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REVIEW

# The role of dexamethasone in peripheral and neuraxial nerve blocks for the management of acute pain

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Dexamethasone has an emerging role as an additive in regional anaesthesia for the management of acute pain. However, outcomes in terms of improvement and prolongation of analgesia, as well as the methods of administration and potential adverse effects, have yet to be clarified. This semi-structured review examines the current literature available with regard to supplemental dexamethasone in regional and neuraxial anaesthesia.

**Keywords:** adverse effects, analgesia, dexamethasone, dosage regimes, regional anaesthesia

## Introduction

Dexamethasone is a glucocorticosteroid with anti-inflammatory properties that is enjoying more widespread use by anaesthesiologists as a systemic, epidural, or perineural analgesic adjunct. It appears that dexamethasone is able to act synergistically with local anaesthetics to achieve a better quality and duration of analgesia, limiting the need for alternative analgesics – particularly opioids.[1–4] Controversy still exists regarding the route of administration of dexamethasone and dose ranges are wide and unstandardised.[1,2,5,6] The safety of this practice is also questioned: long-term glucocorticosteroid use is associated with significant adverse effects, yet the complications associated with a single perioperative dose are not fully appreciated.[1]

We aimed to conduct a semi-structured review of the current literature to assess the role of dexamethasone as an analgesic adjunct with regional techniques. Specifically, the review aimed to:

(1) identify the degree to which dexamethasone reduces pain and prolongs analgesia in the postoperative period when combined with a regional technique;
(2) establish the dose range of a single perioperative dose of dexamethasone;
(3) identify how dexamethasone is administered with regard to route and timing;
(4) describe any side effects associated with its administration during the perioperative period.

## Methods

### *Search strategy and selection criteria*

For the purposes of this review we conducted a semi-structured literature search. On 6 June 2016 RNR, using the OVID search engine, searched the following databases: Embase (1974 to 2016 June 04); Ovid Healthstar (1966 to May 2016); Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to 6 June 2016); and the Cochrane database.

We used the following search terms: *regional anaesthesia*, or *brachial plexus*, *interscalene*, *supraclavicular*, *infraclavicular*, *axillary*, *lumbar plexus*, *femoral*, *3 in 1*, *sciatic*, *popliteal*, *ankle block*, *caudal*, *epidural* or *nerve block*. The 'and' function was used to combine these terms with *dexamethasone*, *corticosteroid*, or *steroid* with the definition exploded. The initial search terms with the keywords with the definition exploded were utilised. We largely restricted the search to human beings and aimed to select publications from the last 5 years or those commonly referenced or highly cited older publications. We restricted the search to the management of acute rather than chronic pain in the perioperative setting.

From these results KG and RNR independently identified publications examining the use of dexamethasone in conjunction with peripheral nerve blocks or neuraxial techniques in the management of acute pain and that focused on dexamethasone's ability to prolong the duration of action of the regional technique employed. From each study identified the following data were extracted: primary author, year of publication, sample size, age group of population, specific form of regional anaesthetic block used, type and dose of local anaesthetic used, route of dexamethasone administration, dose of dexamethasone administered.

The outcomes assessed in this review included: duration of analgesia; time to administration of additional analgesia post block; and specific complications reported due to dexamethasone or regional anaesthesia including: elevated blood sugar, sepsis, and associated long-term nerve damage. The quality of analgesia afforded by the neuraxial or peripheral nerve block and dexamethasone combination was assessed; however, different methods for measurement of this criterion were noted between studies. Further specific comments unrelated to these outcomes but regarding dexamethasone usage in these studies were also included.

