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

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Background. Interscalene brachial plexus block (ISB) provides excellent, but time-limited analgesia. Dexamethasone added to local anaesthetics prolongs the duration of a single-shot ISB. However, systemic glucocorticoids also improve postoperative analgesia. The hypothesis was tested that perineural and i.v. dexamethasone would have an equivalent effect on prolonging analgesic duration of an ISB.

Methods. We performed a prospective, double blind, randomized, placebo-controlled study. Patients presenting for arthroscopic shoulder surgery with an ISB were randomized into three groups: ropivacaine 0.5% (R); ropivacaine 0.5% and dexamethasone 10 mg (RD); and ropivacaine 0.5% with i.v. dexamethasone 10 mg (RDiv). The primary outcome was the duration of analgesia, defined as the time between performance of the block and the first analgesic request. Standard hypothesis tests (t-test, Mann–Whitney U-test) were used to compare treatment groups. The primary outcome was analysed by Kaplan–Meier survival analysis with a log-rank test and Cox’s proportional hazards regression.

Results. One hundred and fifty patients were included after obtaining ethical committee approval and patient informed consent. The median time of a sensory block was equivalent for perineural and i.v. dexamethasone on the duration of ropivacaine analgesia.

Conclusions. I.V. dexamethasone is equivalent to perineural dexamethasone in prolonging the analgesic duration of a single-shot ISB with ropivacaine. As dexamethasone is not licensed for perineural use, clinicians should consider i.v. administration of dexamethasone to achieve an increased duration of ISB.

Keywords: anaesthetic techniques, i.v. regional; anaesthetic techniques, regional, brachial plexus; anaesthetics local, ropivacaine; analgesia, postoperative; analgesics anti-inflammatory, steroid

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Shoulder surgery can be very painful surgery after which the use of opioids is often required. The well-known side-effects of opioids (e.g. respiratory depression, somnolence, nausea, vomiting, and pruritus) limit their use in so called ‘fast track’ surgery and anaesthesia programmes. ISB provides excellent analgesia minimizing the side-effects of opioids and is widely accepted as the gold standard in the management of acute pain after shoulder surgery.1

Although a single-shot ISB is useful for pain relief in the early postoperative period, it is often insufficient as postoperative pain can persist for several days. For patients requiring analgesia for >24 h, a continuous ISB (CISB) can be

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used. The placement of a CISB is more invasive and complex than a single-shot ISB and requires an extensive postoperative follow-up. As there is a trend towards shorter hospital admissions after arthroscopic shoulder surgery, CISB has been promoted in the ambulatory setting. However, the practical problems of the postoperative follow-up limit the use of CISB in an outpatient setting.

The use of additives to local anaesthetics can prolong the duration of a single-shot ISB which can be useful when a CISB is not possible. Various additives such as vasoconstrictors, clonidine, ketamine, and steroids have been studied, but most of them failed to prolong the duration of peripheral nerve blocks. Cummings and colleagues observed a 1.9-fold and 1.5-fold increase in the duration of ISB when dexamethasone was added to ropivacaine and bupivacaine, respectively. Whether the main mechanism of action of glucocorticoids is a systemic anti-inflammatory effect or a local effect on peripheral nerves remains unknown.

We hypothesized that dexamethasone prolongs analgesia after a single-shot ISB regardless of the route of administration. We, therefore, conducted a prospective, double blind, randomized, placebo-controlled study to evaluate the effect of i.v., and perineural dexamethasone on the duration of a single-shot ISB with ropivacaine 0.5% for postoperative analgesia after shoulder surgery.

Methods

The trial was registered on clinicaltrials.be (#B396201110645). The AZ Groeninghe Institutional Review board approved all aspects of the trial (#11 009, 16/02/2011, Chairman Dr. L. Van Lysebeth). The Federal Agency of Medicines and Health Products has been informed regarding the study protocol with the ‘off-label’ use of dexamethasone. It did not request an Investigational New Drug approval. Written informed consent was obtained from all patients. All patients planned for arthroscopic shoulder surgery (rotator cuff repair and shoulder decompressions) were eligible for inclusion in the study. Exclusion criteria were: age <18 yr, brachial plexus neuropathies, severe bronchopulmonary disease, coagulopathies, systemic glucocorticoid use, pregnancy, routine use of opioid medications, intolerance for one or more medications of the study protocol and diabetes. All the patients were operated by the same surgeon (J.V.C.) and the ISB was performed by experienced staff anaesthetists, with at least 10yr experience with interscalene blocks.

