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Adjuvants in peripheral nerve blocks – the current state of knowledge

Wojciech Gola, Marek Zając, Adam Cugowski

Department of Anaesthesiology and Intensive Therapy, St. Lukas Specialist Hospital in Końskie, Poland

Abstract

Regional anaesthetic techniques are an indispensable element of acute and postoperative pain management. The benefits of regional blocks are particularly noticeable in trauma and orthopaedic, joint reconstruction or thoracic surgical procedures. Depending on the local anaesthetic (LA) used, the duration of analgesia is limited to a maximum of 12–16 hours. There are several methods affecting the prolongation of analgesia, e.g. continuous techniques with catheters, liposomal forms of LAs or adjuvants. Due to numerous limitations and problems associated with the use of continuous techniques, lack of approval or availability of liposomal LAs, the optimal measure to prolong the duration of postoperative analgesia is the use of adjuvants. The present study aims to collect and systematise the current knowledge about the most common adjuvants used for nerve / plexus blockades and intravenous regional anaesthesia.

Key words: adjuvants, regional blocks, intravenous regional anaesthesia.

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CORRESPONDING AUTHOR:

Wojciech Gola, Department of Anaesthesiology and Intensive Therapy, St. Lukas Specialist Hospital in Końskie, 41B Gimnazjalna St., 26-200 Końskie, Poland, e-mail: golawojtek@gmail.com

Regional anaesthetic techniques are an essential element in acute and postoperative pain management [1]. Perineural deposition of a local anaesthetic leads to reversible blockade of sodium channels and temporary inhibition of nociceptive conduction. Nerve conduction blockade is based on the all-or-none law; hence, regional anaesthesia is the most efficacious form of analgesia. The benefits of regional analgesic techniques are particularly noticeable in trauma-orthopaedic, large-joint reconstructive and thoracic surgical procedures (Table 1) [2].

Depending on the local anaesthetic (LA) used, the duration of analgesia is limited to a maximum of 12–16 hours. For most scheduled procedures (usually performed between 8 a.m. and 3 p.m.), the blocking effect ends in the late evening or night [3, 4]. In most departments, compared to daytime, night hours are associated with a smaller staffing of medical personnel who can respond quickly to pain reported by the patient, which creates a risk of lack of optimal pain control. The imperative in the treatment of postoperative pain is to provide the patient with optimal analgesia and comfort, especially during the period of the most severe complaints, i.e. on the first postoperative day, including night hours. Hence, many techniques are used in clinical practice to prolong standard analgesia after perineural deposition of LA. These techniques include:

- continuous nerve/plexus block followed by an infusion of a local anaesthetic,
- liposomal forms of local anaesthetics,
- intravenous or perineural delivery of adjuvants.

Continuous peripheral nerve blocks are widely used in clinical practice. Despite many advantages, there are also many factors significantly limiting their routine use (Table 2) [5–7]. Apart from organizational or logistics problems regarding care and supervision, the limitations are predominantly associated with high continuous block failure rates. Their causes can be divided into primary and secondary. The former mainly include the factors related to difficulties during implantations of continuous block sets. The latter encompass the factors that affect the functioning of a correctly established set: dislocation or spontaneous migration of the catheter, as well as LA leaks along the catheter

TABLE 1. Benefits of regional anaesthetic techniques in trauma-orthopaedic surgery

Better pain management
Shorter hospital stays
Lower treatment costs
Reduced perioperative morbidity and mortality
Improved function of the affected joint
Reduced risk of surgical site infection
Reduced demands for homologues blood transfusions
Lower incidences of persistent postoperative pain
Improvement of patient's satisfaction

TABLE 2. Problems associated with the use of continuous peripheral nerve blocks

Organizational and logistics problems
Possible catheter migration/spontaneous dislocation
Local anaesthetic leak along the catheter channel
Equipment problems – infusion pump dysfunctions
Catheter infections
Neurological complications
Higher daily dose of local anaesthetic
The risk of local anaesthetic systemic toxicity (LAST)

working channel. Secondary factors are the main reason for the failure of continuous blocks. According to current literature, spontaneous migration or LA leakage occurs in 30–40% of correctly implemented sets [5, 6]. An important element affecting the effectiveness of continuous infusion is the proper pump operation. Moreover, the risk of systemic toxicity of local anaesthetics, likely to occur during their continuous perineural delivery, should be taken into consideration.

