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Effect of dexamethasone on the duration of interscalene nerve blocks with ropivacaine or bupivacaine

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Editor's key points

- This trial demonstrates a difference in block prolongation between local anaesthetics.
- Dexamethasone significantly prolongs the analgesic effect of plain ropivacaine and bupivacaine used as a single-injection interscalene block.
- Block duration was longer with plain bupivacaine than ropivacaine.
- Further studies have to reveal the safety of dexamethasone for perineural use.

Background. Pain after shoulder surgery is often treated with interscalene nerve blocks. Single-injection blocks are effective, but time-limited. Adjuncts such as dexamethasone may help. We thus tested the hypothesis that adding dexamethasone significantly prolongs the duration of ropivacaine and bupivacaine analgesia and that the magnitude of the effect differs among the two local anaesthetics.

Methods. In a double-blinded trial utilizing single-injection interscalene block, patients were randomized to one of four groups: (i) ropivacaine: 0.5% ropivacaine; (ii) bupivacaine: 0.5% bupivacaine; (iii) ropivacaine and steroid: 0.5% ropivacaine mixed with dexamethasone 8 mg; and (iv) bupivacaine and steroid: 0.5% bupivacaine mixed with dexamethasone 8 mg. The primary outcome was time to first analgesic request after post-anaesthesia care unit discharge. The Kaplan–Meier survival density estimation and stratified Cox's proportional hazard regression were used to compare groups.

Results. Dexamethasone significantly prolonged the duration of analgesia of both ropivacaine [median (inter-quartile range) 11.8 (9.7, 13.8) *vs* 22.2 (18.0, 28.6) h, log-rank $P<0.001$] and bupivacaine [14.8 (11.8, 18.1) and 22.4 (20.5, 29.3) h, log-rank $P<0.001$]. Dexamethasone prolonged analgesia more with ropivacaine than bupivacaine (Cox's model interaction term $P=0.0029$).

Conclusions. Dexamethasone prolongs analgesia from interscalene blocks using ropivacaine or bupivacaine, with the effect being stronger with ropivacaine. However, block duration was longer with plain bupivacaine than ropivacaine. Thus, although dexamethasone prolonged the action of ropivacaine more than that of bupivacaine, the combined effect of dexamethasone and either drug produced nearly the same 22 h of analgesia.

Keywords: anaesthetic techniques, regional; anaesthetics local, bupivacaine; anaesthetics local, ropivacaine; hormones, glucocorticoid

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Pain after orthopaedic surgery can be intense.[1] In particular, managing pain after shoulder procedures poses a challenge to both anaesthesiologists and orthopaedic surgeons. In an effort to improve analgesia and facilitate mobilization, regional anaesthesia in the form of an interscalene approach to the brachial plexus is often used, either as an adjunct to general anaesthesia or as the primary anaesthetic. The use of an interscalene block as the primary anaesthetic increases the proportion of patients suitable for post-anaesthesia care unit (PACU) bypass and decreases immediate postoperative pain.[2] However, analgesia is short-lived, usually lasting less than 24 h.

Investigators have tried mixing local anaesthetic with adjuvant drugs in an attempt to prolong analgesia from nerve blocks. Adjuvants including epinephrine, clonidine,[3][4] opioids,[5][6] ketamine,[7][8] and midazolam[9] have met with limited success. However, the glucocorticoid dexamethasone appears to be effective in a small number of preclinical[10][11] and clinical[12–15] studies. Why dexamethasone would prolong regional anaesthesia is a subject of much discussion. Steroids induce a degree of vasoconstriction, so one theory is that the drug acts by reducing local anaesthetic absorption. A more attractive theory holds that dexamethasone

increases the activity of inhibitory potassium channels on nociceptive C-fibres (via glucocorticoid receptors), thus decreasing their activity.[16 17]

Whether adjuvant dexamethasone prolongs analgesia with plain ropivacaine or bupivacaine, and whether the effect differs among these commonly used anaesthetics, remains unknown. We thus sought to determine the effect of dexamethasone, as an adjuvant for either ropivacaine or bupivacaine, on the duration of analgesia from interscalene blocks for painful shoulder procedures. Specifically, we tested the hypothesis that adding dexamethasone significantly prolongs the duration of ropivacaine and bupivacaine analgesia and that the magnitude of the effect differs among the two local anaesthetics.

Methods

This trial was registered on ClinicalTrials.gov (# NCT00801138). An inquiry to the US Food and Drug Administration regarding the need for an Investigational New Drug approval went unanswered. The Cleveland Clinic Institutional Review Board approved the trial, including the use of perineural dexamethasone. Written informed consent was obtained from 218 patients who were undergoing moderately to severely painful shoulder procedures (e.g. rotator cuff repair, shoulder arthroplasty) at three locations in the Cleveland Clinic Health System. Premedication consisted of 1–2 mg i.v. midazolam and 50 µg i.v. fentanyl.

