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EDITORIAL

Adjuvants to local anesthetics: Current understanding and future trends

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Abstract

Although beneficial in acute and chronic pain management, the use of local anaesthetics is limited by its duration of action and the dose dependent adverse effects on the cardiac and central nervous system. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action. A large array of opioids ranging from morphine, fentanyl and sufentanyl to hydromorphone, buprenorphine and tramadol has been used with varying success. However, their use has been limited by their adverse effect like respiratory depression, nausea, vomiting and pruritus, especially with its neuraxial use. Epinephrine potentiates the local anesthetics by its antinociceptive properties mediated by alpha-2 adrenoreceptor activation along with its vasoconstrictive properties limiting the systemic absorption of local anesthetics. Alpha 2 adrenoreceptor antagonists like clonidine and dexmedetomidine are one of the most widely used class of local anesthetic adjuvants. Other drugs like steroids (dexamethasone), anti-inflammatory agents (parecoxib and lornoxicam), midazolam, ketamine, magnesium sulfate and neostigmine have also been used with mixed success. The concern regarding the safety profile of these adjuvants is due to its potential neurotoxicity and neurological complications which necessitate further research in this direction. Current research is directed towards a search for agents and techniques which would prolong local anaesthetic action without its deleterious effects. This includes novel approaches like use of charged molecules to produce local anaesthetic action (tonicaine and n butyl tetracaine), new age delivery mechanisms for prolonged bioavailability (liposomal, microspheres and cyclodextrin systems) and further studies with other drugs (adenosine, neuromuscular blockers, dextrans).

Key words: Local anesthetics; Adjuvants; Neurotoxicity; Opioids; Ketamine; Midazolam; Alpha-2 adrenoreceptor antagonists

Core tip: The use of local anaesthetics in acute and chronic pain is limited by its duration of action and the dose dependent adverse effects. Adjuvants or additives are often used with local anaesthetics for its synergistic effect by prolonging the duration of sensory-motor block and limiting its cumulative dose requirement. Various drugs like opioids, epinephrine, alpha-2 adrenergic antagonists, steroids, anti-inflammatory drugs, midazolam, ketamine, magnesium sulfate and neostigmine have been used to potentiate the effect of local anesthetics. Due its potential adverse effects, current research is exploring newer drugs and delivery mechanisms to prolong the duration of action of local anesthetics.

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INTRODUCTION

From time immemorial, alleviation of acute and chronic pain has continued to perplex medical professionals. The early success of pharmacologic endeavors in pain mitigation involved extensive use of opioids. Although reasonably successful, it was often associated with systemic complications like nausea, vomiting, respiratory depression, sedation, delayed recovery of bowel functions and hyperalgesia. In an effort to reduce the need and adverse effects of systemic opioids, the perineural (intrathecal, epidural or peripheral nerve blocks) use of local anesthetics have gradually evolved over time.

Although beneficial in acute and chronic pain management, local anaesthetics do have the potential to produce deleterious effects like cardiac arrhythmias, central nervous system depression, seizures, respiratory depression, hypertension and allergic reactions[1-4]. By prolonging the duration of sensory-motor block and limiting the cumulative dose requirement of local anaesthetics, co-administration of adjuvants has the potential to improve efficacy of perineural blocks and decrease local anaesthetic toxicity. The terms, local anaesthetic "adjuvants" or "additives", have often been used interchangeably. They contribute in their own special manner to potentiate the analgesic effect of the local anaesthetics[5]. The armamentarium of local anesthetic adjuvants have evolved over time from classical opioids to a wide array of drugs spanning several groups and varying mechanisms of action.

The aim of this editorial is to have a comprehensive look at the various local anesthetic adjuvants which have been studied till date, ascertain the evidence for their safety and efficacy in perineural use, discuss various novel approaches in local anesthetic usage and highlight the present lacuna in knowledge for directing future research on the subject.

DISCUSSION

Opioid

Opioids are the most frequently used local anesthetic adjuvants and their use in neuraxial blocks have evolved over the last 50 years[6]. The opioids potentiate antinociception of local anesthetics by G protein coupled receptor mechanisms by causing hyperpolarisation of the afferent sensory neurons[7]. The dose, site of injection, lipophilicity and the acid-base milieu of the site of drug deposition determine the extent of efficacy of the block[8,9].

Morphine: Use of preservative free morphine with or without local anesthetics has been used extensively in neuraxial blocks across all age groups[10,11]. Intrathecal Morphine in the dose range of 100-200 μg has exhibited good analgesic efficacy, especially in obstetric and orthopedic subsets[12,13]. Similarly epidural morphine has also been used over a wide dose range (1-5 mg) and has exhibited efficacy in diverse population subsets[14-17]. The hydrophilic nature of neuraxial Morphine results in cephalad spread, thereby increasing the area of analgesia. However the adverse effect of its use in neuraxial blocks includes respiratory depression (early and late), nausea, vomiting, pruritus and urinary retention. Specifically, there is evidence to suggest that intrathecal morphine administration of doses lower than 100 μg results in lesser adverse effects in elderly patients[13]. The use of Morphine in peripheral nerve blocks is presently not recommended as studies have failed to show any advantage over intravenous (Ⅳ) and intramuscular (IM) routes. Their adverse effects persist irrespective of the route of administration[18-22].

Fentanyl: Intrathecal fentanyl in the dose range of 10-25 μg has also been shown to prolong the duration and extent of sensory block with a favorable adverse effect profile in comparison to morphine[23-25]. However, epidural fentanyl does not necessarily follow the same pattern and a higher incidence of adverse effects have been observed with its use[26]. The addition of epinephrine 2 μg/mL to neuraxial local anesthetic-fentanyl mixtures has also been investigated. However, it was demonstrated that thoracic neuraxial instillation resulted in lesser nausea but its lumbar neuraxial administration didn't reduce any opioid related adverse effects[27-29]. Numerous studies have however failed

to conclusively prove the efficacy of fentanyl as an adjuvant in peripheral nerve blocks[30-35].

Sufentanyl: Intrathecal sufentanyl in the dose of 5 μg as an adjuvant to local anesthetics has shown good efficacy, however, for lesser adverse effects, the dose range needs to be lower (around 1.5 μg)[36,37]. The epidural dose of sufentanyl is 0.75-1 μg/mL and has been shown to be strikingly effective in ameliorating pain in various patient subsets[38-40].

Other opioids: Hydromorphone and Buprenorphine: Hydromorphone has been shown be an efficacious adjuvant in both intrathecal and epidural routes at the dosages of 100 μg and 500-600 μg respectively[41,42]. It is preferred in patients with renal insufficiency and had a better adverse effect profile when compared to morphine[43,44].

Buprenorphine has also been used in intrathecal (75-150 μg) and epidural routes (150-300 μg) with reasonable efficacy[5,45]. Additionally, it has also shown good efficacy when used in a dose of 0.3 mg as an adjuvant to peripheral nerve blocks[46-48].

Tramadol: Tramadol is a weak opioid agonist having sodium and potassium channel blocking actions as well as ancillary actions such as blockage of uptake of norepinephrine and serotonin[49-51]. Intrathecal tramadol in doses ranging from 10-50 mg has been in used different subsets with varying success[52-57].

Epidural tramadol in doses of 1-2 mg/kg presented itself as an attractive alternative to morphine for postoperative analgesia without any respiratory depressant effect[58]. Epidural tramadol has given good results for amelioration of pain in various patient subsets ranging from obstetric patients and abdominal surgeries to pediatric patients for lower abdominal procedures[59-63].

The incidence of nausea and vomiting remains a concern. However, incidence was less with lower doses. Other adverse effects like itching and sedation are less frequent[58,62]. Tramadol when used as an adjuvant in peripheral nerve blocks has shown conflicting and contradictory results with an unknown safety profile[64-67]. A couple of studies have shown Tramadol to increase the analgesic efficacy[64,66]. However, there have been other studies which have shown limited or no benefit of Tramadol when used as an adjuvant to local anesthetics for peripheral nerve blocks[65,68-72]. Hence, except for postoperative epidural infusions, present day anesthesia practice does not recommend routine use of Tramadol as a local anesthetic adjuvant.

Adverse effects of neuraxial opioids: The troublesome adverse effects of neuraxial opioids include pruritus, nausea, vomiting and respiratory failure, especially in elderly patients. This has prompted studies to determine the upper safe limit of administration of these drugs. The effects are more profound when the drug is deposited in the intrathecal space resulting in recommendations to reduce intrathecal dosage to avoid respiratory depression[73]. The pruritus produced by neuraxial opioids is dose dependent and responds well to Naloxone 200 μg and Ondansetron 4-8 mg[24,37,74].

Epinephrine

Epinephrine is one of the oldest additives to local anesthetic solutions with a recommended dosing of 0.5-1.0 μg/kg in a concentration of 5-10 μg/mL[75,76]. In addition to its vasoconstrictive actions, it also seems to have intrinsic antinociceptive properties mediated by alpha-2 adrenoreceptor activation[77]. A matter of concern with the use of continuous infusion of neuraxial epinephrine has been the association of severe neurologic complications as well as evidence of intrinsic neurotoxicity attributed to epinephrine[78-82]. Its use in neuraxial anesthesia is limited to being used as an additive to caudal Bupivacaine administration and for the detection of inadvertent intra vascular placement of epidural and other perineural catheters[83,84]. In peripheral nerve blocks, Epinephrine has shown certain analgesic benefits with short and intermediate acting local anesthetic such as lidocaine, but similar effects have not been observed with long acting local anesthetic such as Bupivacaine and Ropivacaine[85,86]. The effect of Epinephrine in peripheral blocks seems to be largely dependent on its vasoconstrictive action as perineural Epinephrine alone doesn't seem to cause any sensory or motor block[82,87,88].

Epinephrine has however had a significant role in preventing inadvertent intravascular administration of local anesthetic solutions; however the recent surge in routine use of ultrasonography in nerve blocks has made such use largely redundant. There is significant evidence indicating potential neurotoxicity with the perineural use of Epinephrine, especially in patients with diabetes mellitus, hypertension and in smokers[80,87]. Current recommendations allow use of epinephrine in peripheral blocks only when ultrasonography is not available or where needle tip and local anesthetic spread are not visualized[85].

Alpha 2 adrenoreceptor antagonists

Alpha 2 adrenoreceptor antagonists (Clonidine, Dexmedetomidine) are one of the most widely used class of local anesthetic adjuvants which give satisfactory effect in neuraxial and peripheral blocks.

Clonidine: Clonidine is an imidazole derivative with selective partial agonist properties which inhibits nociceptive impulses by activation of postjunctional alpha-2 adrenoreceptor in the dorsal horn of spinal cord[89]. In neuraxial blocks, it has a local effect on blockage of sympathetic outflow while in peripheral nerve blocks it prolongs duration of analgesia by

hyperpolarisation of cyclic nucleotide gated cation channels[87,90].

Clonidine was first used in 1984 in epidural blocks[91]. Epidural clonidine in doses of 25-50 μg/h has been found to have beneficial effects in various study populations like spine instrumentation and orthopedic procedures[92-96]. Caudal administration of clonidine in pediatric age groups has also exhibited significant prolongation of the duration of analgesia with minimal cardiorespiratory perturbations[97-99]. Intrathecal administration of clonidine has evolved in terms of dosing from the initial phases of higher doses (150 μg) to routine use of lesser doses (15-40 μg) in present day practice to avoid its cardiovascular adverse effects. Intrathecal Clonidine supplementation of local anesthetic solutions result in increased segmental spread of sensory block, delayed regression of such blocks and decrease the failure rate and analgesic supplementation required in various surgical subsets[100-103]. It has also peculiarly shown benefits in alcoholics undergoing surgery by preventing postoperative alcohol withdrawal symptoms[104]. Use of clonidine in neuraxial blocks had been plagued by the adverse effects like sedation, bradycardia and hypotension, thus necessitating a gradual evolution to present day recommendations of lower dosages[93,105,106].

There have been a plethora of studies investigating efficacy of Clonidine as a local anesthetic adjuvant and results have shown varying outcomes[107-112]. A meta analysis by Pöpping *et al*[113] demonstrated prolongation of peripheral nerve block duration by 2 h when clonidine was used as an adjuvant. McCartney *et al*[114] analyzed 27 well designed studies (15 positive, 12 negative) and found that clonidine prolonged peripheral nerve blockade best in amalgamation with intermediate acting local anesthetics such as mepivacaine and lidocaine. Lesser potentiation was observed with bupivacaine and levobupivacaine while ropivacaine produced the most disappointing results. Interestingly upper extremity blocks fared better in comparison to the lower extremity blocks when clonidine was used as an adjuvant[114]. The extensive studies by McCartney and Pöpping presented convincing evidence suggesting significant association of increased doses with hemodynamic manifestations such as hypotension and bradycardia. Hence a dose of 0.5 μg/kg with a maximum of 150 μg is the recommended maximum dose of clonidine for use as an adjuvant in peripheral blocks[113,114]. Subsequently there has been evidence suggesting that clonidine as an adjuvant is beneficial in popliteal sciatic block and in specific circumstances such as axillary blocks in patients with chronic renal failure and patients undergoing paronychia surgery (analgesia in infected tissue)[115,116]. The heterogeneity of results, especially in routine brachial plexus blocks, suggest that until further well directed research shows unequivocal evidence to advocate the use of Clonidine as an adjuvant to local anesthetic, it cannot be routinely recommended for perineural use[117-120].

Dexmedetomidine: Dexmedetomidine is a 7 times more selective alpha-2 receptor agonist in comparison to clonidine and has a similar mechanism of blocking hyperpolarisation activated cation channels[121,122].

Intrathecal (5-10 μg) and epidural dexmedetomidine (1 μg/kg) as an adjuvant to isobaric bupivacaine or in combination with commonly used local anaesthetics (like ropivacaine) have been investigated for its analgesic efficacy in various patient subsets[123-129]. A meta-analysis on intrathecal dexmedetomidine has shown that its use has been associated with prolonged duration of block and improved post-operative analgesia without any associated hypotension or other adverse events, especially when used at doses less than 5 μg[130]. A qualitative review and meta-analysis on the role of dexmedetomidine in neuraxial blocks had concluded that it is a favorable local anesthetic adjuvant providing prolonged anesthesia and analgesia and decrease the need for rescue analgesics; however, it is often associated with a higher incidence of bradycardia[131]. Comparative evaluation of dexmedetomidine and clonidine has revealed the superiority of dexmedetomidine when used as an adjuvant for epidural or intrathecal administration[132,133].

