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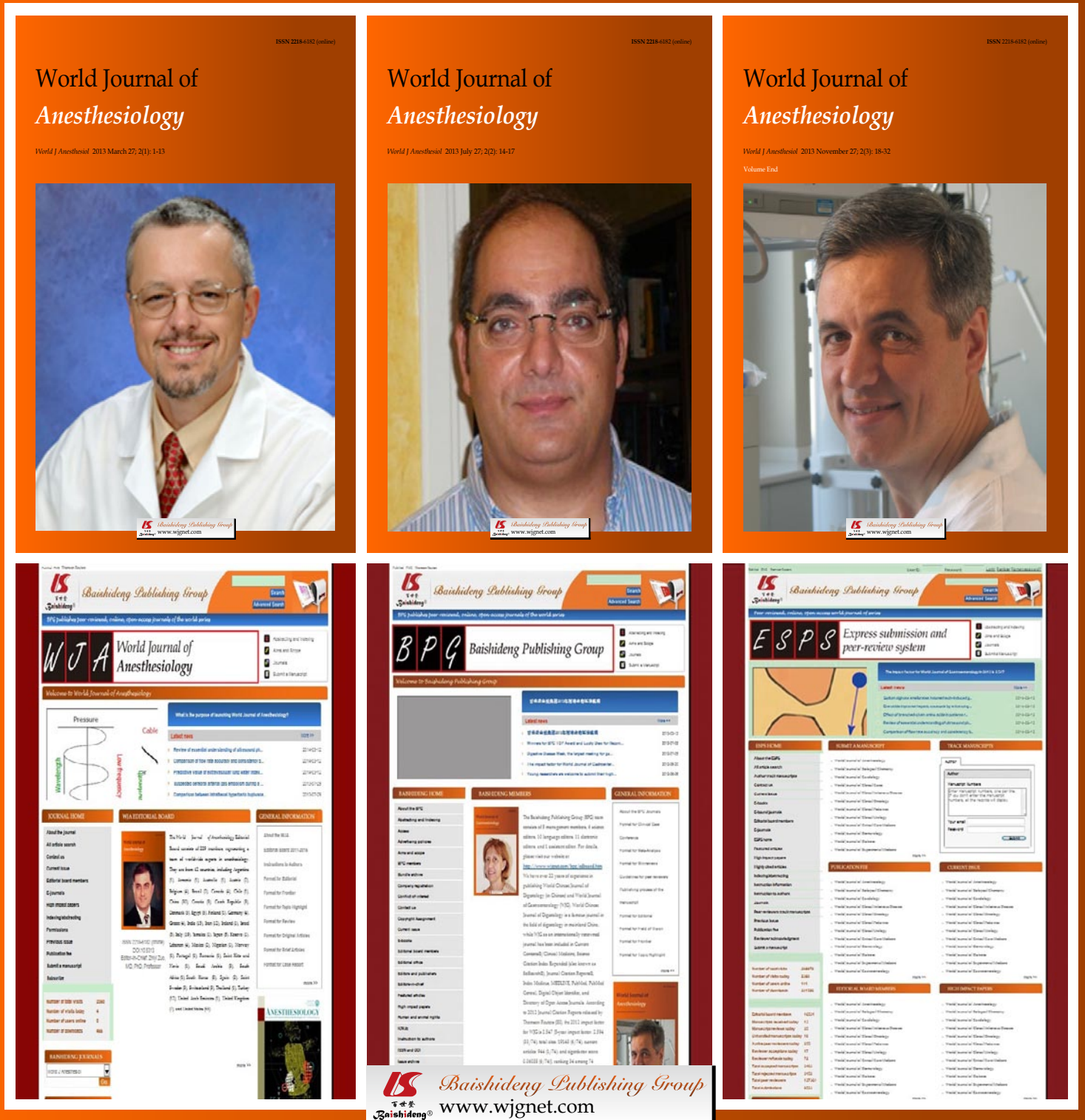

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DIAGNOSTIC ADVANCE

Clinical pharmacology of intravenous paracetamol in perinatal medicine

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Abstract

Clinical pharmacology aims to predict drug-related effects based on compound and population specific pharmacokinetics (PK, concentration-time), and pharmacodynamics (PD, concentration-effect). Consequently, dosing needs to be based on the physiological characteristics of the individual patient. Pregnancy and early infancy hereby warrant focused assessment. The specific characteristics of both subpopulations will be illustrated based on observations on intravenous (*iv*) paracetamol PK and PD collected in these specific populations. At delivery, there is a significant higher paracetamol clearance (+ 45%, L/h) when compared to non-pregnant observations. This higher clearance is in part explained by a proportional increase in oxidative metabolite production, but mainly an increase in glucuronidation. When focusing on PD, an association between maternal paracetamol exposure and atopy in infancy and fetal gastroshizis has been reported. In early infancy, paracetamol clearance is significantly lower and mainly depends on size (weight 0.75), while also the distribution volume is higher (L/kg). Reports on hepatic tolerance, haemodynamic stability and impact of body temperature have been published while the concentration effect profile for analgesia seems to be similar between neonates and children. Similar to maternal exposure, there are reports on the association with atopy. Studies on the use of paracetamol to close the patent ductus arteriosus are ongoing. At least, these observations provide evidence on the need to study commonly administered anesthetics in such specific subpopulations with specific focus on both population specific PK and PD to further improve patient tailored pharmacotherapy.

Key words: Pregnancy; Newborn; Intravenous paracetamol; Pharmacokinetics

Core tip: Although urgently needed to further improve patient tailored pharmacotherapy, data on the clinical pharmacology in pregnant women and young infants are limited, even for commonly used drugs like paracetamol. We summarize the available observations on both pharmacokinetics and pharmacodynamics of intravenous paracetamol in pregnant women and early infancy to illustrate the relevance of subpopulation specific observations. This includes differences in metabolic routes of elimination, in (side) effects (*e.g.*, analgesia, hypotension, atopy) and in potential indications (patent ductus arteriosus).

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INTRODUCTION

Clinical pharmacology in special populations

The general pharmacokinetic principles of disposition

and elimination of drugs apply, irrespective of population specific characteristics[1-5]. However, pregnancy and early infancy warrant a tailored approach. This is because important alterations in physiology affect drug disposition up to clinical relevance. Pregnancy results in extensive alterations in pharmacokinetics (PK, concentration-time profile) with a subsequent extensive inter-individual variability in drug response[6-8]. In general, renal elimination capacity is increased throughout pregnancy (*i.e.*, higher glomerular filtration rate, higher active tubular transport). Similar, the basal metabolic activity is also increased. This commonly results in higher drug metabolism (phase I and phase II processes), although these changes are in part also iso-enzyme specific. This, although rarely, even may result in reduced enzymatic activity (CYP1A2 and CYP2C19) during pregnancy[6,8]. Finally, changes in body weight or binding capacity (protein changes, pH) likely will affect the volume of distribution. Similarly, duration of pregnancy, co-morbidity (*e.g.*, pre-eclampsia) or labor itself may further affect variability in drug disposition[6,8].

Early infancy is another very specific population. When we consider the physiological changes and the subsequent between individual variability in characteristics, we need to take into account that maturational changes are most prominent in infancy[7,9]. Consequently, drug disposition in early infancy differs substantially from children or adults as a result of these physiology-related maturation in absorption, distribution and subsequent elimination, either through metabolic elimination or through primary renal elimination (ADME, PK)[7,9]. In general, neonates have an overall low clearance capacity. Between subject variability can be explained by covariates such as size, weight organ function, co-administration of drugs, genetic polymorphisms, growth restriction or disease characteristics[9]. Consequently, focused studies in peripartum and in early infancy to unveil clinical relevant covariates are needed[8,9]. This is even true for a commonly administered compound like paracetamol.

Paracetamol

Paracetamol, *N*-acetyl-*P*-aminophenol (acetaminophen), is a readily available antipyretic and analgesic agent. It is the most often prescribed drug for treatment of mild to moderate pain or fever in infants, including neonates and can be administered by oral, rectal but also by intravenous route[1-5]. In the therapeutic concentration range, paracetamol is metabolized by the liver to paracetamol-glucuronide (47%-62%) and paracetamol-sulphate (25%-36%) as main metabolites, subsequently eliminated by renal route. Only 1%-4% is excreted unchanged in urine, and about 8%-10% of paracetamol is oxidized to 3-hydroxy-paracetamol and the (hepatic) toxic metabolite *N*-acetyl-*P*-benzoquinone-imine[3-5].

Paracetamol is perceived to have a good efficacy-to-safety ratio as analgesic in a wide range of patient populations[10-15]. However, since paracetamol is one of the most commonly used drugs to treat pain or fever, knowledge on the covariates of paracetamol disposition remains crucial to avoid toxicity through unanticipated variability[16-20]. In addition to oral and rectal formulations, several intravenous (*iv*) formulations became available more recently[21-25]. Such a formulation enables the administration of paracetamol when the enteral route cannot (yet) be used and should improve the predictability by the reduction in variability related to absorption[26-29].

Clinical pharmacology aims to predict drug-related effects based on drug, population and patient specific PK, concentration-time, and pharmacodynamics (PD, concentration-effect): drug dosing needs to be based on the physiological characteristics of the individual patient[8,9]. As mentioned earlier, this necessitates focused studies in specific populations, including peripartum and early infancy.

Consequently, we aim to summarize our studies on aspects of PK and PD of intravenous paracetamol either at delivery and in early infancy. For both subpopulations, this will be combined with a topical review on the clinical pharmacology of paracetamol in these patients.

CLINICAL PHARMACOLOGY OF PARACETAMOL AT DELIVERY AND IN POSTPARTUM

Despite pregnancy and peripartum related changes in PK and PD and the clinical relevance to have such data, most of the drugs administered by anaesthetists have not been extensively evaluated in this specific population. This is also true for commonly administered analgesics like *iv* paracetamol.

Paracetamol PK and metabolism

Following study registration (EudraCT 2010-020164-37) and approval by the Ethics Committee of the University Hospitals Leuven, women who were scheduled to undergo a (semi) elective Caesarean delivery were recruited. The administration of *iv* paracetamol started with a loading dose of 2 g over 15 min shortly after delivery of the newborn. Blood samples from a dedicated peripheral *iv* catheter were collected 1, 2, 4 and 6 h after loading dose administration. These samples were centrifuged and plasma was stored at -20 ℃ until high performance liquid chromatography analysis was performed. Using this approach, 36 paracetamol-time profiles following delivery were available for PK analysis[14,15].

These data were compared to data either published by Gregoire *et al*[30] in 14 women, and 23 additional PK profiles collected in young female volunteers. As illustrated in Figure 1, there is a significant increase in paracetamol clearance (L/h) in peripartum when compared to non-pregnant PK profiles (median clearance 19.6 compared to 13.3 L/h, + 45%)[11,14,21,22]. Table 1 provides a selective overview on paracetamol clearance estimates reported

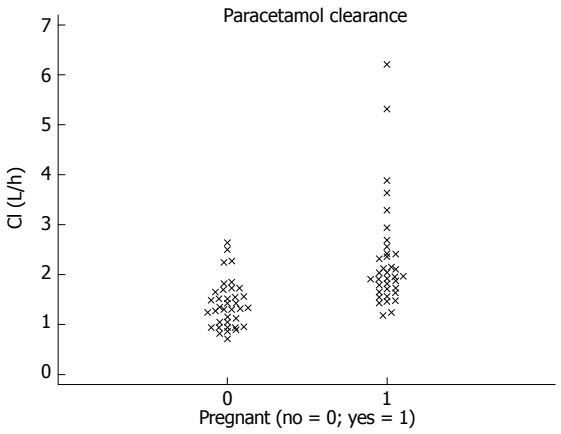

Figure 1 Individual clearance paracetamol estimates in young women at delivery compared to similar individual paracetamol clearance estimates in non-pregnant women.

in different cohorts of adults, including healthy volunteers[30,31]. In essence, this overview suggests that there are additional covariates of paracetamol clearance in adults, including disease severity, age, gender and pregnancy.

More recently and using a more sophisticated population PK modeling approach, we confirmed this a substantially higher paracetamol clearance in women at delivery compared to a subset of the same women 12 wk postpartum[6,14]. More importantly, we were able to document that this increase in total paracetamol clearance at delivery is due to a disproportional increase in glucuronidation clearance and a proportional increase in clearance of unchanged paracetamol and in oxidation clearance without any changes in the absolute sulphation clearance, resulting in a proportional decrease. These pharmacokinetic observations at delivery and in postpartum are of pharmacodynamic (analgesia, toxicity) relevance.

The link between paracetamol plasma concentration and the level of analgesia has not yet been fully described, but McNicol *et al*[18] recently reported on single dose *iv* paracetamol or propacetamol for prevention or treatment of postoperative pain based on a systematic review. Paracetamol (*iv,* 1 g) results in about 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness. Based on the paracetamol disposition (increased clearance) observed at delivery, it might be considered to decrease the time interval between consecutive paracetamol doses (at present guidelines q6h) or increase the dose (at present 1 g) in the immediate postpartum to mimic the time-concentration profile aimed for in the non-pregnant adult. However, such an approach will also results in higher oxidative metabolism (hepatotoxity) during pregnancy and is not without risk, and may explain the specific issues (gastroshizis, atopy of infancy) discussed below[32-35].

Specific pregnancy related issues as reported in literature

Epidemiological data suggest a link between perinatal paracetamol exposure and the risk to develop asthma[32,33]. This included maternal consumption of acetaminophen during pregnancy. To further illustrate this, the Avon Longitudinal Study explored the impact of both nuclear erythroid 2 p45-related factor 2 polymorphism and glutathione S-transferase (GST, M1, T1, and P1) polymorphisms in the mothers and their infants to search for genotype-phenotype concordances[32]. It was hereby documented that the antioxidant genotype of the infant did not modify associations between infant acetaminophen use and asthma phenotypes. In contrast, the increased risk of asthma and wheezing associated with late gestation acetaminophen exposure in the presence of maternal GSTM1 was further enhanced when GSTM1 was also present in the infant. Consequently, it seems that maternal antioxidant gene polymorphisms modify the relation between prenatal acetaminophen exposure and childhood asthma, strengthening evidence for a causal, polymorphisms related association[32,33]. This fits quite well with the pregnancy related differences in metabolic routes of paracetamol elimination during pregnancy since associated with higher formation of oxidative metabolites[14,32,33].

