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Dexamethasone a Promising Adjuvant in Brachial Plexus Anesthesia? A Systematic Review

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Abstract

The benefit of adjuvant dexamethasone in regional anesthesia has recently been the focus of investigation as clinical reports suggest improved block characteristics. However, its use remains off label and few large randomized controlled trials have been completed. A systematic review was undertaken to highlight current research efforts and findings in this area. The authors searched for randomized clinical trials evaluating dexamethasone as admixture in brachial plexus nerve blocks. Eleven trials involving brachial plexus block met inclusion criteria (953 patients, 456 received dexamethasone). Local anesthetic agents studied included lidocaine, mepivacaine, bupivacaine and ropivacaine. Dosing ranged from 4 to 10 mg with the majority of trials using 8 mg (9 trials). Permanent nerve injury or serious complications were not reported in any trial. Trials consistently demonstrated significant prolongation of analgesia (1.5 to 4.0 times) regardless of which local anesthetic was utilized. The effect of dexamethasone on block onset was variable and its clinical benefit unclear. Dexamethasone consistently reduced postoperative pain scores and early opioid consumption (≤ 48 hours), but did not impact total opiate consumption. The most recent evidence raises the possibility of a systemic mechanism of action, potentially eliminating the need for perineural administration. In conclusion, adjuvant dexamethasone significantly prolongs the duration of analgesia when used in brachial plexus nerve blockade and has not been associated with any adverse complications to date. Large clinical trials with particular focus on systemic versus perineural administration are required to better evaluate the clinical use and safety profile of this promising adjuvant in regional anesthesia.

Keywords: Anaesthetics local; Anaesthetic techniques-regional-brachial plexus; Analgesics anti-inflammatory-steroid; Local anaes; Regional anaesthesia

Introduction

Regional anesthesia serves an important role in facilitating ambulatory anesthesia and reducing immediate postoperative pain [1]. Uncontrolled pain, nausea and vomiting are common causes for delayed discharge and unanticipated hospital admission [2,3]. The duration of sensory nerve blockade, and therefore analgesia with single shot regional anesthesia is relatively short lived. Prolonging blockade time and thus analgesia could potentially benefit both patients and the healthcare system. Numerous perineural adjuvants have been used with local anesthetics in regional anesthesia in an attempt to optimize block characteristics and improve clinical outcomes [4,5]. The ideal adjuvant that acts to prolong anesthesia and improve clinical outcomes while maintaining a favorable side effect profile, remains undiscovered. Glucocorticoids have been shown to prolong nerve blockade in proportion to their rank-order anti-inflammatory potency, an effect that can be mitigated by the corticosteroid antagonist cortexolone [6]. Recent research has focused on the addition of the glucocorticoid dexamethasone as a local anesthetic adjuvant in regional anesthesia. Although the exact mechanism of dexamethasone's action is unknown, preliminary studies suggest its addition can impressively prolong the duration of analgesia with minimal adverse effects. It has been suggested that dexamethasone may prolong block duration by increasing the activity of inhibitory potassium channels on nociceptive C fibers [7] or by causing vasoconstriction via glucocorticoid receptor mediated nuclear transcription modulation [8]. Dexamethasone's suppression of inflammatory mediators, including prostaglandins (PGE_2), may also play a role. Indirect evidence has supported the assumption that dexamethasone acts locally [6,9-11] however recent studies have suggested a systemic effect may be responsible for its clinical effect and intravenous administration may give similar results [12,13]. Regardless of its specific mechanism, the best evidence suggests its action is via indirect mechanisms rather than by directly inhibiting neurotransmission [14]. Although many studies have been reported, they have been completed in isolation, are preliminary in nature and involve small patient populations. This systematic literature review was therefore undertaken to evaluate the adjuvant use of dexamethasone in brachial plexus nerve blocks with a focus on block characteristics, clinical outcomes and safety and with the ultimate goal of guiding future research.

Methods

MEDLINE, EMBASE and Cochrane Register of Controlled Trials databases from 1946 to August 2013 were searched using the MeSH (Medical Subject Headings) terms: *local anesthesia, nerve block, local anesthetics, regional anesth*, anesthesia conduction* combined with the binary operator OR. The result was combined with the MeSH term *dexamethasone* using the binary operator AND. The search was limited to human and clinical trial or controlled clinical trial or meta-analysis or multicenter study or randomized control trial. Any randomized trial involving the use of dexamethasone as admixture with any local anesthetic in a single shot brachial plexus nerve block was included. Abstract only papers, non-English language, experimental delivery

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models including microspheres or liposomes, neuraxial techniques, intravenous regional anesthesia, non-brachial plexus nerve blocks and animal trials were all excluded. Bibliographies of relevant articles were reviewed for abstracts not identified during the initial search of databases.

