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Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials

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Editor's key points

- In this systematic review of 9 studies and 801 patients, the authors demonstrate the reliable prolongation of sensory and motor block after local anaesthesia brachial plexus block via the addition of dexamethasone to the injectate.
- No adverse events of significance have been demonstrated, although it is likely that considered studies have not been powered to detect such events.
- The effect on block duration of systemic dexamethasone remains to be investigated.

Background. Brachial plexus nerve blocks (BPBs) have analgesic and opioid sparing benefits for upper extremity surgery. Single-injection techniques are limited by the pharmacological duration and therapeutic index of local anaesthetics (LAs). Continuous catheter techniques, while effective can present management challenges. Off-label use of perineural dexamethasone as an LA adjuvant has been utilized to prolong single-injection techniques. The objectives of this systematic review and meta-analysis are to assess the contemporary literature and quantify the effects of dexamethasone on BPB.

Methods. The authors searched for randomized, placebo-controlled trials that compared BPB performed with LA alone with that performed with LA and perineural dexamethasone. Meta-analysis was performed using a random effects model with subgroup analysis stratified by LA (long *vs* intermediate). The primary outcome was duration of sensory block or analgesia; the secondary outcomes were motor block duration, opioid consumption, and BPB complications.

Results. Nine trials (801 patients) were included with 393 patients receiving dexamethasone (4–10 mg). Dexamethasone prolonged the analgesic duration for long-acting LA from 730 to 1306 min [mean difference 576 min, 95% confidence interval (CI) 522–631] and for intermediate from 168 to 343 min (mean 175, 95% CI 73–277). Motor block was prolonged from 664 to 1102 min (mean 438, 95% CI 89–787). The most recent trial demonstrated equivalent prolongation with perineural or systemic administration of dexamethasone compared with placebo.

Conclusions. Perineural administration of dexamethasone with LA prolongs BPB effects with no observed adverse events. The effects of systemic administration of dexamethasone on BPB must be investigated.

Keywords: anaesthesia adjuvants; dexamethasone; nerve block

Brachial plexus nerve blocks (BPBs) for upper extremity surgery provide superior analgesia and reduce opioid consumption.[1 2] Painful procedures previously requiring inpatient hospital admission for pain control, such as shoulder surgery, are now commonly performed as ambulatory procedures facilitated by BPB analgesia. Inevitably, the effects of single-injection BPB dissipate after several hours unmasking the moderate-to-severe pain of the surgical insult. Efforts to prolong BPB duration by increasing local anaesthetic (LA) dose are limited by their narrow therapeutic window and indeed may not be effective as recent studies have demonstrated equivalent analgesic duration with volumes as low as 5 ml.[3–5] A broad cross section of surgical patients consistently rank postoperative pain as their highest concern highlighting the necessity for prolonged postoperative analgesia.[6 7] As a result, strategies to prolong BPB analgesia beyond the pharmacological duration of the LA used include placement of indwelling perineural catheters to allow prolonged infusion or the co-administration of adjuvants such as epinephrine, $\alpha 2$ agonists (i.e. clonidine and dexmedetomidine), midazolam, or the corticosteroid dexamethasone.[8–10] Indwelling catheter techniques can be very effective and provide analgesia for several days, but their utility is limited by technical

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challenges with placement, inherent secondary failure rate, difficulties with catheter removal, or rarely infection.[11–13] Furthermore, not all anaesthetists have the subspecialty training required to perform advanced indwelling catheter techniques nor is there universal capability to administer and manage an outpatient perineural catheter programme.

LA adjuvants act by several mechanisms. They may cause local vasoconstriction limiting systemic uptake or they may have direct effects on peripheral nerves. In addition, they may also act systemically by anti-inflammatory effects. A meta-analysis by Pöpping and colleagues[10] determined that clonidine, as an adjuvant for peripheral nerve block (PNB), prolonged the duration of postoperative analgesia by 122 min [95% confidence interval (CI), 74–169]. This was at a cost of an increased risk of sedation [odds ratio (OR) 2.28, 95% CI 1.15–5.41], hypotension (OR 3.61, 95% CI 1.52–8.55), and bradycardia (OR 3.09. 95% CI 1.10–8.64), known side-effects of systemic clonidine. Similar results have been demonstrated with dexmedetomidine.[14]

It is widely believed that dexamethasone improves the quality and duration of PNB over LA alone. This is thought to be mediated by attenuating the release of inflammatory mediators, reducing ectopic neuronal discharge, and inhibiting potassium channel-mediated discharge of nociceptive C-fibres.[15–17] The addition of dexamethasone may provide patients who are otherwise not eligible for extended, continuous perineural techniques, to experience an extended period of analgesia compared with LA BPB alone. However, dexamethasone is not approved for perineural administration by the United States Food and Drug Administration (FDA), Health Canada (HC), the European Union (EU), nor any other regulatory body. There are no systematic reviews or meta-analyses estimating the effect of dexamethasone on BPB duration and the incidence of complications (prolonged nerve palsy, hyperglycaemia, and infection) associated with its use in the contemporary literature. If anaesthesiologists are to be confident in utilizing off-label dexamethasone as a BPB adjuvant, a good estimate of the expected positive and negative effects must be available to make informed decisions.

Methods

Reconciliation of study procedures

All activities including the literature search, inclusion of studies, grading study quality, and extraction of data were carried out independently and in duplicate by two authors (S.C. and R.R.). Disagreements between reviewers were resolved through discussion with a third reviewer experienced in the field of regional anaesthesia (C.J.L.M.).

