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Local anaesthetic adjuncts for peripheral nerve blockade

Neel Desai[a,b] *and Eric Albrecht*[c]

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Purpose of review
Moderate-to-severe pain is common and remains a significant problem. Compared with opioid analgesia alone, single-shot peripheral nerve blockade has been associated with improved pain relief and the potential of decreased side effects. Single-shot nerve blockade, however, is limited by its relatively short duration of action. In this review, we aim to summarize the evidence related to local anaesthetic adjuncts for peripheral nerve blockade.

Recent findings
Dexamethasone and dexmedetomidine exhibit characteristics that most closely resemble the ideal local anaesthetic adjunct. In upper limb block, dexamethasone has been demonstrated to be superior to dexmedetomidine regardless of administration route for the duration of sensory and motor blockade as well as the duration of analgesia. No clinically significant differences between intravenous and perineural dexamethasone were found. Perineural and intravenous dexamethasone have the potential to prolong sensory blockade to a greater extent than motor blockade. The evidence indicates that the mechanism of action of perineural dexamethasone in upper limb block is systemic in nature. Unlike perineural dexmedetomidine, intravenous dexmedetomidine has not been shown to result in differences in the characteristics of regional blockade compared with local anaesthetic alone.

Summary
Intravenous dexamethasone is the local anaesthetic adjunct of choice, increasing the duration of sensory and motor blockade as well as the duration of analgesia by 477, 289 and 478 min, respectively. In view of this, we recommend consideration of the intravenous administration of dexamethasone at a dose of 0.1–0.2 mg/kg for all patients undergoing surgery whatever the level of postoperative pain, mild, moderate or severe. Further research should focus on the potential synergism of action between intravenous dexamethasone and perineural dexmedetomidine.

Keywords
local anaesthetic adjuncts, local anaesthetics, nerve block, postoperative pain

INTRODUCTION

Moderate-to-severe pain after surgery is common and remains a significant problem [1]. Unsurprisingly, the presence of uncontrolled pain can cause decreased patient satisfaction, increased pulmonary and cardiac complications, delayed ambulation and the occurrence of chronic pain. Opioids may be administered for the relief of pain but are themselves associated with adverse side effects including respiratory depression, nausea and vomiting, constipation, pruritus and secondary hyperanalgesia [2]. Given this, the concomitant utilization of peripheral nerve blockade rather than opioid analgesia alone has been related to improved pain relief with the potential of reduced side effects [3].

Single-shot peripheral nerve blockade, however, is limited by its relatively short duration of action of 8–14 h [4,5]. Once the effects of the peripheral nerve blockade resolve, the patient is often left with rebound and residual pain as the influence of postoperative noxious operative stimuli persists [6]. The sequelae of this rebound pain include the increased

[a]Department of Anaesthesia, Guy's and St Thomas' NHS Foundation Trust, [b]King's College London, London, United Kingdom and [c]Department of Anaesthesia, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Correspondence to Professor Eric Albrecht, MD, Program Director, Department of Anaesthesia, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. E-mail: eric.albrecht@chuv.ch

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KEY POINTS

- Moderate-to-severe pain after surgery is common, and single-shot peripheral nerve blockade has been associated with improved pain relief compared with opioid-based analgesia alone.
- Single-shot peripheral nerve blockade remains limited by its restricted duration of action and the development of rebound pain on its resolution.
- In upper limb block, perineural and intravenous dexamethasone have been demonstrated to be superior to perineural and intravenous dexmedetomidine for the duration of sensory and motor blockade as well as the duration of analgesia.
- In upper limb block, perineural and intravenous dexamethasone do not result in clinically significant differences in the characteristics of the ensuing regional blockade.
- In upper limb block, intravenous dexamethasone has proved to be the local anaesthetic adjunct of choice, increasing the duration of sensory and motor blockade as well as the duration of analgesia by 477, 289 and 478 min, respectively.

consumption of opioids, overnight sleep disturbance, and the presence of difficulties in compliance with elements of enhanced recovery and physiotherapy protocols. In view of the restricted duration of action of peripheral nerve blockade and the problem of rebound pain, strategies have been explored to prolong the analgesic benefits of single-shot peripheral nerve blockade beyond the normal period of 8–14 h. The use of local anaesthetic adjuncts represents one such important and simple technique, and will form the basis of this review.