Study outcomes and data were extracted from each study using an independently generated extraction form. Specific outcomes sought included time to block onset (sensory and/or motor, standardized to minutes), as well as the duration of analgesia (standardized to hours). The specifics around the technique being evaluated (i.e. local anesthetic and dexamethasone dose, type of block) were also extracted, as well as the incidence and nature of any complications, study specific duration of analgesia definition, follow up duration and study outcomes with respect to postoperative analgesic use. Selected articles were scored for methodological quality using the Jadad score [15].

The literature search, study evaluation and data extraction were conducted independently by two reviewers (CN, LM) and any disagreement between the two was resolved by consensus. In any instances where consensus could not be reached, another reviewer (MK) was consulted to resolve the disagreement.

Results

Twenty studies were assessed for eligibility, nine of which were ultimately excluded and eleven trials were included in this review. The PRISMA diagram in Figure 1 outlines the search and screening process. The quality of studies varied greatly with awarded Jadad scores ranging from zero to five with a median score of five (Table 1). Given the small number trials and qualitative nature of this review, no studies were excluded based on quality score. Table one outlines the interventions studied, analgesia outcomes and complications reported in the included trials.

Dosing

The dosing of dexamethasone varied between 4 and 10 mg with the majority of studies evaluating an 8 mg dose. Although nine studies used the same dose of dexamethasone (8 mg), the effective concentration of dexamethasone varied greatly owing to the different volumes of local anesthetic used for nerve blockade across the trials. The concentration of dexamethasone in the included studies varied anywhere from 0.1 to 0.45 mg/ml as total injected volumes ranged from 20 to 50 ml (Table 1).

Block onset

Dexamethasone had a variable effect on the time to block onset with five trials finding a significant reduction in latency time [16-20] and two trials demonstrating no significant difference [21,22]. The remaining four trials in this review did not report block onset times [13,23-25]. Of the five trials reporting a shorter time to block onset, four of these demonstrated a significant reduction in both sensory and motor block onset with perineural adjuvant dexamethasone, however, the absolute reduction in onset time ranged from 1.8 [17] to 3.65 minutes. Shrestha et al. did not specify how they measured block onset nor whether it was sensory or motor in their low quality trial [16] One trial reported a reduction in sensory but not motor block onset time [17]

Duration of analgesia

The duration of analgesia was the primary end point for every trial in this review however there was marked inter-study variability in its definition and measurement (Table 1). Adjuvant dexamethasone significantly prolonged the duration of analgesia in all eleven trials