Search strategy

The following electronic databases were searched: (i) MEDLINE (1946–April 2013), (ii) EMBASE (1980–April 2013), and (iii) Cochrane Central Register of Controlled Trials (2005–April 2013). The initial search terms with the keywords *regional anaesthesia, brachial plexus*, *interscalene, supraclavicular, infraclavicular, axillary*, or *nerve block* with the definition exploded were utilized. The 'and' function was used to combine these terms with *dexamethasone, corticosteroid, or steroid* with the definition exploded. The identified abstracts were screened and full-text articles meeting the selection criteria were retrieved. The references of all retrieved articles were manually searched to identify any other studies not found in the electronic search. All available abstracts from major international meetings including the American Society of Regional Anesthesia (ASRA—2005–2012), the European Society of Regional Anaesthesia (ESRA—2007–2012), and the American Society of Anesthesiologists (ASA—2000–2012) annual meetings were examined and published protocols on the trial registration site www.clinicaltrials.gov.

Selection criteria

Studies meeting the following criteria were included: (i) prospective study with randomized allocation; (ii) comparison of LA with perineural dexamethasone (intervention) with that without (control) in single-injection BPB regional analgesia or anaesthesia for upper extremity surgery; and (iii) studies only assessing adult (>18 yr old) patients. Attempts were made to contact study authors, particularly for meeting abstracts, to elicit information regarding methodology, missing data, and other study details relevant to this review. Abstracts were planned for inclusion if they were low risk of bias. Studies were planned for inclusion regardless of whether regulatory approval (United States Investigational New Drug or national equivalent) was sought by authors.

Data extraction

Two reviewers performed data extraction independently and in duplicate. The following patient characteristic data were extracted: primary author, year of publication, specific surgical population, sample size, specific type of BPB, nerve localization technique, type and dose of LA, and dose of perineural dexamethasone. Specific extracted outcomes and risk of bias assessments are detailed in the following sections. Where data were reported as median and interquartile range (IQR), authors were contacted to obtain raw data and the mean and standard deviation (SD) were determined to enable meta-analysis. If this was not possible, the mean and SD were estimated from the median and range according to the method described by Hozo and colleagues.[18] As a last resort, the SD was estimated from the IQR by the method described by the Cochrane Handbook for Systematic Reviews (IQR=1.35SD).[19] In the case of multiple groups with differing doses of perineural dexamethasone, these groups were combined and compared with patients receiving no perineural dexamethasone. In the case where systemic dexamethasone was administered, these patients were included in the control or no perineural dexamethasone group.

Outcomes to be assessed

The important patient outcomes extracted were: (i) duration of analgesia or sensory block; (ii) duration of motor block; (iii) cumulative 72 h opioid consumption; and (iv) complications associated with BPB or dexamethasone including persistent nerve palsy lasting >1 week, infection at the site of BPB, and

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perioperative hyperglycaemia (defined as within 1 week of surgery). We specifically did not examine block quality as it is assessed in an extremely heterogeneous manner including subjective descriptions to the use of numerical scales.

Assessment for risk of bias and methods for measuring heterogeneity

Each included study was assessed for risk of bias according to the Cochrane Collaboration's Risk of Bias Tool for randomized controlled trials.[19] Heterogeneity was assessed using the I^2 statistic for each individual outcome. Studies were pooled in the meta-analysis using a random effects model. For significant heterogeneity ($I^2 > 50\%$), subgroup analysis was planned based on the following a priori hypothesis.

A priori hypothesis to explain heterogeneity (subgroup analysis)

The a priori hypothesis to explain heterogeneity is that the effects of dexamethasone on BPB depend on the type of LA utilized. Specifically, we hypothesized that dexamethasone exerts a greater absolute effect on long-acting (ropivacaine, bupivacaine, and levobupivacaine) compared with intermediate-acting (lidocaine and mepivacaine) LAs.

Analysis and plans to summarize results

Meta-analysis was performed with RevMan 5.2 (Cochrane Library, Oxford, UK) using a random effects model. The Summary of Findings table was generated using GRADEpro, the GRADE working group guideline development tool (www.http://ims.cochrane.org/revman/gradepro). Data from trials with more than two intervention groups receiving different perineural doses of dexamethasone were combined into a single group as described by the Cochrane handbook.[20] Continuous outcomes with units in time are presented in minutes. Both absolute duration and relative duration of increase are presented as a weighted mean difference estimate with 95% CI. Opioid consumption is expressed in oral morphine equivalents (conversion according to Canadian Compendium of Pharmaceuticals) with the weighted mean difference and 95% CI between the dose used in groups. Dichotomous outcomes are presented as ORs. Differences were considered statistically significant if $P<0.05$ and the 95% CI excluded 0 for the standardized mean difference or 1 for the OR.

Results

The search yielded 132 records after removal of duplicates identified between databases. Nine of the 132 identified records were included in the systematic review and meta-analysis with dexamethasone doses from 4 to 10 mg (8 studies utilizes doses of 8 mg).[8 21–28] Two full-text studies were excluded.[29 30] The study flow chart is presented in Figure 1. The details of BPB including intervention arms, sample size, guidance modality, outcomes assessed, and pertinent comments are detailed in Table 1. One study randomized patients into four different groups (ropivacaine ± dexamethasone and bupivacaine ± dexamethasone).[8] Because each LA used had a separate control group without double counting of participants, the ropivacaine and bupivacaine groups were considered separate studies for the meta-analysis. One study randomized patients to interscalene brachial plexus block (ISB) with LA alone, with systematic dexamethasone, and perineural dexamethasone.[28] One study received Investigational New Drug Approval (IND),[22] while two studies contacted regulatory authorities with one study receiving no response from authorities,[8] and a second study informed that IND was not necessary.[28] The corresponding author of each study identified for inclusion in our search was contacted to obtain further information regarding either methodological issue related to risk of bias or to acquire data to allow better determination of mean and SD from median and IQR. There was no response from authors of two of the studies.[25 27] Authors of one study provided the entire data set,[22] while two provided the mean and SD.[8 28] Data to refine risk of bias assessments were received from the authors of five studies.[21 23 24 26 28] One study provided information in graphical form that reported statistically significant prolongation of dexamethasone over control. Attempts to contact the corresponding author failed and without a measure of central tendency and variation, we could not include these data in the meta-analysis.[29] A second study did not specifically examine the outcomes sought for this review.[30] Attempts to contact the corresponding author to determine whether these outcomes were recorded but not reported were unsuccessful (Table 1). In addition to standard forest plots provided with meta-analyses, the results are presented in a Summary of Findings table (Table 2).

