ISSN 2218-6182 (online)

World Journal of *Anesthesiology*

World J Anesthesiol 2015 March 27; 4(1): 1-9

Published by Baishideng Publishing Group Inc

WJA World Journal of Anesthesiology

A peer-reviewed, online, open-access journal of anesthesiology

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2011-2015

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WJA World Journal of Anesthesiology

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Four-monthly Volume 4 Number 1 March 27, 2015

EDITORIAL

World Journal of Anesthesiology
Volume 4 Number 1 March 27, 2015

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NAME OF JOURNAL
World Journal of Anesthesiology

ISSN
ISSN 2218-6182 (online)

LAUNCH DATE
December 27, 2011

FREQUENCY
Four-monthly

Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-85381891
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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
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Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
March 27, 2015

INSTRUCTIONS TO AUTHORS
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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5313/wja.v4.i1.1

World J Anesthesiol 2015 March 27; 4(1): 1-4
ISSN 2218-6182 (online)

EDITORIAL

Anesthesia and acupuncture

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Author contributions: Litscher G as editorial board member was invited by the Editor-in-chief to write this editorial; he drafted the manuscript; all authors contributed substantially to the conception and design and approved the final version of the manuscript; Simonis H and Kröll W revised it critically for content.
Supported by The Austrian Federal Ministries of Science, Research and Economy and of Health and by Eurasia-Pacific Uninet (project "Evidence-based high-tech acupuncture and integrative laser medicine for prevention and early intervention of chronic diseases").
Conflict-of-interest: None.

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Fax: +43-316-38513908
Received: November 6, 2014
Peer-review started: November 9, 2014
First decision: December 17, 2014
Revised: December 22, 2014
Accepted: December 29, 2014
Article in press: December 29, 2014
Published online: March 27, 2015

Abstract

Using acupuncture instead of anesthetics to induce analgesia was performed in China many years ago in surgical anesthetization. Although many medical units in China's cities and rural areas are applying these techniques in operations, it should be pointed out that acupuncture anesthesia is still in the process of development and is of next to no practical and even less scientific value in the western world. However, acupuncture-assisted anesthesia can be useful also in countries other than China.

Key words: Anesthesia; Acupuncture; Anesthesiology; Acupuncture-assisted-anesthesia; Sedation

Core tip: Acupuncture anesthesia has been converted into acupuncture-assisted anesthesia in China. Acupuncture-assisted anesthesia reduces the demands of anesthetics and the post-operative complications and has a potential organ protective effect.

Litscher G, Simonis H, Kröll W. Anesthesia and acupuncture. *World J Anesthesiol* 2015; 4(1): 1-4 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i1/1.htm DOI: http://dx.doi.org/10.5313/wja.v4.i1.1

INTRODUCTION

Using acupuncture instead of anesthetics to induce analgesia was performed in China many years ago in surgical anesthetization. Although many medical units in China's cities and rural areas are applying these techniques in operations, it should be pointed out that acupuncture anesthesia is still in the process of development and is of next to no practical and even less scientific value in the western world[1]. However, acupuncture-assisted anesthesia can be useful also in countries other than China.

The objective of this editorial is to present the

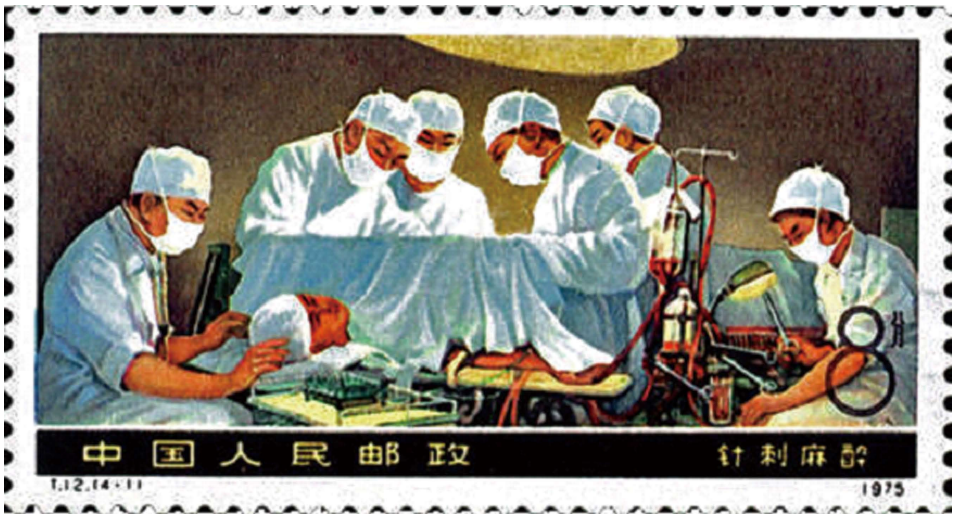

Figure 1 "Acupuncture anesthesia" stamp.

experience with acupuncture-assisted anesthesia that can be found in the scientific literature. Showing traditional approaches to anesthesia may help to tackle problems that are still evident, such as postoperative nausea and pain. Evolution is usually a combination of conservatism and innovative thinking. The editorial should provide an open-minded account of experiences with acupuncture-assisted anesthesia, balanced with skepticism.

FIRST REPORTS ON EVIDENCE AND PERSPECTIVE

For many thousands of years, acupuncture has been proven effective in relieving pain[2]. Acupuncture anesthesia developed from acupuncture analgesia[2].

Two of the first reports concerning acupuncture-assisted anesthesia came from the Shanghai First People's Hospital dated August 30 and September 5, 1958[2,3]. Doctors of Chinese and Western medicine worked together and learned from each other. Dr. Yin Huizhu carried out a tonsillectomy with acupuncture anesthesia without further use of anesthetics[2,3]. In the same year, electroacupuncture anesthesia was used for the first time at the 4th People's Hospital of Xi'an[3]. A pneumonectomy under acupuncture anesthesia was performed in 1960 at the First Tuberculosis Hospital of Shanghai[2]. After this event, many satisfactory results were also obtained in other operations (cardiac surgery, total laryngectomy, cesarean section, surgery on the anterior cranial fossa, *etc.*)[2]. In 1971, Xinhua News reported about acupuncture anesthesia. The headline was "The Chinese medical personnel and scientists successfully invented acupuncture anesthesia", and it was stated that more than 400000 surgical patients had undergone acupuncture anesthesia[3]. On July 26, 1971, even the New York Times published one of the first articles - "Now, let me tell you about my appendectomy in Peking …" - in the Western world on acupuncture anesthesia. Richard Nixon was the first United States President to visit China. At about that time, acupuncture started to become known to people outside Asia. As a consequence, in March 1972, Professor Johannes Bischko from Austria was the first surgeon in the West to perform a tonsillectomy with only acupuncture analgesia[4]. In 1975, as a sign of special recognition, a memorial stamp for the invention of acupuncture anesthesia was issued in China. The stamp shows a scene from the operating theater, and below it is written "acupuncture anesthesia"[5] (Figure 1).

By 1980, many surgeries had been performed under acupuncture anesthesia[2]. From 1986 to 2000, three Chinese national key projects were carried out, supported by the Chinese central government. Famous hospitals, *e.g.,* from Beijing, Shanghai and Chengdu, participated in these studies. In these years, acupuncture mainly played a cooperating role in combination with drugs. Therefore, acupuncture combined with selected drugs was named "acupuncture-drug balanced anesthesia" or "acupuncture-balanced anesthesia"[2]. Because of several reforms in China and the import of modern anesthetic technology, acupuncture-induced anesthesia began to be deemed inadequate. Meanwhile, in China the term "acupuncture anesthesia" has been replaced by "acupuncture-assisted anesthesia" (similar to "acupuncture-balanced anesthesia"). The main goal of this "acupuncture-assisted anesthesia" is the reduction of the dosage of anesthetics, a reduction of the related complications and the protection of the involved organs like brain and heart.

In a documentary from 2006, which is part of a BBC series hosted by Kathy Sykes and has been released on the internet[6], a patient in China is having open heart surgery without general anesthesia, but with acupuncture "instead" (Figure 2). However, the report is massively biased to exaggerate the role of acupuncture. It is casually mentioned that the patient

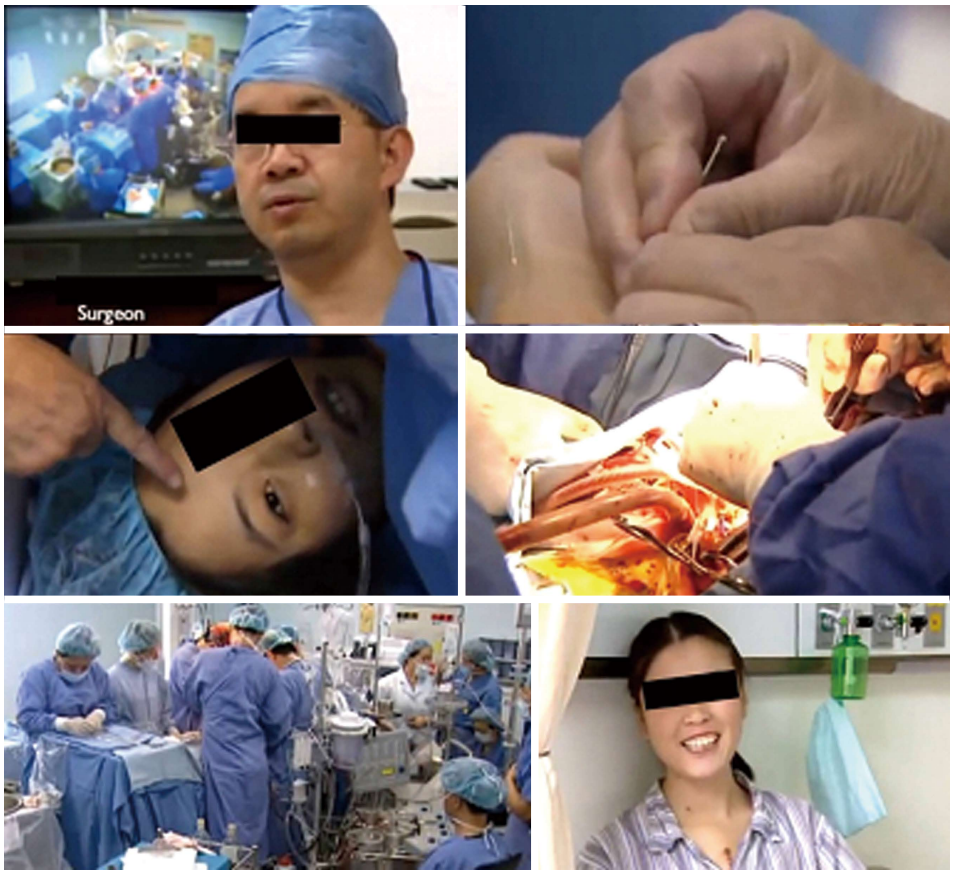

Figure 2 The photos show cardiac surgery under acupuncture-drug balanced anesthesia at the Renji Hospital, Shanghai[6].

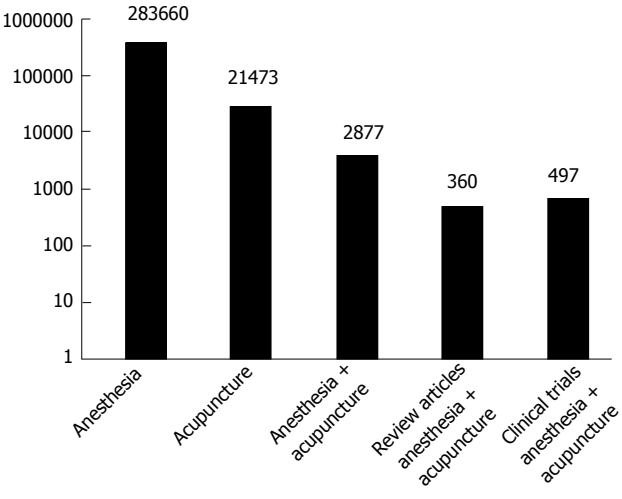

Figure 3 Scientific database research.

had undergone sedation and local anesthesia (her chest was numbed), as if this was a tiny detail[7]. There is no mention of whether or not you could have the same procedure with conscious sedation and local anesthesia, but without the acupuncture[6,7].

The scene in the BBC documentary[6,8] which shows the 21-year-old patient undergoing heart surgery punctured with needles left viewers under the strong impression that acupuncture was providing immense pain relief. However, Singh reported in "The Telegraph"[9] that "in addition to acupuncture, the patient had a combination of three very powerful sedatives (midazolam, droperidol, fentanyl) and large volumes of local anaesthetic injected into the chest"[9].

Although acupuncture-assisted anesthesia for open heart surgery has declined in recent years, there is a renewed interest in it due to the escalating medical costs. Zhou *et al*[10], for example, came to the conclusion that a combined acupuncture-medicine anesthesia strategy can reduce the postoperative morbidity and medical costs in patients undergoing open heart surgery under cardiopulmonary bypass[10].

It is the authors' opinion that acupuncture-anesthesia alone will never be used in the western world, since modern technology offers better and safer possibilities. However, acupuncture does represent a very good method to alleviate the side-effects of anesthesia such as post-operative nausea and vomiting, pain and dizziness, which has been shown in several studies[1,11-13].

A literature research in the scientific database PubMed (Oct 31, 2014) shows many studies concerning the topic "anesthesia and acupuncture"; there are also almost 500 clinical trials on this topic (Figure 3). Several review articles, *e.g.*, the paper by Lee *et al*[14] in *Pain*, concluded that "This review does not support the use of acupuncture as an adjunct to standard anesthetic procedures during surgery"[14].

CONCLUSION

Acupuncture anesthesia has been converted into acupuncture-assisted anesthesia in China. Acupuncture-assisted anesthesia reduces the demands of anesthetics and the post-operative complications and has a potential organ protective effect. Therefore, acupuncture may be an excellent adjunct to reduce peri- and postoperative pain. This conclusion, however, has to be explored in detail in further scientific studies.

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L- Editor: A **E- Editor**: Wu HL

World Journal of Anesthesiology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5313/wja.v4.i1.5

World J Anesthesiol 2015 March 27; 4(1): 5-9
ISSN 2218-6182 (online)

EDITORIAL

Benzodiazepine in spinally mediated analgesia

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Conflict-of-interest: There is no conflict of interest.

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Telephone: +81-3-57810700
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Received: December 8, 2014
Peer-review started: December 9, 2014
First decision: December 26, 2014
Revised: January 5, 2015
Accepted: January 15, 2015
Article in press: January 19, 2015
Published online: March 27, 2015

Abstract

Since benzodiazepine/γ-amino butyric acid receptor was found in the spinal cord, there have been many studies to investigate analgesic effects of midazolam, a water-soluble benzodiazepine in the spinal cord. In animal experiments, intrathecal midazolam has analgesic effects on visceral pain, thermal pain, and inflammatory pain, and it has synergistic or additive effects with different kinds of analgesics acting on different receptors. In human study, intrathecal midazolam has analgesic effects on back pain, somatic pain, but not visceral pain. The analgesic effect lasts long and intrathecal midazolam induces sedation, which is the effect in the brain. Epidural midazolam is less studied than intrathecal midazolam. Epidural midazolam has segmental analgesia for postoperative pain, and adding midazolam to bupivacaine increased duration of analgesia. It also induces sedation, which might be the effects of midazolam coming from cerebrospinal fluid to the brain. Some histopathological studies in animals showed neurotoxicity of midazolam, while there are no toxic side effects in many human studies of intrathecal and epidural midazolam. Therefore, we need clinically relevant animal studies for neurotoxicity and analysis of complications in patients already studied with intrathecal and epidural midazolam to give final conclusion.

Key words: Spinal cord; Analgesia; Benzodiazepine; Neurotoxicity; Intrathecal; Epidural

Core tip: Intrathecal or epidural midazolam has analgesic effect acting on benzodiazepine/γ-amino butyric acid receptor in the spinal cord. Many clinical and animal studies showed no harmful side effects, while in some animal experiments, neurotoxicity was found. Therefore, we need further evidence to bring it into clinical application.

Nishiyama T. Benzodiazepine in spinally mediated analgesia. *World J Anesthesiol* 2015; 4(1): 5-9 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i1/5.htm DOI: http://dx.doi.org/10.5313/wja.v4.i1.5

INTRODUCTION

The first spinal analgesia was done in 1898 by August Bier using cocaine[1]. Since then many local anesthetics has been used for spinal anesthesia without neurotoxicity studies. Recent decades, morphine, hydromorphone, fentanyl and sufentanil are also administered intrathecally with a few neurotoxicity studies, too. Intrathecal opioids induce many side

effects; respiratory depression, nausea, vomiting, sedation, pruritis, constipation, urinary retention, cognitive impairment, and headache. Therefore, to avoid these side effects, other agents such as baclofen, clonidine, etc. for intrathecal use have been enthusiastically investigated.

The benzodiazepine/γ-amino butyric acid (GABA)$_A$ receptor coupling in the spinal cord has a great role in analgesic mechanisms[2]. Therefore, since 1980's, many clinical and animal studies have been performed to investigate analgesic effects of intrathecal midazolam, a water-soluble benzodiazepine[3,4] as substitution for opioids. However, clinically intrathecal midazolam is not widely used because some animal experiments showed neurotoxic results[5-7]. The review by Yaksh *et al*[8] pointed that intrathecal midazolam is neurotoxic, therefore, it should not be used in human, while some animas studies showed no neurotoxicity.

Now United States Food and Drug Administration (FDA) approves only morphine, ziconotide, and baclofen for human intrathecal use. However, no neurotoxicity studies were found for ziconotide and only a few have been performed for baclofen and morphine. Therefore, the reason of the FDA approval for only these three agents, and why the review by Yaksh *et al*[8] targeted only midazolam and did not deny using other agents intrathecally are not clear.

This article summarizes clinical and experimental evidences of spinally mediated analgesia by benzodiazepines, especially midazolam.

ANALGESIC MECHANISMS

GABAergic neurons and GABA$_A$ receptors exist in the spinal cord dorsal horn and they inhibit the conductance of pain signals from periphery to central nervous system. The decrease of this inhibition induces pain[9]. The analgesic effects of benzodiazepines are mainly mediated *via* benzodiazepine/GABA$_A$ receptors in the spinal cord[10,11]. Midazolam decreases excitatory synaptic transmission at the benzodiazepine/GABA$_A$ receptor in interneuron, then decreases excitability of spinal dorsal horn neurons[12], and increases duration and amplitude of GABAergic synaptic current by acting on the benzodiazepine/GABA$_A$ receptor in substantia gelatinosa neurons[13]. Thus, intrathecal midazolam induces segmental analgesia[11]. Midazolam also acts on δ receptors in the spinal cord to release endogenous opioid[14], and directly acts as an agonist at κ opioid receptors[15], but does not have a local anesthetic action[4].

BASIC RESEARCH

In 1987, Goodchild *et al*[4] showed that intrathecal midazolam had analgesic effects in rat, and in 1993, analgesic effects of intrathecal midazolam on visceral pain in rabbits were reported by Crawford *et al*[16]. Another benzodiazepine, chlordiazepoxide has also spinally mediated analgesic effects[17].

Many studies have shown interaction between intrathecal midazolam and other agents acting on different receptors. In the isolated neonatal rat spinal cord, midazolam and alfentanil had synergistic depression of nociceptive neurotransmission[18]. Intrathecal midazolam potentiated analgesic effects of intrathecal morphine, but intracerebroventricular midazolam inhibits analgesia by intracerebroventricular morphine, which are mediated by GABA$_A$ receptors in the spinal cord and brain, respectively[19]. Intraperitoneally administered midazolam had analgesic effect on inflammatory acute and facilitated pain, but not on acute thermal pain, while intrathecal midazolam had analgesic effects on both thermal and inflammatory pain in rat[20]. The 50% effective dose for thermal pain was higher than that for inflammatory pain, therefore, the dose of intraperitoneal midazolam used in this study was not enough dose to have spinally mediated analgesia for thermal pain. Intrathecally administered midazolam has synergistic or additive analgesic effects with N-methyl-D-aspartate receptor antagonist, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonist[21,22], clonidine, α2-adrenergic receptor agonist[23], bupivacaine[24], and serotonin[25] on thermal and inflammatory pain in rat. However, intrathecal midazolam and nicotinic cholinergic agonist had antagonistic effects on thermal acute pain, while they have synergistic or additive effects on inflammatory pain[26]. From these animal studies, intrathecal midazolam is effective analgesic.

NEUROTOXICITY

Before clinical application of intrathecal agents, neurotoxicity must be investigated. However, many spinally or epidurally administered agents; lidocaine, morphine, etc. in human have not been studied enough for their neurotoxicity. Lidocaine is neurotoxic at high concentrations[27], and even at clinical concentrations it changed neurophysiology[28]. In spinal anesthesia, lidocaine induced abnormal neurological symptoms[29]. No histological changes were reported with epidural morphine[30,31], while inflammatory response and fat cell necrosis by epidural morphine were reported[32]. Morphine also induces apoptosis in the brain and spinal cord[33], and neuron death[34]. Fentanyl is absent from neurotoxicity studies. Even natural peptides and amino acids are neurotoxic when administered at high concentration[35].

Some animal studies observed neurotoxicity of intrathecal midazolam[36-40]. Werdehausen *et al*[41] showed that adding midazolam to lidocaine increased neuronal cell death by additive induction of mitochondrial apoptosis. However, other animal studies showed no neurotoxicity of intrathecal midazolam[5-7]. Even a continuous intrathecal infusion of midazolam for 43 d in sheep and pigs showed no histopathological changes in the spinal cord[6]. Many of these studies used

intrathecal catheter, which itself might induce some histopathological changes in the spinal cord. The direct administration of midazolam 10 mg on the cat spinal cord, which dose is quite higher than clinical doses, did not induce any histopathological changes including inflammatory changes[42]. This study did not use any catheters, therefore, it excluded the influence of physical changes. However, observation period in this study was only 6 h after administration. The acidic pH of midazolam might have some damage to the spinal cord, but midazolam administered intrathecally does not decrease pH of cerebrospinal fluid less than 7[43]. Therefore, acidity of midazolam could be neglected.

Neurological symptoms did not increase with intrathecal midazolam in human study by Ho *et al*[44]. The cohort study of safety of intrathecal midazolam investigating 1100 patients showed no neurological and urologic adverse symptoms by intrathecal midazolam[45], and many other clinical studies cited below showed no irreversible adverse effects. Therefore, discussion about neurotoxicity of midazolam did not finish yet until large clinically mimetic animal neurotoxicity studies. In addition, follow up of the patients received intrathecal or epidural midazolam is necessary.

CLINICAL STUDIES

Spinal administration

Intrathecal midazolam has analgesic effects on chronic back pain[46,47] and somatic pain, but not visceral pain[3]. The effect of intrathecal midazolam was segmental and had no effects on sympathetic tone and reflexes[48]. The duration of analgesia by intrathecal midazolam was less than 6 h, which became longer than 6 h by adding diamorphine[49]. Prochazka *et al*[47] showed that analgesic effects on chronic low back pain lasted 9.7 wk, while in 13% no analgesia was obtained. The duration of sensory block by intrathecal midazolam lasted for 72 h in the study by Goodchild *et al*[3]. Many studies showed that adding intrathecal midazolam to bupivacaine increased duration of analgesia[48-55]. Only one study showed no change in the duration of analgesia by adding intrathecal midazolam to bupivacaine, while duration of motor block lasted longer without changing the duration of sensory block[56]. Yegin *et al*[53] reported that the onset and recovery from sensory and motor blocks were not altered, while Wu *et al*[57] showed fastened recovery of motor function. Therefore, intrathecal midazolam might increase duration of analgesia by bupivacaine, but duration of motor and sensory block might not always increase. Intrathecal midazolam induced sedation[53,58] and decreased nausea and vomit[44,54,58], which are the effects in the brain not in the spinal cord, and they are advantages for pain management.

Epidural administration

In comparison with intrathecal midazolam, only a few studies have been performed for epidural midazolam. The first report of epidural benzodiazepine was by Lin *et al*[59], which showed that epidurally administered diazepam by mistake induced reversible motor and sensory block and analgesia.

Epidural midazolam induced wide range of analgesic dermatomes[60-64], and fastened onset of sensory block and time to peak effect, and prolonged duration of motor and sensory blocks of epidural lidocaine[65]. Continuous epidural administration with bupivacaine, midazolam increased analgesic effect[66-68]. This combination potentiated analgesic effect of epidural morphine, but inhibited that of fentanyl[69]. This different effect with morphine and fentanyl might be due to their different lipophilicity. Midazolam antagonized the effect of fentanyl in the brain, but potentiated the effect of morphine in the spinal cord.

Epidural midazolam induced sedation, but serum concentration of midazolam was less than that induces sedation. Therefore, midazolam went into the brain by cerebrospinal fluid[70]. However, in an animal study, after epidural administration of midazolam, concentration of midazolam in cerebrospinal fluid was only 3% of that in serum[71], while it might be enough concentration to induce sedation in the brain.

CONCLUSION

Intrathecally or epidurally administered midazolam has analgesic effect by acting on the benzodiazepine/$GABA_A$ receptor in the spinal cord. It induces sedation and decreases nausea and vomit, which are the advantage induced by the action in the brain. Neurotoxicity of midazolam is still controversial, while no clinical neurotoxicity was found. Therefore, further clinically mimetic animal neurotoxicity study is necessary.

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Published by **Baishideng Publishing Group Inc**
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ISSN 2218-6182 (online)

World Journal of *Anesthesiology*

World J Anesthesiol 2015 July 27; 4(2): 10-48

Published by Baishideng Publishing Group Inc

WJA World Journal of Anesthesiology

A peer-reviewed, online, open-access journal of anesthesiology

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WJA World Journal of Anesthesiology

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Four-monthly Volume 4 Number 2 July 27, 2015

World Journal of Anesthesiology
Volume 4 Number 2 July 27, 2015

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NAME OF JOURNAL
World Journal of Anesthesiology

ISSN
ISSN 2218-6182 (online)

LAUNCH DATE
December 27, 2011

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Four-monthly

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World J Anesthesiol 2015 July 27; 4(2): 10-12
ISSN 2218-6182 (online)

EDITORIAL

Critical importance of tracheal tube cuff pressure management

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Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: None.

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Received: January 25, 2015
Peer-review started: January 30, 2015
First decision: April 10, 2015
Revised: April 29, 2015
Accepted: May 27, 2015
Article in press: May 28, 2015
Published online: July 27, 2015

Abstract

The ideal range for tracheal tube cuff pressures is usually taken to be between 20 to 30 cm H_2O. This is easily measured with a cuff pressure manometer and should be measured in each instance. The importance of tracheal tube cuff pressures is highlighted by the spectrum of airway complications that can occur with incorrect cuff pressures. High cuff pressures can result in complications ranging from sore throat and hoarseness to tracheal stenosis, necrosis, and even rupture. In such cases, the postulated causative factor is diminished blood flow to tracheal mucosa due to excessive cuff pressure on the tracheal wall. This hypothesized ischemic injury then produces healing fibrosis months or even years later. On the other hand, cuff pressures that are too low place the patient at risk for aspiration of gastric contents and consequently, aspiration pneumonitis and pneumonia. This is why the authors recommend that cuff pressures be measured following all intubations.

Key words: Tracheal tube cuff pressure; Tracheal injury; Tracheal stenosis; Patient safety; Intubation

Core tip: The ideal range for tracheal tube cuff pressures is typically between 20 to 30 cm H_2O and is easily measured with a cuff pressure manometer. The importance of tracheal tube cuff pressures is highlighted by the spectrum of complications that can occur: high cuff pressures can result in complications ranging from sore throat and hoarseness to tracheal stenosis, necrosis, and even rupture, while cuff pressures that are too low place the patient at risk for aspiration and consequently, aspiration pneumonitis and pneumonia.

Feng TR, Ye Y, Doyle DJ. Critical importance of tracheal tube cuff pressure management. *World J Anesthesiol* 2015; 4(2): 10-12 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/10.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.10

Anesthesiologists who spend the bulk of their clinical time in ear-nose-throat (ENT) and bronchoscopic pro-

cedures (such as the third author) see a surprising number of cases of tracheal stenosis that appear to be related to prior tracheal intubation. In such cases, the postulated causative factor is diminished blood flow to tracheal mucosa due to excessive cuff pressure on the tracheal wall. This hypothesized ischemic injury then produces healing fibrosis months or even years later[1-4]. However, despite a substantial body of published literature dealing with cuff pressure monitoring[5-8], routine monitoring of endotracheal tube (ETT) cuff pressure in clinical practice is rarely done and no established guidelines exist to direct its measurement[9].

The ideal range for ETT cuff pressures is typically between 20 to 30 cm H_2O[10-13] and is most reliably assessed with direct continuous manometers during the operative period[14]. One can easily and inexpensively display real-time cuff pressures using an ordinary patient monitor with invasive pressure capability as follows[5]. An ordinary pressure transducer is first electronically connected to the pressure channel of the monitor and zeroed. Next, the hydraulic end of the transducer is connected to the pilot balloon/cuff inflation line of the ETT using air-filled tubing and a three-way stopcock. A 10 mL syringe inserted in the side arm of the stopcock allows air to be added or removed. Finally, a male plug ("dead ender") is placed in the remaining port of the pressure transducer to seal the system (Ordinarily this port is hooked up to a high-pressure fluid source to make a flush system).

Despite this, few anesthesiologists use such methods in daily clinical practice and typically rely on less quantitative methods to estimate the cuff pressure (Table 1), often with poor compliance. Additionally, these commonly used techniques are much less accurate and often poor estimates of ETT cuff pressures[9,14]. This dilemma is not remedied by clinical experience, as studies have shown that inaccurate cuff pressure assessments can occur in the hands of even the most seasoned anesthesiologists[11,15]. On the contrary, Wujtewicz *et al*[15] concluded that anesthesiologists may be worse at estimating cuff pressure than a decade ago.

The importance of ETT cuff pressures is highlighted by the spectrum of complications that can occur outside the ideal pressure range. High cuff pressures can result in complications ranging from sore throat and hoarseness[16,17] to tracheal stenosis, necrosis, and even rupture[18-21]. Conversely, lower cuff pressures place the patient at risk for aspiration and consequently, aspiration pneumonitis and pneumonia[22,23]. Although certain complications such as tracheal stenosis remain rare entities, the serious morbidity associated with the disease should be balanced against the ease and low expense of intra-operative cuff pressure monitoring.

Despite the large body of literature dealing with cuff pressure monitoring and the relative ease with which accurate intra-operative cuff pressure monitoring can be implemented, there remains a lack of guidelines and recommendations regarding the issue. Given the fact that studies have shown cuff pressures over 30 cm H_2O occur in about 50% of cases where cuff inflation was performed using pilot balloon palpation[24], it raises the question of why mandatory monitoring is not standard of practice. As a profession, should we not be more vigilant with regards to tracheal tube cuff pressures? We say yes.

Table 1 Common techniques for assessing endotracheal cuff pressures[5,9,24]

Method	Description
Minimal occlusive volume technique	Determination of volume of air to inject into cuff based on how much is required to eliminate audible end-inspiratory leak with positive pressure ventilation
Minimum leak technique	Determination of volume of air to injection into cuff based on how much is required to auscultate a small end-inspiratory leak
Predetermined volume technique	Injection of pre-determined volume of air to inflate cuff
Palpation technique	Palpation of pilot balloon after inflating endotracheal cuff
Direct intracuff pressure monitoring	Use of a pressure transducer to directly provide a quantitative pressure reading

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P- Reviewer: DeSousa K, Hadianamrei R, Higa K, Spasojevic SD
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Yan JL

World Journal of Anesthesiology

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DOI: 10.5313/wja.v4.i2.13

World J Anesthesiol 2015 July 27; 4(2): 13-16
ISSN 2218-6182 (online)

EDITORIAL

Translating the expression of pain in the face of uncertainty: The importance of human pain experiments for applied and clinical science

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Conflict-of-interest statement: Eric Kruger and Jacob M Vigil do not report any conflict of interest in the ideas associated with or the production of this manuscript.

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Received: January 28, 2015
Peer-review started: January 31, 2015
First decision: March 20, 2015
Revised: April 12, 2015
Accepted: May 5, 2015
Article in press: May 6, 2015
Published online: July 27, 2015

Abstract

This brief commentary attempts to provide a concise synthesis of social psychology experiments that inform an interpretation of clinical pain. From a social perspective the expression of pain is a complex phenomenon that is greater than the patient's physiology. Numerous experiments show that pain is modulated by social and contextual factors. These experiments point to the role of the listener as a social agent that can modulate the patient's expression. Within the clinical setting the patient's pain experience can be understood as the uncertainty of physical damage and their expression as an attempt to reduce that uncertainty. How successfully this occurs is in part dependent on the empathetic reception of the provider. Chronic pain is a state that is challenging to effectively model in humans but may persist in patients due to an inability to receive effective empathetic reception at the critical time of need (at or near onset). Rather than focusing on pain's alleviation future avenues of pain interventions may do well by turning attention to the most effective ways to impart a message that the patient will be "okay" in a genuinely empathetic manner.

Key words: Pain; Social psychology; Uncertainty; Fear; Catastrophizing; Contextual modulation; Health; Medicine; Pain management

Core tip: The experience of pain has much to gain from a social psychology perspective where experiments modulate the patient's context and affect their expression. Clinicians and providers should understand that listening sends powerful social cues back to the patient in terms of empathetic feedback. When this feedback is provided in a timely fashion (at or near the time of onset) and in combination with ruling out serious medical pathology a clinician can provide powerful signals that changes patient's experience of pain.

Kruger E, Vigil JM. Translating the expression of pain in the face of uncertainty: The importance of human pain experiments for applied and clinical science. *World J Anesthesiol* 2015; 4(2): 13-16 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/13.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.13

Pain is difficult to study. Typically, clinical pain originates at a specific time and location that is far removed from the controlled confines of a healthcare setting. Experimental pain studies fill the gap between healthcare settings and real-life conditions. Historically, experimental pain studies have focused on medical treatments to decrease discomfort. More recently, social scientists have begun to explore the social and contextual contingencies that surround the experience and expression of pain. Findings thus far reveal a rich but complicated relationship between pain-evoking stimulus and the context in which it occurs. Here we briefly review a social psychological perspective of pain expression and how that perspective might inform interventional philosophy for clinical practice.