The use of liposomal forms of LAs is limited by registration issues, availability and price of drugs; hence, it is not a routine method used to prolong the peripheral block. Liposomal bupivacaine has not been approved for use by the European Union. In the USA, it has been approved for infiltrative anaesthesia, and only for interscalene brachial plexus blocks [8, 9].

Intravenous or perineural use of adjuvants is another measure to prolong regional block. In the literature, there is an arbitrary classification of drugs that prolong the peripheral block into "old" and "new" adjuvants (Table 3). The "old" adjuvants include adrenaline, sodium bicarbonate, clonidine, buprenorphine, tramadol, midazolam and magnesium sulphate, while dexamethasone and dexmedetomidine are among the "new" adjuvants.

ADRENALIN

Adrenaline is one of the oldest adjuvants used in clinical practice. Administered perineurally, it does not directly affect nerve conduction, but it causes a decrease in the absorption of LA into blood vessels, as a result, the time of LA contact with nerve fibres is prolonged. It is most often used in a dose of 2.5–5 μg mL^{-1} of LA solution. Prolonged block after perineural adrenaline deposition ranges from 33 to 100 mins (average: 60 mins) [10]. Applied as an adjuvant, adrenaline is a relatively safe drug. Studies in rats have not showed an increase in the percentage of either histological or functional nerve damage after perineural administration of a mixture of lidocaine and adrenaline [11]. It should be remembered, however, that adrenaline may potentiate the vasoconstrictor effect, especially in relation to long-acting LAs, thus prolonging the toxic effect of LA on axons [12, 13]. This is particularly important in the case of patients with pre-existing blood supply disorders, e.g. diabetes [14].

TABLE 3. Classification of adjuvants

Old	New
Adrenalin Sodium bicarbonate Clonidine Buprenorphine Tramadol Ketamine Midazolam	Dexamethasone Dexmedetomidine

The addition of adrenaline to LA is mainly used as an indicator of the intravascular administration of LA. Adrenaline also limits the distribution of LA to the central compartment, thus reducing the risk of local anaesthetic systemic toxicity [12, 15]. Due to the negligible effect of prolonging block duration, adrenaline is currently used mainly as an adjuvant to improve the safety profile of the LA and an indicator of unintended intravascular delivery of LA.

SODIUM BICARBONATE

Sodium bicarbonate ($NaHCO_3^-$) is used as an adjuvant to accelerate the block onset. The mechanism of action of sodium bicarbonate is to increase the pH of the solution and thus facilitate the dissociation of the LA to an alkaline form, which is fat-soluble and diffuses into the nerve fibre, where re-ionization and reversible blocking of sodium channels occur. The use of sodium bicarbonate as an adjuvant does not increase the duration of analgesia but can only shorten the time of its occurrence [16]. The most common problem associated with the use of $NaHCO_3^-$ in a solution is the precipitation of LA. To avoid this, the right dose of adjuvant in the solution should be used [16]. For lidocaine, the standard dose should be 1 mL $NaHCO_3^-$ per 10 mL LA, and in the case of bupivacaine, 0.1 mL $NaHCO_3^-$ per 10 mL LA. No clinical effect has been demonstrated for the bicarbonate-ropivacaine combination [18].

α-2 ADRENORECEPTOR AGONISTS (CLONIDINE, DEXMEDETOMIDINE)

α-2 adrenoreceptor agonists are a group of drugs that have a sedative and analgesic effect. Two substances from this group are mainly used in clinical practice, i.e. clonidine and dexmedetomidine, which are characterized by, among others, different binding selectivities for α-1 and α-2 receptors.

Clonidine was primarily used as an antihypertensive agent. It has a much lower selectivity for α-2 receptors, compared to dexmedetomidine.

Dexmedetomidine is an S-enantiomer of medetomidine, primarily used in veterinary medicine. It is characterized by much greater selectivity for α-2 adrenergic receptors (α-2 : α-1 = 1600 : 1), which makes it practically a pure agonist of this receptor subpopulation. For comparison, the selectivity of clonidine for α-2 adrenergic receptors over α-1 adrenergic receptors is only 200 : 1 [19].