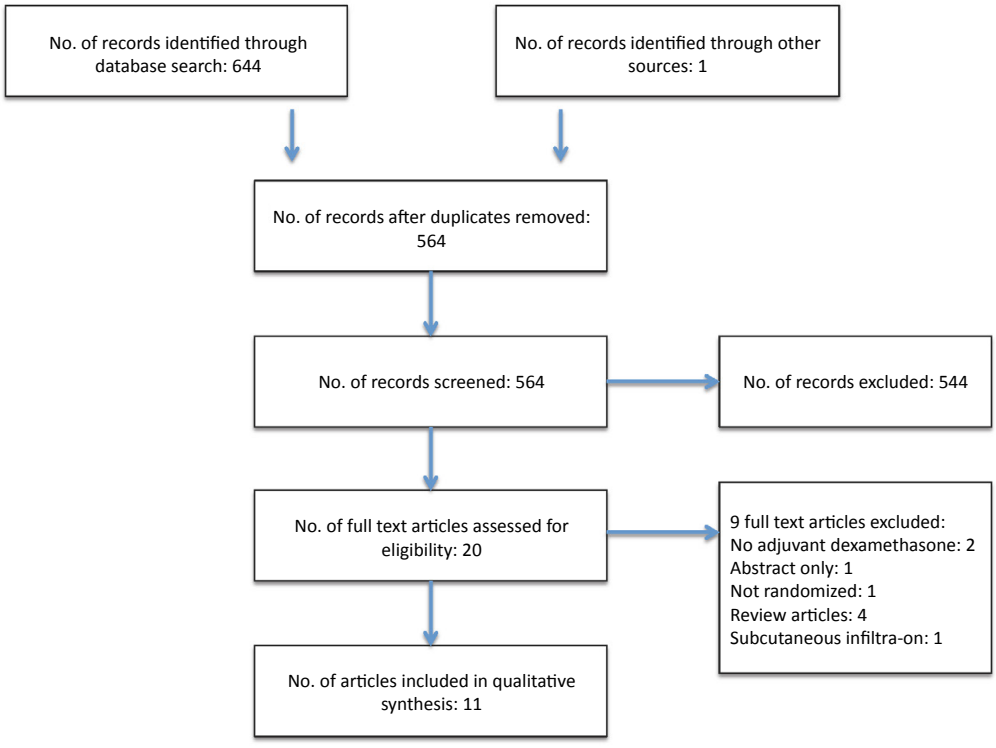

Figure 1: Prisma diagram of screening process.

regardless of the local anesthetic agent used or type of block performed (Table 1). Shrestha et al. [16] reported adjuvant dexamethasone resulted in four times the duration of analgesia compared to the control group. This was considerably longer than the other trials included in this review and furthermore, they did not report the doses of local anesthetic agents used nor how they defined the duration of analgesia. Exclusion of this trial yields a range from 1.5 [22,24] to 2.6 [18] times prolonged analgesia in the adjuvant dexamethasone groups. Trials using bupivacaine reported a range of prolongation of analgesia from 1.5 to 2.3 times [17,23-25]. Cummings et al. [24] and Desmet et al.

Author	Year	Size	Jadad	Intervention studied	Block	Onset	Duration of analgesia definition	Duration of analgesia	Complications	Analgesic outcome
Desmet et al. [13].	2013	n=144	5	a) 0.5% ropivacaine, saline b) 0.5% ropivacaine, 10 mg dexamethasone c) 0.5% ropivacaine, saline + 10 mg IV dexamethasone Vol=32 ml	Interscalene	N/A	Onset to VRS >2/4	a) 12.6 (10.6-15.2) hrs* b) 23.4 (16.9-28.5) hrs* c) 21.3 (18.3-33.9) hrs* a vs. b P<0.0001 a vs. c P<0.0001 b vs. c P>0.05	Group a - 1 wound infection Group b - 1 deltoid hypoaesthesia secondary to C4/5 disc herniation.	48 hr paracetamol use a vs b/c P<0.0001 48 hr diclofencac use a vs. b/c P=0.03
Biradar et al. [20].	2013	n=58	5	a) 1.5% lidocaine (7 mg/kg) w/ epi, saline b) 1.5% lidocaine (7 mg/kg) w/ epi, 8 mg dexamethasone Vol=not stated	Supraclavicular	Sensory a) 16 ± 2.3 min** ω b) 13.4 ± 2.8 min** P=0.001 Motor a) 18.7 ± 2.8 min** b) 16.0 ± 2.7 min** P=0.001	Time to first surgical site pain	a) 2.65 ± 0.34 hrs** b) 5.43 ± 0.98 hrs** P=0.001	None post-operatively	N/A
Tandoc et al. [23].	2011	n=90	5	a) bupivacaine 0.5% w/ epi b) bupivacaine 0.5% w/ epi, 4 mg dexamethasone c) bupivacaine 0.5% w/ epi, 8 mg dexamethasone Vol=40 ml	Interscalene	N/A	Discharge to NRS >3/10	a) 13.3 ± 4.0 hrs** b) 21.6 ± 2.4 hrs** c) 25.2 ± 1.9 hrs** P<0.05 a vs. b/c P>0.05 b vs. c	1 pneumothorax. No other complication within 1 year follow up.	Opiate Use POD1 + 2 a vs b/c P<0.01 POD3 P>0.05 Total NSAID Use b vs. c P<0.05
Cummings et al. [24].	2011	n=218	5	a) 0.5% ropivacaine b) 0.5% bupivacaine c) 0.5% ropivacaine, 8 mg dexamethasone d) 0.5% bupivacaine, 8 mg dexamethasone Vol=32 ml	Interscalene	N/A	Onset to VRS >2/10	a) 11.8 (9.7-13.8) hrs* b) 14.8 (11.8-18.1) hrs* c) 22.2 (18.0-26.6) hrs* d) 22.4 (20.5-29.3) hrs* P<0.001	None at 14 days	No difference in total 3 day opiate consumption P>0.15
Vieira et al. [25].	2010	n=88	5	a) 0.5% bupivacaine w/ epi, 75 mcg clonidine b) 0.5% bupivacaine w/ epi , 75 mcg clonidine, 8 mg dexamethasone Vol=20 ml	Interscalene	N/A	Not specified	a) 13.9 (12.1-18.1) hrs* b) 24.3 (22.1-31.8) hrs* P<0.0001	None at 48 hours	POD1 opiates P<0.0001 Total opiates P>0.05 Pts free of opiates POD1 P<0.0001
Parrington et al. [22].	2010	n=45	5	a) 1.5% mepivacaine, saline b) 1.5% mepivacaine, 8 mg dexamethasone Vol=32 ml	Supraclavicular	Sensory a) 10 ±4 mins** b) 9 ± 5 mins** P=0.779 Motor a) 8 ± 3 mins** b) 8 ± 3 mins** P=0.846	Time to first surgical site pain	a) 3.8 (3.5-4.4) hrs* b) 5.5 (3.8-7.5) hrs* P=0.008	None at 14 days. Transient numbness/ tingling in hand, with no difference in incidence between groups.	Opiates in PACU P=0.020 Opiates POD1, POD7, POD14 P>0.05
Golwala et al. [19].	2009	n=60	2	a) 2% lignocaine, 0.5% bupivacaine w/ epi, distilled water b) 2% lignocaine, 0.5% bupivacaine w/ epi, 8 mg dexamethasone Vol=35 ml	Supraclavicular	Sensory a) 11.8 ± 0.84 mins** b) 9.07 ± 0.79 mins** P<0.05 Motor a) 12.79 ± 0.79 mins** b) 10.86 ± 0.65 mins** P<0.05	Injection to VAS 5/10	a) 4-6 hrs b) 12-18 hrs P<0.001	No complications in immediate post-operative period	N/A

