Dexamethasone Added to Mepivacaine Prolongs the Duration of Analgesia After Supraclavicular Brachial Plexus Blockade

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Background and objectives: Corticosteroids have been used successfully to prolong the duration of local anesthetic action after peripheral nerve and epidural blockade. We hypothesized that the addition of dexamethasone to mepivacaine would prolong the duration of analgesia after ultrasound-guided supraclavicular brachial plexus block for patients undergoing upper-limb surgery.

Methods: After Federal Health Department and institutional review board approval, 45 adult patients undergoing elective hand or forearm surgery under supraclavicular brachial plexus block were randomized to receive either 30 mL mepivacaine 1.5% plus dexamethasone 8 mg (4 mg/mL), or 30 mL mepivacaine 1.5% plus 2 mL normal saline. The primary outcome measure was duration of analgesia. Secondary outcomes included onset times of sensory and motor blockade, pain and satisfaction scores, analgesic consumption, and block-related complications.

Results: Patient characteristics were similar between groups. The median duration of analgesia was significantly prolonged in the Dexamethasone group (332 mins; interquartile range, 225–448 mins) compared with the Normal Saline group (228 mins; interquartile range, 207–263 mins; P = 0.008). The onset times of sensory and motor block were similar between the groups. Complications were minor and transient and did not differ between groups at 2 weeks postoperatively.

Conclusions: The addition of dexamethasone to mepivacaine prolongs the duration of analgesia but does not reduce the onset of sensory and motor blockade after ultrasound-guided supraclavicular block compared with mepivacaine alone.

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Brachial plexus blockade for ambulatory upper-limb surgery can significantly reduce pain and nausea, allowing for faster discharge from the hospital when compared with general anesthesia.1 However, any reduction in pain provided by single-shot brachial plexus blockade may be short-lived, and the challenge remains to prolong the duration of analgesia while minimizing adverse effects. Local anesthetic adjuncts such as opioids, clonidine, neostigmine, and corticosteroids have all studied previously in an attempt to prolong the duration of analgesia after peripheral nerve blockade with varying degree success.23

Animal and preliminary human studies4–9 investigate the analgesic efficacy of dexamethasone added to local anesthetic agents have been encouraging. Our objective was to determine whether the addition of dexamethasone to mepivacaine would prolong the duration of analgesia after supraclavicular brachial plexus block for patients undergoing ambulatory upper-limb surgery. We hypothesized that the addition of methylprednisolone to mepivacaine would significantly prolong the duration of analgesia after ultrasound-guided supraclavicular brachial plexus block compared with mepivacaine alone.

METHODS

This clinical trial was registered on clinicaltrials.gov (registration no. NCT00802009). Approval for the use of methylprednisolone for the purpose of the present study was obtained from the Canadian Federal Health Department. After University Health Network Research Ethics Board approval and informed consent were obtained, 45 American Society of Anesthesiologists I–III patients presenting for elective hand or forearm surgery under brachial plexus block were randomized to receive 30 mL mepivacaine 1.5% plus dexamethasone (4 mg/mL) (Dexamethasone group) or 30 mL mepivacaine plus 2 mL normal saline (Normal Saline group). Randomization followed a computer-generated randomization table, which was concealed in sealed opaque envelopes. Patients were blinded as to their group allocation. Patients scheduled for surgery of less than 30-min duration or more than 120-min duration; with a history of hypersensitivity to local anesthetic or dexamethasone, peripheral neuropathy, ulceration, diabetes mellitus, coagulopathy, an inability to informed consent or contraindication to use were excluded from the study.