CONCEPT OF LOCAL ANAESTHETIC ADJUNCTS

In single-shot peripheral nerve blockade, local anaesthetic adjuncts have been defined as the concomitant administration of one or more drugs around the peripheral nerve or plexus, into a fascial plane or systemically by intravenous injection [7]. The characteristics of the ideal local anaesthetic adjunct include: availability as a preservative-free solution; chemical compatibility with local anaesthetics and accompanying adjuncts; described mechanism of action; effectiveness in all modalities of peripheral nerve blockade; facilitation of decrease in effective dose of local anaesthetic; evidence of dose–response relationship; reduction in time to onset of motor and sensory blockade; improvement of quality of sensory blockade; increase in duration of sensory blockade and no prolongation of motor blockade; differential sensorimotor blockade prolongation; increase in duration of analgesia; and the absence of systemic adverse consequences as well as chondrotoxic, myotoxic and neurotoxic side effects.

Table 1. Summary of evidence for local anaesthetic adjuncts that have demonstrated limited benefit, increased neurotoxicity and side effects

Local anaesthetic adjunct	Evidence
Midazolam	Limited effectiveness on perineural administration Neurotoxicity demonstrated *in vitro* and *in vivo* No increase in neurological symptoms after intrathecal injection in humans
Fentanyl	Conflicting findings for effectiveness on perineural administration Possible efficacy if administered with bupivacaine Side effects include hypercapnia, bradycardia and sedation
Morphine	Conflicting findings for effectiveness on perineural administration No evidence of perineural superiority over systemic administration
Tramadol	Conflicting findings for effectiveness on perineural administration No evidence of perineural superiority over systemic administration
Ketamine	Lack of effectiveness on perineural administration Neurotoxicity demonstrated *in vitro* and *in vivo* Side effects include drowsiness, hallucinations and nausea
Neostigmine	Lack of effectiveness on perineural administration Neurotoxicity demonstrated *in vitro* and *in vivo* Side effects including nausea and vomiting

Many local anaesthetic adjuncts have been investigated to date. Some have clearly exhibited limited benefit, increased neurotoxicity and side effects (Table 1) [8] and other historical local anaesthetic adjuncts have similarly limited evidence to support their use and/or are inferior to the more novel local anaesthetic adjuncts (Table 2) [9–13]. The novel local anaesthetic adjuncts of most recent interest are dexmedetomidine and dexamethasone, and their characteristics have been compared with the ideal local anaesthetic adjunct (Table 3).

DEXMEDETOMIDINE

Dexmedetomidine is an α-2 adrenoreceptor agonist and nonselective imidazoline derivative with a α-2 : α-1 activity ratio of 1620 : 1 [14]. Its mechanism of action after perineural administration is not likely to be because of its effect on α-2 adrenoreceptors as

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Table 2. Summary of historical local anaesthetic adjuncts

Local anaesthetic adjunct	Mechanism of action	Duration of analgesia (min)	Onset of sensory blockade (min)	Duration of sensory blockade (min)	Onset of motor blockade (min)	Duration of motor blockade (min)	Block failure	Pain scores at less than or equal to 24 h	Cumulative opioid consumption at 24 h (morphine equivalents in mg)	Side effects
Adrenaline	α-1 adrenoreceptor-medicated vasoconstriction	+66	ND	Increased/ND	ND	Increased/ ND	ND	Not studied	Not studied	Hypertension Tachycardia
Buprenorphine	Concentration-dependent block of voltage-gated sodium channels, inhibiting the generation of action potentials Interaction with MOP opioid receptors on the axons of unmyelinated C fibres	+518	ND	Increased/ND	−0.3	+13	Not studied	Decreased	Not studied	PONV (RR 5) Pruritus (RR 6)
Clonidine	Block of hyperpolarization-activated nucleotide-gated channels, inhibiting the cation currents that reestablish the neuronal resting potential	+123	−2	+74	ND	+141	ND	Decreased/ND	Not studied	Bradycardia (OR 3.1) Arterial hypotension (OR 3.6) Orthostatic hypotension (OR 2.3) Sedation (OR 5.1)
Magnesium	Calcium antagonist Effects of its positive divalent charge on the neuronal membrane potential	+125	ND	+107	−1	+90	ND	Decreased	Decreased	ND

The data associated with indices of block characteristics and incidence of side effects following their perineural administration have been extracted from meta-analyses and their included trials. ND, no difference; OR, odds ratio; RR, risk ratio.