Yadav et al. [18].	2008	n=90	3	a) 1.5% lignocaine w/ epi b) 1.5% lignocaine w/ epi, 500 mcg neostigmine c) 1.5% lignocaine w/ epi, 4 mg dexamethasone Vol=24 ml	Supraclavicular	Sensory a) 10.6 ± 3 mins** b) 10.4 ± 2.5 mins** c) 8.9 ± 2.2 mins** P=0.028 c vs. a/b Motor a) 17.3 ± 4.3 mins** b) 17.2 ± 4.0 mins** c) 14.7 ± 3.5 mins** P=0.020 c vs. a/b	Onset of block to first perception of pain	a) 2.94 ± 0.89 hrs** b) 3.8 ± 0.88 hrs** c) 7.57 ± 1.8 hrs** P<0.0001 a vs. b/c P=0.016 b vs. c	None reported post-operatively	Lower 12 hr analgesic requirements P=0.001
Shrestha et al. [17].	2007	n=60	5	a) bupivacaine 2 mg/kg, 2 mg/kg tramadol b) bupivacaine 2 mg/kg, 8 mg dexamethasone Vol =not stated	Supraclavicular	Sensory a) 18.47 ± 2.03 mins** b) 16.67 ± 2.34 mins** P<0.05 Motor a) 13.93 ± 1.66 mins** b) 12.90 ± 1.49 mins** P>0.05	VAS of >8/10 or intolerable pain	a) 7.55 ± 1.20 hrs** b) 17.14 ± 3.24 hrs** P<0.05	None at 6 months	N/A
Movafegh et al. [21].	2006	n=60	5	a) 35 ml 1.5% lidocaine, saline b) 35 ml 1.5% lidocaine, 8 mg dexamethasone Vol=36 ml	Axillary	Sensory a) 11 ± 4 min** b) 14 ± 5 min** P>0.05 Motor a) 22 ± 8 min** b) 26 ± 7 min** P>0.05	Injection to first perception of pain	a) 1.6 ± 0.6 hrs** b) 4.0 ± 1.3 hrs** P<0.01	N/A	N/A
Shrestha et al. [16].	2003	n=40	0	a) 2% lidocaine w/ epi, 0.5% bupivacaine b) 2% lidocaine w/ epi, 0.5% bupivacaine with 4-8 mg dexamethasone Vol=40-50 ml	Supraclavicular	Block (motor/sensory unspecified) a) 18.15 ± 4.25 mins** b) 14.5 ± 2.10 mins** P<0.05	Not defined	a) 3.16 ± 0.48 hrs** b) 12.75 ± 5.33 hrs** P<0.05	None reported, period undefined	N/A

