Narrative Review

Perineural Adjuvants for Peripheral Nerve Blocks: What the Evidence Now Supports

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ABSTRACT

The single-injection peripheral nerve block is limited by a mismatch between the duration of the block and the duration of the pain it is intended to treat. Adjuvant drugs added to the local anesthetic solution are the most widely used response to this problem, and two — dexamethasone and dexmedetomidine — now dominate practice. This review examines what the accumulated randomized and meta-analytic evidence actually supports. Dexamethasone reliably prolongs analgesia by several hours, with network and pairwise meta-analyses converging on a modest superiority of the perineural over the intravenous route that is smaller than earlier trials suggested and, for many clinicians, smaller than the argument for avoiding off-label perineural administration. Dexmedetomidine prolongs sensory and motor blockade and improves block quality, at the cost of dose-dependent bradycardia, hypotension and sedation. Direct and network comparisons of the two agents give a small and inconsistent advantage to dexamethasone. Older adjuvants — clonidine, buprenorphine, magnesium, midazolam, opioids — have either smaller effects or worse side-effect profiles, and network meta-analyses of upper limb blockade place them below the two principal agents. We also consider the reframing of the problem introduced by the recognition of rebound pain, which suggests that prolonging a block may matter less than managing its resolution, and the alternative offered by extended-release local anesthetic formulations. Practical dosing recommendations and the unresolved questions of neurotoxicity and off-label use are addressed.

Keywords: perineural adjuvant; dexamethasone; dexmedetomidine; peripheral nerve block; rebound pain; regional anesthesia

INTRODUCTION

A single injection of a long-acting local anesthetic around a peripheral nerve produces analgesia lasting roughly eight to sixteen hours. The pain of a shoulder arthroplasty, a bimalleolar fixation or a mastectomy lasts considerably longer. The three available responses to this mismatch are a continuous catheter, an extended-release formulation, and an adjuvant added to the injectate. Catheters are effective but require infrastructure, carry their own complications and are unsuitable for many day-case pathways; extended-release formulations remain expensive and their comparative efficacy is contested. Adjuvants are cheap, immediately available, and require no additional technique, which explains why they have become near-universal.

The literature on adjuvants is unusually large and unusually noisy, with many small single-centre randomized trials of heterogeneous design. The picture that emerges from the syntheses is, however, reasonably consistent, and it is that picture rather than any individual trial that should guide practice [1].

DEXAMETHASONE

Dexamethasone is the most studied adjuvant and the most widely used. Its mechanism is incompletely understood; proposed contributions include local vasoconstriction reducing systemic uptake, attenuation of ectopic neuronal discharge through an effect on potassium channels in nociceptive C fibres, and a systemic

anti-inflammatory action independent of the site of administration. The last of these matters because it predicts that intravenous administration should also prolong the block — and it does.

A Cochrane review confirmed that dexamethasone as an adjuvant to peripheral nerve blockade prolongs analgesia, while noting that the quality of evidence for the comparison between routes was low [2]. The route question has since been examined repeatedly. Early meta-analyses favoured the perineural route by a margin of several hours [3–5]. Subsequent and more rigorously conducted syntheses have narrowed that margin considerably: a systematic review restricted to the analgesic duration endpoint found a statistically significant but clinically modest perineural advantage [6], a meta-analysis with trial sequential analysis restricted to the interscalene block reached a similar conclusion [7], and an analysis restricted to lower limb blockade found the two routes broadly comparable [8]. A meta-analysis restricted to brachial plexus blockade likewise reported a small perineural advantage [9].

Individual randomized trials illustrate why the picture is mixed. Rosenfeld and colleagues found no clinically important difference between routes for shoulder surgery [10], whereas Kahn and colleagues demonstrated that even a low perineural dose prolonged interscalene analgesia more than a systemic dose [11]. Trials in ankle block [12] and sciatic block [13] have reported differing results. The reasonable summary is that both routes work, that perineural administration is probably slightly better, and that the difference is small enough that a clinician who prefers to avoid off-label perineural administration of a preparation not licensed for that route is not sacrificing much. Where perineural administration is used, a preservative-free preparation should be chosen and the dose kept low; 4 mg is as effective as higher doses in most reports, and intravenous dosing is usually 4–8 mg.

DEXMEDETOMIDINE

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, prolongs blockade by a mechanism that is thought to involve hyperpolarization-activated cation current inhibition in peripheral nerves as well as a central effect after systemic absorption. The first systematic review to establish its facilitatory effect on both neuraxial and peripheral blockade appeared over a decade ago [14], and a later review restricted to brachial plexus blockade confirmed a substantial prolongation of sensory and motor block and an improvement in block quality [15]. A systematic review of α2-agonists as a class reached compatible conclusions and clarified that the effect is not confined to dexmedetomidine [16].

The characteristic problem is haemodynamic. Bradycardia and hypotension are dose-dependent and are reported consistently across trials, as is sedation; these effects reflect systemic absorption and are the main constraint on dose. Typical perineural doses of 50–100 µg, or 0.5–1 µg/kg, represent the usual compromise. As with dexamethasone, the question of whether the perineural route is superior to the intravenous has been examined, and a meta-analysis found the perineural route to give the greater prolongation [17].