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Table 3. Comparison of the characteristics of an ideal local anaesthetic adjunct with perineural dexamethasone and dexmedetomidine

Characteristics of an ideal local anaesthetic adjunct	Dexamethasone	Dexmedetomidine
Available as a preservative-free preparation	+	+
Chemically compatible with local anaesthetics	+[a]	+
Plausible mechanism of action	+	+
Effective for all peripheral nerve blocks	+	+
Evidence of dose response relationship	+	−
Increase in the duration of sensory blockade	+	+
No prolongation of motor blockade	−	−
Differential sensorimotor blockade prolongation	+	−
Increase in the duration of analgesia	+	+
No significant systemic adverse consequences	+	−
No chondrotoxic, myotoxic and neurotoxic side effects	+	?

?, unclear; −, no; +, yes.
[a]Dexamethasone has been shown not to have *in vitro* compatibility with ropivacaine.

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they are not present on peripheral neurones, and instead involves the inhibition of hyperpolarization-activated nucleotide gated channels (Fig. 1). In the refractory phase of the neuronal action potential, cation currents secondary to these hyperpolarization-activated nucleotide gated channels re-establish the resting potential of the neurone, facilitating the resumption of normal function.

In a meta-analysis analysing the effects of perineural dexmedetomidine in the context of brachial plexus block, data from 32 trials and 2007 patients were included [15]. Most trials administered long-acting local anaesthetic, such as bupivacaine, levobupivacaine and ropivacaine, either alone or in combination with short-acting local anaesthetic. Perineural dexmedetomidine was demonstrated to decrease the mean time to onset of sensory blockade from 20 to 11 min and the mean time to onset of motor blockade from 21 to 13 min. Further, it increased the mean duration of sensory and motor blockade by 228 and 192 min, respectively, with high certainty of evidence. The mean duration of analgesia was prolonged by 264 min with moderate certainty of evidence. Perineural dexmedetomidine reduced the oral morphine equivalent consumption by 10 mg and increased the patient satisfaction. It can, however, increase the odds of bradycardia, hypotension and sedation. Bradycardia and hypotension were found to be transient and reversible and did not necessitate anaesthetic intervention. Interestingly, one of the included trials indicated that perineural dexmedetomidine may extend the sensory blockade without prolonging motor blockade, suggesting that it has the potential to provide a greater inhibitory effect on Aδ and C fibres compared with motor neurones [16]. Even though no dose–response relationship for perineural dexmedetomidine was reported, the optimal dose, at which the duration of sensory blockade was maximized and the hemodynamic side effects were minimized to zero, was shown to be 50–60 μg [15]. In the setting of femoral and sciatic nerve block, a randomized controlled trial confirmed that the influence of perineural dexmedetomidine was similar in femoral and sciatic nerve block to that shown in brachial plexus block [17].

The evidence with respect to the neurotoxic potential of perineural dexmedetomidine is not consistent [18,19]. In an *in vivo* study that assessed the effect of dexmedetomidine at high dose when coadministered with bupivacaine in rats, it was revealed to be neuroprotective with the presence of decreased perineural inflammation [18]. This finding may be a result of the inhibition of activated nuclear factor NK-κB [20], and its secondary downstream proinflammatory cytokines, and the modulation of mast cell degranulation [21]. In an *in vivo* study, which evaluated the influence of dexmedetomidine at high dose when coadministered with ropivacaine in the same animal model, it was uncovered to be neurotoxic [19].