Table 1: epi: Epinephrine; hrs: Hours; IV: Intravenous; mcg: Microgram; *Mean ± Standard Deviation; **Median (inter-quartile range 25-75th); ml: Milliliter; mins: Minutes; NRS: Numeric Rating Scale; ns: Not Statistically Significant; PACU: Post Anesthetic Care Unit; POD: Post-Operative Day; VAS: Visual Analogue Scale; vs.: Versus; Vol: volume; VRS: visual Rating Scale; w/: with.

[13] reported 1.9 times prolongation for ropivacaine. [13] Parrington et al.[22] reported 1.5 times prolongation for mepivacaine. Biradar et al. [20] Movafegh et al. [21] and Yadav et al. [18] reported 2.0, 2.5 and 2.6 times prolongation for lidocaine respectively. Desmet et al. also reported 1.7 times prolongation in the systemically administered, intravenous dexamethasone group.

Post-Operative Analgesic Requirements

Five trials reported the analgesic requirements after surgery [18,22-25]. Tandoc et al. found a significant reduction in opiate consumption on post-operative day (POD) 2 (P<0.01) but no difference on POD3 [23]. Parrington et al. found a significant reduction in post-anesthetic care unit (PACU) fentanyl requirements (P=0.020) in the adjuvant dexamethasone group but no significant difference between groups on POD1, POD7 or POD14 [22]. Vieira et al. found a significant reduction in POD1 opiates (P<0.0001) with adjuvant dexamethasone, but the difference in total opiate consumption did not reach significance [25]. Vieira et al. also found there were significantly more patients in the adjuvant dexamethasone group who did not consume any opiates on POD1 (P<0.0001) or POD2 (P<0.01) [25]. Cummings et al. found no significant difference between groups in total 72 hour opiate consumption, though they reported significantly lower pain scores with movement in both of the dexamethasone groups on POD1 [24] Yadav et al. found significantly less rescue analgesic requirement at 12 hours in the dexamethasone group (P<0.001) [18]. Seven trials reported post operative pain scores [13,18-20,22,24,25]. All seven trials reported lower pain scores in the immediate post operative period while only Desmet et al [13]. were able to demonstrate lower scores beyond 24 hours.

Safety

In total, 456 patients received adjuvant dexamethasone and the only major complication reported in any of the included trials was a single pneumothorax [23]. Only four trials followed their patients beyond the immediate postoperative period [13,17,23,24]. Parrington et al. [22] reported the most frequent adverse effect in their study of supraclavicular blocks was numbness or tingling in the hand, which was transitory and was not significantly different between dexamethasone and control groups. Cummings et al. [24] reported no major complications at 14 days, Shrestha et al. [17] reported no major complications at six months and Tandoc et al. [23] reported no major complications at one year. During their six month follow up Desmet et al. [13] reported one patient in the dexamethasone group with persistent hypoaesthesia over the deltoid at four months, however further investigation found a disc herniation at C4/5. The Desmet et al. study also reported one wound infection in the post-operative period;

however, this occurred in the control (non-dexamethasone) group.

Satisfaction

Four trials reported patient satisfaction scores [13,22,23,25]. Satisfaction scores were generally high regardless of grouping and all four trials reported no significant difference between groups. Tandoc et al. [23] did describe a single 'strongly dissatisfied' patient in the dexamethasone group, which corresponded to a patient-reported motor block of more than 72 hours duration. Although not a direct measure of patient satisfaction, Yadav et al. [18] reported significantly higher surgeon satisfaction scores in the dexamethasone group versus lignocaine control for supraclavicular blocks in upper extremity surgery.

Discussion

Much research has been devoted to the use of adjuvant agents in regional anesthesia, with recent studies focusing on the off label use of perineural dexamethasone. This preliminary systematic review supports further research into the use of adjuvant dexamethasone in brachial plexus blocks to elucidate its potential benefits including significantly prolonging the duration of analgesia, reducing pain scores and reducing opioid consumption. In addition to prolonging the duration of analgesia when compared to local anesthetic alone, the preliminary studies included in this review also suggest possible superiority of dexamethasone in prolonging the duration of analgesia when compared to other adjuvants such as clonidine, [25] neostigmine [18] and tramadol [17]. Perhaps the most important finding in this review is the possibility that systemic administration may have similar effects on the duration of analgesia compared to perineural administration, a finding that demands further study as it is based on a single trial [13].