Using a computer generated random number table, patients were randomized in three-treatment groups: ropivacaine 0.5% (Group R), ropivacaine 0.5% and perineural dexamethasone 10 mg (Group RD), and ropivacaine 0.5% with i.v. dexamethasone 10 mg (Group RDiv). Sealed opaque envelopes with the study group allocation were opened before the blocks were performed. Medication was prepared by a staff member who was not involved in the study and delivered in unidentifiable syringes.

Patients were premedicated with lorazepam 2.5 mg p.o. 1h before the surgical procedure, monitored with electrocardiography, pulse oximetry and non-invasive arterial pressure, and sedated with i.v. midazolam (2 mg) and sufentanil (2.5 μg).

After skin disinfection and infiltration with lidocaine 1%, the interscalene brachial plexus was identified using a short bevel 50 mm, 22 gauge stimulating needle (Stimuplex A; B. Braun Melsungen AG, Germany) connected to a Stimuplex (Stimuplex-HNS II A; B. Braun Melsungen AG, Germany) nerve stimulator. The initial setting was a current of 0.8 mA with a stimulating frequency of 2 Hz. The direction of the needle was similar as in the modified lateral approach of Borgeat and Ekatodramis was applied in all patients. Contractions of the biceps, triceps, or any muscle contraction of the hand or forearm with a current of 0.3–0.5 mA indicated correct placement of the needle. A 2 ml solution containing normal saline for Groups R and RD and 10 mg dexamethasone for Group RD was administered perineurally. Then, without repositioning the needle, all patients received 30 ml ropivacaine 0.5%. At the time of the ISB, a 2 ml solution containing normal saline for Groups R and RD and dexamethasone 10 mg for Group RDiv was administered i.v. Thus, all patients received an ISB with 30 ml of ropivacaine 0.5% with an i.v. and perineural solution of 2 ml containing the study drugs according to randomization.

All brachial plexus injections were administered slowly with repeated aspiration to prevent or detect early intravascular injection.

General anaesthesia was induced and maintained using propofol (target controlled infusion 3–5 μg ml⁻¹), remifentanil (loading dose 1 μg kg⁻¹, continuous infusion 0.05–0.3 μg kg⁻¹ min⁻¹), and cisatracurium (0.15 mg kg⁻¹). Patients were intubated and ventilated with an oxygen/air admixture. Maintenance of anaesthesia was left to the discretion of the attending anaesthesiologist. Intraoperatively, no other analgesics were administered. At the beginning of the procedure finger stick blood glucose was measured.

On arrival in the recovery room pain was evaluated using a 4-point verbal rating score (VRS) (1=no pain, 2=mild pain, 3=moderate pain, and 4=severe pain). Paracetamol i.v. (1 g) was administered for VRS≥2 or on patient request. In case of insufficient analgesia, diclofenac i.v. (50 mg) was administered. Rescue analgesia with piritramide i.m. (15–20 mg) was administered if necessary. Piritramide is a synthetic opioid with relatively fast onset after i.m. administration (15–20min) with the duration of action of 4–6h. It has a relative potency of 0.7 compared with morphine. A motor block was evaluated using a 3-point motor block score (MBS) (1=unable to move fingers, 2=able to move fingers but weaker than the non-operated arm, and...
Categorical variables were assessed using frequency tables and a MBS of 3 on arrival in the recovery room the ISB was qualified as failed.

Recovery room discharge criteria were stable vital parameters, absence of nausea and vomiting, and a VRS<2. VRS, MBS, and blood glucose concentrations were assessed upon recovery room discharge.

The morning after surgery, all patients were reassessed for pain, motor block, and overall satisfaction. The timing and dosage of analgesics was recorded and also the quality of sleep (1=no sleep disturbance because of pain, 2=sleep disturbance because of pain). Patients were contacted by telephone on Day 2 after surgery to evaluate the same parameters. Patient satisfaction concerning the procedure was assessed using a 2-point scale (1=satisfied, 1 would want the same anaesthesia/analgesia method for the next surgery, 2=unsatisfied, 1 would want a different anaesthesia/analgesia method for the next surgery). Specific reasons for dissatisfaction were noted. A telephone assessment 3–4 months after surgery was performed to detect late complications. All postoperative scoring was performed by an independent, blinded investigator.

