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NON NARCOTIC ADJUVANTS TO LOCAL ANESTHETICS

Anaesthesiology

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ABSTRACT

As ambulatory surgery is gaining popularity, there is a need to facilitate earlier hospital discharge and improve postoperative pain control. As the shift is gaining from inpatient to outpatient day care surgery, the use of intravenous patient controlled analgesics and continuous epidural infusions has seen a steady decline. Multimodal analgesic regimens using non-opioid analgesics (e.g., local anesthetics, nonsteroidalantiinflammatory drugs, cyclooxygenase inhibitors, acetaminophen, ketamine, α 2-agonistsetc) are here to stay as these opioid-sparing techniques lead to reduced nausea, vomiting, constipation, urinary retention, respiratory depression and sedation. Non-narcotic analgesic techniques coupled with local anesthesia is associated with improved quality of recovery and a pain freepost operative period. Opioids are difficult to procure due to stringent anti narcotic stance of various governments due to abuse potential and anesthesiologists are opting for non narcotic adjuvants in their regional procedures the world over. A wide array of non opioiddrugs are available to achieve this and it would be prudent to have a working knowledge of these newer adjuvants for daily practice.

KEYWORDS

Adjuvants, local anesthesia

INTRODUCTION:

Over the last two decades, there has been considerable revival of interest in the use of regional anesthesia techniques for surgery and pain management. In order to counterbalance the side effects of subarachnoid block and epidural, new adjuvants to local anesthetics keep on adding to the list. These combinations allow for a reduction in doses of both classes of drugs, thus lessening the likelihood of side effects attributable to each. The "Combination Wisdom", has brought a new era to the regional anesthesia and especially relevant in the case of outpatients and daycare surgery patients where prolongation of anesthesia is of greater importance.

The non narcotic adjuvants used are detailed herewith:

(1) Neostigmine

Neostigmine methylsulfate is a synthetic carbamic acid ester which reversibly inhibits the enzyme Acetylcholine esterase (AChE) that makes more Acetylcholine molecules available at cholinergic receptors. Neostigmine is an anticholinesterase drug that inhibits hydrolysis of acetylcholine by competing for attachment at the esteratic site on acetylcholinesterase. This increased concentration of acetylcholine becomes available to bindat muscarinic and nicotinic receptors in the dorsal horn of spinal cord. Neostigmine being a quaternary amine, does not cross blood-brain-barrier. By intrathecal (IT) and epidural route, it provides analgesia via M1 and M2 receptors in the spinal cord, inhibiting the breakdown of acetyl choline (Ach). ACh induces analgesia by increasing cyclic guanidinomono phosphate by generating nitric oxide.Muscarinic receptors mediate analgesia in the dorsal horn of the spinal cord, and neostigmine produces analgesia when administered to both the intrathecal and epidural space.Autoradiographic studies have shown muscarinic binding in substantiagelatinosa and to a lesser extent in lamina 2 and lamina 5 of dorsal gray matter of spinal cord. Neostigmine also displays peripheral and supraspinal analgesic activity, however the dose necessary to achieve this is higher .(1,2)

The addition of 50 mcg neostigmine to bupivacaine in spinal anesthesia prolongs the duration of sensory and motor block and significantly increases the incidence of nausea and vomiting and the time until discharge criteria are achieved. Smaller doses of neostigmine, 6.25 and 12.5 mcg/kg, does not significantly prolong sensory and motor block but does increase the incidence of nausea and vomiting. The addition of 500 µg Neostigmine as adjuncts with Lidocaine in Epidural anesthesia reveals significant finding regarding and intensity of motor block. Large doses of intrathecal neostigmine alone can cause lower-extremity motor weakness in animals and volunteers (>or= to 150 mcg) because of an acetylcholine-mediated reduction in motor neuron outflow. (3,4)

Nausea and vomiting is delayed in onset (60-90 min after spinal injection), severe, repetitive, prolonged (2-6 h), and resistant to pharmacologic therapy. Ondansetron is ineffective and propofolis effective only briefly in treating nausea and vomiting. This is observed with doses greater than 50 mcg neostigmine alone. Nausea (50%) and vomiting (16.5%) occurs with intrathecal/epidural doses as small as 10 mcg. Because central neuraxial anesthesia (epidural and spinal) alone is associated with nausea and vomiting, the interaction of spinal anesthesia and intrathecal neostigmine may explain severe nausea and vomiting with such small doses 6.25-50 mcg of neostigmine.(5)