Dexamethasone is a non-particulate steroid that has been shown in animal studies to be non-neurotoxic [26,27] and may even be cytoprotective [28]. One exception to these findings is that Williams et al. [29] found that bathing isolated rat sensory neurons in a solution of ropivacaine combined with high dose dexamethasone (133 mcg/ml), clonidine and buprenorphine exacerbated the neurotoxicity associated with ropivacaine. They reported that dexamethasone alone or in combination with ropivacaine had no influence on cell death after 24 hours of exposure. This study suggests that although individual adjuvants may not be neurotoxic, combinations may be and urges caution. The relevance of this in vitro study to clinical practice remains unknown, but certainly warrants further study on the neurotoxicity of combinations of agents. Previously, neurotoxicity of corticosteroids has been shown to be related to particle size [26] or vehicles, preservatives and excipients [30]. Caution is urged when choosing a particular dexamethasone formulation; use of preservative free formulations seems prudent and should be encouraged. Recent evidence has suggested that caution be advised in diabetic patients as pre-existent underlying neuropathy is common and could theoretically be exacerbated by dexamethasone [31,32]. The outcomes associated with perineural dexamethasone in this population remain unknown [33] and await further study *in vitro* and *in vivo*.

While dexamethasone is not approved for perineural use, this application is well described in textbooks [34-36] and peer-reviewed literature. There has been no reported incidence of neurotoxicity, nor an increased incidence of complications or side effects associated with perineural use of dexamethasone in humans in the literature, notwithstanding inclusion in this review. Furthermore, the 456 subjects of this systematic review who received dexamethasone as admixture in brachial plexus nerve blocks had no permanent neurological complications. Note is made, however, that only four trials included follow up beyond the immediate post-operative period, which is a considerable limitation when interpreting the safety data in this review. Major neurological complications in regional anesthesia are rare and thus are difficult to study. A further limitation of this review exists in that none of the trials were adequately powered to detect differences in complication rates and 456 patients is inadequate to declare perineural dexamethasone safe for routine use [37]. And yet, from the available data we can cautiously conclude that perineural adjuvant dexamethasone is not overtly neurotoxic at 8 mg and has potential for safe use in this application. Regardless, adequately powered safety studies with long term follow up, examining the perineural use of dexamethasone have not been conducted and perineural use of dexamethasone remains 'off-label'. These authors recommend that full disclosure of this uncertainty be included in the consent process with patients prior to its clinical use. A full discussion of the issues surrounding this topic have been discussed elsewhere [38].

While dexamethasone used as an adjuvant in brachial plexus blocks clearly prolongs the duration of blockade, the magnitude of prolongation was highly variable among trials. Often a multifold difference was reported, with this review reporting ranges from 1.5 [22,24] to 4 times [16] the duration of analgesia. Possible explanations for this variability include varying definitions of duration, the use of different local anesthetic agents (Table 1) and their inherent block characteristics (e.g. duration of effect) and the potential for differential impact upon these characteristics by adjuvant dexamethasone. Although formal dosing studies have yet to be completed, research to date as supported by the studies meeting criteria for inclusion in this review, almost uniformly use a standard dose of 8 mg. Although the dose of dexamethasone was fairly consistent across all studies, the actual concentration of dexamethasone exposed to the nerve varied greatly. It is not yet clear whether dose and/or concentration play a role in the efficacy of dexamethasone. This factor not only warrants further study, but could be a significant contributor to the varied results between studies. Further explanation for the wide range in prolongation of analgesia could include limitations of the studies such as high block failure rates [25] and high dropout rates [25], as well as design flaws such as unblinded investigators [19] and potential bias from patient-reported block resolution.

The effect of dexamethasone on the latency of block onset is still unclear based on the data available with two out of seven trials reporting no significant difference. It would be anticipated that the effect of dexamethasone on latency of onset would be more pronounced with anesthetics with relatively longer latencies inherently (e.g. bupivacaine). The varied anesthetic agents included in this review therefore make it more challenging to draw any meaningful conclusions with respect to this potential effect. However, even if adjuvant dexamethasone is associated with a statistically significant reduction in time to onset of blockade, the clinical effect is modest based on the 1.8 [17] to 3.65 [16] minute reductions being reported.

