Dose-dependency of dexamethasone on the analgesic effect of interscalene block for arthroscopic shoulder surgery using ropivacaine 0.5%

A randomised controlled trial

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BACKGROUND Dexamethasone prolongs the duration of single-shot interscalene brachial plexus block (SISB). However, dose-dependency of dexamethasone as an adjuvant for SISB remains insufficiently understood.

OBJECTIVE The objective of this study is to evaluate the effect of different doses of dexamethasone on the duration of SISB using ropivacaine 0.5%.

DESIGN A randomised, double-blind controlled trial.

SETTING Single university tertiary care centre.

PATIENTS One hundred and forty-four patients scheduled for elective arthroscopic shoulder surgery were allocated randomly to one of four groups.

INTERVENTIONS Patients received 12 ml of ropivacaine 0.5% in 0.9% saline (control group), or containing dexamethasone 2.5, 5.0 or 7.5 mg for SISB.

MAIN OUTCOME MEASURES The primary endpoint was the time to the first analgesic request. Pain scores and adverse effects were also assessed up to 48 h postoperatively.

RESULTS Inclusion of dexamethasone 2.5, 5.0 and 7.5 mg resulted in significant ($P < 0.001$) increases in time to the first analgesic request by factors of 1.6, 2.2 and 1.8, respectively. The percentages of patients not requiring analgesics in the first 48 h postoperatively with dexamethasone 0.0, 2.5, 5.0 and 7.5 mg were 3, 22, 39 and 33%, respectively ($P < 0.001$). There were no significant effects on pain scores or incidences of adverse effects.

CONCLUSION Dexamethasone demonstrated significant beneficial dose-dependent effects on duration to the first analgesic request, the number of patients not requiring analgesics and analgesic use in the first 48 h after SISB for arthroscopic shoulder surgery. There were no significant effects on pain scores or incidences of adverse effects.

TRIAL REGISTRATION The trial was registered with the Clinical Trial Registry of Korea: https://cris.nih.go.kr/cris/index.jsp. Identifier: KCT0001078

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prolonging the duration of SISB have proved unsatisfactory. However, dexamethasone has been found to extend the duration of SISB-induced analgesia significantly.7–10 The doses of dexamethasone have varied in different studies such that the dose–dependency relationship on the duration of sensory block with ropivacaine SISB remains unknown. Until now, most studies concerning SISB have used relatively large volumes of local anaesthetic, although they combined general anaesthesia and SISB for ASS.7–11 In the present study, we used 12 ml of ropivacaine 0.5% based on our experience of more than 5 years and on previous results.12,13 In this double-blind, randomised and prospective trial, we investigated the effects of different doses of dexamethasone as a perineural adjuvant on the duration of analgesia induced by ropivacaine SISB.

Patients and methods
Ethical approval for the study (ECT 13-43A-29) was provided by the local ethics committee of Ewha Womans University, Seoul, Korea (Chairperson, Professor W.B. Pyun) on 18 December 2013. The trial was registered with the Clinical Trial Registry of Korea with an assigned number of KCT0001078, and written informed consent was obtained from all patients. Patients aged 20 to 70 years with American Society of Anaesthesiologists’ (ASA) physical status 1 or 2, scheduled for elective ASS, were enrolled. Exclusion criteria were patient refusal, presence of coagulopathy, infection at the site of the block, any neurological deficit in the surgical limb, severe lung disease, contralateral diaphragmatic paralysis, systemic glucocorticoid use, chronic opioid use, peptic ulcer disease, uncontrolled diabetes mellitus and a known allergy to ropivacaine.

A total volume of 12 ml study drug was made with the final concentration being ropivacaine 0.5%. Patients were allocated randomly to one of four groups to receive an injection of 12 ml of a solution containing 8ml of ropivacaine 0.75% (60 mg) and 4 ml of 0.9% saline or dexamethasone for SISB using a computer-generated randomisation table:

(1) ropivacaine 5 mg ml⁻¹ with 0.9% saline (control);
(2) ropivacaine 5 mg ml⁻¹ with dexamethasone 2.5 mg;
(3) ropivacaine 5 mg ml⁻¹ with dexamethasone 5.0 mg;
(4) ropivacaine 5 mg ml⁻¹ with dexamethasone 7.5 mg.

An anaesthesiologist blinded to the dose assignments prepared all of the study drugs. The patients and attending anaesthesiologists participating in the study were unaware of the dose assignments.