Our understanding of pain has been drastically overhauled during the last 50 years. Before this remaking, the Cartesian model of perception guided medical reasoning as follows: a pain stimulus leads to a pain experience, which leads to pain's expression. Initially, this framework fit nicely with medicine's imperative to reduce signs and symptoms (pain's expression) by eliminating the organic cause of the stimulus. However, as empirical observations accumulated, pain's elimination did not follow. Further, the stories of soldiers expressing little pain at war and medicine's inability to find the organic origins of pain both confounded and challenged 20th century investigators. It was the original work by Melzack and Wall that began to dismantle the Cartesian relationship between stimulus, perception and expression[1].

What was originally viewed as an obligatory relationship between stimulus and expression can now be understood as two fundamental parts: stimulus and its relationship to experience and the relationship of that experience to pain's expression. The reaction to aversive stimulus has been called the expression of pain - an objective and quantifiable behavior that occurs alongside the private aversive sensational experience.

Clinicians might not consider the relationship between the sensation and the expression of pain a necessary division but it demands considerable attention. Our own private experience serves a clear example of this difference - how often do we express pain differently in different social contexts? The distinction between internal and external causes of pain perception and the voluntary and involuntary expression pain is what psychology pain experiments seek to explain.

Psychological research has shown the limits of introspection for understanding human behaviors. Social psychologists have long shown that explicit verbal questioning of a subject does not lead to an accurate description of the causes of their behavior[2-4]. The experience of pain is not exceptional in this respect. Individuals given an identical stimulus will report their pain differently based on the immediate social context they are embedded[5-8]. Further this difference in reporting occurs outside the direct awareness of the subject[9]. So where physiology has shown that a pain stimulus does not necessitate a painful experience, social psychology has shown that the pain experience does not necessitate pain's expression.

The challenge for clinicians is to synthesize these diverse findings in a way that allow for their parsimonious use in the clinical setting. In order to do this we encourage the reader to take on a broader view than simply the medical treatment for the alleviation of pain. From a social psychological perspective, pain's expression could be viewed as accomplishing one very important biological goal: to decrease the immediate uncertainty that accompanies the pain experience *via* facilitating social contact and closeness.

Several animal and human studies of experimental pain have shown that uncertainty is a powerful modulator of pain's expression[10-12]. From the human perspective this uncertainty can best be understood in both the fear and catastrophizing constructs that have been applied to pain[13,14]. Both constructs uniquely help the clinician understand the aspects of uncertainty that the patient faces. This view is also supported by findings which demonstrate that areas commonly associated with processing affective behaviors - the insula, amygdala and cingulate - also process uncertainty[15,16]. The cognitive and behavioral overlap between the shared aspects of physical and social pain[17] has also been observed in social experiments[18,19].

Returning to the division between the experience and expression of pain, the difference between the patient who chooses to express their pain and the one who does not may amount to the uncertainty that accompanies the aversive stimulus, as well as the uncertainty of social defection (social harm) of other people in the immediate context. Humans are the quintessential social animal and seek interpersonal certainty in their social environment. The patient seeks this certainty (about the present and future environments) when the expression of pain occurs[20]. The updating of expectations can be due to characteristics of a health provider's interaction (implicit) as well as their explicit message. In other words what mediates whether an individual accepts a persistent pain experience as an inevitable part of the human experience or goes onto develop a chronic expression of pain can be the result of two dimensions: interpersonal trust (*i.e.*, safety and certainty in the social interaction) and the uncertainty of the aversive stimulus.

The dimensions of social and physical uncertainty interact during pain's assessment, which can both potentiate pain expression (*e.g.*, low uncertainty of social agents; intimacy-induced hyperalgesia) and attenuate pain expression (*e.g.*, high uncertainty of social agents; fear-induce hypoalgesia). Following this reasoning, it is the uncertainty of one's physical condition that accompanies the aversive experience that motivates the patient to find a sympathetic ear to express their pain, and the perception of trustworthiness (lack of threat) of people in the immediate social context that moderates the translation of pain sensations into momentary pain expression[21].

To put this in a more clinically concrete example, the clinician who does not engender the patient's trust

is likely to inhibit the patient's expression. Likewise a clinician who earns more of the patient's trust will in turn receive more of the patient's expression. A clinician may be tempted to hope that the inhibition of a patient's expression is the same as experiencing less pain. Yet no such guarantee can be given. Further, the only way to for the clinician to encourage a dialogue about the significance and the meaning of one's pain - in order to reduce the averseness of physical uncertainty - is by its expression. Therefore in crafting an empathetic dialogue it is imperative for a clinician to work at earning the patient's trust.

Turning to interventions for pain, in the absence of signs of serious pathology, perhaps the best treatment is the genuine message by providers that the patient is physically safe (*i.e.*, physical damage is not continuing to occur) and that there is no reason to expect that a recovery will not occur. This might be as simple as saying "you're alright" but often might involve more than just direct explicit messaging. For example, the use of therapeutic touch, empathetic listening or allowing the patient to fully tell their story may all be necessary parts of the therapeutic ritual (referred to as the placebo mechanism) that may provide the contextual security the patient is seeking[22,23]. Further, rather than the provider following the inclination to provide immediate relief we strongly feel that having open empathetic conversations about the relation of the pain experience to patients' values and functioning is the best way proceed.

Finally, we find ourselves full-circle by concluding that acute pain and chronic pain are different, each in terms of their precipitating stimuli, contextual influences and associations with other aspects of affect (*e.g.*, emotional valence). Experimental social manipulations of pain are performed acutely and no model exists to experimentally induce chronic pain in humans. Additionally, chronic pain represents an unruly challenge to the patient-provider relationship. For example, one challenge may be to reinterpret the patient's expression, an expression that could have persisted because the uncertainty in one's condition was never fully addressed. Instead of allowing for expression to occur providers may be tempted to promise relief alongside treatment and while this promise may provide the temporary certainty that the patient craves, when the pain returns, doubt is likely to creep back in. Repeated enough times, the patient in this situation may become caught in a cycle. Breaking this cycle may not necessarily be about fixing the patient but improving the provider's ability to form an open and empathetic discourse about pain.

We humbly accept that treatment of pain is a course that is littered with challenges and even this parsimonious perspective will not fully account for all the variability encountered along the way. A social psychological perspective has much to contribute to the study of pain. Given the extensive evolutionary history that the expressive role of pain has played in our survival and its biological robustness it may be counterproductive and even professionally stifling to consider a world where the elimination of human pain is possible. As providers we cannot control nor predict and thus must remain tentative about the unanticipated physical, social and/or emotional traumas that our patients can and will experience. However, after the patient's expression of pain to an empathetic clinician and serious disease related pathology is ruled out, what remains for the clinician is building a relationship that allows for the genuine forecasting that life is (and will be) alright for the patient. It is when this message is delivered carefully, responsibly and empathetically that the patient can learn to face the uncertainty of the experience of pain with less averseness.

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P- Reviewer: Boucek C, Rodella LF **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Yan JL

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5313/wja.v4.i2.17

World J Anesthesiol 2015 July 27; 4(2): 17-29
ISSN 2218-6182 (online)

REVIEW

Pharmacokinetics and pharmacodynamics of lignocaine: A review

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Conflict-of-interest statement: There are no conflicts of interests declared by any of the authors.

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Received: November 2, 2014
Peer-review started: November 4, 2014
First decision: November 27, 2014
Revised: March 20, 2015
Accepted: April 10, 2015
Article in press: April 14, 2015
Published online: July 27, 2015

Abstract

Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. Being an amide-type local anesthetic and Class 1b antiarrhythmic, lignocaine is most frequently used clinically for its anesthetic and antiarrhythmic benefits. However, lignocaine has important antinociceptive, immuno-modulating, and anti-inflammatory properties. Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects. In addition we review the dosing regimes and infusion kinetics of lignocaine in the clinical setting. Finally, we review the evidence for ligocaine's modulation of the inflammatory response during major surgery and its specific effects on cancer recurrence. These indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth.

Key words: Lignocaine; Humans; Pharmacokinetics; Pharmacodynamics; Adult

Core tip: Lignocaine is a widely used amide-type local anesthetic and Class 1b antiarrhythmic. In addition to its anesthetic and antiarrhythmic effects, lignocaine has

important analgesic, antinociceptive, immuno-modulating, and anti-inflammatory properties. Understanding the pharmacokinetics and pharmacodynamics of lignocaine will enable clinicians to safely prescribe lignocaine in a variety of clinical settings.

Weinberg L, Peake B, Tan C, Nikfarjam M. Pharmacokinetics and pharmacodynamics of lignocaine: A review. *World J Anesthesiol* 2015; 4(2): 17-29 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/17.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.17

INTRODUCTION

Lignocaine, commonly referred to as "Lidocaine", is an amide local anesthetic agent and a Class 1b antiarrhythmic. Lignocaine is an essential drug on World Health Organisation essential drug list, considered efficacious, safe and cost-effective for any health-care system. Despite its ubiquitous use in medicine and surgery, there are few detailed reviews of its pharmacokinetics and pharmacodynamics. We present a focused synopsis of lignocaine's pharmacological composition, indications for use and mechanisms of action, focusing on its anti-inflammatory, immuno-modulating and analgesia effects.

SEARCH

Search strategy

Information pertaining to the pharmacokinetics and pharmacodynamics of lignocaine was examined by performing a literature search of PubMed, Embase and MEDLINE (*via* Ovid), pharmacology textbooks and online sources. Only articles in the English language and human studies were considered. There were no date restrictions applied to the MEDLINE and Central searches. The last search update was in November 2014. The online databases were searched for the following terms: "lidocaine", "lignocaine", "humans", "pharmacokinetics", "pharmacodynamics", "adult". Specifically, clinical information relevant to the pharmacokinetics and pharmacodynamics of lignocaine was included in this literature review.

Search results

Using a combined search strategy, a total of 7311 articles were revealed. A further search confining the results to "humans" and "English language" revealed 216 information sources and titles, of which 81 references were examined for analysis. A detailed review was undertaken that included the screening of manuscript or abstract titles against the key search criterion. A total of 120 articles were included in this review.

BACKGOUND

Nils Löfgren, Bengt Lundqvist, and Holger Erdtman were the three pioneers who were instrumental in the development of LL30, later developed into the solution known today as "lignocaine". Lignocaine, as detailed by Professor Wildsmith[1-3], was first synthesized in 1942, approved for use in humans and launched in 1948 in Sweden, patented in United States in 1948, and launched in 1949 after Food and Drug Administration approval. Lidocain and Xylocain were the original proprietary and trade names chosen for LL30: Lidocain because it is an acetanilide, and Xylocain because m-xylidide is the major reagent in its synthesis. In the United States the "e" was added to each, hence the names Xylocaine and Lignocaine. Lignocaine was the generic name in the United Kingdom from 1950 until Recommended International Non-proprietary Names were required by European law. The name was derived from the Greek "xylo", or the Latin, "ligno", both meaning "wood" originally[4].

Interestingly, cardiologists discovered the antiarrhythmic effects of lignocaine accidentally during surgical procedures requiring the local anesthetic's use. Previous pharmacologic screening for novel cardiovascular drugs led to the discovery of anti-arrythmic and local anesthetic activity of local anesthetic agents. In this context it was demonstrated that local anesthetic agents were effective in suppressing ventricular arrhythmias, a property common to all Class 1 antiarrhythmic agents.

PHARMACOLOGICAL COMPOSITION

Lignocaine, 2-diethylaminoaceto-2',6'-xylidide ($C_{14}H_{22}N_2O$), is a amide local anesthetic and a Class 1b antiarrhythmic agent according to the Vaughn Williams classification[5]. A Class 1b antiarrhythmic agent binds to open sodium channels during phase 0 of the action potential, therefore blocking many of the channels when the action potential peaks. Lignocaine is a stable, crystalline, colourless solid whose hydrochloride salt is water soluble[6]. Solutions for injection are available with or without adrenaline. All lignocaine solutions should be protected from light and maintained at a room temperature of approximately 25 degree Celcius or 77 degree Fahrenheit[7].

INDICATIONS

The indications of lignocaine include the requirement for local, neuraxial, regional or peripheral anesthesia by infiltration, block or topical application, or the prophylaxis or treatment of life-threatening ventricular arrhythmias. It has also been extensively used for chronic and neuropathic pain management, and more recently as an intravenous infusion for the management of postoperative analgesia and surgical recovery.

MECHANISM OF ACTION

Local anesthetic blockade

Similar to other local anesthetics, the mechanism of action of lignocaine for local or regional anesthesia is by

reversible blockade of nerve fibre impulse propagation[7]. Some local anesthetic is removed by tissue binding and circulation when lignocaine is infiltrated near a nerve[8]. The remaining anesthetic enters the nerve cells by diffusion through membranes. Lignocaine then binds to sodium channels, causing a conformational change that prevents the transient influx of sodium, therefore depolarisation[9]. All potentially excitable membranes are affected, however sensory fibres are blocked preferentially because they are thinner, unmyelinated and more easily penetrated[10]. Lignocaine's onset of action is rapid, and blockade, whilst dependent of dose given, concentration used, nerves blocked and status of the patient, may last for up to 5 h when administered as a peripheral nerve block[7].

Antiarrhythmic effects

An important indication for lignocaine is prophylaxis or treatment of life-threatening ventricular arrhythmias. The mechanism of action of lignocaine for its antiarrhythmic action is by direct effect on mammalian Purkinje fibres. By decreasing the slope of phase 4 and changing the excitability threshold, lignocaine reduces automaticity[9]. This results in a decrease of both the action potential length and the refractory period duration of the Purkinje fibres[11]. The PR interval, QRS and QT durations are not commonly effected by lignocaine[9]. There is no evidence of any important interactions between lignocaine and the autonomic nervous system, thus lignocaine has minimal effect on autonomic tone[11].

Antinociceptive effects

The antinociceptive effects of lignocaine are thought to be attributable to the blockade of neuronal sodium channels and potassium currents[12,13], and the blockade of presynaptic muscarinic and dopamine receptors[14,15]. Local anesthetics have also been shown to block sodium and potassium currents centrally at a spinal cord level, specifically targeting the spinal dorsal horn neurons, in addition to their generally accepted peripheral nerve blockade[13]. The mechanisms of these actions at the molecular level are complex and further characterization will be integral in our understanding of central neuraxial anesthesia.

Anti-inflammatory effects

Lignocaine has potential utility as a potent anti-inflammatory agent, although to date well-designed studies are lacking to substantiate its use in most clinical settings. A variety of lignocaine's actions on inflammatory cells have been described. Accumulating data suggests that lignocaine's powerful anti-inflammatory properties may be superior in many ways to nonsteroidal anti-inflammatory drugs and steroids, the traditional anti-inflammatory agents[16,17]. However lignocaine is not approved for this specific indication and potential risks of toxicity (see below), particularly in unmonitored patients, may negate its beneficial antiflammatory effects. Unfortunately, the specific molecular mechanisms involved in the migration of polymorphonuclear granulocytes and free radicals are not well known. Sodium channel blockade can be however excluded. Firstly, because *in vivo* local anesthetic solutions are active at lower concentrations than those required for blockade of the sodium channel, and secondly because sodium channels *in vitro* are often not even detectable in the cell lines that are being investigated[17].

Whilst lignocaine's antinociceptive effects are thought to be secondary to the blockade of neuronal sodium channels and potassium currents[12,13], and the blockade of presynaptic muscarinic and dopamine receptors[14,15], its anti-inflammatory effects are complex and multifactorial. *In vitro* pre-incubation of human polymorphonuclear granulocytes or monocytes with varying concentrations of lignocaine have been reported to inhibit leukotriene B4 release[18], Both leukotriene B4 and prostaglandin E2 can induce edema; therefore the blockade of these cells may explain lignocaine's beneficial effects on tissue inflammation and edema prevention[19]. In these studies, the treatment of the peritoneum with intravenous local anesthetic solutions resulted in a reduction of the amount of Evans blue-albumen extravasated from areas of inflammation, with histological examinations supporting these clinical findings. However, in the perioperative setting, development of edema is complex and multifactorial. To evaluate the effects of intravenous lignocaine on the development of edema in this setting, further clinical studies are required.

Lignocaine has been documented to block the release of interleukin-1 (IL-1), an inflammatory mediator acting on polymorphonuclear granulocytes, which in turn activates phagocytosis, respiratory burst, degranulation and chemotaxis[16,17]. This reduction in the release of interleukins may also contribute to lignocaine's anti-inflammatory effects. *In vitro*, lignocaine, at concentrations of 0.2-20.0 mmol/L, has been shown to inhibit IL-1 production in peripheral blood mononuclear cells[18]. *In vivo* studies have shown that at high micromolar concentrations, lignocaine can inhibit histamine release from human leukocytes, mast cells, and cultured basophils[20]. Accordingly, the anti-inflammatory actions of lignocaine are thought to be attributable to lignocaine's direct effects on macrophage and polymorphonuclear granulocyte function, in addition to its inhibition of the release of several critical markers of the inflammation cascade.

Arachidonic acid (released from phospholipids) and the subsequent generation of bioactive eicosanoids have a critical function in the regulation of tissue preservation and the patho-physiological response to organ injury and ischemia[21]. This critical sequence of biological processes is modified by lignocaine's action on the enzymes phospholipase A2, cyclooxygenase and lipoxygenase. Lignocaine interacts in a dual manner with phospholipase A2; causing inhibition of its activity at high concentrations and stimulating activity at lower concentrations[22,23]. Lignocaine has been shown to inhibit

spontaneous prostaglandin biosynthesis, in early *in vitro* studies[24,25]. Lignocaine administration significantly inhibited prostanoid release and biosynthesis from human gastric mucosa in response to experimental damage[26-28]. In dogs with cardiac arrhythmias the release of prostaglandin was seen to be inhibited during systemic administration of lignocaine[29]. Lastly, topical lignocaine has been shown to inhibit prostaglandin release when used clinically for the treatment of burns in an animal model[30], confirming other studies that report reduced prostaglandin release from gastric mucosa as a result of lignocaine intervention[26]. These inhibitory effects on prostaglandin release may explain some of the powerful antinociceptive and anti-inflammatory effects of intravenous lignocaine described in patients with severe burns[31,32].

Numerous *in vivo* and *in vitro* studies demonstrate the effects that lignocaine have on thromboxane B2 release[26,28,33]. Lignocaine has an inhibitory effect on thromboxane induced platelet aggregation, which may contribute to reduced incidence of venous thrombosis[34,35]. In addition, early studies demonstrate that lignocaine at low concentrations can powerfully inhibit the release of histamine from activated mast cells[36,37]. Lignocaine also has important effects on oxygen free radical production. The inhibition of free oxygen radical formation (such as superoxide anions) by lignocaine has been eloquently demonstrated in clinical trials[38,39]. The mechanism of action of this direct scavenging effect is due to lignocaine's interaction with protein and phospholipid membranes, the interference with mitochondrial radical formation[40], and the prevention of free radical production[41].

Antibacterial activity

Lignocaine has also been shown to possess antibacterial activity[16]. The potent effects of lignocaine on antimicrobial activity are related to lignocaine's concentration and pharmacological structure. Structure is of lesser importance as both amide and ester type local anaesthetics can inhibit bacteria in high enough concentrations[42]. Lignocaine has been shown to have important inhibitory actions on various strains of bacterium, including important Gram-positive cocci such as *Staphylococcus aureus* and *Streptococcus pneumonia*, and Gram-negative bacteria such as *Haemophilus influenza* and *Pseudomonas aeruginosa*[16,43-46]. Lignocaine's anti-bactericidal effects are poorly understood, however complex interactions between the local anesthetic solutions and the bacterial wall[47] or with macromolecules at the surface of the bacterium[44] have been implicated. Functional changes, which include the alterations in the membrane proteins and reductions of membrane fluidity that may be induced by electrostatic interactions between anionic membrane components and cationic local anesthetics, have been implicated mechanisms[45,48,49]. Consequently, various cell and membrane functions such as the DNA binding properties of the cell and membrane-bound ATPase activity may be inhibited[50,51]. The immunomodulating and anti-inflammatory effects of lignocaine are summarized in Table 1.

PHARMACOKINETICS

History

One of the earliest studies evaluating the pharmacokinetic properties of lignocaine was by Friden[52] in 1965. It was observed that lignocaine displayed a rapid onset of action, but of very short duration (between 10-20 min) after the intravenous administration of either 50 or 100 mg boluses doses. In the same year, Beckett *et al*[53,54] reported that lignocaine had a half-life of approximately 10 to 20 min one hour after the administration of an intravenous bolus. Two years later, Gianelly *et al*[55] reported that patients with occlusive coronary artery disease who were administered a continuous intravenous lignocaine infusion, without an initial loading dose, achieved acceptable plateau plasma concentrations within a 30 to 60 min period, suggestive of a 10 to 20 min half-life. Rowland *et al*[56] studied the ability of intravenous lignocaine to control ventricular arrhythmias in order to understand its disposition kinetics, and thus was able to establish safe and effective dosage regimens. Rowland reported a rapid early fall in lignocaine plasma levels after the administration a 50 mg bolus dose. The mean half-life was 7 min. However, they also reported a significantly slower phase (a mean half-life of 108 min), related to the drug's elimination. After a 4-h lignocaine infusion, the average elimination time of 108 min was similar to the elimination half-life of 96 to 108 min reported by Beckett *et al*[54]. Rowland found that lignocaine was primarily eliminated by metabolism, since urine collected 24 h after the bolus contained less than 4% of unchanged lignocaine. The range of elimination half-life was relatively narrow (73 to 133 min) among the subjects evaluated[56]. Beckett *et al*[54] also put forward that de-ethylation of lignocaine to monoethylglycine xylidide was the drug's primary metabolic pathway.

Absorption

Lignocaine's pharmacokinetics have been studied in a variety of clinical models, which include healthy volunteers, subjects with chronic pain syndromes, and patients with cardiac failure[56-59]. The speed of onset of lignocaine is 1 to 5 min after local infiltration, and 5 to 15 min after peripheral nerve blockade. Lignocaine's absorption is dependent upon the total dose administered, the route by which it is delivered, and blood supply to the site of injection[7]. In 1972, Scott *et al*[57] found that upon injection of lignocaine 400 mg, serum levels were highest following infiltration of vaginal mucosa and lowest following subcutaneous abdominal infiltration. Major nerve blocks and epidurals result in intermediate peak plasma levels. Irrespective of the administration site, peak serum levels occurred 20 to 30 min following injection. The addition of adrenalin (1:200000) to the local anesthetic solution reduced peak levels and delayed the rate of absorption.

Table 1 Immuno-modulating and anti-inflammatory effects of lignocaine

Effects	Immuno-modulating and inflammatory actions
Anti-nociceptive and analgesic effects[12,16,17,34,101]	Interaction with nociceptive pathways
	Blockade of neuronal sodium channels
	Blockade of potassium currents
	Muscarinic receptor antagonist
	Blockade of dopamine receptors
	Glycine inhibitor
	Reduction in excitatory amino acids
	Reduction in thromboxane
	Release of endogenous opioid peptides
	Reduction in neurokinins
	Release of ATP-adenosine triphosphate
Wound healing effects[19,38, 39,102-104]	Retardation by reduction of mucopolysaccharide and collagen synthesis
	Reduction in recruitment and metabolic response of
	Inhibition of thrombus formation
	Antithrombotic activity
	Inhibition of platelet aggregation *via* blockade of calcium influx
	Mobilization of intracellular calcium stores
	Inhibition of oxygen free radical production
	Inhibition of inflammatory cytokines
	Inhibition of vascular permeability
	Inhibition of edema formation
Inhibition of immune cell mediators from monocytes[18,105]	Inhibition of interleukin 1α
	Inhibition of interleukin β
	Inhibition of interleukin 8
	Inhibition of tumor necrosis factor
Inhibition of immune cell mediators from neutrophils[18,24-26,28,33,102,106]	Inhibition of prostaglandins
	Inhibition of thromboxanes
	Inhibition of leukotrienes
	Inhibition of lysosomal enzymes
	Inhibition of free radicals
Inhibition of immune cell mediators from mast cells[36]	Inhibition of histamine release
Anti-bactericidal effects[16-18,43-46,107]	Inhibitory actions on *Pseudomonas aeruginosa*
	Inhibitory actions on *Escherichia coli*
	Inhibitory actions on *Staphylococcus aureus*
	Inhibitory actions on *Haemophilus influenza*
	Inhibitory actions on *Mycobacterium tuberculosis*
Anti-viral and anti-fungal effects[16,17,108]	Inhibitory actions on Herpes simplex virus
	Inhibitory actions on *Candida albicans*
Clinical effects in inflammation-related disease[109-117]	Protective effects in acute lung injury
	Protective effects in septic shock
	Protective effects in cardiac ischemia
	Beneficial effects in ischemia-reperfusion injuries
	Protective effects in interstitial cystitis
	Protective effects in ulcerative colitis
	Protective effects in ulcerative proctitis
	Protective effects in burn injuries
	Accelerated return of bowel function in major surgery
	Blockade of airway hyperactivity in asthma
	Treatment of intractable hiccups
	Beneficial effects in traumatic brain injury

Protein binding

When lignocaine is given intravenously to normal subjects, the volume of distribution is 0.6-4.5 L/kg[60]. The plasma binding of lignocaine is inversely proportional to the drug concentration. It is 60% to 80% protein-bound at concentrations of between 1 and 4 mcg/mL[7]. Binding fraction also depends on the plasma levels of the acute phase reactant alpha-1-glycoprotein[9]. Lignocaine has been shown to cross the placenta and blood-brain barrier by simple passive diffusion. Given that proportion of maternal protein binding is greater than that foetal protein binding, the maternal total plasma concentration will be higher, however free lignocaine concentrations will remain the similar in both mother and fetus[7]. Fetal lignocaine concentration may be increased by transmembrane pH gradients, such as fetal acidosis, and associated ion trapping[9]. Lignocaine may exist in ionised or unionised form depending on the pH of the environment. As a weak basic drug, lignocaine tends to be more unionised and able to cross cell membranes in basic media[10]. In fetal acidosis lignocaine crosses the placenta in unionised form, becomes ionised given the acidic environment of the fetal circulation and becomes "trapped", thus increasing fetal lignocaine concentration.

Metabolism and elimination

Lignocaine is dealkylated in the liver by the cytochrome P450 system forming numerous metabolites. Monoethylglycine xylidide and glycine xylidide are the key active metabolites, both of which have reduced potency but have comparable pharmacologic activity to lignocaine[9]. The only reported metabolite of lignocaine found to be carcinogenic in a rat model is 2, 6-xylidine[61]. Its pharmacologic activity is unknown. After the intravenous administration of lignocaine, monoethylglycine xylidide and glycine xylidide concentrations equate to approximate 11% to 36%, and 5% to 11%, respectively, of the total plasma lignocaine concentrations[62].

Hepatic blood flow appears to be a limiting factor in lignocaine's metabolism. The rate of metabolism is slower reduced in patients with congestive cardiac failure, chronic liver disease and hepatic insufficiency, and after acute myocardial infarction[63]. Lignocaine and its metabolites are predominantly renally excreted. Less than 10% of lignocaine is excreted without being metabolised[53,64].

The total body plasma clearance of lignocaine in healthy volunteers has been reported to be approximately 10-20 mL/min per kilogram[62]. The majority of lignocaine elimination occurs in the liver, and since the total body plasma clearance of lignocaine is about 800 mL/min and hepatic blood flow is about 1.38 L/min[65,66], up to 60% of an oral dose is metabolised before entry into the systemic circulation. This accounts for the low plasma lignocaine concentrations observed following a the oral administration of 500 mg lignocaine hydrochloride[67].

Elimination half-life is defined as the rate at which a local anesthetic is removed from the blood. Therefore, the time necessary for 50% reduction in lignocaine blood level is one half-life; two half-lives equates to a 75% reduction, three half-lives to an 87.5% reduction, four half-lives to a 94% reduction, five half-lives to a 97% reduction and six half-lives to a 98.5% reduction. The half-life of lignocaine has been shown to be approximately 100 min following either an infusion lasting less than 12 h or a bolus injection. In this setting lignocaine demonstrates linear pharmacokinetics[56]. However, following an intravenous infusion greater than 12 h, lignocaine exhibits nonlinear, or time-dependent pharmacokinetics. Patients who received prolonged lignocaine infusions following a myocardial infarction, were found to have lignocaine concentrations that continued to rise for approximately 48 h, with the half-life extending up to 4 h[68].

Maximum doses

The maximum doses for lignocaine is based primarily on manufacturer recommendations and animal studies. Animal studies are frequently used to calculate a drug's therapeutic index. This is derived or calculated from the median toxic dose and median effective dose ratio. It is important to note that the complexities found within human populations are not replicated in animal studies. General recommendations based on site of administration, use of vasoconstrictors, and patient factors such as age, hepatic, renal, cardiac diseases, and pregnancy have been attempted. However due to the lack of quality data, specific recommendations regarding generic maximum doses cannot be definitively made. Furthermore, recommended doses from manufacturers vary between countries. The intrathecal ED50 of lignocaine for a motor block (defined as the development any motor block in either leg within a five-minute-period) has been shown to be approximately 13.7 mg (95%CI: 13.1-14.4 mg)[69]. According to most manufacturers recommendations, the maximum dose of lignocaine for infiltration and regional nerve block techniques is 300 mg (approximately 4.5 mg/kg) or 500 mg (7 mg/kg) with 1:200000 adrenalin (based on a 70 kg patient). However, for neuropathic pain treatment in human subjects, the ED50 and ED90 of lignocaine has been reported as 372 mg and 416 mg respectively, although the resulting plasma levels were not evaluated[70]. Generally, however, from animal data, the ED50 of intravenous lignocaine for CNS toxicity is approximately 19.5 mg/kg (95%CI: 17.7-21.3 mg/kg) and 21 mg/kg (95%CI: 19.0-23.4 mg/kg) for electrocardiographic evidence of cardiac toxicity[71].

Infusion kinetics

As discussed above, plasma concentrations of lignocaine differ widely, depending on the total dose administered, the method and route of delivery, and the vascularity of the site where it is injected. Plasma levels of between 0.5 and 5.0 mcg/mL (2-20 μmol/L) are required for many of reported clinical effects after both intravenous or subcutaneous administration[72]. A infusion of intravenous lignocaine administered at a dose of 2 to 4 mg/min results in plasma levels of between 1 and 3 mcg/mL after 150 min[73]. After 15 min of the same infusion, a 2 mg/kg intravenous bolus of lignocaine leads to peak plasma levels of 1.5 to 1.9 mcg/mL[74]. Subcutaneous lignocaine infusions may be advantageous over intravenous drug delivery methods because plasma levels are more stable, and therapeutic benefit may be achieved whilst avoiding the toxic effects of peaks and troughs associated with episodic drug administration or a prolonged continuous intravenous infusion[75].

The aim of an intravenous lignocaine infusion is to achieve a therapeutic steady-state concentration while minimising systemic toxicity. The pharmacokinetic implication of using a lignocaine bolus dose prior to a continuous infusion is important. This technique increases plasma concentrations allowing therapeutic ranges to be achieved more quickly. Hsu *et al*[59] evaluated the lignocaine's pharmacokinetics during 2-d infusion in patients who underwent cardiac surgery. These researchers concluded that lignocaine plasma concentrations are more accurately described using a two-compartment pharmacokinetic model, and advocated that lignocaine infusions should be dosed by body weight, with the infusion dose reduced after 24 h to avoid toxicity. The authors advocated that the ideal lignocaine continuous infusion protocol is a bolus/loading dose of 1 mg/kg, then an infusion at 50 mcg/kg per minute

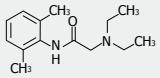
Systematic name	2-(diethylamino)-N-(2, 6-dimethylphenyl)acetamide (International Union of Pure and Applied Chemistry nomenclature)
Class	Amide
Vaughan Williams classification	Class IB antiarrhythmic agent
Molecular formula	$C_{14}H_{22}N_2O,HCl,H_2O$
Structural formula	
pKa	7.86
Molecular mass	234.34 g/mol
Pregnancy Class	Australia: Class A United States: Class B
Trade names	Xylocaine
Preparation	Clear and colorless Sterile and preservative-free Isotonic
Mechanism of action and effects	Myocardial depolarization: decreases Myocardial automaticity: decreases Ventricular excitability during diastole: decreases (by a direct action on Purkinje network) Autonomic system: no effect Contractility: no effect Blood pressure: no effect Atrioventricular conduction: no effect Absolute refractory period: no effect[9,118]
Distribution	Intravenous route: volume of distribution: 0.6 to 4.5 L/kg Transdermal route: lignocaine 5% patch[119] Approximately 70% bound alpha-1 glycoprotein Absorption: depends on duration of application and the surface area When 2100 mg (3 × lignocaine 5% patches) applied over intact skin for 12 h: dose absorbed: 64 ± 32 mg; C_{max}: 0.13 ± 0.06 mcg/mL; T_{max}: 11 h
Protein binding	60% to 80% protein bound
Biotransformation	90% hepatic Metabolites: monoethylglycinexylidide and glycinexylidide (less potent toxic effects[120]) Following intravenous dosing, monoethylglycinexylidide and glycinexylidide in plasma range from 11% to 36%, and from 5% to 11% of lignocaine concentrations Transdermal application (lignocaine 5% patch): negligible metabolite concentrations[119]
Half-life	60 to 120 min Dose-dependent Biphasic distribution phase (7 to 9 min after intravenous loading dose) During prolonged (approximately 24 h) intravenous infusions: > 3 h Time to steady-state plasma concentration Limited data regarding subcutaneous infusion.
Therapeutic plasma concentration	1.5 to 5 mcg/mL > 5 mcg/mL: toxic effects described
Duration of action	Intravenous route: 10 to 20 min
Elimination	Renal excretion: 10% unchanged Not reliably removable by dialysis Systemic clearance: 10-20 mL/min per kilogram

Figure 1 Summary of the pharmacokinetics of lignocaine.

infusion for the first hour, then 25 mcg/kg per minute for the second hour, then 12 mcg/kg per minute for the following 22 h, and finally 10 mcg/kg per minute for the remaining 24 h. The pharmacokinetics of lignocaine are summarised in Figure 1.