A similar illustration, but looking for genotype/phenotype concordance following maternal acetaminophen exposure and fetal gastroshizis has been elaborated by Leeder *et al*[34,35]. The author hereby also stressed that besides the maternal compartment, placental transfer and metabolism, fetal drug disposition and the developmental context also contribute to the fetal concentration/time and concentration/effect profile[34,35].

PARACETAMOL IN EARLY INFANCY

Paracetamol is also commonly prescribed to treat moderate pain in neonates and infants. Similar to other populations, an *iv* formulation may reduce variability related to absorption, and can be considered when enteral routes are not available[36]. Aspects of PK and PD of *iv* paracetamol in (pre)term neonates were collected and reported in literature[37-39]. The PK observations were recently pooled[40].

Based on this pooled population pharmacokinetic analysis in 943 paracetamol observations from 158 neonates, pharmacokinetic estimates (between-subject variability, %) were central distribution volume 51.9 L/70 kg (21.6%), peripheral distribution volume 22.7 L/70 kg and clearance 5 L/h per seventy kilogram (40%)[40]. Covariates predicted about 61% of the paracetamol clearance variability. Weight was the most important covariate of clearance, with only a very minimal additional contribution of postmenstrual age (2.2%)[40]. We hereby mainly confirmed earlier clearance estimates in a further extended cohort of (pre)term neonates[25,36].

Paracetamol clearance, described using allometric scaling was one third of the mature value reported in adults (16.2 L/h per seventy kilogram)[40]. Clearance maturation is slow before 40 wk PMA and matures rapidly

Table 1 Median paracetamol clearance estimates as reported in different cohorts of adults

Ref.	Dose	Adults	Paracetamol (L/h)
Owens *et al*[11]	1 g, repeated q6h	20 patients, major abdominal surgery	
		Day 1 of surgery	10.8
		Day 2 or 3 after surgery	16.65
Kulo *et al*[14]	2 g *iv*, followed by 1g, q6h	Caesarean delivery, 39 women	21.1
	2 g *iv*, single dose	8/39, paired analysis, 18 wk postpartum	11.7
Liukas *et al*[21]	1 g, single dose	40 patients, different age cohort, orthopedic surgery	
		20-40 years, median weight 81 kg	22.3
		60-70 years, median weight 83 kg	20.9
		70-80 years, median weight 82 kg	16.2
		80-90 years, median weight 68 kg	13.5
de Maat *et al*[22]	1 g *iv*, repeated dose	38 medium and intensive care unit adult patients	23.65
		26/38, medium care	20.84
		12/38, intensive care	39.78
Gregoire *et al*[30]	2 g *iv*, followed by 1g, q6h	26 healthy male and female volunteers	15.9
Depré *et al*[31]	0.5 g *iv*, single dose	12 healthy male volunteers	20.04

afterwards with a maturation half-time of 52 wk PMA to reach 90% of adult rates at one year of life (equal to 92 wk PMA). Moreover, when compared to other pediatric populations, the distribution volume is higher in neonates. The increased volume of distribution in neonates supports the use of a larger initial dose (loading dose) of *iv* paracetamol in neonates if one aims to attain a given threshold paracetamol concentration sooner since a higher distribution volume results in a proportionally lower peak concentration[7].

The combined observations of clearance and distribution volume result in the advice to consider a loading dose (20 mg/kg) in neonates, followed by 5, 7.5 or 10 mg/kg per six hours in extreme preterm, preterm and term cases respectively. Figure 2 provides the predicted concentration-time profile for a 36 wk postmenstrual age individual patient based on a loading dose of 20 mg/kg, followed by 10 mg/6 h[40].

Although these dosing suggestions are higher when compared to the registered dosing, the combined loading dose + maintenance (20 mg/kg, followed by 20-40 mg/kg per twenty four-hours) has been evaluated on different pharmacodynamics aspects, including both pain reduction as well as safety (hepatotoxicity, haemodynamics and body temperature)[7,10,37-39].

There were no signs of hepatic intolerance during and following repeated administration of intravenous paracetamol[39]. In addition and as part of the PARA-NEO study (www.clinicaltrials.gov, NCT00969176), we reported on the hemodynamics following *iv* paracetamol (loading dose, 20 mg/kg) administration[38]. In contrast to the negative hemodynamic effects in adult intensive care unit patients, there were no hemodynamic alterations in neonates[22,38]. Similarly, neonates remained normothermic, while temperature reduction - most pronounced within the first 2 h after administration - was observed in neonates with fever[37].

More recently, we also reported on the paracetamol concentration-effect relation in neonates, based on prospective collection in 19/60 neonates included in the PARA-NEO study received monotherapy with *iv* paracetamol to treat mild to moderate pain (*e.g.*, alprostadil administration, delivery related trauma)[10]. Using repeated measures ANOVA, there was a trend ($P = 0.02$) for lower pain scores within 30 min after administration, with a slight increase in pain scores from 5 to 6 h (Figure 3)[10]. Further analysis hereby suggests a similar paracetamol effect compartment concentration in neonates compared to children.

Specific issues reported in literature

In addition to the above mentioned aspects of clinical pharmacology of paracetamol in early infancy, epidemiological data also suggest a link between paracetamol exposure in early infancy and the risk to develop asthma similar to the link between maternal exposure and atopy in early infancy[32,33]. From a safety aspect, we would like to point to the dosage errors (10 fold error) reported following the introduction of the *iv* paracetamol formulation in neonatal intensive care unit, with serious adverse events in individual cases[41]. These errors re-illustrate the risks associated with the introduction of a new compound in this specific population.

Finally, standard pharmacologic closure of the patent ductus arteriosus currently involves the administration of 1 of 2 cyclooxygenase inhibitors: either indomethacin or ibuprofen. However, both of these drugs can be associated with potentially significant adverse effects. There have been a limited number of case reports describing the association of paracetamol exposure and closure of a patent ductus arteriosus[42,43]. At present, there are some study protocols registered who will focus on this research question in preterm neonates (< 1500 g). Until such data become available, we consider this a hypothesis in the need for validation before efficacy/safety comparative trials can be considered.

GENERAL DISCUSSION

Clinical pharmacology aims to predict PK and PD to improve the effect/side-effect balance in every individual

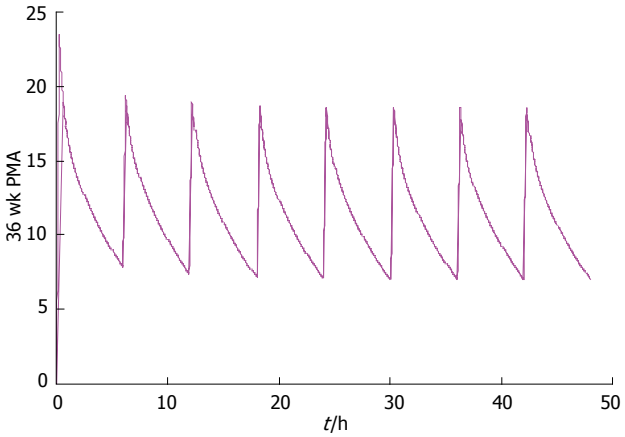

Figure 2 Concentration-time profile estimated based on the pooled pharmacokinetic study in neonates. The profile estimates are based on an initial loading dose (20 mg/kg) of *iv* paracetamol, followed by 10 mg/kg q6h in a newborn of 36 wk postmenstrual age[40].

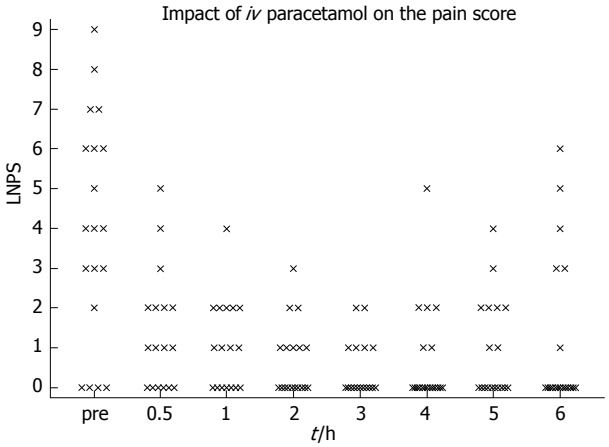

Figure 3 Individual pain scores (Leuven Neonatal Pain Score, range 0-14) as collected following *iv* paracetamol (20 mg/kg) administration. Only observations in 19/60 treated with *iv* paracetamol (monotherapy) while included in the PARANEO study were reported[10].

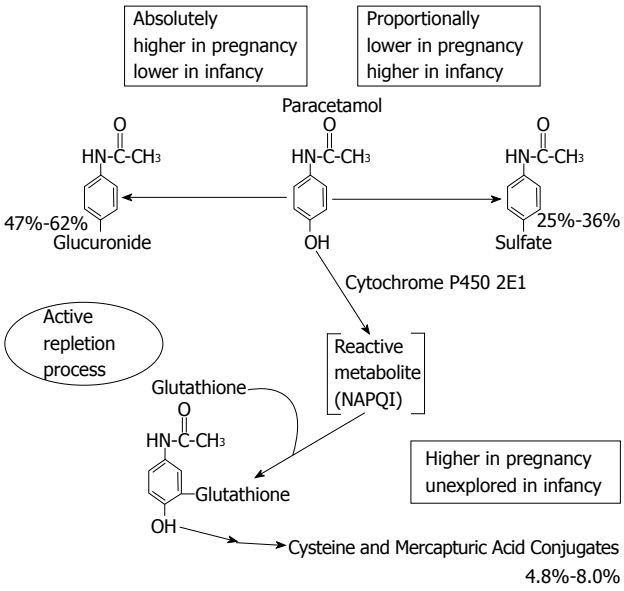

Figure 4 Paracetamol metabolism in the human, hereby indicating the changes in paracetamol drug metabolism at delivery and in early infancy.

patient. Extensive physiological alterations in pregnancy and postpartum or infancy can lead to clinically relevant changes in drug disposition and subsequent effects. This relates to the metabolic route, the pharmacokinetics (distribution volume and clearance), and the subsequent level of analgesia.

The available data reported on drug disposition in the pregnant and non-pregnant state indicate that these pharmacokinetic differences might be of pharmacodynamic relevance. Therefore, we aimed to perform additional paired PK studies in earlier and later than 3 mo postpartum stages to fully elucidate the way how pregnancy induced paracetamol disposition changes return to pre-pregnancy values[6,14]. We hereby were able to describe that the higher paracetamol clearance ad delivery is mainly due to higher glucuronidation and oxidation. In contrast, in neonates, the glucuronidation capacity is still limited, resulting in proportional higher sulphation and primary renal clearance while the contribution of oxidative metabolites to overall paracetamol clearance remains to be explored (Figure 4)[1,6,7,14].

Analgesia of paracetamol is mediated through inhibition of prostaglandins synthesis in the central nervous system (cyclo-oxygenase Ⅲ and Ⅱb). Analgesic effects also involve inhibitory action at the level of spinal nitric oxide and serotonergic pathways[1-5]. Paracetamol is believed to be an effective antipyretic at plasma concentrations between 10 and 20 mg/L and these concentrations have also been suggested to provide analgesia[1-5]. To result in effective analgesia, this means that the distribution volume needs to be considered to attain a sufficient plasma concentration at the initiation of treatment.

At delivery, the distribution volume (L) is proportionally higher due to the higher body weight at delivery, without additional relative (L/kg) changes. As mentioned earlier, the relation between plasma paracetamol concentration and the level of analgesia has not yet been fully described. Intravenous paracetamol (1 g) provides around 4 h of effective (pain relief, opioid sparing) analgesia with a subsequent decrease in effectiveness to 6 h[18]. Similarly, an intraoperative loading dose of two grams compared to one gram following minor hand or third molar surgery respectively provided better analgesia (VAS score) in the first 24 h after the intervention[44]. The higher distribution volume at delivery supports the use of a loading dose of 2 g instead of the recommended 1 g of *iv* paracetamol at delivery in the absence of contra-indications. This should be followed by 1 g *iv* paracetamol q6h to maintain these concentrations within this analgesic range while avoiding both accumulation and overproduction of oxidative metabolites[6,14].

Adequate management of pain is also in neonates a major issue, not only from an ethical perspective, but also to improve short and long term outcome[1,10]. Effective treatment of pain in this population is still in part ham-

pered due to the limited volume of data on the PK and PD of analgesics prescribed. To a certain extent, this is even true for paracetamol.

Based on their body composition, the distribution volume for paracetamol is proportionally (L/kg) higher in early infancy when compared to children or adults[40]. Similar to the rationale to use a loading dose at delivery, this pharmacokinetic variable supports the use of a loading dose (20 mg/kg). Although only based on a very limited number of observations, we recently were able to document that this loading dose approach does result in effective pain reduction up to 6 h[10]. Based on the lower clearance in early infancy, this loading dose should be followed by a maintenance dose of either 20-40 mg/kg per twenty-four hours, divided to result in intermittent administration hereby using a 6-12 h time interval[7,40].

Obviously, further studies on the pharmacodynamics of paracetamol in early infancy are urgently needed similar to the recent work of Capici *et al*[27] on the pharmacodynamics of *iv* paracetamol in children following adeno-tonsillectomy. These authors compared the time until rescue medication after adeno-tonsillectomy in children was needed after paracetamol administration. They hereby were able to document that a 6 h interval of intravenous administration (20 mg/kg) should not be exceeded. The time until rescue medication was needed was shorter after intravenous administration (6 h) compared to rectal (40 mg/kg) administration (10 h), potentially in part reflecting the slower and more variable absorption after rectal administration. Since the time until rescue medication was the main outcome variable of this study, no final conclusions on the safety/effectiveness balance during repeated rectal or intravenous administration of paracetamol can be drawn based on this study. Such studies should result in safer and more effective prescription and use of drugs in early infancy. This even is true for frequently administered drugs like paracetamol since still important issues on its use remain to be unveiled.