Risk of bias assessment for included studies

Four of the nine studies had low risk of bias for all elements, while one had a single element that was unclear risk of bias. Of the remaining four, two had at least three elements with an unclear risk of bias and two had one element rated at high risk of bias. The specific reviewers' judgements for risk of bias are detailed in Figure 2. The majority of studies were low risk for bias with respect to sequence generation, allocation concealment, and blinding. With respect to attrition bias, seven were judged to be low risk; two were of unclear risk because the specific distribution of BPB failure among patient groups was not reported; and another study did not report on any BPB failures.[23 25] A single study was at high risk of bias for selective outcome reporting because specific *P*-values for hypothesis testing were not provided.[23] A single study was rated high risk of other potential sources of bias because no information was provided about patients with failed BPB.[24]

There are no trials registered that have been completed or terminated that are not currently published. The protocols of six of the nine studies were not published a priori. All unpublished trials on www.clinicaltrials.gov are currently in progress. Funnel plot analysis demonstrates that for the outcome of sensory block duration, the point estimate of effect for the effects of dexamethasone demonstrates five studies higher and lower than the estimated effect. When assessed on the basis of a priori subgroups, the individual studies cluster around the point estimates (Supplementary Appendix S1).

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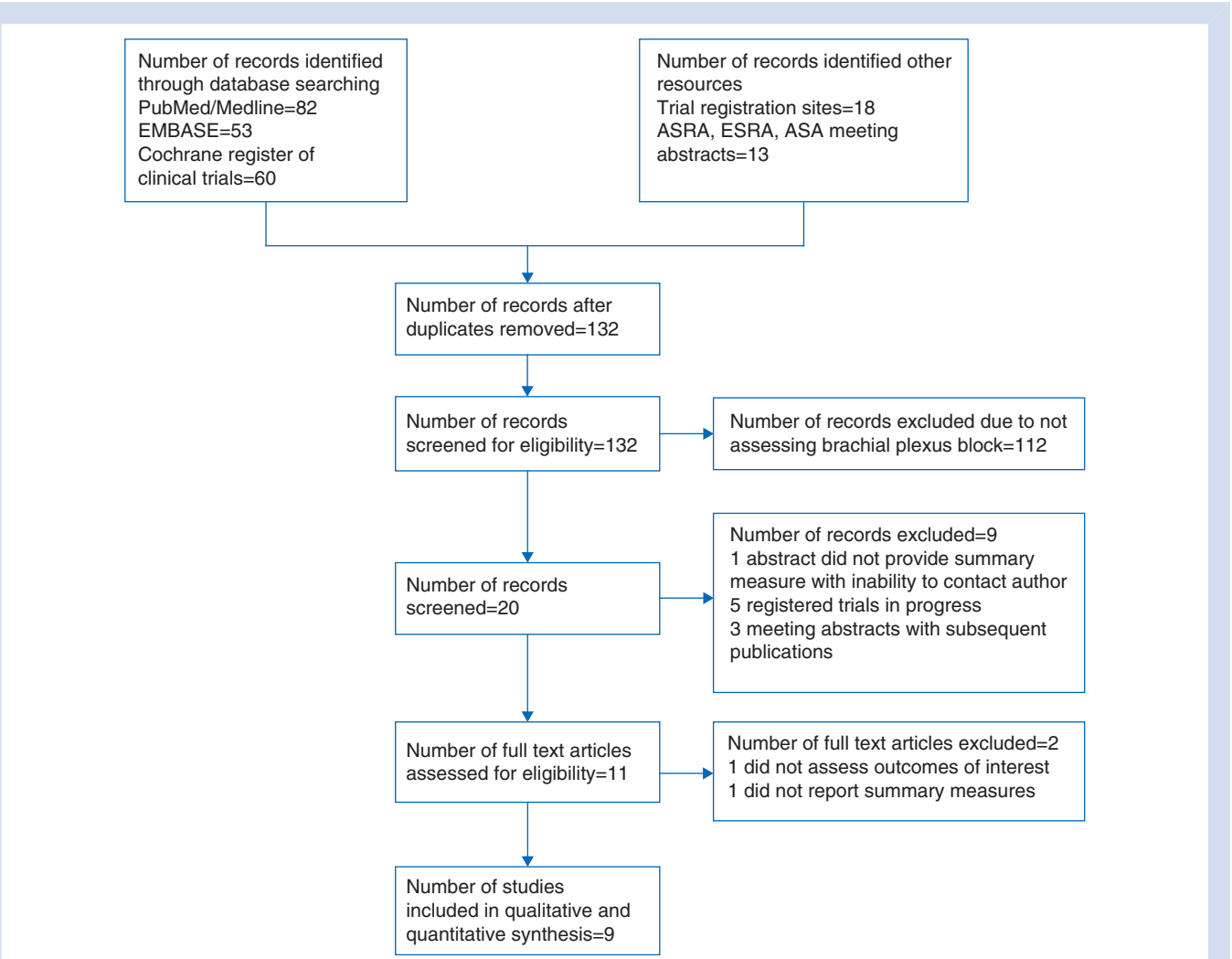

Fig 1 PRISMA flow diagram of search, included/excluded studies. ASRA, American Society of Regional Anesthesia and Pain Medicine; ESRA, European Society of Regional Anaesthesia.

