Systemic versus perineural dexamethasone as an adjuvant to bupivacaine in combined femoral and sciatic nerve blocks in lower-limb vascular surgeries: a prospective randomized study
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Background and aim
Various peripheral nerve block techniques have been described to deliver anesthesia and analgesia that allow better functional recovery and shortened hospital stay following major lower-limb surgeries. We aimed to compare the possible effect of perineural dexamethasone versus systemic dexamethasone after nerve stimulator-guided combined femoral and sciatic nerve blocks in lower-limb vascular surgeries.

Patients and methods
After obtaining approval from the ethical committee of Kasr Al-Ainy University Hospital and obtaining written informed consent, 63 patients aged 18–70 years were randomly allocated into three equal groups. Group P received perineural dexamethasone plus bupivacaine 0.5%, group I received intravenous dexamethasone plus perineural bupivacaine 0.5%, and group B received perineural bupivacaine 0.5% alone. We compared the onset and duration of sensory and motor blockade, duration of analgesia, and hemodynamic changes.

Results
Sensory and motor block onset showed nonsignificant difference between the three groups. Sensory block duration was significantly longer in group P than in groups I and B. Motor block duration was significantly prolonged in groups P and I when compared with group B. Motor block duration was longer in group P than in group I; however, the difference was statistically nonsignificant (p-value 0.34). The duration of analgesia was significantly longer in group P than in the other groups, and significantly longer in group I compared with group B.

Conclusion
The use of equal doses of perineural or intravenous dexamethasone as an adjuvant in single injection combined femoral and sciatic nerve blocks is associated with extended duration of sensory and motor blocks, extension of postoperative analgesia duration, and reduced postoperative analgesic requirements.

Keywords:
anesthesia, dexamethasone, nerve block, perineural, regional

Introduction
A variety of peripheral nerve block (PNB) techniques have been described to provide anesthesia and effective analgesia with a decreased incidence of systemic drawbacks, permitting better functional recovery and shortened postoperative hospital stay following major lower-limb surgeries.

Continuous PNBs have superseded epidural blocks as the analgesic gold standard following some lower-limb surgeries such as vascular surgeries as they can cover analgesia for 48–72 h postoperatively, avoiding possible complications associated with neuroaxial blocks. Generally, proximal sciatic nerve, femoral nerve, and lumbar plexus blocks were found superior for usage in the inpatient setting [1]. PNBs provide multiple benefits in high-risk patients in the form of cardiovascular stability and decreased opioid requirements [2,3].

A documented side effect of continuous nerve block is persistence of motor blockade, a drawback that might delay patient ambulation. When formulating a plan for postoperative pain control following lower-limb surgery, however, consideration must be given to the frequent side effects associated with alternative modalities of analgesia, such as systemic opioids (postoperative nausea and vomiting, sedation, pruritus, and constipation), and the observation that

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inadequate analgesia can lead to painful restriction of limb movement [2].

Nerve localization in the lower limb is performed using either ultrasonography or peripheral nerve stimulation (PNS). Ultrasonographic nerve localization provides numerous possible advantages when performing femoral, popliteal, and distal sciatic nerve blocks; however, neurostimulation remains a useful and frequently used aid to lower-limb regional anesthesia [4,5].

Many studies have been carried out to investigate the effect of different local anesthetic (LA) adjuvants and their effects on the quality of nerve blockade and duration of analgesia [6,7].

Corticosteroids have been successfully used to prolong the duration of LA action after peripheral nerve and epidural blockade. Considering systemic mechanisms of action, along with theoretical safety concerns about perineural dexamethasone, the investigation of parenteral dexamethasone as an alternate to the perineural route has been prompted.

Aim of the work
This study was designed to explore and compare the possible effect of perineural versus systemic dexamethasone on the duration of sensory and motor block after nerve stimulator-guided combined femoral and sciatic nerve blocks in patients undergoing lower-limb vascular surgeries.

Patients and methods
This double-blinded randomized controlled study is a single-institutional clinical trial that was conducted in Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University, between June 2013 and January 2015. After reading the Helsinki Declaration and following its guidelines in this investigation and after obtaining the approval of the ethical committee in Kasr Al-Ainy University Hospital and registering at http://www.clinicaltrials.gov (NCT02576782) 63 patients of both sexes, of ASA physical status I, II, and III, 18–70 years old, undergoing lower-limb vascular surgery were included in the study. Patients were excluded if they had bleeding disorders, neurological deficits involving lumbar or sacral plexuses, if they were allergic to LA, had an infection at the injection site, were on sedative or antipsychotic drugs, and/or had a BMI above 35.