Patients were randomized, using a factorial approach, to single-injection interscalene blocks with four drug combinations: (i) ropivacaine: 30 ml (0.5%) ropivacaine mixed with 2 ml (0.9%) saline (placebo); (ii) bupivacaine: 30 ml (0.5%) bupivacaine mixed with 2 ml (0.9%) saline (placebo); (iii) ropivacaine and steroid: 30 ml (0.5%) ropivacaine mixed with dexamethasone 8 mg (2 ml); and (iv) bupivacaine and steroid: 30 ml (0.5%) bupivacaine mixed with dexamethasone 8 mg (2 ml). The dose of 8 mg was chosen because it has been used previously for perineural injection and is within the dose range used clinically for postoperative nausea.

Computer-generated treatment assignments, with random block size, were stratified by clinical site and the invasiveness of the surgical procedure (open vs arthroscopic). Randomization assignments were stored in sealed, sequentially numbered opaque envelopes and opened immediately before the blocks were performed.

Inclusion criteria were patients aged 18–75 yr undergoing painful shoulder procedures such as rotator cuff repair, shoulder arthroplasty, and subacromial decompression. Exclusion criteria were contraindication to interscalene block (severe lung disease, contralateral diaphragmatic paralysis, and coagulopathy), pregnancy, pre-existing neuropathy involving the surgical limb, systemic use of corticosteroids for 2 weeks or longer within 6 months of surgery, and chronic opioid use (>30 mg oral oxycodone equivalent per day).

Patient (age, gender, and co-morbidities) and morphometric (height and weight) characteristics of participating patients were recorded. Patients, clinical personnel, and study staff were blinded to group allocation. To maintain blinding, medications were prepared by an experienced assistant uninvolved with the study or care of study patients. All blocks were performed by attending anaesthesiologists skilled in the interscalene approach. The choice of block technique (nerve stimulator, ultrasound, or both) was left to the discretion of the attending anaesthesiologist. Both block techniques used 50 mm-long-insulated needles (Stimuplex A, B Braun, Melsungen, Germany). The ultrasound technique consisted of an in-plane posterior approach at the level of the cricoid cartilage. The nerve roots/trunks were identified as hypoechoic structures between the anterior and middle scalene muscles. Local anaesthetic was injected and needle position readjusted as necessary to ensure appropriate spread. The nerve stimulation technique used was described by Winnie,[18] with muscle contraction at a stimulating current of <0.4 mA (2 Hz, 0.1 ms duration) considered evidence of appropriate needle position.

After incremental injection of the designated local anaesthetic mixture, patients were evaluated at 5 min intervals for 15 min for the development of sensory and motor block. Sensory block was assessed by loss of sensation to pinprick over the deltoid muscle. Motor block was assessed by failure to abduct the shoulder, the so-called 'deltoid sign'.[19]

Per our routine, patients were given general anaesthesia along with their interscalene blocks. The type of airway management, antiemetic prophylaxis, and intraoperative opioid use were left to the discretion of the attending anaesthesiologist with the provision that no other corticosteroids be administered.

The severity of postoperative pain was assessed by a blinded study team member using a verbal response score (VRS) upon admission to the PACU. Patients reporting pain scores >2 were given i.v. morphine (2 mg) every 5 min until comfortable. After discharge from the PACU, supplemental analgesia for inpatients consisted of acetaminophen 325–650 mg with oxycodone 5–10 mg orally every 4 h as needed for a pain VRS >4, administered by the nurse caring for the patient. Pain unrelieved by oral medication (VRS persistently >4) was treated with i.v. morphine. Outpatients received a prescription for oral acetaminophen with oxycodone and were instructed to delay administration of analgesics until they felt that their pain warranted medication.

A blinded observer interviewed patients each morning for 3 days after operation, either in the hospital or by telephone. Subjects were given a medication diary to record the required data. Data collected included time of block duration (the primary outcome; defined as time from the onset of sensory block to the first administration of supplemental analgesic medication after PACU discharge), and secondary outcomes: time to a significant increase in shoulder discomfort, maximum VRS with rest and movement, and total opioid consumption. The time to initial analgesic use was determined from the medical record for inpatients and by patient report for those already discharged. The times and VRS scores for secondary outcomes were based on patient

reporting of the corresponding events at the daily interview. Other data collected included time to discharge. A member of the study staff contacted patients at 14 days after operation to assess for any late or persistent complications such as residual sensory or motor block. Total opioid doses were converted to oral oxycodone equivalents according to conversion rates derived from the American Pain Society.[20]

Statistical analysis

Patients who retained deltoid sensation were deemed to have failed blocks, but were analysed in their assigned groups according to intention-to-treat principles (specifically, coded as having the outcome at a time of 0 h). The primary outcome measure was the duration of analgesia, defined as the interval between the onset of sensory block and the initial PACU use of opioid analgesia for surgical site pain.

Baseline characteristics were compared using standard descriptive statistics. Continuous values were assessed for normality and are presented as mean or median [interquartile range (IQR)] as appropriate. Categorical data are presented as per cent of total. The duration of analgesia (defined as time from the onset of sensory block to the first use of opioid analgesia) was analysed by the Kaplan–Meier survival analysis and Cox's proportional hazards modelling (stratified by clinical site). The significance levels for each analysis were adjusted for the α spent during interim analyses. A Bonferroni's correction was applied for the two multiple comparisons (steroid effect within each local anaesthetic). Secondary outcomes included time to a significant increase in shoulder discomfort, maximum VRS with rest and movement, and total opioid consumption. The Kaplan–Meier analysis and unpaired *t*-tests or Wilcoxon's rank-sum tests were used as appropriate.