The analgesic effects of neostigmine is due to its action on muscarinic receptors identified on peripheral nerves. The use of neostigmine in PNBs has not been associated with improvements in postoperative analgesia. Neostigmine at 500 µg had no effect on sensory and motor blockade but is associated with a relatively high incidence of side effects. Neostigmine (500 µg) added to lidocaine in axillary blocks does not increase duration of postoperative analgesia and offers little benefit.Neostigmine added to local anesthetic for IVRA has also been disappointing. 500 µg of neostigmine added to prilocaine 0.5% hastens sensory and motor block onset and offset with prolonged time to first analgesic request. (6)

Overall, neostigmine appears disappointing as an analgesic adjuvant for peripheral nerve block or IVRA. Neostigmine, however, has been used successfully as an analgesic adjuvant for intra-articular use after knee arthroscopy. 500 µg is more effective than 2 mg of intra-articular morphine. The effectiveness of the intra-articular cholinergic analgesic pathway compared with the poor results with perineuronal application may be related to the presence of the inflammatory response in the intra-articular space, increasing the analgesic efficacy of acetylcholine by a mechanism that is yet to be defined.

The use of neostigmine as an adjuvant in neuraxial anesthesia is associated with a reduction in the dose of local anesthetic during labor analgesia and postoperative analgesia following cesarean section. The risk of nausea is increased with intrathecal neostigmine but not with epidural neostigmine. The use of neuraxial neostigmine is associated with a decrease in the risk of pruritus but there was no increase in the incidence of hypotension, dizziness or sedation and no incidence of abnormal fetal heart rate patterns or Apgar scores.Neuraxial administration of neostigmine significantly reduces local anesthetic consumption without serious adverse side effects to the mother or fetus. However, neostigmine is only recommended for epidural administration as intrathecal use significantly increases the incidence of maternal nausea and vomiting.(7)

Adrenaline alone

(200–1000 mg), injected into the lumbar CSF in obstetric patients,

caused spinal analgesia sufficient for vaginal delivery, without any signs of spinal cord ischaemia, even after1000 mg.

9 Thus, it is documented that adrenaline is a spinal analgesic in its own right. It has also been demonstrated that adrenaline acts via a 2-adrenoceptors (a 2A), inhibiting presynaptic transmitter release from C- and Ad-fibers, and causing postsynaptichyperpolarisation of the transmission cells of the substantiagelatinosa of the spinal cord dorsal horn. 11,12,43,44

Although adrenaline is metabolised by COMT in spinal meningeal cells 45 , the results of Bromage et al and Curatolo et al strongly indicate thatepidurally administered adrenaline in bolus doses of 50 mg (5 mg/ml) penetrates the dura and arachnoidea mater in sufficient amount to cause spinal cord effects

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Anesthesiologists often add epinephrine to lidocaine during peripheral nerve block procedures. The advantage of this practice is twofold. First, it reduces the LA plasma concentration and thus minimizes the possibility of systemic toxicity, and second, it improves the quality and prolongs the duration of peripheral nerve block. Most anesthesiologists accept the idea that epinephrine mediates this prolongation of LA action by its vasoconstrictive actions. By stimulating α-adrenergic receptors on the neural vasculature, epinephrine mediates contraction of the vascular smooth muscle, reduces local blood flow, and thereby slows clearance of lidocaine from the nerve. It appears that epinephrine binds to those adrenergic receptors located on the extrinsic plexus of vessels in the epineural space. These vessels then cross the perineurium and anastomose with the intrinsic circulation in the peripheral nerves responsible for the direct clearance of the LA from within the nerve, the "effector compartment" for neural blockade.(8)

The vasoconstrictor effect of epinephrine can prolong the action of local anesthetic and also decrease blood supply to the neural tissue to a threshold associated with nerve damage in patients with diabetes or compromised vascular integrity. Anesthesiologists prefer to continue using epinephrine as an intravascular marker to detect any inadvertent intravascular injection during nerve block placement, especially when an out-of-plane ultrasound technique or a blind peripheral nerve stimulation technique is used. The dilution of epinephrine to 2.5 µg/mL can be an effective marker for intravascular injection and is associated with few side effects. It has been suggested that this dose may also transiently increase peripheral nerve blood flow, presumably by β-adrenergic effects