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CASE REPORT

Anesthetic management of patient with hypertrophic cardiomyopathy and automatic implantable cardioverter defibrillator with a hand fracture

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Abstract

A 26-year-old male with a history of hypertrophic cardiomyopathy (HCM) and ventricular arrhythmias s/p automatic implantable cardioverter defibrillator (AICD) placement presented for open reduction and internal fixation of an open third metacarpal fracture and extensor tendon repair. He underwent successful surgery after placement of an ultrasound-guided infraclavicular brachial plexus block with ropivacaine 0.5% as the main anesthetic. This case report discusses the anesthetic management of patients with HCM and AICD, different approaches available for brachial plexus blockade, and potential complications of anesthesia and surgery in this group of patients.

Key words: Hypertrophic cardiomyopathy; Automatic implantable cardioverter defibrillator; Brachial plexus block; Hand fracture; Ropivacaine

Core tip: The anesthetic management of patients with hypertrophic cardiomyopathy (HCM) and automatic implantable cardioverter defibrillator (AICD) can be very challenging. We present a case of a 26-year-old male who presented for open reduction and internal fixation of an open right hand fracture. He underwent successful surgery after placement of an ultrasound-guided infraclavicular brachial plexus block with ropivacaine 0.5% as the main anesthetic.

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INTRODUCTION

The anesthetic management of patients with hypertrophic cardiomyopathy (HCM) and automatic implantable cardioverter defibrillator (AICD) can be very challenging. We present a case of a 26-year-old male who presented for open reduction and internal fixation (ORIF) of an open right hand fracture. We discuss anesthetic implications of patients with HCM and AICD, different approaches to brachial plexus blockade, and potential risks and complications pertinent to this group of patients.

CASE REPORT

A 26-year-old Caucasian male, 70 inches tall and weighing 105 kg, presented for incision and drainage, ORIF of an open right third metacarpal fracture, and extensor tendon repair after injuring his hand at home while fixing his garage door. He had a history of hypertrophic cardiomyopathy and ventricular arrhythmias s/p insertion of an automatic implantable cardioverter defibrillator two years ago. His vital signs were a blood pressure of 99/50 mmHg, heart rate of 50, respirations of 16 per minute, and oxygen saturation of 99% on room air. Electrocar-

diogram showed sinus bradycardia (HR 54) with sinus arrhythmia and occasional premature ventricular contractions. His preoperative hemoglobin and hematocrit were 15.0 and 42.6 g/dL, respectively, and his electrolytes were normal. His physical examination was otherwise normal. At home the patient took metoprolol 100 mg by mouth once a day. The patient reported that the AICD had discharged twice in the past year during periods of increased physical activity. He did not have any problems with normal physical activity and denied chest pain or shortness of breath on exertion. He denied additional medical history and had never undergone an anesthetic.

After discussion with the patient and his family, the decision was made to perform a brachial plexus block. The AICD was interrogated by the company representative and found to be working properly. We proceeded by performing a right ultrasound-guided infraclavicular brachial plexus block with 40 mL of ropivacaine 0.5% without the use of a nerve stimulator.

Once in the operating room, adhesive external defibrillating pads were placed and the AICD device was turned off due to the expected use of electrocautery during surgery. The patient underwent successful surgery with the brachial plexus block as the main anesthetic and light sedation. Of note, his electrocardiography (ECG) showed premature ventricular contractions throughout the procedure but his hemodynamics were stable throughout. The AICD device was turned back on after the procedure was finished. He recovered well and was discharged home the next morning.

DISCUSSION

This was a challenging case due to the following factors: management of a patient with hypertrophic cardiomyopathy, management of a patient with an AICD *in situ*, the risks of using of peripheral nerve stimulation for performance of a nerve block in patients with AICD, and potential effects on the cardiovascular system of brachial plexus blockade. Careful consideration of each issue separately was important in avoiding complications in this patient. These issues are addressed separately below.

HCM

HCM is a genetic cardiac disorder that is the most common cause of sudden cardiac death in the young[1]. It is characterized by heterogeneous left ventricular hypertrophy and patients often present with diastolic dysfunction that is reflected by elevated left ventricular end-diastolic pressures in spite of often hyperdynamic ventricular function. Clinical course is determined by the following factors: dynamic obstruction to left ventricular outflow, diastolic dysfunction, impaired coronary vasodilator reserve and myocardial ischemia, and supraventricular and ventricular arrhythmias[2]. Anesthetic goals for these patients are: minimize sympathetic activation, expand intravascular volume in order to avoid hypovolemia, and minimize decreases in left ventricular afterload. Reported adverse events for patients with HCM undergoing noncardiac surgery include: congestive heart failure, hypotension, arrhythmias, and myocardial infarction[3].

Our patient had a history of arrhythmias for which he had the AICD placed previously. His electrocardiogram showed sinus arrhythmia and occasional premature ventricular contractions which were concerning. He did not have any history of chest pain and was able to do normal daily activities and work without limitation. The biggest concern was that both episodes where his AICD had discharged previously took place during periods of increased stress and excitement. We all agreed that avoiding a general anesthetic was the best course of action in this case.

AICD

Patients presenting for noncardiac surgery with AICD *in situ* are becoming more common every day. During surgery, the AICD should be deactivated in order to avoid accidental discharge or damage to the device cause by electrocautery or any device that generates a pulse current, including peripheral nerve stimulators[4]. Other patient factors may affect the function of an AICD. Electrolyte abnormalities may cause the actions of an AICD to fail. In addition, patient positioning, positive pressure ventilation, and shivering may affect the functionality of the AICD.

It is important to place external defibrillating pads on the patient while the device is turned off. In our patient, we first applied the external defibrillating pads and turned on the monitoring function of the external defibrillating device. Then, we turned off the AICD device immediately before surgery. Once surgery was finished, we turned the AICD back on and it was found to be functioning properly.

Peripheral nerve stimulation and AICD

Once the decision was made to perform a brachial plexus block in this patient, we needed to take into consideration the potential effects of a nerve stimulator on the AICD device. Manickam *et al*[5] described a set of recommendations with regards to the use of peripheral nerve stimulation in patients with pacemakers. The same issues apply to AICD. If stimulation cannot be avoided, the ground electrode should be placed as far away as possible from the device and stimulation should be done well away from the device (at least 6 inches). Stimulating pulses should be no more than 0.2 milliseconds in duration and the rate of stimulation should not be faster than 1 Hz[5].

Although the surgery and nerve block were to be performed on the right side, away from the AICD, it was decided that it would be best to avoid the use of peripheral nerve stimulation if possible. With the assistance of ultrasound, we were able to visualize the structures and place the local anesthetic around the nerves to provide a surgical block while avoiding the use of nerve stimulation.

Stellate ganglion block after brachial plexus block

Stellate ganglion block is a technique used to diagnose and treat complex regional pain syndrome of the upper extremity. It is performed by local anesthetic injection around the sympathetic chain at the C6 level. Inadvertent blockade of the stellate ganglion may occur during blockade of the brachial plexus and the most common clinical presentation is Horner's syndrome. Horner's syndrome presents as ptosis, miosis and anhidrosis of the ipsilateral face. This commonly resolves within a couple of hours without clinical significance. Reassurance of the patients is all that is needed. A recent study by Tran *et al*[6] found the incidence of Horner's syndrome in ultrasound-guided supraclavicular blocks to be 37%, compared to 5% for infraclavicular and 0% for axillary blocks. However, a report on 510 consecutive ultrasound-guided supraclavicular blocks showed an incidence of Horner's of only 1%[7]. All in all, the more distal blocks have less incidence of this side effect.

Fujiki *et al*[8] studied hemodynamic effects of stellate ganglion block on healthy volunteers. They found that: (1) autonomic innervation of the sinus node is mainly through the right-sided stellate ganglion; (2) pharmacologic right-sided stellate ganglion block may attenuate not only sympathetic but also parasympathetic activity; and (3) following right stellate ganglion block the decrease in both the sympathetic and parasympathetic influence on the sinus node may inconsistently counterbalance and change the RR interval. Left-sided stellate ganglion block changed none of the heart rate variability indices studied.

Although the effects of stellate ganglion blockade on heart rate and electrical conduction may be clinically insignificant in healthy patients, these effects could potentially be detrimental in patients with cardiac disease, especially with history of arrhythmias. Therefore, it is probably best to avoid this side effect in patients with cardiac disease.

We chose an ultrasound-guided infraclavicular block due to our familiarity and success with the technique. Both a supraclavicular and an axillary block would also have been adequate for this surgical procedure. Since the surgery was on the right arm, opposite the AICD device, we were not as concerned with the needle insertion site. If the patient had needed surgery on his left arm, an ultrasound-guided axillary block would have been our choice, as we would want to avoid nerve stimulation and needle placement anywhere near the chest.

In conclusion, a patient with HCM and AICD who required an anesthetic for repair of this hand was successfully managed by placement of an ultrasound-guided brachial plexus nerve block. Consideration of the multiple issues which may arise is important in the management of these patients. Patients presenting for surgery with these medical problems are becoming more and more common. Special consideration should be taken regarding the method of nerve block placement in patient with an AICD in place. Potential hemodynamic effects of anesthetic techniques in patients with HCM and AICD should be considered at all times. Future studies should look at which anesthetic techniques best maintain hemodynamics in patients with HCM and AICD undergoing a variety of surgical procedures.

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CASE REPORT

Management of a patient with perioperative saddle embolus

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Abstract

Pulmonary embolism is a major cause of morbidity and mortality. Risk factors include venous stasis, endothelial injury, and hypercoagulability. Prevention centers on the use of sequential compression devices and anticoagulation in the hospital patient. This is the case of a 45-year-old male who presented for open reduction and internal fixation of tibia plateau fracture. He developed a saddle embolus during the perioperative period which was diagnosed in the recovery room after workup for the cause of his poor oxygenation. A chest computed tomographic scan showed an extensive saddle embolus with partial occlusion of the bilateral main pulmonary arteries and all segmental pulmonary artery branches. This case report discusses his diagnosis, management and clinical course. In addition, risk factors, treatment and prevention for pulmonary embolus and described.

Key words: Venous thromboembolism; Pulmonary embolus; Saddle embolus; Tibia fracture; Anesthesia

Core tip: The case report describes the diagnosis, management and treatment of a 45-year-old male who developed a saddle pulmonary embolus during open reduction and internal fixation of tibia plateau fracture. The incidence of pulmonary embolism, risk factors, and treatment and prevention choices are discussed.

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INTRODUCTION

Venous thromboembolism clinically manifested as deep vein thrombosis and pulmonary embolism, is a common cause of increased morbidity and mortality. Pulmonary embolism (PE) can manifest in a variety of clinical settings ranging from acute shortness of breath in the emergency department to intraoperative cardiovascular collapse, hypoxemia in the recovery room, to respiratory distress in the intensive care unit. In the perioperative setting, it is critical for the anesthesiologist to have a high index of suspicion for PE as symptoms and signs are often vague and non-specific. To do so, one must know the medical and surgical risk factors that can increase the probability of PE as well as the prophylactic measures that can be used to diminish the risk. In addition, it is critical to know the management of pulmonary embolism in the perioperative setting.

CASE REPORT

A 45-year-old African American male was admitted to the hospital with a left tibia plateau fracture after a motor vehicle accident. He had no other injuries from the accident and had no previous medical history other than 20 pack-year history of smoking tobacco. The patient was admitted and started on enoxaparin 40 mg subcutaneously once a day for deep venous thrombosis prophylaxis. On hospital day 3 he underwent open reduction and internal fixation of the left tibia plateau fracture. The surgical procedure was uneventful. A laryngeal mask airway was

used initially, but was subsequently switched to an endotracheal tube after difficulty with placement and difficulty maintaining adequate ventilation and oxygen saturation. After placement of the endotracheal tube, ventilation and oxygenation went back to normal and the procedure proceeded as planned.

The patient was subsequently extubated at the end of surgery. Although he was awake and was ventilating well, he continued to have O_2 saturations in the mid 80 to 90 s with 100% non-rebreather mask along with sustained tachycardia in the 110 to 120 s even after adequate pain control. An arterial blood gas was drawn in the post anesthesia care unit and it showed a pH of 7.40, pCO_2 of 41.6 mmHg, pO_2 of 61.0 mmHg, bicarbonate of 25.1 and oxygen saturation of 91%. A chest X-ray was taken showing an interval development of a right upper lobe opacity concerning for pneumonia or aspiration when compared to his admission chest X-ray. A computed tomography scan of the chest was performed and an extensive saddle embolus with partial occlusion of the bilateral main pulmonary arteries and all segmental pulmonary artery branches with significant thrombus burden. In addition, a right upper lobe dense airspace consolidation with peripheral ground glass opacification along the right posterior segmental bronchus and bronchus intermedius which was suspicious of infarction was found. An echocradiogram was then performed showing a severely dilated right atrium and right ventricle. However, he had normal left ventricular function and his ejection fraction was between 55%-60%. Bilateral lower extremity Doppler studies showed occlusive thrombi in the left common femoral and superficial femoral veins.

The patient was started on a heparin infusion and subsequently had an inferior vena cava filter placed. He remained in the intensive care unit for several days until his oxygen demand was reduced from 100% oxygen *via* non-rebreather mask to nasal cannula. He never required intubation to support his oxygenation and ventilation and remained hemodynamically stable throughout his hospital stay. He was transitioned to the regular nursing floor without need for oxygen supplementation and soon discharged on warfarin with follow up at the Pulmonary and Orthopedics clinics. On follow up, he had returned to normal function and recovered from his surgical procedure well.

DISCUSSION

Our patient was able to fully recover from an event that can often be lethal. It is unknown at which point after his tibia fracture the patient developed his blood clot and pulmonary embolism. We were able to begin treatment as soon as the diagnosis was made. It also helped that our patient was healthy and physically fit before this event took place.

The incidence of mortality after pulmonary embolism has been reported to be as high as 300000 per year[1]. This number understates the significant morbidity including chronic pulmonary hypertension, disability, and impaired quality of life that affects survivors. It is estimated that the economic burden of pulmonary embolism is greater than $1.5 billion a year in healthcare costs with estimates stating that each pulmonary embolism results in additional healthcare costs in excess of $30000[1]. The three-month mortality of pulmonary embolism has been stated as high as 15%-18%[1]. While most patients with acute pulmonary embolism survive, possible long term sequelae include chronic thromboembolic pulmonary hypertension and chronic leg pain and swelling.

It is important for all medical personnel to be aware of patients at higher risk for developing venous thromboembolic disease. Risk factors that acutely increase the risk of pulmonary embolism include orthopedic surgeries, especially total hip and knee replacement, surgery for hip fractures, as well as trauma and spinal cord injuries. Acute medical morbidity, especially malignancy is also a major risk factor.