Since 2004, when it was first used as a local anaesthetic adjuvant in Ⅳ regional anaesthesia, the use of dexmedetomidine in peripheral nerve blocks have evolved with burgeoning evidence of considerable utility in such situations[134]. There have been multiple studies claiming increased effectiveness of use of dexmedetomidine and this has been consolidated in a meta-analysis examining the effectiveness of dexmedetomidine as a peripheral nerve block adjuvant[135].

The meta-analysis examined primarily brachial plexus blocks at doses of 0.75 μg/kg, 1.0 μg/kg, 30 μg and 100 μg and found significant prolongation of motor block and reduced requirement of rescue analgesics[135]. The studies in this review did not reveal any increase in the incidence of hypotension as a significant adverse effect. However, reversible bradycardia was observed in less than 10% of the patients. Sensory block prolongation was not statistically significant[135].

Subsequently, there have been studies in supraclavicular, interscalene, cervical plexus and ulnar nerve blocks where dexmedetomidine has been shown to increase quality and duration of analgesia of commonly used local anaesthetics like ropivacaine and bupivacaine[136-141]. An interesting study found that dexmedetomidine fared significantly better than clonidine when used as a adjuvant in supraclavicular blocks[142]. Neuro-toxicity of dexmedetomidine, especially when used in perineural spaces is a valid

concern. Surprisingly, preliminary evidence seems to suggest that dexmedetomidine has potential for neuroprotection, especially when compared with lidocaine and bupivacaine[143,144].

Hence current evidence seems to suggest that dexmedetomidine is effective when used as an adjuvant in peripheral nerve blocks in doses of 1 μg/kg. The adverse affect profile seems to be acceptable with known complications such as hypotension and bradycardia which are responsive to conventional therapies[145].

Steroids

Dexamethasone: Dexamethasone is a potent anti-inflammatory agent which has been investigated in the last decade for its role as an adjuvant to local anaesthetics in neuraxial as well as peripheral nerve blocks.

The mechanisms by which steroids potentiate the analgesic effects seem to be different from its intrinsic anti-inflammatory mechanism[146,147]. There is also evidence to show that the local action on nerve fibres and systemic effects, both potentiate dexamethasone's analgesic properties[148,149].

A study examined the effect of intrathecal dexamethasone in a dose of 8 mg (preservative free) with standard doses of hyperbaric bupivacaine 0.5% in orthopedic surgeries. It was shown to significantly prolong the duration of sensory block in spinal anaesthesia without any significant adverse effects[150].

Epidural dexamethasone in dose range of 4-8 mg has also been investigated for its analgesic efficacy and a recent meta-analysis has looked at its effectiveness[151]. The meta-analysis showed the advantages of the use of dexamethasone as an adjuvant to epidural local anaesthetics. However, it also highlighted the need of further well powered studies to establish its safety in terms of neurological complications[151].

Dexamethasone in a dose range of 1, 2, 4 and 8 mg has largely shown to be efficacious as a local anaesthetic adjuvant in a variety of blocks such as supraclavicular and inter-scalene brachial plexus block, ankle block and TAP block[152-155]. In fact, a meta-analysis exploring the use of dexamethasone as an adjuvant in brachial plexus block has found it to significantly prolong the duration of block of conventional local anaesthetic solutions[156]. A recent study by Liu *et al*[157] demonstrated that perineural dexamethasone (1, 2 and 4 mg) prolonged the duration of analgesia and motor blockade of bupivacaine in patients receiving supraclavicular brachial plexus nerve block for ambulatory shoulder surgery. This effect was despite the fact that most patients in the study population as well as control group received intravenous dexamethasone as well, hence refuting the assumption that perineural dexamethasone produced analgesia because of systemic absorption[157]. However, in some studies the use of perineural dexamethasone has not produced desirable results and it continues to be debated whether the analgesia produced by dexamethasone is related to its systemic effects[158-160].

Other anti-inflammatory agents

Other than dexamethasone, there have been very few studies on anti-inflammatory agents as perineural local anesthetic adjuvants. Neurotoxicity of neuraxial or perineural non-steroidal anti-inflammatory drugs (NSAIDs) as adjuvants has been a major concern. Although there are studies showing prolongation of the effect of local anaesthetics with epidural instillation of Parecoxib and Lornoxicam[161,162], the use of epidural Lornoxicam has also shown "histopathological signs of neurotoxicity". There is very little research evidence available on the use of anti-inflammatory medications in peripheral nerve blocks and further studies are warranted. Until new evidence comes up, their use cannot be recommended for neuraxial and peripheral nerve blocks.

Other drugs

Midazolam: Neuraxial midazolam acts on the benzodiazepine receptors on the gray matter of the spinal cord, the highest concentration of which is found on the lamina Ⅱ of the dorsal horn. The analgesic effect of neuraxial midazolam is caused by the spinal suppression of sensory functions and its anti-nociceptive effect mediated by GABAergic and opioid receptor mechanisms[163-168].

Intrathecal midazolam in a dose of 1-2.5 mg has been shown to be effective in providing prolonged post-operative analgesia without significant adverse effects in adults undergoing orthopedic, urological and lower abdominal surgeries, parturients undergoing caesarean sections and children undergoing urologic procedures[169-178]. Prochazka reported the safe use of intrathecal midazolam as a useful adjuvant for prolongation of analgesia in 775 patients over a period of 10 years[179].

Studies have found that epidural midazolam in doses of 50 μg/kg potentiates the effect of bupivacaine in patients undergoing upper abdominal surgery[180]. Similarly, it has also been found to potentiate the effect of caudal epidural bupivacaine by increasing the time to first analgesic requirement and decreasing the need for post-operative analgesia in children undergoing inguinal herniotomy[181].

Neurotoxicity of intrathecal and epidural midazolam in animal models has been a concern[182-184]. However, its use in a cohort study in 1100 patients by Tucker *et al*[185] conclusively proved that neuraxial midazolam is not associated with any adverse neurological or bladder-bowel symptoms in conventional therapeutic doses. Midazolam is not currently recommended for use in peripheral nerve blocks[145].

Neostigmine: Intrathecal neostigmine has been found

to cause analgesia by muscarinic receptor mediated mechanisms[186-188]. Studies have reported its usage in the dose of 5-10 μg to as high as 50-150 μg in the intrathecal route with increased doses showing greater association with nausea and vomiting, bradycardia, agitation and restlessness[189-196].

Epidural neostigmine in the doses of 1 μg, 2 μg and 4 μg have also been investigated and have been found to be efficacious local anaesthetic adjuvants[197,198]. Studies on the use of neostigmine as a peripheral nerve block adjuvant have been very few and have exhibited very little clinical prolongation of anaesthesia and have shown to be associated with troublesome gastrointestinal adverse effects. Currently its use in peripheral nerve blocks is not recommended[199].

Neurotoxicity of perineural neostigmine remains a concern, especially because animal studies have shown mixed results and human studies have essentially found the adverse effect to be related to its dose, with doses less than 50 μg not being associated with any adverse effects[200-203].

Ketamine: Ketamine, a NMDA receptor antagonist has been explored for its local anesthetic properties[204]. Preservative free forms of ketamine are recommended for neuraxial use because of the evidence of neurotoxicity due to its preservative[205]. Ketamine has been shown to exert analgesic effects by epidural, caudal and spinal routes by a multitude of mechanisms involving N-methyl-D-aspartate (NMDA), Cholinergic, adrenergic and 5-hydroxytryptamine receptors or 5-HT receptors[206-213].

Intrathecal and epidural ketamine has been studied most commonly in patients undergoing caesarean section, prostate surgeries and orthopedic procedures. It has been found to potentiate the effect of local anaesthetics by shortening the onset of sensory and motor block, but simultaneously decreasing the duration and extent of motor block[214-219]. This effect profile of intrathecal ketamine (early onset and decreased duration of action) has led to its use in day care surgeries wherein the early return of full motor power could be advantageous[220].

Caudal ketamine in a dose of 0.5 mg/kg has been studied in children undergoing lower abdominal surgeries and has prolonged the duration of analgesia without significant adverse effects[221]. A systematic review of caudal ketamine use concluded that though efficacious, there are uncertainties related to its neurotoxicity[222]. The association of neuraxial ketamine use with troublesome adverse effects which seems to be a dose dependant phenomenon with lower doses associated with lesser systemic effects[219,223].

Use of ketamine in peripheral nerve blocks has shown it to be associated with unacceptably high incidence of adverse affects such as psychotomimetic sequelae (hallucinations, drowsiness, nausea) without any increase of block duration. Currently, ketamine is not recommended for use in peripheral nerve blocks[224].

Magnesium sulfate: Magnesium sulfate is an NMDA receptor antagonist and inhibitor of voltage gated calcium channel. It had been investigated for its analgesic properties in a variety of clinical scenarios and routes of administration[225]. It had been shown to reduce the postoperative analgesic requirements in a variety of cases.

Intrathecal administration of magnesium sulfate has been shown to suppress nociceptive impulses in neuropathic pain and potentiates opioid anti-nociception in animal studies[226,227]. In humans, profound motor and sensory block for up to 3-27 h was reported in orthopedic, general surgery and gynecological procedures[228]. The duration of spinal opioid analgesia in patients requesting analgesia for labor was significantly prolonged by co-administration of magnesium sulfate with no effect on motor block, sensory block or the incidence of adverse effects like pruritus[229]. Magnesium sulfate has been used in doses of 25-100 mg along with opioids (fentanyl/sufentanyl) with or without local anaesthetic agents (lidocaine, bupivacaine, levobupivacaine and ropivacaine)[225].

A rapid onset of sensory block has been reported with epidural administration of magnesium sulfate as an adjuvant to local anaesthetic agents in thoracic and orthopedic surgeries with a lower incidence of post-operative shivering, nausea and vomiting[230-232]. A faster onset of action, longer duration of actions and reduced breakthrough pain with no change in adverse effects or fetal outcome was observed when magnesium sulfate was used as an adjuvant in labor analgesia[233].

Magnesium sulfate has been used as an adjuvant to local anaesthetics in interscalene and supraclavicular brachial plexus block, axillary block, femoral nerve block and popliteal nerve block. It has shown to increase the duration of analgesia without any adverse effects[234-237].

The adverse effects of neuraxial use of magnesium sulfate has been reported in isolated cases and are restricted to bradycardia, hypotension, sedation, headache, disorientation or periumbilical burning pain[238,239].

Animal studies were the first to report neurological complications and pain at injection site in a dose dependant manner, especially at dose more than 2-3 mg/kg[240]. Although neurodegenerative changes on intrathecal administration of magnesium sulfate into the rat spine have been reported[241], histological evidence of direct neuronal injury is lacking in canine models, thus suggesting that the neurological injury associated with the use of magnesium sulfate in neuraxial blocks may be species specific[242,243]. The

lack of well defined neurotoxicity studies for the use of magnesium sulfate precludes any recommendation for its use as an adjuvant to local anaesthetic agents[145].

FUTURE TRENDS

There has been an ongoing search for agents and techniques which would prolong local anaesthetic action without its deleterious effects, primarily systemic toxicity and neurotoxicity. Butyl-amino-benzoate is an ester local anaesthetic agent, which though not strictly an adjuvant, has shown to provide pain relief for up-to 14 wk by novel mechanisms such as blockade of sodium and potassium channels[244-247].

Another novel approach has been to use charged molecules to produce local anaesthetic action, as with tonicaine and n butyl tetracaine[248-251]. Although onset is slow because of the time required to penetrate neuronal membranes, the duration of action is prolonged because of charge properties. However, more human trials are required before these novel local anesthetics can be used in routine clinical practice.

Recent advancement in the world of perineural local anaesthetic use has been the progress in new age delivery mechanisms such as liposomal, microspheres and cyclodextrin systems. Liposomes are microscopic lipid vesicles ranging in size from 0.02-40 μm which have the advantage of acting as a reservoir of drug with low bioavailability resulting in prolonged analgesic effects without systemic toxicity[252-254]. Liposomal local anesthetics have been used in multiple routes[255,256] and had shown prolonged analgesia with less motor block in various populations[257-259]. However there are concerns about their potential toxicity because of the compounds, their metabolites and breakdown of the liposomal core[260]. Microspheres and cyclodextrins are also alternatives drug delivery systems which have shown initial promises in animal models[149,261-264].

Among other adjuvants, adenosine showed initial promise because of its analgesia mediated at the spinal adenosine receptors and inherent anti-inflammatory actions without any neurotoxicity in initial animal studies[265-267]. However human studies using intrathecal adenosine (0.5-1.0 mg) as well as its use as an adjuvant to local anaesthetic solutions in peripheral nerve blocks have shown no additional benefit[268-270]. Dextrans, a complex branched polysaccharides derived from sucrose, had been hypothesized to form water soluble complexes with local anesthetics and thereby prolonging the duration of analgesia by sustained action at the store of its deposition, as well as by altering the local pH favorably[271,272]. Human studies on the use of dextrans as a local anaesthetic adjuvant have been mixed, some showing advantage and others being inconclusive and there remains a need for further high powered studies[273-276].

Neuromuscular blocking drugs have also been explored as local anaesthetic adjuncts and have shown promising results in peri-bulbar blocks and intravenous regional anaesthesia with good results[277-281]. However there have been concerns of such use being associated with local anesthetic toxicity and prolonged motor blockade[282].

A summary of commonly used local anaesthetic adjuvants is given in Table 1.

CONCLUSION

Adjuvant to local anesthetics is an evolving and exciting field of anesthesia practice with new technology promising to improve patient satisfaction and safety. While opioids continue to be the most commonly used local anesthetic adjuvant in clinical practice, alpha-2 receptor antagonists, especially dexmedetomidine, has been shown to potentiate the effect of local anaesthetics with an acceptable safety profile. Use of adjuvants to local anesthetic should take into consideration the available evidence and the advocated safe dose ranges, its effective routes of administration, the adverse effect profile of use of such adjuncts as well as preparedness to manage life threatening complications such as Local Anesthesia Systemic Toxicity (LAST). Its users should be aware of its neurotoxicity potential following perineural use and watch for its clinical implications. Search for newer molecules and techniques allowing for lesser perineural doses of local anesthetic, enhanced analgesic effect and improved safety profile are expected to guide further studies in future to fill up the present lacuna in evidence about the use of adjuvant for local anaesthetics.

