Ultrasound-Guided Single-Injection Infraclavicular Block Versus Ultrasound-Guided Double-Injection Axillary Block: A Noninferiority Randomized Controlled Trial

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BACKGROUND: Single-injection ultrasound-guided infraclavicular block is a simple, reliable, and effective technique. A simplified double-injection ultrasound-guided axillary block technique with a high success rate recently has been described. It has the advantage of being performed in a superficial and compressible location, with a potentially improved safety profile. However, its effectiveness in comparison with single-injection infraclavicular block has not been established. We hypothesized that the double-injection ultrasound-guided axillary block would show rates of complete sensory block at 30 minutes noninferior to the single-injection ultrasound-guided infraclavicular block.

METHODS: After approval by our research ethics committee and written informed consent, adults undergoing distal upper arm surgery were randomized to either group I, ultrasound-guided single-injection infraclavicular block, or group A, ultrasound-guided double-injection axillary block. In group I, 30 mL of 1.5% mepivacaine was injected posterior to the axillary artery. In group A, 25 mL of 1.5% mepivacaine was injected posteromedial to the axillary artery, after which 5 mL was injected around the musculocutaneous nerve. Primary outcome was the rate of complete sensory block at 30 minutes. Secondary outcomes were the onset of sensory and motor blocks, surgical success rates, performance times, and incidence of complications. All outcomes were assessed by a blinded investigator. The noninferiority of the double-injection ultrasound-guided axillary block was considered if the limits of the 90% confidence intervals (CIs) were within a 10% margin of the rate of complete sensory block of the infraclavicular block.

RESULTS: At 30 minutes, the rate of complete sensory block was 79% in group A (90% CI, 71%–85%) compared with 91% in group I (90% CI, 85%–95%); the upper limit of CI of group A is thus included in the established noninferiority margin of 10%. The rate of complete sensory block was lower in group A (proportion difference of 12% [95% CI, 2–22]; P = 0.0091), as was surgical success rate (82% [95% CI, 74%–89%] vs 93% [95% CI, 86%–97%]; proportion difference of 11% [95% CI 1–20]; P = 0.0153). Sensory block onset was also slower in group A (log rank test P = 0.0020). Performance times were faster in group I (231 seconds [95% CI, 213–250]) than in group A (358 seconds [95% CI, 332–387]; P < 0.0001). No statistically significant difference was observed for vascular puncture, paresthesia during block performance, or procedure-related pain. No neurologic complication was noted at follow-up.

CONCLUSIONS: We failed to demonstrate that the rate of complete sensory block of the double-injection axillary block is noninferior to the single-injection infraclavicular block. However, the rate of complete sensory block at 30 minutes is statistically significantly lower with the axillary block. The ultrasound-guided single-injection infraclavicular block thus seems to be the preferred technique over the axillary for upper arm anesthesia.
ultrasound-guided axillary block technique, with a perivas-
cular injection posterior to the axillary artery and an injection
around the musculocutaneous nerve, has a comparable suc-
cess rate with the multiple perivascular injection technique
with faster procedural time and fewer needle passes.14,15
Because it is performed in a superficial location, it also enables
better needle visualization and may improve the safety pro-
file in case of vascular puncture. However, the efficacy of this
newer and simplified double-injection axillary block in com-
parison with single-injection infraclavicular block has not
been established clearly. When one considers its safety pro-
file, the double-injection axillary block could indeed become
the block of choice for the upper limb surgery if shown to be
noninferior to the single-injection infraclavicular block.

The objective of this study was to compare the rate of complete sensory block 30 minutes after ultrasound-guided
single-injection infraclavicular block with a double-injec-
tion ultrasound-guided axillary block. We hypothesized
that the double-injection ultrasound-guided axillary block
would show rates of complete sensory block at 30 minutes
noninferior to the single-injection ultrasound-guided infra-
clavicular block.