A good approach to understanding all the risk factors that predispose patients to pulmonary embolism is to understand Virchow's triad[2]. Virchow's triad states that venous stasis, endothelial injury, and hypercoagulability will increase the risk of thrombosis[2]. Venous stasis can occur when patients are immobile (*i.e.*, spinal cord injury, trauma, orthopedic fractures) or when there is a problem with the pump (*i.e.*, heart failure). Surgical procedures are a major culprit to endothelial injury, as are invasive catheter-based procedures including angiograms and placement of transvenous pacemakers. Hypercoagulability can be hereditary such as deficiency or mutation of certain factors (prothrombin, protein C, protein S) or from pro-inflammatory states (malignancy, myeloproliferative syndromes, antiphospholipid antibodies, hyperhomocysteinemia, heparin-induced thrombocytopenia, acquired immunodeficiency syndrome (AIDS), burns, lupus, oral contraceptives)[1].

Orthopedic patients have a high risk from development of deep vein thrombosis and pulmonary embolism. A study by Geerts *et al*[3] showed an incidence of deep venous thrombosis (DVT) of 69% in patient with lower extremity fractures. This made our patient with a tibia fracture at high risk for development of DVT. As is customary with most trauma patients at our hospital, he was on enoxaparin for DVT prophylaxis up until the morning of his surgery. However, it did not prevent him from developing a saddle pulmonary embolus.

When acute pulmonary embolism is present, parenteral anticoagulation with either low molecular weight heparin or unfractionated heparin should be administered, unless contraindicated[4,5]. The primary indications for placement of an inferior vena cava filter are contraindications to anticoagulation, risk of major bleeding during anticoagulation, and recurrent embolism while receiving adequate therapy[4]. Filters are also considered in cases of massive pulmonary embolism, with the thought being that additional thrombotic burden may be life threatening. In cases of massive pulmonary embolism with cardiovascular collapse, requiring cardiopulmonary

resuscitation and blood pressure support, mortality is much higher. A retrospective review performed at Texas Heart Institute by Konstantinov *et al*[6] showed that emergency treatment using cardiopulmonary bypass may be beneficial. Rapid recognition and treatment are very important to prevent severe morbidity and mortality after pulmonary embolism.

Current methods used to prevent DVT and PE have significantly reduced the incidence of fatal PE[7]. Treatments that combine mechanical prophylaxis such as, sequential compression devices or inferior vena cava filters, with low molecular weight heparin appear to be most effective[7]. However, even patients on appropriate prophylaxis are still developing DVT and PE. Future research will hopefully help with better prevention and treatment of pulmonary embolism.

In conclusion, we presented the case of a 45-year-old male who developed a saddle pulmonary embolism after tibia fracture during the perioperative period. Prompt diagnosis and treatment prevented morbidity and mortality in this patient.

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Statistical data

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Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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CASE REPORT

Electrochemotherapy and heart function: Treatment in a patient with implantable cardioverter defibrillator/pace-maker

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Abstract

Electrochemotherapy (ECT) is a recently described therapy that relies on the permeation of cancer cell membranes by electrical pulses to enhance cytotoxic drug penetration. It has been successfully used in the treatment of primary and metastatic skin cancer. Systemic chemotherapy is the most commonly used therapeutic strategy, and the prevailing orientation calls for the administration of the maximum tolerated dose; however, considerable limitations exist including toxicities to healthy tissues and low achievable drug concentrations at tumor sites. We reported a case of an 83-years-old patient with a laterocervical metastasis of a squamous epidermoidal lip cancer. The patient had a complex medical history and an implantable cardioverter defibrillator (ICD)/pace-maker. The lesion was localized in the supraclavicular right side with a distance from the pace-maker/ICD about 5 cm, but the nodule was not deeply located. The ECT was performed under general anesthesia and particular attention we put on the interference with the functioning of the heart. The synchronization algorithm currently implemented in Clinoporator Vitae device coupled with the external triggering device AccuSync proved to be effective in preventing external stimulation of the heart during the so-called vulnerable period of the ventricles. As a result all electroporation pulses in our study were delivered outside the vulnerable period and no heart arrhythmias or any other pathological morphological changes were observed. The safety of treatment was demonstrated also by absence of side effects during and after ECT.

Key words: General anesthesia; Electrochemotherapy; Pace-maker; Implantable cardioverter defibrillator; Tumor ablation; Metastatic skin cancer

Core tip: We reported a case of treatment with electrochemotherapy (ECT) for a metastatic skin cancer in a patient with a complex cardiological history. The safety of the treatment was demonstrated by absence of side effects during and after ECT.

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INTRODUCTION

Electrochemotherapy (ECT) is a therapeutic technique that relies on high-intensity electrical currents to reversibly increase cell membrane permeability (electroporation)

and to enhance the penetration of cytotoxic drugs into neoplastic cells[1].

Bleomycin sulphate has been successfully used in combination with ECT in primary skin cancer, in the treatment of metastases of melanoma and squamous cell carcinoma, such as in Kaposi's sarcoma[2]. ECT is reported as an efficient and safe method, it causes only minor side effects in the patients such as transient lesions in areas in direct contact with the electrodes and acute localized pain due to contraction of muscles next to the electrodes. When tumor nodule is too large or is in the neck the ECT is painful and needs general anesthesia.

Mali *et al*[3] studied the effects of ECT of tumors located close to the heart and they examined the influence of electroporation pulses on functioning of the heart of human patient by analyzing the electrocardiogram. They found no arrhythmias or other pathological morphological changes during the application of electrical pulses and the only demonstrated effect was a transient R-R interval decrease.

Mir *et al*[4] defined the standard operating procedures in order to safely and conveniently treat by ECT patients with cutaneous and subcutaneous nodules. In the section "patient selection" the authors covered the criteria that must be checked during the pre-inclusion visit for the treatment by ECT and the presence of a pace-maker was considered a precluding element for a treatment on the anterior chest wall.

Here we present a case of 83-years-old male patient with laterocervical metastasis of a squamous epidermoidal lip cancer, with an implantable cardioverter defibrillator (ICD)/pace-maker undergoing to ECT.

CASE REPORT

A 83-years-old male (body weight: 71 kg; height: 168 cm) was admitted to our Ear Nose Throat Surgical Unit for the ECT treatment of a laterocervical metastasis, a massive lesion, measuring 43 mm in diameter, aching, extended into the submandibular gland region, masseter and platysma muscle. In 2010, the patient was operated for a squamous epidermoidal lip cancer removal in the same University Hospital. His medical history was significant for a post-ischemic dilatative cardiomiopathy, permanent atrial fibrillation, chronic renal failure and chronic obstructive pulmonary disease. Past surgical history included: inguinal hernia repair in 1956, myocardial revascularization and left ventricular aneurysmectomy in 1985, biventricular pace-maker/ICD implant in 2009 (St. Jude Medical). In addition to oral anticoagulant therapy, the usual treatment was: digoxin 0.125 mg 1 cp/die, carvedilol 25 mg 1 cp × 2, perindopril arginine 10 mg 1 cp/die, candesartan cilexetil 8 mg 1 cp/die, furosemide 25 mg 1 cp × 3, metolazone 10 mg 1 cp/die, ezetimibe/simvastatin 10/40 mg 1 cp/die, pantoprazol 40 mg 1 cp/die, sertraline 50 mg 1 cp/die. Preoperative evaluation of the patient revealed a good blood pressure control, mild dyspnoea, permanent atrial fibrillation. A trans thoracic echocardiography showed global hypokinesia with a dilated left ventricle, aortic-mitral and tricuspidal regurgitation, pulmonary arterial pressure of 50 mmHg and left ventricular ejection fraction 35%. Chest X-ray revealed cardiomegaly, ventilatory stripes and micronodular opacities with calcifications. A subsequent abdomen computed tomography scan was positive for abdomen harvest fluid. Laboratory data showed: haemoglobin 9.1 g/dL, hematocrit 30.1%, red-blood-cells 3.35 × 10^6/μL, creatinine 1.6 mg/dL, glycaemia 115.3 mg/dL, urea 111.5 mg/dL, prothrombin time 54%, partial thromboplastin time 38.9 s, international normalized ratio 1.44. Other haematological parameters were within the normal range.

The procedure was performed under general anesthesia. The patient was considered in class Ⅲ of American Society of Anesthesiologists physical status classification[5] and showed predictive elements of a difficult airway (Mallampati score Ⅲ, a reduced extent of the mouth opening and a reduced motility of the neck with a flexion-extension angle < 90°). After the positioning of a large-diameter *iv* cannula, the patient was monitored (SpO_2, EKG, non-invasive blood pressure) and a magnet was placed on the ICD (it was located near the neoplastic mass < 10 cm). Two pads were applied and connected to an external cardioverter/defibrillator unit. We started the infusion of remifentanil 0.05-0.10 μg/(kg•min) (Ultiva 5 *iv* 5 mg, GlaxoSmithKline S.p.A., Verona, Italy) and propofol (Propofol Ibi 1% 10 mg/mL, Istituto Biochimico Italiano, Milan, Italy), 2-3 mg/(kg•h) giving supplemental oxygen through a nasal cannula at the rate of 4 L/min. After 5 min and adequate atomization of topical 4% lidocaine (Ecocain 10 g/100 mL spy, Molteni Dental, Florence, Italy), we performed an awake fiberoptic tracheal intubation. After the intubation, the induction of anesthesia was obtained with propofol (Propofol Ibi 2% 20 mg/mL, Istituto Biochimico Italiano, Milan, Italy) 1.5 mg/kg and cis-atracurium 0.1 mg/kg (Nimbex 2, GlaxoSmithKline S.p.A., Verona, Italy). Desflurane 5%-6% (Suprane, Baxter S.p.A, Rome, Italy) in a mixture of oxygen/air (60%/40%) and remifentanil 0.1-0.2 μg/(kg•min) was used for the maintenance of anesthesia and a large oropharyngeal cannula was inserted in the mouth to prevent tongue lesions during the electric pulses delivering. Five minutes after the induction, a needle electrode (type Ⅲ, six needles forming an hexagon and one needle at its center with an 8 mm gap between them) was inserted into the metastatic nodule and connected to the electrical pulse generator (Cliniporator Vitae, Igea, Modena, Italy) which generates square-wave electric pulse of variable amplitude with 1-5000 Hz delivery frequencies. In the same time, another operator administered *iv* bleomycin sulphate (TEVA API, LGM Pharma, Sicor S.r.l. Milan, Italy) at a concentration of 1000 UI, 0.25 mL (250 UI)/cm^3 slowly and, 8 min after, a run of 4 square-wave electrical pulses (1000 V amplitude, 5000 Hz, 100 microseconds per pulse) was delivered. The procedure

was repeated three times and the duration of ECT was approximately of 40 min. Throughout the treatment all parameters resulted stable and we didn't observed complications. At the end of ECT treatment we stopped the infusion of remifentanil and the administration of desflurane, the patient returned rapidly to a spontaneous breathing and the endotracheal tube was removed after 5 min. The patient was transferred to the post-anesthesia care unit and was monitored for 24 h. The patient was discharged from the hospital after the revision of the pacemaker/ICD.

DISCUSSION

Recently the ECT was considered as part of strategies for the control of cancer. This technique has been demonstrated to be an effective and well-tolerated therapy for cutaneous and subcutaneous lesions of different histological types with response rate of 80% and long lasting complete responses of 70%[6,7]. The present case report illustrates the difficulty in the management for cancer control in a patient with several organ dysfunctions. Surgery, radiotherapy and chemotherapy are invasive therapeutic approaches and are associated with significant adverse effects and they was not suitable for our patient.

The pace-maker/ICD constituted another limit for ECT. The American Society of Anesthesiologist published an updated task force Practice Advisory in conjunction with the Heart Rhythm Society in 2011 that provides expert recommendations for perioperative management of patients with cardiac implantable electronic devices[8]. According these notices, a magnet can be secured over the pulse generator of an ICD to suspend the arrhythmia detection function of the ICD and prevent discharge. The main caveat to the routine use of magnets to temporarily deactivate an ICD revolves around whether or not there is a possibility that the magnet response of the ICD is programmed to ignore magnet application. It depends on medical technology company and the kind of device: some devices haven't such an option and magnet application should reliably deactivate the device while its removal reactivates it. Other devices have the option of programming the magnet response to off, which underscores the need to know how an implanted device is programmed. Even when the ICD has been deactivated by a magnet, its pacemaker function is not affected. In patients with a Pacemaker the application of the magnet has different consequences. Indeed when a magnet is secured over the pulse generator, the device paces in asynchronous mode (AOO, VOO, DOO), that is, the device paces at a frequency higher than the patient's spontaneous. In asynchronous pacing if the patient is not entirely pmk-dependent, a parasystolic rhythm given by the spontaneous activity could occur and it's likely to compete with the rhythm stimulated by the device. A stimulus delivered during the vulnerable period of a spontaneous cycle could lead to a dangerous arrhythmia. Although this possibility is rare and avoided thanks to a higher pacing rate, it should be evaluated from time to time what is the management more appropriate for each individual patient[9].

An increased probability for electroporation pulses interfering with the heart function is present. In recently published studies on non-thermal irreversible electroporation, different minor and major hemodynamic and cardiologic changes due to unsynchronized irreversible electroporation pulse delivery were reported, such as systolic hypertension, supraventricular tachycardia, ventricular tachycardia with pressure drop, ventricular fibrillation and changes in T wave[10]. Deodhar *et al*[11] showed that unsynchronized irreversible electroporation pulses delivered at less than or equal to 1.7 cm from the heart provoked fatal events whereas pulses delivered more than 3 cm from the heart did not provoke any changes on the electrocardiogram. On the other hand, they reported that synchronized irreversible electroporation did not provoke any events at more than 1.7 cm distance from the heart.

The lesion in our patient was localized in the cervical right side with a distance from the pace-maker/ICD < 10 cm, but the nodule was not deeply located. The choice to perform a general anesthesia was been dictated by the clinical evaluation of the patient: tumor nodule with large dimension, painful, unpleasant sensation during procedure for muscle contraction in a patient with particular cardiac conditions and better administration of oxygen during the procedure. Our operating modalities, general anaesthesia and ECT were performed without complications. The synchronization algorithm currently implemented in Clinoporator Vitae device coupled with the external triggering device AccuSync proved to be effective in preventing external stimulation of the heart during the so-called vulnerable period of the ventricles. As a result all electroporation pulses in our study were delivered outside the vulnerable period and no heart arrhythmias or any other pathological morphological changes were observed.