The clinical effect following the intravenous administration of α-2 adrenoceptor agonists is the result of their effect on both peripheral and central α-2 receptors. The sedative effect is associated with the stimulation of receptors located in the locus coeruleus in the brainstem. However, the analgesic effect is associated with the stimulation of receptors located in the dorsal root of the spinal cord, which inhibits the secretion of stimulants, substance P and glutamine [20]. Common side effects of this drug group include hypotension and bradycardia [20–22].

Under physiological conditions, the expression of α-2 receptors in peripheral nerve axons is absent [23]. Therefore, after perineural supply in addition to LA, clonidine and dexmedetomidine prolong analgesia time in a multidirectional and extremely complex mechanism, both by direct action on the peripheral nerve, but also by central influence [20]. The direct effect on peripheral fibres results, among others, from the properties similar to LA and inhibition of the formation of action potential in type C fibres, as well as hyperpolarization associated with the activation of intracellular cationic current (acting on cyclic nucleotide-gated cation (CNG) channels [20]. In the case of clonidine, a reduction in central redistribution of LA by α-1 adrenergic receptor-mediated vasoconstriction has also been suggested [24].

Clonidine

As an addition to medium- and long-acting LAs, clonidine in a dose of 150 μg increases the analgesia duration in the range of 74–169 mins (122 mins on average) [20]. However, after perineural administration of clonidine, the risk of hypotension, bradycardia, as well as excessive sedation is significantly higher [21, 22]. In addition, a greater potential for neurotoxicity after combining clonidine with ropivacaine has been observed in animal model studies, as compared to ropivacaine alone [25].

Dexmedetomidine

Dexmedetomidine used together with LA in a dose of 50–60 μg prolongs the analgesia duration from 5 to 7 hours (average: 6 hours) [26]. However, episodes of hypotension and bradycardia are significantly more frequent [26–28]. At a dose of 0.5 μg kg^{-1}, after both perineural and intravenous administration, dexmedetomidine shows a similar action profile in terms of prolonged analgesia [28]. The study in an animal model has shown neuroprotective effects of peripherally administered dexmedetomidine. The addition of this drug to ropivacaine almost halves the neurotoxicity of LA [29].

OPIOIDS AS ADJUVANTS IN PERIPHERAL NERVE BLOCKS

Inflammation induces the expression of opioid receptors in peripheral nerve fibres and on immune response cells. In addition, significant amounts of endogenous opioids are released, which is aimed at balancing and silencing the increased nociception process induced by inflammation. Nevertheless, the trauma and inflammation-induced ability to express opioid receptors and the production of endogenous opioids by the immune system is a time-delayed process and usually takes up to 96 hours after injury [30]. The injury to the nerve tissue in the dorsal root ganglion (DRG) results in an increased production of opioid receptors, followed by their axonal transport in microtubules towards the peripheral nerve endings, where they are incorporated into the nerve fibre membrane.

Over the years, numerous studies have been conducted to determine the benefits of perineural delivery of opioids as adjuvants to LA, but it is still extremely difficult to determine whether the analgesic effect after perineural administration of opioids is the result of their effect only on the peripheral opioid receptors, or is a central action occurring after redistribution of the drug to the central compartment. The explanation of this problem is extremely important from the clinical point of view. The pure peripheral effect of an opioid, in addition to improving anti-nociception, would also be associated with reduced incidences of side effects of this group of drugs. Otherwise, with the significant coexistence of central influence, perineural administration would have no clinical validity. The analysis of studies and reports on the effectiveness and benefits of perineural opioid delivery brings ambiguous results and does not allow recommending this form of delivery of these drugs [31, 32].

An exception is buprenorphine, which has been shown to extend the duration of analgesia after being deposited perineurally in combination with LA.

Buprenorphine

Buprenorphine is a partial agonist of the mi type opioid receptors. The distinguishing feature of buprenorphine is high receptor affinity and lipophilicity, which allows it to easily penetrate the neuronal membrane. Used perineurally in a dose of 0.1–0.3 mg as an addition to LA, it increases the duration of analgesia from 6.44 to 10.85 hours (8.5 hours on aver-

age) [33, 34]. This effect is not observed in the case of block with the use of LA alone and systemic delivery of buprenorphine, which clearly indicates the peripheral mechanism of the drug action. However, it should be remembered that perineural administration of buprenorphine induces postoperative nausea and vomiting (PONV), which significantly limits its use in clinical practice [33].