Duration of analgesia or sensory block

Analgesic duration or sensory block was reported by all nine included studies (801 patients, 393 receiving perineural dexamethasone). All the studies reported statistically significant prolonged analgesia with the addition of perineural dexamethasone compared with without (Fig. 3).[8 21–28] The definition of postoperative analgesic duration was variable and reported as verbal rating scale (VRS)>0,[21] VRS>3,[22 25–27] VRS>7,[23] time to first analgesic request,[8 28] and in one study it was not defined.[24] The overall estimate of the effects of dexamethasone on the prolongation of analgesic duration is 410 min (95% CI 282–539, $P<0.00001$) from a baseline of 479 min without dexamethasone. However, there was a large degree of heterogeneity ($I^2=98\%$). When analysed according to the a priori subgroup hypothesis, dexamethasone had a greater absolute effect on long-acting LAs (test for subgroup differences $P<0.00001$). For long-acting LAs, the pooled estimated prolonging effect is 576 min (95% CI 515–625, $P<0.00001$) from a baseline of 730 min without dexamethasone with low heterogeneity ($I^2=29\%$). The relative effect of dexamethasone on long-acting LAs is 1.79 (95% CI 1.71–1.86). For intermediate-acting LAs, the pooled effect of dexamethasone is estimated at 175 min (95% CI 73–277, $P<0.00001$) from a baseline of 168 min with significant heterogeneity ($I^2=98\%$) while the relative effect is 2.04 (95% CI 1.43–2.65).

Sensitivity analysis did not significantly change the pooled results. For long-acting LAs, removing the two studies most at risk of bias[23 24] changed the point effect estimate by 30 min to 546 min (95% CI 438–654) with moderate heterogeneity ($I^2=54\%$). Excluding the study at highest risk of bias from the intermediate-acting LA reduced the point estimate and narrowed the 95% CI (124 min, 95% CI 87–161), but still had significant heterogeneity ($I^2=98\%$). Sensitivity analysis stratifying by BPB type did not result in significant changes either.

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Table 1 Outcomes of interest reported by studies. Ax, axillary block; Bupi, bupivacaine; Clon, clonidine; Dex, dexamethasone; epi, epinephrine; FDA, United States Food and Drug Administration; HC, Health Canada; IND, Investigational New Drug Approval; Levo, levobupivacaine; Lido, lidocaine; LM, landmark; Mepiv, mepivacaine; *n*, number of patients in group; PNS, peripheral nerve stimulation; SC, supraclavicular; Tram, tramodol; US, ultrasound; VRS, verbal rating scale for pain

Study ID	Arms	*n*	Regulatory approval	Guidance	Outcomes of interest							Comments
					BPB type	Sensory block	Motor block	Opioid	Nerve palsy	Infection	Hyperglycaemia	
Included studies												
Shrestha and colleagues[24]	Lido 1%/Bupi 0.25%+epi (1:200 000) 40 ml Lido 1%/Bupi 0.25%+epi (1:200 000) 40 ml+Dex 8 mg	20 20	None	LM	SC	Yes	No	No	No	No	No	Specific definition of duration of analgesia not defined
Movafegh and colleagues[21]	Lido 1.5% 36 ml Lido 1.5% 36 ml+Dex 8 mg	30 30	None	PNS	AX	Yes	Yes	No	No	No	No	Sensory block defined as time to VRS>0 Motor block defined as time to complete recovery
Shrestha and colleagues[23]	Bupi 0.5% 2 mg/kg+Tram 2 mg kg^{-1} Bupi 0.5% 2 mg/kg+Dex 8 mg	30 30	None	LM	SC	Yes	Yes	No	No	No	No	Sensory block defined as time to VRS≥8 Motor block defined as strength to overcome gravity
Yadav and colleagues[27]	Lido 1.5%+epi (1:200 000) 24 ml Lido 1.5%+epi (1:200 000)+Dex 4 mg	30 30	None	LM+PNS	SC	Yes	No	No	No	No	No	Sensory block defined as time to VRS>3
Parrington and colleagues[22]	Mepiv 1.5% 30 ml Mepiv 1.5% 30 ml+Dex 8 mg	21 24	Yes (HC)	US	SC	Yes	No	Yes	Yes	No	No	Sensory block defined as time to VRS≥4 or time to first analgesic request Opioid consumption reported at 8 h, 1, 7, 14 days—cumulative 1 day consumption used in analysis
Vieira and colleagues[26]	Bupi 0.5%+epi (1:200 000)+Clon 75 μg 20 ml Bupi 0.5%+epi (1:200 000)+Clon 75 μg+Dex 8 mg 20 ml	44 44	None	US	ISB	Yes	Yes	Yes	No	No	No	Sensory block defined as time VRS≥4 Motor block defined as time to first movement Opioid consumption reported at 24 and 48 h—cumulative 48 h consumption used in analysis
Tandoc and colleagues[25]	Bupi 0.5%+epi (1:200 000) 40 ml Bupi 0.5%+epi (1:200 000)+Dex 4 mg 40 ml Bupi 0.5%+epi (1:200 000)+Dex 8 mg 40 ml	28 28 30	None	PNS	ISB	Yes	Yes	Yes	No	No	No	Low and high dose dexamethasone groups combined Sensory block defined as time to VRS>3 Motor block defined as time to abducting arm 2 in. Opioid consumption reported at