ADVERSE REACTIONS AND TOXICITY

Generally, lignocaine toxicity can result when either the correct dose of lignocaine is inadvertently administered or delivered *via* the intravascular route, or when doses, even if given by the correct route, are excessive[76]. There are a number of factors that influence or directly affect the severity of lignocaine toxicity. These include the vascularity of the site of injection, speed of the injection, acid base status, and underlying hepatic or renal impairment. Lignocaine is metabolised by the liver, therefore severe hepatic dysfunction will significantly increase the both the risk and severity of toxicity[9]. In addition, given that lignocaine is protein bound, severe hypoalbuminemia may also predispose to toxicity risk[9]. Acidosis increases the risk of toxicity because due to lignocaine dissociating from plasma proteins[7]. Lignocaine's pharmacokinetics and antiarrhythmic effects may be potentiated or altered by beta-blockers, ciprofloxacin, cimetidine, clonidine, and phenytoin[6]. Beta-blockers such as propranolol and metoprolol can reduce lignocaine's metabolism, whilst cimetidine and amiodarone reduce its clearance. Lignocaine's interactions with phenytoin and ciprofloxacin are thro-

Table 2 Adverse effects of lignocaine toxicity

System	Effects
CNS	Biphasic effects
	Early: CNS excitation with seizures
	Late: CNS depression, termination of convulsions, reduced level of consciousness, leading to respiratory depression and/or arrest
	Mechanism: Local inhibition of inhibitory CNS pathways (CNS stimulation), then inhibition of inhibitory and excitatory pathways (CNS inhibition)
	Symptoms and signs
	Anxiety
	Dizziness or light headed
	Confusion
	Euphoria
	Tinnitus
	Blurring of vision or diplopia
	Nausea and vomiting
	Twitching and tremors
	Seizures with reduced consciousness
Cardiovascular	General effects
	Conduction block of neural impulses
	Prevention of passage of sodium through sodium channels
	Stabilization of excitable membranes
	Prevention of the initiation and transmission of nerve impulses
	Attenuation of phase 4 diastolic depolarization
	Reduction in automaticity
	Reduction in absolute refractory period
	Increase in the ratio of effective refractory period: action potential duration
	Decrease in action potential duration
	Ventricular fibrillation threshold: raised
	Higher serum concentrations
	Blockage of sodium channels
	Depression of rate of depolarization during phase 0 of the cardiac action potential
	Re-entrant arrhythmias
	Suppression of conduction through the sinus and atrioventricular nodes
	Symptoms and signs
	Bradycardia
	Hypotension
	Cardiovascular depression
	Cardiac arrest
Respiratory	Symptoms and signs
	Tachypnea
	Respiratory depression
	Respiratory arrest
Allergic reactions	Extremely rare
	Symptoms and signs
	Cutaneous lesions: urticaria, edema
	Anaphylaxis

CNS: Central nervous system.

ugh their effects on the liver's cytochrome system.

Adverse effects of lignocaine and other amide local anesthetic agents are similar in nature[7]. These are summarised in Table 2. Low plasma concentrations of lignocaine (less than 5 mcg/mL) are used in the clinical setting to suppress cardiac ventricular arrhythmias and status seizures, but seizure activity may be induced at higher concentrations. Seizures result from selective depression of central nervous system inhibitory tracts. As plasma lignocaine levels increase, all pathways are suppressed, resulting in respiratory arrest, cardiovascular collapse and coma[76]. Lignocaine toxicity may commence at concentrations greater than 5 mcg/mL, although convulsive seizures most often occur at concentrations greater than 10 mcg/mL. The adverse systemic effects of lignocaine toxicity are summarised in Table 2.

CARCINOGENICITY AND MUTAGENICITY

Toxicity studies of 2, 6-xylidine, a lignocaine metabolite, have documented the development of nasal cavity adenomas and carcinomas in rats[6,77]. Nasal tumors were reported with daily doses of 900 mg/m^2 (150 mg/kg) 2, 6-xylidine, but not with low dose (15 mg/kg) or control animals.

LIGNOCAINE AND CANCER OCCURRENCE

Whilst clear *in vitro* and *in vivo* evidence exists for

the anti-inflammatory properties of lignocaine and its modulation of the inflammatory response during major surgery, the question of whether lignocaine can influence cancer outcomes following cancer surgery is a debatable topic. The indirect effects of local anesthetics in tumor development may stem from the reduction of neuroendocrine responses to the stress response elicited by major surgery and tissue damage, enhanced preservation of immune-competence, in addition to opioid-sparing effects of modulating tumor growth[78]. The plasma concentrations of local anesthetic agents, even when administered as part of a regional anesthetic technique or from infiltration around neoplastic tissue, are frequently in the millimolar range. These concentrations have been shown to have cytotoxic properties *in vitro*[79]. Other actions of local anesthetic agents on cancer cells may be through direct sensitisation of chemotherapy[80]. Protection against tumor cell invasion and suppression of tumor proliferation has been found with the infiltration of local anesthetic agents[79]. Furthermore, local anesthetics can modulate tumor biology[81], and lignocaine has been suggested to be a potent demethylating agent with cancer treatment potential[81].

A retrospective study in patients with breast cancer who received paravertebral anesthesia with local anesthetic solutions during mastectomy showed considerable benefit with regard to metastatic spread[82]. These promising finding could not however be replicated in abdominal cancer patients[83-85]. When epidural anesthesia with a local anesthetic solution was utilized as part of a standardised anesthetic, Gupta *et al*[86] reported a reduction in all-cause mortality after resection of rectal cancer; but not after resection of cancer of the colon. Intraoperative epidural analgesia has been linked to increased three and five-year survivals, and increased recurrence-free interval in patients with from ovarian malignancy[87]. Patients with cervical cancer showed no significant survival effect associated with epidural anesthesia during brachytherapy[88], however the use of epidural anesthesia in patients hepatocellular carcinoma undergoing percutaneous radiofrequency ablation was not associated with a significant decrease in survival[89]. The equivocal results of these small observational studies indicate that there is distinct biological heterogeneity of the cancers being investigated, or that regional anesthesia with local anesthesia has no effect.

Multiple factors can hamper perioperative immune competence. Surgery itself can result in significant cytokine and neuroendocrine responses, which can impair several immune functions and attenuate the adverse effects of natural killer cell function. Natural killer cells play an important role in preventing tumor spread[90]. Lignocaine may reduce the stress response to surgery; hence enhance natural killer cell response[91]. Perioperative immune competence may also be influenced by opioids, which have been shown to suppress multiple immune functions, including both humoral and cellular immune function[92-95]. If lignocaine is used as part of a patient's anesthesia regime, less opioid may be required, resulting in less immune compromise. Appropriate analgesia may also reduce metastatic spread of cancer through preservation of natural killer cell function[96]. Finally, morphine is pro-angiogenic and may promote the release of factors that enhance tumor growth[97]. Lignocaine, therefore, may help to maintain immune function in the perioperative period by minimising the need for postoperative opioids and reducing general anesthesia requirements.

The use of lignocaine in patients with prostate cancer remains equivocal[98-100]. Wuethrich *et al*[98] performed a retrospective study examining prostate cancer-related outcomes and the effects of the anesthesia technique in patients undergoing open radical retropubic prostatectomy. The authors reported a reduction in the risk of clinical cancer progression in a cohort of patients receiving epidural analgesia. However, there were no statistical differences in overall survival, cancer-specific survival, and biochemical recurrence-free survival. Similarly Biki *et al*[99] investigated recurrence of cancer of the prostate in men who underwent open prostatectomy under a general anesthetic with postoperative opioid for analgesia, or general anesthetic with epidural anesthesia/analgesia. They observed a significantly reduced risk of biochemical cancer recurrence when open prostatectomy surgery was performed with general anesthesia in combination with epidural analgesia. In contrast to these two retrospective analyses, more recently Tsui *et al*[100] performed an observational study investigating disease free-survival in patients undergoing open radical retropubic radical prostatectomy. There was no difference in clinically evident or biochemical occurrence of prostate cancer when comparing epidural and control groups. In summary, the question of whether lignocaine can modulate cancer recurrence has not yet been answered unequivocally. It is probable that only specific cancer types may be affected by the tumor-suppressive effects of lignocaine[81].

CONCLUSION

Lignocaine is a unique amide local anesthetic and a Class 1b antiarrhythmic agent with ubiquitous use in medicine and surgery. Its use as a local and regional anesthetic agent and for the treatment and prophylaxis of life-threatening ventricular arrhythmias is well known. However, accumulating data suggests that in addition to its sodium channels properties, lignocaine possesses a wide range of *in vitro* and *in vivo* immunomodulating, anti-inflammatory and anti-cancer effects that show immense promise in a variety of other clinical applications. These effects are often exerted at lower concentrations than needed for sodium channel blockade, and result from lignocaine's complex interactions with other cellular systems[16,17,34].

The clinical applications of utilising lignocaine in the pharmacological armament for treating inflammatory conditions such as inflammatory bowel disease, acute lung injury, sepsis, burns, peritonitis, infections, myocardial infarction and reperfusion injury, and cancer recurrence

continue to be areas of intense clinical research. In the context of anesthesia, patients where perioperative epidural analgesia is contraindicated, intravenous infusion of lignocaine could also be considered as an alternative intervention to modulate the postoperative inflammatory responses[17,34]. Lignocaine may be an important pharmacological agent in the influence and modulation of these responses in the practice of modern perioperative medicine. Finally, defining the roles of lignocaine in these clinical settings are necessary to obtain a more detailed appreciation of the complex mechanisms of lignocaine's clinical utility. Maximizing lignocaines's clinical benefits with its risks of toxicity and harm must be of paramount importance at all times. Well-designed large scale clinical trials are awaited to assess whether the immuno-modulating, anti-inflammatory, analgesic, and anticancer effects of lignocaine observed in both *in vitro* and *in vivo* experiments and small clinical trials can be safely applied to routine clinical practice[17].

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P- Reviewer: Ajmal M, Gelman S, Ozcengiz D, Shorrab AA
S- Editor: Gong XM **L- Editor**: A **E- Editor**: Yan JL

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DOI: 10.5313/wja.v4.i2.30

World J Anesthesiol 2015 July 27; 4(2): 30-38
ISSN 2218-6182 (online)

ORIGINAL ARTICLE

Observational Study

Transthoracic echocardiography assists appropriate pulmonary artery catheter placement: An observational study

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Author contributions: Tan CO conceived and designed the study, was involved in data collection, analysed and interpreted data, drafted and revised the manuscript, gave approval for the final manuscript, and agrees to be accountable for all aspects, accuracy and integrity of the work involved; Weinberg L and Story DA assisted in conceptualisation and design of the study, was involved in data collection, analysed and interpreted data, revised the manuscript, gave approval for the final manuscript, and agrees to be accountable for all aspects, accuracy and integrity of the work involved; McNicol L assisted in design of the study, revised the manuscript, gave approval for the final manuscript, and agrees to be accountable for all aspects, accuracy and integrity of the work involved.

Institutional review board statement: This study was approved by the Austin Health Human Research and Ethics Committee (H2012/04776) and was carried out in compliance with the Helsinki Declaration on research involving human participants.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment. All study data was de-identified for analysis.

Conflict-of-interest statement: There were no conflicts of interest to declare.

Data sharing statement: We hereby regretfully decline to have the following data components of our study placed in the Dryad Repository: Technical appendix; Statistical code; Raw dataset.

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Received: April 6, 2015
Peer-review started: April 8, 2015
First decision: April 27, 2015
Revised: May 12, 2015
Accepted: June 1, 2015
Article in press: June 2, 2015
Published online: July 27, 2015

Abstract

AIM: To investigate the utility of transthoracic echocardiography in confirming appropriate pulmonary artery catheter (PAC) placement.

METHODS: Three commonly used transthoracic echocardiography (TTE) views were used to confirm PAC position in 103 patients undergoing elective cardiac surgery - the parasternal short axis right ventricular inflow-outflow view; the subcostal short axis right ventricular inflow-outflow view; and the parasternal short axis ascending aortic view. All PACs were inserted by the managing anesthesiologist under pressure waveform guidance alone, who was blinded to all sonographic information. A sonographer blinded to all pressure waveform information confirmed visualisation of an "empty" PA before PAC insertion, and visualisation of the PAC balloon in the main PA (MPA) or right PA (RPA) after attempts at placement were complete. Agreement, sensitivity and specificity of TTE in confirming appropriate PAC placement was compared against pressure waveform

guidance as the "gold standard". The successful view used was compared against patients' anthropomorphic indices, presence of lung hyperinflation, and insertion of PAC during positive pressure ventilation. Agreement between TTE and pressure waveform guidance was analysed using Cohen's Kappa statistic. The relative proportion of total RPA seen by subcostal *vs* parasternal TTE views was also compared with a further 20 patients' computed tomography (CT) pulmonary angiograms (CTPA), to determine efficacy in detection of distal RPA PAC placement.

RESULTS: Appropriate positioning of the PAC balloon, and its to-and-fro movement consistent with a non-wedged state, within the MPA or RPA was confirmed by TTE in 98 of the 103 patients [sensitivity 95% (95%CI: 89%-98%)], and absence of the PAC balloon before insertion correctly established in 100 patients [specificity 97% (92%-99%)]. This was in very good agreement with pressure waveform guidance [Cohen's Kappa 0.92, (0.87-0.98)]. The subcostal view was the best view to visualise the PAC tip when it was placed in the right pulmonary artery (OR 70, $P < 0.0001$), was more successful in patients with COAD (OR 9.5, $P = 0.001$), and visualized 61% (*vs* 44% by parasternal views, $P < 0.001$) of mean RPA lengths compared with CTPA; however the parasternal views were more successful in patients with higher body mass indexs (OR 0.78 for success with subcostal views, $P < 0.001$). There was a trend towards insertion during intermittent positive pressure ventilation favoring visualisation by subcostal views (OR 3.9, $P = 0.08$). The subcostal view visualized a greater length of the RPA than parasternal views (3.9 cm *vs* 2.9 cm, $P < 0.0001$). PACs were more often placed in the MPA than RPA (80 *vs* 18 patients). Three patient's pulmonary arteries were not visible by any TTE view; in a further 2 patients, despite pre-insertion visualisation of their pulmonary arteries, the PAC balloon was not visible by any view with TTE where correct placement by pressure waveform was unequivocal.

CONCLUSION: TTE can assist appropriate PAC placement by visualization of an unwedged PAC balloon in the PA.

Key words: Transthoracic echocardiography; Pulmonary artery catheter; Main pulmonary artery; Right pulmonary artery; Pulmonary artery rupture; Intensive care unit

Core tip: Transthoracic echocardiography (TTE) is an efficacious adjunct to pressure waveform guidance for guiding appropriate pulmonary artery catheter (PAC) placement. With the required equipment and expertise, TTE is a rapid and safe tool for confirming whether the PAC is placed too far (the PAC balloon seen beyond the proximal RPA) or not far enough (the body of the PAC seen in the right ventricle but the PAC balloon not seen in the main PA or right PA). This application may assist in reducing complications related to PA rupture or PAC induced arrhythmias.

Tan CO, Weinberg L, Story DA, McNicol L. Transthoracic echocardiography assists appropriate pulmonary artery catheter placement: An observational study. *World J Anesthesiol* 2015; 4(2): 30-38 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/30.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.30

INTRODUCTION

Pulmonary artery catheters (PACs) are variably used in critical care[1] and cardiac anesthesiology[2]. In proficient hands, complication rates are low[3] but include a 1:650-1:4300 risk of death secondary to pulmonary arterial rupture[4], with inappropriate balloon inflation or catheter advancement beyond the main pulmonary artery (MPA) as presumed contributory factors. Conversely, failure to advance the PAC beyond the right ventricle (RV) may result in endocardial irritation and arrhythmias; these complications may occur not only during insertion but also subsequently due to retrograde catheter migration. Pressure waveform analysis, X-ray guidance, and transesophageal echocardiography (TEE)[5] have all been used to confirm placement of the tip of the catheter in the PA. Pressure waveform analysis is the most commonly used technique[6] because of its accuracy and accessibility. Pressure waveform guided placement is usually straightforward, however fast or irregular heart rates, low pulmonary pressures, or gross waveform distortion by widely varying intrathoracic pressures may make pressure waveforms difficult to interpret. This situation occurs more frequently in the ICU setting where patients requiring PACs often display severely abnormal haemodynamic states, at times also with tachyarrhythmias.

TEE is an ultrasound modality that offers advantages over transthoracic echocardiography (TTE) but is semiinvasive, and its use is difficult to justify for PAC placement as a primary indication. Portable X-ray offers ideal information on PAC position but may not be immediately available during PAC insertion and also utilises ionising radiation. TTE however is non-invasive, utilises no ionising radiation, and is usually immediately available in most critical care settings. It has also been used to successfully visualise PACs in a small sample in a non-surgical scenario[7]. We aimed to explore how TTE could serve as an adjunct to pressure waveform guidance for confirmation of PAC placement in the MPA or RPA, as well as how TTE could assist in ideal final positioning of the PAC tip in the MPA to assist prevention of hazardous distal or proximal PAC migration.

We hypothesized that: (1) use of three basic TTE views could reliably confirm PAC placement in the MPA or RPA when pressure waveform analysis is used as the primary technique; (2) particular TTE views

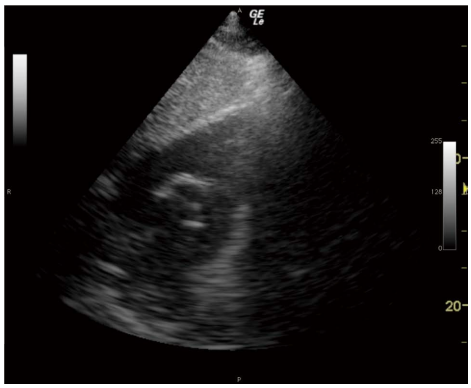

Figure 1 Subcostal right ventricular inflow outflow view confirming absence of the pulmonary artery catheter from the main pulmonary artery and right pulmonary artery prior to pulmonary artery catheter insertion. Cardiac chamber identification labels have been omitted for clarity.

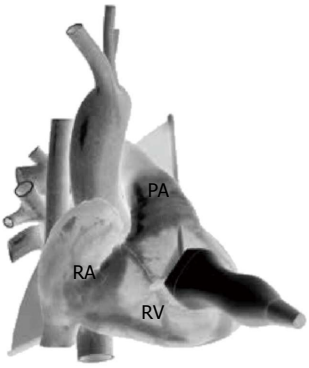

Figure 2 Parasternal right ventricular inflow outflow view, anterior projection. Schematic diagram demonstrating transthoracic echocardiogram probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (http://pie.med.utoronto.ca/TTE). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery.

could visualise a greater proportion the distal RPA as determined by CTPA, assisting confirmation of ideal PAC placement proximal to the RPA 1st division; and (3) that other factors including: chronic obstructive airways disease (COAD), body mass index (BMI), concomitant intermittent positive pressure ventilation (IPPV) or final PAC position influenced which echocardiographic view used to successfully visualise the MPA, RPA and PAC.

MATERIALS AND METHODS

This study was approved by the Austin Health Human Research and Ethics Committee (H2012/04776) and was carried out in compliance with the Helsinki Declaration on research involving human participants. Written informed consent was obtained from all participants. We recruited 103 cardiac surgery patients who were planned for PAC insertion as part of their anaesthesia care. The PACs inserted were the Swan-Ganz VIP+ (Edwards Lifesciences, CA, United States). Information on patients BMI and previous diagnosis

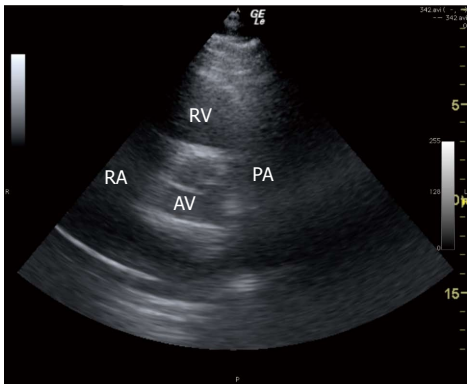

Figure 3 Parasternal right ventricular inflow outflow view, sonogram. RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; AV: Aortic valve.

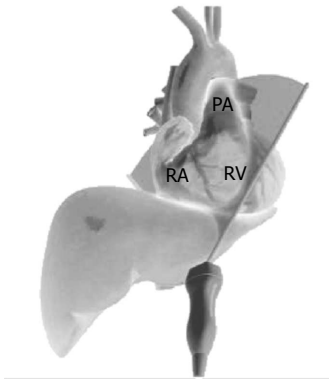

Figure 4 Subcostal right ventricular inflow outflow view, antero-inferior projection. Schematic diagram demonstrating TTE probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (http://pie.med.utoronto.ca/TTE). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery.

of COAD or asthma were obtained preoperatively. The study protocol was as follows.

All PACs were inserted preoperatively by observation of the pressure waveform during advancement of the catheter.

A single anesthesiologist experienced in TTE, who was not the patient's treating anesthesiologist at the time, performed all ultrasound examinations and was blinded to all pressure waveform information obtained during PAC insertion.

Three commonly used TTE views were used in the following sequential order to visualize the MPA and right pulmonary artery (RPA) prior to PAC placement.

The MPA and RPA were visualised and confirmed as "empty" of the catheter before PAC insertion to establish the specificity of the technique (Figure 1).

The 3 TTE views used were: (1) the parasternal short axis right ventricular inflow-outflow (PSRVIO) view (Figures 2 and 3); (2) the subcostal short axis right ventricular inflow-outflow (SCRVIO) view (Figures 4 and 5); and (3) the parasternal short axis ascending aortic (PSAscAo) view (Figures 6 and 7).

These particular views were selected as they offer

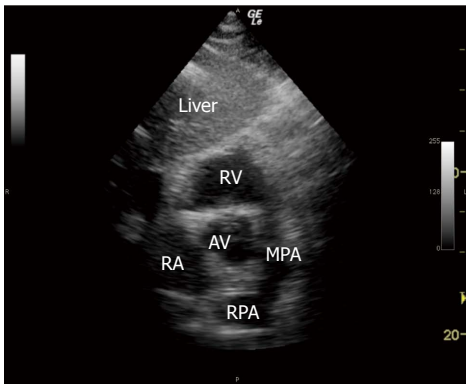

Figure 5 Subcostal right ventricular inflow outflow view, sonogram. RA: Right atrium; RV: Right ventricle; MPA: Main pulmonary artery; RPA: Right pulmonary artery; AV: Aortic valve.

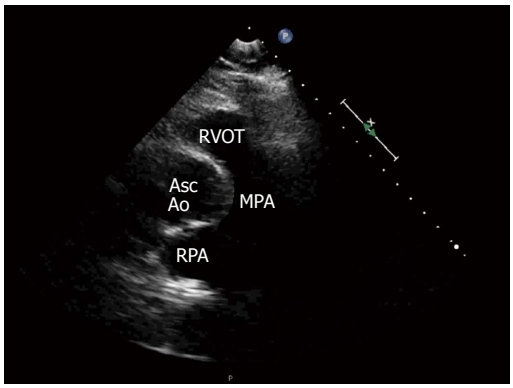

Figure 7 Parasternal ascending aorta short axis view, sonogram. RVOT: Right ventricular outflow tract; AscAo: Ascending aorta; MPA: Main pulmonary artery; RPA: Right pulmonary.

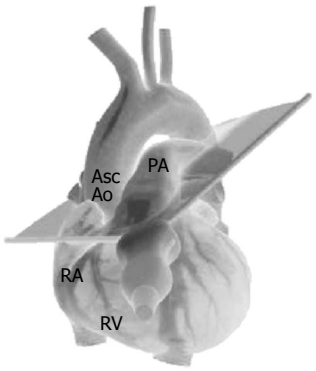

Figure 6 Parasternal ascending aorta short axis view, left anterior oblique projection. Schematic diagram demonstrating TTE probe position and alignment of scanning plane. Reproduced in part with permission from Toronto General Hospital, Perioperative Interactive Education Virtual TTE (http://pie.med.utoronto.ca/TTE). TTE: Transthoracic echocardiogram; RA: Right atrium; RV: Right ventricle; PA: Pulmonary artery; AscAo: Ascending aorta.

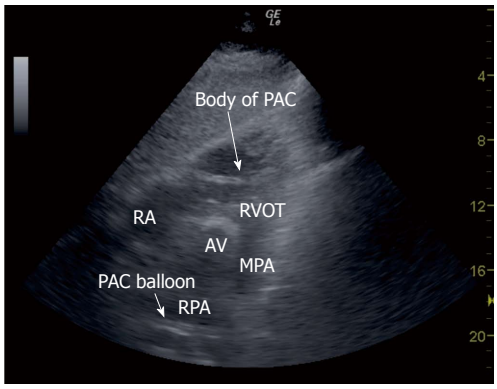

Figure 8 Subcostal right ventricular inflow outflow view showing the body of a pulmonary artery catheter in the right ventricle. RA: Right ventricle; RVOT: Right ventricular outflow tract; AV: Aortic valve; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PAC: Pulmonary artery catheter.

optimal visualisation of the MPA and RPA, with the structures in question positioned in the near field.

Patients in whom none of the three TTE views of the MPA and RPA were attainable were noted and included in the results of the study.

The sonographer was then notified by the proceduralist inserting the PAC that attempts at insertion had begun.

The sonographer then used the same TTE view that was successfully used to visualise the MPA and RPA to examine for the appearance of a PAC balloon or tip, and the right ventricular outflow tract (RVOT) visualised to examine for the presence of the body of the PAC line (Figure 8).

The sonographer was notified by the proceduralist inserting the PAC that attempts at correct placement were complete. The sonographer was not given any information about presumed success or failure of appropriate PAC placement according to pressure waveform information.

If the PAC balloon or tip were not already seen in the PA, or PAC body in the RVOT, then any of the 3 remaining views not used were henceforth utilised in the above described sequence to examine for those structures.

If either PAC line in the RVOT or PAC balloon in the PA were seen by TTE, the case was recorded as a "test positive" for the first view used that, in the above sequential order, was able to identify those structures. We did not attempt to visualise PAC structures further by different views once positively identified. If not seen, the case was recorded as a "test negative".

If the PAC balloon had not been seen in the MPA or RPA by any of the 3 designated TTE views, but examination of the RVOT positively identified the body of the PAC, the PAC tip was presumed to be placed in the distal RPA beyond the view of TTE.

All sonograms were recorded and de-identified, then reviewed independently at a later date by a second anesthesiologist skilled in perioperative TTE to confirm absence or presence of the PAC balloon or tip in the PA, and PAC body in the RVOT. The second assessor was blinded to the diagnosis of "test positive" or "test negative" by the initial sonographer. Disagreement between observers was recorded as interobserver variability.

A single portable ultrasound machine (LogiqE, GE, New York) and 2-5 MHz phased array ultrasound probe (3S, GE, New York) was used to perform each

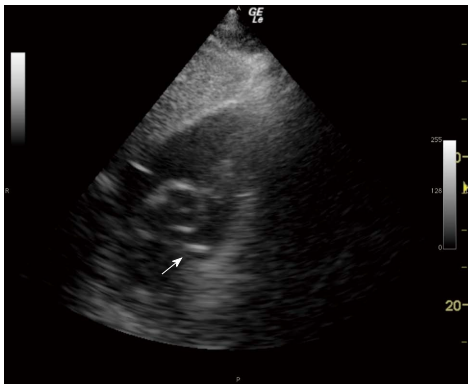

Figure 9 Subcostal right ventricular inflow outflow view confirming presence of the pulmonary artery catheter balloon in the main pulmonary artery after pulmonary artery catheter insertion (arrow). Cardiac chamber identification labels have been omitted for clarity. Movie clip 1: Subcostal right ventricular inflow outflow view showing appearance of pulmonary artery catheter balloon in the main pulmonary artery as it is appropriately placed.

sonogram. The probe was positioned on the praecordium and subcostal region carefully under the patient's sterile drapes. PAC balloon position was identified by the hyperechoic appearance of its air-filled balloon and motion away from the transducer in concert with ventricular systole (Figure 9, Movie Clip 1). The body of the PAC was identified as a hyperechoic line positioned between and distinct from the RVOT free wall and anterior border of the aortic root (Figure 8). Insertion was performed by a cardiac anesthesiologist or a supervised cardiac anaesthesiology registrar, both of whom were blinded to all sonographic information. In keeping with the majority practice in our department of PAC insertion until PA pressure waveforms were observed, in all cases bar those inserted by a single anesthesiologist, PACs were advanced until this point, the balloon then deflated, and the catheter position secured. The remaining practitioner deliberately obtained a pulmonary capillary wedge pressure waveform before balloon deflation, 1-2 cm withdrawal, and fixation of catheter position. Patients were awake and spontaneously ventilating or anaesthetised and positive pressure ventilated (IPPV) as per the cardiac anesthesiologist's preference. Difficulties in placing the PAC under pressure waveform guidance were recorded by the inserting proceduralist but not communicated to the sonographer at any time.

To establish how TTE could assist in confirming a PAC placed potentially too distally or proximally, the distance from MPA bifurcation to the furthest point of RPA visualisation in each sonogram was also measured and compared between views. This was then compared with the dimensions of the RPA at its narrowest point, and its 1st divisions, measured from the CT pulmonary angiography scans (CTPA) of 20 adult patients. With this information the approximate expected wedge position was estimated by comparison of the known width of the inflated PAC balloon[8]. TTE measurements were performed offline (Pixmeo, Geneva, Switzerland). CTPA RPA measurements were taken at the narrowest points of the vessels with the midpoints of bifurcation (MPA to RPA, RPA to 1st divisions) used as measurement endpoints. CTPA measurements were performed *via* Impax Web1000 (Agfa, Mortsel, Belgium).

Statistical analysis

All calculations were performed using SPSS V21 (IBM, New York, United States) statistical software. As described by Gwet[9], based on a mimimum limit of agreement of 70% between TTE and pressure waveform guidance by Cohen's Kappa statistic, 51 subjects were required. We chose a convenient sample of 100 patients anticipating difficulty in obtaining appropriate MPA and RPA views. Continuous data was assessed for normality by histogram frequency distribution analysis and the Kolgomorov-Smirnoff normality test, and was considered suitable for parametric testing using unpaired *t*-tests, or one-way ANOVA for multiple groups. Single independent variable, binary outcome data was analysed with Fisher's Exact test. Multivariate logistic regression was used to identify the effect of simultaneous patient factors and PAC position in the MPA or RPA on likelihood of successful TTE views used. We reported this study using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[10].

RESULTS

One hundred and three patients were recruited (Table 1). Three patients' pulmonary arteries were not visible in any of the 3 TTE views [2% (95%CI: 1%-8%)]. Appropriate placement of the PAC balloon within the MPA or RPA was confirmed by TTE in 98 patients [sensitivity 95% (95%CI: 89%-98%)], measured against pressure waveform guidance as the "gold standard". Absence of the PAC balloon in the MPA or RPA before PAC insertion was correctly established by TTE in 100 patients [specificity 97% (95%CI: 92%-99%)]. Confirmation of correct PAC placement by TTE was in very good agreement with pressure waveform guidance [Cohen's Kappa 0.92, (95%CI: 0.87-0.98)]. There was no interobserver disagreement found regarding presence or absence of the PAC balloon. Visualisation of the body of the PAC in the RVOT was confirmed in 76 patients [74% (95%CI: 63%-82%)] more often by parasternal than subcostal views (69% *vs* 21%, $P < 0.0001$). PACs were more often placed in the MPA than the RPA and the PAC balloon most often seen in the PSRVIO view (Table 1).

All PACs were successfully floated into the MPA or RPA. When the PAC was visualised during insertion, the PAC balloon was easily visible in its transition from RV to PA. Three patients suffered from rapid atrial fibrillation preoperatively, making the pressure waveform transition from RV to PA difficult to interpret. In these instances the balloon was clearly seen on TTE in the MPA. In 2 patients, despite detection of the body of the PAC in the RVOT and clear confirmation of correct placement in the PA by pressure waveform analysis, the inflated balloon of the PAC was not visible by TTE; in one of

Table 1 Patient study parameters

Parameter	Number (proportion or 95%CI) or mean (SD or 95%CI)	
Age (yr)	67 (10)	
BMI (kg/m^2)	29.6 (5.6)	
IPPV during PAC insertion	24 (24%)	
Diagnosis of COAD or Asthma	28 (28%)	
Final PAC position in MPA	80 (72%-88%)	$P < 0.0001$
Final PAC position in RPA	18 (13%-29%)	$P < 0.0001$
TTE view in which PAC was seen		
PSRVIO	52 (43%-63%)	$P < 0.0001$
SCRVIO	33 (26%-45%)	$P < 0.0001$
PSAscAo	13 (6%-24%)	$P < 0.0001$

BMI: Body mass index; IPPV: Intermittent positive pressure ventilation; COAD: Chronic obstructive airways disease; PAC: Pulmonary artery catheter; MPA: Main pulmonary artery; RPA: Right pulmonary artery; TTE: Transthoracic echocardiography; PSRVIO: Parasternal right ventricular inflow outflow view; SCRVIO: Subcostal right ventricular inflow outflow view; PSAscAo: Parasternal ascending aorta short axis view.

these patients, despite good visualisation of the PA in all 3 views, and in the other where only the PSRVIO view was able to be obtained. Neither of these 2 patients had a preoperative diagnosis of COAD, were positively pressure ventilated, or had a BMI over 30.

Successful PAC visualisation by subcostal views compared to parasternal views was more likely in patients with preoperative diagnoses of COAD, PAC insertion during IPPV and PAC positioning in the RPA (Table 2), but less likely in patients with higher BMI. All factors except insertion during IPPV reached statistical significance in the multivariate logistic regression model.

Length of RPA visualised by TTE and CTPA measured dimensions of the RPA and its 1st divisions at their narrowest points are presented in Tables 3 and 4. The SCRVIO view consistently visualised a greater length of the RPA compared with parasternal views, and hence a greater proportion of the complete RPA as established by CTPA (61% *vs* 45% of the complete RPA length respectively, $P < 0.0001$).

DISCUSSION

The use of TTE in acute medicine continues to enjoy rapidly increasing uptake and application in many areas of acute care[11]. Point-of-care ultrasound machines now offer high quality imaging and are smaller and more affordable, making their use in the critical care setting ideal. Although now superseded, the point-of-care machine used in our study was fully enabled to perform quantitative spectral and colour Doppler analyses. Focused TTE training for critical care physicians outside of conventional cardiology and sonography training has demonstrated utility in assisting clinical decision making[12,13].