SAS statistical software version 9.2 (SAS Institute, Cary, NC, USA) and R software version 2.11.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Sample size considerations

From our prior experience and Casati and colleagues,[21] we expected a block duration (and standard deviation) of 11 (5) h for each local anaesthetic. We projected a maximum of 436 patients at the 0.10 significance level to detect an interaction of 3 h or more between the two factors with 90% power, including an adjustment for interim analyses. This sample size also ensured having adequate power to test the main effect of dexamethasone (given that the test for interaction proved non-significant) and ample power to detect a difference of 3 h or more in block duration for each of the two multiple comparisons planned in the case of significant interaction. To allow the trial to stop early in the event of a larger-than-anticipated treatment effect, interim analyses were planned at sample sizes of 73, 145, 218, 290, and 363 and a final analysis, if necessary, at $n=436$. To maintain an overall α of 0.1 for the interaction, stopping boundaries were calculated using the γ-spending

approach of Hwang and colleagues,[22] with γ parameters of -4 for efficacy and -2 for futility.

Results

At the third interim analysis ($n=218$), the efficacy boundary for interaction between dexamethasone and the type of anaesthetic was crossed ($P\leq0.0087$). In the light of this, the trial's Executive Committee (D.I.S., A.K., and J.E.D.) stopped the study.

Patients were enrolled between December 2008 and October 2010. Figure 1 details the patient flow through the study. Baseline covariates were well balanced across the groups (Table 1). Seven patients did not have the primary outcome (opioid use) and were right-censored in the analysis. They were evenly distributed across the randomized groups.

Primary outcome

Dexamethasone significantly prolonged the duration of analgesia of both ropivacaine [median (IQR): 11.8 (9.7, 13.8) *vs* 22.2 (18.0, 28.6) h, log-rank test $P<0.001$, interim analysis-adjusted significance level of 0.0022] and bupivacaine [14.8 (11.8, 18.1) *vs* 22.4 (20.5, 29.3) h, log-rank test $P<0.001$, Fig. 2]. On the basis of the stratified Cox's model for time to first opioid use, the block resolution rate among patients given ropivacaine with dexamethasone was 0.17 times [95% confidence interval (CI) 0.08, 0.39] that among patients given ropivacaine alone. For bupivacaine, the block resolution rate in patients given dexamethasone was 0.44 times (95% CI 0.23, 0.83) that of patients receiving bupivacaine alone. The effect of dexamethasone in prolonging block duration was significantly stronger in ropivacaine than bupivacaine (interaction term $P=0.0029$ at an interim analysis-adjusted significance level of 0.0087).

Analysing the primary outcome of block duration using ultrasound or nerve stimulation, the choice of technique had no appreciable effect on the primary outcome of block duration. In the ultrasound-guided patients, the Kaplan–Meier curve estimates for median block duration were 12.3 *vs* 22.4 h for ropivacaine and 14.7 *vs* 23.7 h for bupivacaine. For patients with nerve stimulation-guided blocks, the median estimates were 11.8 *vs* 21 h for ropivacaine and 15.4 *vs* 25.2 h for bupivacaine.

Secondary outcomes

Consistent with its effect on the primary outcome of first opioid use, dexamethasone significantly prolonged the length of time until the patients' first report of surgical site pain. For ropivacaine, the median time (IQR) to surgical site pain was 11.9 (9.2, 13.8) h without dexamethasone and 22.3 (18.0, 27.2) h with dexamethasone (log-rank test $P<0.001$). The corresponding times for bupivacaine were 14.7 (13.4, 17.9) and 25.7 (21.7, 29.2) h (log-rank test $P<0.001$).