Continued

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Table 1 *Continued*

Study ID	Arms	*n*	Regulatory approval	Guidance	Outcomes of interest							Comments
					BPB type	Sensory block	Motor block	Opioid	Nerve palsy	Infection	Hyperglycaemia	
												48 and 72 h—cumulative 72 h consumption used in analysis
Cummings and colleagues[8]	Ropi 0.5% 30 ml Ropi 0.5%+Dex 8 mg 30 ml Bupi 0.5% 30 ml Bupi 0.5%+Dex 8 mg 30 ml	54 54 56 54	None*	US or PNS	ISB	Yes	No	Yes	Yes	Yes	No	Sensory block defined as time to first analgesic request Opioid consumption reported at 72 h *Authors contacted FDA inquiring about IND approval but no response received*
Desmet and colleagues[28]	Ropi 0.5% 30 ml Ropi 0.5% 30 ml+Dex 10 mg i.v. Ropi 0.5% 30 ml+Dex 10 mg	46 49 49	None*	PNS	ISB	Yes	No	No	Yes	Yes	Yes	Group receiving systemic (i.v.) dexamethasone combined with placebo group Sensory block defined as time to first analgesic request Analgesic consumption reported for paracetamol and diclofenac *European Federal Agency of Medicines and Health Products did not request IND application*
Excluded studies												
Golwala and colleagues[29]	Lido 1%/Bupi 0.25%+epi (1:200 000) 35 ml Lido 1%/Bupi 0.25%+epi (1:200 000) 35 ml+Dex 8 mg	30 30	None	LM	SC	Yes	No	No	No	No	No	No point estimate of effects provided in publication No response from author
Kim and colleagues[30]	Levo 0.5%+epi (1:400 000) 10 ml Levo 0.5%+Dex 8 mg 10 ml	30 30	None	US+PNS	ISB	No	No	No	No	No	No	No response from author

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Table 2 LA alone or with dexamethasone for BPB. *Patient or population*: patients undergoing upper extremity surgical procedures with BPB anaesthesia or analgesia. *Settings*: in-hospital surgical procedures on upper extremity. *Intervention*: LA with dexamethasone for BPB. GRADE Working Group grades of evidence. *High quality*: further research is very unlikely to change our confidence in the estimate of effect. *Moderate quality*: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low quality*: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. *Very low quality*: we are very uncertain about the estimate. *Rated up for evidence because analgesia/sensory block prolonged by large effect. †Rated down because of wide 95% CI (imprecision) around point estimate with significant heterogeneity. ‡Rated down because wide 95% CI (imprecision) around point estimate with significant heterogeneity. ¶Rated down because of inconsistency of effect. §Baseline rate of transient nerve palsy in BPB is <3% and persistent nerve palsy is exceedingly rare

Outcomes	Illustrative comparative (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	LA alone for BPB (control)	LA with dexamethasone for BPB (intervention)				
Duration of analgesia or sensory block—long-acting LA	The mean duration of analgesia or sensory block—long-acting LA alone was *730 min*	The mean duration of analgesia or sensory block—long-acting LA with dexamethasone was *576 min longer* (95% CI: 515–625 longer)	1.79 (1.71–1.86)	636 (6 studies)	⊕⊕⊕⊕ *High**	
Duration of analgesia or sensory block—intermediate-acting LA	The mean duration of analgesia or sensory block—intermediate-acting LA alone was *168 min*	The mean duration of analgesia or sensory block—intermediate-acting LA with dexamethasone was *175 min longer* (95% CI: 73–277 longer)	2.04 (1.43–2.765)	165 (3 studies)	⊕⊕⊕⊖ *Moderate†*	
Duration of motor block	The mean duration of motor block in LA alone group was *664 min*	The mean duration of motor block in LA with dexamethasone group was *438 min longer* (95% CI: 89–787 longer)	1.67 (1.13–2.19)	294 (4 studies)	⊕⊕⊕⊖ *Moderate*	
Opioid consumption	The mean opioid consumption in LA alone was *83.0 mg oral morphine equivalent*	The mean opioid consumption in LA with dexamethasone was *14.7 mg less* (95% CI: 38.0 less to 8.6 more)	0.82 (0.54–1.10)	439 (4 studies)	⊕⊕⊖⊖ *Low‡,¶*	
Persistent nerve palsy	See comment	See comment	Not estimable	407 (3 studies)	See comment	Outcomes assessed in three studies with zero counts in all cells§
Hyperglycaemia within 1 week of BPB	See comment	See comment	Not estimable	144 (1 study)	See comment	Statistically significant, but clinically irrelevant elevation in blood glucose (5.1 mg dl^{-1}, $P=0.0095$). No patients were hyperglycaemic
Infection at BPB site within 1 week	See comment	See comment	Not estimable	216 (0)	See comment	Outcomes in one study with zero counts in all cells

Duration of motor block

The duration of motor block was reported by four studies (294 patients, 162 receiving perineural dexamethasone).[21 23 25 26] Three studies reported statistically significant prolongation associated with dexamethasone (Fig. 4).[23 25 26] The definition of motor block duration included time to first movement[26]; ability to abduct the arm 2 in.;[25] ability to overcome gravity;[23] or complete motor recovery.[21] The overall estimate of the effects of dexamethasone on the prolongation of motor block is 438 min (95% CI 89–787, $P=0.01$) from a baseline of 664 min with significant heterogeneity ($I^2=98\%$). The test for subgroup differences was not significant ($P=0.19$). Sensitivity analysis did not change the overall significance of dexamethasone prolonging BPB.