The anesthesiologist involved in the performance of an ultrasound-guided brachial plexus block was blinded as to allocation. For the purposes of the present study, a trained anesthesiologist assistant prepared and masked the local anesthetic solutions. Upon arrival in the block room, an intravenous line of normal saline 0.9%, oxygen at 6 to 8 L/min via face mask standard monitoring were initiated. Patients were intravenously administered midazolam 0.03 to 0.04 mg/kg before the brachial plexus blockade. All ultrasound-guided supraclavicular blockade were performed by staff resident anesthesiologists, or fellow residents under direct staff supervision, using our previous described technique.10,11 In brief, the brachial plexus was viewed as a compact group of nerves (trunks and/or divisions) over the first rib, lateral and posterior to the subclavian...
A sterile 22-gauge insulated needle (Stimuplex; B. Braun Medical, Bethlehem, Pa) was advanced in-plane with the ultrasound beam until the tip was at the junction of the first rib and the subclavian artery. After a negative aspiration, the local anesthetic solution was administered incrementally, ensuring expansion of the brachial plexus sheath.

An anesthesiologist blinded to the patient’s group allocation provided intraoperative care as per the usual standard of care in our institution with low-dose midazolam (1–3 mg), fentanyl (1–2 µg/kg), and/or propofol at conscious sedation doses (25–75 µg/kg per min).

**Block Evaluation**

A trained research assistant who was blinded to group allocation evaluated sensory loss and motor blockade every 5 mins after injection of local anesthetic and every 10 mins after completion of surgery until discharge from the postanesthesia care unit (PACU). The extent of sensory loss was tested in the median, radial, ulnar, and musculocutaneous nerve distributions and evaluated using a 3-point score: 0 = normal sensation, 1 = loss of sensation to pinprick (ie, analgesia), or 2 = loss of sensation to light touch (ie, anesthesia). The extent of motor blockade was tested in the distribution of the radial (thumb abduction), ulnar (thumb adduction), musculocutaneous (flexion of the elbow in supination and pronation), and median nerves (thumb opposition) and evaluated using a 3-point score where 0 = normal movement, 1 = paresis, and 2 = absent movement.

Block success was defined as loss of sensation to pinprick (sensory score ≤1) in each of the radial, ulnar, median, and musculocutaneous nerve distributions measured 20 mins after the end of local anesthetic injection. For patients in whom block success was not achieved after 20 mins, a supplemental rescue nerve block could be performed at the discretion of the attending anesthesiologist, and the patient was excluded from data analysis.

In the event of inadequate analgesia intraoperatively, a standardized algorithm dictated that the surgeon first infiltrate the surgical skin site with lidocaine 1%–2% or bupivacaine 0.25%–0.5% without epinephrine, followed by conversion to general anesthesia if necessary.

The onset time for sensory and motor blockade was defined as the time between the start of local anesthetic injection and the loss of sensation to pinprick (sensory score = 1) and paresis (motor score = 1) in the distributions of all 4 peripheral nerves, respectively.

During postoperative recovery in the hospital, pain (verbal response score ≥4 or patient request for analgesic) was treated with fentanyl 25-µg increments every 5 mins as needed. Once oral intake was initiated, patients received 1 of 2 combined oral analgesic preparations (acetaminophen 300 mg/codeine 30 mg) or (acetaminophen 325 mg/oxycodone HCl 5 mg) per tablet if intolerant of codeine. Upon discharge from the hospital, patients received a prescription for Tylenol 3 as needed or Percocet if intolerant to codeine.

A home diary (Appendix, Supplemental Digital Content 1, http://links.lww.com/AAP/A20) was provided to complete and return to the study investigators using a stamped, return-addressed envelope. For the first 24 hrs (during waking hours), patients were requested to document hourly visual analog scale (VAS) 0–100 mm pain scores and analgesic consumption. Eight hours postoperatively and on postoperative day (POD) 1, 7, and 14 relative to time and date surgery ended, patients were requested to document their VAS pain scores, total daily oral analgesic consumption since discharge from the hospital, the presence of nausea or vomiting, presence of weakness in the operative arm, presence of paresthesia (‘numbness or tingling”) in the operative extremity, and VAS for satisfaction pertaining to their pain relief after surgery. All patients received telephone calls on POD 1, 7, and 14 to remind them to complete and return the diary.