DEXAMETHASONE

Dexamethasone is a potent and long-acting glucocorticoid with minimal mineralocorticoid activity. Its mechanism of action after perineural administration is likely to be because of its effect on glucocorticoid receptors on the neuronal membrane (Fig. 1). The expression of inhibitory potassium

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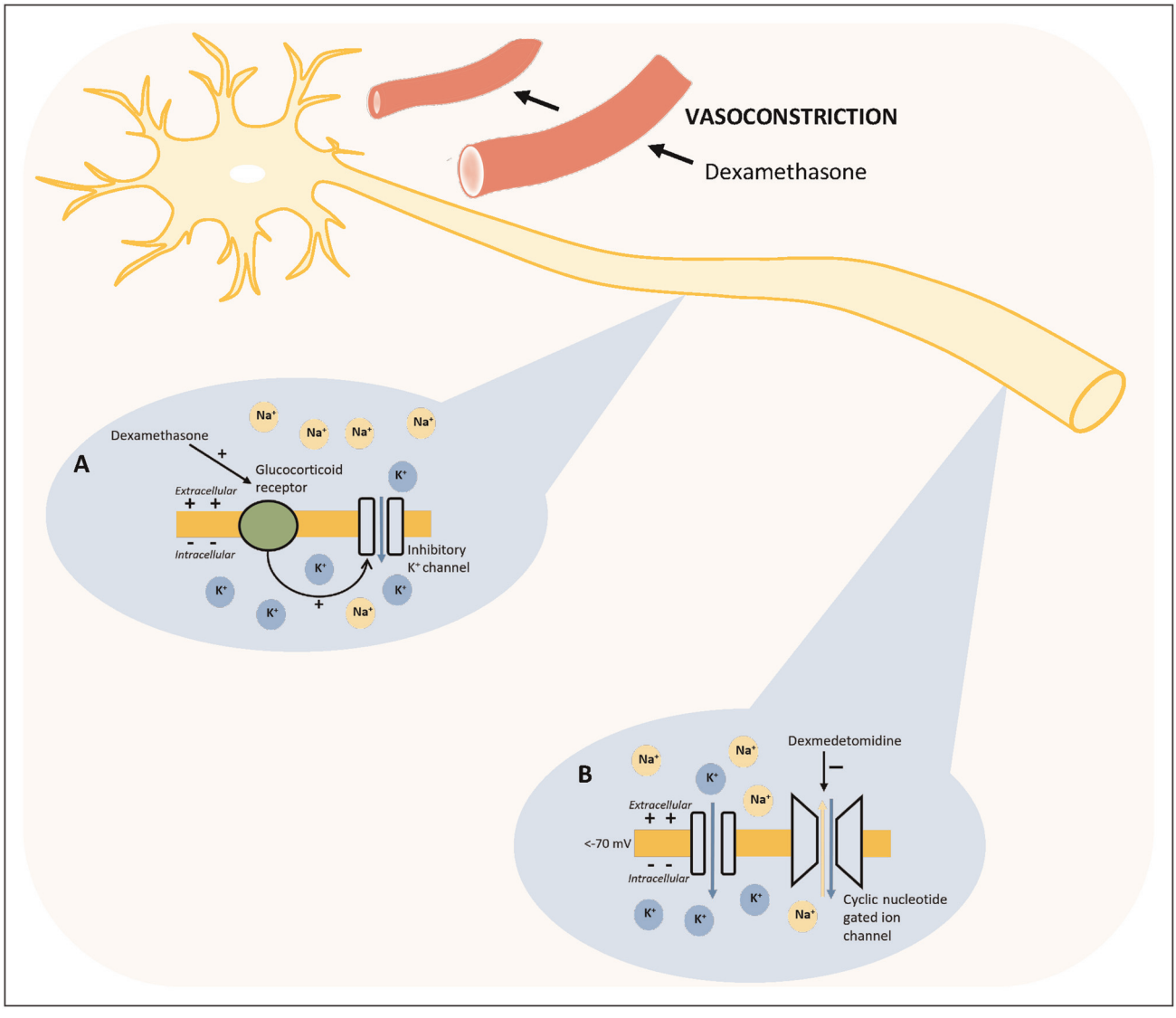

FIGURE 1. Mechanisms of action of local anaesthetic adjuncts on the cell membrane of neurones and the blood vessels. (a) Dexamethasone stimulates glucocorticoid receptors, increasing the expression of inhibitory potassium channels and decreasing the excitability of neurones. (b) Dexmedetomidine inhibits the hyperpolarization-activated nucleotide-gated channels, maintaining the neurone at a more negative potential and hyperpolarized state.

channels is increased and the excitability of unmyelinated C fibres decreased. Further, perineural dexamethasone may cause localized vasoconstriction and, following absorption into the vasculature, reduce systemic inflammation. Unlike bupivacaine and lidocaine, ropivacaine is not compatible with dexamethasone and the combination crystallizes *in vitro* owing to the alkalinity of dexamethasone.