Table 1 Summary of the commonly used local anaesthetic adjuvants

Name of drug	Routes and dosages	Adverse effects	Recommendations for use	Mechanism of action
Morphine[12,22]	Intrathecal: 100-200 μg Epidural: 1-5 mg Peripheral nerve block: 75-100 μg/kg	Pruritus Nausea vomiting Respiratory failure	Useful in neuraxial blocks Not recommended for peripheral nerve blocks	
Fentanyl[23-26,30-35]	Intrathecal: 10-25 μg Epidural: 2-4 μg/mL Peripheral nerve block	Same adverse effects as morphine Adverse effect profile slightly favourable in neuraxial use Increased sedation, bradycardia and hypotension	Useful in neuraxial blocks Not recommended in neuraxial blocks due to inconsistent results	Spinal opioid receptor
Sufentanyl[36-40]	Intrathecal: 1.5-5 μg Epidural: 0.75-1.0 μg/mL Not used in peripheral nerve blocks		Efficacious in neuraxial blocks	Local action in peripheral nerve blocks
Hydromorphone[41-44]	Intrathecal: 100 μg Epidural: 500-600 μg Not used in peripheral nerve blocks	Better adverse effect profile than Morphine	Useful in neuraxial blocks	
Buprenorphine[5,45-48]	Intrathecal: 75-150 μg Epidural: 150-300 μg Peripheral nerve block: 300 μg		Good efficacy in neuraxial and peripheral nerve block routes	
Tramadol[49-72]	Intrathecal: 10-50 mg Epidural: 1-2 mg/kg Peripheral nerve block: 1-5 mg/kg	Nausea and vomiting	Present evidence supports use in epidural infusions Poor evidence in peripheral nerve block studies	Weak opioid agonist actions Sodium/potassium channel blocking actions Blockade of norepinephrine and serotonin uptake
Clonidine[89-121]	Intrathecal: 15-40 μg Epidural: 25-50 μg Peripheral nerve block: 0.5-5 μg/kg (150 μg is the maximum allowed dose in PNB)	Sedation Bradycardia Hypertension Adverse effects show association with dose	Good quality evidence to support use in neuraxial blocks especially at lower dosages In PNB prolongs block with Bupivacaine but poor efficacy with Ropivacaine and levobupivacaine Additional benefit in Alcohol withdrawal	Activation of post junctional alpha-2 receptors in dorsal horn of spinal cord
Dexmeditomidine[122-147]	Intrathecal: 5-10 μg Epidural: 1 μg/kg Peripheral nerve block: 20-150 μg	Sedation Bradycardia Hypertension Adverse effects show association with dose	Prolongation of neuraxial and peripheral nerve blocks with good efficacy of use	Mechanism similar to Clonidine
Dexamethasone[148-161]	Intrathecal: 8 mg Epidural: 4-8 mg Peripheral nerve block: 1-8 mg	Adverse effects minimal Advantageous to prevent ponv Troublesome paresthesias with PNB use	Efficacious in neuraxial blocks, however better studies required Prolongs nerve blockade in PNB	Local action on nerve fibers
Midazolam[164-184]	Intrathecal: 1-2.5 mg Epidural: 50 μg/kg diluted in 10 mL of saline	Sedation Respiratory depression	Neurotoxicity is a major concern in neuraxial and peripheral nerve routes Not recommended for routine neuraxial and PNB use	GABAergic and opioid receptor mechanisms
Neostigmine[185-202]	Intrathecal: 5-10 μg to 50-150 μg Epidural: 1, 2 and 4 μg Peripheral nerve block-not investigated	Neuraxial use associated with bradycardia, restlessness PNB use associated with gastrointestinal adverse effects	Lower dosages recommended for neuraxial use Not recommended for PNB use (neurotoxicity in animal models)	Enhancement of endogenous acetylcholine at nerve terminal

Ketamine[203-223]		Neuraxial use associated with nausea, vomiting and hallucinations	Neuraxial use-shortens onset and duration of anesthesia	NMDA receptor antagonists shown to have local anesthetic properties
		PNB use associated with psychomimetic sequelae	Not recommended for PNB use	Cholinergic, adrenergic and 5HT mechanisms
Magnesium[224-238]	Intrathecal: 25-100 mg	Headache	Prolongs analgesia and quality of block by all perineural routes	NMDA receptor antagonism
	Epidural: 50-100 mg	Cardiovascular disturbances	However more studies required to determine minimal effective doses	Voltage gated calcium channel blockade
		Nausea vomiting	Not recommended for routine use	

PNB: Peripheral nerve block; NMDA: N-methyl-D-aspartate; 5HT: % hydroxyl-tryptamine.

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MINIREVIEWS

Treatment of sepsis: What is the antibiotic choice in bacteremia due to carbapenem resistant *Enterobacteriaceae*?

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Abstract

Sepsis is one of the major challenges of today. Although gram-positive bacteria related infections are more prevalent in hospital setting, the highest mortality rate is associated with gram-negative microorganisms especially *Enterobacteriaceae*. *Enterobacteriaceae*, including *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp. and *Serratia* spp. Resistance to β-lactams in *Enterobacteriaceae* is primarily attributed to the production of B-lactamase enzymes with subsequent antibiotic hydrolysis and to a lesser extent by alteration of efflux pump or porins expression. Carbapenem resistant *Enterobacteriaceae* (CRE) and *Acinetobacter baumannii* are the most notorious pathogens due to the high incidence of morbidity and mortality especially in the immunocompromised patients in the intensive care unit. The most appropriate antimicrobial therapy to treat CRE is still controversial. Combination therapy is preferred over monotherapy due to its broad-spectrum coverage of micro-organisms, due to its synergetic effect and to prevent development of further resistance. Current suggested therapies for CRE resistance as well as promising antibiotics that are currently under investigation for winning the war against the emerging CRE resistance are reviewed and discussed.

Key words: Carbapenem resistant *Enterobacteriaceae*; Sepsis; Bacteraemia; Bacteremia; Treatment; Antibiotics

Core tip: Carbapenem resistant *Enterobacteriaceae* (CRE) is the most notorious pathogens contributing to a significant morbidity and mortality rate in septic patients especially in the intensive care unit. The most appropriate antimicrobial therapy to treat CRE is still controversial. This review is conducted to discuss the

effectiveness of available therapies at this moment and to elaborate on different promising drugs that are still under investigation in order to win the combat on rising antimicrobial resistance.

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INTRODUCTION

Sepsis is a global healthcare problem and one of the major challenges that health care practitioners face worldwide[1]. It has become one of the major causes of death and its incidence is continuing to rise making it a huge burden in terms of increased morbidity and mortality, prolonged hospital stay, increased risk of having antimicrobial resistance and increasing hospital cost. It was estimated that the incidence of septic cases increased 13.7% each year over a period of 22 years[2-4]. Sepsis is newly re-defined as a life-threatening organ dysfunction due to a dysregulated host response to infection. Septic shock is defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities substantially increase mortality[5].

Sepsis is a medical emergency; hence, antimicrobial treatment should be started as soon as sepsis is suspected. To prevent development of further complications and progression of the patient into septic shock and multi organ failure, profound knowledge of the causative pathogens is needed to select the proper antibiotic treatment. To reduce sepsis associated mortality, it has been widely advocated to start empirical antibiotic therapy from the first hour following sepsis identification. This strategy leads to a reduction in mortality of 13.7%[6-8]. The most common primary site involved in sepsis is the respiratory tract, mainly pneumonia, followed by genitourinary tract infections. Other sites involved are the abdomen, wound and soft tissue infections, the central nervous system (CNS) and the cardiovascular system. In some cases, the source origin is unknown (Table 1)[6,9,10]. However, the most commonly isolated pathogens depend on the infection site. In wound infections *Staphylococcus aureus* and coagulase negative staphylococci was found to be the most causative organism of both meningitis and pneumonia, while *Escherichia coli* is the most prevalent cause of urinary tract infections (UTI) related sepsis[11,12]. Regarding blood stream infection (BSI), coagulase negative staphylococci *and E. coli* are the notable organisms isolated[10].

In the intensive care unit (ICU) setting, the most common isolated pathogens causing severe sepsis are *S. aureus* followed by Pseudomonas infection, Enterobacteriaceae and fungal infection, respectively. Acinetobacter baumannii was involved in 9% of all infections[10]. But in general, gram negative pathogens are the most commonly found in sepsis patients[2,4,11,13].

Although gram-positive bacteria related infections (especially *Staphylococcus*) are more prevalent in the hospital setting (62.2%), the highest mortality rate is associated with gram-negative micro-organisms. *Enterobacteriaceae* are the most common microorganisms in gram-negative sepsis[14].

EPIDEMIOLOGY OF *ENTEROBACTERIACEAE*

Enterobacteriaceae, a family of Gram negative pathogens, includes E. coli, Klebsiella spp., Proteus spp., Enterobacter spp. and Serratia spp. These organisms account for half of the bacteremia's that are usually caused by overspill of bacteria from their primary sites[14]. *E. coli* and *K. pneumoniae*, in particular, are the major community and hospital acquired pathogens that usually cause intra-abdominal infections, urinary tract infections and primary bacteremia[15]. The emergence of multi-drug resistant microorganisms has become one of the most important hazards that health care is facing worldwide. Development of such resistance can be attributed to many risk factors including previous ICU admission, presence of a central venous catheter especially in hemato-oncology patients who are receiving chemotherapy, presence of an indwelling catheter insertion, prolonged use of antibiotics, prolonged hospital stay, hospitalization in an area endemic for multidrug resistance (MDR) and a history of previous colonization or infection with these microorganisms[16,17]. Resistance to β-lactams in *Enterobacteriaceae* is primarily attributed to the production of B-lactamase enzymes with subsequent antibiotic hydrolysis and to a lesser extent by alteration of efflux pump or porins expression[18]. One of the main causes of *Enterobacteriaceae* resistance is extended spectrum beta-lactamases (ESBL) production. ESBLs are plasmid encoded enzymes that are able to hydrolyze penicillins, broad-spectrum cephalosporins with an oxyiminoside chain, *e.g.*, cefotaxime, ceftazidime and ceftriaxone as well as oxyimino-monobactams such as azetreonam. However, they are ineffective against cephamycins or carbapenems and their antimicrobial activity is inhibited by clavulanic acid[19,20]. The main problem concerning ESBL-producing bacteria is that they usually acquire multiple antimicrobial resistance mechanisms causing not only resistance to cephalosporins but also to aminoglycosides and fluoroquinolones, which further narrows the choices of finding an effective therapeutic agent[21].

Regrettably, these organisms belonging to the β-lactamases producing *Enterobacteriaceae* have acquired new genetic mutations and became resistant to

Table 1 The most common sites of infection and mortality rates in sepsis

Site of infection	Mortality (%)
Blood stream infection	34.2
Respiratory	22
Genitourinary	8.2
Wound and soft tissue infection	10.55
Abdomen	10.25
CNS	17.4
Device related	9.5
Endocarditis	25.95
Others	7.05

Table was modified from the ref. [9]. CNS: Central nervous system.

Table 2 Resistance mechanisms of carbapenemase producing *Enterobacteriaceae*

Class	Genetic mutation	Clavulanic acid inhibition
Class A	Chromosomal encoded (NmcA, Sme, IMI-1, SFC-1) Plasmid encoded (IMI-2, GES, KPC)	Partially inhibited
Class B	Metallo-β-lactamase (IMP, VIM and NDM-1, SIM, GIM, SPM)	Resistant to clavulanic acid
Class D	Plasmid encoded oxa-48	Resistant to clavulanic aci

KPC: *K. pneumoniae* carbapenemases; OXA: Oxacillin-hydrolising; NDM: New Delhi metallo-beta-lactamase. Table was modified from the ref. [22].

carbapenem antimicrobial therapy.

These carbapenemase producing *Enterobacteriaceae* are classified into group A, B and D. β-lactamases micro-organisms based on the type of gene mutation (Table 2). Class A and D have a serine based hydrolytic mechanism, but class B consists of metallo- β-lactamase[22-24].

Carbapenem resistant *Enterobacteriaceae* (CRE) and *A. baumannii* are the most notorious pathogens due to the high incidence of morbidity and mortality especially in the immunocompromised patients in the ICU. The incidence of CRE was reported in various countries worldwide including East Asia, India, USA and many European countries. A multicenter study, conducted in Shanghai, China, revealed a high proportion of ESBL type *E. coli* as a cause of bloodstream infections. In addition, it was noted that the most common involved gene was CTX-M (CTX-M-15 CTX-M-14 and CTX-M-55, respectively). No carbapenemases producing *Entero-bacteriaceae* were reported[25]. On the contrary, in Turkey a retrospective study evaluating ICU patients over ten years, showed that antibiotic resistance most dramatically increased due to carbapenem resistant *A. baumannii* followed by *Pseudomonas* spp, *E. coli* and *K. pneumoniae,* respectively. In addition, a reduction in methicillin resistant *S. aureus* (MRSA) prevalence from 96% to 54% was noticed[26]. In the United States, it was reported in CRE outbreaks that resistance, especially to *K. pneumoniae* and to a lesser extent other *Enterobacteriaceae*, were important in CRE resistance[27].

A case control study in New York showed that the majority of deaths due to bacteremia in neutropenic oncology patients were caused by CRE infections in 53%, of which gram negative *Enterobacteriaceae* was found in 13%-18% of the patients. Independent risk factors for increased CRE susceptibility were: Previous use of β -lactam antibiotics (*e.g.*, 3rd or 4th generation cephalosporins or carbapenems) within the last 30 d; receiving trimethoprim-sulfamethoxazole or glucocorticoids at the time of onset of blood stream infection and having previous CRE infection isolate[27]. In order to avoid development of more resistance, it is crucial to be selective in the choice of antibiotics. Choosing the proper antibiotic regimen should be based on clinical findings supported by rapid diagnosis[22].

Goodman *et al*[16] tried to develop a clinical decision tree to predict whether a patient with bacteremia was infected with an ESBL-producing pathogen. They retrospectively studied a cohort of patients with bacteremia in Johns Hopkins hospital to identify clinical criteria to diagnose those patients with ESBL bacteremia, especially gram negative *Enterobacteriaceae*, to avoid misuse of antibiotics in the future. The clinical criteria were: A history of ESBL colonization or infection in the last 6 mo with chronic usage of indwelling venous catheter or dialysis, patient age ⩾ 43 years, recent hospitalization in an ESBL high-burden area and a history antibiotic use for ⩾ 6 d in the previous 6 mo. They made a clinical decision based on these five yes-or-no questions. When the patient had a history of ESBL colonization or infection in the last 6 mo with chronic usage of indwelling venous catheter or dialysis they had a 92% chance of being ESBL positive. With these criteria, positive predictive value was 90.8% and negative predictive value was 91.9%. In addition, they found that 43% of patients with an ESBL positive culture had received chemotherapy in the recent history.