Corticosteroids (Dexamethasone)

The mechanism responsible for prolonging block duration after the use of dexamethasone as an adjuvant to LA is multidirectional and extremely complex (Table 4) [35, 36]. Administered perineurally with LA, dexamethasone in a dose of 4 mg prolongs the effect of short- and medium-acting LAs by 3–5 hours (average: 4 hours), and of long-acting LAs by 7–9 hours (average: 8 hours) [37]. Moreover, an increase in the dose of dexamethasone has not been found to cause a statistically significant difference in action [38]. In addition to lengthening the duration of analgesia, the use of dexamethasone shortens the onset time of block [27], and, which has been observed in studies on animal models, has a protective effect on the nerve cells [39]. It is worth noting, however, that after adding dexamethasone to ropivacaine, the former crystallizes in the solution, which creates a potential danger for the patient, making this combination not applicable in clinical practice (such a reaction was not observed for lidocaine and bupivacaine) [40]. Current studies show that intravenous administration of dexamethasone has an equivalent effect of prolonged analgesia as perineural delivery [41]. In the case of intravenous route, the optimal effect of prolonged analgesia is obtained by administering a dose of 0.1–0.2 mg kg^{-1} one hour prior to surgery [1]. An important benefit associated with this administration route of dexamethasone is also a reduction in the incidence of PONV [42]. Moreover, the use of dexamethasone before induction of general anaesthesia has been demonstrated to significantly reduce the patient's need for both intraoperative and postoperative opioids [1, 43, 44]. In patients administered iv dexamethasone to increase peripheral block duration, or as a co-analgesic, no increase in the percentage of neurological complications, infections, or prolonged wound healing was observed, but only a small, transient, clinically insignificant increase in blood glucose levels [27]. A common limitation of preoperative intravenous administration of dexamethasone may be the frequent occurrence (50–70%) of severe, burning perineal pain, especially when the drug is administered quickly at a low volume. This can be prevented by diluting the drug in 50 mL 0.9% NaCl and giving it by intravenous infusion over 10–15 minutes [1, 43, 44].

TABLE 4. Mechanisms responsible for prolonging block duration after dexamethasone

Decrease in C-nociceptive activity (direct effect on glucocorticoid receptor)
Inhibition of potassium channels
Local vasoconstrictive effect
Systemic anti-inflammatory effect
Agonistic effects on central α-2-adrenergic receptors
Peripheral nerve fibre hyperpolarization support
Synaptic transmission block
Reduction of perineural inflammation

Tramadol

Tramadol is a weak MOR agonist. It is distinguished by an inhibitory effect on noradrenaline reuptake and a stimulating effect on the secretion of serotonin in the CNS [45]. Both noradrenaline and serotonin are extremely important substances in the descending anti-nociceptive system of the spinal cord. As an adjuvant to LA, tramadol has been used both in epidural anaesthesia and in nerve and plexus blocks [46, 47]. At present, due to contradictory reports regarding the effectiveness of perineural tramadol delivery, it is not recommended to use this adjuvant in routine clinical practice [48, 49].

Ketamine

Ketamine is a *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, which only slightly prolongs the peripheral nerve block. Due to high incidences of adverse effects, such as hallucinations, dizziness, nausea and vomiting, perineural administration of this drug is not recommended [49, 50].

Midazolam

Midazolam, a water-soluble benzodiazepine, is an indirect γ-aminobutyric acid receptor agonist. Initially studied as an adjuvant of spinal and epidural anaesthesia, midazolam has not been approved for perineural use due to its neurotoxicity and lack of clinically significant evidence of prolonging the duration of LA [49, 51].

ADJUVANTS USED IN INTRAVENOUS REGIONAL ANAESTHESIA

Intravenous regional anaesthesia (IVRA) was first described in 1908 by the father of regional anaesthesiology August Bier [52]. This quite simple and safe technique of anaesthesia is most often used for minor and short soft tissue procedures on the forearm and hand, much less frequently for the lower leg and foot procedures. IVRA is also indicated

for the management of the complex regional pain syndrome (CRPS) [53].

To optimize analgesia, increase tourniquet tolerance and prolong postoperative analgesia, the use of an intravenous adjuvant to LA may be considered. Over the years, many different substances have been used for this purpose, including opioids, α-2 adrenergic receptor agonists, striated muscle relaxants, neostigmine, alkalizing drugs ($NaHCO_3$), non-steroidal anti-inflammatory drugs, and corticosteroids [17].