Sample size considerations
At the time of our study, no studies were published concerning the effect of dexamethasone on interscalene plexus blocks with ropivacaine. Based on our experience with ropivacaine 0.5%, we assumed a block duration of 720 min with a standard deviation (sd) of 500 min. A difference of 360 min between the treatment and the control group was considered clinically relevant and a sample size (power=90% and α=0.05) of 42 patients per group was calculated (two-sample t-test). To correct for failed blocks and patient drop out, 50 patients per group were included in the study.

Statistical analysis
The primary endpoint was the length of the sensory block defined as the time between the performance of the block and the first administration of analgesia. Secondary outcomes were pain scores, MBSs, analgesic need, sleep disturbance, and overall satisfaction as measures for patient comfort. Finally, pre- and postoperative blood glucose measures were analysed and compared between groups. Descriptive statistics are used to present baseline characteristics for the three groups. Standard hypothesis tests (t-test, Mann–Whitney U-test) were used to compare these baseline values between treatment groups. Continuous variables were assessed for normality and are presented as mean (sd) or median with interquartile range (IQR) as appropriate. Categorical variables were assessed using frequency tables and χ² or Fisher’s exact test. The interval between the onset of the sensory block and the initial use of analgesia was analysed by Kaplan–Meier survival analysis with a log-rank test and Cox’s proportional hazards regression to estimate likelihood ratios adjusted for covariates. The primary analysis is the comparison between survival curves. All other statistical tests are secondary and performed at the 5% significance level, without correction for multiple testing, and should be interpreted accordingly.

All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC, USA).

Results
From March to December 2011, 234 patients presented for arthroscopic shoulder surgery, 84 were ineligible because of exclusion criteria or refusal to participate, and 150 patients were enrolled in the study. Six patients had no primary or secondary outcome result because of inadherence to the protocol. These patients were not included in the intention-to-treat (ITT) analysis. Figure 1 presents the allocation process according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

A total of 144 patients were included for the ITT analysis (Group R n=46, Group RD n=49, Group RD iv n=49). Five patients, evenly distributed over the three study groups (Group R n=2, Group RD n=1, Group RD iv n=2) were deemed to have failed blocks, but were analysed in their assigned groups according to ITT principles. These patients were given the outcome at the time of recovery. Eleven patients did not require analgesics during the first 48 h after operation (no primary outcome). These patients were also evenly distributed over the three study groups (Group R n=2, Group RD n=4, Group RD iv n=5, respectively) and were censored in the survival analysis. The mean age of the study population was 52 (14) yr, the mean body mass index (BMI) was 27.2 (4.4), and 45% were men. There were significantly more cuff repairs in men than in women (78.9 vs 59.5%, P=0.002) but the different procedures were equally distributed in the three groups (Table 1).

Dexamethasone significantly prolonged the duration of analgesia, independent of the mode of administration. In Group R, the primary endpoint of the study was reached after a median of 757 min with an IQR of 635–910 min, for Groups RD and RDiv this was 1405 (1015–1710) and 1275 (1095–2035), respectively. Kruskal–Wallis followed by the correction for multiple testing showed statistically significant differences between Groups R and RD (P<0.0001), Groups R and RDiv (P<0.0001), but not between Groups RD and RDiv. Kaplan–Meier curves for the first analgesic request with patients not receiving any analgesics after 48 h censored to the right are presented in Figure 2. Significant differences between these curves (log-rank test) were obtained between Group R and the combined groups RD and RDiv (P<0.0001), but not between Groups RD and RDiv (P=0.6254).

A Cox proportional hazards model for time to first analgesic was performed using the following variables: study group, sex, age, and type of surgery. Patients included in Group R had a 3.91 times (95% CI 2.63–5.81) higher probability for analgesic need during the first 48 h compared with patients in Groups RD and RDiv (P<0.0001). None of the other variables differed significantly.
When pain scores were dichotomized in VRS scores 1 and 2 (no to mild pain) vs VRS scores 3 and 4 (moderate to severe pain), there was a significant difference between groups after 24 and 48 h \((P < 0.0001)\) (Figs 3 and 4).

There was a statistically significant difference in analgesic use in the three groups. We only present the data for paracetamol and diclofenac as only seven patients needed opioids. Of note is that five of these patients had blocks that were qualified as failed. The mean paracetamol use (in gram) in Group R was 3.8 compared with 2.6 in Group RD and 2.3 in Group RDiv during the first 48 h \((P = 0.0001)\). The mean diclofenac use after 48 h was also significantly different: 101 mg for Group R compared with 59 and 56 mg for Group RD and RDiv \((P = 0.03)\).

