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Does dexamethasone have a perineural mechanism of action? A paired, blinded, randomized, controlled study in healthy volunteers

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Abstract

Background: Dexamethasone prolongs block duration. Whether this is achieved via a peripheral or a central mechanism of action is unknown. We hypothesized that perineural dexamethasone added as an adjuvant to ropivacaine prolongs block duration compared with ropivacaine alone, by a locally mediated effect when controlled for a systemic action.
Methods: We performed a paired, blinded, randomized trial, including healthy men. All subjects received bilateral blocks of the saphenous nerve with ropivacaine 0.5%, 20 ml mixed with dexamethasone 2 mg in one leg and saline in the other, according to randomization. The primary outcome was the duration of sensory block assessed by temperature discrimination in the saphenous nerve distribution. Secondary outcomes were sensory block assessed by mechanical discrimination, pain response to tonic heat stimulation, and warmth and heat pain detection thresholds.
Results: We included 20 subjects; one had a failed block and was excluded from the paired analysis. Block duration was not statistically significantly longer in the leg receiving dexamethasone when assessed by temperature discrimination (primary outcome, estimated median difference 1.5 h, 95% confidence interval −3.5 to 0, P=0.050). For all other outcomes, the duration was statistically significantly longer in the leg receiving dexamethasone, but the median differences were <2.0 h. Individual subject analysis revealed that only eight subjects had a block prolongation of at least 2 h in the leg receiving dexamethasone perineurally.
Conclusion: Perineural administration of dexamethasone 2 mg showed a modest and inconsistent effect of questionable clinical relevance on block duration.
Clinical trial registration. NCT01981746.

Key words: anaesthetics; local; dexamethasone; lower extremity; nerve block

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Editor's key points

- Perineural injection of dexamethasone is thought to prolong the duration of local anaesthetic block.
- It is uncertain if this is a local or a systemic effect.
- Healthy volunteers received bilateral saphenous nerve blocks with ropivacaine, with the addition of dexamethasone on one side.
- Block duration for temperature discrimination (primary outcome) was not significantly extended by dexamethasone.

Postoperative pain is often treated by peripheral nerve blocks, but block duration limits the effectiveness of a single injection. In an attempt to prolong block duration, anaesthetists have added different adjuvants (e.g. dexamethasone, clonidine, dexmedetomidine, opioids, and epinephrine) to the local anaesthetic. Currently, dexamethasone seems to be the most promising of these adjuvants, and recent systematic reviews have shown that perineural dexamethasone prolongs analgesia by approximately 8–10 h compared with placebo.[1–3]

However, systemic administration of dexamethasone also provides analgesia,[4] making the absence of a systemic control an important limitation to these studies. This has led to the inclusion of a control group receiving dexamethasone i.v. in recent studies, which in turn have demonstrated comparable effects of i.v. and perineural dexamethasone on duration of analgesia.[5–8] Nonetheless, perineurally administered dexamethasone might exert its effect systemically via vascular absorption. Hence, one important question remains unanswered: does dexamethasone have any local perineural effect or is the mechanism of action solely systemic? Considering the potential augmentation by perineural dexamethasone on local anaesthetic-induced neurotoxicity[9] and the finding that dexamethasone does not directly affect the action potentials in A- and C-fibres,[10] this enigma needs to be resolved.

In the present study, we aimed to investigate whether perineural dexamethasone prolongs block duration, in an experimental model, controlling for any systemically mediated effect. By administering bilateral blocks simultaneously, any systemic effect (caused by systemic absorption from the perineural dexamethasone) will affect both blocks equally in each subject; hence, any difference between blocks must be attributed to a local effect. We hypothesized that perineural dexamethasone as an adjuvant to ropivacaine prolongs block duration compared with ropivacaine alone, by a locally mediated effect. Our primary outcome was the duration of sensory block assessed by temperature discrimination in the saphenous distribution. Secondary outcomes were sensory block assessed by other measurement tools; mechanical discrimination, pain response to a tonic heat stimulation, warmth detection threshold (WDT), and heat pain detection threshold (HPDT).