Patients were randomly allocated to one of three equal study groups using Excel 2010 (Microsoft Corp., Redmond, Washington, USA). The randomization sequence was concealed in opaque sealed envelopes that were kept by the senior anesthesia staff. The envelope was opened at the beginning of the operation before block initiation. All groups received 22 ml for each of femoral and sciatic nerve blocks plus 4 ml intravenously.

(1) Group P: 21 patients received 20 ml bupivacaine 0.5% and 2 ml (8 mg) dexamethasone in each block, plus 4 ml normal saline (NS) intravenously.

(2) Group I: 21 patients received 20 ml bupivacaine 0.5% and 2 ml NS in each block, plus 4 ml (8 mg) dexamethasone intravenously.

(3) Group B: 21 patients received 20 ml bupivacaine 0.5% and 2 ml NS in each block, plus 4 ml NS intravenously.

The primary outcome of this study was to detect the difference between the three groups regarding the duration of sensory blockade (measured from the time of sensory loss until the time of its regain). Secondary outcomes included the duration of motor blockade (measured from the time of motor loss until the time of its regain), duration of analgesia (measured from the time of sensory loss until the time of demand for the first dose of rescue analgesia), onset of sensory and motor blockade [where the onset of sensory block was measured from the time of each block completion until the time of sensory loss in the dermatomal distribution of the blocked nerve (tested by pin prick) and onset of motor blockade was measured from the time of each block completion until attaining a motor block equal to 2 or 3 on the modified Bromage scale [8] in femoral and sciatic nerve blocks, respectively]. Changes in heart rate (HR), arterial blood pressure (ABP), respiratory rate, and oxygen saturation (SpO2) were also considered as secondary outcomes.

Patients were subjected to systematic preoperative assessment including history taking, physical examination, and review of routine investigations. The visual analogue pain score (VAS) was explained to all candidates (0=no pain and 10=worst intolerable pain).

On arrival at the preparation room a peripheral intravenous cannula (18 G) was inserted under LA (1 ml lidocaine 2% using a 27-G needle), and the patients were premedicated using 1–2 mg midazolam intravenously. The patients were then transferred to
the operating room where basic monitoring (ECG, noninvasive blood pressure, and pulse oximetry) was initiated. Baseline HR, ABP, SpO2, and respiratory rate were recorded as preblock values.

Femoral nerve block was performed using PNS (Model ES400; Life-Tech, Stafford, Texas, USA). The patient was placed in the supine position with both legs extended and the thigh slightly abducted and externally rotated, permitting femoral artery palpation. The anterior superior iliac spine and pubic tubercle were identified and marked. Then a line was drawn between them, representing the inguinal ligament.

Under strict aseptic measures subcutaneous infiltration of 2–3 ml of lidocaine 2% at the needle insertion site was performed, followed by advancement of a 22-G, short-bevel, 5-cm long, insulated stimulating needle 1–2 cm immediately lateral to the pulse of the femoral artery and 1–2 cm below the inguinal ligament. The nerve stimulator was initially adjusted to deliver 1.0 mA.

When a visible or palpable twitch of the quadriceps muscle (patellar twitch) was observed, the stimulating current was gradually decreased until twitches were still seen or felt at 0.2–0.4 mA, which was the best response suggestive of a successful femoral nerve localization.

After a negative aspiration for blood, 20 ml of LA and 2 ml of NS or dexamethasone were injected slowly while applying distal pressure, allowing proximal spreading of LA in the femoral sheath.

Sciatic nerve block was performed using the same PNS, following the classic approach of Labat. The patient was placed in the lateral position, where the limb to be blocked is topmost with the foot positioned over the dependent leg, with minor flexion of the hip and knee. A line was drawn from the posterior superior iliac spine to the greater trochanter, and a second line was drawn from the greater trochanter to the sacral hiatus (Winnie’s modification). Under strict aseptic measures subcutaneous infiltration of 2–3 ml lidocaine 2% was carried out at the needle insertion site (intersection of a perpendicular line from the midpoint of the first line and the second line), followed by insertion of a 22-G, short-bevel, 10-cm long, insulated stimulating needle.