We conducted a prospective observational study of focused transthoracic echocardiography used to confirm appropriate pulmonary artery catheter placement in the main or right pulmonary artery in patients undergoing elective cardiac surgery. Consistent with our hypotheses

Table 2 Influence of patient factors and pulmonary artery catheter position on successful pulmonary artery catheter visualisation by subcostal views[1]

	Odds ratio	*P*-value	95%CI
Diagnosis of COAD or Asthma	9.5	0.001	2.5-36
Insertion during IPPV	3.9	0.08	0.8-17.8
BMI (kg/m^2)	0.78	< 0.0001	0.67-0.89
RPA PAC position	70.0	< 0.0001	9.6-502

[1]Data are expressed as [number, (proportion)] or [mean, (SD)]. COAD: Chronic obstructive airways disease; IPPV: Intermittent positive pressure ventilation; BMI: Body mass index; RPA: Right pulmonary artery; PAC: Pulmonary artery catheter.

Table 3 Transthoracic echocardiogram length of right pulmonary artery visualised

TTE	Length (cm)		*P*-value
	Mean (SD)	Range	
Parasternal views: RPA	2.9 (0.8)	1.2-4.8	< 0.0001
SCRVIO view: RPA	3.9 (0.8)	2.8-5.6	

Data are presented as mean (SD). TTE: Transthoracic echocardiogram; RPA: Right pulmonary artery; SCRVIO: Subcostal right ventricular inflow outflow.

Table 4 Computerised tomographic pulmonary angiogram measurements of the right pulmonary artery and 1st divisions

CTPA	Length (cm)		Width (cm)	
	Mean (SD)	Range	Mean (SD)	Range
RPA	6.4 (1.0)	4.5-8.1	2.0 (0.4)	1.1-2.6
RPA 1st division (anterior)			0.8 (0.02)	0.4-1.4
RPA 1st division (posterior)			0.7 (0.02)	0.4-1.3

Data are presented as mean (SD). CTPA: Computerised tomographic pulmonary angiogram; RPA: Right pulmonary artery.

we found that: (1) Use of three basic TTE views could reliably confirm appropriate PAC placement in most patients, by direct visualisation of a mobile "to-and-fro" PAC balloon in MPA or RPA, and by the presence of the body of the PAC catheter in the RVOT confirming adequate PAC advancement; (2) Subcostal TTE views visualised a greater proportion of the RPA as defined by CTPA than parasternal TTE views, allowing more reliable estimation of ideal ("not too far") PAC positioning; and (3) that patient factors and final PAC position affect the type of echocardiographic view successfully used for PAC visualisation.

Tempe *et al*[14] demonstrated a mean distance from PA to wedge pressure trace of 6.8 cm. The MPA is known to be approximately 5 cm in length; as our data suggests that as the mean length of the RPA is 6.4 cm, in the majority of cases a PAC would wedge in proximal-to-mid RPA. Such a wedge position is consistent with our CT pulmonary angiogram data suggesting that small RPAs at their distal narrowest point may not accommodate an inflated PAC balloon (Table 3), as

the balloon is purported to be 1 cm in diameter when inflated[8]. Hence a PAC placed approximately halfway between the origin of the MPA and 2 cm beyond the MPA bifurcation should have the least likelihood of migrating too distally to spontaneously wedge in the RPA, as well as too proximally causing RV irritation. Even the TTE parasternal views, which visualized less of the RPA than the SCRVIO view, consistently visualized the proximal RPA (Table 3). Hence successful use of any view that captures the PAC balloon, together with visualization of its to-and-fro motion over the cardiac cycle, should confirm placement of a PAC balloon within this "safe" depth of proximal to mid RPA.

Use of parasternal views also offered good visualization of the body of the PAC in the RVOT more frequently; this was most likely because the lie of the PAC in the RVOT is perpendicularly aligned to the incoming ultrasound beams, and is in the near field, in these views. In practice, if the body of the PAC is seen in the RVOT, but to-and-fro movement of the PAC balloon is not seen in the MPA or RPA, it is highly likely that the balloon is wedged; additionally, if the catheter is not seen in both the RVOT and the PA/MPA in this instance, then the PAC must be inserted "not far enough" (*i.e.*, placed proximal to the RVOT). Hence, TTE should be used to: (1) confirm that a PAC is not unintentionally wedged; (2) confirm that a PAC is inserted distal to the RVOT; (3) assist "ideal" PAC balloon final positioning approximately 3-4 cm beyond the origin of the MPA; and (4) confirm subsequently by repeat examination that proximal or distal PAC migration has not occurred if the monitored PAC pressure waveforms become equivocal.

Where the PACs were placed in the RPA, the SCRVIO was significantly better at visualizing the PAC balloon than parasternal views. This may be because the caudo-cranial direction of the ultrasound beams from the SCRVIO are well aligned with the final path taken by the PAC from RVOT to RPA (Figures 5 and 6).

In the 2 patients where the balloon of the PAC was not seen when an obvious PA waveform was displayed, one case was most likely because the SCRVIO was not obtained and the PAC positioned in the RPA. In the other patient, despite good visualization of the MPA and RPA in both parasternal and subcostal views, the PAC balloon was not seen. It is possible that further non-standard views not utilised in this study, such as the parasternal long axis RV outflow view[15], may have assisted in PAC visualisation.

Although serious complications are rare with the use of PACs, should pulmonary artery rupture occur, the associated mortality is up to 70%[16]. The important pressure waveform transitions to recognize during insertion are the changes from RV to PA, and if this is unrecognized, the transition from PA to wedge. Even in experienced hands these changes can occasionally be obscure. Patients who have received a sedating premedication can partially obstruct their airway and create large baseline swings in their intrathoracic, and hence cardiac, pressures. Right ventricular systolic failure and hypovolemia may also reduce the pulse pressures in RV and PA whilst raising the central venous pressure a, c and v waves. Absolute changes between systolic and diastolic pressures from RA, RV, PA and then to wedge are difficult to appreciate in these circumstances. The dicrotic notch seen in a PA pressure trace may be subtle and hidden within an underdamped pressure trace, and the falling diastolic phase seen when in the PA can be hard to distinguish from the flat or rising diastolic phase of the RV during rapid and/or irregular heart rates; for example in rapid atrial fibrillation or other supraventricular tachycardias. All of these confounders may mislead even experienced practitioners in identifying appropriate PAC placement; in our study 3% of patients had rapid atrial fibrillation making pressure waveform interpretation difficult. These situations will be more frequent in the emergency cardiac surgery or intensive care setting. Scenarios in which TTE would provide utility in confirming appropriate PAC placement are summarized in Table 5.

Our study is limited by its single centre sample and observational design. Selection bias cannot be excluded as only elective patients in whom a PAC was deemed necessary for the operative procedure were included in the study. The moderate sample size used also precludes any conclusions when lack of a statistical difference between compared samples was found. The designation of TTE in the study as an adjunct to pressure waveform guidance, rather than as a sole alternative was purposeful; in most cases, insertion of a PAC is straightforward with the latter technique. Whilst we have not investigated a direct comparison between the two insertion techniques, we believe this would not have practical significance as use of pressure waveform guidance should remain the proceduralist's insertion technique of choice. Catheter migration due to unfolding PAC loops, changes in patient position, and/or unintentional catheter manipulation is known to occur after insertion. To take full advantage of the potential for TTE to assist in the prevention of PAC related complications, repeated examinations would be required to exclude further PAC migration into the RPA or regression back to the RVOT. The sequential, rather than systematic use of TTE views from PSRVIO to PSAscAo then SCRVIO may have also skewed the proportion of "true positive" views in favor of the parasternal approach. This was again a deliberate aspect of the study design as the author's experience in teaching TTE is that parasternal views are more intuitive and easier to apply in a beginner's hands. Finally, the fact that in 3 patients no TTE views were obtained is a reminder that despite the excellent sensitivity and specificity of the technique when the MPA and RPA are visualized, there remains a very small proportion of patients in whom the technique will not provide useful information.

We conclude that TTE is a highly sensitive and

Table 5 Situations where utilisation of transthoracic echocardiogram for pulmonary artery catheter positioning may be of assistance

Timing	Utility
Pre-insertion	Identify RV dilation, suggesting a longer than standard PAC insertion distance until the MPA/RPA is reached by the PAC balloon
	Identify small calibre MPA/RPA dimensions, usually associated with hypovolemia, and possibly predisposing to shorter depths of insertion from RV to "wedge"
	Quantify RA, TV and PV abnormalities and/or degree of regurgitation prior to PAC insertion
Insertion	Establish absence of the body of the PAC within the RVOT, suggesting PAC coiling or failure of passage past the TV
	Establish presence of the body of the PAC within the RVOT, confirming that the PAC balloon (1) is not coiled in the RV and (2) must be either in or distal to the MPA/RPA
	Visualisation of an "un-wedged" PAC balloon by the appearance of "to-and-fro" movement of the echogenic air-filled PAC balloon in the MPA or RPA
	Imply a wedge position and/or "too distal" placement of the PAC balloon if (1) the body of the PAC is seen within the RVOT and (2) the PAC balloon is not seen in the MPA or RPA
	Optimise final PAC balloon position to distal MPA/proximal RPA
Post-insertion	Repetition of the above TTE signs to identify proximal or distal migration of the PAC from the initial insertion point
	When in doubt, confirmation of the PAC balloon inflation status by visualisation of the "to-and-fro" movement of the echogenic air-filled PAC balloon
	Quantify possible contribution of decline in RV/TV/PV function with presence of the PAC

TTE: Transthoracic echocardiogram; BMI: Body mass index; PAC: Pulmonary artery catheter; MPA: Main pulmonary artery; RPA: Right pulmonary artery; RV: Right ventricle; PA: Pulmonary artery; RVOT: Right ventricular outflow tract.

specific second line technique when confirmation of appropriate PAC placement is required. Visualization of the air-filled PAC balloon in the MPA or RPA, together with its free "to-and-fro" movement, assists in confirming that a PAC is not wedged, whereas visualization of the body of the PAC in the RVOT confirms PAC placement beyond the RV. TTE used to guide final PAC positioning approximately 3-4 cm beyond the MPA origin, and used again as needed in the postoperative period, could assist in reducing the incidence of complications related to proximal or distal migration. Parasternal views are useful in patients with higher BMI, for PACs placed in the MPA and for visualisation of the PAC body, whereas subcostal views are more successful for PACs placed in the RPA. With the appropriate equipment and an available pracitioner with experience in perioperative TTE relevant to obtaining views of the pulmonary artery, use of focussed TTE as an adjunct to pressure waveform guidance may assist in reducing complications related to PAC malposition.

COMMENTS

Background

With the advent of point-of-care ultrasound machines with high quality imaging, more and more applications of ultrasound in critical care are finding their place. Transthoracic echocardiography (TTE) in particular was previously the sole domain of cardiologists and cardiac sonographers; however with the use of a focussed TTE examination critical care physicians can obtain reliable and useful information. Appropriate placement of pulmonary artery catheters (PAC) is usually a routine procedure with the use of pressure waveform guidance, but can be challenging in certain circumstances. The authors explored how focussed TTE could assist in confirming appropriate PAC placement.

Research frontiers

Other examples of new applications of point-of-care ultrasound (U/S) in critical care include U/S diagnosis of pneumothorax, U/S localisation of the cricothyroid membrane for cricothyrotomy, and U/S estimation of stomach residual volumes to assist decision making on pre anaesthesia aspiration risk.

Innovations and breakthroughs

Point-of-care TTE utilised by critical care physicians has added great value to cardiovascular aspects of clinical decision making (Potter A. Echocardiography in acute medicine: a clinical review. *Br J Hosp Med* 2010; 71: 626-630). Guidance on degree of volume replacement, requirement for administration of inotropes or vasocstrictors, and postoperative level of care planning decisions have all been assisted by information by TTE (Cowie B. Three years' experience of focused cardiovascular ultrasound in the peri-operative period. *Anaesthesia* 2011; 66: 268-273). However, use of echocardiography to guide invasive procedures outside of U/S guided regional anaesthesia has been restricted to case series of transoesophageal echocardiographic confirmation of PAC placement (Tempe DK, Datt V, Banerjee A, *et al* (2004). Case 5: Transesophageal echocardiography-guided insertion of a pulmonary artery catheter. *J Cardiothorac Vasc Anesth* 2004; 18: 657-662). This study is the first of its kind to be used in a large sample in the perioperative context demonstrating the utility of the less invasive transthoracic modality. The authors have successfully shown how TTE can safely and efficaciously confirm appropriate TTE placement.

Applications

With appropriate training and available equipment, PAC positioning in the main or right pulmonary artery can be confirmed reliably when PAC insertion by pressure waveform methods are equivocal. This can be performed rapidly and safely in time critical situations. Other applications of the technique may include pre-insertion quantification of right heart conditions that may be affected by PAC insertion, as well as post-insertion assessment of placement when catheter migration may have occurred.

Terminology

TTE: Transthoracic echocardiogropahy; TEE: Transesophageal echocardiography; RV: Right ventricle; RVOT: Right ventricular outflow tract; RA: Right atrium; PAC: Pulmonary artery catheter; PA: Pulmonary artery; MPA: Main pulmonary artery; RPA: Right pulmonary artery; PSRVIO: Parasternal right ventricular inflow-outflow view; SCRVIO: Subcostal right ventricular inflow-outflow view; PSAscAo: Parasternal ascending aorta short axis view; CTPA: Computerised tomographic pulmonary angiogram; COAD: Chronic obstructive airways disease; IPPV: Intermittent positive pressure ventilation; ICU: Intensive care unit; BMI: Body mass index; ANOVA: Analysis of variance statistical test.

Peer-review

This is an interesting and well conducted study reinforcing the usefulness of TTE during invasive procedure.

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P- Reviewer: Schoenhagen P, Sicari R **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Yan JL

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DOI: 10.5313/wja.v4.i2.39

World J Anesthesiol 2015 July 27; 4(2): 39-43
ISSN 2218-6182 (online)

CASE REPORT

Anesthesia for bronchoscopic amniotic membrane grafting to treat non-healing bronchial dehiscence

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Author contributions: Feng TR designed and drafted the case report and revised the manuscript; Gildea TR performed the bronchoscopic procedure and provided manuscript revisions; Doyle DJ provided anesthesia for the procedure and revised the manuscript.

Institutional review board statement: The Cleveland Clinic Foundation Institutional Review Board indicated that they do not require consent or approval for case reports where the patient is not identifiable.

Informed consent statement: Despite repeated attempts, we were unable to reach the family of the patient, who is now deceased. The Cleveland Clinic Foundation Institutional Review Board indicated that consent it not required from deceased patients.

Conflict-of-interest statement: None.

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Received: February 2, 2015
Peer-review started: February 2, 2015
First decision: March 6, 2015
Revised: April 24, 2015
Accepted: May 7, 2015
Article in press: May 8, 2015
Published online: July 27, 2015

Abstract

Airway complications after lung transplantation remain a significant cause of morbidity and mortality. Many of these occur at the anastomotic sites, which are susceptible due to poor collateral circulation. Of the possible complications, bronchial dehiscence is particularly formidable. These cases have been successfully treated bronchoscopically with metallic stents, which likely promote healing through granulation tissue formation. However, limited options exist in cases where the dehiscence fails to heal following stent placement. Here, we present the case report of a 65-year-old male who developed bronchial dehiscence status post bilateral lung transplantation for idiopathic pulmonary fibrosis that failed to heal with simple stent placement. Eventually, the patient underwent amniotic membrane grafting with stenting as a novel therapy for non-healing bronchial dehiscence, for which we describe the anesthetic management. His anesthetic plan included inhalational induction with sevoflurane, propofol infusion for total intravenous anesthesia, rocuronium for muscle relaxation, and closed-circuit assisted ventilation. His existing tracheostomy was used as the airway for oxygenation and induction. In summary, our anesthetic plan for the lung transplant patient was effective; future amniotic membrane grafting for bronchial dehiscence through bronchoscopy may follow a similar technique. Ultimately, the choice of anesthesia in this patient population requires judicious consideration of the requirements of the procedure as well as the pathophysiology of the transplanted lung.

Key words: Bronchial dehiscence; Amniotic membrane;

Grafting; Bronchoscopy; Lung transplantation; Anesthesia

Core tip: Bronchial dehiscence is a significant airway complication following lung transplantation and most commonly occurs at anastomotic sites due to poor collateral perfusion. This complication is often difficult to treat, especially when widespread. Severe disease has been treated with the temporary placement of metallic stents within the airway to promote healing, but limited options exist when stenting fails. This case report presents the anesthetic considerations for a lung transplant patient undergoing bronchoscopic placement of an amniotic membrane graft as a novel solution for non-healing bronchial dehiscence after multiple failed attempts with metallic stent placement.

Feng TR, Gildea TR, Doyle DJ. Anesthesia for bronchoscopic amniotic membrane grafting to treat non-healing bronchial dehiscence. *World J Anesthesiol* 2015; 4(2): 39-43 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/39.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.39

INTRODUCTION

Since the first human lung transplantation, improvements in patient selection, surgical technique, and immunosuppression have led to increased overall survival[1-3]. Nevertheless, airway complications remain an important cause of morbidity and mortality[4,5]. The incidence of complications at most centers ranges from 7%-18% with a 2%-4% mortality rate[1]. These complications arise partly because bronchial arterial circulation is not reestablished during transplantation and requires approximately 2 wk for rearterialization[4-6]. Thus, initial bronchial perfusion depends on retrograde collaterals from the pulmonary artery, making the anastomotic sites particularly susceptible to ischemia[1,4,5,7].

Of the anastomotic complications, dehiscence is particularly difficult to treat, especially when widespread and clinically significant[2]. Partial dehiscence is often managed conservatively with surveillance and aggressive antibiotic therapy. More severe cases have been treated with temporary placement of metallic stents, which promote healing through excessive granulation tissue formation[1]. Other methods have also been used, including endoscopic application of cyanoacrylate glue[8] and surgical repair with homograft aorta[9].

Here, we present the anesthetic management of a lung transplant recipient with non-healing bronchial dehiscence treated with the novel application of amniotic tissue grafting *via* bronchoscopy. As interventional bronchoscopic procedures have become more sophisticated and capable of treating more severe disease, anesthesia for bronchoscopy has evolved alongside them. In providing anesthesia for such patients, thorough preoperative evaluation with ample consideration of transplanted lung physiology and requirements within the bronchoscopy suite setting is imperative.

CASE REPORT

A 65-year-old male underwent bilateral lung transplantation for end-stage lung disease secondary to idiopathic pulmonary fibrosis. Though he tolerated the procedure well, his immediate post-operative course was complicated by cardiac insufficiency, pulmonary hypertension, acute kidney injury, hypotension, and coagulopathy. He soon underwent percutaneous tracheotomy due to debilitation and extended ventilation requirement.

Three weeks later, he developed acute hypoxic decompensation with sepsis, pneumomediastinum and pneumothorax. Bronchoscopy revealed partial dehiscence of the right anastomosis with a large fistula into the mediastinum. A non-covered metallic stent was placed in the right main stem bronchus and was subsequently replaced and repositioned several times. However, the dehiscence continued to worsen and extend. Pseudomonas aeruginosa was also isolated from the bronchial wash and treated with antibiotics. The decision was made to place an amniotic membrane graft *via* bronchoscopy.

Pre-anesthetic assessment demonstrated a patient status post tracheostomy and ASA class IV, weighing 78 kg. His blood pressure was 119/57 mmHg, pulse was 90 beats/min, temperature was 35.5 ℃, and arterial oxygen saturation was 99% on 4 L *via* tracheostomy collar. He had bilateral chest tubes in place and bilateral rhonchi on auscultation. His hemoglobin and hematocrit were 8.7 g/dL and 26.3%, respectively. Serum electrolytes were within normal limits. Chest X-ray showed no pneumothoraces.

His tracheostomy was used as the airway for oxygenation and for pure sevoflurane inhalational induction at 5 L/min over 2-3 min. We then switched to total intravenous anesthesia (TIVA) using a propofol infusion, starting at 125 mcg/kg per minute and rate adjusted to a Bispectral Index of less than 50 throughout the case. Following induction, the patient's blood pressure dropped to 82/51 mmHg, which was treated with propofol titration to 100 mcg/kg per minute and 200 mcg of phenylephrine. A 50 mg dose of rocuronium was given for paralysis.

After the patient was anesthetized and stabilized, rigid bronchoscopy was performed. A closed circuit was attempted due to the large fistula into the mediastinum; wet gauze was packed into the mouth to facilitate ventilation and limit circuit leaks. The stent was peeled out of granulation tissue with forceps and then removed with flexible instruments. A 2 cm by 4 cm EpiFix amniotic tissue graft was draped over a balloon and deployed over the fistula and the defect in the posterior wall and the mediastinal fistula of the right main bronchus as planned. An uncovered Ultraflex stent was passed through the rigid bronchoscope into the right main stem bronchus

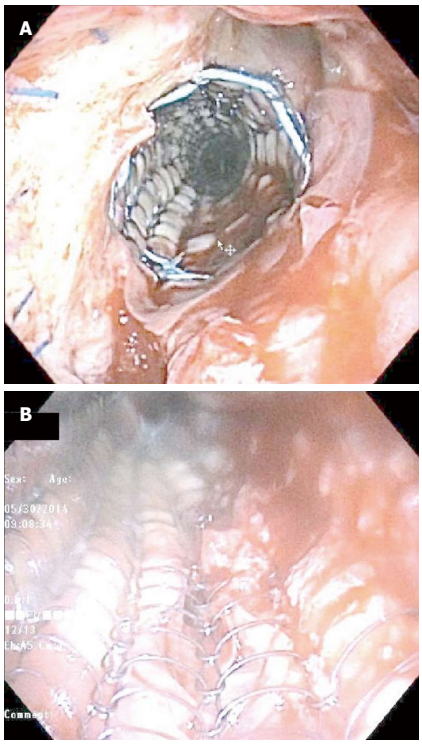

Figure 1 Two views of a bronchoscopically placed amniotic membrane graft underneath a self-expanding metallic stent used for treatment of bronchial dehiscence after lung transplantation. The image (A) shows the blue-colored sutures used for the bronchial anastomosis as well as the stent covering the graft, while the image (B) provides a view from inside the stent.

and was deployed over the amniotic tissue. However, the amniotic tissue was dislodged and required repositioning; its final location was under the stent and partially covering the fistula, which was the best positioning possible (Figure 1).

Throughout the case, a high oxygen flow rate of 15 L/min was maintained due to expected circuit leaks and suctioning from bronchoscopy. An assisted ventilation setting was used with a respiratory rate of 12-15 respirations/min. Two more 10 mg doses of rocuronium were given during the case. Due to a down-trending blood pressure, the patient was started on a phenylephrine infusion at 30 mcg/min; he was later titrated to 40 mcg/min.

Prior to emergence, the propofol infusion rate was decreased to 75 mcg/kg per minute and 5 mg of neostigmine with 0.6 mg of glycopyrrolate were given for reversal of rocuronium. Ondansetron 4 mg was given for nausea prophylaxis. Once the patient was confirmed to be breathing spontaneously at 14 respirations/min, he was switched to blow-by oxygen through mask on 6 L/min. He was transported to the post-anesthesia care unit (PACU) without any post-operative complications. His blood pressure in the PACU was 103/42 mmHg with a pulse of 70 beats/min, temperature of 35.1 ℃, and oxygen saturation of 100% on room air.

Weeks later, the patient passed away due to complications related to liver failure and sepsis; bronchoscopy cultures prior to death were negative.

DISCUSSION

Management of airway complications varies depending on clinical symptoms and severity, and can range from medical management to interventional bronchoscopy to open surgical repair[1]. Among the various methods to treat airway complications, stent placement is becoming increasing popular and is effective for several types of complications[1,7]. The different types of stents and their associated advantages and disadvantages have been described at length in the literature[1,6,7,10-13]. In bronchial dehiscence, bronchoscopically deployed uncovered metallic stents have been useful in treatment, as they promote excessive granulation tissue formation that provides a platform for healing[6]. They also have the added benefit of preventing stenosis through a constant outward radial force, which is important at the anastomosis due to its tendency to become stenotic upon healing[2,6].

Amniotic membrane grafts are processed from human placenta and comprise the innermost layer of the amniotic cavity. Due to its anti-inflammatory, stem cell proliferating, and epithelialization-promoting effects, these grafts are particularly useful in healing and have been used in ophthalmology and for reduction of post-laminectomy epidural adhesions[14-17]. Furthermore, Kheirkhah *et al*[18] demonstrated its antibacterial effects in treating acute Pseudomonas keratitis. Though its mechanism of action is poorly defined, its structure and properties likely lend to epithelia cell migration and attachment[15]. Thus, in this case report, amniotic tissue was bronchoscopically placed as a potential substrate to treat the bronchial dehiscence and Pseudomonas infection.

As bronchoscopic procedures gradually became more sophisticated, anesthesia for bronchoscopy evolved alongside them. The increasing complexity and duration of bronchoscopic cases inevitably require deep sedation or general anesthesia[19,20]. Rigid bronchoscopy is most often performed under general anesthesia with neuromuscular blockade[19]. TIVA is preferred with a continuous variable rate infusion of propofol, as this is thought to minimize undesirable cardiorespiratory effects compared to bolus doses[19,21]. The benefits of propofol are its rapid onset (< 2 min) and rapid offset (< 15 min)[19,22,23]. It has also been shown to have the lowest complication rate and improved patient neuropsychometric recovery[22], as well as improved tolerance, total amnesia, and decreased cough[19,21]. Drug choice for neuromuscular blockade depends on the required duration of action; typically rocuronium or vecuronium is used[19,23].

The choice of inhalational induction *vs* intravenous induction depends on both clinical circumstance and patient preference. Our patient's existing tracheostomy lent itself well to inhalational induction with sevoflurane since this merely involved connecting the tracheostomy tube to the patient breathing circuit. The switch to TIVA is typically made once the rigid bronchoscope is placed

to prevent room contamination, as the anesthetic circuit is not closed[19,24]. Gauze packing in the nose and mouth can help with circuit leakage[19]. A study by Thwaites *et al*[25] comparing sevoflurane to propofol use on induction demonstrated a significantly slower onset with sevoflurane, but a lower incidence of apnea and shorter time to establish spontaneous ventilation[25]. Other advantages of sevoflurane included smoother transition to maintenance, less associated hypotension, and earlier emergence[25]. However, patient preference appeared to lean towards propofol[25].

Several ventilation strategies can be employed during bronchoscopic procedures, including spontaneous ventilation, high-frequency jet ventilation, and closed-circuit positive pressure ventilation[19]. Spontaneous ventilation is typically ideal[19,24]; thus, muscle relaxants are only recommended for coughing, movement, or dangerous airway manipulation[24]. Unfortunately, spontaneous ventilation is often not feasible due to the deeper sedation required for cough and sympathetic drive suppression during bronchoscopy[19]. Jet ventilation is a poor choice due to the added risk of further dissecting into the mediastinum through the fistula. The high airflow would also make amniotic tissue graft positioning difficult due to the graft's paper-like consistency and propensity to become displaced. Furthermore, an attempt to maintain a closed circuit is recommended in patients with airway fistulas due to the possibility of further exacerbation of existing pneumomediastinum and pneumothorax.

In lung transplant recipients, thorough consideration of transplanted lung physiology is also prudent. In the immediate post-operative month, total lung capacity and FEV_1 tend to decrease; significant improvement in respiratory function and gas exchange of the transplanted lungs is only gradually seen with time[26]. Furthermore, transplanted lungs are highly susceptible to pulmonary edema from fluid overload as lymphatic drainage is interrupted during harvesting[26]. In single lung transplants, ventilation and perfusion in the native and transplanted lungs may also be unequally distributed due to a difference in compliance[26]. In single lung transplants for emphysema, ventilator flow is mostly directed toward the more compliant native lung, whereas the opposite is true for single lung recipients with pulmonary fibrosis[26]. Bilateral transplantation does not appear to require ventilator precautions other than avoiding barotrauma due to an overall decrease in compliance[26]. Barotrauma and aggressive tracheobronchial stimulation can be avoided with gentle intubation and moderate-to-deep anesthesia[26]. Fiberoptic bronchoscopic intubation may also be helpful in avoiding complications at the site of bronchial anastomosis[26].

In conclusion, our anesthetic plan for the lung transplant patient was effective for the procedure; future amniotic membrane grafting for bronchial dehiscence through bronchoscopy may follow a similar technique. Ultimately, the choice of anesthesia in this patient population requires judicious consideration of the requirements of the procedure as well as the physiology of the transplanted lung.

COMMENTS

Case characteristics

A 65-year-old male with a history of bilateral lung transplantation complicated by bronchial dehiscence that failed treatment with metallic stent placement, who underwent bronchoscopic amniotic membrane grafting as a novel therapy for non-healing bronchial dehiscence.

Clinical diagnosis

He initially presented with acute hypoxic decompensation with sepsis, pneumomediastinum and pneumothorax, and bronchial dehiscence of the right anastomosis with a large fistula into the mediastinum was confirmed *via* bronchoscopy. Prior to his procedure, he was hemodynamically stable and presented with a tracheostomy, bilateral chest tubes, and bilateral rhonchi on physical exam.

Laboratory diagnosis

Hemoglobin 8.7 g/dL; hematocrit 26.3%; serum electrolytes within normal limits.

Imaging diagnosis

Chest X-ray showed no pneumothoraces pre-procedurally.

Treatment

The patient underwent bronchoscopic placement of an amniotic membrane graft underlying a stent as a potential substrate to treat the non-healing bronchial dehiscence and superimposed Pseudomonas infection.

Related reports

The reported cases of amniotic membrane grafting as a treatment have been mainly in the domain of ophthalmology and for the reduction of post-laminectomy epidural adhesions; use of amniotic membrane grafting for the treatment of bronchial dehiscence has not been reported in the literature and the anesthetics for this procedure has not been discussed.

Experiences and lessons

This case report outlines an anesthetic plan that was successful for the grafting procedure and can be used as a guideline in the future when bronchoscopically treating non-healing bronchial dehiscence with amniotic membranes. In this patient population, it is particularly important to carefully consider the comorbidities of the patient, the requirements of the procedure, and the physiology of the transplanted lung.

Peer-review

This is an interesting case report on the anesthetic management of bronchoscopic amniotic membrane grafting. The procedure is new for this kind of application and thus the paper is original and has merit. The report will be a useful reading for all anesthesiologist involved in lung surgery. The manuscript is well written and easily readable.

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P- Reviewer: Luchetti M, Tanabe S **S- Editor**: Ji FF **L- Editor**: A
E- Editor: Yan JL

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DOI: 10.5313/wja.v4.i2.44

World J Anesthesiol 2015 July 27; 4(2): 44-48
ISSN 2218-6182 (online)

CASE REPORT

Bradycardia and hypotension during pediatric scoliosis surgery-hypovolemia or spinal shock?

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Author contributions: All authors contributed to this paper.

Institutional review board statement: Research Ethics Board approval was waived for this case report.

Informed consent statement: Written informed consent was obtained to submit this manuscript and publish the imaging details.

Conflict-of-interest statement: The authors have no conflict of interests to report.

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Received: January 20, 2015
Peer-review started: January 21, 2015
First decision: February 7, 2015
Revised: March 31, 2015
Accepted: April 27, 2015

Article in press: April 29, 2015
Published online: July 27, 2015

Abstract

We present the case of a 13-year-old boy undergoing scoliosis repair utilizing skull-femoral traction who developed sudden, sustained bradycardia and hypotension during scoliosis repair, associated with loss of somatosensory evoked potentials and motor evoked potentials to all four limbs. A diagnosis of spinal shock and hypovolemia was made after ruling out primary cardiac causes, sepsis, anaphylaxis and intra-spinal pedicle screw placement. Acute complications of surgical scoliosis repair are reviewed along with anatomy of the sympathetic nervous system. In this case spinal shock may have been due to hypovolemia as well as spinal cord manipulation during T12 vertebral column resection that was needed to effect scoliosis correction. Treatment included volume expansion and inotropic support. Anesthesiologists caring for these patients should be mindful of the possibility of spinal shock during correction of severe scoliosis, particularly when vertebral column resection is undertaken.

Key words: Spinal shock; Scoliosis; Hemorrhagic shock; Vertebral; Sympathectomy

Core tip: A child undergoing scoliosis repair developed sudden bradycardia and hypotension, associated with loss of somatosensory and motor evoked potentials to all four limbs. Spinal shock and hypovolemia were diagnosed after ruling out other causes. Acute complications of scoliosis repair are reviewed along with sympathetic nervous system anatomy. Spinal shock was likely due to hypovolemia and spinal cord manipulation during vertebral column resection that was needed to effect scoliosis correction. Treatment included volume

expansion and inotropic support. Anesthesiologists should be mindful of the possibility of spinal shock during correction of severe scoliosis, particularly when vertebral column resection is undertaken.

Karsli C, Strantzas S, Finnerty O, Holmes L, Lewis S. Bradycardia and hypotension during pediatric scoliosis surgery-hypovolemia or spinal shock? *World J Anesthesiol* 2015; 4(2): 44-48 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i2/44.htm DOI: http://dx.doi.org/10.5313/wja.v4.i2.44

INTRODUCTION

Surgical correction of scoliosis may be associated with complications such as spinal cord or nerve root injuries[1], hypovolemic shock, superior mesenteric artery syndrome[2] and subtle sympathetic trunk/chain lesions[3]. We present a case of acute intraoperative spinal shock likely exacerbated by hypovolemia during thoracic vertebral column resection (VCR).

CASE REPORT

Our patient was a 13-year-old male with Prader-Willi syndrome and severe scoliosis, Cobb angle 128 degrees, (Figure 1A) who presented for posterior spinal instrumentation and fusion with the use of skull-femoral traction. Anesthesia was maintained with propofol and remifentanil to optimize somatosensory somatosensory evoked potentials (SEP) and motor evoked potentials (MEP) monitoring throughout the case. The use of skull-femoral traction to aid in deformity correction was abandoned after repeated alerts in MEP monitoring during the surgical exposure. With attempted rod insertion, the MEPs were completely abolished from the lower extremity muscle groups bilaterally, and responses from the abdominal recti were decreased in amplitude by more than 50% of baseline. The mean arterial blood pressure was elevated to aid the patient tolerate saggital plane correction of the spine. However, with the persistent absence of MEPs, the decision was made to eliminate the corrective forces by removing the rod. This resulted in an immediate return of all MEPs. With each subsequent attempt at rod insertion there was an associated loss of MEPs and the responses normalized only when attempts to correct the scoliosis were abandoned. It was decided to proceed with a vertebral column resection at the level of T12 in an effort to aid with the reduction of the severe curvature.