Methods

Recruitment

We performed a paired, blinded, randomized, controlled trial in healthy volunteers. The study protocol was prospectively approved by the Committees of Biomedical Research Ethics for the Capital Region (H-3-2014-145), the Danish Medicine Agency (2014-004879-23), and the Danish Data Protection Agency and registered at clincialtrials.gov (NCT02351804). The Copenhagen GCP (Good Clinical Practice) unit monitored the study.

We conducted the study at Gentofte University Hospital, Denmark, during February 2015. Written informed consent was obtained from all subjects before inclusion. Inclusion criteria were men aged 18–30 yr, with a BMI of 18–30 kg m^{-2} and an ASA grade of I. Subjects presenting with allergy to local anaesthetics, alcohol or drug abuse, inability to cooperate, neuromuscular pathology, previous trauma or surgery to the leg, diabetes mellitus, or as non-Danish speakers were excluded from the study. Subjects were also excluded if they had taken opioids or steroids within the last 4 weeks or any analgesic during the last 48 h.

Block performance

We blocked the saphenous nerve by using a subsartorial approach with ultrasound-guided injection of the study medication in the adductor canal. This approach was chosen because of the high success rate in blocking the saphenous nerve by this technique.[11] Under ECG and pulse oximetry monitoring, we performed the blocks at the midthigh level under ultrasound guidance (Logiq e, R6 ultrasound unit; GE, Waukesha, WI, USA) with a linear 12L ultrasound probe. In the short-axis view, we identified the superficial femoral artery deep to the sartorius muscle. At this level, the saphenous nerve is usually seen lying at the junction between the artery, the vastus medialis muscle, and the sartorius muscle. The needle was advanced in plane until the needle tip was in the perineural position. The study medication was then deposited anterolateral to the artery.

Study medication

All subjects received bilateral blocks. We injected ropivacaine 0.5%, 20 ml plus isotonic saline, 0.5 ml in one leg (ROPI-SAL treatment) and ropivacaine 0.5%, 20 ml plus dexamethasone 4 mg ml^{-1}, 0.5 ml in the opposite leg (ROPI-DEX treatment), according to randomization.

The pharmacy prepared a computer-generated randomization list (1:1 ratio, blocks of 10) and packed the study medication in identical, sealed, opaque boxes, one for each subject. The boxes were first opened upon inclusion into the study. Each box contained one vial of isotonic saline and one vial of dexamethasone 4 mg ml^{-1}, one labelled 'right leg' and the other 'left leg', according to randomization. Two assistants, not involved in the trial, prepared two identical syringes labelled with the subject's identification number and right or left leg. Under double verification, they filled the syringes with the study medication according to the randomization sequence. The prefilled syringes were handed over to the anaesthetist performing the blocks (U.G.). Dexamethasone and saline are both transparent liquids, indistinguishable from each other. Hence, we ensured allocation concealment and blinding to treatment of all subjects, outcome assessors, the anaesthetist performing the blocks, and all other personnel. Blinding was maintained until completion of data collection. Group allocation was coded during statistical analysis and was first broken upon completion of the first draft of this manuscript.

Evaluation of sensory block

We assessed sensory block by using five different measurement tools to test afferent impulses via Aδ- and C-fibres. All sensory tests were performed within the saphenous nerve distribution;

in the medial part of the lower leg, distal to the tibial tubercle, and proximal to the medial malleolus. We validated these tests in a previous pilot study, all showing high sensitivity and specificity (80–100%) in differentiating block of the saphenous nerve from no block. Mechanical discrimination was assessed using pinprick, and temperature discrimination by assessing cold sensation to an alcohol swab. For both tests, we used the lateral part of the thigh as a reference area and dichotomized the response as normal (corresponding to the sensation in the reference area) or abnormal (blunt or absent). We assessed warmth and heat pain detection thresholds using a computer-controlled thermode (2.5 cm^2; Thermotest; Somedic A/B, Hörby, Sweden). The temperature of the thermode was raised by 1°C every second, and the subjects were instructed to push a button at the first sensation of warmth or pain, respectively, thereby terminating the stimulation. We used the same thermode in the tonic heat stimulation test. In this test, the temperature of the thermode was increased to 45°C for 30 s, and the subjects were asked to report the maximal pain experienced during the test, using a visual analog scale (VAS, 0–100 mm).