Another score has been developed to identify patients with high suspicion of CRE or ESBL-BSI so antibiotic therapy might be started on time to reduce mortality (Table 3). Risk factors were chemotherapy in the last 3 mo, foreign invasive device, absence of peripheral vascular disease, reduced level of consciousness, hospitalization of > 3 d and age < 65 years old. With a total score ⩾ 32 patients were considered as high risk for CRE BSI infections and required antimicrobial therapy targeted for CRE BSI infections. Although this test showed a lower sensitivity and specificity, its negative predictive value might prevent needless use of toxic antibiotics[28].

The Carba NP test is such a rapid diagnostic with a very high sensitivity and specificity that can differentiate between class A, B and C CRE. In addition, other promising tests such as PCR assay and matrix assisted laser desorption ionization might facilitate CRE diagnosis. In addition, fast gram-negative blood culture assays and film array blood culture can help

Table 3 Bed side risk score for carbapenem resistant *Enterobacteriaceae*

Risk factor	Score (points)
History of chemotherapy in the last 3 mo	19
Invasive devices	10
Absence of peripheral vascular disease	10
Impairment of level of consciousness at the time of illness	9
Hospitalization for 3 or more days before development of BSI	7
Age < 65 years old	6

Table was modified from the ref. [28]. BSI: Blood stream infection.

in identifying carbapenemase genes within two hours[29,30]. However, deciding on the most appropriate antibiotic choice in bacteremia due to CRE can be very challenging.

TREATMENT OF CRE

The most appropriate antimicrobial therapy to treat CRE is still controversial. No consensus has been reached regarding the optimal choice of antibiotic therapy. As a consequence of the evolving broad spectrum antibiotic resistance, the old fashioned antibiotics, previously discarded because of their side effects, *e.g*., polymyxin E (colistin), polymyxin B, aminoglycosides and fosfomycin, have reappeared, because of effectiveness to some extent[31,32]. Despite the numerous publications on the subject, no consensus has been reached even on the preference of monotherapy or combination therapy[33].

Monotherapy vs combination therapy for treatment of sepsis

In a study conducted in a mice sepsis model, no significant difference was shown between colistin monotherapy and tigecycline monotherapy in treating carbapenem-resistant *K. pneumoniae*. In addition, combination of both colistin and tigecycline did not show superiority over monotherapy[34]. However, several studies suggested that combination therapy might be superior to monotherapy in terms of mortality rates. A review conducted by Falagas *et al*[35] described a cohort of 692 patients in which majority had confirmed *Klebsiella pneumoniae* carbapenemase producing *K. Pneumoniae* (KPC-KP) isolates and most of them related to bacteraemia. Mortality rate among those who received combination antimicrobial therapy ranged from 50% to 67% with the lowest rate associated with combination of tigecycline and gentamicin and highest rate with colistin and carbapenem (50% mortality rate in combination of tigecylcine with gentamicin, 64% in tigecycline-colistin and 67% for carbapenem-colistin combination). Patients who received colistin monotherapy had a mortality rate of 57% and patients who received tigecycline monotherapy 80%. The superiority of using combination therapy was shown in only three studies. No hard conclusions can be drawn from this review to decide on the use of single agent or combined therapy. Except in the critically ill patients, it is preferable to use combination therapy with superiority of tigecycline and gentamicin as a first choice, but randomized clinical trials need to confirm this statement.

But even with combination therapy, mortality rate remains high in patients with CRE related bacteremia. The underlying illness of the patient remains the most important risk factor for mortality. Tumbarello *et al*[36] showed the lowest mortality rate in patients with KPC-KP related sepsis using combined antimicrobial regimens especially those containing meropenem (when MIC $\leqslant$ 8 mg/L).

In a retrospective cohort study by Tumbarello *et al*[36] it was shown that combined therapy was superior to monotherapy in treating KPC-KP infection. Survival in patients with blood stream infection (mainly septic patients) with KPC-KP receiving monotherapy had a mortality rate of 54.3% while those receiving a combination therapy had a mortality rate of 34.1%. The same study demonstrated that a combination of tigecycline or colistin with meropenem had a better outcome compared to other combination therapies (12.5% mortality rate compared to 16.6% for tigecyclin, gentamicin with meropenem, 57% for colistin-gentamicin, 50% for tigecyclin-gentamicin and 30.4% tigecycline and colistin combination therapy).

Interestingly, in a prospective study by de Maio Carrilho *et al*[37] in patients with infections caused by KPC-KP (but also *Enterobacteriaceae* and *E. coli*) regimens of three or more antibiotics did not show any improved survival in comparison to regimens with two antibiotics. Moreover, monotherapy was just as effective as combination therapy in patients with UTI. Other independent risk factors such as dialysis, older age and septic shock seem to influence patient outcome more than monotherapy *vs* combination therapy.

Nevertheless, taken all current evidence into account, combination therapy can have a significant association with a lower mortality rate and increase the cure rate compared to monotherapy in the septic patient since each drug has its own mechanism of action, which can create a synergistic environment while combating resistant bacterial strains. The limited number of antimicrobial agents currently available to treat CRE will be further discussed in this review.

Colistin

Colistin is one of polymyxin antibiotics with bactericidal activity against Gram-negative bacterial infection[38]. Although the usage of this antibiotic was banned for many years due to its nephrotoxicity and neurotoxicity effect, it was reintroduced again due to emergence of MDR microorganisms. However, the use of colistin in treating CRE infection is still controversial[39].

Qureshi *et al*[40] retrospectively evaluated a cohort of 41 patients admitted to the ICU from two different

hospitals in the United States with almost similar clinical and demographic variables. Of the 41 patients who developed bacteremia with a KPC-producing *K. pneumoniae*, seven patients died before initiating treatment. Among those who received combination therapy with carbapenem/tigecycline or carbapenem/colistin 28 d survival was significantly higher than in those on monotherapy (2 out of 15 patients receiving combination therapy died compared to 11 out of 19 patients receiving monotherapy).

Regarding the optimal dose for colistin, Gibson *et al*[41] showed that use of high dose colistin (> 4.4 mg/kg per day) in patients with CRE bacteremia was associated with a better clinical outcome, *i.e*., reduction of leucocyte < 12000 cells/mm^3, no fever for 48 h and hemodynamically stable without any vasopressor. Also a better microbiological outcome was demonstrated, *i.e.,* eradication of CRE on day 7 after starting colistin.

Unfortunately, although still rare, colistin resistant CRE species are emerging in China, United States and different European countries. It is most often observed in *Enterobacteriaceae* harboring the *mcr-1* gene along with carbapenemase resistant gene[42-44].

Despite the fact that some investigators showed that development of colistin resistant CRE did not correlate with an increased mortality compared to patients without colistin resistant CRE[37], others have found that having colistin resistant KP is an independent risk factor of death especially in those with bacteremia[36,43].

Colistin seems to be a good alternative in vulnerable patients (without any evidence of renal impairment) especially when combined with other antibiotics such as carbapenems. However, it is very important to pay extra-attention for colistin resistant strains.

Carbapenems

Despite the fact of developing resistance to carbapenems anti-microbial therapy, they still can be of use especially in combination with other antimicrobial agents in colistin resistant *Enterobacteriaceae*. In a review by Bassetti *et al*[45], it was recommended that patients with KPC-KP and a MIC of isolate between 8 mg/L-16 mg/L or < 8 mg/L should receive a high dose of carbapenem containing therapy with a prolonged infusion together with colistin, tigecycline or an aminoglycoside. The underlying reason was prevention of developing new resistance to the rest of CRE antimicrobial therapy

In a case report on ertapenem and meropenem combination therapy, it was reported that an elderly patient with KPC-producing *E. coli* isolated from surgical site and nosocomial pneumonia with a contra-indication to colistin use due to a recent renal transplantation was started on combination therapy with ertapenem and meropenem showing good response. Unfortunately, the patient died later due to hemorrhagic shock[46].

In order to have a better outcome in colistin resistant *Enterobacteriaceae*, double carbapenem treatment was introduced. In two patients with carbapenemase-producing K. pneumoniae who were also colistin resistant, a combination of meropenem 2 g every 8 h and ertapenem 1 g every 24 h were given. In a third patient, dosages were adjusted for renal function. Both patients showed clinical improvement and also *in vitro* bactericidal activity was maintained up to 24 h. In conclusion, in such select cases like resistance to colistin, where options to treat CRE related sepsis are limited, a combination of two carbapenem antibiotics could be beneficial[47].

In a trial performed by Cprek *et al*[48] ertapenem/carbapenem double therapy (consisting of one gift of 1 g ertapenem given daily 1 h before administration of meropenem 2 g or doripenem 500 mg and the rest of the daily doses of meropenem or doripenem given normally) a favorable outcome was observed with maximum benefit in patients with CRKP bacteremia (43%) followed by pneumonia, intraabdominal, UTI and skin associated CRE infections.

Taking these observations into account, a combination of two carbapenems can be effective and even superior to other combination regimens in bacteremia patients due to its synergistic effect.

Tigecycline and other tetracyclines

Tetracyclines are a group of antibiotics that exhibit bacteriostatic activity by reversible binding to 30S ribosomes that interfere with protein synthesis. It is widely used due to its coverage of both gram-positive and gram-negative bacteria as well as some anaerobes and parasites[49]. Tigecycline is a glycylcycline, which is a tetracycline derivative and exhibits broad spectrum activity covering many organisms including MDR pathogens[50]. Many studies were conducted to evaluate the efficacy of tetracyclines mainly tigecycline in treating CRE related sepsis. A systematic review demonstrated that tigecycline did not significantly improve sepsis related mortality[51]. However, combination therapy containing tigecycline did significantly improve survival. In addition, it was found that administration of high dose regimen was associated with better outcome compared to standard dose tigecycline in combination therapy.

Administration of tigecycline monotherapy was associated with a high mortality rate[52]. Tigecycline might have a role in the treatment of CRE if it is used as a part of combination therapy particularly with aminoglycoside group or colistin[52]. Other tetracyclines, minocycline and eravacycline, are also studied in the treatment of CRE. Although high dose intravenous minocycline (200 mg twice daily) can be effective in carbapenem resistant *A. baumannii* up to 74%, its efficacy is less when dealing with CRE with only 12% of the CRE susceptible to minocycline[53]. Another promising agent is eravacycline, belonging to the fluorocyclines. *In vitro* it showed a potent effectiveness to MDR organisms[54]. An ongoing phase 3 clinical trial with eravacycline (GNITE4) might give us more data on its effectiveness[55]. The preliminary results suggest

that there is no place for the use of tetracyclines in the treatment of CRE related sepsis; however the definitive results have not been published until now.

Aminoglycosides

The antibiotic group of aminoglycosides consists of gentamicin, amikacin, streptomycin, paromomycin, streptomycin and plazomicin, the last one still under clinical research. This group covers mainly gram negative and to some extent gram-positive pathogens and Mycobacteria[56]. It is usually used in combination with other antimicrobial agents in serious infections due to its synergistic effect[57]. The major side effects are ototoxicity and nephrotoxicity together with its narrow therapeutic window it can limit its use[58]. Aminoglycosides (especially gentamicin and amikacin) have shown their efficacy in treating carbapenem resistant KP UTI compared to other carbapenem resistant antimicrobial treatment (88% clearance compared to tigecycline and colistin), but its role in carbapenem resistant bacteremia as monotherapy is still uncertain[58]. A retrospective cohort study demonstrated that administration of gentamicin is an independent factor, which can improve 30 d mortality mainly in cases of KPC-KP related sepsis.

Especially in patients with both Carbapenem and colistin resistant KP, it decreased the mortality rate to 20.7% in comparison to 61.9% in patients treated with non-gentamicin containing therapy[59].

In conclusion, the role of aminoglycosides, mainly gentamicin, was studied previously particularly in combination with tigecycline with promising results. Now, it can be considered as a good option in the CRE patient with sepsis. Regarding the rest of aminoglycoside group antibiotics, further prospective studies are recommended.

Fosfomycin

The same might be applied for fosfomycin which has shown only its effectiveness in the treatment of patients with CRE UTI, but up until now no sufficient data exists supporting the use of fosfomycin either as a monotherapy or as part of a combination therapy in treating sepsis[58]. In a study by Bowers *et al*[60], 68 patients were treated with intravenous fosfomycin either in combination with colistin or with tigecycline. Effectiveness was demonstrated in 54.2% of patients at day 14. Mortality rate was 37.5% at day 28, with the highest mortality in having bacteremia; ventilator associated pneumonia and CRE KP isolates or *P. aeruginosa* isolates. Interestingly, three patients developed fosfomycin resistance shortly after treatment.

PROMISING NEW TREATMENTS

Alternative combination regimens can be considered in the future as curative agents in CRE related sepsis, but further clinical trials and prospective studies are required to assess its effectiveness. Fortunately, many new promising drugs might win the current battle against the current CRE resistance. One of them is plazomicin that belongs to the group of aminoglycosides. Recently, a phase 3 clinical trial was published showing efficacy of plazomicin. It was demonstrated that plazomicin significantly reduced mortality rate and reduced complications in patients with severe infection including CRE bacteremia, ventilation associated pneumonia and hospital acquired pneumonia related to CRE compared to colistin (28 d mortality rate was 11.4% in the plazmicin group compared to 40% in the colistin group). It also showed that plazomicin has the same efficacy of ertapenem in treating UTI[61], therefore it might play an important role in ceftazidime-avibactam combination therapy. In a recent study by Wu *et al*[62], three patients with CRE bacteremia (one patient with septic shock and one patient with suspected endocarditis) were successfully treated with ceftazidime-avibactam combination therapy. Combination of ceftazidime-avibactam is effective against oxa-48 and KP CRE[63].

Another option in the battle of CRE might be the addition of vabobactam to meropenem. Vabobactam is a boronic acid beta-lactamase inhibitor, which acts mainly on the serine carbapenamase and it has shown its efficacy in treating complicated UTI including those caused by CRE in phase 1 and 2 trials. A phase 3 trial is still ongoing now. In addition, its role in treating bacteremia needs further investigation[64].

In addition, combination of relebactam with imipenem and cilastatin is a promising option. Relebactam belongs to same group of vabobactam antibiotics. A phase 3 trial is designed to compare this combination with piperacillin/tazobactam in the treatment of complicated UTI. Its role in treatment of bacteraemia has not been investigated up until now[65].

One of the promising discoveries that can help in reducing the rate of CRE resistance is the peptide-conjugated phosphorodiamidate morpholino oligomer. It is a neutral DNA analogue which can inhibit gene expression of carbapenemases. It has been demonstrated that PRMO can target NDM1 (class B carbapenemases). It was shown that in combination with meropenem, it improved patient survival up to 92% because it re-established meropenem function[66].

CONCLUSION

The most appropriate antibiotics to treat CRE related sepsis is still debatable. Combination therapy is preferred over monotherapy in most of the studies due to its broad-spectrum coverage of organisms, its synergetic effect and to prevent development of further resistance.