On arrival at the operating room, standard ASA monitors were used throughout the surgery. All patients received a standardised SISB under ultrasound guidance (SonoSite; M-Turbo; SonoSite; Bothell, Washington, USA). The blocks were performed by one experienced anaesthesiologist and were facilitated by sedation using intravenous midazolam (1 to 3 mg) and fentanyl (25 to 50 μg). The patient was placed in a supine position with the head turned away from the side to be blocked. Using a linear probe (5 to 12 MHz), hypoechic nerve roots or the superior trunk located between the anterior and middle scalene muscles were identified in the short-axis view. After sterile skin preparation, the point where the C5, C6 and C7 roots or superior trunk were most visible was selected. A 50-mm, 22 gauge insulated needle (Stimuplex A; B-Braun, Melsungen, Germany) was used, and the tip was advanced towards the C5 and C6 roots or superior trunk within the sheath using the in-plane method. After localisation and negative aspiration, all patients received SISB with 12 ml of the study solution according to the group allocation.

After intravenous injection of glycopyrronium 0.2 mg, general anaesthesia was induced using thiopentone 4 mg kg⁻¹ and fentanyl 1 to 2 μg kg⁻¹. Tracheal intubation was facilitated using racuronium 0.6 mg kg⁻¹. Anaesthesia was maintained using a 50% oxygen in air mixture and sevoflurane (1.0 to 1.5 minimum alveolar concentrations) to maintain the bispectral index value between 40 and 60 and SBP within 20% of the baseline value. Patients were placed in the lateral decubitus position, and all of the operations were performed by one surgeon. Patients were extubated in the operating room after reversal of residual muscle relaxation.

In the recovery room, patients were assessed by an anaesthesiologist for pain score, weakness, numbness and complications or side effects such as nausea, vomiting, dizziness, respiratory difficulties and Horner syndrome. The patients underwent chest radiography to rule out phrenic nerve palsy. A doctor blinded to the groups visited the patients and evaluated pain using a numerical rating scale (NRS; 0, no pain; 10, most severe pain imaginable) up to 48 h from the time of arrival in the recovery room. The patients were given i.v. tramadol 100 mg, up to three times a day when NRS was at least 3 or analgesia was requested. In the case of insufficient analgesia, patients were treated with i.v. ketorolac 30 mg up to 90 mg a day. Individual doses given were recorded.

Statistical analysis
The Statistical Package for the Social Sciences (SPSS; 18.0, Chicago, Illinois, USA) was used for statistical analysis. The primary endpoint was the time to the first analgesic request, defined as the interval between SISB and the first administration of analgesic. Secondary outcomes included the number of patients not requiring analgesics, analgesic use, pain scores and incidences of arm weakness, arm numbness and adverse effects for 48 h postoperatively. From our prior experience and that of Cummings et al.,8 we expected a block duration of 10 h with ropivacaine alone, and an 11-h difference between
the control and treatment groups was considered clinically significant. Therefore, a sample size of 32 patients ($\alpha = 0.05$, power = 80%) per group was calculated (log-rank test). Correction for dropouts suggested $n = 36$ patients per group. Continuous variables were analysed by analysis of variance or the Kruskal–Wallis test after assessment for normality and are presented as mean ± SD or as median and interquartile range (IQR) as appropriate. Categorical variables were analysed using the $\chi^2$ or Fisher exact tests. The time to the first analgesic request was analysed by Kaplan–Meier survival analysis with the log-rank test and the Cox proportional hazards model to estimate likelihood ratios adjusted for covariates. The Bonferroni correction was applied for three comparisons against the control group and the corrected $P$ values are presented. The secondary outcomes (number of patients who did not require analgesics, and the incidences of arm weakness, numbness and adverse effects) were analysed using linear-by-linear association $\chi^2$ test. Tramadol and ketorolac use and pain scores were analysed using the linear regression test after conversion to the van der Waerden normal scores because those data were not normally distributed. A $P$ value less than 0.05 was considered statistically significant.

**Results**

One hundred and fifty-nine patients were assessed for eligibility and 15 were ineligible because of the exclusion criteria or patient refusal; in total, 144 patients were included in the analysis. Figure 1 illustrates the allocation process according to the Consolidated Standards of Reporting Trials (CONSORT) statement. Baseline covariates were well balanced across the randomised groups (Table 1). Perioperative clinical details such as the pre-operative pain score, duration of operation and anaesthesia and type of surgery were distributed evenly among the four groups (Table 2).

Dexamethasone significantly (log-rank test $P < 0.001$) prolonged the duration of analgesia. Kaplan–Meier curves were used to measure the time to the first analgesic request during the first postoperative 48 h. In the control group, the time to first analgesic request was a median (IQR) of 11.0 (8.2 to 14.4) h. Compared with the control group, dexamethasone doses of 2.5, 5 and 7.5 mg resulted in times to first analgesic request of 17.3 (12.2 to 22.0) h ($P = 0.005$), 24.2 (15.8 to 49.8) h ($P < 0.001$) and 19.9 (15.5 to 49.6) h ($P < 0.001$), respectively. A Cox proportional hazards model for the time to the first analgesic request was performed including the following variables: dexamethasone dose, sex, age and type of surgery. None of the variables except dose of dexamethasone was significant (Fig. 2).