Subjects were familiarized with all tests before assessments. We collected baseline values immediately before block performance. Post-block assessments were performed at 1 and 4 h post-block, thereafter hourly for as long as abnormal sensation persisted. All tests were performed at all time points, with the following two exceptions. First, when sensation started to recover (corresponding to VAS pain scores >0 mm in the tonic heat stimulation test) we decreased the interval for assessing temperature discrimination to 30 min (primary outcome). Second, although the cut-off points for the WDT and HPDT tests (maximal temperature of 52°C) have been validated in other settings and are considered to be safe, we were still concerned about risking burn injuries as a result of the many frequent and repeated tests in an anaesthetized area. Thus, the WDT and HPDT were not assessed as long as pain scores were zero during the tonic heat stimulation test.

We considered the temperature and mechanical discrimination ability to be recovered fully when sensation corresponded to that in the reference area. Pain scores during the tonic heat stimulation test were considered to be normalized when the VAS scores were <10 mm below the pre-block baseline value. For the WDT and HPDT test, the values had to return to baseline or <2°C above baseline to be considered normalized.

Outcomes

The primary outcome was block duration assessed by temperature discrimination (alcohol swab). The secondary outcomes were block duration assessed by mechanical discrimination, pain scores during tonic heat stimulation, WDT, and HPDT. Finally, we compared maximal pain scores during tonic heat stimulation at 4 h post-block and 1 h after block resolution (after normalization of VAS scores) to evaluate potential rebound pain.

Sample size calculation

Most studies investigating the effect of adjuvants to local anaesthetics have been performed in a clinical setting, using time to first pain or first administration of analgesics as the outcome. Marhofer and colleagues[12] performed an experimental study similar to ours, directly assessing ulnar block duration by pinprick in healthy volunteers. They found that the duration of an ulnar block assessed by pinprick was 350 (SD 54) min in the group receiving ropivacaine alone, and 555 (SD 118) min in the group receiving ropivacaine plus perineural dexmedetomidine. To compensate for the uncertainty in the SD, we assumed an SD of 150 min, and considered a 120 min block prolongation to be clinically relevant. With a significance level of 0.05% and a power of 90%, 18 subjects would be needed to detect a difference of 120 min. To compensate for dropouts, we planned to include 20 subjects.

Statistical analysis

Data were analysed using SPSS version 19.0 (SPSS, Chicago, IL, USA). Histograms, box plots, Q-Q plots, and the Shapiro–Wilk test were used to assess whether the pairwise differences were normally distributed. Data are presented as the mean (SD) or median (range). Data for the primary end point (temperature discrimination) showed a skewed distribution, but data for most of the secondary outcomes had normal distributions (mechanical discrimination, tonic heat stimulation test, HPDT, and rebound pain). However, because small data sets have low power in detecting deviations from normality we performed non-parametric Wilcoxon signed-rank tests for all comparisons, and the difference in medians was calculated using the Hodges–Lehman estimator with a constructed 95% confidence interval (CI). A two-sided P-value of <0.05 was considered statistically significant.

Results

We included 20 subjects, but one subject had an incomplete block in one leg (only partial loss of sensation), and was excluded from the paired analysis. Furthermore, block duration was unexpectedly long (up to 37 h), and two subjects had to leave before complete block resolution, because of other appointments (ROPI-SAL $n=1$ and ROPI-DEX $n=1$). We instructed these two subjects in how to assess temperature discrimination after discharge every hour until normal sensation occurred (primary outcome). One of the subjects had completed the measurements for the secondary outcomes before leaving, but for the other person we have missing data for the secondary end points. Thus, data from 19 subjects were included in analyses of the primary outcome (including the two self-reported results), and data from 18 subjects were included in analysis of the secondary outcomes. There were no adverse or serious adverse events in the study. Subjects' characteristics are presented in Table 1.