In severely ill patients with co morbidities, a combination of two or more antibiotics is preferred. One of the best treatments up until now has been a combination of meropenem, tigecycline and colistin. A second option might be the combination therapy with

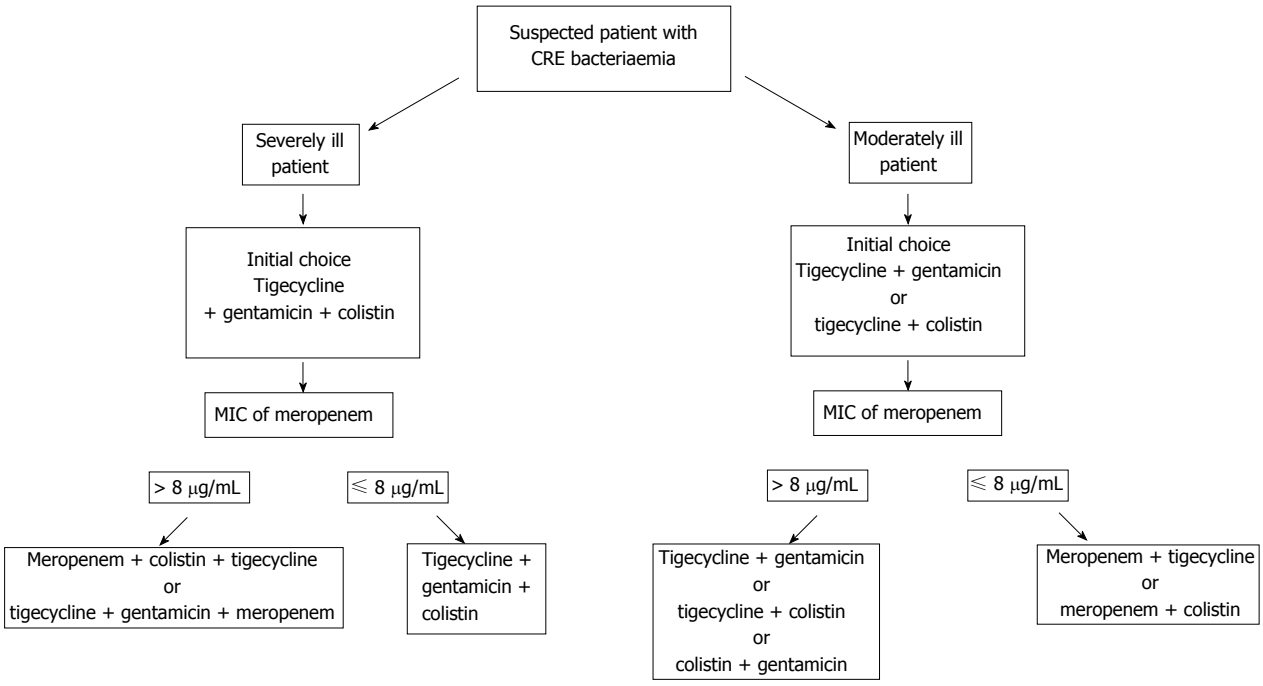

Figure 1 Suggested algorithm for antibiotic choice in patient with bacteriaemia of carbapenem resistant *Enterobacteriaceae*[1]. [1]The algorithm is based on the following references: [35,36,40,45,51,59]. CRE: Carbapenem resistant *Enterobacteriaceae*.

tigecycline, gentamicin and meropenem. In moderately ill patients, it is recommended to administer the combination of tigecycline and gentamicin. If the MIC is less than 8 μg/mL, it is advisable to switch to a carbapenem containing therapy. In case of colistin resistance, a combination of two carbapenems can be used (*e.g.*, ertapenem with meropenem or ertapenem with doripenem) besides the combinations shown in the algorithm (Figure 1). Many promising antibiotics are currently under investigation. The most optimal treatment still needs to be determined to win the battle against the emerging CRE resistance.

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CASE REPORT

Vertebroplasty and delayed subdural cauda equina hematoma: Review of literature and case report

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Abstract

Vertebroplasy is considered an alternative and effective treatment of painful oncologic spine disease. Major complications are very rare, but with high morbidity and occur in less than 1% of patients who undergo vertebroplasty. Spinal subdural hematoma (SDH) is an extremely rare complication, usual developing within 12 h to 24 h after the procedure. We report the case of a tardive SDH in an oncologic patient who underwent VP for Myxoid Liposarcoma metastasis. Trying to explain the pathogenesis, we support the hypothesis that both venous congestion of the vertebral venous plexus of the vertebral body and venous congestion due to a traumatic injury can provoke SDH. To our best knowledge, only 4 cases of spinal subdural hematoma following a transpedicular vertebroplasty have been previously described in International literature and only one of them occurred two weeks after that surgical procedures. Percutaneous verteboplasty is a well-known treatment of pain oncologic spine disease, used to provide pain relief and improvement of quality life and is considered a simple surgical procedure, involving a low risk of complications, but related to high morbidity, such as SDH. Therefore it has to be performed by experienced and skilled surgeons, that should also recognize possible risk factors, making SDH more risky.

Key words: Subdural hematoma; Liposarcoma; Surgery; Radiotherapy; Vertebroplasty

Core tip: This is an original paper about a rare complication of vertebroplasty: A subdural hematoma. In literature there are only 4 cases described. To our knowledge thid is the first case in which this complication occur after 20 d. In this work we try to explain the pathogenesis and the importance of a correct and rapid diagnosis, and, if needed, an emergency treatment.

Tropeano MP, La Pira B, Pescatori L, Piccirilli M. Vertebroplasty and delayed subdural cauda equina hematoma: Review of literature and case report. *World J Clin Cases* 2017; 5(8): 333-339 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i8/333.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i8.333

INTRODUCTION

Myxoid liposarcoma is the most common subtype of liposarcoma, accounting for 10% of all adult tissue sarcomas[1]. The frequency of bone metastasis arising from liposarcoma has been reported to be 14% and 17%[2]. In one of the largest series, which analyze specifically the development of bone metastases, the incidence of spinal metastases was 83%[2]. Treatment options included: Surgical excision, chemotherapy, adjuvant radiotherapy, surgical decompression of spinal metastasis after having their surgery elsewhere.

The first percutaneous vertebroplasty in an oncological patient, was performed at the University Hospital of Amiens, France, to fill a vertebral void after the removal of a benign spinal tumor, then it was quickly adopted also for use in metastatic vertebral lesions and hematologic malignancies such as multiple myeloma and lymphoma. Clinical studies documented the effectiveness of VP as an alternative treatment of painful oncologic spine disease[3].

The first vertebroplasty was performed by Galibert in 1987 for a C2 hemangioma[4]. The first series was reported in 1997 and since[5], it has become a very common surgical technique for the symptomatic treatment of painful osteoporotic vertebral fractures, wedge-compression fractures, vertebral malignancies and painful vertebral angiomas.

The goal is to provide pain relief and bone strengthening, injecting cement or calcium phosphate bone cement into the vertebral body, *via* a transpedicular or an extrapedicular approach under fluoroscopic guidance. There is strong evidence of pain relief and improvement in the patient's quality life. Percutaneous vertebroplasty is usually performed in the thoracic and lumbar vertebrae and rarely in the cervical vertebrae and cervico-thoracic junction. Absolute contraindications are: Unstable fractures with posterior element involvement, bleeding disorders, active local infections and sepsis[6]. Relative contraindications are: clinical conditions not allowing to lie prone, neurological signs and symptoms due to vertebral body collapse or tumor extension[7].

Major complications are very rare, but with high morbidity and occur in less than 1% of patients who undergo vertebroplasty. The most common are anaphylaxis and hypotension due to an adverse reaction to the cement, pneumothorax, pulmonary embolism due to cement leakage, spinal cord compression following the cement leakage, epidural or subdural hematoma, vertebral injury, infections and death[8,9]. Most often, complications occur during surgery or immediately following surgery. Late-developing complications are infection, adjacent vertebral body fractures and recurrent fracture; they appear within days to weeks following surgical procedure. Spinal subdural hematoma (SDH) is an extremely rare complication, usual developing within 12 h to 24 h after the procedure. To our knowledge, to date, only 4 cases have been previously reported in International literature[10,11], where only one of them occurred two weeks following transpedicular vertebroplasty[12]. We report the case of a tardive SDH in an oncologic patient who underwent VP for Myxoid Liposarcoma metastasis.

CASE REPORT

We report the case of a 63-year-old man who presented to our emergency department with bilateral inferior limb numbness and weakness, mainly to the left leg and complaining of bladder retention. Neurological assessment revealed a 1/5 monoparesis of the left inferior limb and 3/5 monoparesis of the right, as well hypoesthesia and dysesthesia in the same region. Perineal reflexes were absent. The patient was on anticoagulants.

Three weeks prior to the onset of neurological symptoms, the patient underwent percutaneous VP of L1 and L3 vertebrae, in an oncology institute, for pathological compression fractures, due to secondary localization of a retroperitoneal myxoid liposarcoma, removed several years before. VP was indicated by an oncologist and performed at the above-mentioned institute of oncology. Pathological anamnesis revealed that the patient underwent surgery several times for the removal of a retroperitoneal liposarcoma. In 1997 the patient underwent the first surgical procedure for the removal of the lesion located in the upper left quadrant of the retroperitoneal space. During the same procedure, the left colon was also removed. In 2004 a second surgical procedure was performed for the removal of a local relapse of the lesion as well as for the removal of the spleen. In February 2005 a follow up abdominal magnetic resonance imaging (MRI) showed the presence of another local relapse of the pathology. In consequence, another surgical excision of the lesion was performed, including excision of the pancreatic tail. The procedure was proceeded by the administration of a chemotherapeutic protocol consisting of Antracicline and Ifosfamide. In November 2011 another surgical excision was performed. It included the left part of the diaphragm as well as a portion of the small intestine and the left half of the transverse colon. Furthermore, on November 2013 the patient underwent cyberknife radiotherapy.

Upon admittance at our emergency department for paraparesis, an emergency spinal MRI with gadolinium was obtained. Results showed the presence of a high signal lesion in the intradural extramedullary space, at the conus medullaris (Figure 1). Furthermore,

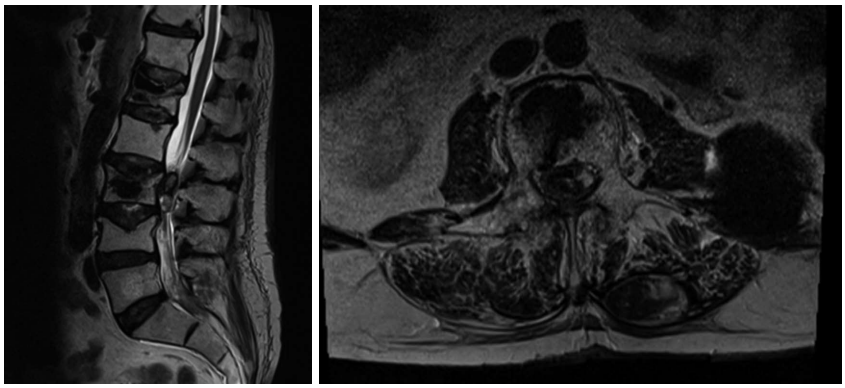

Figure 1 T2 weighed magnetic resonance imaging of the lumbar tract of the spinal column on sagittal and axial planes. The images reveal the presence of a lesion located within the spinal channel at L2-L3. It is not possible to establish if it is located within the intradural or extradural space by the mere observation of the MRI. Note the needle trajectory inside the spinal channel at L1 on the right side.

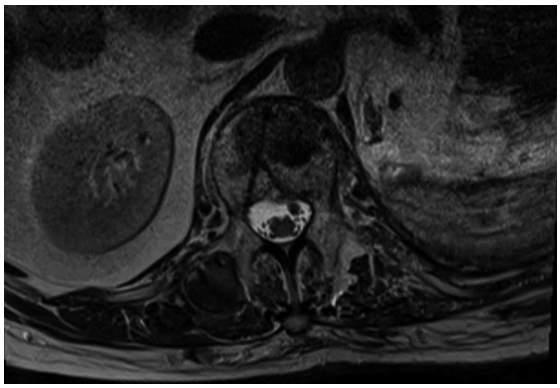

Figure 2 T2 weighed magnetic resonance imaging of the L1 vertebra on axial plane. As the image show, the trajectory of the needle used to perform the vertebroplasty passes within the spinal channel on the left side.

the trajectory of the needle used to perform the vertebroplasty was detected at L1 and L3 levels and it suggested that the needle had passed through the dura into the subarachnoid space and then into the vertebral body (Figure 2). An emergency decompressive bilateral laminectomy of L2 and L3 vertebrae was performed. No epidural bleeding was observed. A longitudinal durotomy revealed a blood clot, tightly adherent to the cauda equina rootlets (Figure 3). The hemorrhagic lesion was completely removed with the assistance of a surgical microscope (Figure 4). After the procedure, neurological symptoms progressively disappeared and 5 d later, the patient completely recovered both motor and sensory deficits, as well as bladder functions. Postoperative MRI documented adequate surgical decompression and removal of the intradural lesion (Figure 5). Histological examination confirmed the haemorrhagic origin of the lesion, constituted by clots and fibrin, with no evidence of tumor.