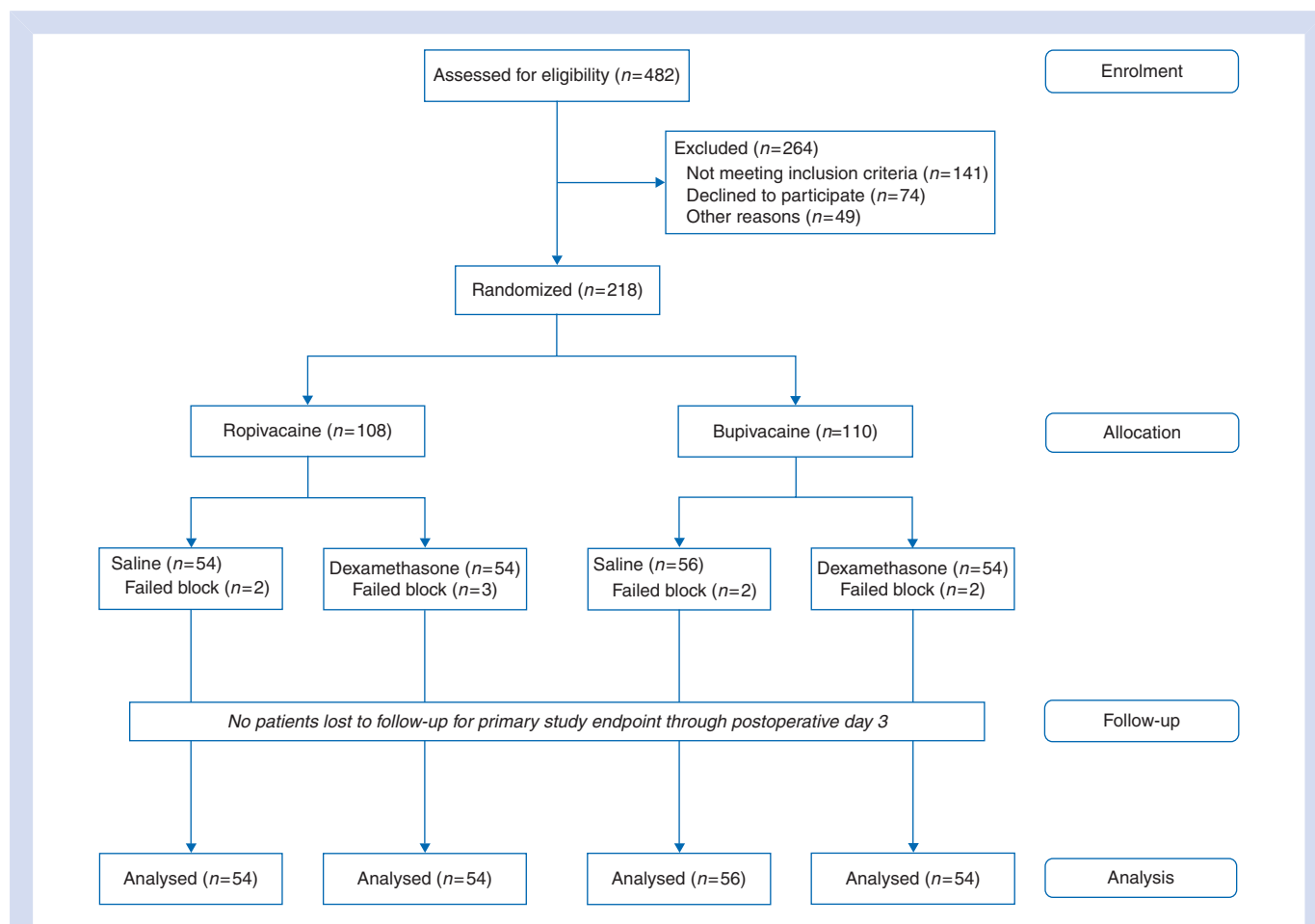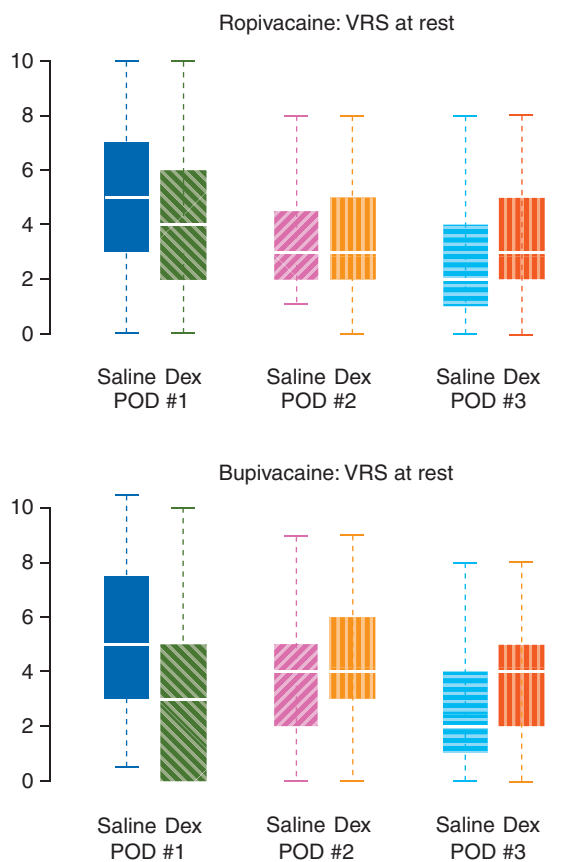The median maximum VRS pain scores at rest (shown in Fig. 3) were significantly lower in the bupivacaine plus

Fig 1 CONSORT study diagram.

Table 1 Summary of patient characteristics by treatment group. Data are presented as per cent or median (IQR)