METHODS
Population
This prospective, randomized, single-blinded study was first approved by our institutional Research Ethics
Committee (PEJ-666) and was conducted in 2 academic hos-
pitals of the CHU de Québec (Hôpital de l’Enfant-Jésus and
Hôpital du Saint-Sacrement). Written informed consent was
obtained from each participant. This study was registered to
ClinicalTrials.gov (NCT01761175). Patients aged 18 years
or older with ASA physical status I to III, who previously
agreed to a regional anesthesia technique for their surgery
at or distal to the elbow, were considered for eligibility.
Patients with a body mass index >40 kg/m², weight <45
kg, who were allergic to any medication used in the study
protocol, who had contraindications to regional anesthesia,
who had previous neurologic deficit in the operated arm,
who had severe renal or hepatic failure, were pregnant, or
were breast-feeding were excluded.

Intervention
An IV line and standard monitoring were installed on all
patients. Premedication was administered up to 2 mg mid-
azolam if deemed necessary. The randomization sequence
in either group A (axillary block) or group I (infraclavicular
block) was generated by a third party not involved in the
study by the use of a computer-generated random sequence
(www.randomizer.org), then sealed in prenumbered opaque
envelopes. All blocks were performed by a certified anes-
thesiologist or a senior resident in their regional anesthesia
rotation under direct supervision by one of the investiga-
tors with specific expertise in regional anesthesia. All blocks
were performed using a L10-5 linear probe (Model z.one
SmartCart, ZONARE, Mountain View, CA).

Ultrasound-Guided Infraclavicular Block
Patients were in a supine position with their arm adducted.
The ultrasound probe was positioned under the clavicle,
medial to the coracoid process, in a parasagittal plane. After
a local anesthetic skin wheal, with the use of an in-plane
technique, a 20-gauge 8.89-cm Tuohy needle was advanced
to the posterior side of the axillary artery (6-o’clock posi-
tion) until a fascial click was perceived, then 30 mL of 1.5%
mepivacaine was injected, with the goal of a crescent-
shaped distribution around the artery.2

Ultrasound-Guided Axillary Block
Patients were in a supine position with their arm abducted
to 90°. The ultrasound probe was placed to obtain a trans-
verse image of the axillary artery at the level of the conjoint
tendon of the latissimus dorsi and teres major muscles.
After a local anesthetic skin wheal, with an in-plane tech-
nique, a 20-gauge 8.89-cm Tuohy needle was advanced to
the posterior side of the axillary artery, where 25 mL of 1.5%
mepivacaine was injected to obtain a posterosomedical spread
of the solution around the artery, then 5 mL of the same
solution was injected around the musculocutaneous nerve.
If the musculocutaneous nerve was not distinctly visual-
ized, all the 30 mL was injected posterosomedical to the artery.

Data Collection
Preoperatively, the following data were collected: age, sex,
weight, height, ASA physical status, and medical, surgical,
and anesthesia history. During bloc performance, imaging
time (the time elapsed from the moment the probe is in contact
with the patient to the insertion of the Tuohy needle), needle-
ing time (from the insertion of the needle to its complete removal),
and performance time (sum of imaging and needling time) were collected. The amount of midazolam received, any aspiration of blood or paresthesia, and procedure-related pain on a visual analog pain scale were recorded. During surgery, the type and length of surgery, tourniquet use and its duration, administration of sedatives or analgesia, infiltration of local anesthetics, or general anesthesia were collected. Any potential complication related to the regional anesthesia technique (i.e., local anesthetic toxicity, pneumothorax, local anesthetic allergy, hematoma at the puncture site, neurologic injury, infection, or abscess at the puncture site) was sought.

Follow-Up
Patients were contacted at 24 hours and 1 month after their surgery by an investigator blinded to the technique. Standardized questions were asked about patient’s satisfaction and potential complications (Table 1, Supplemental Digital Content 1, http://links.lww.com/AA/B254).