Sensory block assessed by temperature discrimination (primary outcome) lasted for a median of 23 (range 17–37) h in the ROPI-DEX group compared with 21 (14–30) h in the ROPI-SAL

Table 1 Subjects' characteristics. Values are reported as number of subjects or mean (SD)

Characteristic	Value
Number of subjects	20
Age (yr)	24 (3)
Height (cm)	182 (8)
Weight (kg)	77 (11)
BMI (kg m^{-2})	23 (3)

Table 2 Block duration. Data are presented as median (range). HPDT, heat pain detection threshold; ROPI-DEX, group receiving dexamethasone 2 mg added to ropivacaine 0.5%; ROPI-SAL, group receiving saline added to ropivacaine 0.5%; WDT, warmth detection threshold

Test	ROPI-DEX duration (h)	ROPI-SAL duration (h)	Estimated median difference	95% Confidence interval	P-value
Temperature discrimination	23 (17–37)	21 (14–30)	1.5	0.0–3.5	0.050
Mechanical discrimination	23 (17–29)	22 (14–28)	1.0	0.5–3.0	0.005
WDT	22 (16–27)	18.5 (15–25)	2.5	1.0–4.0	0.006
HPDT	22 (16–28)	19 (14–28)	2.0	0.0–4.0	0.027
Tonic heat stimulation	22 (16–28)	20 (14–27)	2.5	0.5–4.0	0.006

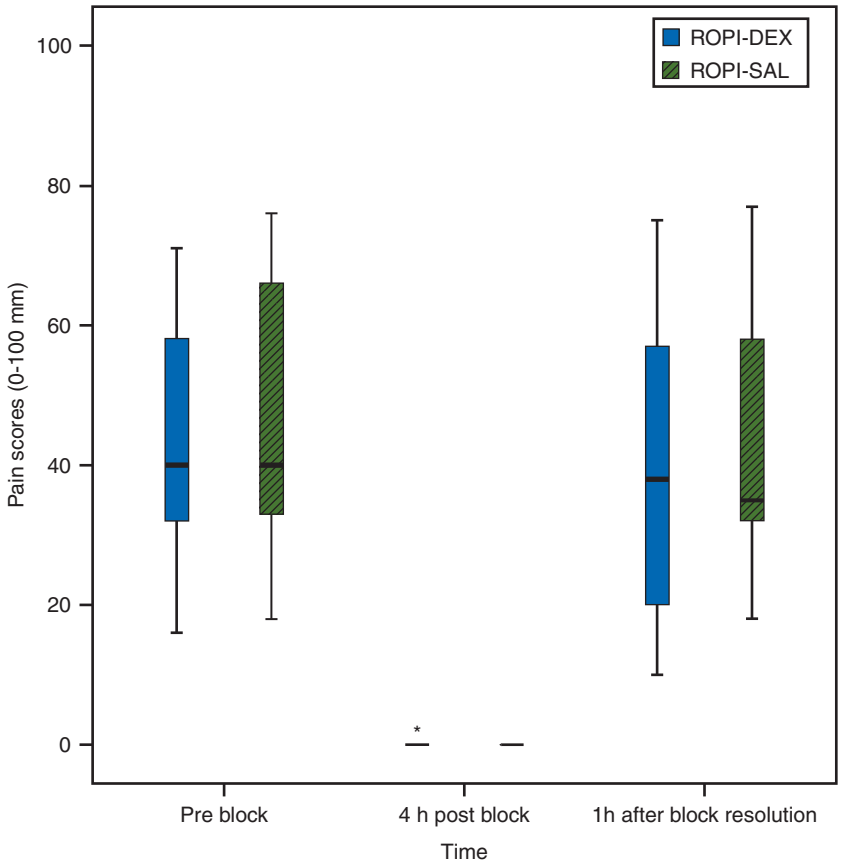

Fig 1 Effects of perinerual dexamethasone on visual analog pain scores. Pain scores were assessed during tonic heat stimulation pre-block, during block (4 h post-block), and 1 h after block resolution (rebound pain). There was no difference in pain scores between treatments, neither during block (estimated difference of 0 mm, 95% CI 0–0, P=0.32) nor after block resolution (estimated difference of 1.5 mm, 95% CI − 3.5 to 7, P=0.54).

group, with an estimated difference of 1.5 h (95% CI 0.0–3.5), P=0.050. An intention-to-treat analysis including the subject with a partial block did not alter the results substantially; estimated difference of 1.5 h (95% CI 0.0–4). For all other outcomes, the duration was statistically significantly longer in the ROPI-DEX group compared with the ROPI-SAL group (Table 2). There were no statistically significant differences in pain scores during tonic heat stimulation (4 h post-block); median values 0 (0–3) *vs* 0 (0–0) mm for ROPI-DEX and ROPI-SAL, respectively (Fig. 1), with an estimated difference of 0 mm (95% CI 0–0), P=0.32. Neither were there statistically significant differences in pain scores after block resolution (rebound pain, 1 h after block resolution); 37 (10–75) mm for ROPI-DEX *vs* 35 (18–77) mm for ROPI-SAL (Fig. 1), with an estimated difference of 1.5 mm (95% CI −3.5 to 7), P=0.54.