Adding epinephrine to intrathecal or regional anesthetics prolongs analgesia and motor block by no more than 60 minutes. The impact of adding epinephrine to epidural local anesthetics or to a combined spinal-epidural remains uncertain. *However, it is recommended that the use of epinephrine for nerve blocks done without ultrasound guidance, or blocks in which the needle tip and local anesthetic spread is not adequately visualized, as a safety measure to detect intravascular injection.*

Decreases in blood flow and the increased duration of analgesia with epinephrine are due to the $\propto_1$-adrenoceptor agonist effect of epinephrine. Some local anesthetics, including lidocaine and ropivacaine, will also cause vasoconstriction and are synergistic with epinephrine. Whether the effect of epinephrine is simply due to decreased systemic uptake leading to a greater effect of the local anesthetic on the peripheral nerve is still not completely understood; however, perineural epinephrine alone does not cause sensory or motor blockade.

The controversy surrounding widespread use of epinephrine in combination with local anesthetics is the argument as to whether it is protective or harmful. There is no question that epinephrine can be a valuable marker for the detection of intravascular injection, and many believe that the early detection of intravascular injection greatly outweighs the potential neurotoxic or myotoxic effects. The increased use of ultrasound worldwide allows for visualization of the needle tip and real-time assessment of local anesthetic spread; however, unintentional intravascular injection of local anesthetic with subsequent cardiovascular collapse using ultrasound has still been reported and remains a legitimate concern. The addition of epinephrine to local anesthetics may increase the potential neurotoxicity, which may be especially concerning in those patients at higher risk for nerve injury (i.e., patients with diabetes mellitus, hypertension, and/or a history of smoking). The use of epinephrine as an additive for test dose purposes in out-of-plane ultrasound blocks or nerve stimulator blocks is recommended. Beta blockade may limit the use of epinephrine as a marker of intravascular injection. Avoidance of high volume blocks, use of in-plane ultrasound guidance, slow injections, and limited sedation with constant assessment of central nervous system excitatory effects are likely equally or more important for limiting potential cardiotoxicity. (9,10)

3. Alpha$_2$-adrenoceptor agonists:
These receptors are located on primary afferents of both peripheral and spinal nerve endings, on the superficial laminae of the spinal cord, and within several brainstem nuclei implicating analgesic action at peripheral, spinal, and brainstem sites in animals. The effects ofintrathecal α_2-adrenoreceptor agonists is mainly achieved by inhibiting the release of C-fiber transmitters and substance P, and hyperpolarizing post-synaptic dorsal horn neurons, and the analgesic effect has a good correlation with their binding affinity to the spinal α_2 adrenergic receptors.

(a)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. Because α2- receptors are not present on the axon of the normal peripheral nerve, the mechanism of analgesia of clonidine may be related to the drug's ability to block cation current through hyperpolarization-activated cyclic nucleotidegated channels that subsequently prevent neurons from generating action potentials. This current normally functions to restore nerves from a hyperpolarized state to resting potential for a subsequent action potential. The effect appears to be more profound on C-fibers (pain fibers) than A∝-fibers (motor fibers), thereby making the effects potentially more sensory specificMinor degrees of nerve conduction blockade at both local and central sites are produced with high concentrations of clonidine. Because multiple sites of action have been identified for clonidine, mixed results in demonstrating clonidine's effect on analgesia have been reported when used as an adjuvant with local anesthetics. (11,12,13)

Clonidine appears to improve the duration of analgesia with intermediate but not long-acting local anesthetics. Side effects such as

hypotension and bradycardia are dose dependent and limited when doses are kept to 150 µg or less. 150 µg of clonidine increases postoperative analgesia of longacting anesthetics by more than 2 hours. Furthermore, when clonidine is added to ropivacaine, motor blockade has a shorter duration than when added to bupivacaine. This implies that clonidine may provide long-lasting analgesia without prolonging the duration of motor blockade. In peripheral nerve blocks it prolongs duration of analgesia by hyperpolarisation of cyclic nucleotide gated cation channels. Clonidine also produces a minor degree of nerve conduction blockade (C-fibers) at high concentrations and hence the enhancement of peripheral nerve block when added to local anesthetics. (14,15,16)