Sample Size Calculation
Considering a rate of complete sensory block of 90% for the infraclavicular and the axillary blocks, and a noninferiority margin of 10%, a sample size of 224 patients was needed to evaluate the noninferiority of the axillary block in comparison with the infraclavicular block at 30 minutes, with a power of 80% and an α-error of 5% (1-sided hypothesis). The margin of noninferiority was determined by consensus by a panel of clinical experts in regional anesthesia from our institution. A 10% difference in sensory block rate was considered a clinically significant difference.

Statistical Analysis
Statistical analyses were conducted according to the intention-to-treat principle. For the primary outcome, the noninferiority of the double-injection ultrasound-guided axillary block was considered if the limits of the 90% confidence intervals (CIs) were within a 10% margin of the rate of complete sensory block of the infraclavicular block. Sensitivity analyses on the primary outcome measures were performed after to evaluate the robustness of the findings. Secondary outcomes were expressed as 95% CIs based on a 2-sided hypothesis. Newcombe-Wilson score CIs with continuity correction were used for single proportion and difference of proportions. Proportions were analyzed with the χ² or Fisher exact tests, and continuous variables were analyzed with the Wilcoxon test. Imaging, needling, and performance times were log-transformed, and CIs were generated by the Cox method and were analyzed with the Student t test. The installation of the block over time was analyzed with the log rank test on KaplanMeier survival curves. Analyses were performed with the Statistical Analysis System (version 9.4, SAS Institute, Cary, NC).

RESULTS
Among the 284 patients screened between September 2012 through February 2013, 224 patients were assigned randomly to either group I (112 patients) or group A (112 patients; Fig. 1). Patient characteristics were comparable between groups (Table 1). One patient in group I had an anatomic variation precluding the successful performance of the block at 30 minutes. After unsuccessful attempts, the patient was then out of protocol and the anesthetic plan was left to the attending anesthesiologist, who performed an axillary block. One patient assigned to group I inadvertently had an axillary block performed. The first patient was considered a failure for the primary outcome measure; data from the second patient were analyzed in group I, as per the intention-to-treat analysis.

At 30 minutes, the rate of complete sensory block was 91% (90% CI, 85%–95%) in group I compared with 79% (90% CI, 71%–85%) in group A (Fig. 2). The upper limit of the CI of group A is thus included in the established 10%
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...However, the rate of complete sensory block was statistically significantly greater in group I compared with group A (P = 0.0091). Other block characteristics are presented in Table 2. The onset of complete sensory and motor block was faster in group I (Fig. 3; Fig. 1, Supplemental Digital Content 2, http://links.lww.com/AA/B255). The data for the sensory and motor block installation for major nerves are available in supplemental digital content (Figs. 2–9, Supplemental Digital Content 3–10, http://links.lww.com/AA/B256, http://links.lww.com/AA/B257, http://links.lww.com/AA/B258, http://links.lww.com/AA/B259, http://links.lww.com/AA/B260, http://links.lww.com/AA/B261, http://links.lww.com/AA/B262, http://links.lww.com/AA/B263). Nine of the 11 rescue blocks in group A were performed on the median nerve. In 10 patients in group A, the musculocutaneous nerve could not be visualized; 30 mL of local anesthetics were injected posterior to the axillary artery.

One patient in group A showed mild signs of local anesthetic toxicity (tinnitus, dizziness, and tongue numbness), which subsided with the administration of midazolam. One patient in group I had a mild hematoma at the puncture site after block completion, which subsided progressively within 3 weeks. No neurologic sequelae related to the block performance were noted. Patient satisfaction did not differ between the 2 groups.

Per-Protocol Analyses
We conducted a per-protocol analysis in which data from the patient in group I having had the wrong block performed were considered in group A for the analysis. This analysis showed a comparable rate of complete sensory block of (101/111) 91% (90% CI, 85%–95%) in group I compared with (89/113) 79% (90% CI, 71%–85%) in group A at 30 minutes (proportion difference of 12% [95% CI, 2%–22%]; P = 0.0108).