Individual subject analysis of block duration, assessed by temperature discrimination, revealed that only eight subjects had a block prolongation of at least 2 h in the leg receiving dexamethasone perineurally. In the remaining 11 subjects, the difference between treatments was either <2 h, or block duration was longer in the leg receiving ropivacaine mixed with saline (Fig. 2).

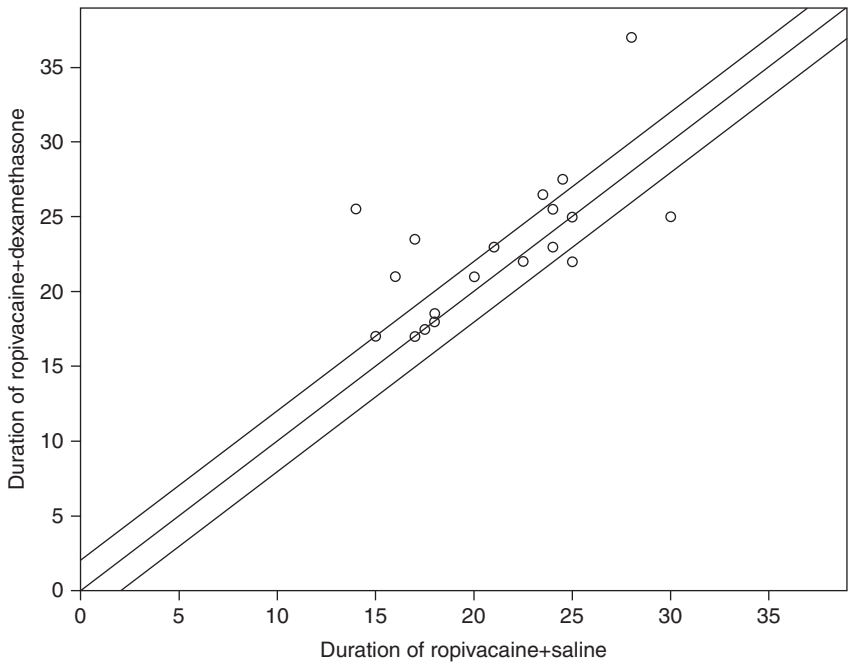

Fig 2 Individual subject analysis of block duration assessed by temperature discrimination. In this scatter plot, each dot in the coordinates represents one subject. The position on the horizontal axis represents the duration of block in the leg receiving ropivacaine plus saline, and the position on the vertical axis represents the duration in the leg receiving ropivacaine + dexamethasone. In only eight subjects did perineural dexamethasone prolong block duration by at least 2 h (the *a priori* considered level of clinical relevance).

Discussion

In this experimental study, we aimed to resolve the question of whether perineural dexamethasone has a locally mediated effect on block duration or not. Using an experimental model, strictly controlling for any systemically mediated effects, we found that adding perineural dexamethasone to ropivacaine has only a modest effect on block duration compared with ropivacaine alone. Although the difference in our primary outcome did not reach statistical significance ($P=0.050$), block duration was longer in the leg receiving perineural dexamethasone in all secondary outcome analyses. Albeit being statistically significant, the estimated median difference ranged from only 1.5 to 2.5 h (Table 2). Furthermore, block duration was longer than anticipated in both groups, questioning the clinical relevance of our *a priori* defined 120 min prolongation (corresponding to ~10% prolongation). Another important point to note is that the effect of dexamethasone was unevenly distributed. For our primary outcome, co-administration of dexamethasone resulted in block prolongation of ≥120 min in only eight out of 19 subjects (42%, 95% CI 0.23–0.54; Fig. 2). The remaining 11 subjects (58%, 95% CI 35.81–80.19) receiving perineural dexamethasone showed a less pronounced effect or even shorter duration of the block compared with ropivacaine alone.