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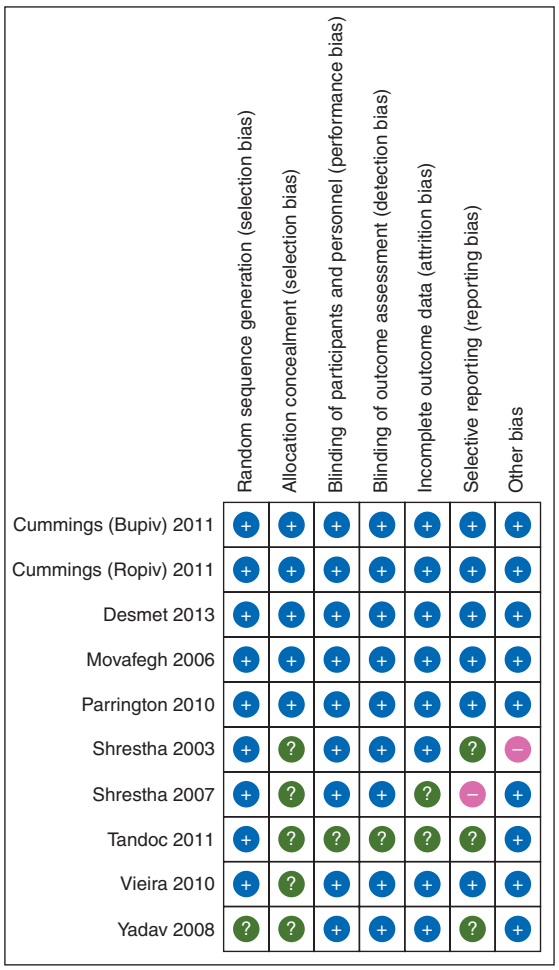

Fig 2 Authors' judgements regarding risk of bias for included studies. blue circle, low risk of bias; green circle, unclear risk of bias; pink circle, high risk of bias.

Opioid consumption

Opioid consumption up to 72 h was reported by four studies (439 patients, 234 receiving dexamethasone).[8 22 25 26] Pooled results did not demonstrate a statistically significant reduction in opioid consumption with a point estimate of 14.7 mg less oral morphine equivalent (95% CI −38.0 to 8.6, P=0.22) (Fig. 5). Opioid consumption was measured at different time points in all four studies ranging from 24 h to 2 weeks.

Complications associated with BPB

Three studies evaluated the incidence of persistent nerve palsy up to 2 weeks,[8 22] and 6 months[28] after BPB (407 patients; 180 receiving perineural dexamethasone). No events were recorded in either arm, and therefore, no effect can be estimated. Given that the rate of persistent nerve palsy after BPB is extremely low, it was not unexpected that among only 407 patients, no events were observed. A single study evaluated perioperative blood glucose concentrations and determined that dexamethasone use increased blood glucose concentrations (up to 5.1 mg dl^{-1}, P=0.0095), but this was not clinically relevant.[28]

Discussion

This systematic review and meta-analysis of nine randomized controlled trials demonstrates that the addition of dexamethasone to LA for PNBs prolongs the duration of sensory block/analgesia. The addition of dexamethasone to long-acting and intermediate-acting LAs prolongs sensory block by ~10 h and 3 h, respectively. The absolute effect was greater in the long-acting compared with intermediate-acting LAs. This is in contrast to other adjuvants such as clonidine or epinephrine that demonstrate the opposite. Off-label perineural additives to prolong intermediate-acting LAs are of marginal clinical benefit, since long-acting LAs exceed the purported duration. These studies may have been 'proof of concept' studies or those that incorporated normal clinical practice in local centres.

While our meta-analysis displayed clear benefits in terms of duration of analgesia, other outcomes are less clear. Prolonged analgesia without prolonged motor block is desirable both for surgeons and for anaesthesiologists. The data indicate that the prolongation of motor block was similar in magnitude to that of sensory block. Given that one of the purported mechanisms of dexamethasone is to specifically inhibit nociceptive C-fibre transmission and perhaps spare motor function, this result is suboptimal. This suggests that dexamethasone may still have a direct effect on nerve transmission that is not yet elucidated.

While there was a trend towards decreased consumption, we did not find a significant difference in cumulative opioid consumption. There are likely several reasons for this. First, cumulative 72 h consumption is too long a time frame over which to expect differences in opioid consumption, particularly when the duration of analgesia does not last that long. The 72 h period was selected to allow the inclusion of the maximum number of studies assessing opioid consumption, whereas only two studies assessed 24 h opioid consumption, a more suitable time frame in the context of the intervention. Secondly, varying analgesic protocols likely influenced opioid consumption, with some trials employing multimodal-opioid sparing adjuncts while others did not. Further study, specifically assessing 24 h opioid consumption will likely refine the estimated opioid sparing benefits.

We did not seek to specifically examine the effects of dexamethasone on analgesic quality because of the subjective nature of the outcome. It is less reliable than duration of analgesia. Given that we were concerned about the variable definitions with respect to duration of sensory block and analgesia in the included studies and that the definitions of analgesic quality were even more heterogeneous, this outcome was not included in the meta-analysis. Nonetheless, several studies did report that LA with perineural dexamethasone resulted in patients reporting qualitatively 'better' analgesia or lower pain scores than without.[8 26–30]