Table 3 summarises the pain scores and analgesic requirements during the first postoperative 48 h. There was a dose-dependent increase in the number of patients not requiring analgesics for the first postoperative 48 h with dexamethasone ($P < 0.001$). Likewise, there were dose-dependent reductions in the uses of tramadol ($P = 0.003$) and ketorolac ($P < 0.0001$) with dexamethasone. There were no dose-dependent effects on NRS at each time point. The other secondary outcomes are...
summarised in Table 4. There were no significant differences in the incidences of arm weakness, numbness or adverse effects including nausea, vomiting, dizziness, phrenic nerve palsy, Horner syndrome and hoarseness during the study period. During the second postoperative 24 h, arm weakness was observed in one patient who had received dexamethasone 2.5 mg and arm numbness was noted in three patients who had received 5 mg. However, all neurological signs had resolved by the following day. At day 14 of follow-up, no patient reported persistent symptoms such as weakness, paraesthesiae or numbness of the arm.

Discussion

Our results have shown that perineural dexamethasone significantly prolongs the analgesia induced by ropivacaine SISB and that this effect is dose-dependent. Although the most noticeable prolongation of analgesia was observed with dexamethasone 5 mg, there was a significant dose-dependent increase in the number of patients not requiring analgesics with dexamethasone. There was also a beneficial dose-dependent effect on analgesic use. This randomised study was designed to minimise possible biases by using a single anaesthesiologist and surgeon. The types of surgery were also distributed evenly among the groups. Furthermore, a Cox proportional hazards model revealed that the type of surgery did not affect our results.

Previous authors have performed SISB using 20 to 40 ml of 0.5 to 0.75% ropivacaine or bupivacaine for SISB, but we used 12 ml of ropivacaine 0.5% (60 mg) for SISB. In the study by Desmet et al., SISB was performed with 30 ml of ropivacaine 0.5% followed by general anaesthesia for ASS. They reported a high incidence of Horner syndrome and hoarseness, although the duration of analgesia and the amount of analgesics used were comparable with our results using a lower volume of ropivacaine 0.5%. No patient experienced Horner syndrome or hoarseness in our study. We evaluated doses of perineural dexamethasone up to 7.5 mg. In a previous study using SISB as surgical anaesthesia for ASS, Tandoc et al. used 40 ml of bupivacaine 0.5%. They found that doses of 4 and 8 mg of perineural dexamethasone prolonged sensory blocks to 21.6 ± 2.4 h and 25.2 ± 1.9 h, respectively, although these were not significantly different. This result is comparable with our study, which showed an analgesic duration of 24.2 (15.8 to 49.8) h with dexamethasone 5 mg and no further additional benefit with 7.5 mg.

The mechanisms behind the beneficial effect of dexamethasone and the route of administration remain to be determined. It has been suggested that the effect is mediated by direct blockade of transmission in nociceptive C-fibres, reducing the release of inflammatory mediators and ectopic neuronal discharge, and upregulation of potassium channels. Recently, the route of dexamethasone administration has been debated and several studies have reported that intravenous dexamethasone can produce opioid-sparing effects under various situations, and that there was no difference in the analgesic effect between perineural and systemic administration. This reduces the probability that dexamethasone exerts its action by a direct perineural effect. However, some evidence has suggested that dexamethasone exerts its activity via a perineural effect. Whereas a meta-analysis of 24 randomised trials suggested that a single dose of intravenous dexamethasone at doses less than 0.1 mg kg⁻¹ did not produce an opioid-sparing effect, even 2.5 mg of perineural dexamethasone prolonged the length of the sensory block in our study. Kawanishi et al. demonstrated that 4 mg of perineural dexamethasone as an adjuvant for SISB using 20 ml ropivacaine 0.75% produced a significant advantage over intravenous dexamethasone administration.