Table 1: Characteristics of eligible studies included in the review

| Author | Year | Sample size | Age group | Type of regional block | Type and dose of local anaesthetic | Route of dexamethasone administration | Dexamethasone dose |
|---|---|---|---|---|---|---|---|
| Fredrickson[3] | 2013 | 126 | 16–80 yrs | 60 Sciatic/58 ankle blocks | 30 ml 0.5% Bupivacaine | Systemic–intramuscular | 8 mg |
| Rahagdale[8] | 2014 | 80 | >18 yrs | Sciatic nerve blocks | 0.45 ml/kg Bupivacaine 0.5% with adrenaline | Perineural or intravenous | 8 mg |
| Vermeylen[9] | 2016 | 72 | >18 yrs | Popliteal sciatic blocks | 30 ml Ropivacaine 0.75% +/– clonidine 100 mcg | Perineural | 5 mg |
| Cummings[13] | 2011 | 218 | 18–75 yrs | Interscalene blocks | 30 ml 0.5% Ropivacaine or bupivacaine | Perineural | 8 mg |
| Movafegh[14] | 2006 | 60 | >18 yrs | Axillary blocks | 34 ml 1.5% Lignocaine | Perineural | 8 mg |
| Parrington[15] | 2010 | 45 | >18 yrs | Supraclavicular blocks | 30 ml 1.5% Mepivacaine | Perineural | 8 mg |
| Shrestha[16] | 2007 | 60 | >18 yrs | Supraclavicular blocks | Bupivacaine +/– tramadol 2 mg/kg | Perineural | 8 mg |
| Shrestha[17] | 2003 | 40 | >18 yrs | Brachial plexus blocks | 40–50 ml Local anaesthetic +/– adrenaline | Perineural | 8 mg |
| Tandoc[18] | 2011 | 90 | >18 yrs | Interscalene blocks | 40 ml 0.5% Bupivacaine | Perineural | 8 mg vs. 4 mg |
| Vieira[19] | 2010 | 88 | >18 yrs | Interscalene blocks | 20 ml 0.5% Bupivacaine with adrenaline and 75 mcg clonidine | Perineural | 8 mg |
| Yadav[20] | 2008 | 90 | >18 yrs | Supraclavicular blocks | 23 ml 1.5% Lignocaine with adrenaline +/– neostigmine | Perineural | 4 mg |
| Desmet[21] | 2013 | 150 | >18 yrs | Interscalene blocks | Ropivacaine 0.15% | IV and perineural | 10 mg |
| Liu[22] | 2015 | 89 | >18 yrs | Supraclavicular blocks | 30 ml Bupivacaine 0.25% | Perineural | 1 mg; 2 mg; 4 mg |
| Desmet II[23] | 2015 | 240 | >18 yrs | Interscalene blocks | 30 ml Ropivacaine 0.5% | Intravenous | 1.25 mg; 2.5 mg; 10 mg |
| Woo[24] | 2015 | 144 | >18 yrs | Interscalene blocks | 12 ml Ropivacaine 0.5% | Perineural | 2.5 mg; 5 mg; 7.5 mg |
| Abdallah[25] | 2015 | 75 | >18 yrs | Supraclavicular blocks | 30 ml Bupivacaine 0.5% | IV and Perineural | 8 mg |
| Shah[26] | 2015 | 53 | 18–60 yrs | Infraclavicular blocks | 1.5% Lignocaine with adrenaline +/– clonidine 150 mcg | Perineural | 8 mg |
| Hong[2] | 2010 | 77 | 1–5 yrs | Caudal blocks | Ropivacaine 1.5 ml/kg | Systemic – intravenous | 0.5 mg/kg |
| Kim[11] | 2014 | 80 | 6 months–5 yrs | Caudal blocks | Ropivacaine 0.15% 1.5 ml/kg | Perineural | 0.1 mg/kg |
| Murni[12] | 2015 | 64 | 3–10 yrs | Caudal blocks | Levobupivacaine 0.25% 0.75 mg/kg and paracetamol 30 mg/kg | Intravenous | 0.5 mg/kg |
| Naghipour[10] | 2013 | 70 | >18 yrs | Thoracic and lumbar epidurals | Bupivacaine 0.5% titrated and 50 mcg fentanyl | Perineural | 8 mg |
| Akram[27] | 2015 | 180 | >18 yrs | Bier's Blocks | Lignocaine +/– ketorolac 30 mg | Intravenous | 8 mg |
| Hassani[28] | 2015 | 50 | 20–55 yrs | Bier's Blocks | Lignocaine 3 mg/kg | Intravenous | 8 mg |