Use of clonidine in neuraxial blocks has been plagued by the adverse effects like sedation, bradycardia and hypotension, thus recommendations of lower dosages. This is likely due to systemic absorption of the medication and stimulation of the α2-receptors.A dose of 100 µg clonidine may produce mild, treatable side effects also seen with other anesthetics; Hence it may be prudent to use (to avoid hypotension) lower range of doses of the drug for patients in the sitting position with spontaneous ventilation, as is commonly the case with arthroscopic or "mini-open" shoulder surgery. (17,18)

(b)Dexmedetomidine:

It is a selectivelipophilic alpha-2 receptor agonist in comparison to clonidine, it has a similar mechanism of blocking hyperpolarisation activated cation channels.Dexmedetomidine has a high affinity for α2-receptors and is 8 times more selective for α2- than α1-receptors (1620:1) than clonidine is (200:1) .α-2 Adrenoceptorsare subdivided into four subtypes: α-2A, α-2B, α-2C, and α-2D. The α-2A, α-2B, and α-2C adrenoceptorsare well identified pharmacologically. They are differentially distributed in central and peripheral cells and tissues, and have different physiological functions and pharmacological activities. Thus, oxymetazoline hydrochloride (oxymetazoline), is a specific agonist for α-2A adrenoceptor, yohimbine hydrochloride (yohimbine), an α-2A, α-2B, and α-2C adrenoceptor antagonist, and prazosin hydrochloride (prazosin), an α-1, α-2B, and α-2C adrenoceptor antagonist have been utilized to explore the mechanism of the peripheral effect of α-2 adrenoceptor agonists on the anesthetic action of a local anesthetic. an α-2 adrenoceptor agonist combining with lidocaine enhances local anesthetic action via α-2 adrenoceptors, not via α-1 adrenoceptors. Dexmedetomidine binds α-2A, α-2B, and α-2C adrenoceptors with high affinity. Hyperpolarization-activated cation currents normally bring neurons back to the resting potential and normal functional activity during the refractory phase in an action potential. By blocking these currents, dexmedetomidine can accentuate inhibition of neuronal conduction and produce analgesia. (19,20,21)

This increase in selectivity and agonism of α2-receptors intensifies the sedative and analgesic effects of dexmedetomidine, causing hypotension and bradycardia. Although its mechanism of action in PNBs remains unclear, it is hypothesized that dexmedetomidine produces analgesia by blocking the hyperpolarization-activated cation current in the peripheral nerve, preventing an action potential from generating and rendering the nerve refractory to stimulation. Dexmedetomidine (150 µg) hastens onset time of sensory and motor blockade, extends mean duration of analgesia by 240 minutes, and decreases pain scores for the first 24 hours after surgery. Dexmedetomidine in ulnar nerve blocks prolongs sensory and motor blockade by 205 and 248 minutes, respectively. Interestingly, sensory blockade and motor blockade are also clinically prolonged after IV administration of 20 µg of dexmedetomidine by 45 and 90 minutes, respectively without any hemodynamic side effects. Perineuraldexmedetomidine prolongs the time to first analgesia and prolongs the mean duration of motor blockade by 268 minutes and the duration of sensory block by 284 minutes. A wide range of doses (30 µg to 100 µg) are being used and side effects include bradycardia, hypotension, and sedation. Further research is needed to establish the most effective dose associated with the fewest side effects. (22,23)

The greatest concern about the intrathecal application of Dexmedetomidine is its neurotoxicity as it has been seen to cause moderate to severe demyelination of white matter when it was administered by epidural route at a dose of up to 6.1 $\mu g \cdot kg^{-1}$ in rabbits.

Clonidine and dexmedetomidine prolong the duration of analgesia by 123 and 345 minutes, respectively. Although an optimal dose has not been established for dexmedetomidine, clonidine up to 150 µg has been demonstrated to prolong analgesia with the fewest side effects.Dexmedetomidine is seen to be superior to sufentanil in analgesic effect and duration in first-stage labor during epidural analgesia when combined with 0.1% ropivacaine. The addition of dexmedetomidine to lidocaine for maxillary and mandibular nerve blocks significantlyshortens the onset of action and prolongs the block duration with better postoperative analgesia in terms of the need for fewer analgesics in the postoperative period.(24,25,26,27,28)