COMPARING THE TWO, AND THE REST

Direct comparison of dexamethasone with dexmedetomidine has been undertaken in a PRISMA-compliant systematic review, which found dexamethasone to give a somewhat longer duration of analgesia with fewer haemodynamic effects [18]. A network meta-analysis restricted to supraclavicular brachial plexus blockade compared both agents by both routes and reached a similar ranking [19], as did a Bayesian network meta-analysis restricted to the interscalene block [20] and a network meta-analysis in a paediatric population [21].

The broader comparison across all adjuvants is best captured by two network meta-analyses. Xuan and colleagues, examining the prolongation of local anesthetic duration across all peripheral blocks, ranked dexamethasone and dexmedetomidine above the alternatives [22]. Schubert and colleagues, restricting the analysis to single-injection upper extremity blockade, reached the same conclusion and provided a useful ranking of the older agents [23]. A qualitative systematic review remains a helpful summary of the pharmacology of the whole class [1].

Of the older adjuvants, buprenorphine has the best evidence for meaningful prolongation but a high incidence of nausea; a randomized trial of dexamethasone and buprenorphine added to sciatic blockade illustrates both the benefit and the cost [24]. Clonidine prolongs blockade modestly and shares dexmedetomidine's haemodynamic effects without matching its efficacy. Magnesium, midazolam, ketamine and perineural opioids have either weak evidence, unacceptable side effects, or unresolved neurotoxicity concerns, and none can be recommended for routine use.

REBOUND PAIN: A DIFFERENT FRAMING OF THE PROBLEM

The recent recognition of rebound pain has changed how the adjuvant question should be posed. Rebound pain — the abrupt, often severe increase in pain as a block resolves — affects a substantial proportion of patients after single-injection blockade and is now the subject of a dedicated literature [25]. If a block simply defers the onset of pain rather than reducing its total burden, then prolonging the block by four hours may accomplish less than ensuring that scheduled multimodal analgesia is in place before it wears off.

Dexamethasone appears to attenuate rebound pain as well as prolong the block, plausibly through its anti-inflammatory action, and a randomized controlled trial comparing intravenous with perineural dexamethasone specifically for the reduction of rebound pain after interscalene blockade found both effective [26]. This gives an additional and perhaps stronger reason to use dexamethasone than duration alone, and it partially neutralizes the route debate, since a systemic anti-inflammatory effect does not depend on perineural placement.

EXTENDED-RELEASE FORMULATIONS

Liposomal bupivacaine and other extended-release preparations represent the alternative solution to the same problem, and the relevant question for a clinician choosing between strategies is whether they outperform a conventional local anesthetic plus an adjuvant. A recent randomized controlled trial comparing liposomal bupivacaine with ropivacaine plus dexamethasone in suprainguinal fascia iliaca blockade for hip arthroplasty addresses this comparison directly [27], and a broader review situates these formulations alongside perineural additives and catheters as the three available routes to a longer block [28]. On present evidence the cost differential is not matched by a proportionate clinical advantage.

SAFETY AND PRACTICAL RECOMMENDATIONS

All perineural adjuvant use is off-label. Preservative-free preparations should be used; preservatives, particularly bisulphites and benzyl alcohol, are the component most often implicated in experimental neurotoxicity. The relevant clinical safety framework remains the practice advisory on neurologic complications in regional anesthesia, which emphasizes that most perioperative nerve injury is multifactorial and that avoidable contributions include intrafascicular injection and high injection pressure [29].

In practice, a defensible default is dexamethasone 4 mg — perineural where institutional practice permits, intravenous 4–8 mg otherwise — added to a long-acting local anesthetic, with dexmedetomidine 50–100 µg reserved for patients in whom corticosteroid is contraindicated or in whom the additional block density is specifically desired, and with haemodynamic monitoring appropriate to that choice. Whatever adjuvant is used, scheduled paracetamol and a non-steroidal anti-inflammatory drug should be started before the block resolves.

CONCLUSION

Two adjuvants have survived rigorous synthesis: dexamethasone, which prolongs analgesia by several hours and appears to blunt rebound pain, and dexmedetomidine, which prolongs and deepens blockade at a haemodynamic cost. The difference between perineural and intravenous dexamethasone is real but small,

and smaller than a decade of enthusiastic trials implied. The more useful shift in thinking is away from extending the block as an end in itself and toward planning for its resolution.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception, literature search and appraisal, interpretation of the evidence, and manuscript preparation and revision.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

ETHICS STATEMENT

This article is a narrative review of previously published literature. It does not report any study involving human participants or animals performed by the author, and therefore ethics committee approval and informed consent were not required.

ARTIFICIAL INTELLIGENCE DISCLOSURE

Artificial intelligence tools were used to assist with literature retrieval and language editing. All scientific content, interpretation, and conclusions are the responsibility of the author, who has reviewed and verified the final manuscript.

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