During the VCR there was an acute, complete loss of the left lower extremity MEPs and a significant reduction in amplitude of the right lower extremity MEPs to less than 10% of baseline (Figure 2A). Blood loss during the VCR was significant and over the next hour an estimated 60 mL/kg bleeding occurred. This was associated with a drop in mean arterial pressure from 70 to 35 mmHg and a slight increase in heart rate from 60 to 70 BPM. Coinciding with the drop in mean arterial pressure, the remaining small response from the right lower extremity MEPs disappeared. At this time, the upper extremity and abdominal rectus MEPs remained at baseline bilaterally. Aggressive fluid resuscitation included a total of one blood volume, comprising red blood cell concentrate: fresh frozen plasma at a ratio of 2:1. A dopamine 10 mcg/kg per minute infusion was initiated to address hypotension resistant to volume resuscitation and transfusion. Despite this, hypotension persisted and the heart rate remained between 60 and 70 BPM. With this the left and right upper extremity MEPs slowly declined in amplitude to less than 10% of baseline and the abdominal rectus responses were lost. This was followed by a complete loss of the upper extremity and greater than 50% amplitude decrease in the lower extremity SEP on both sides. The electroencephaography demonstrated burst suppression indicating global hypoperfusion.

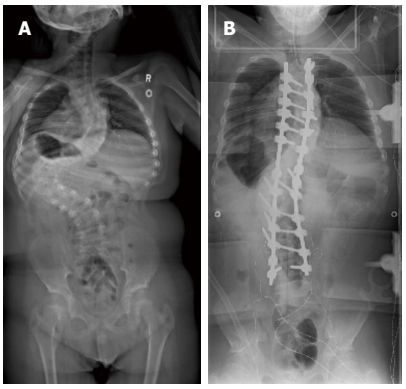

Figure 1 A-P X-ray of the patient. A: Preoperative A-P X-ray of the patient with severe scoliosis, Cobb angle 128 degrees; B: Postoperative A-P X-ray showing spinal instrumentation and final correction.

With the instrumentation secured (Figure 1B) and continued fluid resuscitation with inotropic support, the mean arterial pressure improved over the next 20 min coinciding with partial return of MEPs, first in the right lower extremity followed by the left and right upper extremity. No improvement was seen from the left lower extremity MEPs (Figure 2B). Soon after, the left and right SEPs displayed recovery in both the upper and lower extremities. An intraoperative echocardiogram out-ruled hypovolemia or a primary cardiac cause for the decreased output and serum electrolytes and hemoglobin were in the normal range. With other causes ruled out, a diagnosis of acute intraoperative spinal shock was made. Upon emergence from anesthesia the patient was noted to be purposefully moving all but the left lower limb. This clinical presentation was consistent with the intraoperative findings of persistent complete loss of the left lower extremity motor evoked potentials.

Soon after intensive care unit admission dopamine was replaced with a norepinephrine infusion to maintain mean arterial pressure between 60 and 80 mmHg. Vasopressor support was discontinued on post-operative day 2 and the patient was transferred to the ward.

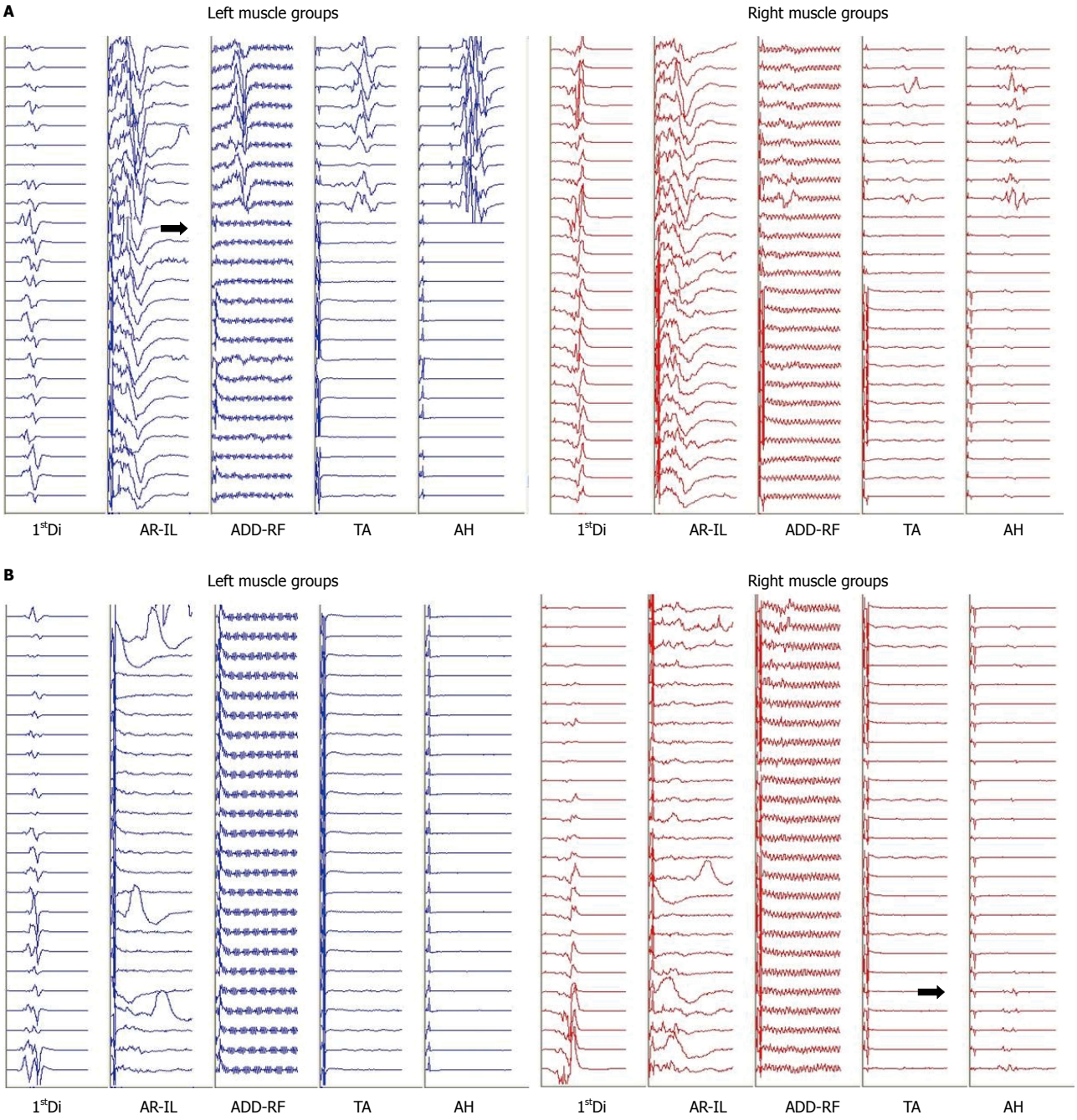

Figure 2 Motor evoked potentials during vertebral column resection (A) and at surgical closure (B). A: Abrupt loss of the left and right lower extremity motor evoked potentials (MEPs) during the vertebral column resection (dark arrows). Transcranial electric stimulation is delivered between two subdermal needle electrodes inserted 2 cm anterior to C1-C2 (International 10-20 System) overlying the motor cortex region. Trains of 5 to 9 pulses, spaced at an interstimulus interval ranging from 1.1 to 4.1 ms, are delivered with constant voltage (200-500 V) at the anode. Resultant compound muscle action potentials are recorded using subdermal needle electrodes, in a bipolar montage. These myogenic responses are recorded bilaterally from the first dorsal interosseous muscles (1st Di) in the upper extremity and lower extremity MEPs are recorded from the left and right abdominal rectus-iliopsoas (AR-IL), adductors-rectus femoris (ADD-RF), tibialis anterior (TA), and abductor hallucis (AH) muscles. Muscle groups are linked on occasion in order to maximize nerve root coverage. These unaveraged compound muscle action potentials are recorded through a 30-1000 Hz bandpass filter and are displayed in a 100 ms window; B: Closing left and right MEP responses. The dark arrow indicates the onset of a very small recovery of the right AH. There are no responses present from the left lower extremity muscle groups. Upon emergence from anesthesia the patient was noted to be purposefully moving all but the left lower limb coinciding with his MEP responses. Intermittent responses recorded from the left and right AR-IL were a result of movement artifact. Stimulation and recording parameters are similar to Figure 2A.

Some motor function had returned to the left leg by that time and the heart rate and blood pressure returned to pre-operative values. Clinical neurologic examination revealed a left sided Brown-Séquard syndrome at the T12-L1 level.

DISCUSSION

To our knowledge, this is the first reported case of acute intra-operative spinal shock in a pediatric patient undergoing scoliosis repair. This was a diagnosis of

exclusion, as many other confounding factors were present. There was significant blood loss during the VCR with hypovolemic shock and the absence of tachycardia in response to hypotension suggests a possible autonomic cause. The use of remifentanil may have clouded the overall clinical picture and delayed the diagnosis of spinal shock in this case as it often results in a relative bradycardia. However the authors feel the persistent bradycardia was not due to remifentanil as rises in heart rate were seen in response to incision and during deeper dissection earlier in the case. Trauma to the spinal cord as a result of a breached pedicle screw was out ruled using electrophysiological stimulation intraoperatively, and visual inspection of the X-rays post-operatively. It is possible during the VCR there was an insult to the left side of the spinal cord indicated by reductions in MEPs, and then confounded by ischemia during hemorrhagic shock. Despite aggressive resuscitation to normovolemia on ECHO, the need for inotropic support indicates a more sinister cause for the persistent shock. Given the acute and persistent loss of the left lower extremity motor evoked potentials during the VCR, and the clinical diagnosis of Brown-Séquard syndrome postoperatively, involvement of the spinal cord appears likely.

Spinal or neurogenic shock occurs usually after a serious injury to the spinal cord resulting in rapid loss of sympathetic output with persistent, relatively unopposed vagal tone causing the typical clinical picture of bradycardia with hypotension. The sympathetic nervous system includes preganglionic neurons in the lateral horn of the spinal cord from T1 to L2/3. Preganglionic axons exiting the spinal cord enter the white rami communicantes to join a network of the sympathetic chain, which run on either side of the vertebral bodies. Postganglionic axons follow the arterial tree to distal organs providing a constant balance between vasoconstriction and vasodilatation depending on clinical needs. Subtle sympathetic lesions have been reported after scoliosis repair and include altered sweating and sympathetic skin responses and an increase in temperature. We feel in this case two factors were at play: (1) a temporary but significant disruption in sympathetic activity due to spinal manipulation or vertebral column resection; and (2) hypovolemia from blood loss. The hypovolemia likely intensified the clinical picture of spinal shock. It is interesting that a single discrete injury at the level of T12 caused such rapid neurogenic shock. This scenario is more likely seen in high thoracic or cervical cord injuries. Hypovolemia leading to spinal cord ischemia likely aggravated the neurogenic shock. In caring for these patients the anesthesiologist should be mindful of this possibility and be prepared to treat spinal shock with fluids and vasopressor/inotropic support such as norepinephrine and dopamine.

Vertebral column resection is a challenging procedure that is reserved for patients with severe, rigid spinal deformity. Conventional methods such as posterior only instrumentation, or posterior instrumentation with anterior release, may not be adequate and a more aggressive method may be required[4]. It is associated with a higher degree of intraoperative blood loss and carries a risk of spinal or nerve root injuries, however, it has been performed safely and with excellent outcomes in several case series[5-7]. In our particular case, VCR was performed after it was determined that the patient could not tolerate the saggital corrective forces placed on the spinal cord by either skull-femoral traction or rod placement, as demonstrated by repeated MEP alerts. MEPs are highly sensitive in detecting ischemia to the anterior two-thirds of the spinal cord, and specifically the corticospinal tracts[7]. Vertebral column resection reduces both the coronal and saggital curves and aides in decompression of the spinal cord and reduces traction of the anterior spinal artery. Because of the high risk associated with VCR it is imperative that MEPs and SEPs be monitored to provide real time feedback and direct key surgical decisions[7].

COMMENTS

Case characteristics

A child undergoing scoliosis repair developed sudden bradycardia and hypotension.

Clinical diagnosis

The clinical findings coincided with loss of somatosensory and motor evoked potentials to all four limbs.

Differential diagnosis

A diagnosis of spinal shock and hypovolemia was made after ruling out primary cardiac causes, sepsis, anaphylaxis and intra-spinal pedicle screw placement.

Laboratory diagnosis

Somatosensory and motor evoked potentials identified the acute neurologic changes, and intraoperative echocardiography ruled out primary cardiac causes.

Imaging diagnosis

X-ray was used to rule out intraspinal pedical screw placement as a cause.

Treatment

Fluid resuscitation as well as inotrope and vasoconstrictor therapy was required to treat the hypotension and spinal shock.

Related reports

Spinal shock in pediatric scoliosis repair using vertebral column resection has not yet been reported.

Term explanation

Vertebral column resection is a surgical technique which involves resecting a or some segmental vertebral columns in their entirely in order to facilitate correction of severe scoliosis. It is associated with increased surgical blood loss and possible neurologic complications.

Experiences and lessons

In caring for pediatric patients undergoing scoliosis surgery the anesthesiologist should be mindful of the possibility of spinal shock and be prepared to treat it with fluids and vasopressor/inotropic support such as norepinephrine and dopamine.

Peer-review

It is an interesting case.

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P- Reviewer: Noll-Hussong M, Wong KL **S- Editor**: Gong XM
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Published by **Baishideng Publishing Group Inc**
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ISSN 2218-6182 (online)

World Journal of *Anesthesiology*

World J Anesthesiol 2015 November 27; 4(3): 49-90

Published by Baishideng Publishing Group Inc

WJA World Journal of Anesthesiology

A peer-reviewed, online, open-access journal of anesthesiology

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2011-2015

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World Journal of Anesthesiology

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Four-monthly Volume 4 Number 3 November 27, 2015

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World Journal of Anesthesiology
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NAME OF JOURNAL
World Journal of Anesthesiology

ISSN
ISSN 2218-6182 (online)

LAUNCH DATE
December 27, 2011

FREQUENCY
Four-monthly

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http://www.wjgnet.com

PUBLICATION DATE
November 27, 2015

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2218-6182/g_info_20100722172951.htm

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DOI: 10.5313/wja.v4.i3.49

World J Anesthesiol 2015 November 27; 4(3): 49-57
ISSN 2218-6182 (online)

REVIEW

Zygapophysial joint pain in selected patients

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Author contributions: Klessinger S solely contributed to this paper; he wrote the complete manuscript.

Conflict-of-interest statement: No conflict of interest is declared by the author.

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Received: May 3, 2015
Peer-review started: May 7, 2015
First decision: July 30, 2015
Revised: September 2, 2015
Accepted: September 10, 2015
Article in press: September 16, 2015
Published online: November 27, 2015

Abstract

The zygapophysial joints (z-joints), together with the intervertebral disc, form a functional spine unit. The joints are typical synovial joints with an innervation from two medial branches of the dorsal rami. The joint capsule and the surrounding structures have an extensive nerve supply. The stretching of the capsule and loads being transmitted through the joint can cause pain. The importance of the z-joints as a pain generator is often underestimated because the prevalence of z-joint pain (10%-80%) is difficult to specify. Z-joint pain is a somatic referred pain. Morning stiffness and pain when moving from a sitting to a standing position are typical. No historic or physical examination variables exist to identify z-joint pain. Also, radiologic findings do not have a diagnostic value for pain from z-joints. The method with the best acceptance for diagnosing z-joint pain is controlled medial branch blocks (MBBs). They are the most validated of all spinal interventions, although false-positive and false-negative results exist and the degree of pain relief after MBBs remains contentious. The prevalence of z-joint pain increases with age, and it often comes along with other pain sources. Degenerative changes are commonly found. Z-joints are often affected by osteoarthritis and inflammatory processes. Often additional factors including synovial cysts, spondylolisthesis, spinal canal stenosis, and injuries are present. The only truly validated treatment is medial branch neurotomy. The available technique vindicates the use of radiofrequency neurotomy provided that the correct technique is used and patients are selected rigorously using controlled blocks.

Key words: Zygappophyseal joint; Facet joint; Low back pain; Medial branch block; Radiofrequency neurotomy; Interventional pain therapy; Chronic pain

Core tip: This review emphasizes the importance of the zygapophysial joints (z-joints) as a pain generator. Taking the historic or the physical examination are not helpful in identifying z-joint pain. The prevalence of z-joint pain increases with age, and it often comes along with other pain sources. The focus is on the significance of z-joint pain in elaborated patient groups in which z-joint pain is clinically relevant but does not occur as an isolated and independent disease. Diagnostic methods and the treatment with radiofrequency neurotomy are discussed.

Klessinger S. Zygapophysial joint pain in selected patients. *World J Anesthesiol* 2015; 4(3): 49-57 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/49.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.49

INTRODUCTION

The smallest functional motion consists of two vertebrae, all adjoining ligaments between them, and three joints. First, there is the interbody joint, which consists of the intervertebral disc and the vertebral endplates. The other two joints are the paired zygapophysial joints (z-joints), which are formed by the articulation of the inferior and superior articular processes of two adjacent lumbar vertebra. The nomenclature of the small joints of the vertebral spine is inconsistent. Facet joint is commonly used in North American literature to describe paired synovial joints between the posterior elements of adjacent vertebrae. The joints are also known as z-joints, zygapophyseal joints, apophysial joints, or posterior intervertebral joints. Because a facet is simply a small articular surface and, as such, pertains to any small joint, in this review the term z-joint is used.

The existence of pain deriving from the z-joints is discussed controversially. In the existing literature there is no support for the existence of a facet syndrome. There are no typical examination findings or diagnostic proofs to justify the term "syndrome". Z-joint pain is defined as pain originating from any structure essential to the function and the configuration of the lumbar facet joints, including the capsule, synovial membrane, hyaline cartilage surfaces, and bony articulations[1].

This review provides an overview about the clinical presentation and treatment of z-joint pain with emphasis on selected patients and diagnosis.

Prevalence

The proposal that the lumbar z-joints might be a source of back pain had initially been communicated more than 100 years ago by Goldthwaith[2] in 1911. In 1933, the term "facet joint syndrome" was introduced[3]. With the implementation of successful operations of herniated discs by Mixter[4] in 1934, the focus was directed away from the z-joints and towards the intervertebral discs. The prevalence of zygapophysial pain is very difficult to specify. In the literature, studies with different prerequisites are found. In original prevalence studies the prevalence was 10%-20%[5]. Later studies reported prevalence rates of 27%, 31%, 38%, and 45%[6-9]. The recent investigation by DePalma *et al*[10] found a prevalence for z-joint pain of 31%. One reason for the incongruity between the different studies is the difference in the age of the groups studied. There is an increasing prevalence with a maximum of more than 40% up to age 70[10]. In patients with thigh pain, older age was even more predictive of z-joint pain with a predicted probability of more the 50% in 60-year-old patients and more than 85% in patients over 80 years old[11].

Anatomy

Although the z-joints are small, they show the features typical of synovial joints[12]. This means the facets are enclosed by a capsule. The surface of the facets is covered by cartilage, a typical synovium, and even a meniscoid exists. The z-joints of the lumbar spine are innervated from the medial branches of the dorsal rami of the spinal nerves at the same level and from the level above. The medial branch of the dorsal ramus in the lumbar spine runs over the base of the transverse process at the junction of the superior articulating process (Figure 1)[13-15]. The lumbar dorsal rami have the same number as the vertebra from which they originate. In their course, these nerves traverse structures and innervate joints caudad the segment of origin[16]. Subsequently, each medial branch passes under the mamillo-accessory ligament[17]. This ligament is responsible for the consistent location. It can be large and sometimes ossified, particularly at lower levels[17]. Outside the ligament, the medial branch sends branches to innervate the z-joint, multifidus muscle, interspinal muscles, and the interspinous ligaments[18]. The z-joints are involved in all principal movements of the spine. Possible movements are axial compression/distraction, flexion/extension, axial rotation and lateral flexion. Horizontal translation does not occur as isolated movement[19].

Symptoms

Pain originating from the z-joints results from noxious stimulation and is therefore a somatic pain. Z-joint pain is often associated with pain in the buttock or in the leg. However, in this case, it is a somatic referred pain and not a radicular pain. Referred pain occurs because of a misperception of the region of the signal that reaches the brain by a convergent sensory pathway[20]. Somatic referred pain is perceived deeply. It is diffuse and hard to localize and it is aching in quality[21]. Pain at the beginning of a movement is typical for joints. Therefore, the z-joints often hurt when moving from a sitting to a standing position or while sleeping when turning from one side to the other. Morning stiffness with difficulty to put on socks in a standing position and pain early in the morning that is relieved during the next hours and with walking will be reported often.

Diagnosis

No historic or physical examination variables exist to identify a z-joint as the pain source[22,23]. Target joints can be recognized by the pain pattern, local tenderness over the area, and provocation of pain with deep pressure. The neurological examination is usually normal. Pain is the most common reason why patients undergo imaging of the spine[24], however, the the routine use of radiological imaging to diagnose z-joint pain is not supported by evidence in the literature[25-30]. The majority of

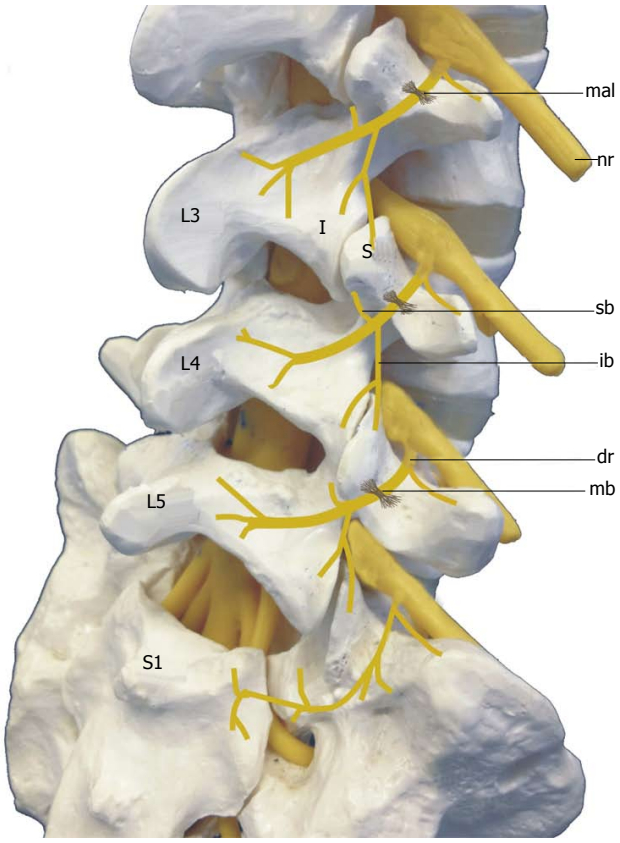

Figure 1 Lumbar medial branch anatomy. Left anterior oblique illustration (L3 to S1): Spinous processes. mal: Maillo-accessory ligament; nr: Nerve root; I: Inferior articular process; S: Superior articular process; sb: Superior branch from medial branch; ib: Inferior branch of medial branch; dr: Dorsal ramus; mb: Medial branch[13,14].

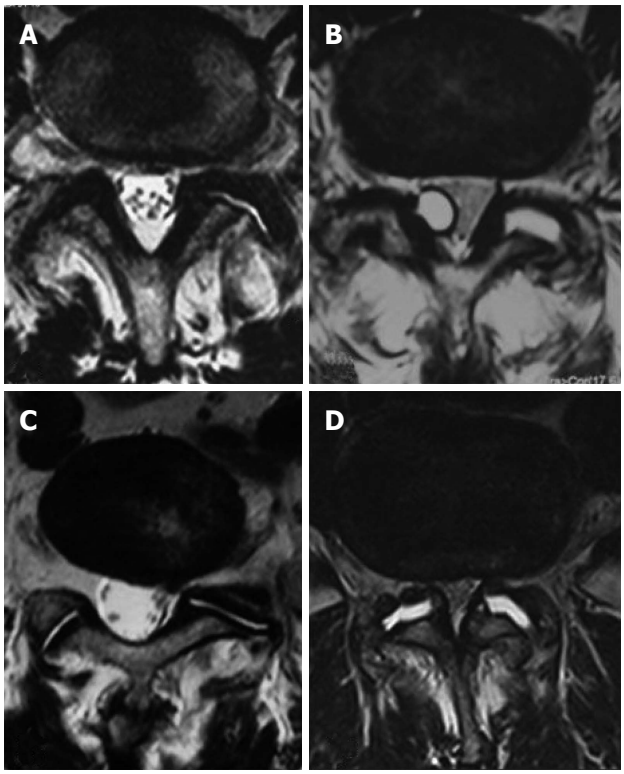

Figure 2 Examples of magnetic resonance imaging findings concerning the zygapophysial joints. A: Degenerative changes; B: Synovial cyst of the z-joint and increased joint volume; C: Asymmetric joint gap; D: Increased joint volume[13,14]. Z-joint: Zygapophysial joint.

clinical investigations testify no correlation between the clinical symptoms of low back pain and degenerative changes observed on radiological imaging, including radiographs, magnetic resonance imaging (MRI) (Figure 2), computed tomography (CT), single-photon emission computed tomography (SPECT), and radionuclide bone scanning[28-30]. Specifically, the association between degenerative changes in the lumbar z-joints and symptomatic low back pain remains unclear and is a subject of discussion[25-28].

The most accepted method[31] for diagnosing z-joint pain are controlled medial branch blocks (MBBs). MBBs are a diagnostic tool designed to test whether the pain stems from the z-joint because the medial branch innervates it[32]. They are the most thoroughly validated of all spinal interventional procedures[33,34]. The target nerve (medial branch of the dorsal ramus) is anaesthetized with a small volume of local anesthetic. The medial branch cannot be regarded as mediating the pain, if the pain is not relieved after a MBBs, this means the z-joint is not the pain source. A new suggestion about the pain source is necessary. If case of a positive answer, the pain source is recognized and a good chance of obtaining pain relief after denervation of the nerve is expected[35,36]. Single diagnostic blocks are not valid because they have an unacceptable high false-positive rate of 25%-45%[5-9,31]. To reduce the possibility of responses being false-positive, controlled blocks are mandatory[29]. Uncontrolled blocks or intra-articular blocks lack validity[31].

Therapy

No specific conservative treatment for z-joint pain exists. Patients with z-joint pain are treated in the same way as patients with low back pain emerging from a different pain source. Guidelines only exist for radiofrequency denervation of the z-joints, published by the International Spine Intervention Society[16]. Radiofrequency denervation is the direct consequence after the diagnosis of z-joint pain has been validated by controlled MBBs and it is the only validated treatment for pain mediated by the medial branches[29]. Percutaneous radiofrequency neurotomy offers pain relief by denervation of the painful joints. It is a percutaneous therapeutic procedure in which a radiofrequency electrode is used to coagulate the medial branches of the lumbar dorsal rami, or the L5 dorsal ramus, in order to relieve back pain mediated by these nerves (Figure 3)[14].

The available data vindicate the use of lumbar medial branch neurotomy provided that the correct surgical technique is used and patients are selected rigorously using controlled blocks[16,31]. There are no data that vindicate any other technique[16]. If the criterion for a positive response to diagnostic blocks is raised to complete relief, some 56% of patients

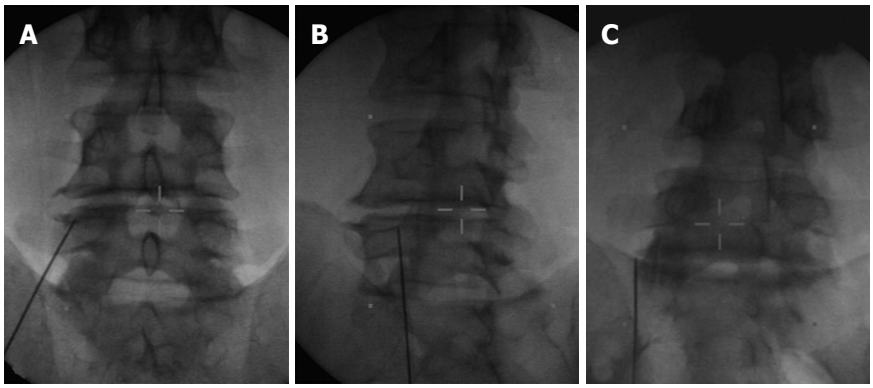

Figure 3 Different views of an electrode placed for an L4 medial branch neurotomy. A: Antero-posterior view; B: Corresponding oblique view; C: Antero-posterior view of an electrode placed for an L5 medial branch neurotomy[14].

obtain complete relief of pain[37]. They return to their normal activities, and the need for other health care is eliminated.

SELECTED PATIENTS

Particularly well studied is z-joint pain in patients without comorbidities. In this group of patients, diagnostic standards can be applied best and success rates after a specific therapy can be measured. In this review, the significance of z-joint pain is elaborated in patient groups in which z-joint pain is clinically relevant but does not occur as an isolated and independent disease. It is thus expected that diagnostic and therapeutic methods are only partially successful. For the patients, this can nevertheless make a significant difference in their daily lives.

Degeneration

During life, changes occur to the intervertebral disc and to the z-joints called spondylosis or osteoarthrosis. After the fifth decade, the subchondral bone of the z-joint gets thinner[38]. Severe or repeated pressure may result in erosions and focal thinning of the cartilage (Figure 4). These changes are not a disease per se but an expression of the morphological consequences of stress applied to the disc and the joints during life. The incidence of osteoarthrosis is just as great in patients with symptoms as in patients without symptoms[39,40]. Additional factors must be present to make the z-joints a pain source.

Z-joints are commonly altered by osteoarthritis. The arthritis is usually secondary to disc degeneration or spondylosis[41], but in 20% of cases it can be totally independent[42]. This condition is believed to be a possible cause of z-joint pain[43-46]. Inflammatory mediators, such as cytokines, prostaglandins, and neuropeptides, increase within the joint and the dorsal root ganglion in joint inflammation and arthritis[47-49]. Specifically, prostaglandin E2 has been identified as a key mediator of inflammation and amplified neuronal excitability[50-52].

Synovial cysts arise from the z-joint capsule of the lumbar spine (Figure 2B)[53]. They contain serous, gelatinous, or hemorrhagic fluid and are sometimes lined with synovium[54]. The development is related to degenerative spondylosis, segmental instability, and perhaps trauma[54,55]. They are a cause of back pain and radiculopathy, with z-joint degeneration being the most common cause for cyst formation[56].

A temporary one-sided load is often found in the context of knee or hip problems with appropriate gait disturbance or when walking with crutches. These patients often develop z-joint pain without structural changes. The reason is unusual strain or overuse of the joint. The treatment prognosis is good. Facet tropism (asymmetry of the facet angles) may have an association with degenerative changes in the spine, either as the cause of degenerative changes or as the result of abnormal loads produced by degeneration[57]. These degenerative changes can be a cause of back pain[57]. The clinical significance of facet tropism is not yet well proven[57-62].

Elderly patient

Degenerative changes are more common in older age. The joints can be affected by osteoarthritis, which is believed to be a possible cause of z-joint pain[43-46]. Compared with other sources of low back pain (*e.g.*, discogenic pain or sacroiliac joint pain), z-joint pain becomes the most important pain source[11]. However, there is often an image of mixed pain of various causes. Especially in combination with discogenic changes, spinal canal stenosis and degenerative spondylolisthesis several pain sources might exist.

Spinal canal stenosis

Patients with a spinal canal stenosis on the one hand have a symptomatology coming from the stenosis and the compression of the nerves in the dural sac. These symptoms are called claudicatio spinalis and are manifested in a restricted walking distance with pain, a sensory disturbance in the legs, or even neurologic deficits. On the other hand the most important reason for the development of a spinal canal stenosis is the

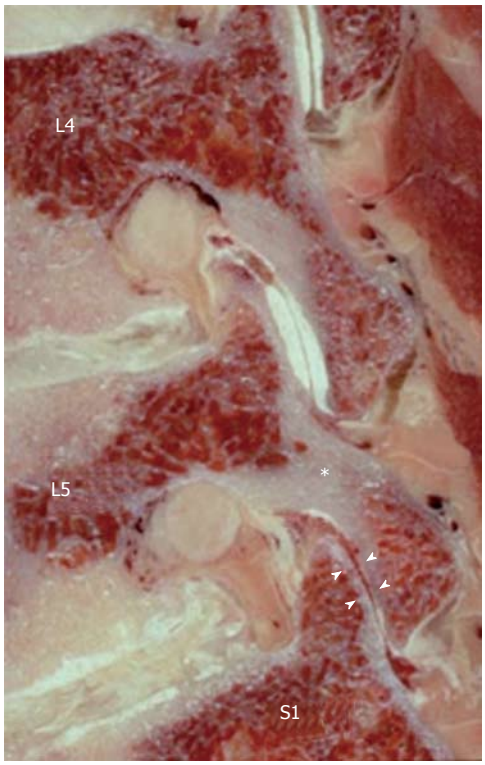

Figure 4 Sagittal section through the neuroforamina of a severely degenerated lower lumbar spine of a 70-year-old man. The z-joints are in a subluxated position due to the loss of segmental height. The pars interarticularis of L5 is being eroded superiorly by the inferior articular process of L4 and inferiorly by the superior articular process of S1 (*). Such pars erosion is a prerequisite for the development of degenerative spondylolisthesis. There is no cartilage in the L5/S1 z-joint (arrow heads). Z-joints: Zygapophysial joints.

destruction of the z-joints[63]. Therefore, patients suffer at the same time from pain deriving from the z-joints. Epidural steroid injections are commonly used to relieve symptoms caused by lumbar spinal stenosis[64,65]. Treatment of z-joint pain as described above, including radiofrequency neurotomy is an alternative for patients for whom back pain is prominent and for patients with high risk of bleeding[66].

Spondylolisthesis

The loss of the normal structural support as seen in arthritis of the z-joints is the main local reason that probably leads to the development of degenerative vertebral slippage[67,68]. It seems to be obvious that morphological deformities of z-joints in the lumbar spine are an important cause of low back pain and segmental instability and a predisposing factor in the development of degenerative spondylolisthesis[69-71]. One of the most probable sources of pain related to degenerative spondylolisthesis are degenerated and subluxated z-joints and segmental instability which causes tension in the z-joint capsule and ligaments[67,70]. Spinal instability is often indicated by an increase of the joint volume[72], or synovial cysts associated with degenerative spondylolisthesis and z-joint osteoarthritis can be found[73]. An increased amount of fluid in the joint gap seen on axial MRI (Figure 2D) is significantly suggestive of spondylolisthesis[74].