4. MIDAZOLAM:

Synthesized in 1976 by Walsar, midazolam was the first water soluble benzodiazepine. In 1986, high density GABA A receptors were discovered in lamina II of the dorsal horn of the spinal cord and, in the 1990s intrathecal midazolam use was commenced as it released endogenous opioids at the spinal delta receptors. (29,30)

Midazolam exerts its effect by occupying benzodiazepine receptor that modulates γ-amino butyric acid (GABA), the major inhibitory neurotransmitter in the brain. Benzodiazepine receptors are found in the olfactory bulb, cerebral cortex, cerebellum, hippocampus, substantianigra, inferior colliculus, brain stem, and spinal cord. There are two types of GABA receptors; benzodiazepine receptors are part of the benzodiazepine-GABAA-chloride channel receptor complex. Benzodiazepine binding site is located on the γ2 subunit of the GABA receptor complex . With the activation of the GABAA receptor, gating of the channel for chloride ions is started after which the cell becomes hyperpolarised and resistant to neuronal excitation. (331,32,33)

The hypnotic effects of benzodiazepine are mediated by alterations in the potential dependent calcium ion flux Hypnotic, sedative, amnesic, and anticonvulsant effects are mediated by α1 GABA receptors and anxiolysis and centrally acting muscle relexant properties are mediated by α2 GABA receptors The anxiolytic effect of midazolam is via its action at mammillary body. Presumably midazolam exerts its anxiolytic property like other benzodiazepines by increasing glycine inhibitory neurotransmitter. Midazolam also possesses anticonvulsant action which is attributed to enhanced activity of GABA on the brain's motor circuit. It exhibits a muscle relaxant effect via its action at the glycine receptors in the spinal cord. Midazolam administered via intrathecal or epidural routes can produce analgesia, probably due to its GABA mediated action. Other mechanisms of action including its interaction with opiate receptors have also been proposed.Intrathecal benzodiazepine-induced analgesia is spinally mediated. Binding sites are GABA receptors, abundantly present in the dorsal root nerve cells, with the maximum concentration found within lamina II of the dorsal nerve cells, a region that plays a prominent role in processing nociceptive and thermoceptive stimulation. (343,35,36)

The first step in the metabolism of midazolam is hydroxylation. The two metabolites formed are α-hydroxymidazolam and 4-hydroxymidazolam, both are pharmacologically active. The α-hydroxymidazolam is as potent as the parent compound and may contribute significantly to the effects of the parent drug when present in sufficiently high concentrations. 4-Hydroxymidazolam is quantitatively unimportant. Both metabolites are rapidly conjugated by glucuronic acid to form products which have been considered to be pharmacologically inactive. On the other hand; glucuronidated α-hydroxymidazolam, the main metabolite of midazolam, has a substantial pharmacological effect and can penetrate the intact blood–brain barrier. The elimination half-time of α-hydroxymidazolam is about 70 min. However, it can accumulate in patients with renal failure.(37,38)

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.A high concentration of type-II benzodiazepine receptors is found in the substantiagelatinosa of the human spinal cord, leading to the hypothesis that they may have a role in sensory pathways. Midazolam acts by facilitating the action of the inhibitory neurotransmitter c-aminobutyric acid (GABA). It may also have a central antinociceptive effect via the activation of spinal delta opioid receptors. (39)

When used intrathecally, midazolam 1– 2 mg has been shown to

potentiate the analgesic effects of intrathecal bupivacaine for 2–6 h and intrathecal fentanyl by 50 min. Intrathecal midazolam delays the time to request rescue analgesia without any increase in the duration of motor blockade. Similar improvements in pain scores are seen with the addition of midazolam to bupivacaine for adult epidurals and paediatric caudal epidurals, although there is an increased incidence of sedation. When used in conjunction with bupivacaine for a supraclavicular nerve block, midazolam 50 lg.kg)1 is associated with improved postoperative pain scores and decreased analgesic requirements for up to 24 h. Intra-articular midazolam provides 4 h of additional analgesia after arthroscopy. 2 mg of intrathecal midazolam does not increase the occurrence of symptoms suggestive of neurological damage when compared with conventional therapies.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. Intrathecal midazolam is a useful adjuvant for prolongation of analgesia.(40)

Epidural midazolam in doses of50 µg/kg potentiates the effect of bupivacaine in patients undergoing upper abdominal surgery. Similarly, it potentiates 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.

Neurotoxicity of intrathecal and epidural midazolam in animal models was a concern. However, 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.