Most evidence and scientific reports support the use of non-steroidal anti-inflammatory drugs as adjuvants to IVRA. Most studies concern ketorolac: its addition to lidocaine in a dose of 20 mg significantly improves tourniquet tolerance and extends the time of postoperative analgesia without inducing any significant adverse effects [54, 55].

As for opioids (fentanyl, sufentanil, morphine) as adjuvants to IVRA, most studies do not confirm improvement of the analgesic effect and, therefore, their use is not recommended [56]. The addition of 50–100 mg tramadol to a 0.5% lidocaine solution accelerates the occurrence of sensory block and increases tourniquet tolerance [57]. Nevertheless, the use of tramadol as an adjuvant of IVRA is limited by an intense pain during injection and skin changes (urticaria) developing at the injection site of the mixture of LA with tramadol [57].

Studies on the use of α-2 adrenergic receptor agonists as an addition to a 0.5% lidocaine solution may indicate improvement in tourniquet tolerance and postoperative analgesia. The use of dexmedetomidine in a dose of 0.5 μg kg^{-1} with a 0.5% lidocaine solution accelerates sensory and motor blocks, increases tourniquet tolerance, improves analgesia, and extends tourniquet tolerance time [58]. Similar effects have not been observed after clonidine (2 μg kg^{-1}), with a significant decrease in blood pressure additionally observed in this group after the release of the tourniquet [59].

Neuromuscular blocking agents may be added to LA in IVRA to achieve deeper motor block required for bone surgery. Non-depolarizing neuromuscular blocking agents, such as atracurium, pancuronium and mivacurium, are most commonly used in clinical practice [60, 61].

Furthermore, one of the indications for IVRA is the management of complex regional pain syndrome (CRPS). Due to the pathophysiology of this disease entity, adjuvants with the potential of chemical sympathectomy are used. They inhibit the post-ganglionic adrenergic neurons, the storage of noradrenaline in synaptic vesicles (guanethidine, reserpine), and the secretion of noradrenaline (bretylium). The clinical trials on guanethidine in CRPS did not demonstrate evident benefits compared to placebo [62]. Otherwise, the bretylium effects reducing pain severity and improving limb blood flow were more pronounced [53].

CONCLUSIONS

Due to numerous limitations and problems associated with continuous nerve and plexus blocking techniques, the use of adjuvants is a good and safe way to prolong postoperative analgesia – both in intravenous and perineural administration routes (Table 5). Of all the adjuvants used in clinical practice, the most optimal clinical effect with the best safety profile is that of dexamethasone. Perineural administration in a dose of 4 mg and intravenous supply (one hour before surgery) in a dose of 0.1–0.2 mg kg^{-1} are equivalent and, in the case of block with long-acting LA, increase the time of analgesia by an average of 8 hours. This gives the clinician an opportunity to provide patient comfort and optimal pain management throughout the first postoperative day, including night hours. An additional benefit of intravenous dexamethasone is the reduction in postoperative nausea and vomiting. When deciding on perineural delivery of an adjuvant, it should be borne in mind that none of the drugs discussed in this study (except for adrenaline) has been approved for perineural administration and all will then be used off label – except as indicated in the summary of product characteristics. It should also be remembered that the perineural route is restricted only for medications without preservatives. Considering the above and the clinical efficacy and safety profile, the authors of this study recommend iv dexamethasone as the adjuvant of choice for nerve and plexus blocks. In the case of IVRA, non-steroidal anti-inflammatory drugs are still the adjuvants of choice, the addition of which to lidocaine extends the time of tourniquet toler-

TABLE 5. Summary of the most common adjuvants

Adjuvant	Perineural dose	Medium block extension (hours)	Side effects
Adrenaline	2.5–5 μg mL^{-1}	1	–
Clonidine	150 μg	2	Hypotension Bradycardia Sedation
Buprenorphine	0.1–0.3 mg	9	PONV
Dexmedetomidine	50–60 μg	5	Hypotension Bradycardia Sedation
Dexamethazone	4 mg	8	Slight increase in glycaemia

PONV – postoperative nausea and vomiting

ance and prolongs postoperative analgesia, without inducing adverse side effects. Ketorolac is the representative of this group with the best documented activity in IVRA. Unfortunately, it is not available in Poland.

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