The nerve stimulator was initially set to provide 1.5 mA, to allow recognition of twitches of the gluteal muscles and stimulation of the sciatic nerve. Twitches of the gluteal muscles were detected first, indicating shallow needle position. Once the gluteal twitches disappeared, response of sciatic nerve stimulation was detected.

When contractions of the hamstrings, calf muscles, foot, or toes were observed, the stimulating current was slowly reduced until twitches were still visible or felt at 0.2–0.5 mA. This was the ideal response suggestive of successful sciatic nerve localization.

Following both nerve blocks; the onset and duration of sensory and motor blockade were recorded. Patients were closely monitored to detect possible side effects (LA toxicity, hematoma). HR, SpO2, and ABP were recorded every 5 min during the first 15 min, and then every 15 min. Sensory and motor blockade was assessed by an independent blinded anesthetist. Postoperatively, patients were transferred to the postanesthesia care unit and then to the intermediate-care unit. Patients were monitored for 24 h following the block and data recording was continued until the first dose of rescue analgesia.

Statistical analysis
Using F-tests, analysis of variance (ANOVA): Fixed effects, omnibus, one-way analysis, and assuming that the mean duration of the sensory block of bupivacaine was 4 h, a two-tailed α-error probability of 0.05, and β-error probability of 0.2 (power of 80%), a total sample size of 63 patients, randomly allocated into three equal groups (21 patients each), was calculated as being required to detect a presumed minimum clinically significant difference of 10% in the duration of sensory block (effect size f=0.404). Statistical power calculations were performed using computer program G*Power 3 for Windows (Franz Faul, Universität Kiel, Germany).

Collected data were presented as mean±SD, numbers, and percentages as appropriate. Categorical variables were analyzed using the χ²-test. One-way ANOVA univariate two-group repeated-measures ‘mixed-design’ ANOVA with post-hoc Dunnett’s test as appropriate was performed. Statistical analysis was
carried out using the computer program SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA), version 20, 2011. $P$ values less than 0.05 were considered statistically significant.

Results
Sixty-three patients fulfilling the inclusion criteria were enrolled in this study. They received combined femoral and sciatic nerve blocks. Those patients were randomly allocated into three equal groups: group P received perineural dexamethasone plus bupivacaine 0.5%, group I received systemic (intravenous) dexamethasone plus perineural bupivacaine 0.5%, and group B received perineural bupivacaine 0.5% alone.

Demographic data did not show statistically significant difference between the three studied groups (Table 1).

Regarding sensory and motor block onset, there was a nonsignificant difference between patients of all groups (Table 2). Groups P and I showed delayed sensory block regression, with significant differences when compared with group B ($P<0.001$ each). Similar results were found as regards the motor block duration, where it was significantly prolonged in groups P and I when compared with group B ($P<0.001$ each) (Table 3).

In addition, sensory block duration was significantly longer in group P when compared with group I ($P=0.03$). Motor block duration was longer in group P than in group I; however, the difference was statistically nonsignificant ($P=0.34$) (Table 3).

When comparing the duration of analgesia following nerve block administration, a significant difference was found between group P and each of group I ($P=0.002$) and group B ($P<0.001$). Furthermore, there was a significant difference in the duration of analgesia between group I and group B ($P<0.001$) (Table 4).

Perioperative hemodynamic profiles showed no significant difference between the three groups. Transient hypotension (a drop of the mean ABP $\geq 20\%$ of the baseline values) occurred in three patients of group P (14.3%) and in four patients of group B (19%). In contrast, three patients of group I (14.3%) showed hypertensive episodes (a rise in mean ABP $\geq 20\%$ of the baseline values), whereas it was noticed in only one patient of each of group P (4.8%) and group B (4.8%). Neither bradycardia, desaturation, bradypnea, nor tachypnea was recorded in any patient in any of the studied groups.

The nerve blockade administered was successful in all patients. None of the patients required rescue analgesia intraoperatively or postoperatively in the postanesthesia care unit. No block-related complications were recorded in any patient.

Discussion
In this study we compared the effect of perineural dexamethasone with bupivacaine 0.5% versus intravenous dexamethasone with perineural bupivacaine 0.5% as regards the onset and duration of motor and sensory block as well as duration of analgesia. Sensory and motor block onsets showed nonsignificant difference among the patients. Use of perineural dexamethasone significantly prolonged the duration of sensory block and the analgesia duration when compared with other groups. Motor block duration was significantly higher in the perineural group when compared with the bupivacaine group.