Characteristic	Level	Ropivacaine, $n=54$	Bupivacaine, $n=56$	Ropivacaine+Dex, $n=54$	Bupivacaine+Dex, $n=54$
Clinical site	Euclid (%)	50	50	48	46
	Hillcrest (%)	11	14	15	17
	Strongsville (%)	39	36	37	37
Age (yr)		55 (44, 65)	60 (51, 68)	59 (49, 68)	58 (53, 64)
BMI (kg/m^2)		29 (26, 34)	29 (26, 33)	29 (25, 34)	28 (26, 32)
Gender	Female (%)	39	34	39	41
	Male (%)	61	66	61	59
ASA classification		II (II, III)	II (II, III)	II (II, II)	II (II, III)
Ethnicity	Caucasian (%)	89	98	96	91
Procedure type	Arthroscopic (%)	43	41	44	41
Procedure	Rotator cuff repair (%)	54	55	54	61
	Arthroplasty (%)	17	21	20	22
	Other (%)	30	23	26	17
Failed block (%)		0	4	6	4
Ultrasound-guided (%)		69	69	72	69
Nerve stimulator used (%)		34	30	33	39
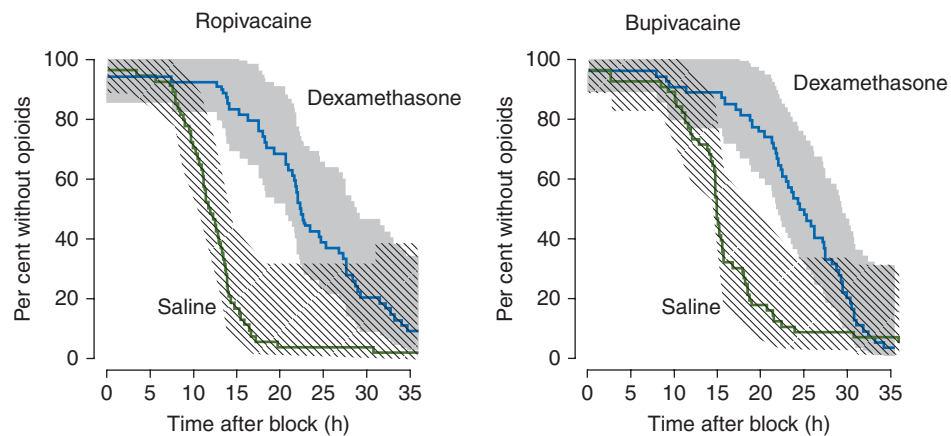
Fig 2 Comparison of block durations for ropivacaine and bupivacaine with dexamethasone or placebo. Data presented as the Kaplan–Meier survival density estimates; shaded areas represent 95% pointwise confidence intervals adjusted for interim analyses and multiple comparisons.

Fig 3 Maximum VRS pain scores at rest. Solid horizontal lines represent medians and boxes represent IQRs. Whiskers extend to the range of the data.

dexamethasone group compared with saline on postoperative day 1 (3 *vs* 5, Wilcoxon's rank-sum test *P*<0.001 at an adjusted significance level of 0.025), but not in the

ropivacaine groups. The only other significant difference was on postoperative day 3 in the bupivacaine group: the dexamethasone group had a significantly higher maximum VRS pain score than saline (median 4 *vs* 2, *P*=0.014).

The median maximum VRS pain scores with movement on postoperative day 1 (shown in Fig. 4) were significantly lower in both the ropivacaine plus dexamethasone (5 *vs* 7, *P*=0.005) and bupivacaine plus dexamethasone groups (4 *vs* 5.5, *P*=0.01) compared with saline. There were no significant differences on postoperative days 2 and 3.

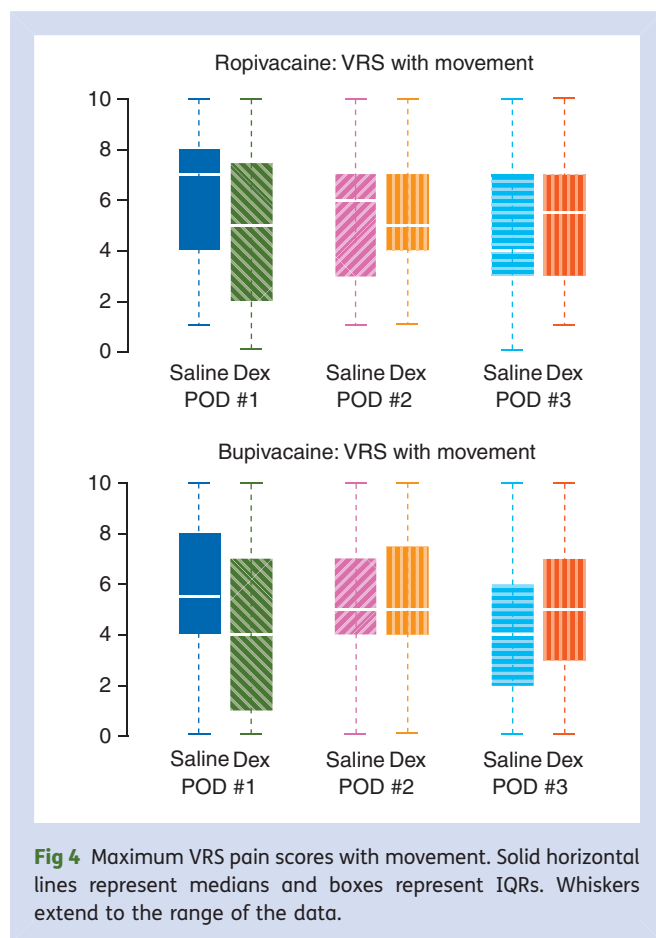Total 3 day opioid consumption was not significantly different between the randomized groups (Table 2).

Safety

At the 14 day interview, no patient reported persistent numbness, paraesthesias, or weakness of the operative limb. There were also no reports of persistent hoarseness, respiratory difficulty, injection site infection, or haematoma.