## Results

The search yielded a total of 15 studies. Frederickson, Rahangdale and Vermeylen all described the use of perineural dexamethasone in lower limb peripheral nerve blocks in an adult population.[4,8,9] Naghipour examined the use of perineural dexamethasone in thoracic and lumbar epidurals;[10] and Hong, Kim and Murni explored systemic dexamethasone in conjunction with caudal blocks in a paediatric group.[2,11,12] Choi's systematic review and meta-analysis examined its use in nine studies in conjunction with different forms of brachial plexus blocks via both systemic and perineural approaches. [4] These nine studies were examined on an individual basis for the purposes of this review.[13–21] Liu, Desmet II, Woo, Abdullah and Shah also examined the addition of dexamethasone to brachial plexus nerve blocks and Akram and Hassani described its use in upper limb Bier's blocks.[22–28]

All studies illustrated a prolonged analgesic duration of regional technique in the presence of dexamethasone administration with minimal side effects.[2,4,8–28] However, many of the studies employed different primary outcomes – time of regional sensory and motor block duration; time to additional analgesia; postoperative pain scores and postoperative opioid consumption – to establish this analgesic prolongation, making direct comparison difficult. This prolongation of analgesia appears independent of dose of dexamethasone employed or route administered.[2–4,8–28] Adverse side effects reported with the use of

**Table 2:** Outcomes assessed: dexamethasone's ability to augment analgesia when used in conjunction with regional anaesthesia

| Author | Primary outcome | Analgesia duration | Block analgesia quality | Time to additional analgesia | Secondary outcomes | Complications associated with dexamethasone |
|---|---|---|---|---|---|---|
| Fredrickson[3] | Analgesic quality and duration | Increased analgesia at 24 h vs. no change at 48 h | No difference | – | – | Nil noted |
| Rahagdale[8] | Analgesic duration | Prolonged 13 (perineural) vs. 8 (iv) vs. 6 h (control) | – | – | No difference postoperative opioid consumption | Nil noted |
| Vermeylen[9] | Analgesic duration | Prolonged by 9 h | – | – | – | Nil noted |
| Cummings[13] | Analgesic duration and postoperative pain scores | Prolonged 1.9x with ropivacaine and 1.4x with bupivacaine | Median maximum verbal response pain score significantly lower on day 1 post-surgery | – | Reduced post operative nausea and vomiting<br>No significant reduction in opioid use over 72 h postop | Nil observed during 14 day follow-up |
| Movafegh[14] | Analgesic duration | Prolonged 242+/–76 vs. 98+/–33 min | – | – | – | Nil noted |
| Parrington[15] | Analgesic duration | Prolonged 332 vs. 228 min | – | – | No difference in analgesia onset time | Nil noted |
| Shrestha[16] | Analgesic duration | Prolonged 1028 vs. 453.17 min | – | – | Superior to tramadol as regional adjuvant | Nil noted |
| Shrestha[17] | Analgesic quality and duration | Prolonged 834 vs. 274 min | No difference | – | Faster onset of analgesia noted | Nil noted |
| Tandoc[18] | Analgesic duration | Prolonged 21.6 (4 mg) and 25.2 (8 mg) vs. 13.3 h (control) | – | – | Reduced additional analgesic requirements during 48 h<br>No significant difference between the two dexamethasone dosages with regard to outcome | Nil noted at 4 weeks of follow-up |
| Vieira[19] | Analgesic duration and postoperative pain scores | Prolonged 1457 (dexamethasone) vs. 833 min (control) | Lower median verbal analogue scores at 24 h (3 vs. 6) | – | Reduced opioid use during first 24 h<br>Similar pain scores at 48 h | Nil noted |
| Yadav[20] | Analgesic duration and postoperative pain scores | Prolonged 454.2 +/– 110.7 (dexamethasone) vs. 176.5 +/– 53.5 (neostigmine) minutes | Lower visual analogue pain scores at 12 h | – | Reduced additional mean analgesic requirements | Nil noted |
| Desmet [21] | Analgesic duration | Prolonged 1405 (perineural) and 1275 (intravenous) vs. 757 min | – | – | Equivalency between perineural and intravenous doses | Nil noted |
| Liu[22] | Analgesic quality and duration | Prolonged 22.3, 23.3, 21.2 h vs. 12.1 h | Significant prolongation of motor blockade also noted | – | Low dose vs. higher dose produce similar duration of prolongation analgesia | Nil noted |
| Desmet II[23] | Time to first postoperative analgesic request | – | – | Prolonged 17 h and 20 h vs. 12.2 h | 1.25 mg dexamethasone failed to prolong time to first analgesia vs. control | Not recorded |
| Woo[24] | Time to first postoperative analgesic request and pain scores | – | No significant effect on pain scores | Increased time to first request by factors 1.6; 2.2 and 1.8 | Increased percentage of patients requiring no addition analgesia in first 48 h | Nil noted |
| Abdallah[25] | Analgesic duration and post operative pain scores | Prolonged 25 h vs. 13 h | Reduced pain scores in both IV and PN groups | – | Reduced postoperative opioid consumption and improved satisfaction | Nil noted |
| Shah[26] | Analgesic quality and duration | Prolonged 304 (dex) vs. 217(control) min | Prolonged sensory and motor blockade | – | No difference in satisfaction scores and 24 h opioid requirements | Nil noted |