Peribulbar block using a combination of lidocaine 2% and hyaluronidase 15 IU/mlplus midazolam 50 µg/ml results in shorted onset time of the sensory block.

Intrathecal midazolam appears to improve perioperative analgesia and it can be useful and safe adjunct to bupivacaine for intrathecal analgesia during different surgical operations. A study on the analgesic and sedative effects of intrathecal 2mg preservative free midazolam in perianal surgery under spinal anesthesia found that the addition of bupivacaine produces a more effective and longer analgesia with a mild sedative effect. Postoperative pain relief following intrathecal administration of 1mg preservative free midazolam with bupivacaine in patients scheduled for elective lower abdominal, lower limb, and endoscopic urological surgeries provides longer duration of postoperative analgesia when compared to intrathecal bupivacaine alone, without prolonging time for dermatomal regression. The addition of preservative-free midazolam to bupivacaine intrathecally results in prolonged postoperative analgesia without increasing motor paralysis. The use of intrathecal midazolam also decreases the incidence of postoperative nausea vomiting (PONV). (41)

Benzodiazepines are unique among the group of intravenous anesthetics in that their action can readily be terminated by administration of their selective antagonist flumazenil.

5. Neuromuscular blocking drugs:

Neuromuscular blocking drugs have been used as adjuncts to LAs in peribulbar blocks and in intravenous regional anaesthesia. Vecuronium 0.5 mg has been shown to provide superior ocular and eyelid akinesia than placebo when added to a mixture of lidocaine with adrenaline, bupivacaine and hyaluronidase . The addition of atracurium 5 mg to a lidocaine and bupivacaine mixture resulted in more rapid ocular akinesia but no difference in the frequency of complete akinesia . The addition of atracurium (2 mg) and cisatracurium (0.01 mg.kg)1) to lidocaine and prilocaine for intravenous regional anaesthesia is associated with superior intra-operative analgesia and easier forearm fracture reduction with no adverse side effects. However, the addition of mivacurium 0.6 mg to prilocaine resulted in all patients complaining of symptoms consistent with LA toxicity and all experienced prolonged motor blockade. (42,43,44,45,46)

Adding muscle relaxantrocuronium 5 mg to the local anesthetic mixture (lidocaine, bupivacaine, and hyaluronidase) for peribulbar block provides optimal globe akinesia, shortens the block onset time, and improves the postoperative analgesia.Epidural ropivacaine with rocuronium 0.6mg/kg does not prolong the duration of neuromuscular blockade. (47,48,49)

6. Steroids:

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

(a) Dexamethasone:

Itis a long-acting glucocorticosteroid used predominately for its anti-inflammatory and antiemetic actions. Although its mechanism of action as an adjuvant is not completely understood, it is known that as a glucocorticoid it exhibits anti-inflammatory and analgesic effects through inhibition of phospholipase A2 and activation of glucocorticoid receptors. Locally administered corticosteroids inhibits signal transmission of nociceptive C-fibers, decreases ectopic neuronal discharge, and decreases the release of local inflammatory mediators. Dexamethasone prolongs the mean analgesic duration for long-acting local anesthetics by 576 minutes and prolongs mean motor blockade by 438 minutes. Patients who receive 8 mg of dexamethasone in sciatic blocks report less pain at 24 hours. Dexamethasone 4 mg can extend the duration of analgesia by 10 hours for upper extremity PNBs. Perineural dexamethasone prolongs the duration of analgesia and motor blockade but may not be beneficial when used for lower extremity cases. Preservative components found in pharmaceuticals, particularly polyethylene glycol, have been linked to possible neurotoxic sequelae. Dexamethasone has a potentialto produce transient increases in blood glucose and a potential for subsequent wound infection. Increases in blood glucose concentration of 3.8 mg/dLis, however, clinically not significant.(50,51,52)

4 to 10 mg dexamethasone-containing local anaesthetic solutions have a faster onset of action in brachial blocks and also a significant increase in the duration of analgesia compared with local anaesthetic solutions alone. Dexamethasone significantly decreases postoperative nausea and vomiting and approximately doubles the duration of postoperative analgesia when it is combined with intermediate-acting (lidocaine, mepivacaine) or long-acting (bupivacaine, ropivacaine) local anaesthetic.(53)

(b)Methyprednisolone:

The drug belongs to corticosteroid group and long been used in analgesia. Studies show that depo-methylprednisolone as an adjuvant to 0.5% lidocaine shows excellent result in neuropathic pain resulting from nerve injury. The adjuvant and anesthetic are administered at the proximal site of the injury through peripheral nerve block.(54)

7. Non-steroidal anti-inflammatory drugs (NSAIDs)

Trauma causes the migration of inflammatory cells that release cytokines, primarily IL-6, causing a local inflammatory reaction at the site of injury. When cytokines subsequently reach the blood circulation, a systemic reaction may occur which leads to an increase in C-reacting proteins (CRP), serum amyloid A-protein in the liver as well as T- and B-cell activation in the blood and bone marrow. Later, a compensatory anti-inflammatory response causes inhibition of the pro-inflammatory cytokines. Pro- and anti-inflammatory cytokines serve as immune-modulatory molecules that limit potential injury or excess inflammatory reactions during physiologic conditions. Under pathologic conditions, imbalanced cytokines may cause systemic inflammatory responses or immune-suppression due to a shift in the balance between pro- and anti-inflammatory cytokines. This may result in organ dysfunction, immunity and infection, as well as affecting wound healing and pain after surgery. Similarly, musculo-skeletal trauma, as during surgery, causes an inflammatory response that leads, at first, to an elevation of the pro-inflammatory cytokines in the plasma and later, the anti-inflammatory cytokines step in so that a balanced inflammatory response is seen perioperatively. Osteoarthritis of the hip joint results in an increase in pro-inflammatory mediators, specifically IL-6, IL-8 and TNF-α in the synovial fluid. NSAIDs commonly used for the treatment of osteoarthritis decrease IL-6, TNF-alpha and VEGF in the synovial fluid with an improvement in joint pain and function. Thus, it is possible that local infiltration of ketorolac and local anesthetics periarticularly may reduce pain intensity via local anti-inflammatory effects, and could partly explain the known analgesic effect of NSAIDs. (55,56,57,58)

Non-steroidal anti-inflammatory drugs have been used as adjuncts in intravenous regional anaesthesia. When lornoxicam 8 mg was used in conjunction with lidocaine, the onset time for motor and sensory blocks was decreased and an improvement in postoperative analgesia was noted. Similar benefits in postoperative analgesia have been demonstrated with ketorolac (20–60 mg), tenoxicam (20 mg) and lysine acetylsalicylate (90 mg). (59)

By injecting ketorolac directly into the peri-articular tissues, high concentration of the drug is likely achieved locally and with much lower plasma concentrations. Although some amount of ketorolac is absorbed into the systemic circulation when injected periarticularlyhas systemic anti-inflammatory effects. Ketorolac is known to prolong the local anesthesia in conjunction with regional anesthetics by inhibiting prostaglandin. The drug belongs to the class of parenteral NSAIDs. Studies have shown that addition of ketorolac to another local anesthetic lidocaine (1.73% lidocaine plus IV ketorolac) improves the length of analgesia in peripheral nerve block at ankle in pediatric surgery.

A combination of spinal anaesthesia and locally injected NSAIDs, may provide the correct balance of low pro-inflammatory cytokines in plasma, early mobilization, lower pain intensity and quicker home discharge after surgery.

Tenoxicam is a newer-generation drug-of-choice NSAID in the oxicam group. It is a highly hydrophilic prostaglandin synthesis inhibitor with a peripheral pharmacodynamic action, therefore lacking central effects. It is almost entirely eliminated by linear metabolism. The recommended systemic dose of tenoxicam for postoperative pain is 20-40 mg intravenous or intramuscular every 24 h. The local addition of small dose tenoxicam (2 mg) is effective in reducing the incidence, duration, and severity of postepidural backache, particularly after multiple attempts at needle placement. (61,62)

Ketorolac as a component of intravenous regional anesthesia (IVRA) can suppress intraoperative tourniquet pain and enhance postoperative analgesia. Addition of ketorolac improves IVRA with 0.5% lidocaine both in terms of controlling intraoperative tourniquet pain and by diminishing postoperative pain.