Discussion

Our results demonstrate that dexamethasone significantly prolongs the analgesic effect of plain ropivacaine and bupivacaine used as a single-injection interscalene block and that this effect differs between the two local anaesthetics. This finding is generally consistent with previous studies, but direct comparisons are difficult because of the variety of local anaesthetic mixtures used, different blocks studied, and different methods of evaluating block duration.

The block prolongation we observed (~1.9-fold with ropivacaine and 1.5-fold with bupivacaine) is consistent with that observed when dexamethasone was combined with mepivacaine for supraclavicular blocks.[13] Similarly, Vieira and colleagues[15] observed that adding dexamethasone to a mixture of bupivacaine, clonidine, and epinephrine increased interscalene block duration from 14 to 24 h (1.7-fold prolongation). Their results, however, must be interpreted in

Fig 4 Maximum VRS pain scores with movement. Solid horizontal lines represent medians and boxes represent IQRs. Whiskers extend to the range of the data.

Table 2 Total 3 day opioid consumption in oral oxycodone equivalents (mg). *P-values from Wilcoxon's rank-sum test. Adjusted significance level=0.025

Group	Median (inter-quartile range)	P-value*
Ropivacaine/dexamethasone	79 (45.2, 100)	0.29
Ropivacaine/saline	75 (45.2, 152.5)	
Bupivacaine/dexamethasone	60 (46.7, 105.2)	0.15
Bupivacaine/saline	85 (51.3, 117.6)	

the light of the presence of two α-agonists that were also included in the local anaesthetic mixture.

We were unable to demonstrate the multi-fold prolongation of analgesia found in one study of bupivacaine/lidocaine supraclavicular blocks[14] and a trial of dexamethasone added to epidural bupivacaine.[23] An exaggerated effect may be due to the small size of those trials, as the accuracy with which treatment effects are estimated in smaller studies is often low. The balance of the small body of existing literature, however, supports the more modest—but still highly clinically important—benefit we observed.

As would be expected from longer block duration, maximum VRS pain scores tended to be lower on the first postoperative day. Beyond this time, however, there

appeared to be no lasting difference in pain scores. The significant (but small) difference seen on postoperative day 3 in one group should be interpreted cautiously due to the multiple tests being performed. Total opioid consumption over the first 72 h also did not differ significantly among groups.

This study is the first to examine the effect of dexamethasone on ropivacaine (or plain bupivacaine) for interscalene blocks and is by far the largest trial to date examining the adjunctive use of dexamethasone in peripheral nerve blocks. Our study was also unique, in that we designed it to detect a modest interaction between dexamethasone and the particular local anaesthetic used—an interaction that proved to be both statistically significant and clinically important.

Dexamethasone was more effective in prolonging analgesia from interscalene blocks from ropivacaine than bupivacaine. We note, though, that this effect was muted by the fact that the block duration was longer with plain bupivacaine than ropivacaine (median 14.8 vs 11.8 h). Thus, although dexamethasone prolonged the action of ropivacaine more than that of bupivacaine, the combined effect of dexamethasone and either drug produced nearly the same 22 h of analgesia.

Despite the concern surrounding the 'off-label' use of perineural adjuvants,[24] the safety profile of dexamethasone is promising. No trial has reported neurotoxicity attributable to dexamethasone, although sample sizes to date are insufficient to detect rare outcomes and most studies did not follow patients for weeks after surgery. In our study, with no adverse events detected in 108 patients given dexamethasone, the 95% CI for neurotoxicity is 0–3%. To conclusively demonstrate safety with low event rates would require enormous sample sizes. For example, to demonstrate a doubling of the baseline complication rate of 0.4% with 90% power, a total sample size of roughly 16 000 patients would be required.

Reassuringly, though, animal studies demonstrate no long-term changes in nerve structure or function after local steroid administration.[25] From a mechanistic point of view, toxicity attributed to corticosteroids may in fact be due to the particulate nature[26] or vehicle used[27] in different steroid preparations—neither of which applies to the formulation of dexamethasone (dexamethasone sodium phosphate) we used. Additionally, corticosteroids have a long history of safe use in the epidural space for the treatment of radicular pain arising from nerve root irritation[28] and dexamethasone specifically has been studied as an adjuvant to epidural local anaesthetics.[23] The neurological risk, if any, of dexamethasone thus appears to be small. In fact, the use of dexamethasone as an adjunct to local anaesthesia for nerve blocks is discussed in prominent textbooks.[29][30]

Systemic toxicity from a single dose of dexamethasone is also unlikely. It is effective[31] and widely administered i.v. by anaesthesiologists for prophylaxis against postoperative nausea and vomiting. Concerns about steroid-induced hyperglycaemia have been borne out in high-dose i.v. regimens,[32]

but have not been problematic in our practice (American Society of Anesthesiologists Annual Meeting, October 2009, Abstract A955).

Perineural glucocorticoids are eventually absorbed and exert systemic effects. Given i.v., several steroids have been shown to improve postoperative pain and reduce postoperative nausea and vomiting.[33–36] Any systemic analgesic effect, however, should be minimal due to slow systemic uptake: a human volunteer trial of intercostal bupivacaine and dexamethasone microsphere injection resulted in negligible blood dexamethasone levels.[17] Nonetheless, it remains possible—although unlikely—that some or even all of the block prolongation we observed could have been obtained by i.v. injection of dexamethasone.