Dexamethasone has been shown by three studies [22,24,25] in this review to reduce the early, but not total, post-operative analgesic requirements. Seven trials reported significantly reduced pain scores immediately after surgery while only one trial reported lower scores beyond 24 hours. The effect of adjuvant dexamethasone on post-operative analgesic requirements has yet to be fully elucidated. In particular, comparison to systemically administered dexamethasone in

large, well designed trials has yet to be definitively made. Based on the limited data available dexamethasone reduces analgesic requirements in the immediate post-operative period but a reduction in total analgesic requirements has yet to be proven. The potential effect of adjuvant dexamethasone on this clinically important outcome certainly warrants further investigation. While adjuvant dexamethasone was not found to significantly increase patient satisfaction in the included studies, most patients surveyed were already greatly satisfied, diminishing the possible impact to this factor. The lack of positive impact in this realm should not be seen negatively.

As the mechanism of action of adjuvant dexamethasone remains unclear, the need for basic science research to further advance knowledge in this area should be encouraged. The current assumption is that perineural dexamethasone acts locally. This theory is supported by trials using animal models [6], an epidural study with systemic control, [10] intercostal microsphere trial with plasma concentration measurement [11] and human based intravenous regional techniques [9]. In contrast, previous work has demonstrated that epidural administration of 15 mg of dexamethasone resulted in adrenal suppression for at least one week's duration, suggesting systemic absorption and effect [39]. Furthermore, a recent meta-analysis by De Oliveira et al. [40] demonstrated that intravenous dexamethasone administered intra-operatively in moderate doses (0.11-0.2 mg/kg) decreased postoperative pain. It had been previously assumed that systemic absorption of perineural dexamethasone was an unlikely explanation for the opioid-sparing results highlighted by this review given the comparatively smaller dose that would be potentially absorbed into systemic circulation. Despite the indirect and theoretical evidence to support a local effect, Desmet et al. [13] published a high quality trial demonstrating that systemic dexamethasone prolonged the duration of analgesia with interscalene block to the same degree as perineural administration. Fredrickson et al. [12] published similar results in a trial comparing intravenous versus perineural adjuvant dexamethasone for ankle and sciatic blocks. In most trials duration of analgesia is used as a surrogate for block duration. Systemic dexamethasone has been shown to reduce opiate requirements making systemic action is a plausible explanation for the clinical effects being reported. Large, well-designed studies investigating the systemic versus local effect of dexamethasone on pain outcomes are urgently needed. Systemic dexamethasone has a well-established safety profile [40] and given the lack of robust safety data surrounding perineural administration, subsequent trials confirming the results published by Desmet et al. [13] and Fredrickson et al. [12] may eliminate the need for perineural administration.

There are clearly many limitations to this systematic review, namely the small number of trials included, the small number of total patients exposed to adjuvant dexamethasone and in some cases [16,18,19], the poor quality of the trials. Although the safety of dexamethasone in this application was addressed in many of the included studies, the follow up periods rarely extended beyond the immediate post-operative period, and complications would have only been noted if a subjective complaint was made by a subject. Furthermore, properly designed randomized controlled trials would require prohibitively large sample sizes to be adequately powered detect any subtle, yet relevant, clinical differences in nerve function [24]. Faced with these challenges, perineural safety data will only become known as more trials are published.

Conclusion

The use of adjuvant dexamethasone in brachial plexus nerve blockade is off label as it has not been approved for perineural use. This systematic review demonstrates that there are potential benefits for both patients and the healthcare system that could be realized with its adoption into current regional anesthetic practices. However, currently there is insufficient data to support its use in routine practice. Considering the eleven studies discussed here, there is no clinical evidence that 8 mg perineural dexamethasone has any neurotoxic effects however further study is needed prior to recommending routine use. Adjuvant dexamethasone clearly prolongs analgesia regardless of the local anesthetic or the definition of duration of analgesia. It reduces early post-operative analgesic requirements and has no negative impact on the existing high level of patient satisfaction with this regional technique. Importantly systemic administration of dexamethasone may have similar clinical effects and await confirmatory trials. We conclude that dexamethasone is a promising adjuvant, which clearly and impressively prolongs the duration of analgesia in brachial plexus nerve blockade. As such, we call for large, well-designed, randomized controlled trials to either support or refute its adoption into mainstream clinical practice with particular attention to comparison with systemic administration.

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