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Study or subgroup	LA with dexamethasone Mean (min)	SD (min)	Total	LA alone Mean (min)	SD (min)	Total	Weight	Mean difference I.V. random, 95% CI (min)
Long-acting LA								
Shrestha 2003	765	320	20	190	29	20	10.1%	575.00 (434.18, 715.82)
Shrestha 2007	1028	195	30	453	73	30	11.1%	575.00 (500.49, 649.51)
Vieira 2010	1457	434	44	833	267	44	10.0%	624.00 (473.44, 774.56)
Cummings (Ropiv) 2011	1488	864	54	888	564	54	7.5%	600.00 (324.80, 875.20)
Cummings (Bupiv) 2011	1428	510	54	1044	774	56	8.1%	384.00 (139.87, 628.13)
Tandoc 2011	1408	158	58	798	60	28	11.4%	610.00 (563.66, 656.34)
Desmet 2013	1433	510	49	1160	1263	95	7.2%	273.00 (–18.37, 564.37)
Subtotal (95% CI)			309			327	65.5%	576.46 (522.42, 630.51)
Heterogeneity: τ^2=1366.24; χ^2=8.40, df=6 (P=0.21); I^2=29%								
Test for overall effect; Z=20.91 (P<0.00001)								
Intermediate-acting LA								
Movafegh 2006	242	76	30	98	33	30	11.5%	144.00 (114.34, 173.65)
Yadav 2008	452	54	30	177	54	30	11.5%	275.00 (247.67, 302.33)
Parrington 2010	334	43.5	24	228	36	21	11.5%	106.00 (82.76, 129.24)
Subtotal (95% CI)			84			81	34.5%	174.89 (72.50, 277.28)
Heterogeneity: τ^2=7999.94; χ^2=88.76, df=2 (P=0.00001); I^2=98%								
Test for overall effect; Z=3.35 (P=0.0008)								
Total (95% CI)			393			408	100.0%	410.45 (281.94, 538.96)
Heterogeneity: τ^2=37238.99; χ^2=550.58, df=9 (P=0.00001); I^2=98%								
Test for overall effect; Z=6.26 (P<0.00001)								
Test for subgroup differences: χ^2=46.21, df=1 (P<0.00001); I^2=97.8%								

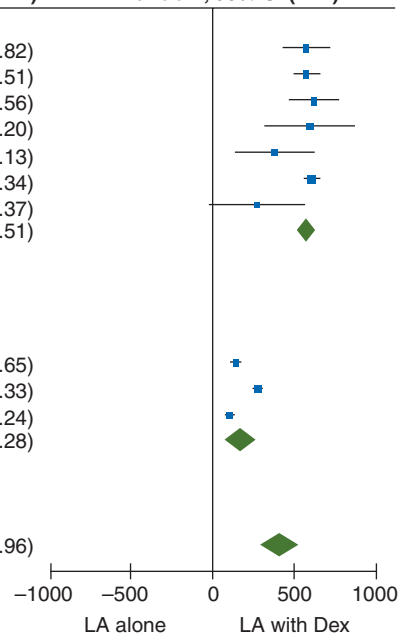

Fig 3 Forest plot demonstrating duration of analgesia/sensory block. Sample size, mean, SD, and the pooled estimate of the mean difference are shown according to subgroup. 95% CIs are indicated as lines for each study and diamonds for pooled estimates. Dex, dexamethasone; LA, local anaesthetic; SD, standard deviation.

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Study or subgroup	LA with dexamethasone Mean (min)	SD (min)	Total	LA alone Mean (min)	SD (min)	Total	Weight	Mean difference I.V. Random, 95% CI (min)	Year
Long-acting LA									
Shrestha 2007	393	99	30	203	31	30	26.3%	190.00 (152.88, 227.12)	2007
Vieira 2010	1374	299	44	827	239	44	25.7%	547.00(433.90, 660.10)	2010
Tandoc 2011	2280	249	58	1476	198	28	25.8%	804.00 (706.61, 901.39)	2011
Subtotal (95% CI)			132			102	77.8%	511.82 (104.17, 919.47)	
Heterogeneity: τ^2=127737.45; χ^2=154.70, df=2 (P<0.00001); I^2=99%									
Test for overall effect; Z=2.46 (P=0.01)									
Intermediate-acting LA									
Movafegh 2006	310	817	30	130	31	30	22.2%	180.00 (–112.56, 472.56)	2006
Subtotal (95% CI)			30			30	22.2%	180.00 (–112.56, 472.56)	
Heterogeneity: not applicable									
Test for overall effect: Z=1.21 (P=0.23)									
Total (95% CI)			162			132	100.0%	437.95 (89.36, 786.55)	
Heterogeneity: τ^2=119991.57; χ^2=155.25, df=3 (P<0.00001); I^2=98%									
Test for overall effect; Z=2.46 (P=0.01)									
Test for subgroup differences: χ^2=1.68, df=1 (P=0.19); I^2=40.5%									

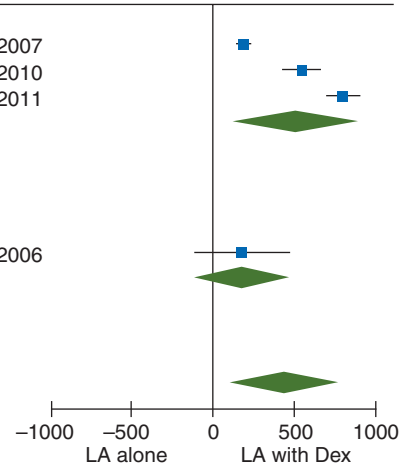

Fig 4 Forest plot demonstrating duration of motor block. Sample size, mean, SD, and the pooled estimate of the mean difference are shown according to subgroup. 95% CIs are indicated as lines for each study and diamonds for pooled estimates. Dex, dexamethasone; LA, local anaesthetic; SD, standard deviation.

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Study or subgroup	LA with dexamethasone Mean (mg)	SD (mg)	Total	LA alone Mean (mg)	SD (mg)	Total	Weight	Mean difference I.V. Random, 95% CI (mg)	Year
Long-acting LA									
Vieira 2010	25	25	44	25	9	44	24.7%	0.00 (–7.85, 7.85)	2010
Tandoc 2011	109.6	15.6	58	146.3	16.9	30	24.8%	–36.70 (–43.96, –29.44)	2011
Cummings (Ropiv) 2011	119	58	54	113	119	54	16.0%	6.00 (–29.31, 41.31)	2011
Cummings (Bupiv) 2011	90	65	54	127	74	54	19.3%	–37.00 (–63.00, –11.00)	2011
Subtotal (95% CI)			210			184	84.8%	–17.99 (–43.67, 7.70)	
Heterogeneity: τ^2=576.17; χ^2=48.99, df=3 (P<0.00001); I^2=94%									
Test for overall effect; Z=1.37 (P=0.17)									
Intermediate-acting LA									
Parrington 2010	31	81	24	27	46	21	15.2%	4.00 (–33.91, 41.91)	2010
Subtotal (95% CI)			24			21	15.2%	4.00 (–33.91, 41.91)	
Heterogeneity: not applicable									
Test for overall effect; Z=0.21 (P=0.84)									
Total (95% CI)			234			205	100.0%	–14.67 (–37.96, 8.63)	
Heterogeneity: τ^2=556.02; χ^2=50.49, df=4 (P<0.00001); I^2=92%									
Test for overall effect; Z=1.23 (P=0.22)									
Test for subgroup differences: χ^2=0.89, df=1 (P=0.35); I^2=0%									

