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Short Topic

Adjuvants in Peripheral Nerve Blocks

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An increase in the use of peripheral nerve blocks (PNBs) has been noted in recent years. Not only do these blocks provide adequate anaesthesia intraoperatively, but they are also now the cornerstone of perioperative pain management. Superior pain control, a significant decrease in opioid requirements as well as opioid-related side effects, improved patient satisfaction, earlier discharge from hospital and increasing use with the advancement of ultrasound technology have contributed to the increasing use of peripheral nerve blocks [1-4].

Regional anaesthesia techniques including PNBs have also become the need of the hour in recent times of the Covid19 pandemic. As per recent practice recommendations (American Society of Regional Anaesthesia May 2020), Regional anaesthesia is preferred to avoid aerosol-generating procedures associated with General anaesthesia [5].

For postoperative pain management, PNBs are used as a single injection or as a continuous catheter infusion. Single-injection nerve blocks are more commonly done as they are technically easier and quicker. They provide superior analgesia in the immediate postoperative period for various procedures in which the pain intensity is high initially and reduces over significantly over time. Oral analgesics may be effective by then as the effect of PNBs is wearing off gradually over 12 to 24 hours. Rebound pain can however be a significant problem [6]. Continuous catheter techniques are not only technically challenging but require greater monitoring and are prone to secondary block failures due to catheter blockage and displacement [7]. They are labour and resource intensive. Hence the need for adjuvants that will help prolong the duration of PNBs and avoid the placement of continuous catheters has been part of the quest of regional anaesthesiologists. Multiple classes of drugs have been tested as adjuvants in the past. Some have stood the test of time and helped improve the practice of regional anaesthesia while others proved more detrimental. Discussed below are some of the adjuvants that have been successfully used (Table 1).

Opioids

Opioids are a class of frequently used local anaesthetic adjuncts. Drugs like morphine, fentanyl, sufentanil have been used for years intrathecally as an adjunct [8, 9]. However, their perineural use in PNBs has not proved as successful [10, 13].

Buprenorphine is another drug from the same group that has been used in PNBs as an adjuvant and has been found to increase the duration of sensory blockade significantly [14, 15]. It is a partial agonist at the Mu Opioid receptor and a Kappa Opioid and Delta Opioid receptor antagonist [16]. It has not received Food and Drug Administration approval for neuraxial or perineural administration. It has been used in the dose of 150-300 mcg [15]. The use of Buprenorphine intravenously or perineurally has been associated with the systemic side effects of Nausea and Vomiting (PONV), sedation and respiratory depression thus limiting its use.

Vasoactive Agents

One of the most common pharmacological adjuncts used in PNBs is adrenaline. Multiple studies are published on the role of adrenaline as an adjunct using different local anaesthetics [17-20]. It is commonly used in the dose range of 2.5-5 mcg/ml. However, due to the local vasoconstrictor effect, it is seen to prolong the duration of the block slightly [21]. The peak plasma level of local anaesthetic is reduced hence higher local anaesthetic recommended doses. It is more commonly used as a marker of intravascular injection.

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Drug Name	Classification	Dose	Limitations
Buprenorphine [15]	Opioids	150-300 mcg	Systemic side effects of PONV, sedation and respiratory depression
Adrenaline [18]	Alpha agonist	2.5-5 mcg/ml	Common use as a marker for unintended intravascular injection
Clonidine [22]	Alpha 2 agonist	1-1.5 mcg/kg	Higher incidence of cardiovascular side effects like bradycardia, hypotension.
Dexmedetomidine [28]	Alpha 2 agonist	0.5-1 mcg/kg	Adverse effects like bradycardia and hypotension
Dexamethasone [34, 35]	Steroid	1-8 mg	Steroid-induced hyperglycaemia
Ketamine [46]	NMDA antagonist	30 mg	Risk of psychomimetic adverse effects
Magnesium Sulphate [50-52]	NMDA antagonist	150-450 mg	Conflicting evidence regarding the effectiveness

Table 1: The adjuvants used successfully

Clonidine is a non-selective imidazole derivative belonging to the alpha-2 adrenoreceptor agonist group. It was used frequently as an adjuvant in PNBs, dose being 1-1.5 mcg/kg. The mechanism of action is thought to be via blockage of hyperpolarization-activated nucleotide-gated channels responsible for cation currents. Clonidine thus maintains A-delta and C fibres in a hyperpolarised state inhibiting their action potential generation. Another possible action could be localised vasoconstriction via its alpha-1 adrenoreceptor action. Multiple RCTs have evaluated the effect of perineural clonidine and found a motor and sensory block prolonging effect [22-24]. However, clonidine is also associated with cardiovascular side effects of bradycardia, hypotension. This requires greater peri-operative monitoring. A meta-analysis of 14 clinical trials done by El-Boghdadly et al covering 868 patients found that perineural dexmedetomidine had a faster onset of block and longer sensory and motor block duration as compared to perineural clonidine [25]. Hence dexmedetomidine is now preferred over clonidine in PNBs.