The safety of the treatment was demonstrated by absence of side effects during and after ECT.

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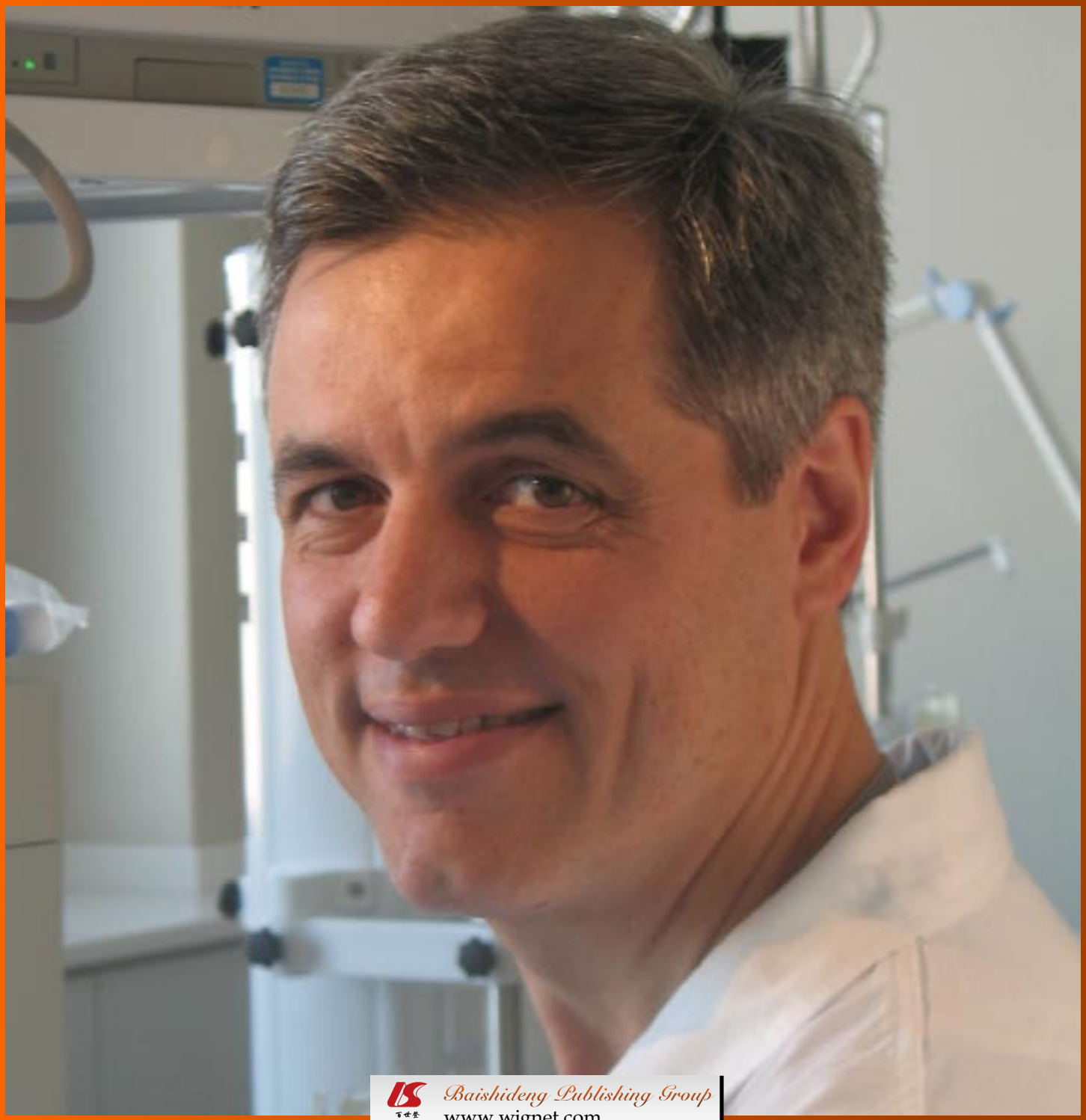

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BRIEF ARTICLE

Comparison between intrathecal hyperbaric bupivacaine and levobupivacaine for ambulatory knee arthroscopy

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Abstract

AIM: To compare the effect of hyperbaric levobupivacaine and bupivacaine on the quality of the block, patient satisfaction, and discharge time in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia.

METHODS: One hundred and thirty-two patients, American Society of Anaesthesiologists Ⅰ or Ⅱ, scheduled for elective ambulatory knee arthroscopy were randomly assigned to four double-blind groups. To achieve a unilateral spinal block, Group BF received 5 mg of hyperbaric bupivacaine plus 20 μg of fentanyl intrathecally, Group LF received 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl intrathecally, Group B received 5 mg of hyperbaric bupivacaine intrathecally, and Group L received 5 mg of hyperbaric levobupivacaine intrathecally. The level and duration of the sensory block, the intensity and duration of the motor block, the time to first analgesic requirement, and the time elapsed until the patient's discharge were recorded. Hemodynamic values and adverse effects were also recorded.

RESULTS: The duration of time needed to reach the T12 dermatome level was significantly longer in Group L [7 (3-20) min] than in Group B [6 (3-12) min] (P = 0.006). The maximum sensory level reached on the side undergoing the operation was significantly higher in Group BF than in Group B (P < 0.05). The intensity of the motor blockade was greater in Group BF than in Group LF and L. Complete recovery from motor blockade occurred earlier in Groups LF [75 (45-165) min] and L [63 (35-120) min] than in Group BF [115 (60-180) min] (P < 0.05). The length of time needed for the sensory block to regress to the level of S2 was shorter in Group L (154 ± 50) than in Group BF (192 ± 66) (P < 0.05). The quality of the block was significantly lower in Group L than in Groups BF, LF and B (P = 0.012, P = 0.003, and P < 0.001, respectively). The time elapsed until Visual Analog Scale ⩾ 4 was significantly shorter in Group L (110 ± 48) than in Groups BF (200 ± 60), LF (156 ± 61) and B (162 ± 52) (P < 0.05). The time elapsed until the patient's discharge was shorter in Groups B (244 ± 54) and L (229 ± 55) than in Group BF (288 ± 64) (P = 0.021 and P = 0.001, respectively). There were no differences among the groups regarding hemodynamic parameters and adverse events, except for pruritus. The occurrence of pruritus was significantly more frequent in Groups BF and LF than in other groups.

CONCLUSION: In conclusion, 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl provided a better spinal anesthesia than 5 mg of hyperbaric levobupivacaine alone.

Key words: Spinal anesthesia; Knee arthroscopy; Outpatient surgery; Bupivacaine; Levobupivacaine

Core tip: Arthroscopic knee surgery is a common procedure performed in the ambulatory setting. The primary goals of the anesthetic techniques used in ambulatory surgery are to reduce anesthetic complications and to allow for early patient discharge. The aim of this study was to compare the effect of low dose hyperbaric bupivacaine and levobupivacaine, with and without fentanyl, on the quality of the block, patient satisfaction, and the time elapsed until discharge in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia.

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INTRODUCTION

Arthroscopic knee surgery is one of the most frequently performed ambulatory orthopedic surgeries. The main goals of the anesthetic techniques used in ambulatory surgery are to reduce anesthetic complications, provide adequate postoperative analgesia and allow for early patient discharge[1].

Spinal anesthesia is often preferred for lower extremity surgery because of the procedure's low level of difficulty, better postoperative analgesia and reduced incidences of nausea or vomiting[2]. Long-acting local anesthetics such as bupivacaine and levobupivacaine have been widely used in ambulatory surgery thanks to the development of the low-dose spinal anesthesia technique[3,4]. However, when small doses of local anesthetics are used, an adjuvant must be given to improve the quality of the block and decrease the risk of a failed block. Different adjuvants such as lipid soluble opioids can be added to the local anesthetics[5].

Levobupivacaine, the S-enantiomer of racemic bupivacaine, is approximately equipotent with bupivacaine when used in a similar concentration and dose. At the same time, levobupivacaine is a weaker cardiac and central depressant[6,7]. Studies comparing the different doses and forms of levobupivacaine and bupivacaine for ambulatory arthroscopic surgery have been published[8,9]. However, there is no study comparing these two drugs in the context of arthroscopic knee surgery.

We hypothesized that levobupivacaine administered *via* spinal anesthesia for arthroscopic knee surgery would provide less motor blockade and earlier patient discharge compared to bupivacaine.

The primary outcome of this study was to compare the effect of low dose hyperbaric levobupivacaine and bupivacaine, with and without fentanyl, on the time elapsed until discharge in patients undergoing arthroscopic knee surgery under unilateral spinal anesthesia. The effect of these anesthetics on the quality of the block and patient satisfaction were also compared as a secondary outcome.

MATERIALS AND METHODS

With the approval of the Institutional Ethical Committee, written, informed consent was obtained from all patients. One hundred and thirty-two patients with American Society of Anaesthesiologists (ASA) physical status Ⅰ or Ⅱ, aged 18-65 years, measuring 150-185 cm in height, and scheduled for elective ambulatory knee arthroscopy were included in this prospective, double-blind, randomized controlled study. The number of patients enrolled in this study was determined by considering the relevant literature[6,10]. Patients were excluded when they met one or more of the following criteria: history of a severe renal, hepatic, or cardiac disease; a neurologic or psychiatric condition; a coagulation defect; sepsis or a local infection at the site of the lumbar puncture; and/or any hypersensitivity to local anesthetics or opioids.

Patients were randomized to one of four groups to receive spinal hyperbaric bupivacaine or hyperbaric levobupivacaine, with or without fentanyl (Figure 1). Randomization was performed using a random number table. The local anesthetic solution was prepared aseptically by an anesthetist who was blinded to the study shortly before the spinal injection. Group BF received 5 mg (1 mL) of hyperbaric bupivacaine (Marcaine Heavy 0.5% AstraZeneca) with 20 μg of fentanyl (0.4 mL), Group LF received 5 mg (1 mL) of hyperbaric levobupivacaine with 20 μg of fentanyl (0.4 mL), Group B received 5 mg (1 mL) of hyperbaric bupivacaine with 0.4 mL of sterile water, and Group L received 5 mg (1 mL) of hyperbaric levobupivacaine with 0.4 mL of sterile water. The hyperbaric levobupivacaine solution was prepared by an anesthesiologist who was not involved in further patient care. This solution was composed of 2 mL of plain 0.75% levobupivacaine (Chirocaine: levobupivacaine hydrochloride, Abbott, United Kingdom), 0.8 mL of 30% dextrose, and 0.2 mL of normal saline solution, achieving a final concentration of 0.5% levobupivacaine with glucose. The total syringe volume was 1.4 mL in all four groups.

Patients received no premedication. Pulse oximetry (SPO_2) values, non-invasive blood pressure (NIBP) measurements, and electrocardiogram (ECG) tracings were monitored in all patients. Heart rate, SPO_2 and NIBP were recorded before spinal anesthesia, every 3 min during the first 15 min of the spinal anesthesia, and then every 5 min during the remainder of the surgery. After inserting a 20 gauge *iv* cannula in the dorsum of the hand, 0.5 mL/kg of 0.9% normal saline was preloaded intravenously in all patients. The patients were placed in the lateral decubitus position, and their operated sides were positioned inferiorly. Spinal anesthesia was performed at the L4-5 intervertebral area using the mid-line approach with a 25 gauge Whitacre spinal needle. Correct needle

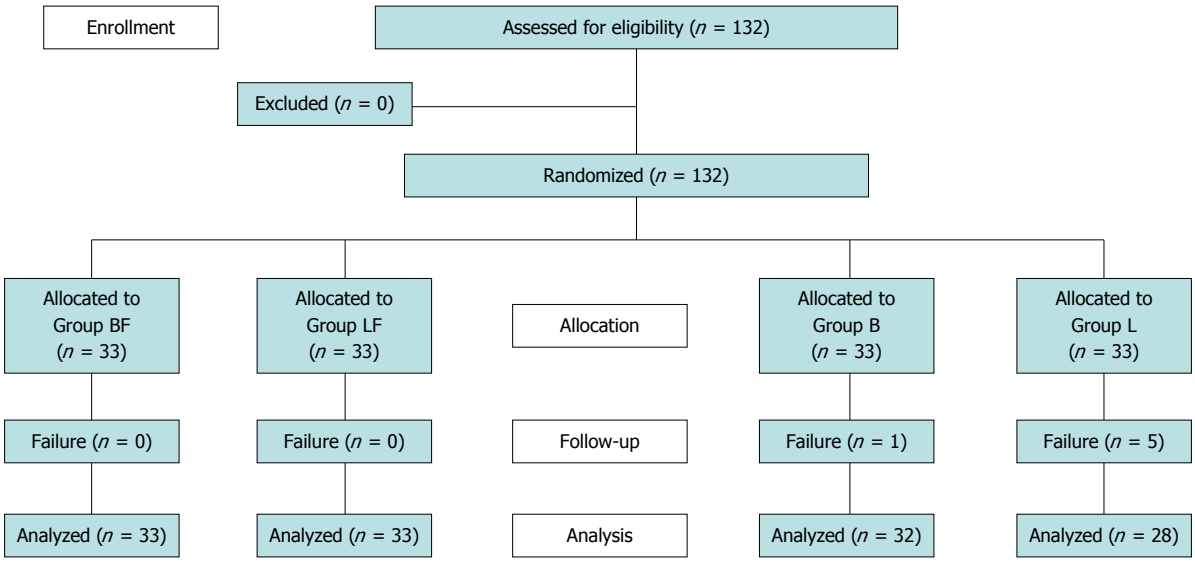

Figure 1 Flowchart. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

positioning was confirmed with the free flow of cerebrospinal fluid, and the anesthetic solutions were injected slowly without barbotage. The lateral decubitus position was maintained for 10 min from the start of the injection to provide selective spinal anesthesia. Afterwards, patients were turned to supine position, and surgery was started as soon as the analgesic level reached T12. In the case of insufficient anesthesia during the procedure, fentanyl (1 μg/kg), midazolam (0.05 mg/kg) or both in *iv* formulations were used. If the pain was not controlled with an *iv* bolus of fentanyl and/or midazolam, general anesthesia was administered. Three liters of oxygen per minute was given *via* nasal cannula until the end of the surgical procedure. The anesthesiologist who performed the spinal anesthesia and evaluated the quality of the block was blinded to the study solution received by each group.