It is well known that patients with degenerative spondylolisthesis also have sources of pain other than the z-joints[75]. In particular, the often additionally present spinal canal stenosis causes symptoms. The second pathology often interlinked with degenerative spondylolisthesis is disk degeneration[67,68], Spondylolisthesis is a characteristic example of concurrent pain sources in the same patient at the same time. The proportion by which the z-joints are involved in the complex symptoms is often difficult to diagnose[76].

Radiofrequency denervation is a rational treatment of low back pain in patients with degenerative spondylolisthesis because morphological deformities of the lumbar z-joints are a predisposing factor in the progress of degenerative spondylolisthesis[70], pathology of the z-joints is a important cause of low back pain within the lumbar spine[69]. An adequate pain reduction can be realized in 65% of the treated patients for a reasonable time[76,77].

Failed back surgery

Z-joints are an important pain source not only in patients with chronic low back pain but also in patients after disc surgery[78-80]. Therefore, a specific therapy against z-joint pain is rational. Continued pain following lumbar spine surgery has been assumed to be secondary to multiple causes, including epidural fibrosis, acquired stenosis, sacroiliac joint pain, and z-joint pain[81-83]. It is difficult in post lumbar surgery syndrome to identify pain-generating structures[84]. The prevalence of z-joint pain in patients with post lumbar laminectomy syndrome is 32%. In patients after disc surgery, the prevalence of z-joint pain is 7% and 28% in patients with persistent back pain after surgery[79].

The reasons why the z-joints are involved even if the joint was untouched during the operation might be inflammatory processes, low-level trauma, changes in disc height, or stretching of the joint capsule[23]. The process of degenerative disc disease, particularly when enhanced by a herniated disc or discectomy, results in progressive loss of intervertebral disc volume and disc height and increased load to the joints, which might be a reason for pain[85]. Z-joint pain can be identified and treated with a radiofrequency neurotomy with a success rate of 58.8%[79] in patients after disc surgery.

After spinal fusion, z-joint pain can occur due to residual mobility in the index segment or in adjacent segments due to overload. Studies on the effectiveness of a specific joint therapy after spinal fusion do not exist.

Injuries

Z-joint pain is expected to appear with repetitive, chronic strains as might be seen in the elderly, or after an acute incident such as tearing the capsule of the joint by extending it beyond its physiologic limits. This

theory is supported by clinical studies showing a higher prevalence of facet arthropathy in elderly patients[86-88] and numerous cases of lumbar facet arthropathy after high-energy trauma[89]. There is also evidence that cervical z-joints can be injured by whiplash injury and can become painful[90]. Studies using double-blind controlled MBBs found that the prevalence of pain deriving from one or multiple z-joints was between 54% and 60% amongst patients with chronic neck pain after whiplash; 27% of consecutive patients with neck pain and/or headache after whiplash had pain stemming from the C2/3 joint[91-93]. The level of symptomatic joints is consistent with the location foreseen by biomechanical studies: joints at C5/6 or C6/7 and at C2/3 are most commonly affected[94-96]. A placebo-controlled trial and several observational studies with long-term follow-up[97-102] have shown that percutaneous radiofrequency neurotomy can eliminate chronic neck pain after whiplash injury stemming from the z-joints in approximately 70% of treated patients.

Lumbar facet dislocation was reported in more than two dozen patients after rapid deceleration injuries[89,103-105]. The mechanism of injury in these cases is supposed to be a combination of hyperflexion, distraction, and rotation[89,103,106,107]. Both in biomechanical studies and in postmortem studies, capsular tears, capsular avulsion, subchondral fractures, intra-articular hemorrhage, and fractures of the articular process have been found[20,108-112]. Fractures of the z-joints cannot be detected on plain radiographs and might be too small to be seen in CT scans[111,112]. Lesions such as capsular tears cannot be detected by radiography, CT, or MRI. It may be that these lesions underlie z-joint pain[1].

CONCLUSION

Z-joints meet all prerequisites to be a pain source. They are often involved in back pain and radiating pain and should not be underestimated. The prevalence of isolated z-joint pain increases with age. In addition, z-joint pain also appears in combination with other common spine diseases, such as disc degeneration, spinal canal stenosis, and spondylolisthesis. If the diagnosis is made with controlled MBBs, radiofrequency denervation is the only validated treatment for pain mediated by the medial branches.

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P- Reviewer: Ahmed AS, Charles B, DeSousa K, Sandblom G, Tufan M
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Jiao XK

World Journal of Anesthesiology

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DOI: 10.5313/wja.v4.i3.58

World J Anesthesiol 2015 November 27; 4(3): 58-65
ISSN 2218-6182 (online)

MINIREVIEWS

Perioperative hypothermia: Causes, consequences and treatment

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Author contributions: All authors substantially contributed to conception and design of the review, drafting the article or making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

Conflict-of-interest statement: All authors deny conflicts of interests with the presented material.

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Received: May 6, 2015
Peer-review started: May 8, 2015
First decision: June 3, 2015
Revised: June 24, 2015
Accepted: July 21, 2015
Article in press: July 23, 2015
Published online: November 27, 2015

Abstract

Perioperative hypothermia, core temperature below 36.0 ℃, transpires due to disruption of thermoregulation by anesthesia coupled with cold exposure to procedural surroundings and cleansing agents. Although most publications have focused on thermoregulation disruption with general anesthesia, neuraxial anesthesia may also cause significant hypothermia. The clinical consequences of perioperative hypothermia are multiple and include patient discomfort, shivering, platelet dysfunction, coagulopathy, and increased vasoconstriction associated with a higher risk of wound infection. Furthermore, postoperative cardiac events occur at a higher rate; although it is unclear whether this is due to increased oxygen consumption or norepinephrine levels. Hypothermia may also affect pharmacokinetics and prolong postoperative recovery times and hospital length of stay. In order to combat perioperative hypothermia, many prevention strategies have been examined. Active and passive cutaneous warming are likely the most common and aim to both warm and prevent heat loss; many consider active warming a standard of care for surgeries over one hour. Intravenous nutrients have also been examined to boost metabolic heat production. Additionally, pharmacologic agents that induce vasoconstriction have been studied with the goal of minimizing heat loss. Despite these multiple strategies for prevention and treatment, hypothermia continues to be a problem and a common consequence of the perioperative period. This literature review presents the most recent evidence on the disruption of temperature regulation by anesthesia and perioperative environment, the consequences of hypothermia, and the methods for hypothermia prevention and treatment.

Key words: Body temperature regulation; Hypothermia prevention; Hypothermia; Hypothermia treatment; Intraoperative care

Core tip: Thermoregulation tightly controls core temperature to ensure optimal organ and enzymatic

function. Anesthesia disrupts normal thermoregulation and, when combined with patient exposure to a cold procedural environment, leads to hypothermia. However, hypothermia is not a benign issue. It is associated with postoperative complications including infection, bleeding, cardiac events, changes in drug metabolism, patient discomfort, and increased length of stay. Although multiple preventive strategies have been explored, their utility varies. This review explores the impact of anesthesia on perioperative hypothermia and the evidence for associated complications and outcomes. Preventative strategies are also examined and future directions for research are discussed.

McSwain JR, Yared M, Doty JW, Wilson SH. Perioperative hypothermia: Causes, consequences and treatment. *World J Anesthesiol* 2015; 4(3): 58-65 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/58.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.58

INTRODUCTION

Normal core body temperature is approximately 37 ℃. As strict temperature control is important for normal organ, enzymatic, and cellular function[1], temperature control is tightly regulated by the body to within 0.2 ℃. This is referred to as the interthreshold range. Within this range, active methods of heating or cooling are not triggered. In addition, a set point temperature exists in which the body maintains steady changes in core body temperature (0.5-1.0 ℃) based on circadian rhythms. Temperature tends to be decreased during sleep and increased with physical activity[1,2].

Precise temperature regulation involves both the peripheral and central nervous systems through behavioral and autonomic triggers. Afferent signals for cold and hot sensations are transmitted *via* A-delta and C nerve fibers, respectively[2,3]. Sensory nerve fibers are thought to sense environmental temperature changes through skin projections[3]. These cutaneous "sensors" are recently characterized as transient receptor potential receptors located in both skin and spinal cord[4]. Temperature signals from the skin, spinal cord, deep abdominal/thoracic tissue, and other parts of the brain coalesce mainly within the anterior spinal cord and travel to the primary area of temperature regulation, the hypothalamus[2-4]. The hypothalamus then activates both behavioral and autonomic responses to temperature changes[3].

The human body tightly controls core temperature through a variety of mechanisms including behavioral modification, autonomic nervous system stimulation, surface skin sweating, and increased heat production *via* shivering and non-shivering thermogenesis[2]. Behavioral changes, such as a change in dress or moving out of the wind, are more influenced by skin temperature. Conversely, autonomic regulation actions including peripheral vasoconstriction or vasodilation are mostly dependent on core temperature[1].

CAUSES OF PERIOPERATIVE HYPOTHERMIA

The human body loses heat to the atmosphere in four ways: radiation, conduction, convection, and evaporation[1,5]. Radiation is the infrared transfer of heat. Conduction involves heat transfer through physical contact with an object (*i.e.,* operating room table). Convection is the movement of heat based on air flow (*i.e.,* cold air blowing over body). Finally, evaporation refers to the loss of heat through sweat from skin or fluid loss from exposure of organs to the open atmosphere. The most significant heat loss, approximately 60%, occurs by radiation[2].

Multiple factors contribute to perioperative hypothermia development. Operating room temperature contributes to intraoperative hypothermia primarily through radiant heat loss. Although most operating rooms have in-room thermostats that are able to control the ambient temperature, disagreements about the optimal temperature settings may occur based on different levels of personal comfort, dress (surgical gowns), and other heat exposure (standing under hot lights)[5]. Additional heat loss occurs through conduction as the patient is positioned on the cold operating room table and through convection by laminar airflow. Further, operative cleansing solutions aid in heat loss through evaporation.

Under normal conditions, the human body would initiate mechanisms to preserve or create heat. However, anesthesia disrupts these homeostatic mechanisms. Concurrently, exposure to the cold procedural environment and vasodilation induced by general or regional anesthesia contribute to intraoperative hypothermia development[2,4].

General anesthesia

Regardless of maintenance with volatile agents, dexmedatomidine, or propofol, general anesthesia impairs autonomic temperature control[2-4]. In fact, it may increase the interthreshold temperature range 5-20 fold, allowing temperatures to vary by 2-6℃.

After induction of general anesthesia, body heat redistributes from the central compartment to the periphery *via* vasodilation, causing heat loss to the environment[6]. Approximately 90% of this heat loss is through the skin *via* radiation and convection, with evaporation and conduction playing smaller roles[3]. This redistribution of heat mainly occurs during the first hour of general anesthesia and is responsible for about 80% of the core temperature drop; however, after induction redistribution continues for at least 3 h, making it the major contributor to intraoperative heat loss during general anesthesia[7]. Ventilation with dry gas, cutaneous heat loss, and cold surgical prep

solutions further contribute to overall intraoperative temperature decline[6,7]. After several hours, core temperature decline stops and autonomic-induced peripheral vasoconstriction occurs in an effort to bring heat back to the body's core. This is often referred to as the plateau phase which may occur 3-5 h into a general anesthetic[3].

Neuraxial anesthesia

The mechanisms of heat loss with neuraxial anesthesia are similar to those of general anesthesia, but they also differ in important ways. Similar to general anesthesia, neuraxial anesthesia impairs autonomic temperature control[7]. Although redistribution during regional anesthesia decreases core temperature approximately half as much as during general anesthesia, it still remains the most important cause of core heat loss during the first hour. Unlike general anesthesia, there is not a temperature plateau phase with neuraxial anesthesia[8]. The blocked portion of the patient's body is unable to shiver or vasoconstrict regardless of the decrease in core temperature. For these reasons, a long case under neuraxial anesthesia may cause more heat loss than general anesthesia[9]. Neuraxial anesthesia also alters behavioral responses to hypothermia[10]. Patients do not feel cold despite being hypothermic, secondary to the peripheral vasodilation in the blocked extremities. Finally, core temperature is often not monitored with neuraxial anesthetics and accordingly hypothermia is not detected. Overall, hypothermia with neuraxial anesthesia may be as significant as with general anesthesia[11].

CONSEQUENCES OF PERIOPERATIVE HYPOTHERMIA

Hypothermia affects over 60% of patients intraoperatively, and its effects are noteworthy[12]. It adversely impacts blood loss, infection risk, and cardiac events, potentially increasing length of hospital stay. It also slows anesthetic drug metabolism and may alter pharmacodynamics, thus contributing to increased post anesthesia care unit (PACU) recovery time.

Blood loss

Studies that attempted to determine whether mild hypothermia leads to increased blood loss and transfusions have given inconsistent results[13]. A recent meta-analysis found that a median patient temperature of 35.6℃ resulted in increased blood loss (4%-26%) and an increased relative risk of transfusion (3%-37%)[13]. Notably, some studies included in the meta-analysis were from the 1990s when blood conservation techniques and transfusion thresholds may have been more liberal. However, in a recent large retrospective study of noncardiac surgeries published in 2015, transfusion requirements increased in proportion to the decrease in temperature and the increased duration of hypothermia[12].

Potential causes for increased blood loss include hypothermia-induced platelet dysfunction and coagulation cascade enzyme dysfunction. To evaluate coagulopathy, prothrombin time (PT) and partial thromboplastin time (PTT) were measured at different temperatures. For a given blood sample, PT and PTT increased from 11.8 ± 0.3 s and 36.0 ± 0.7 s to 12.9 ± 0.5 s and 39.4 ± 1.0 s, respectively, as the temperature of the sample decreased from 37 to 34 ℃[14]. Both PT and PTT continued to increase as temperature further decreased. It is important to note that blood samples are warmed to 37 ℃ prior to performing the lab tests[14]. Therefore, laboratory values may not reflect what is occurring physiologically in the patient.

Surgical wound infection

Mild hypothermia has been associated with increased risk of surgical wound infection due to vasoconstriction and change in oxygen tension. At 34.5℃, thermoregulation leads to peripheral vasoconstriction[12]. When this occurs, oxygen delivery to subcutaneous tissues decreases impairing the strength of the collagen lattice that supports the healing scar[15,16]. Decreased oxygen delivery also impairs chemotaxis, phagocytosis, and antibody production by white blood cells and the immune system[17]. In patients undergoing colorectal surgery, the last intraoperative core temperature was strongly correlated with the incidence of postoperative wound infection. The hypothermic group (34.7 ± 0.6 ℃) had a 19% incidence of wound infections compared with 6% in the normothermic group (36.6 ± 0.5℃)[16].

Length of hospital stay and PACU recovery time

Although most studies show that hypothermia contributes to increasing length of hospital stay and PACU recovery time, results are not consistent. A large study published in 1996 in colorectal surgery patients found that hypothermia (34.7 ± 0.6℃) at the end of surgery delayed patients' ability to tolerate solid food and suture removal by one day compared to patients with normothermia. Hospital length of stay also increased 20% (2.6 d) and length of stay was prolonged even after correcting for the increased risk of infection in the hypothermic group[16].

PACU discharge times are also impacted by hypothermia. Discharge from the PACU was observed to significantly increase by 40 min in hypothermic patients based on a modified Aldrete and Kroulik scoring system[18]. If discharge criteria included normothermia, then recovery was prolonged over 2 h[18].

Drug metabolism

Mild hypothermia impairs temperature-sensitive enzymes that metabolize and clear anesthetic drugs, thus increasing their duration of action; the effect on potency differs depending on the drug. In animal models, moderate-severe hypothermia increases volatile anest-

hetic potency, thus decreasing minimum alveolar concentration (MAC)[19].

The duration of actions of midazolam, morphine, propofol, and several nondepolarizing neuromuscular blocking agents (*e.g.,* vecuronium, rocuronium, atracurium) are prolonged due to the pharmacokinetic effect of hypothermia. In nonsurgical healthy patients, midazolam clearance decreases 11.1% per 1℃ below 36.5 ℃[20]. The same decrease in clearance has been noted for vecuronium[21-24]. Additionally, mild hypothermia can cause a decrease in the twitch response even when neuromuscular blocking drugs are not given[25]. The twitch tension starts to decrease 16% per 1 ℃ once the temperature of the adductor pollicis muscle is below 35.2 ℃[26]. With moderate hypothermia to 30 ℃, morphine also has decreased potency, clearance, and volume of distribution; although, its concentration is elevated in the plasma and cerebral spinal fluid[27,28]. Notably, the efficacy of neostigmine and naloxone seems to be preserved during hypothermia[29].

Shivering and thermal discomfort

If a patient is hypothermic, there is an increased incidence of thermal discomfort, oxygen consumption, vasoconstriction, and shivering[30]. Shivering is four times more dependent on core temperature than skin temperature[30]. However, core normothermia does not guarantee that shivering will not occur. During shivering, all patients are vasoconstricted[30]. In a study by Kurz *et al*[16], intraoperative vasoconstriction, measured by comparing forearm temperature with fingertip temperature, was noted in 74% of hypothermic patients *vs* 6% of normothermic patients. Postoperatively, hypothermic patients experienced persistent vasoconstriction for up to 6 h, decreased thermal comfort, and increased rates of shivering[16]. Although postoperative cutaneous warming decreases thermal discomfort, shivering intensity, and maximum oxygen consumption during shivering, it does not stop or affect the duration of shivering[30]. Fortunately, vasoconstriction and hypothermia usually resolve by postoperative day one[31].

Cardiac events

The mechanism behind the increased postoperative cardiac risk with mild hypothermia is still unclear. Studies are inconsistent in determining whether the increased risk of myocardial infarction is due to shivering or stress hormones[32]. Although plasma catecholamine concentrations increase to three times normal in PACU, this finding has not been proven to be the cause[32]. To further this conundrum, hypothermia is thought to be cardioprotective during cardiopulmonary bypass and after cardiac arrest.

Although normothermia does not change the incidence of intra-operative cardiac events, it does reduce the postoperative risk by 55%[33]. In a study evaluating patients with high risk of coronary artery disease who had abdominal, thoracic or vascular surgery, those who were hypothermic had an increased incidence of postoperative cardiac events, including angina, ischemia, infarction, and cardiac arrest[33]. In the hypothermic group, cardiac events (6.3%) and ventricular tachycardia (7.9%) were significantly greater compared to the normothermic group (1.4% and 2.4%) respectively[33]. Similarly in the first 24 h following lower extremity revascularization surgery, hypothermic patients were significantly more likely to experience myocardial ischemia compared to normothermic patients (36% *vs* 13%, respectively)[34]. However, the incidence of intraoperative cardiac events was similar in the two groups[33]. In contrast, a significant difference in cardiovascular events or mortality was not noted between moderate hypothermic (33.3 ± 0.8 ℃) and normothermic patients undergoing intracranial aneurysm surgery[35].

The mechanism for the increased risk of myocardial ischemia in patients with mild hypothermia remains unclear. Shivering leads to increased metabolic demands but oxygen consumption alone has not proven to be the culprit[34]. Physiologic responses to hypothermia in nonsurgical patients include vasoconstriction[36] and sympathetic nervous system stimulation leading to increased epinephrine, norepinephrine, blood pressure, and heart rate[37,38]; however, stress hormones in surgical patients seem to respond differently. In a study by Frank *et al*[31] examining patients over 60 years old with two or more coronary artery disease risk factors and undergoing thoracic, abdominal, or lower extremity vascular surgery, hypothermic patients had significantly higher norepinephrine concentrations and arterial blood pressures but lower heart rates in the early postoperative period. While postoperative norepinephrine, epinephrine and cortisol concentrations increased in all patients, norepinephrine was significantly higher in the hypothermic group compared to the normothermic group[31]. Alternatively, during cerebral aneurysm surgery, intraoperative norepinephrine and cortisol levels decreased similarly in both the mild hypothermic and normothermic groups, while epinephrine had a significant decrease in the hypothermic group[39]. Intraoperative mild hypothermia also did not affect blood pressure when compared to normothermic patients. The difference between intraoperative and postoperative stress hormone levels may suggest that a time lag exists between stressful stimuli and hormone response; alternatively, anesthetics may attenuate the stress response and protect the myocardium. This would be consistent with the risk of myocardial infarction increasing and occurring postoperatively instead of intraoperatively.

HYPOTHERMIA PREVENTION AND TREATMENT

Hypothermia treatment involves minimizing cold exposure while providing heat sources, such as heat transfer systems or pharmacologic agents, to equalize heat loss. Heat transfer systems may be passive or active.

Passive warming methods include passive insulation, environmental warming, and closed or semi-closed anesthesia systems. Active warming requires heat transfer to the patient through warmed fluids, circuit humidification, radiant heaters, forced or convective air warmers, infrared lights or circulating hot water systems. Alternatively, pharmacologic means may minimize heat loss through medications that decrease heat redistribution or through intravenous nutrients that stimulate metabolism and heat production. A combination of these methods is likely most effective in practice; however, prevention of hypothermia is likely a superior approach to treatment[40-42].

Passive warming

Passive warming methods, including environmental heating and passive insulation, minimize but do not eliminate heat loss. The operating room temperature is the most critical factor influencing heat loss[43,44]. Heat loss increases as the difference between the skin and environment grows. Consequently, the simplest method to reduce heat loss is raising ambient temperature. Unfortunately, most operating room personnel find elevated temperatures intolerable making this approach impractical as a singular solution. Thermal insulation may be accomplished through mass or reflective covering. Reflective coverings prevent radiant heat loss by reflecting radiant heat back to the body. Mass coverings halt airflow between the covering materials. Surgical drapes and blankets are common examples, and covering patients with blankets is a standard practice. Heat loss may be reduced by as much as 33% with a single layer covering; however, prevention of heat loss is limited and multiple blankets are only slightly more effective than one blanket[45-47]. Unfortunately, effective covering of the body surface is often not feasible in the intraoperative setting making passive methods ineffective to prevent hypothermia.

Active warming

Active warming is required in most situations to maintain normothermia. Methods include warming of intravenous fluids, cutaneous warming, pharmacologic vasoconstriction, and intravenous nutrients. Of these choices, cutaneous warming (*e.g.,* forced air warming, electrical resistance, circulating hot water device) is the most widely used[48].

Cutaneous warming: Likely the most common warming system, forced air warming is effective, safe, relatively inexpensive, easy to use[45,49], and superior to many other warming systems[50,51]. Forced air warmers were initially utilized to treat postoperative hypothermia before they were introduced for intraoperative warming. In this method, warmed air is forced into a receptacle, commonly a two-layer blanket, which lies in direct contact with a large surface area of the body. The forced air escapes through pores of the blanket material creating a warm microclimate over the area of contact. Heat transfer is dependent on both the amount of surface area covered and the temperature difference between the skin and blanket. Consequently, the effectiveness is dependent upon utilization of a properly shaped warming blanket, appropriate placement on the body, and selection of a high warming temperature.

The utility and consequences of forced air warmers have also been scrutinized. A recent, large retrospective study of over 58000 patients undergoing noncardiac surgery and utilizing forced air warmers found that 64.4% of patients were hypothermic 45 min after induction and 20% of patients continued to be hypothermic after 6 h of anesthesia[12]. Additionally, much discussion has occurred recently in regard to the potential for bacterial dispersion in the operating room by forced air warmers. However, studies examining contamination with and without forced air warmers did not find a difference[52,53].

Electrical resistance may also be used for heat production by sending an electrical current through a resistant polymer blanket or mattress[54]. These systems utilize conduction and are only effective when the warmed surface directly contacts the skin. This differs from forced air warmers, which create a carrier (air) for heat to travel from the warming blanket to the patient. Benefits of these devices include noiseless operation and slower temperature changes compared to the continuous supply of warmed air required with forced air warmers[54]. While the efficacy of electrical resistance warming blankets are similar to forced air warmers, they are expensive albeit reusable[54-56]. Additionally, an electrical mattress alone is insufficient to prevent hypothermia due to the negligible amount of body surface area contacting the operating table and the low amount of heat transfer[56,57]. Consequently, warming blankets (forced air warming or electrical resistance) must be utilized concurrently to prevent intraoperative hypothermia.

Since water has much greater heat capacity than air, it may be hypothesized that water systems would supply a great amount of heat. However, similar to electrical resistance systems, direct contact must be made with the skin. In addition, these devices have been found to be ineffective with posterior body warming alone[51]. As a result, water-warming blankets have been designed to wrap around the limbs[58] and trunk[59] depending on the surgical procedure. While anterior and posterior warming with water systems have demonstrated improved maintenance of normothermia in large upper abdominal surgeries compared to forced air warming alone, posterior water mattresses combined with anterior forced air warmers are comparable[60]. Further, thermal injury remains a concern for circulating water devices; especially mattresses[61]. Price and technological problems have also largely limited use of these systems.

The timing to initiate cutaneous warming is also important. Hypothermia prevention is less effective after anesthesia induction[40-42]. Warming patients prior to anesthesia induction substantially prevents the decrease

in core temperature caused by redistribution[62]. Pre-warming may also lessen intraoperative heat loss by increasing peripheral tissue temperature to resemble core temperature.

Warming intravenous fluids: Although heating intravenous fluids does not warm patients, it does assist in hypothermia prevention with administration of large volumes of Ⅳ fluids[63]. Multiple different systems and technologies have been developed to warm intravenous fluids and blood products. These include water baths, conductive warming with metal, countercurrent heat exchange, microwave technology, and forced-air warming. All systems provide a range of flow velocities and temperatures with built-in prevention technologies for excessive warming and air detection. However, while 42 ℃ is considered safe for blood administration[64], the safe upper limit is not well defined. Although reports have described heating intravenous fluids to 54 ℃[65], this practice is not studied and should not be utilized.

Pharmacologic vasoconstriction: Pharmacologic means to minimize heat loss caused by core-to-peripheral redistribution have been explored with a predominant focus on maintaining precapillary vasoconstriction. Induction with ketamine was associated with greater core temperatures throughout surgery compared to patients induced with propofol[66]. Similarly, phenylephrine infusion (0.5 μg/kg per minute) initiated immediately prior to general anesthesia induction was associated with a smaller reduction in core temperature compared to controls.

Intravenous nutrients: Administration of intravenous nutrients, such as amino acids and fructose, has been examined to maintain normothermia through endogenous heat production. Protein/amino acid administration increases whole-body heat content by 20% with a significant increase in body temperature in awake subjects[67]. Intravenous infusion of amino acids minimized core temperature decline and postoperative shivering following general anesthesia for open abdominal surgery[68]. Notably, the timing of amino acid administration was variable. In hip arthroplasty patients receiving neuraxial anesthesia, preoperative intravenous amino acid administration one hour prior to surgery elevated subjects' temperatures prior to spinal placement resulting in improved intraoperative normothermia with decreased blood loss compared to control patients receiving saline[69]. Oxygen uptake was also increased in subjects receiving amino acids. Intravenous fructose has also been examined. Patients receiving preoperative fructose infusions demonstrated greater core temperatures after anesthetic induction and throughout the study period[70]. Interestingly, improvement in normothermia was attributed to both amplified metabolic heat production and an elevated threshold for vasoconstriction.

CONCLUSION

Despite the well-documented incidence of perioperative hypothermia, it continues to be a very common and avoidable anesthesia-related complication. Both general and neuraxial anesthesia impair normal physiologic temperature regulation. The consequences of perioperative hypothermia are significant and may include increased intraoperative blood loss, increased chance of surgical wound infection, increased length of PACU and overall hospital stay, decreased patient comfort, and increased rates of cardiac events. Although both passive and active cutaneous warming minimize heat loss and are commonly used strategies in most operating rooms today, these methods do not completely eliminate intraoperative hypothermia.

Few published studies characterize intraoperative temperature patterns. Rather, most publications have focused on postoperative temperatures and outcomes. Consequently, the impact of various normothermia strategies on intraoperative temperature patterns is not well elucidated. This is especially true in patients receiving neuraxial anesthesia, where temperature monitoring is often inconsistent or absent.

As intraoperative hypothermia may be difficult to prevent in many cases, future studies should further characterize intraoperative hypothermia development and the impact on outcomes. Intraoperative characterization should investigate the impact of both preventative strategies and anesthesia type. Postoperative outcome studies should examine the extent and duration of hypothermia and how it relates to negative perioperative outcomes.

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P- Reviewer: Afzal M, Ewers A, Spasojevic SD
S- Editor: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5313/wja.v4.i3.66

World J Anesthesiol 2015 November 27; 4(3): 66-72
ISSN 2218-6182 (online)

MINIREVIEWS

Sugammadex: Role in current anaesthetic practice and its safety benefits for patients

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Author contributions: Copp MV and Barrett TF contributed equally to this work.

Conflict-of-interest statement: Copp MV has in the past received honoraria from MSD for serving as a speaker but none is related to this publication and MSD has not been involved in the writing of this article.

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Received: May 20, 2015
Peer-review started: May 22, 2015
First decision: July 10, 2015
Revised: July 30, 2015
Accepted: August 20, 2015
Article in press: August 21, 2015
Published online: November 27, 2015

Abstract

Sugammadex has revolutionized anaesthetic management of reversal of neuromuscular block (NMB) by way of its unique mechanism of action encapsulating the amino steroid neuromuscular blocking drugs rocuronium and vecuronium. The cholinesterase inhibitors have significant pharmacological and clinical limitations whereas sugammadex allows predictable, safe and rapid reversal from any depth of blockade. The financial cost of sugammadex is significant. Many hospitals in the United Kingdom use clinical guidelines to direct best use of sugammadex in their institutions. Auditing the use of sugammadex provides useful information on which patients are benefiting from sugammadex. The clinical benefits of sugammadex are well understood. No patient should now be subjected to the danger of post-operative residual curarization. Versatility in the ability to reverse NMB has brought opportunities to the anaesthetist in the management of rapid sequence induction using high dose rocuronium with the knowledge that safe reversal of NMB is now possible in the unlikely event of a "can't intubate can't ventilate" situation. Do we still need suxamethonium to be available? The nature of surgery continues to evolve with ever-increasing enthusiasm for minimally invasive laparoscopic techniques. There is evidence to support using a deeper level of NMB to improve the working space and operating conditions in laparoscopic surgery. It is now possible to maintain a deep level of NMB right up until the end of surgery with no concerns about the ability to effect safe reversal of NMB. Vigilance about the possibility of allergic sensitivity to sugammadex needs to be maintained. The increased usage of rocuronium has the potential for rocuronium-induced anaphylaxis. Conversely, there is a potential role for sugammadex in the treatment of rocuronium anaphylaxis. Clinicians who have used sugammadex are struck with the quality of recovery seen in their patients. It is important that the economic implications of the use of sugammadex are fully understood. This article considers the current role of sugammadex in clinical practice outside of routine reversal of NMB and discusses how the addition of sugammadex to the anaesthetic armamentarium brings safety benefits for patients.

Key words: Sugammadex; Neuromuscular block; Clinical benefits; Patient safety; Cost benefit

Core tip: Sugammadex is a new drug to reverse neuromuscular blockade. Its unique mechanism of action has revolutionized the management of neuromuscular block. For the first time anaesthetists have the ability to reverse safely and predictably from any level of neuromuscular blockade transforming its clinical management. Postoperative residual curarisation can be eliminated bringing significant safety benefits to patients. Sugammadex is expensive and anaesthetists need to use it in a cost effective way for appropriate patients and anaesthetic techniques. Clinical guidelines can help in ensuring that sugammadex is used responsibly in current clinical practice.

Copp MV, Barrett TF. Sugammadex: Role in current anaesthetic practice and its safety benefits for patients. *World J Anesthesiol* 2015; 4(3): 66-72 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/66.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.66

INTRODUCTION

Sugammadex was licensed for use by the European Medicines Agency on 29 July 2008 and launched for use in the United Kingdom in November 2008. It is now available for use throughout Europe, Asia, Japan, Australia and New Zealand. The anticipated launch of sugammadex in the United States has been put back after the Food and Drug Administration (FDA) cancelled its meeting in March 2015 of the Anesthetic and Analgesic Drug Products Advisory Committee, which was planned to discuss the resubmission of the New Drug Application for sugammadex.

MSD United Kingdom estimate that in the United Kingdom 70000 patients were given sugammadex last year and it is estimated that globally in excess of 8.9 million patients have been exposed to sugammadex without significant reported adverse events showing it to be a safe, effective and important new drug[1].

CLINICAL ROLE OF SUGAMMADEX

The original clinical trials evaluating sugammadex clearly demonstrate that it achieves faster and more predictable recovery of neuromuscular block (NMB) from a moderate level of NMB as defined by a return of two twitches (T2) of the train of four (TOF) count and from a deep block of NMB at the level of a post tetanic count (PTC) of 1-2. The dose dependent response of sugammadex has also been shown to be effective in reversing safely from a profound level of block immediately after administration of an intubating dose of 1.2 mg/kg of rocuronium as used in a rapid sequence induction (RSI) of anaesthesia[2].

At the launch of sugammadex, emphasis was placed on the rapid and predictable reversal of NMB as compared to reversal with traditional cholinesterase inhibitors. The expectation was that sugammadex might universally replace the cholinesterase inhibitors in everyday clinical practice. The issue for the majority of clinicians and healthcare providers was the financial cost of sugammadex. In the United Kingdom such was the concern about the introduction of sugammadex on pharmacy and operating theatre budgets that many hospitals struggled to get formulary approval. In our own institution a guideline (Table 1) was written in an effort to inform usage in a rational manor to take advantage of the clear clinical benefits whilst trying to contain the likely adverse effect on the operating theatre budget[3].

We audited the use of sugammadex for the first six months after it became available. The aim of the audit was to check adherence to our guidelines and to give a quantitate figure for the overall use of sugammadex to inform effects on the operating theatre pharmacy budget.

In our institution approximately 18000 general anaesthetics are given per annum of which 15% use an NMB. In the first six months of sugammadex being available the drug budget for reversal agents (neostigmine + glycoplyrolate + sugammadex) increased by 60%. In the context of the total theatre pharmacy budget for our institution the overall increase in this budget was less than 1%. This is a reflection of the fact that conventional reversal (neostigmine + glycopyrrolate) is so inexpensive.