DISCUSSION
On the basis of our predefined 10% margin of noninferiority, we cannot exclude that the ultrasound-guided double-injection axillary block is “noninferior” to the ultrasound-guided single-injection infraclavicular block. However, we observed a statistically significant lower rate of complete sensory block at 30 minutes after the double-injection ultrasound-guided axillary block. We also observed a greater surgical success rate and faster performance times with the infraclavicular block.

Previous studies on ultrasound-guided upper limb blocks were designed as superiority studies.2–4 Block rates obtained were then considered comparable between the axillary and the infraclavicular blocks in one of them.4 However, these studies were not designed to evaluate the noninferiority between the techniques, but whether one technique was superior to another. On the contrary, we considered a noninferiority design as being appropriate to evaluate the potential clinical use of the axillary technique in the context where no technique is likely to have a clinically significant greater success rate than the ultrasound-guided infraclavicular block. We believe that the benefit of the axillary block over the infraclavicular block was in its potentially superior safety profile. To lead to practice changes in the field, the success of the axillary block then had to be showed noninferior to the infraclavicular block.

Table 2. Characteristics of the Blocks

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group I (n = 112)</th>
<th>Group A (n = 112)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete sensory block at 30 min, % (90% CI)</td>
<td>91 (85–95)</td>
<td>79 (71–85)</td>
<td>0.0091*</td>
</tr>
<tr>
<td>Complete motor block at 30 min, % (95% CI)</td>
<td>71 (61–79)</td>
<td>54 (44–63)</td>
<td>0.0089*</td>
</tr>
<tr>
<td>Surgical success, % (95% CI)</td>
<td>93 (86–97)</td>
<td>82 (74–89)</td>
<td>0.0153*</td>
</tr>
<tr>
<td>Operator, expert/anesthesiologist/resident, n</td>
<td>30/38/44</td>
<td>34/32/46</td>
<td>0.6674*</td>
</tr>
<tr>
<td>Number of takeovers*, n</td>
<td>1</td>
<td>3</td>
<td>0.6216*</td>
</tr>
<tr>
<td>Imaging time, s</td>
<td>68 (62–75)</td>
<td>117 (104–130)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Needling time, s</td>
<td>161 (147–177)</td>
<td>241 (222–261)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Performance time, s</td>
<td>231 (213–250)</td>
<td>358 (332–387)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Paresthesia, n</td>
<td>11</td>
<td>16</td>
<td>0.3166*</td>
</tr>
<tr>
<td>Vascular puncture, n</td>
<td>2</td>
<td>1</td>
<td>0.6216*</td>
</tr>
<tr>
<td>Block-related pain, VAS 0 to 100</td>
<td>2 (1–4)</td>
<td>2 (1–4)</td>
<td>0.3340*</td>
</tr>
<tr>
<td>Dose of midazolam before the block, mg</td>
<td>2 (1.5–2)</td>
<td>2 (1.5–2)</td>
<td>0.1047*</td>
</tr>
<tr>
<td>Perioperative midazolam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients, n</td>
<td>34</td>
<td>37</td>
<td>0.7002*</td>
</tr>
<tr>
<td>Median dose, mg</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
<td>0.5442*</td>
</tr>
<tr>
<td>Perioperative sufentanil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients, n</td>
<td>8</td>
<td>13</td>
<td>0.2606*</td>
</tr>
<tr>
<td>Median dose, µg</td>
<td>5 (5–6)</td>
<td>10 (5–10)</td>
<td>0.0551*</td>
</tr>
<tr>
<td>No. of patients for pain in the surgical field, n</td>
<td>3</td>
<td>9</td>
<td>0.2031*</td>
</tr>
</tbody>
</table>