In a meta-analysis analysing the effects of perineural dexamethasone in the context of mainly brachial plexus block, data from 29 trials and 1695 patients were included [22]. Most trials administered long-acting local anaesthetic, such as bupivacaine, levobupivacaine and ropivacaine, and intermediate-acting or short-acting local anaesthetic, such as mepivacaine or lidocaine and prilocaine, were given in the remaining trials. Perineural dexamethasone was not demonstrated to decrease the mean time to onset of sensory or motor blockade by a clinically significant amount. It increased the mean duration of motor blockade by 150 and 286 min if injected with short-acting or intermediate-acting and long-acting local anaesthetic, respectively. The mean duration of analgesia was prolonged by 233 and 488 min if injected with short-acting or intermediate-acting and long-acting local anaesthetic, respectively. Perineural dexamethasone decreased the pain score at rest and on movement at 8–12 and 24 h, and reduced the intravenous morphine consumption by 8 mg at 24 h. The results of this meta-analysis were

limited by the presence of funnel plot asymmetry and, therefore, the potential for publication bias or small study effects, and the lack of full evaluation of quality of evidence. Importantly, in brachial plexus block, perineural dexamethasone has a ceiling effect at a dose of 4 mg on the duration of analgesia, irrespective of the duration of action of the coadministered local anaesthetic [23,24]. Perineural and intravenous dexamethasone can, however, increase the postoperative glucose concentration by 0.2 and 1.7 mmol/l, respectively [25,26]. Concerns have been raised in regard to dexamethasone and its influence on delayed wound healing and systemic or wound healing, but the increased occurrence of these side effects was not confirmed in a systematic review [27].

The evidence indicates that perineural dexamethasone is not neurotoxic [22,28–32]. In one in-vitro study that assessed the effect of dexamethasone on mouse neuroblastoma cells, it decreased the cytotoxic potential of bupivacaine [28]. In another *in vitro* study, which evaluated the influence of dexamethasone at high dose when coadministered with ropivacaine on rat dorsal root ganglia, it did not have an increased neurotoxic effect relative to ropivacaine alone [29]. Moreover, in an *in vivo* study where dexamethasone and bupivacaine were coadministered for sciatic nerve block in rats, no subsequent histopathological or neurobehavioral changes were reported [30]. Tellingly, in human trials to date, perineural dexamethasone has not resulted in neurological complications [22,31] and, in fact, neurological sequelae were not revealed in a series of over 2000 intrathecal injections of dexamethasone for posttraumatic visual disturbance [32]. It should be borne in mind, nevertheless, that a sample size of approximately 16 000 patients would be required to show a doubling of the low baseline nerve injury rate of 0.4% [33].

THE PROBLEM WITH PERINEURAL ADMINISTRATION OF LOCAL ANAESTHETIC ADJUNCTS

Concerns have been raised in regard to the possibility of localized muscle or nerve injury subsequent to the perineural administration of local anaesthetic adjuncts. Further, in order to preserve their effectiveness, quality and safety, drugs are licensed by regulatory authorities, such as the European Medicines Agency, Food and Drug Administration and the Medicines and Healthcare products Regulatory Agency, for particular indications, doses, routes of administration and specific patient populations. It is not uncommon in clinical practice, however, to prescribe medications in an off-label manner, that is in a way different to that defined in the label or product licence [34]. In the United Kingdom, for example, the General Medical Council has advised that the prescription of an off-label drug may be indicated should there be adequate evidence or experience of using the medication and when no alternative and licenced drug meets the patient's need. Importantly, the intravenous rather than perineural administration of local anaesthetic adjuncts would obviate all these worries, and the question then arises as to whether intravenous dexmedetomidine and dexamethasone are at least equivalent in efficacy to their perineural counterparts.