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
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<tr>
<td></td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>ASA physical status (1:2)</td>
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<tr>
<td>Values are mean ± SD or count.</td>
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</table>

Table 2 Perioperative data

<table>
<thead>
<tr>
<th></th>
<th>Saline 0.9% (n = 36)</th>
<th>Dex 2.5 mg (n = 36)</th>
<th>Dex 5 mg (n = 36)</th>
<th>Dex 7.5 mg (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative pain (NRS)</td>
<td>2.1 ± 1.4</td>
<td>2.3 ± 1.5</td>
<td>2.1 ± 1.5</td>
<td>2.8 ± 1.7</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>81.3 ± 30.7</td>
<td>79.2 ± 30.8</td>
<td>87.9 ± 49.4</td>
<td>79.3 ± 35.34</td>
</tr>
<tr>
<td>Anaesthetic time (min)</td>
<td>131.4 ± 35.7</td>
<td>131.5 ± 34.4</td>
<td>138.6 ± 52.1</td>
<td>130.8 ± 39.6</td>
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<tr>
<td>Surgery, n (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rotator cuff repair</td>
<td>29 (80.6)</td>
<td>26 (72.2)</td>
<td>24 (66.7)</td>
<td>26 (80.6)</td>
</tr>
<tr>
<td>Labral repair</td>
<td>7 (19.4)</td>
<td>9 (25.0)</td>
<td>8 (22.2)</td>
<td>10 (27.8)</td>
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<tr>
<td>Arthroscopic capsular release</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Greater tuberosity reconstruction</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (8.3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
| Values are mean ± SD or count (%). Data were similar among groups. Dex, dexamethasone; NRS, numerical rating scale.
There have been concerns about the use of perineural dexamethasone. Because trials require large sample sizes to come to reliable conclusions about safety in respect of extremely rare events, there is no alternative but to rely on the results of experimental studies. Several animal experiments have demonstrated no significant long-term adverse effects.\textsuperscript{20,21} Moreover, epidural injections of corticosteroids have long been used to treat radiculopathy and, to date, no clinical trial has reported any neurological complications attributed to dexamethasone.\textsuperscript{16} Neural injury can also be related to needle-induced direct trauma. In our study, we performed SISB under ultrasound guidance using the in-plane approach to minimise the risk of trauma to nerves. The appropriate spread of local anaesthetic within the sheath of the interscalene brachial plexus was ascertained during administration. Thus, local anaesthetics were allowed to spread with sufficient perfusion throughout the brachial plexus and SISB was achieved successfully in all patients without persistent neurological complications.

There are several limitations of the present study. First, our sample sizes are too small to discuss clinical or statistically significant differences between different dexamethasone doses. This study was also not designed to find the optimal dose of dexamethasone. Our results only confirm a significant beneficial dose-dependency with dexamethasone. Second, we focused on outcomes during the acute postoperative period and did not specifically evaluate long-term complication profiles. However, on the day of discharge and on day 14 of follow-up, no patient reported neurological complications. Third, we did not analyse changes in the postoperative blood glucose concentration. One study showed that the elevation of blood glucose after SISB using dexamethasone 10 mg was statistically significant but clinically irrelevant. Fourth, given the extremely low rate of persistent neurological complications and safety concerns with perineural dexamethasone use, further studies are warranted to clarify dexamethasone administration as an adjuvant.

| Pain intensity and analgesic requirements for the first postoperative 48 h |
|-----------------------------|-------------------|-------------------|-------------------|
| Patients not requiring analgesics* | Saline 0.9% (n = 36) | Dex 2.5 mg (n = 36) | Dex 5 mg (n = 36) | Dex 7.5 mg (n = 36) |
| Patients not requiring analgesics* | 1 (2.8%) | 8 (22.2%) | 14 (38.9%) | 12 (33.3%) |
| Tramadol use (n)** | 2 (1 to 3) | 1 (0 to 1) | 1 (0 to 1) | 1 (0 to 1) |
| NRS at 6 h | 1 (0 to 3) | 0 (0 to 1) | 0 (0 to 1) | 0 (0 to 2) |
| NRS at 12 h | 3 (1 to 4) | 1 (0 to 2) | 1 (0 to 3) | 1 (0 to 2) |
| NRS at 24 h | 2 (1 to 3) | 1 (0 to 3) | 2.5 (0.25 to 5) | 1.5 (1 to 4) |
| NRS at 48 h | 1 (0 to 2) | 0 (0 to 1) | 0 (0 to 2) | 0 (0 to 1) |

*Values are median (IQR) or count (percentage). There were no significant differences among groups. Data were similar among groups. Dex, dexamethasone; NRS, numerical rating scale. *P < 0.001 by linear-by-linear association \( \chi^2 \) test. **P < 0.05 by linear regression analysis using the van der Waerden normal scores.
In conclusion, we have shown that perineural dexamethasone has significant beneficial dose-dependent effects on the time to the first analgesic request, the number of patients not requiring analgesics and analgesic use during the first postoperative 48 h when added to 12 ml ropivacaine 0.5% for SISB in ASS.

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Conflict of interest: none.

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References