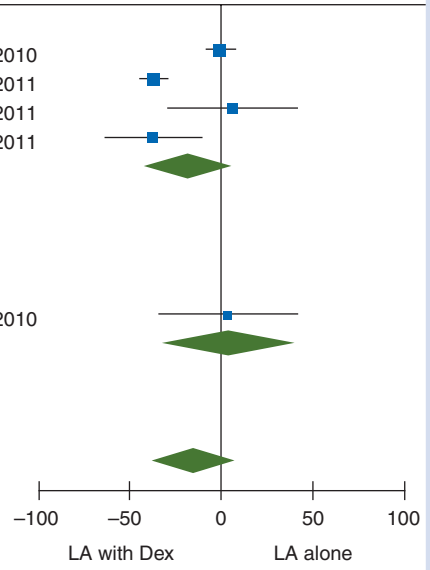

Fig 5 Forest plot demonstrating opioid consumption in oral morphine equivalents (mg). Sample size, mean, SD, and the pooled estimate of the mean difference are shown according to subgroup. 95% CIs are indicated as lines for each study and diamonds for pooled estimates. Dex, dexamethasone; LA, local anaesthetic; SD, standard deviation.

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To date, there are no reports of dexamethasone-induced neuronal damage. To the contrary, *in vitro* murine studies have actually demonstrated that dexamethasone attenuates the neurotoxicity of bupivacaine at a cellular level.[31] At the sensory nerve level, Williams and colleagues[32] demonstrated that ropivacaine and dexamethasone, in clinically relevant concentrations, did not result in increased neurotoxicity. While promising, the absence of evidence of harm is not evidence of absence. The inherent low rate of persistent nerve palsy in contemporary practice as determined by Brull and colleagues[33] suggest that even a significant increase associated with the use of dexamethasone would not be detected with the current number of studies, given that only 393 in this analysis received perineural dexamethasone.

There are limitations to this meta-analysis that likely contribute to the observed heterogeneity. First, the outcomes sought in this review more likely follow a skewed, non-normal distribution as confirmed by authors of the three most methodologically rigorous studies.[8 22 28] As pooling of data for meta-analysis involves normally distributed data, converting median and IQR into mean and SD will introduce a degree of uncertainty in the estimate of effect. Secondly, the varying definitions used by the source studies for outcomes sought also introduce heterogeneity. Though duration of analgesia and sensory block duration were combined, they are not equivalent, particularly when defining the threshold at different VRS levels. However, it was decided a priori to combine them, as they are at least comparable. The same theme repeats with the duration of motor block and opioid consumption where various definitions were used. Thirdly, while there is no clear evidence of publication bias, it cannot be precluded as only three of the nine included studies published protocols on trial registration sites.[8 22 28] These issues with heterogeneous methods of defining outcome measures again highlight the need for standardized outcome measures in regional anaesthesia studies to enable more accurate comparisons. Regardless, all the studies included, however block duration was defined, demonstrated statistically significant increases in duration when perineural dexamethasone was administered in addition to LA.

The most recent study included in this systematic review and meta-analysis published by Desmet and colleagues[28] highlight the need for further investigation into the effects of perineural dexamethasone. It is the first trial to include a systemic dexamethasone group. The authors randomized patients into three groups for ISB: (i) ropivacaine 0.5% alone, (ii) ropivacine 0.5% with systemic dexamethasone (10 mg), and (iii) ropivacaine 0.5% with perineural dexamethasone (10 mg). For the purposes of this meta-analysis, Groups 1 and 2 were combined. However, the authors demonstrated that patients receiving systemic and perineural dexamethasone did not demonstrate statistically significant differences in ISB duration (median block duration: control 757 min, systemic dexamethasone 1275 min, and perineural dexamethasone 1405 min). The conclusion that perineural and systemic dexamethasone are equivalent in terms of prolonging ISB may be overstated and may instead reflect lack of power to demonstrate a difference. To truly confirm equivalency, a properly designed equivalency trial should be conducted. Nonetheless, this study provides compelling reasons to investigate further.

To date, dexamethasone appears to be the best method to prolong analgesia as an adjuvant over clonidine, epinephrine, or midazolam. The value of several additional hours of analgesia is a risk/benefit discussion that anaesthesiologists must have with their patients, given the off-label use of perineural dexamethasone, its effects as determined in this review, and ultimately a decision on the part of the individual anaesthesiologist. Future research should focus on establishing the possible enhanced opioid sparing effects of PNBs with dexamethasone and the relative effects of perineural *vs* systemic dexamethasone administration, and establishing whether the effects can be duplicated in lower extremity PNBs.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Author's contributions

S.C.: study conception, design, data extraction, analysis, interpretation, drafting manuscript, and approval of the final manuscript. R.R.: study design, data extraction, analysis, interpretation, revised draft, and approval of the final manuscript. C.J.L.M.: study conception, data extraction, interpretation, revised draft, and approval of the final manuscript.

Declaration of interest

S.C., R.N.R., and C.J.L.M.: none declared.

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