The quality of anesthesia was assessed by testing for sensory and motor blockade. Sensory blockade was evaluated by pinprick on each side of the mid-clavicular line, and motor blockade was evaluated *via* the 4-point modified Bromage scale (0 = no motor block, 1 = inability to raise extended legs, 2 = inability to flex the knees and 3 = inability to flex the ankle joints). These tests were performed bilaterally every 3 min up to 15 min and then at 5 min intervals until the end of the operation. Postoperatively, these tests were done every 15 min until the sensory block regressed to the level of S2. The following lengths of time were recorded: achievement of a sensory block at the level of T12, maximum spread of the sensory block, highest dermatome level reached, regression to the level of S2, motor blockade levels, regression of the motor blockade, first analgesic requirement and discharge time. Postoperatively, patients who had a Visual Analog Scale (VAS) score ⩾ 4 were given 50 mg of *iv* dexketoprofen trometamol, and the time was recorded as the first analgesic requirement time. Home discharge criteria included stable vital signs, the absence of nausea or vomiting, minimal or no pain, the ability to tolerate liquids by mouth, and the ability to walk and void spontaneously. Complications such as hypotension, bradycardia, nausea, vomiting, shivering and pruritus were also noted.

Hypotension was defined as a decrease in systolic blood pressure > 30% from baseline and was initially treated with a rapid infusion of 250 mL of normal saline. In patients who did not respond to this treatment, 5 mg of *iv* ephedrine was given. Bradycardia was defined as a heart rate < 45 beat/min and was treated with 0.5 mg of *iv* atropine. Nausea and vomiting were treated with 10 mg of *iv* metoclopramide. Pruritus was assessed by a 4-point scale, where 0 = no pruritus, 1 = mild, 2 = moderate, 3 = severe pruritus. Moderate and severe pruritus was treated with *iv* naloxone. Shivering was treated by warming the skin surface. All patients underwent operations by the same experienced surgeon. The satisfaction of the patient and the surgeon regarding the anesthetic technique used was assessed with a 2-point scale, where 1 = satisfied (*i.e.*, "I will accept to undergo the same procedure if it is required in the future") and 2 = unsatisfied (*i.e.*, "I would prefer the use of a different anesthetic technique in future operations").

The quality of the spinal block was evaluated according to the need for additional *iv* analgesics and sedatives: adequate spinal block = neither sedatives nor analgesics were required to complete the surgery; inadequate spinal block = additional analgesia or sedation was required to complete the surgery (0.001 mg/kg bolus of *iv* fentanyl or 0.05 mg/kg bolus of *iv* midazolam); failed spinal block = general anesthesia was required to complete the surgery.

The day after surgery, the patients were contacted *via* telephone by a blinded research assistant and asked whether they had experienced headache, backache, or dysesthesia in the lower limbs or buttocks.

Table 1 Patient characteristics, duration of surgery and failed spinal blocks (*n* = 33)

Variables	Group BF	Group LF	Group B	Group L	*P* value
Gender (M/F)	16/17	13/20	12/21	14/19	0.779
Age (yr)	45 (11)	46 (12)	44 (12)	47 (11)	0.863
Height (cm)	165 (8)	168 (9)	165 (8)	165 (9)	0.664
Weight (kg)	79 (12)	77 (11)	76 (12)	80 (11)	0.253
ASA (Ⅰ/Ⅱ)	25/8	22/11	25/8	26/7	0.699
Duration of surgery (min)	50 (40-60)	60 (35-60)	50 (30-60)	55 (40-60)	0.621
Failed spinal block	0	0	1	5[a]	0.008[a]

Data are presented as the median (min-max), SD, or frequencies. [a]$P < 0.05$ compared with Group hyperbaric bupivacaine plus fentanyl (BF), Group hyperbaric levobupivacaine plus fentanyl (LF) and Group hyperbaric bupivacaine (B). L: Hyperbaric levobupivacaine; M: Male; F: Female; ASA: American Society of Anaesthesiologists.

Table 2 Quality of sensory and motor blocks and post-anesthesia care unit variables per group

Variables	Group BF (*n* = 33)	Group LF (*n* = 33)	Group B (*n* = 32)	Group L (*n* = 28)
Sensory block				
Onset to T12 (min)	6 (3-15)	6 (3-15)	6 (3-12)	7 (3-20)[e]
Highest level of sensory block (dermatome)	T8 (T12-T4)	T10 (T12-T4)	T10 (T12-T4)[a]	T10 (T12-T4)
Time to maximum sensory block (min)	15 (6-35)	12 (6-50)	13 (6-35)	20 (6-40)[c]
Sensory regression	192 ± 66	173 ± 53	179 ± 47	154 ± 50[a]
Motor block				
Time to maximum motor block (min)	9 (3-20)	12 (3-25)	9 (3-25)	12 (3-35)
Motor block regression (min)	115 (60-180)	75 (45-165)[a]	95 (40-150)	63 (35-120)[a,e]
Time to micturition (min)	196 ± 57	174 ± 54	164 ± 45	151 ± 52[a]
Time to VAS ⩾ 4	200 ± 60	156 ± 61[a]	162 ± 52[a]	110 ± 48[a,c,e]
Time to discharge	288 ± 64	260 ± 61	244 ± 54[a]	229 ± 55[a]

Data are presented as the median (min-max) or mean ± SD. [a]$P < 0.05$ compared with Group BF; [c]$P < 0.05$ compared with Group LF; [e]$P < 0.05$ compared with Group B. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine; VAS: Visual Analog Scale.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS 15.0; SPSS, Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was used to assess whether the data were normally distributed. Numerical results were expressed either as a mean ± SD or as a median and range, when appropriate. Nominal data were presented as frequencies. Categorical data in each study group were compared using a χ^2 test or Fisher's exact test. The numerical data were compared between study groups with the Kruskall-Wallis test, followed by the Mann-Whitney *U* test, the Bonferroni correction test, and a One-way ANOVA with the Tukey HSD test. In the case of hemodynamic changes within the study groups, repeated measures analysis of variance was performed. In general, a *P* value of < 0.05 was considered statistically significant. However, the significance level of $P < 0.008$ was determined using a Bonferroni correction for multiple comparison test.

Post-analysis power calculation reached 93%, $\alpha = 0.05$ (1-tailed), with the 33 patients included in Group BF and LF (mean times elapsed until discharge were "288 ± 64" and "260 ± 61", respectively), 32 patients included in Group B (mean time elapsed until discharge was "244 ± 54") and 28 patients included in Group L (mean time elapsed until discharge was "229 ± 55").

RESULTS

There was no statistically significant difference between the four study groups regarding demographic parameters, age, weight, height, sex, and ASA classification (Table 1). Spinal anesthesia was initially successfully performed in all patients. Six patients required conversion to general anesthesia due to an inadequate block level (one in Group B and five in Group L, $P < 0.05$) and were therefore excluded (Figure 1).

A significant difference was found among the study groups when comparing the lengths of time needed to reach the T12 dermatome level and to reach the maximum sensory level ($P = 0.020$, $P = 0.041$, respectively). Reaching the T12 dermatome level took significantly longer in Group L than in Group B ($P = 0.006$). The length of time needed to reach the maximum sensory blockade was significantly longer in Group L than in Group LF ($P = 0.008$). The maximum sensory level of the side undergoing the operation was higher in the Group BF compared to Group B ($P < 0.05$). The sensory block regressed to the level of S2 in a shorter amount of time in Group L than in Group BF ($P = 0.049$) (Table 2).

Although there was no statistical difference between the groups, the motor blockade was not observed in 3 patients from Groups LF and L and 1 patient from Group

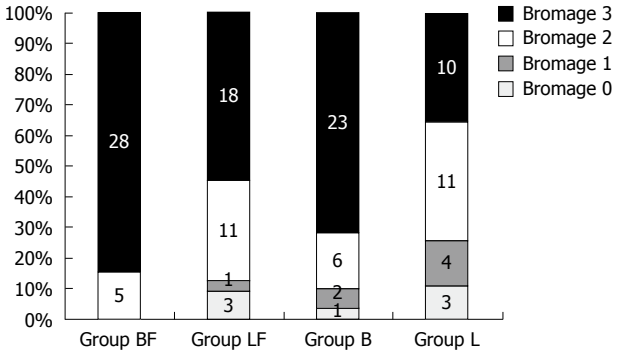

Figure 2 Maximal intensity of motor blockade expressed as a percentage of the population with definite motor block grade. 0 = No motor block; 1 = Inability to raise extended legs; 2 = Inability to flex knees; and 3: Inability to flex ankle joints. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

B. The intensity of the motor blockade was significantly higher in Group BF than in Groups LF and L and higher in Group B than in Group L ($P < 0.05$) (Figure 2). Complete recovery from the motor blockade occurred earlier in Groups LF and L than in Group BF and earlier in Group L than in Group B ($P < 0.05$) (Table 2).

A strictly unilateral sensory block (absence of detectable sensory block on the nonoperative side throughout the study period) was observed in 10 patients within Group BF (30%), 14 patients within Group LF (42%), 17 patients within Group B (53%) and 13 patients within Group L (46%) ($P = 0.30$). A strictly unilateral motor block (Bromage score = 0 on the nonoperative side throughout the study period) was observed in 20 patients within Group BF (60%), 24 patients within Group LF (72%), 23 patients within Group B (72%) and 23 patients within Group L (82%) ($P = 0.32$).

The time elapsed before micturition was significantly shorter in Group L than in Group BF ($P = 0.006$) (Table 2). Because of the inability to spontaneously void, four patients, one from each group, required urinary catheterization.

The time elapsed until VAS $\geq$ 4 was significantly longer in Group BF than in the other three groups and was significantly shorter in Group L than in Groups BF, LF, and B. There was no statistically significant difference between Groups LF and B (Table 2).

The time elapsed until the patient's discharge was significantly shorter in Groups B and L than in Group BF ($P = 0.021$, $P = 0.001$, respectively) (Table 2).

The quality of the block was significantly lower in Group L than in Groups BF, LF, and B ($P = 0.012$, $P = 0.003$, and $P < 0.001$, respectively). The requirement of additional sedation was greater in Group L than in the other groups. Patient satisfaction scores were significantly lower in Group L than on Groups BF and LF ($P = 0.039$). Surgeon satisfaction scores were significantly lower in Group L than in Groups BF, LF, and B ($P < 0.001$, $P < 0.001$, and $P = 0.024$, respectively) (Table 3).

Cardiovascular changes were unremarkable, and no statistically significant differences were found between the study groups regarding heart rate, mean arterial pressure, or hypotensive events. The occurrence of pruritus was significantly more frequent in patients receiving spinal fentanyl, and all cases resolved without treatment. Other side effects were not statistically different between the study groups (Table 4). None of the patients developed bradycardia or emesis in the postoperative period.

Table 3 Intraoperative and postoperative outcomes

Variables	Group BF (n = 33)	Group LF (n = 33)	Group B (n = 32)	Group L (n = 28)
Sedation	0	2	3	11[c]
Patient satisfaction (satisfied/unsatisfied)	33/0	33/0	28/4	24/4[a]
Surgeon satisfaction (satisfied/unsatisfied)	33/0	33/0	29/3	18/10[c]

Data shown are the mean ± SD, median (range) or count. [a]$P < 0.05$ compared with Group hyperbaric bupivacaine plus fentanyl (BF) and Group hyperbaric levobupivacaine plus fentanyl (LF); [c]$P < 0.05$ compared with Group BF, Group LF, and Group hyperbaric bupivacaine (B). L: Hyperbaric levobupivacaine.

Table 4 Frequency of adverse events n (%)

Adverse events	Group BF (n = 33)	Group LF (n = 33)	Group B (n = 32)	Group L (n = 28)	P value
Hypotension	2 (6)	2 (6)	0	0	0.289
Bradycardia	0	0	0	1 (4)	0.317
Emesis/vomiting	0	1 (3)	0	0	0.417
Shivering	6 (18)	5 (15)	7 (21)	6 (21)	0.894
Pruritus	11 (33)[a]	10 (30)[a]	0	1 (4)	< 0.001
Headache	4 (12)	7 (31)	6 (19)	4 (14)	0.754

[a]$P < 0.05$ compared with Group L and Group B. BF: Hyperbaric bupivacaine plus fentanyl; LF: Hyperbaric levobupivacaine plus fentanyl; B: Hyperbaric bupivacaine; L: Hyperbaric levobupivacaine.

DISCUSSION

Our results suggest that 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg fentanyl provided spinal anesthesia of equivalent quality for patients undergoing outpatient arthroscopic knee surgery with unilateral positioning. However, the quality of the block was significantly lower in the group receiving 5 mg of levobupivacaine, and the time elapsed until discharge was significantly longer in the group receiving 5 mg of bupivacaine plus 20 μg of fentanyl.

The positioning of the patient during spinal anesthesia affects the distribution of the drug in the subarachnoid space and therefore affects recovery and discharge[11]. Patients who had received unilateral spinal anesthesia were ready to be discharged on average 42 min earlier than patients who received bilateral anesthesia[4]. Hyperbaric local anesthetic solutions have been often preferred over hypobaric and isobaric solutions in studies regarding unilateral spinal anesthesia. Hyperbaric bupivacaine is commercially available, but hyperbaric levobupivacaine requires the addition of dextrose to a

commercially available plain solution[12]. In the present study, hyperbaric levobupivacaine was obtained by adding glucose to isobaric levobupivacaine to achieve a unilateral spinal block. A recent review article suggested that 4-5 mg of hyperbaric bupivacaine can provide effective spinal anesthesia for knee arthroscopy[4]. Therefore, we compared 5 mg of hyperbaric bupivacaine with 5 mg of hyperbaric levobupivacaine in our study.