The clinical findings of the audit showed that 30% of cases where sugammadex was administered there was a desire to avoid the side effects of neostigmine, in particular the potentially detrimental effect of a tachycardia in patients with known ischaemic heart disease. Sugammadex was used in 28% of cases to help ensure complete reversal of NMB in morbidly obese patients undergoing non-bariatric surgery (at the time of the audit our institution did not have a Bariatric Surgery programme). Sixteen percent of cases were ear nose and throat cases where deep NMB was required right up until the end of surgery. Sixteen percent of cases involved a need to provide optimal surgical conditions with deep NMB up to the end of surgery during laparoscopic surgery. Five percent of cases were to reverse patients with a known difficult intubation in an attempt to avoid airway compromise from any element of residual NMB at extubation. Five percent of cases were ASA 3/4 patients undergoing emergency surgery where it was considered essential to avoid any potential element of residual block that would be likely to significantly compromise patients in the post anaesthesia care unit (PACU).

Most hospitals in the United Kingdom have subsequently used a guideline to help facilitate introduction of sugammadex into clinical practice. It is accepted that morbidly obese patients are at increased risk of postoperative anaesthesia related complications. In

Table 1 Suggested guideline for use of sugammadex

Sugammadex is not to be prescribed for routine reversal from moderate NMB (TOF count > 2)
Clinical situations where avoiding the use of neostigmine and glycopyrrolate potentially gives significant safety benefits to patients, *e.g.*, avoidance of tachycardia/tachyarrthymias in patients with ischaemic heart disease and/or atrial fibrillation. Avoidance of potential bronchospasm in patients with brittle asthma
Concern about residual neuromuscular block (after rocuronium or vecuronium) post-operatively in patients with airway difficulty or respiratory insufficiency that have already been reversed with a max 5 mg dose of neostigmine
Reversal from deep neuromuscular block that would otherwise waste 30 min of theatre time if waiting for a TOF count of 2 to use neostigmine reversal, *e.g.*, when a large dose of rocuronium has been used to provide deep neuromuscular block for a short surgical procedure or the surgery has finished earlier than predicted
In morbidly obese patients where there is a concern about the potential for residual neuromuscular blockade following reversal of NMB drugs
Emergency reversal of rocuronium (1.2 mg/kg) using the sugammadex rescue pack (16 mg/kg) after failed intubation at RSI

NMB: Neuromuscular block; TOF: Train of four; RSI: Rapid sequence induction.

particular, morbidly obese patients undergoing non-bariatric surgery with a history of sleep apnoea are at risk of airway complications in the PACU. It is essential in this group of patients that the muscles of the upper airway, which are some of the most sensitive to the presence of a NMB and hence post-operative residual curarization (PORC), have achieved complete reversal at the time of extubation[4,5]. Sugammadex would seem to be ideally suited to reversal from NMB in this high-risk group of patients. Anaesthetists practising bariatric surgery are debating the use of a deep block technique compared to moderate block with remifentanil and further evidence is required to support the routine use of sugammadex in bariatric surgery.

There is clear evidence that critical respiratory events occur in the PACU as a result of PORC as shown by Murphy and colleagues[6]. In our institution we have recently published a case report of a patient who developed stridor in the PACU as a result of PORC which, when recognized as such, was swiftly and effectively resolved by sugammadex administration[7].

RSI AND CAN'T INTUBATE CAN'T VENTILATE

The traditional purist RSI using thiopentone and suxamethonium alone to induce anaesthesia and achieve endotracheal intubation is less commonly performed in United Kingdom clinical practice today. More often a modified form of RSI is carried out substituting thiopentone for propofol or supplementing the core induction medications with short acting opioids for dose sparing effect and in an attempt to obtund the laryngeal reflex during airway manipulation.

More recently, high dose rocuronium (1.2 mg/kg) has been shown to produce identical intubating conditions as suxamethonium[8]. Given the numerous side effects and contra-indications to suxamethonium this has become an increasingly attractive alternative. However, the use of rocuronium confers an intermediate duration of neuromuscular blockade (60-90 min)[9]. Prior to the introduction of sugammadex this would preclude the option of neuromuscular blocking agent reversal and waking a patient up in the event of a failed intubation, or indeed a Can't Intubate Can't Ventilate (CICV) scenario. However, with its potential to rapidly reverse a deep NMB, the question remains as to whether sugammadex has transformed the safety of a rocuronium based RSI.

Sugammadex reversal of profound NMB has been shown to be significantly faster than spontaneous recovery from suxamethonium[10]. Paton *et al*[11] reported on the successful use sugammadex after induction in a patient with airway difficulties. The key to a successful clinical outcome is early recognition of the CICV situation and administration of the appropriate dose of sugammadex (16 mg/kg) to reverse the intubating dose of rocuronium. It should be noted however, that the decision time to use sugammadex and its preparation in an emergency situation might cause significant delay in achieving full NMB reversal. Bisschops *et al*[12] (2010) demonstrated in simulation the extent of this delay and raise the concern that this may increase patient morbidity and mortality. If sugammadex is to be considered for CICV scenarios it must be readily available to be drawn up and immediately administered. In our trust we have put together an emergency reversal rescue pack stored in emergency theatres. It consists of three 500 mg ampoules of sugammadex, sufficient to recover a 93 kg patient that can be given promptly whilst exact doses are calculated and further sugammadex given as needed.

Individual experience must also be considered in the emergency use of sugammadex. Following its introduction, a number of hospitals in the United Kingdom only made sugammadex available in the theatre for the emergency treatment of a failed intubation. An individual poll conducted by the author at one such hospital found that no anaesthetist had actually ever used sugammadex. The concept that clinicians should use an unfamiliar drug in a difficult and potentially life-threatening situation could be questioned and may be criticised in the event of a poor clinical outcome. It follows that it could be considered unreasonable of an anaesthetist to use rocuronium for an RSI if they have no previous experience of using sugammadex in their own clinical practice.

Finally, we should perhaps be wary of becoming com-

placent with the availability of sugammadex in difficult airway trolleys. Mendonca warns of the risks of relying on sugammadex as a rescue plan in cases of anticipated difficult airway where awake tracheal intubation remains the gold standard[13]. The presence of sugammadex should not be a substitute for thorough pre-operative assessment of the airway, anticipation of difficulty and the presence of well thought out plans for management and back up.

THE END OF SUXAMETHONIUM?

The arrival of sugammadex suggested that it would remove the need for suxamethonium[14]. Indeed the Difficult Airway Society guidelines are currently under review, due for publication in late 2015, and are likely to propose that rocuronium may be better than suxamethonium for RSI[15]. The question has been posed as to whether the availability of sugammadex will bring about the removal of suxamethonium from the anaesthetic drug cupboard. This issue was debated by Professor Mirakur RK and the author at the Annual Meeting of the British Association of Day Surgery[16]. It was agreed that whilst suxamethonium theoretically could be substituted by a rocuronium and sugammadex technique most clinicians feel uncomfortable not having access to suxamethonium, despite its considerable array of clinical side effects, in their clinical practice.

DEEP NMB (PTC 1-2)

Sugammadex provides the anaesthetist for first time ever the ability to safely reverse from any level of NMB. This means that NMB could be maintained right up till the end of surgery without fear of having to prolong anaesthesia whilst waiting until the return of two twitches of the TOF to allow reversal with neostigmine and also fear of putting the patient at the potential risk of PORC.

Laparoscopic surgery is one area where the ability to maintain a deep level of block can bring safety benefits to the patient by improving intraoperative conditions for the surgeon. Over the last decade there has been a significant increase in the number and types of surgery that can be performed laparoscopically. The combined aims of the surgeon and anaesthetist are to do no harm, practice safe surgery, and produce an enhanced recovery for the patient. Major bowel surgery and the majority of gynaecological surgery are now routinely being performed using a laparoscopic technique. Avoiding large abdominal incisions brings real benefits to patients in terms of enhanced recovery.

The anaesthetist has a key role to play in assisting to provide optimal operating conditions for the surgeon right up until the end of surgery. There is evidence that provision of deep NMB can improve the operating conditions for surgeons, in particular the working space in laparoscopic surgery, with improved outcomes for patients[17,18]. In summary a deeper block prevents sudden unexpected patient movement, increases the working space, lowers intra-abdominal pressure and may reduce postoperative pain[19-21].

However, the place for deep NMB in laparoscopic surgery has been questioned with regard to the substantial economic considerations of maintaining deep block as compared to a less intensive block of TOF 1-3. Further evidence is required to ascertain if deep block contributes to better patient outcomes and truly improves surgical operating conditions[22].

HYPERSENSITIVITY TO SUGAMMADEX

One of the concerns consistently preventing approval of sugammadex by the United States FDA regards the potential risk of drug-induced hypersensitivity reactions. Case reports of anaphylaxis following sugammadex administration with confirmatory skin prick testing certainly exist in the literature[23,24]. A recent review article by Tsur and Kalansky[1] (2014) examined these reports in more depth. Of the 15 cases that they identified during a thorough search of the literature 11 underwent skin prick testing and 10 of these were proven to develop sugammadex induced hypersensitivity. Based on these cases they conclude that hypersensitivity reactions to sugammadex usually occur within 5 min of its administration with the appearance of a rash, hypotension and tachycardia being the most frequently shared signs. Of note, all of the patients during this review survived and in the majority of cases there had been no previous exposure to sugammadex. This raises the possibility that patients may have been previously sensitized by cyclodextrins found in food or cosmetics and that previous exposure to the drug itself is not a pre-requisite for hypersensitivity.

Despite the existence of reports of hypersensitivity, sugammadex use appears to be well tolerated and there remain no reports in the literature of deaths associated with its use[9]. Indeed, cyclodextrins are considered to be a relatively inert group of medicines and the doses of sugammadex used clinically are low in comparison to other medicinal products that contain these substances[9]. Current estimates of incidence of hypersensitivity reactions are less than 1%[25]. Ultimately, as with any medication that we administer, we should remain vigilant to the possibility of reaction and hypersensitivity and to have clear guidelines to manage such an event.

SUGAMMADEX IN THE MANAGEMENT OF ROCURONIUM INDUCED ANAPHYLAXIS

Conversely there has been some interest in the role of sugammadex in the management of rocuronium induced anaphylaxis. An allergic reaction to rocuronium is one of the most common causes of anaphylaxis in anaesthesia[9,26]. With the availability of sugammadex it

is foreseeable that there will be an increase in the use of rocuronium as a muscle relaxant of choice. Consequently there may be a rise in the number of cases of rocuronium-induced anaphylaxis. If sugammadex has a role in the management of this potentially life-threatening emergency then its presence in the anaesthetic cupboards can be further justified.

Sugammadex binds rocuronium. Studies have demonstrated that once encapsulated, a rocuronium-sugammadex complex is formed and the epitope of the rocuronium molecule is concealed, preventing its role in facilitating further allergic reaction[27,28]. Current evidence in clinical practice remains at a case report level. Most of these describe an improvement in clinical condition following the administration of large doses of sugammadex immediately, or soon after the recognition of rocuronium induced anaphylaxis. Once an allergic process and mast cell activation have been triggered it is unlikely that encapsulation of the rocuronium will affect the anaphylactic cascade[9]. Despite this, there have been cases where sugammadex has appeared to improve clinical condition even 10 min after rocuronium anaphylaxis, which is more difficult to explain biochemically[29,30]. Of course, sugammadex is only one of a number of treatments given in attempt to attenuate the anaphylactic process and without further evidence it should not be considered a single therapy in itself, however, it's role does appear to be expanding further than first thought.

QUALITY OF RECOVERY

Clinicians with wide clinical experience of sugammadex universally remark on the enhanced quality of recovery of their patients in the PACU who have had NMB reversed with sugammadex. It is difficult to objectively measure the "quality" of recovery from anaesthesia but why do patients who have been reversed with sugammadex subjectively seem to have a superior recovery?

One explanation put forward is the change in excretion of rocuronium. During spontaneous recovery, rocuronium is taken up by the liver and excreted in the bile with no metabolism. After sugammadex reversal, rocuronium will be excreted as a complex with sugammadex *via* the glomeruli in the kidney. As a result, the uptake mechanism in the liver does not have to deal with rocuronium. If another drug or drug metabolite is also removed *via* this liver uptake mechanism, the clearance of that drug will be improved. This hypothesis needs further evaluation. Alternatively, it could simply be that the rapid and complete restoration of muscle tone followed by activation of muscle spindles which results in activation of the arousal centre in the brain. One would expect to see changes in the electroencephalogram if this hypothesis was correct but this has yet to be clinically evaluated. After conventional reversal up to 70% of the NMJ receptors may still be occupied by NMB but still produce sufficient recovery of a TOF to 0.9 indicating a satisfactory clinical recovery[31]. When 100% of receptors are free of NMB following complete removal of rocuronium the increase in muscle tone and muscle spindle activity may contribute to the appearance of enhanced well-being and a better quality of recovery whilst patients are in the PACU.

ECONOMIC CONSIDERATIONS AND COST BENEFIT

In all healthcare environments the cost effective use of resources is paramount. The efficient use of the operating theatres and the PACU is an essential component of the cost effectiveness in any healthcare system. The debate that sugammadex brings economic efficiencies by increased case turnover in the operating room with reduced length of stay in the PACU will depend on the model of healthcare provision being utilized. It is clear that patients who are not fully recovered from NMB in the PACU have a delayed recovery room discharge[32].

There is an ever-increasing drive to improve theatre efficiency and facilitate rapid turnover between patients. Although "anaesthetic time" is often a relatively short part of the overall theatre time for each patient, certain operating lists can provide particular challenges for anaesthetists. Ear nose and throat and thoracic bronchoscopy surgery lists for example, where deep NMB is mandatory to enable surgical manipulation of the airway but with unpredictable, and often short, surgical time have traditionally proved difficult to manage efficiently for the anaesthetist. The side-effects of suxamethonium make it unattractive in these instances despite its rapid onset and offset, mivacurium remains unpredictable and other NMB require a certain timeframe before conventional cholinesterase reversal may be considered.

Short acting opioids such as alfentanil and remifentanil certainly have a role in facilitating such cases, however, they too confer side effects and alone may fail to achieve optimal surgical conditions. Sugammadex allows deep NMB with rocuronium that can then be completely reversed regardless of the duration of surgery. For this reason, in our Trust one of the agreed indications for sugammadex use is reversal from deep NMB that would otherwise waste 30 min of theatre time if waiting for a TOF count of 2 before administering neostigmine reversal (Table 1). The guideline relates to when a dose of rocuronium has been used to provide NMB for a surgical procedure where the surgery has finished earlier than predicted.

The clinical and cost effectiveness of sugammadex for the reversal of muscle relaxation after general anaesthesia in United Kingdom practice following routine and rapid induction of NMB was evaluated by Chambers *et al*[33] who concluded that sugammadex may be a cost-effective option compared with neostigmine+glyco pyrrolate for reversal of moderate NMB. There remain, however, considerable uncertainties about whether the full benefits of sugammadex can be realised in clinical

practice.

The economic benefits of sugammadex depend upon the funding processes of the healthcare system within which it is being used. Paton *et al*[34] have suggested there may be some economic benefit to its use. The reality for most hospitals in the United Kingdom is that it has been a challenge getting sugammadex on to the hospital formulary. The difficulties are compounded depending on whether institutions take a macroeconomic view on budgets where it is accepted that in comparison to overall theatre costs, currently approximately 30 Euros/min, the costs of anaesthesia are small compared to the overall theatre costs. Some institutions take a micro economic view where drug costs are isolated, easy to calculate and more difficult to justify. Savings in theatre turnover time, increased productivity and reduced length of stay in recovery may well offset the cost of using sugammadex in individual cases. Certainly if the use of sugammadex helps avoid a clinical crisis with potential significant morbidity or to prevent an ICU admission then the use of sugammadex can be justified[35].

In practice we have not seen the universal uptake of sugammadex to replace cholinesterase inhibitors simply because the impact upon healthcare budgets would be prohibitive. Anaesthetists are generally cost conscious and although the cost of anaesthesia is small in relation to the resource utilized by our surgical colleagues the cost of drugs is easy to quantify and measure. This has meant that most anaesthetists will use sugammadex for selected cases only. In our own institution the guideline described exists to direct use of sugammadex, which is audited and reviewed on a regular basis.

CONCLUSION

The arrival of sugammadex presented the opportunity to change the practice of anaesthesia[36]. Sugammadex is a significant addition to the anaesthetic armamentarium enabling effective use of and safe recovery from the use of neuromuscular drugs when used as part of the classic anaesthesia triad of hypnosis, analgesia and muscle relaxation.

However, recognizing the reality of the cost implications of a blanket replacement of neostigmine + glycopyrrolate with sugammadex has lead clinicians to look carefully at how best to use this novel drug. Guidelines to direct use have helped to bring sugammadex onto hospital formularies.

The potential benefits of using sugammadex to avoid the well-known side effects of the conventional reversal agents in patients with significant clinical comorbidities are easily understood. The ability to provide a deep level of NMB for short periods of time without fear of an inability to reverse at the end of surgery is suited for certain surgical procedures. There is a belief that provision of a deeper level of block in particular for laparoscopic surgery has clinical benefits improving the operating conditions for surgeons and outcomes for patients but there needs to be further evidence to support this idea.

Sugammadex is a key rescue component of an RSI technique using high dose rocuronium in the rare scenario of a CICV where anaesthetists need to be familiar with its use. However, it would appear that we are not about to see suxamethonium disappear from the anaesthetic drug cupboard just yet. Finally, PORC in the recovery room although rare can be dealt with effectively in patients who have had a full dose of conventional reversal and the option of just waiting for the block to wear off consigned to history.

We suspect that the majority of anaesthetists in busy everyday clinical practice would welcome the chance to replace neostigmine universally with sugammadex but, with the ever-increasing pressure on healthcare budgets globally, this is highly unlikely to happen until sugammadex becomes more affordable.

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P- Reviewer: Armendariz-Buil I, Shorrab AA
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5313/wja.v4.i3.73

World J Anesthesiol 2015 November 27; 4(3): 73-82
ISSN 2218-6182 (online)

MINIREVIEWS

Swine model in transplant research: Review of anaesthesia and perioperative management

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Conflict-of-interest statement: None.

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Received: June 22, 2015
Peer-review started: June 27, 2015
First decision: July 27, 2015
Revised: September 18, 2015
Accepted: October 16, 2015
Article in press: October 19, 2015
Published online: November 27, 2015

Abstract

Pigs are one of most common animal species to be used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to transplantation. Despite this use, in many of the researches in which pigs are selected for transplantation, the anaesthesia used is an adaptation of human anaesthesia and presents some limitations such as a reduced analgesia a limited control in perioperative period. In this review we show some of the most important conditions in the preanaesthetic management and of swine as well as we review of anaesthetic protocols for the most common types of swine model of transplantation.

Key words: Swine; Anesthesia; Transplantation; Animal model; Perioperative management

Core tip: Swine is a common model in research, especially in transplantation studies. A correct management and anaesthesia as well as knowledge of the different protocols in pigs are useful in performing these researches.

Morgaz J, Navarrete R, Granados MM, Gómez-Villamandos RJ. Swine model in transplant research: Review of anaesthesia and perioperative management. *World J Anesthesiol* 2015; 4(3): 73-82 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/73.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.73

INTRODUCTION

Pigs are one of most common animal species used in biomedical models due to their many anatomical visceral similarities with humans, particularly with regards to metabolic or cardiovascular diseases and for liver, lung or heart transplantation[1-4]. These similarities have meant that pigs have become a potential species in xenotrasplantation in primates species[5-7]. Despite this resemblance, different anatomical and physiological aspects should be considered in order to perform a successful anaesthesia technique in swine, especially considering that in these researches major surgical procedures are usually performed. In

Table 1 Normal cardiorespiratory parameters of adult and healthy pigs during anaesthesia

Parameter	Range	Parameter	Range
Heart rate (beats/min)	50-100	Temperature (℃)	36-38
Respiratory rate (breaths/min)	10-20	Haemoglobin (g/dL)	11-16
Systolic arterial pressure (mmHg)	80-140	Et CO_2 (mmHg)	40-45 (mechanical ventilation)
Diastolic arterial pressure (mmHg)	60-120	Arterial pH	7.38-7.50
Mean arterial pressure (mmHg)	40-70	PaO_2 (mmHg)	> 70-80
Cardiac output (mL/kg per minute)	60-140	$PaCO_2$ (mmHg)	35-50 (mechanical ventilation)

$EtCO_2$: End-tidal of carbon dioxide; PaO_2: Partial pressure of oxygen; $PaCO_2$: Partial pressure of carbon dioxide.

addition, the perioperative care and management of pigs should be considered. In Table 1 are shown normal cardiorespiratory parameters of adult pigs during anaesthesia.

PERIOPERATIVE CARE AND GENERAL CONSIDERATIONS

As with other animals of research, an acclimatization period of 5-7 d prior to anaesthesia is necessary to reduce the depressant effect of transport or stress, which could alter the anaesthetic effects of different drugs or parameters related to the research. Before anaesthesia, a solid fast period of 24-48 h is recommended, but water must be maintained. The nervous and sometimes aggressive behaviour of pigs prevents venous cannulation before anaesthesia, and for this reason preanaesthetics must be administered by intramuscular route in almost all cases, alone or sometimes with anaesthetics such as ketamine. Athough piglets and some swine breeds have thinner skin, adult pigs usually have a wide tissue adipose and their skin is generally hard, and for this reason intramuscular administration is carried out using a large and thick needle (longer than 35-40 mm, over 18-20 G), to ensure that drugs are deposited in muscle. A longer onset and a softer effect of drugs are noted if anaesthetics are administered into adipose tissue. The most used anatomical locations for intramuscular administration are the lateral cervical muscle region (behind the ear), semitendinosus-semimembranosus muscle areas (posterior side of hindlimb), and the lumbar muscle area[8-10].

Preanaesthetic protocol

There are several anaesthetic protocols suitable for pigs, which include the combination of a hypnotic with a sedative and/or an analgesic. This approach provides a degree of anaesthetic suitable for the handling of pigs, although sometimes it is not enough for endotracheal intubation and an inhalation induction by mask is necessary to complete the anaesthetic induction. Oxygen administration *via* face mask is recommended because these combinations induce a variable degree of cardiorespiratory depression. Since the preanaesthetic combination is applied intramuscularly, dissociative agents such as ketamine and tiletamine (in commercial combination with zolazepam) are used[8,10-12]. Alphaxalone has also been evaluated as acting like a hypnotic in swine and when administered intramuscularly together with midazolam provides an excellent sedation, although it is only recommended for small pigs due to the large volume used[13].

Ketamine is the hypnotic habitually used because it can be administered intramuscularly and has a rapid onset, although due to its excitatory effects it must always be combined with a sedative and muscle relaxant[8,10,11]. Alfa-2 agonist sedatives (xylazine, medetomidine, dexmedetomidine) are widely used in both veterinary medicine and biomedicine, providing central sedative effects accompanied with muscle relaxation and analgesia[8,12,14]. Some frequent anaesthetic combinations in transplant researches with pigs are shown in Table 2.

Since the surgical techniques of transplant imply an aggressive approach or major procedures in most cases, at the time of designing an anaesthetic protocol it is important to consider the potential pain of the procedure during the surgery and the post-operative period. Transplantation surgery is major surgery that requires the use of an opioid analgesic in premedication and especially during the surgery, in which constant rate infusions of pure opiods (fentanyl or remifentanil), may be necessary[8,14]. Likewise, a multimodal approach must be used and f NSAIDs must be administered as carprofen[8-10].

Anaesthetic induction and tracheal intubation

Venous catheterization is often performed after the intramuscular premedication and often when tracheal intubation has been accomplished. The auricular veins are the most common access in pigs for the administration of additional intravenous anaesthetic drugs, fluid therapy and for obtaining venous blood samples. However, for transplantation surgery, central venous and arterial catheterizations are recommended (usually external jugular veins and femoral artery), because a major management of electrolyte and acid-base status is required. Moreover, a central venous access allows the monitoring of cardiac output control and pulmonary pressures. This advanced monitoring is especially indicated for research, when pigs must be maintained and controlled under intensive care conditions for several hours or days after surgery[8-10,15].

Table 2 Intramuscular preanaesthetic combinations for transplantation surgery in pigs

Dissociative	Sedative	Analgesic (optional)	Time induction	Duration of anaesthesia
Ketamine (5-15 mg/kg), or Tiletamine-zolazepam (5-10 mg/kg)	Medetomidine (5-20 mcg/kg), or Romifidine (60-100 mcg/kg), or Dexmedetomidine (5-20 mcg/kg)	Morphine (0.3-0.5 mg/kg), or Methadone (0.3-0.5 mg/kg)	5-20 min	40-60 min

Table 3 Intravenous anaesthetic induction in pigs

Anaesthetic	Intravenous doses
Propofol	2-5 mg/kg
Ketamine	2-10 mg/kg
Tiopenthone	5-15 mg/kg

Table 4 Minimal alveolar concentration of inhaled anaesthetics in pigs

Anaesthetic	Minimal alveolar concentration
Isoflurane	1.2-2.0
Sevoflurane	2.2-3.5
Desflurane	8.3-10

Table 5 Mechanical ventilation settings for pigs

Tidal volume	10-15 mL/kg
Respiratory rate	10-15 breaths/min
Maximum airway pressure recommendable	20 cm H_2O
Normocapnia (end-tidal CO_2 concentration)	40-45 mmHg

Table 6 Recommended doses of constant rate infusion of drugs in pigs

Drugs	Bolus intravenous	Constant rate infusion
Fentanyl	3-10 μ/kg	10-30 μg/kg per hour
Remifentanyl	10 μ/kg	10-50 μg/kg per hour
Morphine	0.1-0.3 mg/kg	0.1-0.3 mg/kg per hour
Dexmedetomidine	0.5-1 μ/kg	0.5-1 μg/kg per hour
Medetomidine	1-2 μ/kg	1-2 μg/kg per hour
Ketamine	0.5-2 mg/kg	0.1-2 mg/kg per hour
Lidocaine	2 mg/kg	1-3 mg/kg per hour
Midazolam	0.2-0.4 mg/kg	0.2-0.4 mg/kg per hour

Usually it is not possible to perform the intubation after premedication since the metabolization of dissociatives is quick, so the induction of anaesthesia must be completed after the administration of the preanaesthetic combination in order to obtain an adequate relaxation of the laryngopharyngeal structures to perform a tracheal intubation. Propofol (2-5 mg/kg), can be administered intravenously if the ear vein has been catheterized (Table 3). Isofluorane or sevofluorane administration (3%-5%) in oxygen (2-4 L/min) *via* face mask is the most used technique. The use of neuromuscular blocks is initially inadvisable because tracheal intubation is difficult to perform and requires some experience[8-10,15].

Tracheal intubation can be performed in sternal, ventral or lateral recumbency, being a difficult procedure, especially in large pigs because the mouth cannot be opened sufficiently and laryngeal structures are not easily visible. In large pigs a specific straight laryngoscope (15-30 cm length) with a large blade is needed. The diameter of the endotracheal tube oscillates between 7 and 12 mm, depending of the size of the swine. In pigs above 25 kg, the use of a rigid or semi-rigid guide for tracheal tubes avoids bending and facilitates the intubation in sternal recumbency especially. To prevent laryngospasm during tracheal intubation, laryngeal irrigation with local anaesthetic (lidocaine or mepivacaine) is recommended[8-10,15].

Anaesthetic equipment

Pigs can be anaesthetized with human or veterinary anaesthetic machines. A corrugated and reservoir balloon must be selected according to the weight of the pig. Precision vaporizers of isofluorane, sevofluorane or desfluorane can be used attending to minimum alveolar concentration (Table 4), and several fraction of oxyegen can be set up. Mechanical ventilation settings for pigs are similar to other species and are shown in Table 5. For an adequate constant rate infusion of drugs (Table 6), a perfusor or infusion pump must be used.

PIG AS A MODEL OF TRANSPLANT RESEARCH

Swine is used extensively as a transplant model of different organs, but despite the complexity of these surgical procedures, in many researches of transplantation in pigs, special considerations are not taken into account and normal anaesthetic procedures are performed, but with important limitations.

Renal transplantation

In all the experimental kidney transplantation papers reviewed, even in very recently published papers, a lack in anaesthetic control and monitoring has been found. In most of the pig model studies, anaesthetic protocol is not even mentioned in a number of different

papers[16-19]. Other studies describe the drugs and doses, but no description of the quality of anaesthesia or an evaluation of anaesthesia's influence on patient evolution are mentioned. An intramuscular injectable mixture of a sedative and ketamine[20,21] or tiletamine-zolazepam[22] is the method most described for the induction of anaesthesia in pigs for kidney transplantation. The sedatives used were xylazine[20,22] or diazepam and azaperone[21]. Atropine was also added[20] to the injectable mixture to prevent bradycardia and reduce bronchial secretions. The authors another paper[23] used ketamine IM and thiopental IV directly as anaesthesia inductor agents without the previous use of sedatives. In this case the ketamine dose was increased to 5 mg/kg. Other papers administered propofol as a bolus for the induction of anaesthesia and to achieve an adequate depth of anaesthesia for tracheal intubation, either as a unique drug[22] or combined with fentanyl[21].

Atracurium and cisatracurium are frequently used in human kidney transplantation due to the fact that their duration of action is independent of either liver or kidney function, since other muscle relaxants, such as pancuronium, vecuronium or rocuronium, have a prolonged duration of action in patients with end-stage renal disease[24,25]. This is not a problem in experimental kidney transplantation if the recipient pig is healthy. Few authors describe the use of neuromuscular blockers in pigs. In[21] a bolus of cisatracurium after induction (15 mg/kg IV) was used and pancuronium (0.1 mg/kg IV) was used in[22], an experimental study. Anaesthesia maintenance in pigs is mainly performed using volatile agents, such as halothane 1%-2%[20], isoflurane[22,23] or sevoflurane 2%[21], although some other drugs have been used during anaesthesia maintenance to reduce the volatile agent requirements, such as remifentanil (0.08-0.1 mg/kg per hour)[21]. Among all the reviewed papers, only[22] described that the depth of anaesthesia was assessed by a veterinary anaesthetist throughout the procedure and adjusted accordingly.

Pigs were under controlled ventilation during some experimental kidney transplantations[21-23]. A description was found only when volume-controlled ventilation was applied, such as in[21] (minute volume 8 mL/kg; adapted according to blood gas analysis) or[22] (tidal volume 10-15 mL/kg; a peak inspiratory pressure of 25 cm of water; adjusted to achieve normocapnia, end-tidal carbon dioxide level 35-45 mmHg) studies. Fluids are needed in order to maintain optimum central venous pressure (CVP) and pulmonary arterial pressure. During a review of papers, no description of the type and rate of fluids used was found. Only[22] mentioned the use of Hartmann solution and Gelofusin and the internal jugular vein was used for this purpose.

With regard to perioperative pain control, drugs such as morphine, meperidine or oxycodone should be used with caution in patients with renal failure because these agents or their active metabolites depend on renal excretion and may accumulate[26,27]. Fentanyl, sufentanil, alfentanil and remifentanil are safe for renal function[26,28-30]. Post-operative pain is controlled in different ways in humans, and it has been shown that the choice of intraoperative anaesthetic influences post-operative pain control, since patients receiving propofol had better recovery of psychomotor function and used patient-controlled analgesia more effectively than patients receiving halotane or isoflurane[31]. No proper descriptions regarding perioperative and post-operative pain control have been found in the pig kidney transplantation review.

Hypotension may occur after unclamping the iliac vessels and reperfusion of the graft. Because the renal graft function depends on adequate perfusion, every effort should be made to avoid episodes of marked hypotension. Few studies describe the monitoring performed. CVP was measured using the internal jugular vein[22,23]. The brachial[23] or the auricular artery[22] were cannulated for blood pressure measurement. Oxygen saturation, ECG, temperature and end-tidal carbon dioxide were continuously measured during general anaesthesia[21-23]. In addition, full blood count, glucose, creatinine, urea, sodium, potassium, haemoglobin, alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase were measured in one study[21]. Some authors described that the recipient's haemodynamic and metabolic alterations were treated, but no data were published. One paper[23] mentioned that they obtained effecctive anaesthetic maintenance until the experimental end point, and in the[22] study, that the vital signs of all pigs were stable during surgery and the post-operative observation period.

In animal models it has been shown that vessels in the transplanted organ seem to be more sensitive to sympathomimetics, and are thus more likely to compromise renal blood flow to the transplanted kidney, so strong alpha-adrenergic vasoconstrictors, such as phenylephrine, should be drugs used only as a last resort[32,33]. Drugs such as mannitol and dopamine have been used in human kidney transplantation but no references have been found to its use in pigs. Mannitol is usually administered to donors before recovery and to recipients just before unclamping the arterial blood flow, because it may give protection against ischaemic injury and induce osmotic diuresis. The use of a low-dose dopamine (2-3 mcg/kg per minute) to stimulate DA1 dopaminergic receptors in the kidney vasculature to induce vasodilation and increased urine output has been shown to be effective during kidney transplantation[34], whereas other studies have shown no significant improvement[35].

Liver transplantation

Although the initial liver transplantation studies included dogs, pig is the preferred species due to its physiologic and anatomic similarity with humans[36].

Azaperone is a butyrophenone that has been used as a sedative before general anaesthesia for liver transplantation, either as a sole agent at premedication[36,37] or in combination with other drugs, such as ketamine,

diazepam or atropine[21,38,39]. Another pharmacological group used frequently for sedation at premedication in pigs undergoing liver transplantation is that of α2-adrenoceptor agonists, such as xylazine[40-44] or romifidine[45]. Benzodiazepines are also used at premedication for muscle relaxation, generally combined with ketamine and/or a sedative drug since they are minor tranquillizers[21,38,41,46,47]. There are authors that have used parasympatholytic drugs at premedication in pigs undergoing liver transplantation[39,41,43], the main use being as an excessive salivation inhibitor; it is unusual for bradycardia to be a problem in anaesthetized pigs[48].

The most common method is the use of a combination of drugs with different properties to induce a balanced premedication-sedation, such us the administration of sedatives with opioids[49]. Furthermore, the administration of an analgesic before a painful stimulus optimizes the control of pain during the surgery procedure and reduces the dose of analgesic during the post-operative period. In general, mu agonists produce a more profound analgesia and they are recommended for moderate to severe pain and to reduce the necessity of anaesthetics[50]. Several authors have used an opioid at premedication in pigs prior to a liver transplantation[45,51].

Ketamine has been used at premedication in pigs undergoing a liver transplantation by several authors to immobilize the animal and to make easier its manipulation[21,39,40,42,45-47,51,52]. However, ketamine as a sole agent does not induce a surgical anaesthesia, so it would be necessary to combine it with opioids, benzodiazepines and/or sedatives[48]. Another dissociative anaesthetic used in pigs is tiletamine, commercialized with zolacepam, a benzodiazepine[43,44]. Like ketamine, it would be convenient to combine it with other sedative and/or analgesic agents to improve the quality or surgery anaesthesia[48].