(*Continued*)

Table 2: (*Continued*)

| Author | Primary outcome | Analgesia duration | Block analgesia quality | Time to additional analgesia | Secondary outcomes | Complications associated with dexamethasone |
|---|---|---|---|---|---|---|
| Hong[2] | Time to postoperative analgesic request and pain scores | – | Significantly lower CHEOPS* and FLACC* scores in post anaesthetic care unit | Prolonged 646 vs. 430 min | Reduced sedation, shivering and postoperative nausea and vomiting | Nil noted |
| Kim[11] | Time to postoperative analgesic request and pain scores | – | Reduced pain scores at 6 h and 24 h post-surgery | Prolonged 12 h vs. 4h | Greater pain-free group for first 48 h postoperatively – 50% vs. 10% | Comparable to control – vomiting, fever, wound infection and dehiscence |
| Murni[12] | Time to postoperative analgesic request and pain scores | – | Reduced mean pain scores on day 1 and 2 postoperatively | Prolonged 800 vs. 520 min | Reduced frequency of paracetamol rescue on day 2 postoperative | Not recorded |
| Naghipour[10] | Analgesic duration and postoperative pain scores | Prolonged 234.6 vs. 58.1 min | Reduced pain scores | – | Reduced additional pentazocine usage 37.1 mg vs. 73.1 mg | Nil noted |
| Akram[27] | Analgesic duration and time to postoperative pain scores | Unchanged | Reduced pain scores. | Prolonged 524 vs. 122 min | Reduced additional analgesic usage | Not recorded |
| Hassani[28] | Analgesic quality and duration | Prolonged 9.32 vs. 5.60 min | Shorter onset times of sensory and motor blockade | – | Reduced postoperative narcotic consumption | Nil noted |

dexamethasone as a regional anaesthesia adjuvant were limited to hyperglycaemia.[4] However, due to limited sample size and long-term follow-up, data are underpowered to draw firm conclusions regarding complications.[2,4,8–28] Table 1 illustrates the extracted data from suitable studies and Table 2 illustrates the study outcomes from each study.

## Discussion and narrative summary

Dexamethasone is a synthetic glucocorticosteroid with a multitude of clinical applications. It is a potent anti-inflammatory agent, an immunomodulator and has proved useful to the anaesthetist for its anti-emetic properties. Recent interest has focused on its place as an analgesic adjunct in the perioperative period in conjunction with both general and regional anaesthesia.[1–3,6]

Proposed mechanisms by which dexamethasone augments analgesia include a reduction in pro-inflammatory interleukins and tumour necrosis factor – alpha, neuropeptides and bradykinin release at tissue level, thus limiting local oedema and tissue destruction that may generate a pain stimulus; potassium channel permeability modulation; changes in lipid membrane equilibrium and the subsequent alteration in nervous impulse generation and transduction, which may further limit nociception locally at the nerve fibre.[2,3] Furthermore, its ability to down-regulate prostaglandin synthesis contributes to analgesia peripherally and at spinal cord level by limiting sensitisation of nociceptive and inflammatory pathways.[2,3]