The doses of oral codeine or oxycodone consumed by each patient were converted into equianalgesic doses of oral morphine sulfate to facilitate comparison between groups. Equianalgesic conversion ratios were used according to the general monograph for opioids in the Canadian Pharmacists’ Association *Compendium of Pharmaceuticals and Specialties* (36th ed, 2001) as

**FIGURE 1. Consort diagram.**

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Statistical Analysis

The primary outcome measure for this study was the duration of analgesia defined as the time interval between the end of local anesthetic injection and the patient's first report of postoperative pain at the surgical site. Based on previous data by Robaux and colleagues[1] and from our clinical experience, we expected the duration of analgesia to be 180 (SD, 41) min after administration of 30 mL mepivacaine 1.5% alone. To demonstrate that the addition of 8 mg dexamethasone to 30 mL mepivacaine 1.5% would prolong the duration of analgesia by 20%, we calculated that 21 patients were required per group to detect a statistically significant difference between groups with α = 0.05 and 80% power.

Statistical analysis was performed using SPSS for Windows (version 15, SPSS Inc, Chicago, Ill). The normality of data distribution was assessed using the D’Agostino-Pearson test. Data were analyzed using descriptive statistics and are presented as median (interquartile range [IQR]) or mean (SD) as appropriate. For analysis of patient characteristics and comparison between groups, the χ² test and Fisher exact test were used. Continuous data were analyzed using the Mann-Whitney U test for nonparametric and independent Student t test for normally distributed data. The duration of analgesia was analyzed by survival and Cox regression analysis and is presented as Kaplan-Meier survival curves derived using MedCalc Software (MedCalc, Mariakerke, Belgium). In all cases, P < 0.05 was considered statistically significant.

RESULTS

Eighty-one adult patients were assessed for eligibility to participate during the study period. Fifty-eight patients gave informed consent and were enrolled in the study (Fig. 1). Four patients (2 in the Dexamethasone group, 2 in the Normal Saline group) were excluded from the study because of unsuccessful blockade. Five patients (none in the Dexamethasone group, 5 in the Normal Saline group) were excluded from the study because of the unintentional use of nonstudy analgesic medications in the early postoperative period. Four patients in the Dexamethasone group and none in the Normal Saline group were lost to follow-up at 1 week. A total of 45 patients (24 in the Dexamethasone group, 21 in the Normal Saline group) were included in data analysis for our primary outcome.

<table>
<thead>
<tr>
<th>TABLE 1. Type of Surgery with Site of Surgery</th>
<th>Normal Saline Group (n = 21)</th>
<th>Dexamethasone Group (n = 24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42 (16)</td>
<td>43 (14)</td>
<td>0.838</td>
</tr>
<tr>
<td>Sex, male/female, n</td>
<td>11/10</td>
<td>12/12</td>
<td>0.873</td>
</tr>
<tr>
<td>ASA I/II/III, n</td>
<td>6/12/3</td>
<td>12/11/1</td>
<td>0.240</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27 (4)</td>
<td>26 (4)</td>
<td>0.911</td>
</tr>
<tr>
<td>Surgery duration, min</td>
<td>81 (22)</td>
<td>79 (40)</td>
<td>0.769</td>
</tr>
<tr>
<td>Site of surgery elbow/forearm/hand, n</td>
<td>0/4/17</td>
<td>1/2/21</td>
<td>0.387</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD) or number of patients.
ASA indicates American Society of Anesthesiologists; BMI, body mass index.

FIGURE 2. Duration of analgesia. Kaplan-Meier survival curves depict the cumulative pain-free probability expressed as a percentage for patients in both groups after injection of local anesthetic.

Patient characteristics were similar between groups (Table 1). The duration of analgesia was significantly prolonged in the Dexamethasone group (median, 332 mins; IQR, 225-448 mins) compared with the Normal Saline group (median, 228 mins; IQR, 207-263 mins; P = 0.008). The pain-free probability with time after injection was significantly higher in the Dexamethasone group compared with the Normal Saline group (P < 0.0001) (Fig. 2). There were no significant differences in the onset times of sensory (dexamethasone, 9 [SD, 5] mins; normal saline, 10 [SD, 4] mins; P = 0.779) or motor blockade (dexamethasone, 8 [SD, 3] mins; normal saline 8 [SD, 3] mins; P = 0.846).