Table 1 Demographic data of the three studied groups

<table>
<thead>
<tr>
<th></th>
<th>Group P (n=21)</th>
<th>Group I (n=21)</th>
<th>Group B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56±10.5</td>
<td>62±7.5</td>
<td>58±8.5</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (81)</td>
<td>15 (71.4)</td>
<td>16 (76.2)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (19)</td>
<td>6 (28.6)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>82.9±6.1</td>
<td>77.9±7.8</td>
<td>79.4±8.7</td>
</tr>
<tr>
<td>ASA classification [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>7 (33.3)</td>
<td>3 (14.3)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>II</td>
<td>11 (52.4)</td>
<td>14 (66.7)</td>
<td>11 (52.4)</td>
</tr>
<tr>
<td>III</td>
<td>3 (14.3)</td>
<td>4 (19)</td>
<td>5 (23.8)</td>
</tr>
<tr>
<td>Block application time (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>7.8±2.5</td>
<td>8.9±3.1</td>
<td>7.9±3.6</td>
</tr>
<tr>
<td>Sciatic</td>
<td>7.3±2.3</td>
<td>8±3</td>
<td>7.5±2.7</td>
</tr>
<tr>
<td>Duration of surgery (h)</td>
<td>4.5±0.9</td>
<td>4.2±1.1</td>
<td>4.4±0.7</td>
</tr>
</tbody>
</table>

Data are presented as means±SD or n (%). ASA, American Society of Anesthesiologists.
Systemic versus perineural dexamethasone in nerve block  Abdel Naim et al. 573

Table 2 Onset of sensory and motor blockades

<table>
<thead>
<tr>
<th></th>
<th>Group B (n=21)</th>
<th>Group I (n=21)</th>
<th>Group P (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of sensory block (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Femoral</td>
<td>10.48±1.29</td>
<td>9.67±2.94</td>
<td>11.24±2.32</td>
<td>0.092</td>
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<tr>
<td>Sciatic</td>
<td>15.38±1.43</td>
<td>14.71±3.54</td>
<td>16.33±2.61</td>
<td>0.151</td>
</tr>
<tr>
<td>Onset of motor block (min)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femoral</td>
<td>16.43±1.5</td>
<td>15.95±2.69</td>
<td>17.52±2.75</td>
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<tr>
<td>Sciatic</td>
<td>20.38±1.43</td>
<td>19.33±4.4</td>
<td>21.52±3.79</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. P value less than 0.05 is considered statistically significant.

Table 3 Duration of sensory and motor blockades

<table>
<thead>
<tr>
<th></th>
<th>Group B (n=21)</th>
<th>Group I (n=21)</th>
<th>Group P (n=21)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of sensory blockade (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>11.00±1.1</td>
<td>13.55±1.6</td>
<td>14.67±1.6*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Group I</td>
<td>10.79±1.8$^a$</td>
<td>11.29±1.5$^b$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group P</td>
<td>12.39±1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of motor blockade (h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B</td>
<td>8.23±1.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>10.79±1.8$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group P</td>
<td>11.29±1.5$^b$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean±SD. P value less than 0.05 is considered statistically significant. $^a$P<0.05 versus group I and B. $^b$P<0.05 versus group B.

Although it was longer than that in the intravenous group, the difference was statistically nonsignificant (P=0.34). Although systemic dexamethasone prolonged the clinical duration of bupivacaine-induced femoral and sciatic nerve blocks, perineural administration was superior in this context.

Our study outcome correlates well with that of Cummings et al. [9], who added dexamethasone 8 mg to bupivacaine 0.5% or ropivacaine 0.5% in 218 patients undergoing shoulder surgery with interscalene block. They found that the duration of analgesia of both ropivacaine and bupivacaine was significantly prolonged, with a stronger effect for ropivacaine. However, pain scores with movement on the first postoperative day were significantly lower in both the ropivacaine and bupivacaine plus dexamethasone groups.

Movafegh et al. [10] tested the effect of adding 8 mg dexamethasone on axillary brachial plexus block with lidocaine 1.5% in 60 patients scheduled for hand and forearm surgery. Although the onset times of sensory and motor block were equivalent in the two groups, the duration of sensory and motor blockade was significantly longer in the dexamethasone group.