There are several studies comparing the properties of sensory and motor blocks with hyperbaric bupivacaine and levobupivacaine. Luck *et al*[6] reported that spinal anesthesia with 15 mg of hyperbaric bupivacaine and 15 mg of levobupivacaine achieve similar sensory and motor block characteristics in patients undergoing elective surgery. A study conducted by Erdil *et al*[13] compared the effectiveness of 7.5 mg of plain levobupivacaine with bupivacaine plus 15 μg of fentanyl in elderly patients. It was emphasized that the peak sensory block level was found to be significantly higher for bupivacaine than for levobupivacaine and that the length of time needed to reach the T10 sensory level was significantly longer for levobupivacaine than for bupivacaine. The authors suggested that levobupivacaine may not be quite as potent as bupivacaine[13]. In our study, the peak sensory block level was found to be higher for bupivacaine plus fentanyl. Moreover, the length of time needed to reach the T12 sensory block level was longer when using 5 mg of hyperbaric levobupivacaine than when using bupivacaine. Cappelleri *et al*[3] reported that injecting 5 mg of 0.5% hyperbaric levobupivacaine unilaterally was sufficient for short-lasting spinal blocks in patients undergoing outpatient knee arthroscopy[3]. In their study, an inadequate spinal block was observed in one patient receiving 5 mg of hyperbaric levobupivacaine, and none of the spinal blocks failed. However, in our study, sedation was required in eleven patients receiving 5 mg of hyperbaric levobupivacaine, and five patient blocks failed. The length of time required for complete resolution of the sensory block and the time elapsed until the patient was ready to be discharged were slightly longer in the those receiving 5 mg of levobupivacaine in our study compared to the study described above. In our study, the use of 5 mg of hyperbaric levobupivacaine led to fewer motor blocks and a longer time needed to attain a sensory block at the level of T12. These findings could have led to the increased number of patients requiring sedation.

Camorcia *et al*[14] found that spinal levobupivacaine was 29% less potent than bupivacaine in producing motor blocks. In our study, motor block quality and motor block regression time were found to be lower in the levobupivacaine groups than in the bupivacaine groups. Dobrydnjov *et al*[15] studied a restricted spinal block using 6 mg of hyperbaric bupivacaine with or without clonidine for inguinal hernia repairs. In their study, the authors reported a strictly unilateral spinal block in 47% of the patients. Cappelleri *et al*[3] reported a strictly unilateral motor block in 83% of patients who had received 5 mg of hyperbaric levobupivacaine. In our study, there were similar rates of strictly unilateral sensory and motor blocks to these studies.

The use of low dose local anesthetics while limiting the dose of the spinal block may result in an inadequate sensory block. For this reason, the addition of opioids to the local anesthetics can enhance the analgesia and prolong the sensory block without affecting the motor block[16]. Ben-David *et al*[17] demonstrated that the use of a diluted, low-dose bupivacaine is insufficient to provide spinal anesthesia, but the addition of 10 μg of fentanyl provides reliable anesthesia. We observed inadequate sensory and motor blocks in the group receiving 5 mg of hyperbaric levobupivacaine. However, our findings suggest that the quality of sensory and motor blocks is better when using 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl than when using 5 mg hyperbaric levobupivacaine alone.

Casati *et al*[18] reported that the unilateral technique with 8 mg of hyperbaric bupivacaine and 8 mg of hyperbaric levobupivacaine provided adequate spinal blocks for hernia repair procedures. Motor recovery was significantly faster after levobupivacaine, whereas the time elapsed until patient discharge was similar with both agents. Cappelleri *et al*[3] reported that the length of time required for the spinal block resolution and the time elapsed before discharge were shorter with 5 mg of levobupivacaine than with 7.5 mg of levobupivacaine. Although the time elapsed until the patient was discharged was slightly longer in the levobupivacaine group in our study compared to the study by Cappelleri *et al*[3], our results are not substantially clinically different.

Pruritus is a common complication arising from the use of intrathecal fentanyl[17]. Itching arises in 30%-33% of patients receiving 20 μg of fentanyl, and they recover without any treatment. The incidence of side effects such as hypotension and bradycardia is lower with unilateral spinal anesthesia than with conventional bilateral spinal anesthesia[4]. In our study, hemodynamic parameters were within safe ranges during the intraoperative and postoperative periods, and these side effects were observed in less than 4%-6% of the patients. We believe that these side effects are due to the low-dose intrathecal drug and the unilateral spinal block.

A common side effect of spinal anesthesia is urinary retention, which could be due to the fluid therapy used in the treatment of spinal anesthesia-induced hypotension or bilateral blockade of the parasympathetic plexus, which innervates the detrusor muscle. However, urinary retention occurs rarely in unilateral spinal blocks, since hemodynamic stability is better maintained and the function of the detrusor muscle has not been totally blocked[19]. Casati *et al*[18] reported no urinary retention after unilateral spinal anesthesia for inguinal herniorrhaphy. In our study, one patient in each study group complained of urinary retention, and they resumed spontaneous micturition after one catheterization. Moreover, it has been reported that dose-dependent spinal opioids influence bladder function and may cause urinary retention[19,20]. Liu

et al[2] reported that a 20 μg dose of fentanyl did not delay the ability to void. We also found no influence of the use of 20 μg of fentanyl in delaying the return of bladder function.

The main drawback associated with levobupivacaine is that the hyperbaric formulation is not available on the market. Diluting the hyperbaric formulation with dextrose for spinal anesthesia has a potential risk for infection. Furthermore, densities of solutions transformed into hyperbaric formulations can be different from the intended hyperbaric formulation. The density of the anesthetic solutions and the position of the patient are the most important factors affecting the intrathecal spread of the drug[4,12]. A limitation in our study is the fact that the density of levobupivacaine was not measured. However, in a laboratory investigation, McLeod showed that the density of levobupivacaine increases linearly with the addition of 8% dextrose[21].

In conclusion, both 5 mg of hyperbaric bupivacaine and 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl provided adequate and reliable anesthesia for arthroscopic knee surgery in the ambulatory setting. Both solutions provided a high level of patient and surgeon satisfaction without affecting the time elapsed until patient discharge, compared to 5 mg of hyperbaric bupivacaine plus 20 μg of fentanyl. In our opinion, 5 mg of hyperbaric levobupivacaine does not provide sufficient anesthesia for unilateral arthroscopic knee surgery.

COMMENTS

Background

Arthroscopic knee surgery is one of the most frequently performed ambulatory orthopedic surgeries. Spinal anesthesia is often preferred for lower extremity surgery in the ambulatory setting. For decades, lidocaine was the local anesthetic of choice for spinal anesthesia in ambulatory surgeries. However, its use is limited due to the risk of a transient neurological syndrome and neurotoxicity. Therefore, lower doses of long-acting local anesthetics have been used in outpatient surgeries. The comparison of low-dose hyperbaric bupivacaine to levobupivacaine with respect to the quality of the block and the time elapsed until discharge in outpatient knee arthroscopy procedures has not been investigated in the literature.

Innovations and breakthroughs

There are several studies comparing the properties of sensory and motor blockade in hyperbaric bupivacaine and levobupivacaine. This is the first study to compare hyperbaric bupivacaine with hyperbaric levobupivacaine in arthroscopic knee surgeries in the ambulatory setting. In this study, the dose and concentration of levobupivacaine used resulted in an inadequate block and higher sedation requirement for a greater number of patients compared to studies using hyperbaric levobupivacaine.

Applications

The study results suggested that, in knee surgeries in the ambulatory setting, 5 mg of hyperbaric bupivacaine provides a better spinal anesthesia than 5 mg of hyperbaric levobupivacaine. Equivalent spinal anesthesia, postoperative analgesia and recovery were attained with 5 mg of hyperbaric levobupivacaine plus 20 μg of fentanyl without creating any adverse hemodynamic effects.

Terminology

Ambulatory surgery: Ambulatory surgery, also known as outpatient surgery, is surgery that does not require an overnight hospital stay. Unilateral spinal anesthesia: Unilateral spinal anesthesia consists of positioning the patient on the side that will undergo the operation for 10-15 min after the administration of the spinal anesthetic. Hyperbaric local anesthetic: Hyperbaric solutions are typically prepared by mixing the local anesthetic with 5% to 8% dextrose.

Peer review

The methodology of the investigation is sound and can support the outcome.

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CASE REPORT

Suspected cerebral arterial gas embolism during a laparoscopic Nissen fundoplication

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Abstract

We present the first case report known to us of a suspected cerebral arterial gas embolism (CAGE) leading to transient left-sided hemiparesis after a laparoscopic Nissen fundoplication. During the operation there was no evidence of hemodynamic compromise and the end-tidal carbon dioxide level and oxygen saturation had been within normal limits. Radiological studies and transesophageal echocardiography showed no abnormalities. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts.

Key words: Paradoxical gas embolism; Arterial embolism; Laparoscopic Nissen fundoplication; Neurologic deficit; Laparoscopic surgery

Core tip: We present the first case report known to us of a suspected cerebral arterial gas embolism (CAGE) leading to transient left-sided hemiparesis after a laparoscopic Nissen fundoplication. During the operation there was no evidence of hemodynamic compromise and the end-tidal carbon dioxide level and oxygen saturation had been within normal limits. Radiological studies and transesophageal echocardiography showed no abnormalities. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts.

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INTRODUCTION

Carbon dioxide (CO_2) embolism is a well-recognized complication during laparoscopic procedures utilizing CO_2 insufflation for the establishment of a pneumoperitoneum[1]. The clinical presentation of CO_2 embolism ranges from a complete lack of symptoms to neurologic injury, cardiovascular collapse or even death depending on the rate and volume of gas entrapment[2]. CO_2 embolism can be fatal, yet the incidence during laparoscopic surgeries is varied. The true incidence is difficult to determine secondary to subclinical cases and the sensitivity of the detection of gas embolism by available monitors during procedures. Hong *et al*[3] report that the incidence of subclinical embolisms in laparoscopic radical prostatectomies is 17%. Usually, venous embolism manifests in the first few minutes after the start of the gas insufflation during initial establishment of a pneumoperitoneum and it is due to inadvertent venous cannulation with a Veress needle or gas absorption through open venous channels. However, in many cases no noticeable hemodynamic changes are noted since the pulmonary circuit may filter

or reabsorb the small bubbles of CO_2 without causing any embolic obstruction[4]. Conversely, in the presence of intracardiac shunts, such as a patent foramen ovale or septal defect, the CO_2 embolus can reach the left side of the circulation resulting in varied degrees of neurologic or vascular deficits depending on the location where the embolus lodges[5]. Such paradoxical CO_2 embolisms are extremely rare events, especially in the absence of intracardiac shunts. Nevertheless, they could have disastrous consequences.

Herein, we present the first case known to us of a suspected cerebral arterial gas embolism (CAGE) in the absence of intracardiac shunts that led to a transient left-sided hemiparesis after an uncomplicated laparoscopic Nissen fundoplication.

CASE REPORT

A 22-year-old woman with gastroesophageal reflux disease unresponsive to maximal medical management and who failed lifestyle modifications was scheduled for a laparoscopic Nissen fundoplication. The patient also had a past medical history of Hashimoto's thyroiditis and Crohn's disease treated medically. Her past surgical history included two laparoscopic procedures: a bilateral ovarian cystectomy and a cholecystectomy, which had been uneventful. Four months prior to the laparoscopic Nissen fundoplication she had given birth to a healthy boy *via* a normal vaginal delivery.

The patient was brought to the operating room and standard American Society of Anesthesiologists noninvasive monitors (electrocardiogram, noninvasive blood pressure monitoring, oxygen saturation, capnograph, and temperature) were placed. After preoxygenation, the patient underwent a rapid sequence induction with propofol (200 mg) and succinycholine (100 mg) and the trachea was intubated. General anesthesia was maintained with air, oxygen, and sevoflurane. The patient was positioned with a beanbag on the operative table with both lower extremities placed in stirrups. Mechanical ventilation was adjusted to maintain the end-tidal CO_2 between 30-40 mmHg. The patient's abdomen was then prepped and draped. The Veress needle was inserted, a water drop test was performed, and the abdomen was insufflated at the rate of 3 L/min. The intra-abdominal pressure was built up to 18 mmHg according to recommendations set forth by Bhoyrul *et al*[6]. The introducer of the trocar was then removed and the laparoscope was reinserted into the abdominal cavity to inspect the entry area, ensuring that no intra-abdominal injuries were made upon entering the abdominal cavity. The patient was then placed in a sitting position to improve surgical exposure of the hiatus for the operation and the CO_2 insufflation pressure was decreased to 14 mmHg. The surgical and anesthetic course was uneventful. There were no episodes of sudden hypotension, bradycardia, arrhythmia, oxygen desaturation, or decrease in end-tidal CO_2 during the operation. The trachea was extubated without difficulty with the patient awake. In the recovery room, the nursing staff noticed the patient had a left eye ptosis and a left hemiparesis. A thorough neurologic assessment by a senior neurosurgeon in the recovery room demonstrated that the patient could not move her left upper arm and that she had 1/5 strength in her left lower extremity. Preoperatively, the motor strength in all extremities was 5/5. Deep tendon reflexes on the right were 2+ and were absent on the left side of the body. In addition to a diagnosis of possible CO_2 arterial embolism, our evaluation of this patient involved the differential diagnoses of a coagulopathy, intracardiac thrombus with subsequent embolus, cerebral vascular disease, and a hemorrhagic cerebral vascular event. A computed tomography (CT) scan was obtained within 1 h and showed no evidence of a stroke. The stroke team was informed and the patient was transferred by ambulance from the Veterans Administration Hospital to the University hospital in the immediate vicinity (one block away) for definitive care. Upon arrival to the emergency room (ER) of the University hospital, the patient was examined by the same surgical team who performed the laparoscopic procedure, by members of the stroke team, and by the ER attending physician. At this time, the patient had recovered the use of her left upper extremity to gain 3/5 strength and she had also improved her left lower extremity strength to 4/5. Motor strength on the right was unchanged at 5/5 and deep tendon reflexes on the right were 2+. Reflexes on the left side, which were initially absent, were found to be 1+.

A CT angiogram of the intracranial circulation failed to show any significant narrowing or obstruction to cerebral flow. Similarly, a hypercoagulable evaluation failed to show any hypercoagulable disorder. Finally, transesophageal echocardiography did not show any evidence of gas in any of the cardiac chambers or any demonstrable intracardiac shunt on color-flow Doppler imaging. The patient was admitted to the Neurological intensive care unit for monitoring and over a period 24 h she had complete resolution of her neurologic symptoms. She underwent a magnetic resonance imaging (MRI) on postoperative day two which was normal. Supportive treatment with postoperative pain control and fluid management were continued for the entire duration of the patient's hospital stay.