Intraoperative fentanyl requirements were similar between groups (P = 0.645). Patients in the Dexamethasone group had significantly reduced fentanyl requirements in PACU (P = 0.020) (Table 2) and significantly reduced VAS pain scores at 8 hrs after surgery (dexamethasone, 27 [SD, 29]; normal saline, 56 [SD, 2]; P = 0.005) (Fig. 3). At 1 day, 1 week, and 2 weeks after surgery, there were no significant differences in pain scores (Fig. 3) or oral analgesic consumption (Table 2).

<table>
<thead>
<tr>
<th>TABLE 2. Intraoperative and Postoperative Analgesic Consumption</th>
<th>Normal Saline Group</th>
<th>Dexamethasone Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative fentanyl in OR, µg</td>
<td>35 (34)</td>
<td>40 (35)</td>
<td>0.645</td>
</tr>
<tr>
<td>Intraoperative fentanyl in PACU, µg</td>
<td>16 (36)</td>
<td>6 (22)</td>
<td>0.020</td>
</tr>
<tr>
<td>Oral morphine equivalent at 8 hrs, mg</td>
<td>31 (37)</td>
<td>31 (76)</td>
<td>0.996</td>
</tr>
<tr>
<td>Oral morphine equivalent on POD 1, mg</td>
<td>27 (46)</td>
<td>31 (81)</td>
<td>0.874</td>
</tr>
<tr>
<td>Oral morphine equivalent on POD 7, mg</td>
<td>8 (18)</td>
<td>18 (60)</td>
<td>0.559</td>
</tr>
<tr>
<td>Oral morphine equivalent on POD 14, mg</td>
<td>10 (21)</td>
<td>20 (66)</td>
<td>0.585</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD).
OR indicates operating room.

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FIGURE 3. Postoperative pain. Effect of suprACLavicular mepivacaine with and without dexamethasone on pain after surgery. Data are presented as median VAS (0–100) (horizontal bar) with 25th to 75th percentiles (box) and 10th to 90th percentiles (whiskers).

Satisfaction with the pain relief provided for surgery was rated as 29 out of 10 in patients in both groups on arrival in PACU and did not differ between groups at any measured time interval after surgery (Fig. 4).

Postoperatively, a greater number of patients in the Normal Saline group (5 patients) experienced nausea in the first 8 hrs after surgery compared with the Dexamethasone group (0 patients; P = 0.02). The most frequently occurring adverse effect reported was numbness or tingling in the arm or hand 2 weeks after surgery (dexamethasone, 8 patients; normal saline, 5 patients; P = 0.248). Other possible block-related complications reported up to 2 weeks postoperatively were minor and transient and did not differ between groups (Table 3).

DISCUSSION

Our results demonstrate that the addition of dexamethasone to an intermediate-acting local anesthetic such as mepivacaine can prolong the duration of analgesia after brachial plexus blockade. These results are in keeping with the trend of previous studies using dexamethasone and a brachial plexus model.

however, faithful comparisons are challenging because of material differences in design and methodology between studies.

In contrast to previous studies in which dexamethasone was added to local anesthetic for brachial plexus blockade, we were unable to demonstrate a multifold augmentation of the duration of analgesia.

TABLE 3. Postoperative Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Normal Saline Group (n = 19)</th>
<th>Dexamethasone Group (n = 18)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea at 8 hrs</td>
<td>5 (26)</td>
<td>0 (0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Vomiting at 8 hrs</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.653</td>
</tr>
<tr>
<td>Nausea on POD 1</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>0.653</td>
</tr>
<tr>
<td>Vomiting at POD 7</td>
<td>0 (0)</td>
<td>1 (5)</td>
<td>0.296</td>
</tr>
<tr>
<td>Numbness/tingling on POD 14</td>
<td>5 (21)</td>
<td>8 (44)</td>
<td>0.248</td>
</tr>
<tr>
<td>Bruising injection site on POD 14</td>
<td>1 (5)</td>
<td>1 (6)</td>
<td>0.927</td>
</tr>
</tbody>
</table>

Data are presented as number of patients with corresponding percentages in parentheses.