There was no significant difference in MBS in the three groups on admission in the post anaesthesia care unit, and at 24 and 48 h.

During the first night, there was a significant higher proportion of patients with sleep disturbance because of pain in Group R (59%) compared with Group RD (29%) and Group RDiv (22%) \((P = 0.0004)\). Overall satisfaction for the three groups was excellent: 85–98% of the patients would like a similar anaesthesia and analgesia protocol for future shoulder surgery (Table 2).

There was an increase of mean postoperative blood glucose concentrations in both groups receiving dexamethasone with a mean increase of 3.8 (1.2) mg dl\(^{-1}\) for Group RD \((P = 0.026)\) and 5.1 (13) mg dl\(^{-1}\) \((P = 0.0095)\) for Group RDiv. There were no differences in the incidence of hoarseness, dyspnoea, or Horner’s syndrome after operation.

Patients were contacted 2–6 months after surgery. There was one patient in Group RD who complained of hypoaesthesia in the deltoid region 4 months after surgery. However, neurological and radiological examination revealed spinal disc herniation at the level of C4–5 with a disc-radicular conflict. One patient in Group R had a superficial wound infection requiring no further therapy but local incision and drainage.

**Discussion**

The present study demonstrates that dexamethasone effectively prolongs the duration of ropivacaine ISB analgesia. There is, on average, a 1.8-fold increase in the duration of analgesia when dexamethasone is used as an adjunct to ropivacaine 0.5%. This is concordant with other results in the literature.\(^8\) \(^9\) \(^12\) \(^13\) Interestingly, this effect is independent of the route of administration as both perineural and i.v.
administration of dexamethasone produced similar results. Not only the analgesia duration but also the quality of analgesia indicated by outcome measures such as sleep disturbance and postoperative analgesic use were favourably influenced by dexamethasone.

Acute postoperative pain has different components (e.g. nociceptive, inflammatory, and neuropathic because of direct nerve injury) all of them possible targets for postoperative analgesic strategies. The precise mechanism of action of dexamethasone added to local anaesthetics is unknown. Some studies described a direct effect of glucocorticoids on nerve conduction while others reported that dexamethasone induced perineural vasoconstriction with concomitant slower absorption of the administered local anaesthetics. However, such effects of dexamethasone do not explain the results of our study as the systemic
The administration of dexamethasone was equally effective. This interesting observation is in accordance with the work of Yilmaz and colleagues, who could not detect an effect of dexamethasone on the compound action potential of A- and C-fibres in isolated sciatic rat nerves. As a direct effect of dexamethasone on the nerve is unlikely, the anti-inflammatory properties of dexamethasone are probably responsible for prolonged analgesia after ISB. After intracellular uptake, glucocorticoids will activate cytoplasmatic glucocorticoid receptors which will bind to glucocorticoid response elements in the DNA. This leads to both a decreased production of inflammatory proteins (COX-2, iNOS, cytoplasmatic PLA2, interleukins (ILs), inflammatory chemokines, etc.), and an increased production of anti-inflammatory proteins (lipocortin-1 (IL-1) receptor antagonist).

To our knowledge, there are no pharmacokinetic data on the absorption of perineurally administered dexamethasone. Because absorption in the systemic circulation and gene transcription is time consuming, one could argue that clinically relevant anti-inflammatory effects of steroids, would come too late after perineural administration with short-acting local anaesthetics. However, Movafegh and colleagues demonstrated that dexamethasone also prolongs the duration of an axillary block when added to lidocaine (242 vs 98 min). This proves that perineural dexamethasone has a clinical effect within 2 h of administration. Therefore, we should aim further research towards the ideal dose and timing of dexamethasone administration.

We acknowledge that our study has some limitations. First, we did not assess the duration of the sensory block in our patients using repeated neurological examinations. As most patients were treated in an ambulatory setting, it was impossible to perform such an assessment of the sensory block. We, therefore, decided to use the duration until first analgesic request as a marker of the sensory block. With our study protocol, we were unable to discriminate if the prolonged analgesia was associated with a

![Graph](image)