A meta-analysis [11] has confirmed this impression by analyzing nine trials including 801 patients that tested the impact of dexamethasone (4–10 mg) on brachial plexus block. The authors concluded that perineural administration of dexamethasone with LA extends brachial plexus block effects (analgesic duration and motor block), with no detected adverse events. They stated that dexamethasone appeared to be the best means to prolong analgesia as an adjuvant to clonidine, epinephrine, or midazolam.

In contrast to the previous studies in which dexamethasone was added to LA, Shrestha et al. [12] found a statistically significant delay in the onset of action in the LA plus steroid group. This outcome was similar to that published in a recent systematic review carried out by Knezevic et al. [13] that included 14 studies, in which perineural dexamethasone delayed the onset of both sensory and motor block and the prolonged motor block duration. They also stated that smaller doses of dexamethasone (4–5 mg) had a similar effect to higher doses (8–10 mg).

Meanwhile, Noss et al. [14] conducted another systematic review including 11 clinical trials that investigated the efficacy of dexamethasone added to several LA agents in brachial plexus block. They found that the effect of dexamethasone on block onset was variable, with unclear clinical benefit.

Direct antinociceptive effects have been described following local administration of steroids. Johansson et al. [15] demonstrated that locally administered steroids limit the signal transmission of nociceptive C-fibers and change the membrane lipid-phase equilibrium. Remarkably, myelinated nerves were spared from such changes. The biologic half-life of dexamethasone is between 36 and 54 h, and its effects are most obvious in the first 48 h [16].

The analgesic effect of systemically administered dexamethasone likely arises from a diversity of mechanisms,
including peripheral and central anti-inflammatory effects. According to their classical concept of action, steroids bind to intracellular receptors and modulate nuclear gene transcription and protein synthesis [10], ultimately stopping the production of prostaglandins, leukotrienes, and proinflammatory cytokines [17]. However, dexamethasone produces a relatively quick effect, which cannot be explained by the above mechanism [18]. Dexamethasone is also thought to suppress the neuropeptide immune response in injured tissue, thus decreasing the degree of pain [19].

Indirect evidence has supported the assumption that dexamethasone acts locally [20]; the stronger analgesic effect obtained with the perineural route in the present study probably supports a peripheral site of action. However, recent studies have suggested that a systemic effect might be responsible for its clinical effect, and intravenous administration may give similar results [21,22]. Irrespective of its definite mechanism, the finest evidence suggests that its action is through indirect mechanisms rather than by directly inhibiting neurotransmission [23].

The potentiating effect of intravenous dexamethasone on PNB was described by Desmet et al. [21], who studied 150 patients who presented for shoulder arthroscopy under interscalene block using ropivacaine 0.5%, and compared the effect of perineural dexamethasone with that of intravenous dexamethasone. Dexamethasone significantly prolonged the duration of analgesia and decreased analgesic consumption independent of the route of administration. They found the effect of intravenous dexamethasone to be equivalent to that of perineural dexamethasone.

This correlates with the work of Rahangdale et al. [24], who studied 78 patients undergoing ankle and foot surgery under ultrasound-guided sciatic nerve blocks using 0.5% bupivacaine with epinephrine 1 : 300 000, comparing the effect of perineural versus intravenous dexamethasone on block characteristics. There was no significant difference in motor block or analgesia duration between the perineural and intravenous dexamethasone groups.

Kawanishi et al. [25] observed the effects of intravenous and perineural dexamethasone 4 mg on the duration of interscalene brachial plexus block using ropivacaine 0.75% in 39 patients undergoing shoulder arthroscopy. Perineural dexamethasone significantly prolonged the duration of analgesia, even when compared with intravenous dexamethasone.

References

Recommendations
Future studies might involve the combined usage of perineural and intravenous dexamethasone within the safe total maximum dose, as this might improve the quality and duration of block.

Conclusion
The present study demonstrated that, compared with a single injection of combined femoral and sciatic nerve block, the adjuvant use of equal doses of perineural and intravenous dexamethasone in patients undergoing major vascular surgeries is associated with extended duration of sensory and motor blocks, extension of postoperative analgesia duration, and reduced postoperative analgesic requirements. The postoperative analgesic effects of perineural dexamethasone were found superior to those of intravenous administration.

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Nil.

Conflicts of interest
There are no conflicts of interest.