One might question the relative potency of the two local anaesthetics used in this trial. Opinions differ regarding the potency of ropivacaine relative to bupivacaine. Although ropivacaine may be less potent for spinal anaesthesia, there is reasonable evidence that the two drugs are at least roughly comparable for peripheral nerve blocks.[37 38] Possibly explaining some of the confusion in this area, Kee[39] and colleagues studied dose–response curves of the two drugs in the epidural space for labour analgesia. They found that the ED_{50} ratio for bupivacaine:ropivacaine is 0.75. However, for ED_{90}, an endpoint most clinicians find more useful, there was no difference between the drugs. Thus, at the higher concentrations used in this study, potency is probably comparable.

We also allowed the anaesthesiologists performing the blocks to use either ultrasound or nerve stimulation techniques. As noted previously, there was no appreciable difference in block duration between the two techniques. If there were a large difference in the number of failed blocks, this might bias the results of the trial. The small number of failed blocks (ultrasound: 3/147, nerve stimulation: 4/71) are consistent with generally accepted success rates and preclude any meaningful analysis.

Because general anaesthesia was used during these surgeries, intraoperative opioids were allowed to blunt the haemodynamic response to intubation. Compared with the primary outcome of at least 12 h, the duration of action of these intraoperative drugs (principally fentanyl) would be negligible. Thus, this should not significantly affect our results.

Owing to the majority of our patients being discharged before the third postoperative day, our ability to measure opioid consumption by day was limited. Hence, we were only able to compare 72 h opioid use between groups. Given the difference in VRS pain scores, it is quite plausible that there were differences on postoperative day 1 that were obscured by later opioid use. We also did not examine the duration of motor block as many of our patients are discharged home after surgery and resolution of weakness is too subjective to document in the absence of direct evaluation.

In summary, dexamethasone prolonged analgesia from interscalene blocks using ropivacaine or bupivacaine, with the effect being stronger with ropivacaine. However, block duration was longer with plain bupivacaine than ropivacaine. Thus, although dexamethasone prolonged the action of ropivacaine more than that of bupivacaine, the combined effect of dexamethasone and either drug produced nearly the same 22 h of analgesia. This trial is the largest to date and the first to demonstrate a difference in block prolongation between local anaesthetics. Although the toxicity profile of dexamethasone is promising, large studies will be necessary to demonstrate its safety for perineural use.

Acknowledgements

Conflict of interest

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References

1 Rawal N, Hylander J, Nydahl PA, Olofsson I, Gupta A. Survey of postoperative analgesia following ambulatory surgery. *Acta Anaesthesiol Scand* 1997; **41**: 1017–22

2 Hadzic A, Williams BA, Karaca PE, *et al.* For outpatient rotator cuff surgery, nerve block anesthesia provides superior same-day recovery over general anesthesia. *Anesthesiology* 2005; **102**: 1001–7

3 Andan T, Elif AA, Ayse K, Gulnaz A. Clonidine as an adjuvant for lidocaine in axillary brachial plexus block in patients with chronic renal failure. *Acta Anaesthesiol Scand* 2005; **49**: 563–8

4 Duma A, Urbanek B, Sitzwohl C, Zimpfer M, Kapral S. Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study. *Br J Anaesth* 2005; **94**: 112–6

5 Karakaya D, Buyukgoz F, Baris S, Guldogus F, Tur A. Addition of fentanyl to bupivacaine prolongs anesthesia and analgesia in axillary brachial plexus block. *Reg Anesth Pain Med* 2001; **26**: 434–8

6 Fanelli G, Casati A, Magistris L, *et al.* Fentanyl does not improve the nerve block characteristics of axillary brachial plexus anesthesia performed with ropivacaine. *Acta Anaesthesiol Scand* 2001; **45**: 590–4

7 Clerc S, Vuillermier H, Frascarolo P, Spahn DR, Gardaz J. Is the effect of inguinal field block with 0.5% bupivacaine on postoperative pain after hernia repair enhanced by addition of ketorolac or S(+) ketamine? *Clin J Pain* 2005; **21**: 101–5

8 Noyan A. On effects of ketamine to axillary block in hand surgery. *J Reconstr Microsurg* 2002; **18**: 197

9 Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. *Can J Anaesth* 2005; **52**: 822–6

10 Colombo G, Padera R, Langer R, Kohane DS. Prolonged duration local anesthesia with lipid-protein-sugar particles containing bupivacaine and dexamethasone. *J Biomed Mater Res A* 2005; **75**: 458–64

11 Drager C, Benziger D, Gao F, Berde CB. Prolonged intercostal nerve blockade in sheep using controlled-release of bupivacaine and dexamethasone from polymer microspheres. *Anesthesiology* 1998; **89**: 969–79

12 Movafegh A, Razazian M, Hajimaohamadi F, Meysamie A. Dexamethasone added to lidocaine prolongs axillary brachial plexus blockade. *Anesth Analg* 2006; **102**: 263–7

13 Parrington SJ, O'Donnell D, Chan VWS, *et al.* Dexamethasone added to mepivacaine prolongs the duration of analgesia after supraclavicular brachial plexus blockade. *Reg Anesth Pain Med* 2010; **35**: 422–6