This review revealed that dexamethasone is able to significantly prolong the analgesia afforded by a single-shot peripheral or neuraxial nerve block.[8–26,28] Analgesia was achieved through low-dose regimes, with most physicians administering a single perioperative dose of 8 mg.[1,3,8,9,13–19,25–28] Both perineural and systemic dosing is applied with few side effects.[9–11,13–20,22,26] This is in keeping with the findings of Albrecht and Krezevic, both of whom conducted systematic reviews aimed at assessing extent of prolongation of analgesia and incidence of side effects in the use of perineural dexamethasone.[29,30]

### Prolonged duration of analgesia

Of the 15 studies reviewed, all reported a prolongation of the analgesia afforded by the particular nerve blocks administered in the presence of dexamethasone. Naghipour, Liu, Abdallah and Vermeylen all displayed an increase in average analgesic time.[9,10,22,25] Choi's brachial plexus block's analgesia was prolonged by on average 567 min, whilst Naghipour's epidurals were prolonged by 177 min.[4,10] The pain-free interval in Hong's paediatric population was not as easy to quantify, and an indirect measure – time before administration of alternative analgesia – was employed instead. This too was markedly prolonged.[2]

Six studies all indicated a trend to decreased use of opioids in the dexamethasone groups during the postoperative period.[4,10–12,24,25,28] Hong also reported lower Face, Legs, Activity, Cry, Consolability (FLACC) Scores and Children's Hospital of Eastern Ontario Pain Scales (CHEOPS) in the dexamethasone group and an earlier discharge from the PACU.[2] Woo, Abdallah and Kim all reported more patients completely pain free in the first 48 h postoperatively and increased satisfaction scores in those patients receiving dexamethasone.[11,23,24]

The prolongation of analgesia appears independent of local anaesthetic (bupivacaine, lignocaine and ropivacaine were used) and specific form of regional technique employed.[2–4,8–28]

### Route of administration

Great variability was noted in how the dexamethasone was being administered. Seven studies described off-label perineural administration of the drug, whilst Fredrickson advocated systemic administration via an intramuscular route and Hong, Murni and Desmet II suggested an intravenous route instead.[2–4,8–28] These studies collectively noted an increased analgesic time associated with the regional block regardless of route employed.

Three studies attempted to directly compare the efficiency of dexamethasone as an analgesic adjunct via a perineural or a systemic route. All showed no statistically significant difference

between the two but a trend towards greater prolongation in the off-label perineural route.[8,21,25] The limited sizes of these original studies mean that debate still exists on this topic, and further investigation and bigger studies are required to determine which route is more effective in the management of acute pain in association with regional anaesthesia.[23]

Little is reported about timing of dexamethasone administration, with the four studies administering it systemically not detailing the exact point during anaesthesia or recovery at which it was administered.[2,3,12]

## Dosing regimens

Dosing regimens vary, but most employed a fairly low dose in the order of 0.1 mg/kg – with adults in 14 of the studies receiving a single dose of 8 mg.[3,8, 9,13–19,25–28] Low doses in this setting were considered as 0.1 mg/kg versus high doses of more than 0.2 mg/kg.[1] The paediatric group's dosage also ranged between 0.1 mg/kg and 0.5 mg/kg, but instituted a maximum dose of 10 mg.[2,11,12] Dosing ranges do not appear to differ depending on route administered.

There is also no obvious correlation between increased doses and increased adverse effects from the corticosteroids – probably owing to the relatively low doses (in comparison of IV dexamethasone for other uses) being administered as an analgesic additive. Tandoc's study compared dexamethasone doses of 4 mg and 8 mg, whilst Woo compared doses of 2.5 mg, 5 mg and 7.5 mg and Liu used doses of 1 mg, 2 mg and 4 mg to prolong the duration of action of interscalene brachial plexus blocks.[18,22,24] All dexamethasone doses were administered perineurally with brachial plexus blocks. Tandoc showed no significant difference in outcomes between the two doses; however, Woo and Liu indicated an increase in analgesic time experienced and an increase in time to first analgesic request in patients receiving dexamethasone doses in the middle of the spectrum.[22,23] Desmet II used intravenous doses of 1.25 mg, 2.5 mg and 10 mg and illustrated that the highest dose prolonged analgesia to the largest degree, and that doses of 1.25 mg were not useful in prolonging analgesia in this setting.[23] The current move to limit doses in order to limit potential side effects appears appropriate to an extent but further investigation in this arena is necessary.