DISCUSSION

Liposarcoma is a common malignant soft tissue tumor, accounting for 10% to 16% of all sarcomas[1]. It typically affects patients between the fifth and seventh decade of life and usually develops in the extremities or retroperitoneum[13]. It can be classified into five distinct histological subtypes (WHO 1994): Well-differentiated, dedifferentiated, mixed, round cell and pleomorphic. Myxoid liposarcoma (MLS) is the second most common subtype, accounting for 10% of all adult soft tissue sarcoma, occurring more frequently during the fourth and fifth decades of life[14]. It is considered as a clinicopathologically and genetically distinct type, characterized by its common occurrence in young patient, its location in the thigh and the presence of at translocation[12,15,16]. Specifically, it is common associated with TLS-CHOP fusion transcript. Differently from other soft-tissue sarcomas, that show a tendency for metastasis to the lung, MLS has a propensity to spread to extrapulmonary sites, including bone. The frequency of bone metastasis is reported at 14%[2] and 17%[16]. Furthermore, MLS presents often as a multifocal disease, either synchronous or metachronous. The degree to which MLS spreads to bone has not been specifically studied and it is still unclear if skeletal metastasis represents the usual pattern of spread in MLS, or if it is the mark of specific molecular subset. In a large series, including 40 patients who developed skeletal metastasis, 33 (83%) were diagnosed with spine metastasis[2]. The spine metastases demonstrated the typical MRI findings of MLP. T1 weight images were heterogenous with areas go high signal intensity corresponding to the lipid component and low signal to the mixed component, as T2 images as well. The treatment of metastasis is individualized to each patient. Surgical excision is the treatment of choice; chemotherapy and radiotherapy are also utilized. Percutaneous verteboplasty (VP) is a well-known treatment of pain oncologic spine disease, used to provide pain relief and improvement of quality life. It was introduced for the first time to fill a vertebral void after a the removal of a benign spinal tumor, since then it was introduced as a treatment option also for primary and metastatic spinal tumor[17]. During the last few decades, improvement in surgical

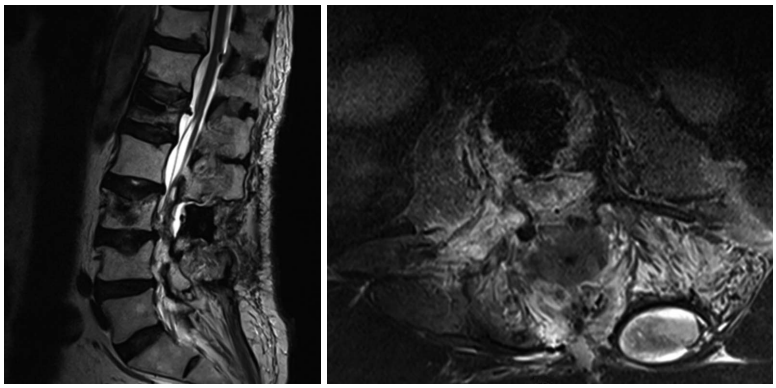

Figure 3 Postoperative T2 weighed magnetic resonance imaging on sagittal and axial plane showing the proper execution of the bilateral laminectomy at L2 L3 as well as the removal of the intradural lesion.

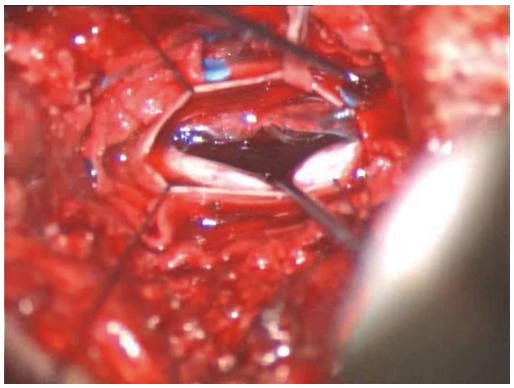

Figure 4 Intraoperative image by microscope, showing the dura mater opened and the hematoma between the radiculae.

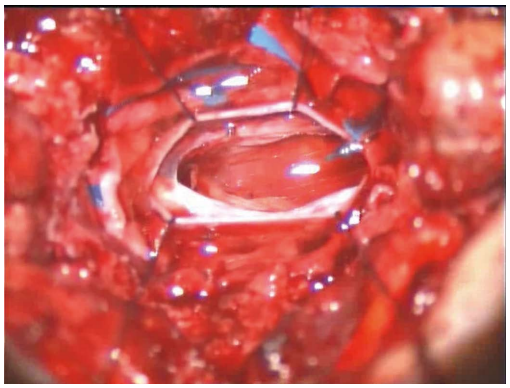

Figure 5 Intraoperative image by microscope, showing the complete removal of the hematoma.

strategies and technologies, have increased disease-free survival rates, in patient with a wide variety of malignant tumors that were once considered inoperable. Despite these advances, many patients present with widespread tumor and minimal life expectancy and surgical or any other aggressive treatment cannot be medically or ethically considered[18]. Palliative strategies are recommended in this cases, such methods include medical management, pain management, vertebroplasty, radiotherapy. Vertebroplasty and Kyphoplasty are usually indicated for the treatment of metastatic spinal tumors without epidural compression, to improve the anterior column stably of the spine in conjunction with medical and radiation therapies and to obtain pain relief[19]. In particular, these conservative procedures are recommended in elderly patients, at high anesthetic risk, because less operating time under anesthesia and minimal blood loss. Randomized, multi centered and controlled trials, demonstrated that the use of VP, specifically for spinal metastasis, had an improvement in pain (among 73% to 100% of patients), mobility and vertebral height restoration[20,21]. To our knowledge, Yang *et al*[22] conduct- ed the largest vertebroplasty study in patients with metastatic spinal disease. A total of 196 patients were treated during the study and a 98.5% improvement in pain was seen, as well as statistically significant improvements in vertebral body height[22].

Percutaneous vertebroplasty is a therapeutic strategy, that gained increasing popularity among the neurosurgical community for the treatment of refractory axial mechanical pain due to osteoporotic fractures, malignancy fractures and painful hemangiomas. With time, the indications for vertebroplasty were extended to include acute traumatic vertebral compression fractures[23]. The therapeutic mechanism of action consists of injecting polymethyl methacrylate into the fractured vertebral body. There is evidence of the ability of vertebroplasty to provide pain relief and improvement of patient's quality of life. Although it is a safe procedure, the rate of major complications is from 0.5% to 1%, when it is conducted by experienced spinal surgeons. Complications reported in literature are often related to the cement extravasation into the epidural space[24] (some series reported up to 20% extravasation rates, occasionally requiring surgical decompression) causing spinal cord compression, or related to the cement migration through the epidural veins to the venous system leading to pulmonary embolism[25]. To our knowledge only 5 cases of SDH, including our own, have been reported in literature (Table 1). Cosar *et al*[10] reported two cases: An 18-year-old man with an acute compression fracture of the L2 and L4 vertebrae (AO Type A1.1), in whom both levels were treated with

Table 1 Cases of spinal subdural hematoma following a transpedicular vertebroplasty reported in literature

Case	Age, gender	Fracture level	Fracture cause	SDH symptoms onset	Symptoms	SDH level	Treatment	Recovery
Lee *et al*[12]	40 yr, female	T11-T12	Traumatic	2 wk	Back pain, radiating both legs	SDH T10-L5	No surgery, corticosteroid therapy	Good
Cosar *et al*[10]	75 yr, female	L1	Osteoporotic	12 h	Paraparesis, incontinence	SDH T12-L3	Laminectomy T12	Good with arachnoiditis
Cosar *et al*[10]	18 yr, male	L2-L4	Traumatic	12 h	Paraparesis	SDH T1-L2	Hemilaminectomy T1-L2	Good with arachnoiditis
Mattei *et al*[11]	49 yr, female	T8	Traumatic	Immediate	Motor deficit left leg	SDH T9-C7	Laminectomy T7-T9	Good
Our case	63 yr, male	L1-L3	Oncological fracture	2 wk	Paraparesis	SDH conus	Laminectomy L2-L3	Good

SDH: Spinal subdural hematoma.

vertebroplasty. The patient complained of severe back pain immediately after the surgical procedure and paraparesis developed in both his legs 12 h later. Postoperative MRI showed spinal SDH extending from T1 to L2, evacuated *via* cross-hemilaminectomy from T-1 to L2. The second case reports a 75-year-old woman with an osteoporotic compression fracture at L1. The patient suffered psychosomatic symptoms with paraparesis 24 h after the procedure. The Postoperative MRI revealed spinal SDH extending from T-10 to L-3, evacuated *via* T-12 laminectomy. Both patients improved after the second surgical procedure, but reported back pain after a few months, with an MRI showing spinal arachnoiditis, controlled with steroids and anti-inflammatory drug therapy. They hypothesized that the spinal SDH developed after puncture of the spinal dura mater and that venous blood began to enter the subdural space slowly after this trauma. This is reasonable, according to the time of onset of symptom presentation.

Lee *et al*[12] reported a 40-year-old female with an acute compression fracture of the T11 and T12 vertebrae, treated with successful transpedicular VP, under continuous visualization with fluoroscopic guidance. After two weeks, during which the patient's conditions were improving, she complained of acute back pain. MRI imaging showed a high signal intensity mass lesion in the intradural extra medullary space, located at the lower thoracic, lumbar and sacral area. No coagulation disturbances were detected. Open surgery was recommended but she refused. Following 10 d of intravenous therapy with dexamethasone, she improved. The authors did not give a precise explanation and concluded that pathogenesis is still unclear. Among possible theories explaining the pathogenesis of SDH after vertebroplasty, the authors hypothesize the increase in thoracic and/or abdominal pressure, due to leakage of bone cement, increasing the pressure within the intraspinal vessels, particularly the valveless radiculomedullary veins, that cross subdural and subarachnoid space (but leakage was not enough), the development after spinal puncture of dura mater, as Cosar *et al*[10] proposed and the possibility that SDH may originate directly from the subarachnoid space, dissecting through the arachnoid membrane and eventually break into the spinal subdural space.

Mattei *et al*[11] reported the case of a 49-year-old woman with a T8 compression fracture, previously treated conservatively and with a VP after 3 mo follow-up, when she complained of severe deep axial pain. After cannulation of the left T8 pedicle and the initial injection of PPMA, a small posterior extravasation of cement to the epidural veins was observed. Surgical procedure was stopped, and, after awaking, she presented diffuse numbness on the left side (both in the superior and inferior limbs) and diffuse weakness in the left leg. An emergency CT scan showed a very small posterior leakage of PMMA towards the epidural space and into the adjacent costotransverse joint and a hyperdense collection anterior to the spinal cord from T7 to the upper cervical spine. decompressive laminectomy was performed, at T8, T7, T9. Postoperative MRI confirmed the presence of SDH. The authors commented on the anatomy of spinal venous drainage and focused on the possible etiologic role of venous congestion caused by the venous obstruction.

SDHs can be divided into traumatic and spontaneous. Traumatic SDHs usually occur after minor spinal trauma, spinal anesthesia lumbar puncture and spinal surgery, especially in the presence of intraoperative dural tears[26,27]. Spontaneous (non traumatic) SDHs are much more rare, with a recent review having identified 106 cases reported in the English literature[28]. Most of them are located anteriorly to the spinal cord, differently from epidural haematomas located posteriorly, at the lower thoracic region and lumbar region. Predisposing factors are considered coagulation abnormalities, anticoagulation therapy, platelet disfunction, polycythemia vera, pregnancy, arterial wall abnormalities and spinal arteriovenous malformations[29-33], but the pathophysiology still remains unclear. The management of SDH is still controversial as well. Some authors propose emergency spinal decompression and evacuation of the hematoma, while other wait for the recovery of incomplete

neurological deficits, especially in the absence of spinal cord compression. Several theories have been proposed to explain the pathogenesis, most of them stressing the anatomy of spinal venous drainage, involving venous congestion. Although some authors have suggested that thin and delicate extra-arachnoid vessels on the inner surface of dura can give rise to SDH, it is confined to specific cases occurring in association with a subarachnoid hemorrhage of traumatic origin[34]. Alternatively, other authors have reported cases of sudden episodes of increased intra-abdominal or intra-thoracic pressure (coughing or straining) associated with SDH, suggesting the presence of a locus minoris resistentiae, that, when submitted to high pressure for venous congestion, would possibly rupture, causing extravasation of blood into the subdural space[35,36]. According to this theory, both venous congestion of the vertebral venous plexus of the vertebral body and venous congestion due to a traumatic injury can provoke SDH.

In conclusion, there are still questions that remain unclear. How can the differences in time of onset be explained? Why do certain SDH cases present immediately following intervention with neurological deficits (within 24 h), while others presented later (2 wk after)? Is it possible that there is no difference, but that the SDH already present in both cases and becomes symptomatic within 24 h or 2 wk. Can we postulate that other conditions are superimposed? Concerning our case, both theories have been proposed. The late onset of SDH at the same level of a vertebral boy previously treated by VP, without extension to the upper and lower levels, is extremely rare. It is most likely related to the wrong insertion of the needle, but also to the anticoagulants, with a delay in the onset probably due to the mechanism of venous congestion. We definitely consider VP a simple surgical procedure, involving a low risk of complications, but related to high morbidity. Therefore it has to be performed by experienced and skilled surgeons. Furthermore, surgical iatrogenic complications must be known, correctly and rapidly diagnosed and, if needed, receive emergency treatment. Experienced surgeons should also consider and evaluate possible risk factors, making SDH more risky.

COMMENTS

Case characteristics

This is the case of a 63-year-old man who presented to our emergency department with bilateral inferior limb numbness and weakness, mainly to the left leg and complaining of bladder retention. Three weeks prior to the onset of neurological symptoms, the patient underwent percutaneous vertebroplasty (VP) of L1 and L3 vertebrae, in an oncology institute, for pathological compression fractures, due to secondary localization of a retroperitoneal myxoid liposarcoma, removed several years before.

Clinical diagnosis

Neurological assessment revealed a 1/5 monoparesis of the left inferior limb and 3/5 monoparesis of the right, as well hypoesthesia and dysesthesia in the same region. Perineal reflexes were absent.

Differential diagnosis

Haemorrhage, concussion injury, spinal contusion, Guillain- Barrè Sindrome.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

A magnetic resonance imaging scan showed the presence of a high signal lesion in the intradural extramedullary space, at the conus medullaris.

Treatment

An emergency decompressive bilateral laminectomy of L2 and L3 vertebrae was performed. A longitudinal durotomy revealed a blood clot, tightly adherent to the cauda equina rootlets. The hemorrhagic lesion was completely removed with the assistance of a surgical microscope.

Related reports

Spinal subdural hematoma is an extremely rare complication, usual developing within 12 to 24 h after the procedure. To our knowledge, to date, only 4 cases have been previously reported in International literature.

Term explanation

Vertebroplasty is usually indicated for the treatment of metastatic spinal tumors without epidural compression, to improve the anterior column stably of the spine in conjunction with medical and radiation therapies and to obtain pain relief.

Experience and lessons

VP a simple surgical procedure, involving a low risk of complications, but related to high morbidity. Therefore it has to be performed by experienced and skilled surgeons. Furthermore, surgical iatrogenic complications must be known, correctly and rapidly diagnosed, and, if needed, receive emergency treatment.

Peer-review

The manuscript reports a rare case and is clear, comprehensive and convincing. It is an interesting review about the complications following the percutaneous vertebroplasty, mainly about the occurrence of spinal subdural hematoma.