Dexmedetomidine belongs to the same class as clonidine. It is eight times more alpha 2 selective than clonidine. It is known to have sedative, analgesic, sympatholytic and anaesthetic sparing properties. Dexmedetomidine provides analgesia via its action at the supraspinal (locus ceruleus) level, spinal level or even at the peripheral adrenoreceptor level by decreasing nociceptive stimulus transmission. It is now being used as an adjunct in peripheral nerve blocks to prolong their duration [26, 27]. The dose used for PNBs is in the range of 0.5-1 mcg/kg [28]. Neurotoxicity effects of dexmedetomidine were not studied until recently. Xue et al performed neurotoxicity studies on sciatic nerve roots of rats [29]. When they compared the apoptotic changes in the nerve cells between ropivacaine alone and ropivacaine with dexmedetomidine, they found significantly lower apoptosis rates in the dexmedetomidine group. Furthermore, higher doses of dexmedetomidine had lower rates of apoptosis. It has been observed that while low doses prolong block duration significantly, high doses also shorten the onset of block action along with prolonging block duration. Different routes of administration of dexmedetomidine have also been studied. Perineural administration has shown to be more effective and associated with lesser hemodynamic side effects as compared to the intravenous route of administration. Researchers have also compared dexamethasone and dexmedetomidine as adjuvant and found that perineural dexamethasone causes the longest block prolongation with the least amount of side effects [30, 31].

Steroids

Another commonly used adjuvant is dexamethasone. Dexamethasone is a potent long-acting steroid with proven efficacy as an adjuvant in various studies [32, 33]. It has been studied in various doses ranging from 1 to 8 mg, the most common being 8 mg [34, 35]. Liu et al compared dexamethasone doses of 1 mg, 2 mg and 4 mg injected perineurally and found no significant difference in the duration of blockade achieved by either of the three doses [36]. This in the light of neurotoxicity reports in animal models of high dose dexamethasone allows for a significant reduction in the routinely used perineural doses [37]. Steroids are believed to have strong anti-inflammatory and analgesic properties, however, the exact mechanism by which it acts as a PNB adjunct is unknown. They are believed to block transmission of nociceptive C-fibres and suppress ectopic neural discharge [38]. Route of administration is another factor that has been studied and is known to affect the length of block prolongation. Multiple studies have been done on animal models as well as human volunteers/ patients comparing the perineural and intravenous route [39-41]. Most of the studies have documented significantly longer durations of analgesia with perineural drug as compared to a drug given via the systemic route. A meta-analysis done by Zorrilla-Vaca et al noted that when doses in the range of 4-

5 mg were used perineurally and intravenously, perineural dexamethasone prolonged the block significantly more [42]. However, when doses of 8 mg or more were used there was no significant difference found in block prolongation.

There is the possibility of post-injection hyperglycaemia even at the doses used in PNB [41-43]. This is particularly disadvantageous in diabetic patients in whom PNBs are frequently used.

A few case reports have been published where a combination of dexamethasone and dexmedetomidine has been used perineurally as an adjuvant. This Dex-Dex combination has shown promising synergistic results with sensory blockade of up to 3-7 days postoperatively and a significant reduction in postoperative opioid consumption. However, the lack of sufficient data on the safety of this combination warrants further investigation and studies [44, 45].

Others

Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist that has been studied as an adjuvant to local anaesthetics via the neuraxial route. Very few studies, however, have been done on the use of ketamine as a peripheral nerve block adjuvant and those done have not shown promising results [46].

Midazolam, a commonly used benzodiazepine has been used as an additive in neuraxial anaesthesia techniques and provides analgesia via its gamma-aminobutyric acid (GABA) receptor agonist action [47]. However, it is not an FDA approved additive and use in the peripheral nerve block has mostly been avoided due to neurotoxic effects seen in animal models [48, 49].

Magnesium Sulphate is another NMDA receptor antagonist that is being used as an adjuvant in peripheral nerve blocks [50]. It is found to have anti-hypertensive, analgesic and anaesthetic sparing properties when used systemically. Recently its use as an adjuvant to peripheral nerve blocks has been practised. However, there are conflicting reports regarding its effectiveness.

Commercially available solutions are acidic so as to increase water solubility and chemical stability. Alkalinisation of the local anaesthetic solution just before injection by addition of sodium bicarbonate (8.4%) would increase the amount of non-ionised drug, reduces the pain on injection and onset time of the block. This may be an advantage during infiltration local anaesthesia but does not provide any practical advantage in plexus blocks [53].

Conclusion

Adjuvants to local anaesthetic agents, whether administered intravenously or perineurally, are a simple and promising alternative to other methods of increasing peripheral nerve block effects. However, none of the currently available adjuvants fulfils all the criteria of an ideal local anaesthetic adjuvant. Dexamethasone and Dexmedetomidine come closest to being a near-ideal option. However, both have associated side effect profiles that restrict their use in specific clinical scenarios. Thus, the search for the ideal adjuvant continues.

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