8. MAGSULF

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. It had been shown to reduce the postoperative analgesic requirements in a variety of cases.Intrathecal administration of magnesium sulfate suppresses nociceptive impulses in neuropathic pain and potentiates opioid anti-nociception in animal studies. In humans, profound motor and sensory block for up to 3-27 h are reported in orthopedic, general surgery and gynecological procedures. (63,67,68,69)

The duration of spinal opioid analgesia in patients requesting analgesia for labor is significantly prolonged by co-administration of magnesium sulfate with no effect on motor block, sensory block or the incidence of adverse effects like pruritus. Magnesium sulfate in doses of 25-100 mg can be used along with opioids (fentanyl/sufentanyl) with or without local anaesthetic agents (lidocaine, bupivacaine, levobupivacaine and ropivacaine).A rapid onset of sensory block occurs 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. A faster onset of action, longer duration of actions and reduced breakthrough pain with no change in adverse effects or fetal outcome is observed when magnesium sulfate was used as an adjuvant in labor analgesia.Magnesium sulfate as an adjuvant to local anaesthetics in interscalene and supraclavicular brachial plexus block, axillary block, femoral nerve block and popliteal nerve blockincreases the duration of analgesia without any adverse effects. Intrathecal administration of magnesium sulfate suppresses nociceptive impulses in neuropathic pain and potentiates opioid anti-nociception and results in profound motor and sensory block for up to 3-27 h in orthopedic, general surgery and gynecological procedures. (70,71,72,73)

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.

9. Verapamil

Verapamil, a synthetic papaverine derivative, is an L type calcium channel blocker. Verapamil has been shown to have potent local anaesthetic activity, reflecting inhibition of fast sodium channels. It induces fast channel blocking effects similar to local anaesthetics.belongs to the calcium channel blocker category that is used as adjuvant to local anesthtics for peripheral nerve block. Verapamil has been used in addition to lignocaine/bupivacaine solution for brachial plexus and exhibited significant result in prolonging the duration of action of local anaesthetic. It lengthens the sensory block by reducing permeability of calcium ion. The use of verapamil in supraclavicular brachial plexus block has been studied extensively and found effective as an adjuvant to levobupivacaine in terms of faster onset and prolonged analgesia. Suggested dose 2.5 mg per 20 ml local anesthetic. (74,75,76)

10.Sodiumbicarbonate

Sodium bicarbonate is added to any local anesthetic solution for alkalization that facilitates the passage of the chemical across the lipid membrane resulting in increased nerve blockade action. Among some of the local anesthetic, bupivacaine may be alkalized with a lower concentration of sodium bicarbonate to prevent the precipitation of bases present in the solution. Hence, it can be safely concluded that the effect of sodium bicarbonate is unclear and it should be used with only selected few peripheral nerve blocks.Alkalinization with sodium bicarbonate reduces pain on injection by increasing pH (acidic solutions *per se* are algogenic), decreases onset time, and perhaps produces a more complete block by elevating the pH of the lidocaine solutions closer to the pK_a of this local anesthetic, thus favoring the proportion of the deprotonated, membrane-permeant form of the local anesthetic.

The addition of 8.4% sodium bicarbonate to 2% lidocaine hydrochloride without epinephrine (1:10, vol:vol) decreases onset time and enhance the depth of epidural block at L4–S1. When bicarbonate is added to 2% lidocaine hydrochloride with epinephrine (1:200,000), neither onset time nor depth of epidural block at L4–S1 roots are altered. Recommended dose is2 mL sodium bicarbonate 8.4% per 20 ml plain local anesthetic for epidural use. (77,78)

11. Adenosine:

Adenosine is known to have various modulatory effects both in the peripheral and central nervous system. Intrathecalinjection of an adenosine agonist was first tested in animals for antinociception in 1984 and tested intrathecally in humans for analgesia in 1995. In doses less than 0.5 mg, adenosinereduces acute nociceptive pain in humans for 24 h, despite itshalf life in human cerebrospinal fluid of less than 2 h. (79,80,81)

Other studies of 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. The most common side effects of the drug are headache and backache. (82,83,84)

12. Dextran

A linear increase in solubility of the local anaesthetic base with increasing concentrations of dextran suggests that the mixture forms soluble molecular complexes. Increasing the molecular weight of dextran prolongs the action of local anaesthetic by forming macromolecules may be formed between dextran and local anesthetic so the later is held in the tissue for longer period. Dextran also reduces vascular uptake of lignocaine from epidural space and that it may prolong the duration of action and is pH dependent.Dextran has been largely replaced with liposomal bupivacaine.(85,86,87,88)

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