The mechanism and site of action by which glucocorticoids exert their effects remain unknown. Perineurally administered dexamethasone is thought to exert its effect by a direct inhibition of signal transmission in nociceptive C-fibres, a local inflammatory effect, and locally induced vasoconstriction prolonging the local anaesthetic effect. However, glucocorticoids also have a central effect, and i.v. injection of dexamethasone in doses as low as 2.5 mg has been shown to prolong block duration.[13] The main strength of the present study is that the bilateral injections ensured an even distribution of the systemic effect of dexamethasone in each subject. Thus, differences between our groups were not influenced by systemically mediated analgesia but solely reflect the local effect of dexamethasone as an adjuvant to ropivacaine. Albeit systemically mediated effects have not influenced differences between the groups, we cannot rule out a potential systemic effect in both groups, and block duration might have been substantially shorter if we had not administered dexamethasone at all. Thus, the present design allows us draw conclusions only on the local effect of dexamethasone, but not its systemic effect.

Most studies investigating perineural administration of dexamethasone use time to first analgesia as a surrogate, without directly measuring block duration. The inclusion of healthy volunteers enabled us to assess block duration directly, every hour/half an hour, throughout the study period. Such frequent measurements throughout the night in a newly operated patient would have been neither feasible nor ethical. The non-surgical setting further ensured that block duration was not influenced by surgical trauma or individual pain responses, but as glucocorticoids also have anti-inflammatory properties, we may be overlooking essential properties of the effect of dexamethasone.

The applied test battery ensured testing of different sensory submodalities: nociception, mechanical sensation, and temperature sensation. We validated these measurement tools in a previous pilot investigation, finding that the thermal

discrimination test had the highest sensitivity and specificity to differentiate block of the saphenous nerve from no block. However, it may be considered a limitation that we assessed only sensory block. Even though no previous studies have indicated a selective motor effect, we cannot exclude a more attenuated perineural effect of dexamethasone on motor block.

The minimal effective and maximal safe doses for perineural dexamethasone remain unknown. Although most previous studies have used perineural doses of 4 (5) or 8 (10) mg dexamethasone, there has been a call for lower doses. The 2 mg dose of dexamethasone used in the present study extrapolates to the 66 $\mu g\ ml^{-1}$ that was less likely to augment local anaesthetic-induced neurotoxicity in cultured rat neurones,[9] and is within the recommended dose range for perineural administration proposed in a recent editorial.[14] However, higher doses might have resulted in a more pronounced and consistent block prolongation in the present study. Considering the increasing evidence that perineural and systemic dexamethasone have similar block-prolonging effects, and that Desmet and colleagues[13] found no statistically significant block prolongation by increasing the systemic dose above 2.5 mg i.v., we find a 2 mg dose for perineural administration relevant to investigate. In contrast, administering ropivacaine 0.5%, 20 ml may be considered excessive for a saphenous block, but we wished to reduce the risk of failed blocks caused by an inadequate volume.

Interestingly, in some subjects the block duration was shorter in the leg receiving dexamethasone. Thus, the peripheral effect of dexamethasone is very variable, and in some subjects, there may be no peripheral effect, making other factors for duration dominant (variable absorption and perfusion in the area, proximity of the injectate to the nerve, etc.). Another and more dreadful explanation may be that dexamethasone has no local effect except in instances where it causes a small nerve injury, leading to the prolonged duration seen in some of the patients.

In the present study, there was no difference in pain scores between treatments at 4 h post-block, indicating that perineural dexamethasone does not improve block density. Kolarczyk and Williams[15] reported transient heat hyperalgesia (rebound pain) in rats after resolution of a sciatic nerve block with ropivacaine, and it has been suggested that dexamethasone may worsen this rebound pain when co-administered with local anaesthetics. In the present study, pain scores 1 h after block resolution were no higher than those seen pre-block, with no difference between groups (Fig. 1). However, previous studies describing this phenomenon included a surgical model. Hence, although the present study did not find any evidence of rebound pain or any effect of perineural dexamethasone, this may be the case only in a non-surgical setting.

Our results are consistent with recent studies showing a modest effect of questionable clinical relevance by perineural administration of dexamethasone.[5–8] These studies controlled for the systemic action by including a control group receiving dexamethasone i.v.[5–8] Although such studies contribute crucial knowledge regarding the efficacy of the two different routes of administration, they do not answer the question of whether the mechanism of action is local or systemic, because systemic absorption after perineural administration is likely to have affected the results.