For anaesthetic induction in pigs undergoing liver transplantation, several studies have used propofol[21,40,46,53,54], etomidate[39] or barbiturates[36,37,44,47]. These drugs produce a faster onset of anaesthesia with short duration of action after the administration of a bolus. Other authors have used an inhalatory anaesthetic through a face mask for the induction of anaesthesia, after a satisfactory premedication[45,51].

Most of the authors have used inhalatory anaesthetics during the maintenance of anaesthesia in pigs undergoing a liver transplantation. Changes in the depth of anaesthesia are faster than with intravenous anaesthetics, with a faster recovery after the anaesthesia procedure[55]. Isoflurane[36,39,40,42,51,54] and sevoflurane[21,41,44] are the anaesthetics most used. None of these anaesthetics are good analgesics, so many authors used them together with continuous infusion of fentanyl[21,36,40,44,45,56] or remifentanil[54]. Other authors described the use of propofol in total intravenous anaesthesia during the maintenance of anaesthesia in pigs undergoing liver transplantation[52], even combined with a continuous infusion of fentanyl because propofol does not have analgesic properties[46,56,57]. In addition, the pharmacological combinations for maintaining the anaesthetic in pigs during a liver transplantation has been described, with ketamine at 15 mg/kg per hour, fentanyl at 0.02 mg/kg per hour and midazolam at 0.9 mg/kg being used[38].

At induction and during the anaesthetic maintenance in pigs undergoing a liver transplantation it is common practice to the use of neuromuscular blocking agents such as pancuronium[36,39,41,45,51], atracurium[45,51], vecuronium[41] and cisatracurium[21]. These agents are indicated to facilitate orotracheal intubation, and are administered together with hypnotic agents to avoid larynx spasm and to provide the fast control of the airway. Other indications included the prevention of spontaneous movement during the maintenance of anaesthesia, reducing the resistance to ventilation and easing surgical access during the surgical procedure[58].

During a liver transplantation, metabolic (acidosis) and cardiovascular changes (hypotension and bradycardia) are usual. To finish the experiences correctly, it is neccesary to understand these alterations, when they are produced and how to correct them. In human medicine, a liver transplantation procedure can be divided in three phases: (1) dissection phase, includes the lysis of adhesion and the removal of the damaged liver; (2) anhepatic phase, includes the implantation of donor liver; and (3) reperfusion phase, including the anastomoses, haemostasis and closure[59]. The ionized calcium levels can decrease during a liver transplantation, mostly during the dissection and anhepatic phases[60]. The exogenous citrate from blood transfusion could be responsible for this low level of ionized calcium and calcium infusions may be required, such as calcium chloride and calcium gluconate[61]. After reperfusion and with the beginning of the functionality of the transplanted liver, the haemostasis of calcium may be corrected and calcium supplementation may no longer be required.

During the anhepatic phase, the donor liver is implanted. If the surgery technique is infracaval interposition, there is a complete vascular occlusion by clamping the hepatic artery and porta, infrahepatic cava and suprahepatic cava veins. Because the inferior cava venous is blocked, a severe hypotension can develop. These haemodynamic effects depend on the patient, so it is advisable to place a previous temporary test clamp on the inferior vena cava to know the haemodynamic response of the animal before realizing the permanent vascular clamping during the anhepatic phase. Once the liver is positioned, the anastomosis of suprahepatic, infrahepatic and portal veins is completed in that order. The anastomosis of the hepatic artery is carried out before reperfusion or after the restoration of blood flow. During this phase hypocalcaemia and acidosis could be observed, so it is important to monitor these parameters closely. Avoid the aggressive infusion rate of fluids in this phase to maintain blood pressure, because this could result in overload of fluids resulting in cardiopulmonar

compromise and liver and intestinal swelling. At the end of this phase the vascular clamps are removed and each anastomosis is observed for the detection of leaks[59]. The withdrawal of the clamps from the portal vein allows blood flow from splanchnic circulation into the donor liver and is the beginning of the reperfusion phase. The most critical point in this phase is the immediate period after the vascular clamps are removed from the liver graft, mainly seconds or minutes after unclamping the portal vein, as is called as reperfusion syndrome[59]. A decrease in cardiac contractility[62], arrhythmias, bradycardia, severe hypotension and hyperkalemic arrest may be observed. The anaesthetic management must be directed at maintaining or recovering cardiovascular stability. The use of epinephrine, atropine, calcium or sodium bicarbonate could be neccesary[59]. Also, the use of methylene blue has been described as attenuating the haemodynamic changes during reperfusion syndrome[63]. In this phase it is common for an alteration in the metabolism of glucose, and progressive hyperglycaeemia may ensue, due to the glycogenolysis by the donor liver, a decrease in glucose use and insulin resistence. In this phase it is possible that coagulopathy may develop, with resultant bleeding[59].

Severe coagulopathy and intraoperative loss of blood are significant problems in patients undergoing liver transplantation. This alteration in the homeostasis, mainly after receiving the donor liver, is multifactorial and inludes hyperfibrinolysis, depletion of coagulation factors, trombocytopenia and platelet dysfunction. The administration of fresh frozen plasma, red blood cells, platelets and cryoprecipitate are the main therapies for blood loss and coagulopatthy during liver transplantation. However, in humans, the use of these blood products during the liver transplantation has been significantly reduced in recent years due to an improvement in surgical technique, intraoperative management and in patient selection[59]. Currently, the administration of haemostatic agents, such as aminocaproic acid, tranexamic acid, *etc.*, are being evaluated as adjunctive therapies[64-69]. It is important to restore diuresis during the procedure to facilitate fluid management and to protect the kidneys during the renal ischaemia in the anhepatic phase. Drugs used to maintain the urine output are loop diuretics, dopamine and mannitol[59].

Most of the pigs used in experimental procedures are euthanized at the end of the surgical procedure. However, some authors keep them alive to continue with the investigation. Authors of[41] described the use of buprenorphine during the post-operative period. Authors of[36] described this period in detail, evaluating the ingestion of the animals and the follow-up treatment with immunosuppression, antibiotics and buprenorphine as analgesic.

Heart transplantation

Porcine models have been used to study cardiovascular disease and transplantation, but have been associated with problems, such as friability of certain organs, anaesthesia difficulties, ventricular fibrillation and oedema[70]. Cardiopulmonary bypass (CPB) models have been described only for two to four hours[71-73] or using swine models not of mature age or body weight, which cannot be considered as true adult size[74] and do not have the same responses to stress as do larger or mature swine[71].

Authors of one paper[75] described a swine model for long-term CPB using an adult pig weighing more than 80 kg. The anaesthesia protocol used for this model was very simple since ketamine and atropine sulphate were given intramuscularly followed by sodium pentobarbital intravenously to maintain a proper level of anaesthesia. Anaesthesia was maintained throughout the entire procedure using sodium pentobarbital in the mechanically ventilated pig. It maintained normothermic CPB and did not develop any previously described problems. Priming the CPB circuit with a combination of more adult blood than crystalloid solution possibly prevented the tissue oedema often seen in such procedures. HR, arterial pressures, urine production, hematocrit, electrolytes, glucose and lactate were within normal range throughout the CPB procedure and were not different from each other from the beginning to the end of CPB. Only the activated clotting time was maintained artificially higher than 1000 s. Prior to the initiation of CPB and throughout the entire procedure and pO_2 was also kept high. Modifications to the procedure, including a higher blood-to-crystalloid ratio in the priming solution, a slightly higher oxygen concentration in the circuit and maintaining the acid base status seemed to contribute to the success of this model.

Recently, the use of porcine cardiac xenografts has become more feasible because of the production of transgenic pig organs expressing human complement regulatory proteins on the endothelium, and continued surgical experimentation involving baboons will contribute to the understanding of the immunological basis for xenograft rejection. Orthotopic pig-to-baboon xenogeneic heart transplantation is the only accepted preclinical animal model for cardiac xenotransplantation[7]. Anaesthetic management of the orthotopic pig-to-baboon model is complicated by ischaemia-reperfusion injury, the use of CPB and the additional immunological processes of xenogeneic transplantation.

A variety of animal experiments[76,77] and human studies[78-80] have investigated the benefits of different anaesthetic regimens in cardiac surgery, suggesting a protective effect of halogenated volatile anaesthetics on the myocardium by mimicking ischaemic preconditioning.

Santerre *et al*[81] described in detail a balanced anaesthetic technique for use in baboons undergoing abdominal porcine cardiac xenografting, and discussed intraoperative monitoring and treatment of the haemodynamic consequences related to infrarenal, aortic cross-clamping. The pharmacological techniques employed were found to be safe and reliable.

Others types of transplant

Swine has been used in other models of transplant such as pancreas[82], cornea[83], duodenum[84], uterus[85], vascularized composite allotransplantation[86], ureter-bladder[87] and lung[88], although in general the anaesthetic considerations are similar to most common transplant in pigs.

CONCLUSION

Swine is a common research model and a complete knowledge of the different protocols of anaesthesia and their perioperative care is important to develop transplant researches without complications. Pigs are excellent models of research and allow a more direct translation of results than laboratory animals, so they will continue to be frequently used in transplant research models.

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P- Reviewer: Mentes O, Wong KL
S- Editor: Tian YL **L- Editor**: A **E- Editor**: Jiao XK

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DOI: 10.5313/wja.v4.i3.83

World J Anesthesiol 2015 November 27; 4(3): 83-90
ISSN 2218-6182 (online)

MINIREVIEWS

Update in perioperative anesthetic management of pheochromocytoma

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Author contributions: All authors had participated drafting the article and making critical revisions related to important intellectual content of the manuscript, and final approval of the version of the article to be published.

Conflict-of-interest statement: None of the authors have any commercial, personal, political, intellectual, or religious interests.

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Received: April 27, 2015
Peer-review started: May 7, 2015
First decision: June 4, 2015
Revised: August 23, 2015
Accepted: September 25, 2015
Article in press: September 28, 2015
Published online: November 27, 2015

Abstract

Pheochromocytoma is a tumor that originates from either chromaffincells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. The perioperative management is quite challenging especially in view of hemodynamic fluctuations. Pheochromocytoma is challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires a through preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication. In this review we review these concepts based on recent evidence for an optimal outcome.

Key words: Phaeochromocytoma; Anaesthesia; Surgery; Analgesia; Drugs

Core tip: The paper is a comprehensive review of the most important pathophysiological and diagnostic issues, preoperative optimization, and anesthesia management of pheochromocytoma. It describes advanced imaging and biochemical techniques for diagnosis and localisation. Once considered nightmare by anaesthesiologist, pheochromocytoma have improved outcome nowadays due to widely available vasoactive drugs, monitors and perioperative care. Also, availability of laparoscopic and robotic adrenal-sparing adrenalectomy has reduced hospital stay and hastened recovery.

Gupta A, Garg R, Gupta N. Update in perioperative anesthetic management of pheochromocytoma. *World J Anesthesiol* 2015; 4(3): 83-90 Available from: URL: http://www.wjgnet.com/2218-6182/full/v4/i3/83.htm DOI: http://dx.doi.org/10.5313/wja.v4.i3.83

INTRODUCTION

Pheochromocytoma is a tumor that originates from

either chromaffin cells in adrenal medulla or in other paraganglia tissues of the sympathetic nervous system. Adrenal is the origin for majority of tumor accounting 80% and rest are from extra adrenal site[1]. Majority of them are benign and may be associated with familial syndromes like multiple endocrine neoplasia (MEN) syndromes, von Recklinghausen disease or von Hippel-Lindau (VHL) syndrome in 10% of the patients. In a few patients pheochromocytoma have been found arising from atypical sites like head and neck, pericardium, inferior mesenteric artery (the organ of Zuckerkandl), aortic bifurcation, other chromaffin tissue in the abdomen, pelvis, and thorax[2,3].

GENETIC MUTATIONS AND PHEOCHROMOCYTOMA

The formerly used rule of 10 for pheochromocytoma (10% of tumors are malignant, bilateral and extra adrenal) is not convincing with present evidence[4]. Pheochromocytoma may occur sporadically in majority of cases but as high as 40% children and 25% adults may have an associated gene mutation[5,6]. Hereditary pheochromocytoma may be associated with MEN type 2 with RET proto-oncogene mutation, VHL syndrome with *VHL* gene mutations, von Recklinghausen disease with *NF1* gene mutation and succinate dehydrogenase subunit D genes mutation in familial non-syndromic pheochromocytoma[5-7]. Despite multiple gene mutations have been associated with pheochromocytoma, the testing for gene mutations in all the cases is not considered appropriate and is not cost effective.

CLINICAL PRESENTATION

The presenting signs and symptoms are primarily due to release of catecholamine or their metabolites in the body[1,8-12]. Most of the pheochromocytoma sites except head and neck tumors (less than 5%) produce, store, metabolize and secrete catecholamines or their metabolites[8]. The usual symptoms include hypertension, palpitations, headache, sweating, fatigue, nausea, weight loss, constipation, flushing, fever and pallor. The prolonged exposure of increased concentrations of catecholamines may result in dilated cardiomyopathy, ventricular failure, myocardial infarction, arrhythmia, stroke or other vascular ischemic symptoms. The classical triad of headache, sweating and palpitations may be seen in up to 40% of patients[9,10]. Headache and hypertension occur in predominantly norepinephrine secreting tumors whereas other symptoms like palpitations, sweating, anxiety, panic etc suggest epinephrine or dopamine secretion[11]. Stimulation of sympathetic nervous system may release neither excessive quantities of norepinephrine into the synaptic cleft. Due to proximity of norepinephrine to its receptors, the response is exaggerated even with small increments and patient may present hypertensive crises.

In addition a number of metabolic derangements like diabetes (decreased insulin and increased hepatic glucose output), lactic acidosis, hypercalcemia (parathyroid adenomas), diarrhea and fluid and electrolyte imbalance (vasoactive intestinal peptide secreting tumors) may also be seen in some patients with pheochromocytoma[10-12]. Some patients may be asymptomatic due to receptor down regulation. In such patients, the sympathetic reflexes may be blunted, leading to severe hypotension and shock during unrelated surgery. The symptoms of pheochromocytoma may also be mimicked by many endocrine (hyperthyroidism, menopausal syndrome, carcinoid), cardiovascular (heart failure, arrhythmias), ischemic heart disease and neurological (migraine, stroke) diseases. So, we need to confirm the diagnosis with further testing[12].

DISCUSSION

Once the signs and symptoms are suggestive of pheochromocytoma, the diagnosis can be confirmed by plasma epinephrine, norepinephrine and urinary catecholamine metabolite [vanillyll mandelic acid (VMA)][1,8,11,13-15]. But since the catecholamines may be released sporadically, these tests have low sensitivity and low specificity. The excessive production of catecholamines is metabolized in the tumor by catechol-o-methyl transferase to metanephrins which can be measured in the plasma[8]. They have a sensitivity of 99% (negative tests rule out pheochromocytoma) and should be carried out as the first test in patients with clinical symptoms and normal catecholamines[11,13]. Also high plasma metanephrin to epinephrine and normetanephrine to norepinephrine ratios are suggestive of pheochromocytoma. The 24 h urinary metanephrins has been found to have high sensitivity (97%) for pheochromocytoma. The product of normalised metanephrin and normetanephrine (100% sensitive and 99% specific) and serum chromogranin A have also been used for diagnostic purpose[14,15].

The other tests reported include clonidine suppression test glucagon stimulation test and selective adrenal vein sampling (not done now days)[13-15]. In clonidine suppression test, plasma epinephrine and norepinephrine are measured before and 3 h after 0.3 mg clonidine. In pheochromocytoma there will be less than fifty percent reduction in epinephrine and norepinephrine and less than 40% reduction plasma metanephrin values[14].

LOCALIZATION

Once the diagnosis is confirmed by history and biochemical testing, we need to localize the tumor to decide the treatment plan[1,8,9,16]. Surgical resection is the only curative procedure for these tumors. Both magnetic resonance imaging (MRI) and computerized tomography (CT) provide accurate and consistent anatomical identification of adrenal tumors as small as

1 cm in the majority of cases[16]. Contrast enhanced CT further increases its sensitivity but MRI is slightly better than CT. Gadolinium enhanced MRI can be used in children, pregnancy and patients with contrast allergy. In extra adrenal, metastatic and recurrent tumors, the sensitivity of both MRI and CT decreases (< 90%)[9,16]. Such cases need to be identified with radio nucleotide [meta-iodobenzyl guanidine (MIBG)] testing. MIBG has specificity as high as 100% but it may be taken up by neuroblastomas, medullary carcinoma thyroid, carcinoid and small cell carcinomas of lung. Also certain drugs like labetolol, reserprine, calcium channel blockers and some tricyclic antidepressants may interfere with uptake of MIBG and give false negative tests.

The positron emission tomography scan are nowadays available and become important in cases where conventional imaging is unable to detect the tumor in patients with positive biochemical testing[16].

PREOPERATIVE PHARMACOLOGICAL CONTROL

The control of symptoms due to excessive release of catecholamines are essential as preoperative pharmacological preparation reduces the mortality to less than 3%[9,10,13,16-23]. The surgery is rarely an emergency and anesthesiologist has time to optimize to control blood pressure, heart rate and arrhythmias. The advantages of preparation are: (1) Decreased vasoconstriction and restoration of vascular volume; (2) Normalization of hematocrit; (3) Symptom control; (4) Reversal of myocardial ischemia; and (5) Reduced intraoperative hemodynamic fluctuations.

Pharmacological agents

Various drugs have been used to achieve the optimal status prior to surgical intervention[16-23]. These include:

Alpha blockers: Phenoxybenzamine is a non-selective α blocker and is considered the main stay of perioperative control. It has a long duration of action and allows twice daily ingestion[16]. It can be administered orally (10 mg twice a day upto 1 mg/kg per day) or intravenous (0.5 mg/kg per day over 5 h for 3 d). It takes 2-3 wk for treatment to be effective. It produces a non-competetive blockade of the receptor that prevents the effects of surges of catecholamines during preoperative period. This also blocks the α2 adrenoreceptor and prevents feedback inhibition exercised by presynaptic adrenergic neurons leading to uninhibited release of norepinephrine at the cardiac sympathetic nerve endings and consequent undesirable chronotropic and inotropic side effects. Also, it is a non competitive blocker and has a long duration of action. Beta-blockers are given to control tachycardia. It may also lead to side effects due to central α2 blockade like somnolence, peripheral edema, headache, stuffy nose, *etc*.

Selective α1 blockers: Doxazosin, prazosin and tetrazosin are also used for optimization and lack reflex tachycardia[16,17]. They may produce profound hypotension due to uninhibited norepinephrine reuptake and its inhibition at postsynaptic α1 receptors. They are usually administered at bedtime with adequate hydration. Doxazosin is administered as a single dose (1-16 mg); prazosin and tetrazosin are administered 4-6/h. A preoperative blockade of 2-3 wk is required to optimize myocardial function.

Beta blockers: β blockers given in perioperative period limit the signs and symptoms due to increased circulating catecholamines (supraventricular and ventricular arrhythmias) and control tachycardia due to α blockade[16]. If a β blocker is started before effective α receptor blockade, the vasoconstrictor effects of α receptor go unopposed may produce dangerous hypertension[19]. Cardio selective agents like atenolol (25-50 mg) and metoprolol (50 mg) are preferred drugs. Labetalol β blockade capability is more than α blockade capability (1:7) and it also interferes with imaging by preventing uptake of ^{131}I MIBG.

Calcium channel blockers: (Amlodipine 10-20 mg/d, nicardipine 30-90 mg/d or verapamil 180-240 mg/d) inhibit NE-induced intracellular calcium influx and prevent catecholamine-induced coronary spasm, myocarditis, and attenuate hypertensive responses to noxious stimuli. They do not produce hypotension and are preferred in normotensive patients with occasional episodes of paroxysmal hypertension[16]. Clevidipine butyrate is an intravenous an ultrashort-acting, third-generation dihydropyridine calcium channel blocker that inhibits calcium influx in arterial smooth muscle, causes arterial vasodilation and decreases in peripheral vascular resistance. It is a novel agent for hemodynamic control in the management of pheochromocytoma before a tumor resection[20]. Clevidipine has a fast onset (1-2 min), is rapidly titratable, has a fast offset (5-15 min), and has proven safety and efficacy for acute perioperative hypertension. Since its preparation contains soybean oil and egg yolk phospholipids, it is contraindicated in patients with soybean, soy product, egg, or egg product allergies and in patients with lipid metabolism deficiencies[20].

Alpha-methylpara tyrosine: Methyl-para-tyrosine (MPT) is a competitive inhibitor of tyrosine hydroxylase (rate-limiting step in catecholamine biosynthesis)[16,18]. This reduces catecholamine stores and their release on stimulation of the tumor. In MPT is especially useful in extensive metastatic disease to control refractory blood pressure or in patients in which conventional drugs are not tolerated due to side effects (heart failure: β blocker and tachycardia: α blocker). Its use in combination with α blocker has shown to result in a better blood pressure control and less need for use of antihypertensive

medication or pressors during surgery. However, its usefulness is limited due to associated side effects like diarrhea, crystalluria, depression, galactorrhea, anxiety and extra pyramidal symptoms.

Magnesium sulfate: It inhibits the release of catecholamine, directly inhibits catecholamine receptors, and is a calcium antagonist. It attenuates catecholamine release due to noxious stimuli (*e.g.*, endotracheal intubation) and abolishes the arrhythmias induced by epinephrine. It also profoundly dilates the arterioles, reduces the peripheral vascular resistance (after load), and exerts minimal effect on venous return (preload)[16,22]. The beneficial effects are more pronounced during the peri-operative period and thus, can be considered an attractive option for catecholamine blockade in patients undergoing tumor resection[22]. It has been found effective for resection of pheochromocytoma in children, during pregnancy and patients presenting with arrhythmias[23]. Its use is associated with sedation, prolonged neuromuscular blockade and muscle weakness.

α2-agonists: Clonidine is a well-known presynaptic α2-adrenoreceptors agonist. It reduces sympathetic tone reduces blood pressure and anesthetic requirements[16]. Dexmedetomidine is a selective α2-adrenoceptor agonist and has sedative and analgesic properties. The decreased BP and heart rate are attributed to the decreased catecholamine levels. It can blunt sympatho-adrenal responses to tracheal intubation and surgical stimuli[21].

PREOPERATIVE MANAGEMENT

The objectives of preoperative evaluation are to ensure adequate α blockade, assess myocardial function, minimize organ complications, ensure normovolemia and correct hyperglycemia and electrolyte abnormalities. Adequacy of blockade is assessed using Roizen's criteria[24]: (1) BP < 160/80 mmHg; (2) Orthostatic hypotension not less than 80/60 mmHg; (3) No more than 1 ventricular premature contractions (VPC) in 5 min; and (4) No new ST-T changes on the ECG over the last week.

The achievement of these parameters suggests an optimization of the patient with regards to effect of catecholamine. Also, the cardiovascular evaluation needs to be done and includes a baseline ECG for evaluation of any myocardial ischemic changes, left ventricular hypertrophy and/or strain. An echocardiogram may further detect ventricular dysfunction, evaluate improvement with therapy and diagnose dilated cardiomyopathy.

ANESTHETIC MANAGEMENT[25-29]

The anesthetic management and monitoring during surgery will depend upon the extent of surgical approach. Traditionally the surgery is performed in open lateral retroperitoneal approach but sometimes transabdominal approach may be required. Recently laproscopic transperitoneal resection of the tumor is being done. Anesthetic plan will depend upon the surgical approach and patient positioning. Good communication between anesthesiologist and surgeon is important during the perioperative period[25].

Premedication

Preoperative sedation and good communication by the anesthesiologist help in decreasing anxiety and prevent marked hemodynamic fluctuations in the immediate perioperative period. Oral benzodiazepines and H2 receptor antagonist can be given. Short acting selective α-1 adrenergic blockers should be administered in the morning of surgery but longer acting drugs (Phenoxybenzamine/doxazosin) should be stopped 12-24 h prior to schedule surgery[25] (Table 1).

Operating room preparation

The infusions of hypotensive drugs [sodium nitroprusside (SNP) 0.01%, nitroglycerine (NTG) 0.1%, esmolol 1 mg/mL and norepinephrine 40 mcg/mL] and vasoactive drugs (magnesium sulfate, labetalol, diltiazem, nicardipine and lidocaine 2%) needs to be prepared in the operating room. Fluids in form of colloids, crystalloids, blood and blood products should be readily available (Table 2).

Anesthesia induction and maintenance

Two large bore (14G) peripheral intravenous access should be secured. The pain and anxiety associated with these procedures can lead to sudden hypertensive response. Invasive lines like radial artery and central venous cannulation should be secured under local anesthetic infiltration supplemented with intravenous midazolam. The monitoring includes continuous electrocardiogram, pulse oximeter, capnograph, temperature and urine output. The invasive monitoring includes central venous pressure and invasive arterial blood pressure monitoring.

Anesthesia induction and tracheal intubation must be smooth and hemodynamic response to intubation should be avoided. Various drugs/techniques have been used to blunt sympathetic response such as nitroprusside, nitroglycerin, magnesium sulfate, urapidil, opioids (fentanyl, remifentanyl), esmolol, nicardipine, and lidocaine have been described.

Induction of anesthesia

Almost all induction agents have been used safely and the choice of drugs depends upon institutional and individual practice. Both thiopentone and propofol are the commonly used drugs during induction of anesthesia. Propofol is preferred because it produces vasodilatation and blunts to the hypertensive response to laryngoscopy and intubation[26]. Etomidate is also recommended due to its cardiovascular stability[27,28]. The use of all the drugs that increase sympathetic tone

Table 1 Drugs commonly used in preoperative preparation of pheochromocytoma

Drug name	Dosages	Additional information
Phenoxybenzamine	60-50 mg	Dizziness, headache, nasal stuffiness peripheral edema and prolonged hypotension (long postoperative blockade)
Doxazosin	2-6 mg	Short acting, no prolonged hypotension
Beta blockers		
Propranolol	80-120 mg	Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension
Metoprolol	50-100 mg	
Labetalol	5-10 mg q5 min	
Calcium channel blockers		
Verapamil	120-240 mg	Careful in patients with n AV blocks, hypovolemia, sinus sick syndrome, and heart failure
Diltiazem	180 mg	
Nifedipine	30-90 mg	Side effects: Elevated liver enzymes, headache, constipation, dizziness, fatigue, edema
Clonidine	0.1-1.2 mg	
Dexmedetomidine	1 mg/kg in 10 min, 0.7 mg/kg per hour infusion	Dizziness, rebound hypertension side effects: depression, anxiety, dry mouth, bradycardia
Magnesium sulfate	1-8 mg loading dose, 1-4 mg/h maint	Potentiates neuromuscular blockade, caution in heart block and renal failure
Urapidil	10-15 mg/h	Caution because of severe hypotension
Alpha methyl-p-tyrosine	1-4 g/d	Crystaluria, extra-pyramidal and psychic disturbances

Table 2 Commonly used drugs during resection of pheochromocytoma

Drug	Dosages	Additional information
Fenoldopam	0.2 mg/kg per minute	Tachycardia, hypokalemia Cautions in patients with CVA
Sodium nitroprusside	1-2 mg/kg per minute	Cyanide toxicity, reflex tachycardia, severe hypotension
Nitroglycerine	25-250 mg/min	Reflex tachycardia, tachyphylaxis Methemoglobinemia, cerebral vazodilation
Nicardipine	5.0 mg/h	Hypotension, bradycardia, heart failure, WPW syndrome
Phentolamine	1-5 mg	Minimum side effects
Beta blockers		Careful in patients with asthma, conduction disturbances, severe heart failure. May cause severe bradycardia and postural hypotension. May potentiate effect of other drugs (like CCB)
Esmolol	5-10 mg × 3 min	
Metoprolol	2.5-5 mg × 2 min	
Labetalol	5-10 mg	
Epinephrine	1-20 mg/min	A and β agonist, positive inotropic, chronotropic effect and increases BP
Norepinephrine	1-30 mg/min	α/β1 agonist, decreases organ blood flow
Dopamine	5-20 mg/kg per minute	α/β/dopamine dose dependent agonist, may cause tachycardia and dysrthymias
Vasopressin	0.1-0.4 units/min	May cause MI

or may precipitate hypertensive crisis, such as ketamine, ephedrine, pancuronium and metoclopramide must be avoided[27,28]. Droperidol may cause hypertensive crisis and should be avoided[29].

Inhalation agents

Sevoflurane is preferred because it is cardio-stability and lack of arrhythmogenic potential[30]. Isoflurane lowers peripheral vascular resistance and blood pressure and can be used[31]. Halothane (arrhythmia potential) and desflurane (sympathetic stimulation) are not preferred in pheochromocytoma[32].

Muscle relaxants

During induction, use of succinylcholine can be hazardous as it may stimulate the autonomic ganglia (cause arrhythmia) and fasciculations due to succinylcholine may squeeze the gland and precipitate hypertensive crisis[33]. Atracurium and tubocurarine release histamine and should be avoided[34]. The recommended drugs are vecuronium, rocuronium and cisatracurium[27,28].

Total intravenous anaesthesia

Propofol and remifenatnyl are hemodynamically safe and decrease heart rate (central vagal nuclei stimulation). Remifentanil is an ultrashort acting opioid and acts by binding to μ-receptors in brain, spinal cord, and peripheral neurons[35]. Propofol is also a short acting drug which acts by increasing inhibitory γ-aminobutyric (GABA) synapses and inhibiting glutamate. Both the drugs together decrease the hemodynamic response during pheochromocytoma resection. The pharmacological profile of these drugs makes total intravenous anesthesia a safe anesthetic choice for such patients[36]. Recently, dexmedetomidine has also being used to provide a satisfactory preoperative sedation and intraoperative hemodynamic control. It also reduces anesthetic requirements and improves postoperative analgesia. Dexmedetomidine has been described recently for pheochromocytoma resection in an adult[27].

Intra operative hypertensive crises

During the intraoperative period, hypertension can occur

during induction, insertion of central lines, intubation, surgical incision, creation of pneumoperitoneum and tumor manipulation[37]. Risk factors for intraoperative hemodynamic instability include large tumor, baseline mean arterial pressure more than 100 mmHg and a high plasma norepinephrine concentration. Hemodynamic crisis may be due to epinephrine or norepinephrine release. Epinephrine induced crisis will present with tachyarrhythmia (paroxysmal supraventricular tachycardia, VPCs and ventricular arrhythmias) with increased systolic blood pressure and diastolic blood pressure (> 100 mmHg)[26,27,37]. Drugs like esmolol (0.5-1 mg/kg intravenous bolus or infusion), labetalol 5-10 mg intravenous, adenosine or intermittent boluses of metoprolol (1-2 mg intravenous) will help in controlling the crises. Amiodarone or lidocaine may be required in patients with poor left ventricular function. Norepinephrine crises are more common and characterized by severe bradycardia with profound hypertension. Rapid intravenous infusion of SNP through the central vein is usually effective, but esmolol needs to be added to control resultant tachycardia. The hypertension can also be controlled by deepening the anaesthesia or use of drugs like nicardipine, NTG, magnesium, *etc*. A combination of nicardipine (titrable short-acting calcium channel blocker) and esmolol (titrable ultrashort acting selective β1-receptor antagonist) can be used as an alternative especially in asthmatic patients[26,27]. Fenoldopam (dopamine1 receptors agonist) is a suitable titrable drug (dose of 0.2 mg/kg per minute) and causes peripheral vasodilatation and reduces blood pressure[37].

After the adrenal gland has been removed, severe hypotension may be result due to blood volume depletion (because of diuretics), residual action of vasodilators, bleeding, catecholamine withdrawal, adrenoceptor down regulation and steroid withdrawal (bilateral adrenalectomies)[26,27]. Initial treatment should be volume replacement upto 2-4 L to restore CVP to 10-12 mmHg. If ineffectivewe may require combination of multiple inotropes like epinephrine, norepinephrine, neosynephrine (pure α-adrenergic agonist), ephedrine, dopamine and vasopressin.

ANALGESIA

Epidural analgesia and spinal anesthesia have been used in patients planned for open procedures with large incisions[26,27]. However, a combination of central neuraxial block with general anaesthesia must be balanced against the risk of hypertension during its placement and possibility of post-excision hypotension[38,39]. Drugs like morphine (histamine release) and pethidine (sympathetic stimulation) are not preferred in pheochromocytoma. Fentanyl is a potent opioid and can be used as bolus (3-5 μg/kg) or infusion (1-2 μg/kg per hour)[27]. Non-steroidal anti-inflammatory drugs provide analgesia in patients with laparoscopic and robotic-assisted adrenalectomy.

Now days, laparoscopic arenalectomy and more recently, robotic-assisted adrenalectomy is being done[40-42]. These may be associated with reduced blood loss and vasodilator use, due to decreased/delicate tissue handling. It also produces less postoperative pain, decreases hospital stay and recovery period. Laparoscopic approach may not be feasible in cases of invasive carcinoma also. Carbon dioxide pneumoperitoneum can induce catecholamine release by a pheochromocytoma, leading to increase mean arterial pressure and central venous pressure[43,44].

POSTOPERATIVE MANAGEMENT

Approximately half of patients remain hypertensive for a few days due to elevated catecholamine stores in adrenergic nerve endings, which tend to persist for 1 wk after resection[26,27]. Persistent hypertension may indicate fluid excess, return of autonomic reflexes, inadvertent ligation of a renal artery, or presence of residual tumor.

Some patients may have persistent hypotension due to blood loss, altered vascular compliance, and residual preoperative adrenergic blockade. Postoperative blood glucose monitoring should be done because hypoglycaemia has been reported. Patient operated for arenalectomy may have postoperative drowsiness/unconsciousness and may be related to hypoglycemia, depletion of CNS catecholamine and multiple episodes of hypertensive crises intraoperatively may lead to cerebrovascular accident[44].

To conclude, pheochromocytoma is a challenging in view of the impact of excessive and depleted catecholamines in the perioperative period. It requires although preoperative evaluation and optimization with meticulous intraoperative management. The postoperative period requires vigilance to prevent any untoward complication.

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P- Reviewer: Fassoulaki A, Feltracco P, Ozcengiz D
S- Editor: Ji FF **L- Editor**: A **E- Editor**: Jiao XK

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