INTRAVENOUS VERSUS PERINEURAL LOCAL ANAESTHETIC ADJUNCTS

To date, one landmark pharmacokinetic study and two randomized controlled trials have indicated that the activity of dexamethasone as a local anaesthetic adjunct may be systemic and not perineural in nature [35–37]. In the pharmacokinetic study, the addition of perineural or intravenous dexamethasone to bupivacaine in brachial plexus block effected a similar average time to maximum plasma concentration as well as maximum plasma concentration, suggesting that most of the perineural dexamethasone was systemically absorbed [35]. In the first randomized controlled trial, the use of dexamethasone as a perineural or intravenous local anaesthetic adjunct to ropivacaine for ulnar nerve block in healthy volunteers did not influence the duration of sensory blockade [36]. If its mechanism of action were to be systemic, then dexamethasone would not have a target site to exert its anti-inflammatory properties, explaining these findings. In the second randomized controlled trial, the addition of dexamethasone as a perineural or intravenous local anaesthetic adjunct to ropivacaine for interscalene brachial plexus block in shoulder arthroscopy did not result in any clinically significant differences in the duration of analgesia between these two modalities of administration [37].

More recently, a seminal network meta-analysis has been published that compared perineural dexmedetomidine, intravenous dexmedetomidine, perineural dexamethasone and intravenous dexamethasone as local anaesthetic adjuncts [38▪▪]. In all, 100 trials and 5728 patients were included, and the inclusion criteria encompassed patients who had had supraclavicular brachial plexus block with long-acting local anaesthetic, such as bupivacaine, levobupivacaine and ropivacaine. Perineural dexmedetomidine was the only local anaesthetic adjunct which was demonstrated to decrease the

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mean time to onset of sensory or motor blockade by a clinically significant amount. Compared with local anaesthetic alone, intravenous dexamethasone, perineural dexamethasone and perineural dexmedetomidine increased the mean duration of sensory blockade by 477, 411 and 283 min, respectively. Relative to local anaesthetic alone, perineural dexamethasone, intravenous dexamethasone and perineural dexmedetomidine increased the mean duration of motor blockade by 294, 289 and 258 min, respectively. Importantly, intravenous dexmedetomidine was not demonstrated to be provide any clinical benefit to local anaesthetic alone, suggesting a solely perineural mechanism of action for this local anaesthetic adjunct as has been evidenced by previous animal [39] and human studies [40]. Consistent with this, a randomized controlled trial found that intravenous dexamethasone and dexmedetomidine were not superior to dexamethasone alone in brachial plexus block for duration of sensory and motor blockade and the duration of analgesia as well as the pain score at rest and on movement and cumulative oral morphine consumption [41]. Further, these results revealed that unlike perineural and intravenous dexmedetomidine, perineural and intravenous dexamethasone have the potential to prolong sensory blockade to a greater extent than motor blockade [38▪▪]. Compared with local anaesthetic alone, perineural dexamethasone, intravenous dexamethasone and perineural dexmedetomidine increase the mean duration of analgesia by 518, 478 and 318 min, respectively. In summary, dexamethasone was superior to dexmedetomidine regardless of administration route in the setting of brachial plexus block, and the characteristics of the resulting regional blockade with perineural dexamethasone was not shown to be clinically different to intravenous dexamethasone. It is possible, however, that perineural dexamethasone may be similar in efficacy to intravenous dexamethasone in upper limb block secondary to its significant systemic absorption in this vascular anatomical location, but the same might not be the case in lower limb block where the systemic absorption is relatively limited. Interestingly, the authors of this systematic review performed a post hoc analysis of the trials included in previous systematic reviews and verified that the perineural route may be superior in lower limb block [38▪▪].

CONCLUSION

In the evolution of our understanding of local anaesthetic adjuncts, most of the evidence to date has accumulated in the setting of upper limb block. Intravenous dexamethasone has proved to be the local anaesthetic adjunct of choice. In view of this, we recommend consideration of the intravenous administration of dexamethasone at a dose of 0.1–0.2 mg/kg for all patients undergoing surgery, whatever the level of postoperative pain, mild, moderate or severe. Further research should focus on the potential synergism of action between intravenous dexamethasone and perineural dexmedetomidine in single-shot peripheral nerve blockade.

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Conflicts of interest

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- ▪ of special interest
- ▪▪ of outstanding interest

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