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CASE REPORT

Pseudotumoral acute cerebellitis associated with mumps infection in a child

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Abstract

Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. It often follows an inflammatory or infectious event, particularly due to varicella virus. Patients could have a wide clinical spectrum on presentation. Some patients may be asymptomatic or present at most with mild cerebellar signs, whereas others may suffer severe forms with brainstem involvement and severe intracranial hypertension mimicking tumor warranting surgical intervention. Imaging techniques especially multimodal magnetic resonance imaging represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. We describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

Key words: Acute cerebellitis; Pseudotumoral cerebellitis; Posterior fossa tumor; Children; Mumps

Core tip: Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. It often follows an inflammatory or infectious event, particularly due to varicella virus. Patients could have a wide clinical spectrum on presentation. Imaging techniques especially multimodal magnetic resonance imaging represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. We describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

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INTRODUCTION

Acute cerebellitis is usually a benign disease[1]. Patients could have a wide clinical spectrum on presentation. Some patients may be asymptomatic[2] or present at most with mild cerebellar signs, whereas others may suffer severe forms related to brainstem compression and severe intracranial hypertension mimicking tumor warranting surgical intervention[3]. The diagnosis and the management of these pseudotumoral forms represent a challenge for clinicians and radiologists to distinguish acute cerebellitis from posterior fossa tumors. The etiopathology of acute cerebellitis remains unknown, although an infectious or postinfectious origin is frequently advocated. Several viral infections maybe associated with cerebellitis in particular varicella virus.

We report a rare case of pseudotumoral cerebellitis secondary to mumps infection which resolved favorably after corticosteroid therapy.

CASE REPORT

A 6-year-old girl presented to the emergency department with a 2-d history of severe headache, nausea and vomiting. There was no family history of neurological disorders and her psychomotor development was normal. She had a history of a recent episode of mumps infection 10 d before presentation, with spontaneous resolution. Upon admission, the patient had an altered consciousness level and was mildly confused (Glasgow Coma Scale = E4 V4 M6). Neurological examination revealed trunk and gait ataxia with bilateral dysmetria on finger-nose tests. The body temperature was 37.5 ℃. Vital signs were initially stable with normal heart and breath rates. Few hours after her admission, she had dysautonomic troubles; her heart rate decreased unexpectedly to 55 beats/min and her arterial pressure dropped to 80/50 mmHg. Therefore, the patient was transferred to the Pediatric Intensive Care Unit for close observation. Brain computed tomography scan showed a cerebellar ill-defined hypodense lesion with mass effect on the fourth ventricle and dilation of the upper ventricular system. A multimodal magnetic resonance imaging (MRI) was performed in order to differentiate between posterior fossa tumor and acute cerebellitis. Brain MRI showed cerebellar high-intensity areas on T2-weighted and FLAIR images predominant on the right side, related to a diffuse edema with mass effect on the fourth ventricle and brainstem, tonsillar herniation and supratentorial hydrocephalus (Figure 1A and B). No bleeding on T2* sequence or diffusion restriction was noted. Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia (Figure 1C). Magnetic Resonance Spectroscopy (TE = 35 ms) showed mildly reduced level of N acetyl aspartate (NAA)/Creatine and normal Choline/Creatine ratios. Doublet of lactate-lipid peak (1.3 ppm) was also found (Figure 2). Biological investigation revealed an hemoglobin concentration of 12.7 g/dL, a white blood cell count of 14280/mm^3 (with 85% neutrophils, 9% lymphocytes and 4.8% monocytes), platelet count of. Erythrocyte sedimentation rate showed moderate increase and was 20 mm/h. C-reactive protein level was above 2 mg/L. Lumbar puncture was not performed because of the risk of cerebellar herniation. Serological tests for Epstein Barr virus, human herpes virus, human immunodeficiency virus, rubella virus, parvovirus B19, measles virus and Mycoplasma pneumoniae in serum were all negative except for the serological test for mumps virus which was positive with IgM and IgG and positive with IgG in the control serology done 10 d later. Post-infectious acute hemicerebellitis was diagnosed on the basis of the MRI features, the clinical symptoms and the biological findings. The patient was treated with mannitol and corticosteroid. She received Ⅳmethylprednisolone 30 mg/kg per day for 3 d followed by oral prednisone 1 mg/kg per day tapered within 1 mo. The evolution was rapidly favorable. Eighteen days after discharge, a brain MRI showed a partial resolution of signal alterations in the cerebellar hemispheres. Complete resolution was confirmed by brain MRI performed 3 mo later.

DISCUSSION

Acute cerebellitis often occurs as a primary infectious, post-infectious, post-vaccination disorder and it may follow a vaccine or drug administration[1]. It is associated with viral or bacterial infections in approximately 24% of the children[4]. Several infectious agents associated with cerebellitis were reported in literature: Varicella-Zoster virus, human herpes virus, Epstein-Barr virus, rubella, pertussis, diphtheria, coxsackie virus, Coxiella burnetti or Mycoplasma pneumoniae[5]. Mumps virus infection causes usually benign diseases and 30% of pediatric cases are asymptomatic[6]. It induces viremia resulting in dissemination of virus to several organ systems, including the central nervous system[7]. Mumps viruses are highly neurotropic, with evidence of central nervous system infection in more than half of all cases of infection[8]. The most common neurological complication of mumps is aseptic meningitis. Severe complications, though rare, include hearing loss in children (5/100000) and encephalitis (incidence of < 2/100000 cases, of which 1% are fatal)[6]. Our patient had an acute cerebellitis post mumps virus infection which is an unusual clinical feature. These severe complications could be explained by the neurovirulence of some mumps virus strains rather than others. This observation has been also shown by Sauder *et al*[7] through the use of different live

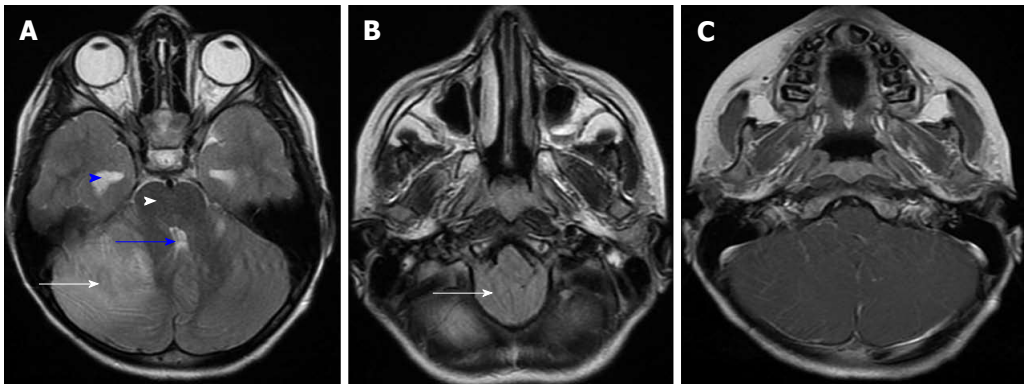

Figure 1 Magnetic resonance imaging: T2 and T1 post contrast images. A and B: Cerebellar hyperintense areas on T2-weighted images predominant on the right side (white arrow in A), related to diffuse edema and producing cerebellar mass-effect on the fourth ventricle (blue arrow) and brainstem (white head arrow), tonsillar herniation (white arrow in B) and supratentorial hydrocephalus (blue head arrow); C: Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia.

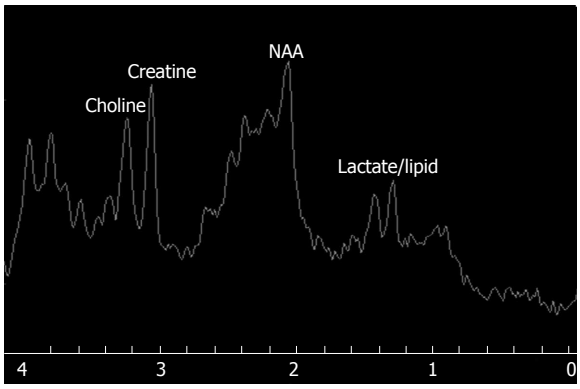

Figure 2 Magnetic resonance spectroscopy (TE = 35 ms) showed mildly reduced N actetyl aspartate/creatine and normal Choline/Creatine ratios. Doublet of lactate/lipid peak (1.3 ppm) was detected. NAA: N actetyl aspartate.

attenuated mumps viruses strains. Our observation is distinctive by its clinical and radiological presentations and by its uncommon infective etiology. It illustrates pseudotumoral feature of acute cerebellitis associated with mumps virus infection. Clinical presentation and radiological features were similar to posterior fossa tumors. The challenge in these cases is to differentiate between posterior fossa tumor and acute cerebellitis. MRI is the study of choice to demonstrate cerebellar pathology, which could be undetected on CT. It confirms acute cerebellitis and leads to a more accurate description of the lesion. Cases of cerebellitis involving only one hemisphere are rare and are more difficult to differentiate from tumors. Magnetic resonance spectroscopy is a valuable tool to exclude tumor by showing normal choline/creatine ratio. Most forms of acute cerebellitis have a good clinical outcome and have no need for specific treatment as they are benign forms. However, some cases, like in our report, could be fulminant and should be treated urgently. These severe forms require to start methylprednisolone bolus with a very close observation of clinical and imaging variables.

We report a child with acute cerebellitis secondary to post-mumps infection. This case illustrates that although mumps infection is a benign infection, it could be associated to a severe and atypical cerebellitis syndrome. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The risk of brainstem compression may be life-threatening and indicate an urgent need for treatment.

COMMENTS

Case characteristics

A 6-year-old girl presented to the emergency department with a 2-d history of severe headache, nausea and vomiting. She had a history of a recent episode of mumps infection 10 d before presentation, with spontaneous resolution.

Clinical diagnosis

Acute cerebellitis.

Differential diagnosis

A multimodal magnetic resonance imaging (MRI) was performed in order to differentiate between posterior fossa tumor and acute cerebellitis.

Laboratory diagnosis

Serological tests for Epstein-Barr virus, human herpes virus, human immunodeficiency virus, rubella virus, parvovirus B19, measles virus and Mycoplasma pneumoniae in serum were all negative except for the serological test for mumps virus which was positive with IgM and IgG and positive with IgG in the control serology done 10 d later.

Imaging diagnosis

Brain MRI showed cerebellar high-intensity areas on T2-weighted and FLAIR images predominant on the right side, related to a diffuse edema with mass effect on the fourth ventricle and brainstem, tonsillar herniation and supratentorial hydrocephalus. Gadolinium-enhanced T1-weighted sequence revealed leptomeningeal enhancement along the cerebellar folia. Magnetic resonance spectroscopy (TE = 35 ms) showed mildly reduced level of N acetyl aspartate (NAA)/Creatine and normal Choline/Creatine ratios. Doublet of lactate-lipid peak (1.3 ppm) was also found.

Pathological diagnosis

Final diagnosis: Post-infectious acute hemicerebellitis.

Treatment

The patient was treated with mannitol and corticosteroid. She received IV methylprednisolone 30 mg/kg per day for 3 d followed by oral prednisone 1 mg/kg per day tapered within 1 mo.

Related reports

Pseudotumoral cerebellitis in childhood is an uncommon presentation of cerebellitis mimicking a brain tumor. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The authors describe a case of pseudotumoral cerebellitis in a 6-year-old girl consequent to mumps infection and review the literature on this rare association.

Term explanation

Acute cerebellitis often occurs as a primary infectious, post-infectious, post-vaccination disorder and it may follow a vaccine or drug administration. It is associated with viral or bacterial infections in approximately 24% of the children.

Experiences and lessons

The authors report a child with acute cerebellitis secondary to post-mumps infection. This case illustrates that although mumps infection is a benign infection, it could be associated to a severe and atypical cerebellitis syndrome. Imaging techniques especially multimodal MRI represent an interesting tool to differentiate between posterior fossa tumors and acute cerebellitis. The risk of brainstem compression may be life-threatening and indicate an urgent need for treatment.

Peer-review

The case report is described very well and will be useful to share with the scientific community.

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CASE REPORT

Atlanto-axial langerhans cell histiocytosis in a child presented as torticollis

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Author contributions: Tfifha M, Mama N and Gaha M contributed to project development, data collection, bibliography review, manuscript writing; Yacoubi MT contributed to data collection and bibliography review; Jemni H and Abroug S contributed to data collection and manuscript writing.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at Sahloul University Hospital Sousse Tunisia.

Informed consent statement: The parents of the patient involved in this study gave their written informed consent authorizing use and disclosure of his protected health information.

Conflict-of-interest statement: All the authors have no conflicts of interests to declare.

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Abstract

Langerhans cell histiocytosis (LCH) is a rare condition mostly seen in children and adolescents. Eosinophilic granuloma (EG) is one of its three clinical entities and is considered as a benign osteolytic lesion. Many reports of patients with spine histiocytosis are well documented in the literature but it is not the case of atlantoaxial localization. We report here a new observation of atlantoaxial LCH in a 4-year-old boy revealed by persistent torticollis. He was successfully treated with systemic chemotherapy and surgery. Inter-body fusion packed by autologous iliac bone was performed with resolution of his symptoms. It is known that conservative treatment is usually sufficient and surgery should be reserved for major neurologic defects in spine EG. In atlantoaxial lesion, surgical treatment should be frequently considered.

Key words: Langerhans cell histiocytosis; Eosinophilic granuloma; Torticollis; Cervical spine

Core tip: Langerhans cell histiocytosis (LCH) is a rare condition mostly seen in children and adolescents. Eosinophilic granuloma is one of its three clinical entities and is considered as a benign osteolytic lesion. Many reports of patients with spine histiocytosis are well documented in the literature but it is not the case of atlantoaxial localization. We report here a new observation of atlantoaxial LCH in a 4-year-old boy

revealed by persistent torticollis.

Tfifha M, Gaha M, Mama N, Yacoubi MT, Abroug S, Jemni H. Atlanto-axial langerhans cell histiocytosis in a child presented as torticollis. *World J Clin Cases* 2017; 5(8): 344-348 Available from: URL: http://www.wjgnet.com/2307-8960/full/v5/i8/344.htm DOI: http://dx.doi.org/10.12998/wjcc.v5.i8.344

INTRODUCTION

Langerhans cell histiocytosis (LCH) is an uncommon disorder characterized by an abnormal accumulation of histiocytes[1]. It includes three clinical entities namely eosinophilic granuloma (EG), Hand-Schûller-Christian syndrome and Letter-Siwe disease[2]. It consists in various clinical manifestations from a single lytic bone lesion to multisystemic lesions with organ dysfunction[3]. EG is a benign osteolytic lesion that commonly affects the skeletal system in a unifocal or multifocal form[2]. Atlantoaxial involvement by LCH is very rare[4,5], especially in a very young child[2,6,7]. The localization makes it difficult to diagnose. Neural deficit in spinal EG can be observed representing a life threatening condition[2,6]. The management is still controversial. We present, herein an unusual and rare case of atlantoaxial LCH with infiltrative mass involving the dens of C2 resulting in torticollis as the first symptom lasting for 3 wk in a 4-year-old boy. EG is discussed and the literature is reviewed.