For the purposes of the present study, we opted to use mepivacaine without epinephrine because of its intermediate duration of action, which would be less likely to mask any pharmacodynamic effect of adjunctive dexamethasone.

Indeed, whereas the absolute increase in the duration of analgesia may be similar for perineural adjuvants (eg, clonidine) regardless of local anesthetic type, the relative increase in the duration of analgesia is far more pronounced with intermediate-acting local anesthetics alone compared with long-acting local anesthetics alone.

Previously published studies are also limited by additional methodological flaws such as an insufficiently powered sample, high block failure rates and unblinded assessments of block success, in addition to relatively short postoperative follow-up times. Finally, varying methods of block assessment and differing definitions of duration of analgesia and block success further render comparison between studies difficult.

We chose to measure the duration of analgesia, defined as the time to first postoperative report of pain at the surgical site, which is arguably a more clinically relevant patient outcome measure in the ambulatory setting than the duration of analgesia (sensory and/or motor blockade) as described in previous studies.

The mechanism of action of corticosteroids in prolonging peripheral neural blockade is not clearly understood and has been postulated and discussed in detail elsewhere.

In brief, the prolongation of analgesic duration after peripheral administration of dexamethasone may be secondary to local action on nociceptive C-fibers mediated via glucocorticoid receptors and the up-regulation of the function of potassium channels in excitatory cells.
The safety of perineural adjuvants has recently been the subject of debate that centers on the potential for neurotoxicity of the adjuvant drug itself or any co-administered preservatives.\cite{17, 16} Dexmethylone is not approved as a perineural adjuvant to local anesthetic by the US Food and Drug Administration or the Federal Health Department in Canada. However, the use of dexametasonase at doses between 4 and 12 mg via the intravenous, perineural, and epidural routes is described in regional anesthesia and pain medicine textbooks.\cite{17, 16, 15, 18} Reports of corticosteroid-mediated neurotoxicity seem to be related to the vehicle polyethylene glycol and the preservative benzyl alcohol in steroid preparations as well as the presence of insoluble steroid particulate matter in the injectate.\cite{19, 20} In vivo and in vitro animal studies have demonstrated that locally applied corticosteroids have no long-term effect on the structure, electrical properties, or function of peripheral nerve fibers and that the extrafascicular and intrafascicular injection of dexamethasone in a rat sciatic nerve experimental model caused no or minimal peripheral nerve damage, respectively, when compared with other steroids such as hydrocortisone or triamcinolone.\cite{21} Although our results suggest similar rates of postoperative neurologic symptoms between groups, the present study was not powered to evaluate safety.

One important limitation of our study is the lack of a systemic dexamethasone arm. However, a randomized controlled trial in healthy human volunteers, which demonstrated an increased duration of analgesia after the intercostal administration of dexamethasone and bupivacaine microcapsules (arguably with greater potential for systemic absorption than brachial plexus blockade), failed to show significant plasma levels of dexamethasone.\cite{22} Nonetheless, it is possible that systemic absorption of the dexamethasone may have accounted for some of the observed effects as evidenced by a statistically significant reduction in postoperative nausea in the Dexamethasone group. In addition, our study did not formally assess the duration of sensory and motor blockade (offset time) as it is our institutional routine practice to send patients home with residual sensory and/or motor blockade. Finally, the frequency of unsuccessful blockade encountered in the present study was comparable to previous prospective and retrospective studies using ultrasound- and non-ultrasound-guided approaches to brachial plexus blockade.\cite{11, 12, 22}

In summary, the addition of dexamethasone to meperoxaïne prolongs postoperative analgesia after supraclavicular blockade for patients undergoing ambulatory upper-limb surgery. Further studies are required to elucidate the mechanism of action, determine the optimal dose, and examine the safety profile of dexamethasone before its routine use as a perineural adjuvant can be advocated.

REFERENCES