In conclusion, the addition of 2 mg of dexamethasone to ropivacaine, for a saphenous block in healthy volunteers, resulted in only an inconsistent and modest block prolongation of questionable clinical relevance.

Authors' contributions

Study conception: P.J., U.G., J.B.D.
Study design: P.J., U.G., Z.J.K.-N., A.R.S., J.B.D.
Participant recruitment and data analysis: P.J., U.G.
Data collection: P.J., U.G., J.K.S.
Data analysis: P.J., U.G.
Writing up the first draft and the final paper: P.J.
Revising drafts and final approval: U.G., Z.J.K.-N., A.R.S., J.K.S., J.B.D.

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Declaration of interest

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References

1. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. *Anaesthesia* 2015; **70**: 71–83
2. Choi S, Rodseth R, McCartney CJ. Effects of dexamethasone as a local anaesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. *Br J Anaesth* 2014; **112**: 427–39
3. De Oliveira GS Jr, Castro Alves LJ, Nader A, Kendall MC, Rahangdale R, McCarthy RJ. Perineural dexamethasone to improve postoperative analgesia with peripheral nerve blocks: a meta-analysis of randomized controlled trials. *Pain Res Treat* 2014; **2014**: 179029
4. De Oliveira GSJ, Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2011; **115**: 575–88
5. Desmet M, Braems H, Reynvoet M, *et al*. I.V. and perineural dexamethasone are equivalent in increasing the analgesic duration of a single-shot interscalene block with ropivacaine for shoulder surgery: a prospective, randomized, placebo-controlled study. *Br J Anaesth* 2013; **111**: 445–52
6. Rahangdale R, Kendall MC, McCarthy RJ, *et al*. The effects of perineural versus intravenous dexamethasone on sciatic nerve blockade outcomes: a randomized, double-blind, placebo-controlled study. *Anesth Analg* 2014; **118**: 1113–9
7. Fredrickson Fanzca MJ, Danesh-Clough TK, White R. Adjuvant dexamethasone for bupivacaine sciatic and ankle blocks: results from 2 randomized placebo-controlled trials. *Reg Anesth Pain Med* 2013; **38**: 300–7
8. Abdallah FW, Johnson J, Chan V, *et al*. Intravenous dexamethasone and perineural dexamethasone similarly prolong the duration of analgesia after supraclavicular brachial plexus block: a randomized, triple-arm, double-blind, placebo-controlled trial. *Reg Anesth Pain Med* 2015; **40**: 125–32

9. Williams BA, Hough KA, Tsui BY, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. *Reg Anesth Pain Med* 2011; **36**: 225–30
10. Yilmaz-Rastoder E, Gold MS, Hough KA, Gebhart GF, Williams BA. Effect of adjuvant drugs on the action of local anesthetics in isolated rat sciatic nerves. *Reg Anesth Pain Med* 2012; **37**: 403–9
11. Marian AA, Ranganath Y, Bayman EO, Senasu J, Brennan TJ. A comparison of 2 ultrasound-guided approaches to the saphenous nerve block: adductor canal versus distal transsartorial: a prospective, randomized, blinded, noninferiority trial. *Reg Anesth Pain Med* 2015; **40**: 623–30
12. Marhofer D, Kettner SC, Marhofer P, Pils S, Weber M, Zeitlinger M. Dexmedetomidine as an adjuvant to ropivacaine prolongs peripheral nerve block: a volunteer study. *Br J Anaesth* 2013; **110**: 438–42
13. Desmet M, Vanneste B, Reynvoet M, *et al*. A randomised controlled trial of intravenous dexamethasone combined with interscalene brachial plexus blockade for shoulder surgery. *Anaesthesia* 2015; **70**: 1180–5
14. Williams BA, Schott NJ, Mangione MP, Ibinson JW. Perineural dexamethasone and multimodal perineural analgesia: how much is too much? *Anesth Analg* 2014; **118**: 912–4
15. Kolarczyk LM, Williams BA. Transient heat hyperalgesia during resolution of ropivacaine sciatic nerve block in the rat. *Reg Anesth Pain Med* 2011; **36**: 220–4

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