**Table 2** Secondary outcome parameters

<table>
<thead>
<tr>
<th></th>
<th>Group R (n=46)</th>
<th>Group RD (n=49)</th>
<th>Group RDiv (n=49)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean paracetamol use (g) at 48 h</td>
<td>3.8</td>
<td>2.6</td>
<td>2.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean diclofenac use (mg) at 48 h</td>
<td>101</td>
<td>59</td>
<td>56</td>
<td>0.03</td>
</tr>
<tr>
<td>Patients with residual motor block at 24 h (n)</td>
<td>1/46</td>
<td>5/49</td>
<td>3/49</td>
<td>NS</td>
</tr>
<tr>
<td>Sleep disturbance at 24 h (n)</td>
<td>27/46</td>
<td>14/49</td>
<td>11/49</td>
<td>0.004</td>
</tr>
<tr>
<td>Percentage of patients satisfied</td>
<td>84</td>
<td>92</td>
<td>94</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of Horner syndrome (%)</td>
<td>45</td>
<td>48</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of hoarseness (%)</td>
<td>30</td>
<td>23</td>
<td>23</td>
<td>NS</td>
</tr>
<tr>
<td>Incidence of dyspnoea (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
prolongation of the sensory block. Although a point deserving further study, it is irrelevant for daily practice. Indeed, for patients, pain is the most important parameter to define satisfaction after surgery.

Secondly, we did not use ultrasound (US) to perform ISB. At the time of the study, we considered our experience with US-guided locoregional anaesthesia insufficient to use a US-based technique. The success rate of our blocks was 97%, which is similar to that reported in the literature.18 We assume that our study results would not have been different with the use of US.19

Thirdly, analgesics were only administered on request and a postoperative regimen with regular analgesic administration might have impacted our secondary outcomes. Such a regimen is often not easy to implement in an ambulatory setting. We think that our study better represents routine clinical practice where patient adherence to pain protocols can be surprisingly low. The overall opioid use in our study groups was very low. In contrast, all patients with failed blocks needed opioids in addition to paracetamol and diclofenac for postoperative analgesia indicating severe postoperative pain emphasizing the efficiency of interscalene blocks in this setting.

Fourthly, there are safety concerns regarding the perineural use of dexamethasone. In the absence of human clinical trials, we can only rely on laboratory research. Williams and colleagues20 studied the effect of ropivacaine and different adjuvants on isolated sensory neurone cell bodies of rats. In contrast to ropivacaine, dexamethasone did not increase cell death after 24 h exposure. There was no increased neurone cell death after 2 h exposure to low-dose dexamethasone and ropivacaine compared with ropivacaine alone. Ma and colleagues21 reported on the protective effect of dexamethasone on bupivacaine-induced neurone injury in rats through a threonine-serine protein kinase B-dependent mechanism. When the electrophysiological, behavioural and histological effects of topical dexamethasone on sciatic nerve in rats was studied, it was discovered that although dexamethasone temporarily attenuated conduction, it had no significant long term effects.14

More than 250 patients received perineural dexamethasone as an adjunct to local anaesthetics in clinical trials. None of the clinical trials reported an increased incidence of serious adverse effects compared with the control groups but all were underpowered to detect an increase in the incidence of serious adverse effect.8–10 12 It is clear that with an incidence of 0.4%, 16 000 patients are needed to reliably detect a doubling of adverse effects.9 So far no safety trial on the use of perineural dexamethasone has been performed and it is highly unlikely that such a trial will ever be conducted. However, local, perineural steroid injection has been used for many years in the treatment of carpal tunnel syndrome and is acknowledged to be an effective and safe therapy.22 We should also caution to extrapolate in vitro and in vivo observations with regard to the possible neurotoxicity of dexamethasone. The isolation technique of neural cell bodies will inherently lead to neural damage, diminish the protective effects of the surrounding vasculature and fibrous tissues and is unable to study the effect on distal axons.18 Neurone isolation techniques commonly used to study detrimental effects of drugs may not fully appreciate the mechanisms of neural injury after peripheral nerve blocks. In clinical practice, neurological damage is the result of multiple factors where there is a complex interplay between neurotoxicity of administered drugs, puncture technique and possible pre-existing neural injury.23

Regarding the inconclusive data on the safety of perineural dexamethasone, we would like to remind clinicians that this ‘off-label’ use needs approval of the appropriate regulatory health institutions. Fortunately, with the results of our trial the debate on the perineural administration of dexamethasone may become obsolete.

In conclusion, this study demonstrates that perineural or i.v. dexamethasone in a dose of 10 mg prolongs significantly the duration of effective postoperative analgesia resulting from a single-shot ISB with ropivacaine 0.5%. We, therefore, propose that i.v. dexamethasone should be considered for routine use in patients having regional analgesia for the postoperative pain management.

Declaration of interest

None declared.

References


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