14 Shrestha BR, Maharjan SK, Tabedar S. Supraclavicular brachial plexus block with and without dexamethasone—a comparative study. *Kathmandu Univ Med J* 2003; **1**: 158–60

15 Vieira PA, Pulai I, Tsao GC, Manikantan P, Keller B, Connelly NR. Dexamethasone with bupivacaine increases duration of analgesia in ultrasound-guided interscalene brachial plexus blockade. *Eur J Anaesthesiol* 2010; **27**: 285–8

16 Attardi B, Takimoto K, Gealy R, Severns C, Levitan ES. Glucocorticoid induced up-regulation of a pituitary K^+ channel mRNA in vitro and in vivo. *Receptors Channels* 1993; **1**: 287–93

17 Kopacz DJ, Lacouture PG, Wu D, Nandy P, Swanton R, Landau C. The dose response and effects of dexamethasone on bupivacaine microcapsules for intercostal blockade (T9 to T11) in healthy volunteers. *Anesth Analg* 2003; **96**: 576–82

18 Winnie AP. Interscalene brachial plexus block. *Anesth Analg* 1970; **49**: 455–66

19 Wiener DN, Speer KP. The deltoid sign. *Anesth Analg* 1994; **79**: 192

20 American Pain Society. *Principles of Analgesic Use in the Treatment of Acute and Cancer Pain*, 5th Edn. Glenview, IL: American Pain Society, 2003

21 Casati A, Fanelli G, Albertin A, *et al.* Interscalene brachial plexus anesthesia with either 0.5% ropivacaine or 0.5% bupivacaine. *Minerva Anestesiol* 2000; **66**: 39–44

22 Hwang IK, Shih WJ, De Cani JS. Group sequential designs using a family of type I error probability spending functions. *Stat Med* 1990; **9**: 1439–45

23 Khafagy H, Refaat A, El-sabae H, Youssif M. Efficacy of epidural dexamethasone versus fentanyl on postoperative analgesia. *J Anesth* 2010; **24**: 531–6

24 Neal JM, Rathmell JP, Rowlingson JC. Publishing studies that involve 'Off-label' use of drugs: formalizing regional anesthesia and pain medicine's policy. *Reg Anesth Pain Med* 2009; **34**: 391–2

25 Johansson A, Dahlin L, Kerns JM. Long-term local corticosteroid application does not influence nerve transmission or structure. *Acta Anaesthesiol Scand* 1995; **39**: 364–9

26 Benzon HT, Chew T-L, McCarthy RJ, Benzon HA, Walega DR. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. *Anesthesiology* 2007; **106**: 331–8

27 Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG. The effect of polyethylene glycol on mammalian nerve impulses. *Anesth Analg* 1987; **66**: 553–9

28 Price C, Arden N, Coglan L, Rogers P. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess* 2005; **9**: 1–58

29 Williams BA, Neumann KJ, Goel SK, Wu C. Postoperative pain and other acute pain syndromes. In: Benzon HT, Rathmell JP, Wu CL, Turk DC, Argoff CE, eds. *Raj's Practical Management of Pain*, 4th Edn. Philadelphia: Mosby Elsevier, 2008

30 Racz GB, Noe CL. Pelvic spinal neuraxial procedures. In: Raj P, Lou L, Serdar E, *et al.*., eds. *Interventional Pain Management*, 2nd Edn. Philadelphia: Saunders, 2008

31 Apfel CC, Korttila K, Abdalla M, *et al.* A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**: 2441–51

32 Pasternak JJ, McGregor DG, Lanier WL. Effect of single-dose dexamethasone on blood glucose concentration in patients undergoing craniotomy. *J Neurosurg Anesthesiol* 2004; **16**: 122–5

33 Bisgaard T, Klarskov B, Kehlet H, Rosenberg J. Preoperative dexamethasone improves surgical outcome after laparoscopic cholecystectomy: a randomized double-blind placebo-controlled trial. *Ann Surg* 2003; **238**: 651–60

34 Nagelschmidt M, Fu ZX, Saad S, Dimmeler S, Neugebauer E. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. *Eur J Surg* 1999; **165**: 971–8

35 Aasboe V, Raeder JC, Groegaard B. Betamethasone reduces postoperative pain and nausea after ambulatory surgery. *Anesth Analg* 1998; **87**: 319–23

36 Kardash KJ, Sarrazin F, Tessler MJ, Velly AM. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. *Anesth Analg* 2008; **106**: 1253–7

37 Casati A, Putzu M. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? *Best Pract Res Clin Anaesthesiol* 2005; **19**: 247–68

38 Casati A, Fanelli G, Magistris L, Beccaria P, Berti M, Torri G. Minimum local anesthetic volume blocking the femoral nerve in 50% of cases: a double-blinded comparison between 0.5% ropivacaine and 0.5% bupivacaine. *Anesth Analg* 2001; **92**: 205–8

39 Kee WDN, Ng FF, Khaw KS, Lee A, Gin T. Determination and comparison of graded dose-response curves for epidural bupivacaine and ropivacaine for analgesia in laboring nulliparous women. *Anesthesiology* 2010; **113**: 445–53