The patient was discharged on the third postoperative day with no residual weakness or deficits, tolerating a clear liquid diet without heartburn, regurgitation, or dysphagia. She was examined postoperatively at 2 wk and 2-mo follow-up in the Surgery and Neurology outpatient clinics. She continued to show no neurologic deficits. The patient has given written consent and has agreed to publication of this case report.

DISCUSSION

CAGE is an exceptionally rare event during laparoscopic surgery. The clinical presentation of CO_2 embolism varies with respect to the rate of entry of the gas and the size of the embolus, which can increase with the use of

nitrous oxide[7]. CO_2 embolus can result in "gas lock" with obstruction to right ventricular outflow, ventilation and perfusion mismatch, cardiac arrhythmias, pulmonary hypertension, and cardiovascular collapse. The diagnosis of a CO_2 embolism can be revealed by the auscultation of a millwheel murmur with a precordial or esophageal stethoscope, decrease in end-tidal CO_2 noted with capnography, increased end-tidal nitrogen, decrease in oxygen saturation by pulse oximetry, electrocardiographic changes, Doppler ultrasonography, transesophageal Doppler, and transesophageal echocardiography[8]. In addition to cardiopulmonary and neurological symptoms seen with CO_2 embolus, patients with CAGE may also experience seizures, headaches, dizziness, and visual field defects.

Radiologic evaluation is not always conclusive in the diagnosis of CAGE. CT scans can distinguish CAGEs from cerebral infarcts or hemorrhages; however, the distinction may be elusive[9]. MRI may show injured tissue with a fluid collection; yet, again, this is not reliable especially if the patient has mild symptoms[10].

The treatment of CAGE is similar to the treatment of a CO_2 embolus. However, the treatment of a patient with CAGE may include the transfer to a hyperbaric oxygen chamber if the patient is stable; placing the patient in the supine position; anticonvulsant medications; and lidocaine[11]. Furthermore, distinct from the treatment of venous gas embolism in which the patients are placed in the Trendelenburg and left lateral decubitus position, patients with CAGE should be placed in the supine position to avoid gas bubbles flowing toward the head and to prevent cerebral edema[12]. However, under general anesthesia with stable cardiopulmonary signs, small cerebral arterial emboli may go undetected until neurological signs are apparent after the emergence from anesthesia, as we encountered in this patient.

The exact cause of CAGE in this case remains unknown. The rapid elimination of CO_2 due to the high solubility of CO_2 in blood as well as a reduction in CO_2 insufflation pressures contributed to the transient nature of this patient's symptoms and the elusiveness of medical studies. The blood/gas solubility of CO_2, nitrous oxide, dissolved oxygen, and nitrogen are 0.60, 0.45, 0.024, and 0.013 mL/mL solvent with 100% gas at 17 degrees Celsius respectively. Furthermore, since the blood solubility of nitrous oxide and CO_2 are similar, discontinuing nitrous oxide will not reduce the size of a CO_2 embolus as it would an air embolus[13].

Intraoperatively, a more urgent intraoperative transesophageal echocardiogram would have been indicated in the setting of hemodynamic compromise[14]. Such a hemodynamic collapse did not occur in this patient perhaps because, as shown by Huang *et al*[15], the gas was released in time without formation of a fatal pulmonary gas lock. Although during the operation we had no evidence of bleeding or vascular injury due to the placement of the Veress needle, we postulate that the initial intra-abdominal pressure of 18 mmHg might have been high enough for the CO_2 to enter and bypass the pulmonary circuit and that, at the same time, was kept brief enough to avoid a pulmonary gas lock. In fact, Eiriksson *et al*[16] demonstrated that high intra-abdominal pressures (16 mmHg) during experimental laparoscopic liver resection in swine reduced bleeding but increased the risk of gas embolism.

Paradoxical embolisms have been demonstrated in patients without intracardiac defects. Bedell *et al*[17] presented a case of a patient in the sitting position undergoing occipital artery to posterior inferior cerebellar artery bypass who developed paradoxical gas embolism in the absence of any intracardiac defect. Bedell *et al*[17] demonstrated transesophageal echocardiographic evidence for the transpulmonary passage of gas from the right to the left side of the circulation. The event confirmed the validity of a 50-year-old theory that attributed a precise pathogenic role to arteriovenous connections, called "*sperrarteries*", within the pulmonary vasculature. According to this theory, the *sperrarteries* bypassed the pulmonary parenchyma and were thought to serve as rapid conduits for absorbed venous air to travel to the arterial side of the circulation[18].

In conclusion, we report, to our knowledge, the first case of suspected CAGE occurring during a laparoscopic Nissen fundoplication causing transient neurologic symptoms. We conclude that CAGE can occur during uncomplicated laparoscopic surgery even in the absence of demonstrable intracardiac shunts and that such an event might be prevented by keeping the CO_2 insufflation pressure set at 15 mmHg with a slow flow rate during the creation of the pneumoperitoneum[19].

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CASE REPORT

Fractured tracheostomy tube obturator: A rare cause of respiratory distress in a tracheostomized patient

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Abstract

Foreign body aspiration is a worldwide health problem which often results in life threatening complications. Tracheostomy tube fracture resulting in airway obstruction is a serious condition which has been reported in the medical literature. We report a rare case of a tracheostomy obturator fractured and lodged in tracheobronchial tree in a patient who presented with acute respiratory distress. Rigid or flexible bronchoscopy is frequently necessary for the diagnosis as well as the treatment. In adults, removal of the foreign body can be attempted during a diagnostic examination with a fiberoptic bronchoscope under lignocaine local infiltration with sedation, which may help to avoid any further invasive procedures. Flexible bronchoscopy should always be considered in foreign body aspiration. A periodic review of the techniques of tracheostomy care, including timely check-ups for signs of wear and tear, can possibly eliminate such avoidable late complications.

Key words: Respiratory distress; Tracheostomy; Foreign body; Aspiration; Bronchoscopy

Core tip: Foreign body aspiration is often a serious medical condition that demands timely recognition and prompt action. Delayed diagnosis and subsequent delayed treatment is associated with serious and sometimes life threatening complications. We describe a case of acute respiratory distress following aspiration of part of the obturator of a tracheostomy tube during a routine change of the tracheostomy tube.

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INTRODUCTION

Foreign body aspiration is often a serious medical condition that demands timely recognition and prompt action. Delayed diagnosis and subsequent delayed treatment is associated with serious and sometimes fatal complications[1]. In adults, however, foreign body aspiration can be tolerated and remain undetected for a long time. We describe a case in which part of the tracheostomy obturator was broken and migrated into the tracheobronchial tree, resulting in acute respiratory distress.

CASE REPORT

A tracheostomized 68-year-old male known to have hypertension and diabetes presented at our emergency room with progressive acute respiratory distress. During a routine change of the tracheostomy tube, medical staff noticed that the tracheostomy obturator was fractured and had migrated into the trachea. The bronchoscopic removal in a referral hospital was unsuccessful. Therefore, the patient was referred to our hospital for further management. Past medical history revealed that the patient had had a cardiac arrest 3 mo earlier due to myocardial ischemia and was successfully resuscitated. After

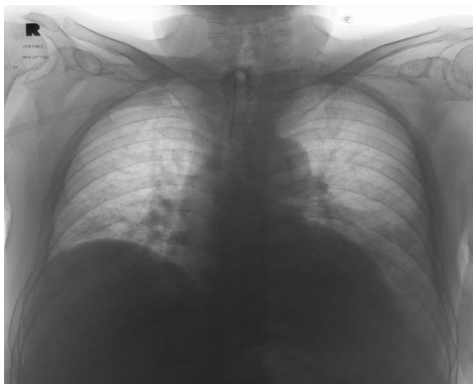

Figure 1 The prominent broncho-pulmonary markings without a radio-opaque foreign body in the right lung.

prolonged cardiopulmonary resuscitation, the patient remained on a ventilator for 3 wk. Thus, the tracheostomy was done after the few unsuccessful attempts of weaning from the ventilator. Pre anesthesia evaluation revealed electrocardiography (ECG) showing periodical supra ventricular tachycardia with antero-lateral ischemic changes, whereas the echocardiography showed a moderately dilated left ventricle with severely impaired systolic function, with an ejection fraction of 10%-25%.

His computed tomography of the brain showed an old infarct and microangiopathic ischemic change. His respiratory rate was 35/minute, O_2 saturation 88%-89% and blood pressure 90/50 mmHg. He was conscious and oriented but both his upper and lower limbs were spastic. Auscultation of the chest revealed decreased breath sounds on the right side. A subsequent X-ray of the chest did not show any foreign body (Figure 1). He was immediately taken to the operating room.

After putting on ECG leads, pulse oximeter, oxygen through a face mask and noninvasive blood pressure measurement, Xylocaine 2% was infiltrated into the trachea through the tracheostomy tube. About 1 mg of Midazolam was given intravenously and 15 mL/h propofol infusion was commenced.

The fiberoptic bronchoscopy revealed a fractured part of the obturator deeply lodged in the right bronchus (Figure 2A). After suction of secretions, the obturator was removed with endoscopic forceps and it was pulled out from the tracheostomy tube with artery forceps (Figure 2B). After the uneventful procedure, the patient was sent to the recovery room. Two days later, the patient was referred back to the primary hospital for long term management.

DISCUSSION

The first case of a fractured, metallic tracheostomy tube was reported by Bassoe *et al*[2] in 1960. Since then, this kind of a complication has been published in the medical literature frequently, with all kinds of tracheostomy tubes (TT). The composition of TTs range from metal, poly vinyl chloride to silicone[3]. A number of factors predispose fracture of one of the flanges of the TT. The most frequent weak points of TT are the junctions between

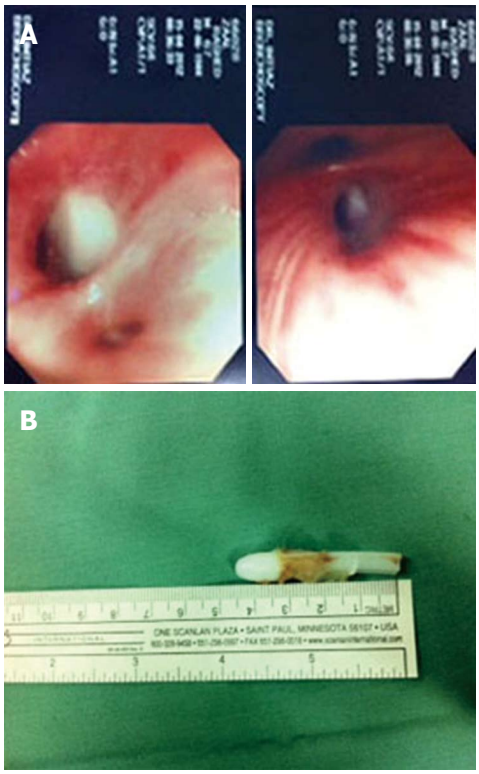

Figure 2 Bronchoscopic view showing the tracheostomy tube obturator lodged in the right main stem bronchus (A) and a tracheostomy obturator after removal from the right main bronchus (B). The length of the broken obturator measures 4.5 cm.

the tube and the neck plate, the distal end of the tube and the fenestration site[4,5]. In our case, it was not the TT but part of the obturator (introducer) which fractured and migrated to the distal trachea and was noticed during a routine change of tracheostomy tube by the staff.

Foreign body aspiration can be a life-threatening emergency. An aspirated solid or semisolid object may lodge in the larynx or trachea. If the object is large enough to cause nearly complete obstruction of the airway, asphyxia may rapidly lead to death[6].

Tracheobronchial foreign body (TFB) aspiration is rare in adults, although the incidence rate rises with advancing age. Risk factors for TFB aspiration in adults are a depressed mental status or impairment in the swallowing reflex[5]. Symptoms associated with TFB aspiration may range from cough, dyspnea, fever and acute asphyxiation with or without complete airway obstruction. In adults, many other medical conditions mimic breathing abnormalities similar to those associated with TFB aspiration. In our case, there was a definitive history of a missing part of the obturator during a change of the TT.

If the history is not suggestive, then only a high index of suspicion can ensure proper diagnosis and timely removal of the foreign body[6]. Initial treatment is airway management. Radiographic imaging may assist in localizing the foreign body. Bronchoscopic removal of the foreign body is necessary to avoid long-term sequelae. Flexible bronchoscopy is effective both in the diagnosis and removal of foreign bodies[7].

Almost all aspirated foreign bodies can be extracted bronchoscopically. If rigid or flexible bronchoscopy is unsuccessful, surgical bronchotomy or segmental resection may be necessary. Chronic bronchial obstruction with bronchiectasis and destruction of lung parenchyma may require segmental or lobar resection.

A pulmonologist or thoracic surgeon with experience in foreign body extraction should immediately perform bronchoscopic inspection and extraction of the object[8].

An anesthesiologist may be needed to maintain adequate ventilation and control of the upper airway during diagnostic and therapeutic procedures. Rigid bronchoscopy is performed with the patient under general anesthesia or heavy sedation[8].

As foreign bodies in the TBT are uncommon in adults, the clinician must be vigilant regarding their possibility. Foreign body aspiration should be considered especially in the etiology of recurrent lung diseases and in the presence of risk factors for aspiration, in particular with different neurological and neuromuscular diseases. They can be safely and successfully removed in the majority of patients by using fiberoptic bronchoscopy under local anesthesia alone or under local anesthesia with sedation. An endotracheal intubation is recommended in cases of a repeated procedure.

An intermittent review of the techniques of tracheostomy care should be done, including timely check-ups for signs of wear and tear which can possibly eliminate such avoidable late complications[9].

Since there are no universally accepted and published standards of care for a tracheostomy tube, the policy should be to provide patients who require an indwelling tracheostomy tube with the following recommendations for home care: (1) Replace the tracheostomy tube every 6 mo; (2) Change/clean the inner cannula every 48 h; (3) Replace the tracheostomy ties weekly; (4) Change the dressing daily; and (5) Use nocturnal humidification[10].

In conclusion, cases of tracheostomy tube fractures and aspiration into TBT have been reported in the literature. We, hereby, report a rare case of the TT obturator that had fractured and migrated to the right main stem bronchus. Proper care and high vigilance when the obturator is removed during suction and cleaning of the TT is of high clinical importance.

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