## Adverse effects

Despite concern regarding neuronal damage – particularly in vulnerable populations – as described in recent murine studies, no evidence of any long-term neuropraxia was documented in any study.[7,31–34] Sepsis – a concern frequently associated with corticosteroid administration – was also not noted to be increased in those patients receiving a dexamethasone adjuvant, nor was local wound site infection.[1,34,35] A clinically insignificant increase in blood glucose was, however, reported in several patients in Choi's review.[4]

This paucity of complications may be falsely reassuring. Studies may be underpowered to reveal complications and there was little long-term follow-up. Only Tandoc and Cummings instituted a follow-up interview for complications outside of the post-anaesthetic care unit – at 4 weeks and 14 days respectively.[13,19] Larger studies regarding the use of perioperative dexamethasone are currently under way, and will shed more light on the incidence of sepsis and local infection.[36]

## Interpretation and guidelines for clinical application

Dexamethasone's ability to augment the analgesia offered by regional single-shot nerve blocks and thus improve the management of acute pain in the perioperative period is supported by all of the literature currently available. However, the literature does lack clarity regarding dexamethasone's route of administration, timing and dosing range for the specific purpose of analgesic additive.

It therefore seems reasonable for clinicians to employ preservative-free dexamethasone from single-use vials together with single-shot peripheral and neuraxial anaesthesia provided that it is administered only once, at a low dose (0.1 mg/kg, to a maximum of 10 mg). A single perioperative dose has been illustrated by all sources reviewed to limit adverse effects whilst still inferring benefit from an analgesic point of view. Without clear evidence to favour a perineural route the preferred route for administration of the drug should remain the FDA-approved systemic intravenous route.

Despite the fact that the current literature suggests that complications are limited, the possibility for adverse effects should always be borne in mind when using a drug. Dexamethasone's proven ability to generate neural damage in animal models, hyperglycaemia and even sepsis with repeated administration should not be discounted.[7,31,33,35] Contamination from multi-use vials and the preservatives contained therein is also of concern when considering potential side effects. Patients at high risk of sepsis or hyperglycaemia should receive dexamethasone only with caution or not at all.

## Implications for future research

Current literature has illustrated dexamethasone's ability to augment analgesia in the perioperative period when combined with regional techniques. However, the long-term safety of this practice still needs to be addressed. The first step for future study would involve monitoring adverse reactions in patients who have received a single perioperative dose of dexamethasone. There should be a focus on the development of local infection in these patients, hyperglycaemia in at-risk patients and the development of neuronal damage in patients receiving perineural dexamethasone. Larger future randomised controlled trials should investigate the relative risk for these adverse outcomes in all patient groups receiving adjunctive dexamethasone. Follow-up studies should assess the development of these side effects during a 24 h period following the perioperative dose – bearing in mind the 190 min half-life of the drug. Long-term follow-up at a point of 3 months post-surgery would provide the optimum time span to conclusively exclude any permanent neuropraxias. The PADDI (Perioperative ADministration of Dexamethasone and Infection) trial is currently under way; it is a large multi-centre randomised control trial, which will provide great insight into the exact risk of sepsis and local infection in patients receiving perioperative steroids.[36]

Once the potential for complications has been reviewed, further information regarding the best application of the drug in this setting should be investigated. The most efficacious dose, the most reliable route and the most appropriate timing of administration all need to be established. Further work in animal models is needed to limit the potential for harm in humans.

## Conclusion

Dexamethasone has potential as an additive in regional analgesia for its ability to prolong the duration of action of analgesia afforded by 'single-shot' peripheral and neuraxial blocks. The routes of administration and dosing ranges are currently controversial but a trend to low dosing and systemic use appear to reduce the potential for complications. A single, intravenous, low-dose (0.1 mg/kg) dexamethasone adjunct may be used perioperatively in conjunction with regional techniques in all non-diabetic patients. However, future studies are required to elucidate the most effective route and optimum dosing range for dexamethasone's use in this field.

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