CASE REPORT

Clinical presentation

A 4-year-old boy without significant medical history was admitted for limited neck motion for 3 wk. The physical examination showed an irreducible torticollis with analgesic attitude of cervical spine. The active and passive mobilization of the neck was painful and no motor or sensory deficit was detected. The general condition of the patient was good, the clinical examination did not show a tumoral syndrome and the neurological examination as well as skin examination and laboratory tests were normal.

Imaging features

The magnetic resonance imaging (MRI) of cerebro-spinal cord uncovered an infiltrative mass involving the dens of C2 which is hypointense on T1 sequence and hyperintense on T2 sequence, extending to the surrounding soft tissues leading to an increase in C1-C2 space, without compression of the spinal cervical cord. Complementary CT showed fragmented dens with important C1-C2 dislocation (Figure 1).

Histologic features

The odontoïd and mass biopsy was performed by endoscopic guidance. Histological features were consistent with inflammatory EG. The positivity of the immunostain by the antibody anti Ps100 and the antibody anti CD1a confirms the diagnosis of LCH (Figure 2).

Treatment and evolution

Initial treatment was started prednisolone 40 mg/m^2 per day orally, with weekly reduction starting from week 4 and intravenous Vinblastine 6 mg/m^2 per week for six weeks. An external immobilization by a cervical collar was maintained during the entire period of chemotherapy.

The evolution was marked by a decrease in pain secondary to the active mobilization of the neck with a persistent passive analgesic position. The control radiologic MRI showed a displaced horizontal fracture of the dens responsible for a posterior wall recoil reducing cervical occipital hinge without intramedullary signal abnormality. The infiltrative process had regressed in size (Figure 3).

A posterior cervical arthrodesis was performed and the spine was stabilized with a metal lacing associated with tricortical iliac crest graft interposed between the posterior arch of C1 and C2. No neuro-vascular complications have been detected.

The patient is still under treatment consisting of prednisolone 40 mg/m^2 per day orally for five days in a week every four weeks and Ⅳ Vinblastine 6 mg/m^2 bolus every four weeks for 12 mo. Repeated CT scans revealed at 5 mo a consolidation of C2 fracture with moderate stenosis of the occipital hinge (Figure 4)

DISCUSSION

Spinal LCH commonly involves vertebral bodies, thoracic spine (54%) being the most common site of involvement followed by the lumbar (35%) and cervical spine (11%)[5]. Cervical vertebral involvement is exceedingly rare[6]. More than half of the cervical LCH lesions affect the C3-C5 vertebrae[4]. Atlantoaxial involvement by LCH is very rare[7]. Less than 15 cases have been reported in the literature. To our knowledge, it was the first Tunisian case of atlantoaxial LCH with odontoid process fracture reported in a 4-year-old child.

Our case present only torticollis as the first symptom, no other neurologic deficit was detected. In fact, pain, restricted range of motion or torticollis are the most common symptoms of cervical LCH[5]. However, the spinal destructive bony lesions etiology in children is extensive. Gaucher's disease, osteogenesis imperfecta, aneurysmal bone cyst, myeloma, tuberculosis, Ewing's sarcoma, osteogenic sarcoma, metastatic lesions, posterior fossa and cervical spinal cord tumors are part of the differential diagnosis of acquired torticollis with such bony lesions[5,7].

Loss of neural function is a rare occurrence with EG. It may result from vertebral collapse and impingement or, less frequently, from extradural extension of the lesion[5]. An asymptomatic case was also reported[2].

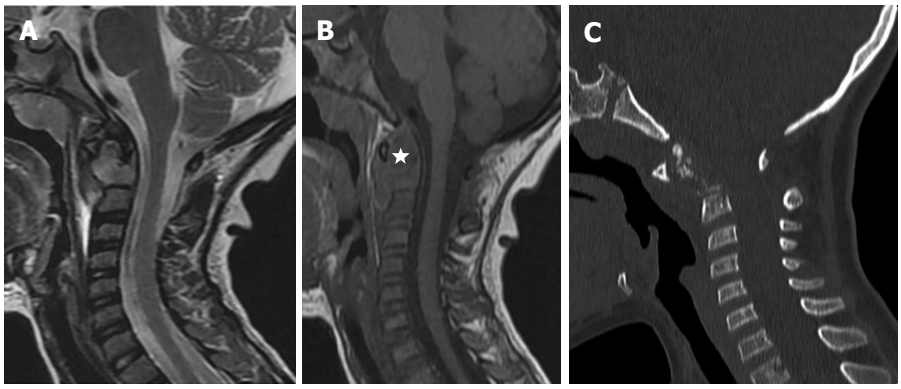

Figure 1 Initial cervical imaging: Sagittal FSET2 (A), SET1 magnetic resonance images (B) and Sagittal thin slice CT image (C). Infiltrative mass involving the dens of C2 hypointense on T1 and hyperintense on T2 sequence, extending to the surrounding soft tissues (star) leading to an increase in C1-C2 space. No compression of the spinal cervical cord. No signal abnormality nor rupture of the posterior longitudinal ligament spine. Complement CT showed fragmented dens with important C1-C2 dislocation.

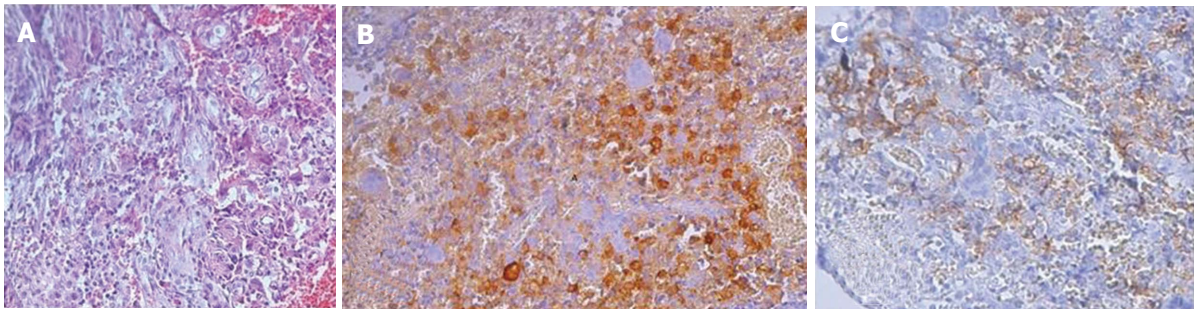

Figure 2 Langerhansien histiocytosis histology. A: Inflammatory granuloma with esinophils and histiocytes with circonvoluted nuclei; B: Positivity of the immunostain by the antibody anti Ps100; C: Positivity of the immunostain by the antibody anti CD1a.

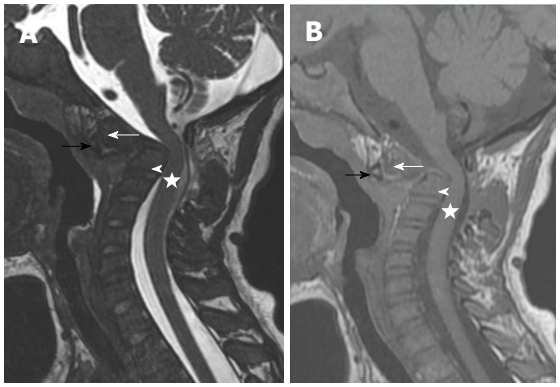

Figure 3 Six weeks follow-up after chemotherapy. Sagittal FSET2 (A), SET1 (B) magnetic resonance images: Displaced horizontal fracture of the dens responsible for a posterior wall recoil reducing cervical occipital hinge without intramedullary signal abnormality. Increase in the shrinkage of the cervical canal despite the regression of the infiltrative process. Black arrow: Anterior arch of C1; White arrow: The upper part of dens process; White arrowhead: The base of the dens; Star: Spinal cord.

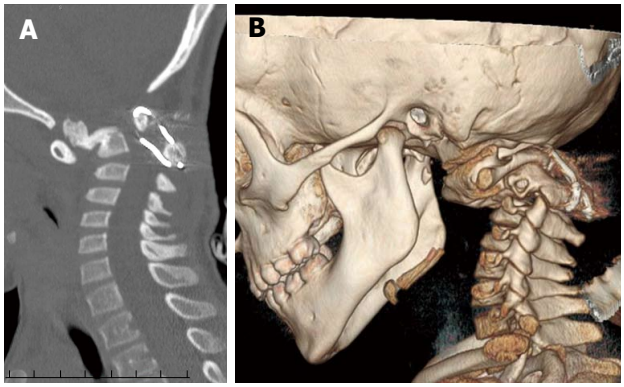

Figure 4 Five months post-operative follow-up. Sagittal thin slice CT image (A) and volume rendering CT image (B): Consolidation of C2 fracture with moderate stenosis of the occipital hing.

Since the atlantoaxial lesion was the only one detected in our case, the biopsy of the spine lesion under endoscopic guidance established the diagnosis. If there were multiple lesions, the most accessible lesion would be the appropriate for biopsy to avoid open biopsy and prevent the possible vertebral growth plate damage[6].

Our case fits into definitive diagnosis of LCH. The histological confirmation is required to establish LCH diagnosis[8]. The Writing Group of the Histiocyte Society identified three levels of confidence in the diagnosis of LCH. A definitive diagnosis, the third group, is established when histology is consistent with a diagnosis of LCH and the lesional cells are shown to express CD1a or to have intracytoplasmic Birbeck granules on electron microscopy[9]. Our patient presents a solitary spinal lesion. Spinal EG, in

the literature, is frequently associated with multiple skeletal lesion[3]. It is recommended that a technetium bone scan or a skeletal survey be performed early in the evaluation of every child with a suspected spinal lesion[3,5].

Within the adult population, displaced type 2 odontoid process fracture can be treated operatively or non-operatively, depending on the patient age, co-morbidities, fracture pattern and displacement[2]. However, the management of such fractures in the pediatric population remains unclear especially in fracture spine due to LCH[10]. With such paucity of literature on this topic, it is unknown whether operative intervention associated with chemotherapy aid fracture union and functional outcome in young child.

In the present case, treatment consisted in chemotherapy (combination of oral prednisone and intravenous vinblastine). The effectiveness of this type of combination was demonstrated by LCH-Ⅰ and LCH-Ⅱ group in systemic LCH but the situation for spine EG remained unclear[1,9]. The infiltrative process has regressed in size with this association. The patient tolerated the treatment of chemotherapy with vinblastine well and showed no serious complications. The decision to continue treatment for one year was made.

Garg *et al*[3] report a spinal LCH in a child successfully treated without any chemotherapy use. The use of chemotherapy to treat solitary EG is still controversial, but it seems safe and effective in some studies. However, localized bone lesions with spontaneous regression are described[8]. The resolution occurred at a rate unaffected by the mode of treatment[6,8].

Despite the absence of the observed neurologic deficit, the young age of the patient and radiologic assessment with displaced horizontal fracture of the dens and compromised spinal stability conducted to surgical excision followed by auto-graft fusion with satisfactory outcome in the present case. The use of surgery in such case is still controversial[1,3,6].

Jiang *et al*[6] argue that mild neurologic deficit could be immobilized under strict observation and surgery should be reserved for major neurologic defects like myelopathy or monoparesis. The authors believe some intervention should be used to prevent possible LCH progress, especially in the C2 vertebral body. In this study, a protocol for the management of suspected LCH lesion of the cervical spine was suggested, the atlantoaxial LCH lesion is not included in this protocol[6].

The radiotherapy was discussed but not applied for our patient. Some bone LCH lesions can be treated by radiotherapy alone[10,11]. However, a non successful radiotherapy performed on a 15-year-old girl presenting C1/C2 lateral LCH mass was reported[6]. Moreover, some authors support that radiotherapy might destroy the potential growth of the endochondral plates[6]. Further research on this topic is recommended.

Atlantoaxial LCH is rare. The diagnosis of the disease was made within a brief time limit with torticollis as the only clinic symptom. A delay in the diagnosis of this disease may lead to progressive neurological deterioration and increasing compression affecting largely the prognosis. Treatment modalities have changed over time depending on the clinical severity of the disease since it is quite varied. The combination of chemotherapy and surgical procedure seems to be effective in such lesion. This hypothesis needs to be improved from each other experiences.

COMMENTS

Case characteristics

A 4-year-old boy without significant medical history was admitted for limited neck motion for 3 wk.

Clinical diagnosis

The physical examination showed an irreducible torticollis with analgesic attitude of cervical spine.

Differential diagnosis

The spinal destructive bony lesions etiology in children is extensive. Gaucher's disease, osteogenesis imperfecta, aneurysmal bone cyst, myeloma, tuberculosis, Ewing's sarcoma, osteogenic sarcoma, metastatic lesions, posterior fossa and cervical spinal cord tumors are part of the differential diagnosis of acquired torticollis with such bony lesions.

Laboratory diagnosis

Laboratory tests were normal.

Imaging diagnosis

The magnetic resonance imaging of cerebro-spinal cord uncovered an infiltrative mass involving the dens of C2 which is hypointense on T1 sequence and hyperintense on T2 sequence, extending to the surrounding soft tissues leading to an increase in C1-C2 space, without compression of the spinal cervical cord. Complementary CT showed fragmented dens with important C1-C2 dislocation.

Pathological diagnosis

The odontoïd and mass biopsy was performed by endoscopic guidance. Histological features were consistent with inflammatory eosinophilic granuloma (EG). The positivity of the immunostain by the antibody anti Ps100 and the antibody anti CD1a confirms the diagnosis of langerhans cell histiocytosis (LCH).

Treatment

Initial treatment was started prednisolone 40 mg/m^2 per day orally, with weekly reduction starting from week 4 and intravenous Vinblastine 6 mg/m^2 per week for six weeks. An external immobilization by a cervical collar was maintained during the entire period of chemotherapy.

Related reports

Atlantoaxial involvement by LCH is very rare. Less than 15 cases have been reported in the literature. To our knowledge, it was the first Tunisian case of atlantoaxial LCH with odontoid process fracture reported in a 4-year-old child.

Term explanation

LCH is an uncommon disorder characterized by an abnormal accumulation of histiocytes. It includes three clinical entities namely EG, Hand-Schûller-Christian syndrome and Letter-Siwe disease. It consists in various clinical manifestations

from a single lytic bone lesion to multisystemic lesions with organ dysfunction.

Experiences and lessons

Atlantoaxial LCH is rare. A delay in the diagnosis of this disease may lead to progressive neurological deterioration and increasing compression affecting largely the prognosis. Treatment modalities have changed over time depending on the clinical severity of the disease since it is quite varied. The combination of chemotherapy and surgical procedure seems to be effective in such lesion.

Peer-review

This is an interesting case report, which seems to provide readers with useful information. The manuscript is well written.

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