Categorical variables are expressed as count and/or percentage.
CI = confidence interval; VAS = visual analog pain scale.
*x* test.
**y** test.
*Defined as one of the investigators (ND, SL, M-JN) with specific expertise in regional anesthesia.
*Number of blocks during which the supervising anesthesiologist had to take over.
*Fisher exact test.
*Values are expressed as mean and 95% CIs generated by the Cox method.
*Student t test.
*Values are expressed as median and the 25%–75% interquartile range.
*Wilcoxon test.
Although we observed, as a secondary analysis, that the difference between sensory block rates was statistically significant, the upper limit of the 90% CI of the sensory block rate of the axillary block was included in the 10% noninferiority margin defined a priori. Thus, we cannot exclude that the true difference between the sensory block rates of the 2 techniques is <10%, and then decide on the rejection or not of the null hypothesis (not noninferiority). According to a landmark review article on noninferiority studies, our results are inconclusive, which means that it is still possible that the true sensory block rate of the axillary block at 30 minutes could be lower than the margin of noninferiority. However, the success rate of the axillary block is statistically worse than that of the infraclavicular block.

The rate of complete sensory block for the double-injection ultrasound-guided axillary technique found in the present study is comparable with those observed in previous trials. Although the surgical success rate for the axillary block observed in our study is comparable with the one observed in a previous study, it is inferior to what was previously found by other investigators. The discrepancies in success rates could result from different injection end points between their technique and our own. Also, a mean number of needle passes of 4 and 3.5 were recorded in the previous studies. For both block techniques, once the needle was in the right position, we could not move or redirect the needle to do a strict single- or double-injection technique to seek for the simplest technique possible.

For the axillary block, our high failure rate in the median nerve territory could be explained by the inability of the local anesthetic solution to spread to the lateral upper quadrant of the artery. A previous study found that with the double-injection axillary block, the rate of sensory block of the median nerve was lower at 10 and 15 minutes compared with quadruple-injection techniques; however, this difference did not persist beyond this point.

Our study has limitations. First, any anesthesiologist in our center could perform the blocks, as well as any resident in his/her regional anesthesia rotation. However, this limitation was deliberate to mimic real-life conditions and increase the external validity of our study. Another limitation of this study is that the attending anesthesiologist was not always blinded to the block performed because of operational and feasibility reasons. This may have therefore influenced the administration of sedation and surgical success but not the assessment of the primary outcome of complete sensory block at 30 minutes, which was evaluated before any analgesia or additional sedation was administered. Furthermore, administration of sedation or analgesia and the reasons of administration were tightly controlled to limit this bias. The main strength of our study is the use of a strict and thorough methodology compared with previous published trials on this topic. All blocks were also directly supervised by 3 of the authors to insure standardized techniques.

In summary, we failed to demonstrate that the rate of complete sensory block at 30 minutes with the double-injection ultrasound-guided axillary block is noninferior to the single-injection ultrasound-guided infraclavicular block. A statistically and clinically significant lower rate of complete sensory block was observed with the axillary block. Thus, when seeking a reliable, easily performed, and successful block, the single-injection ultrasound-guided infraclavicular block must still be considered. However, the axillary block remains a suitable alternative technique. Finally, we designed a noninferiority study based on the assumption that the axillary block could have a potentially improved safety profile, given its compressible location. However, our trial did not show any difference with regard to adverse events, although it was neither designed nor powered to demonstrate a difference in such a rare outcome.

**DISCLOSURES**

**Name:** Ariane Boivin, MD.
**Contribution:** This author helped in study design, conducting the study, data collection, data analysis, and manuscript preparation.
**Attestation:** Ariane Boivin approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

**Name:** Marie-Josée Nadeau, MD.
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**Attestation:** Marie-Josée Nadeau approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript. Dr. Nadeau is the archival author.

**Name:** Nicolas Dion, MD.
**Contribution:** This author helped in study design, conducting the study, and data collection.
**Attestation:** Nicolas Dion approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

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**Attestation:** Simon Lévesque approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

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**Contribution:** This author helped in study design, data analysis, and manuscript preparation.
**Attestation:** Alexis F. Turgeon approved the final manuscript and attests to the integrity of the analysis reported in this manuscript.

This manuscript was handled by: Terese T. Horlocker, MD.
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REFERENCES