Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: a randomized, controlled study


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Background. We compared the effects of clonidine added to levobupivacaine and bupivacaine on axillary brachial plexus block as well as the effectiveness of levobupivacaine alone compared with bupivacaine alone.

Methods. In this prospective, randomized, controlled, double-blind trial, four groups of 20 patients each were investigated, using (i) 40 ml of levobupivacaine 0.5% plus 0.150 mg of clonidine, (ii) 40 ml of levobupivacaine 0.5% plus 1 ml of NaCl 0.9%, (iii) 40 ml of bupivacaine 0.5% plus 0.150 mg of clonidine, and (iv) 40 ml of bupivacaine 0.5% plus 1 ml of NaCl 0.9%, respectively. The onset of motor and sensory block and duration of sensory block were recorded.

Results. There was no significant difference in duration between groups, but a significantly higher variance (P<0.001) was found in the two groups with clonidine than in the two groups without.

Conclusions. These findings suggest responder and non-responder behaviour is a result of the addition of clonidine.

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Since the 1980s clonidine has been used as an adjuvant to local anaesthetics in various regional techniques to extend the duration of block.12 In axillary plexus block, some studies have shown that clonidine prolongs the local anaesthetic block,3–5 whereas other trials found contrasting results.6–9 One study of three different anaesthetics in combination with clonidine reported mixed results.10

The local anaesthetic investigated in this study, levobupivacaine, is the S(–) enantiomer of racemic bupivacaine; less toxic than bupivacaine,11 it has been shown in the animal model to be equally effective in inhibiting proprioception, motor function, and nociception.12 Studies have been carried out on the use of levobupivacaine for brachial plexus block,13 14 but no data are available on the impact of clonidine on levobupivacaine in axillary plexus block or, for that matter, any peripheral nerve block. The combination of clonidine and levobupivacaine has been studied only by Milligan and colleagues, who applied it epidurally and reported that it improved postoperative pain management.15 Finally, plain bupivacaine has not to date been compared with plain levobupivacaine specifically in axillary block.

We therefore investigated time to onset of motor block and of sensory block, and duration of sensory block of:

(i) plain levobupivacaine vs levobupivacaine in combination with clonidine,
(ii) plain levobupivacaine vs plain bupivacaine, and
(iii) levobupivacaine in combination with clonidine vs bupivacaine in combination with clonidine using the axillary perivascular brachial plexus technique.

Methods

The study protocol of this prospective, randomized, controlled, double-blinded, single-centre, parallel-group trial was approved by the Research Ethics Committee of the University Hospital of Vienna. All participants gave written informed consent. Eighty patients, ASA physical status I–III, 18 yr of age or older, undergoing surgery of the forearm or hand, were recruited. Excluded from the study were patients for whom axillary brachial plexus block or the study medications were contraindicated, or who had a history of significant neurological, psychiatric, neuromuscular,
cardiovascular, pulmonary, renal or hepatic disease, or alcohol or drug abuse, as well as pregnant or lactating women. Also barred from the study were patients taking medications with psychotrophic or adrenergic activities and patients receiving chronic analgesic therapy other than simple analgesics (e.g. non-steroidal anti-inflammatory drugs). No pre-medication was given. No additional sedative medication was administered in the first 60 min after injection of the study dose.

After the sample size was estimated from the data of previous studies\(^5\)\(^1\)\(^3\)\(^1\)\(^4\)\(^1\) using an alpha level of 0.05 and a beta power of 0.90 to detect a significant difference of 2 h in duration of block, four groups (\(n=20\)) were investigated: Group 1 (levobupivacaine-clonidine) received 40 ml of levobupivacaine 0.5% plus 1 ml (0.150 mg) of clonidine; Group 2 (levobupivacaine) received 40 ml of levobupivacaine 0.5% plus 1 ml of NaCl 0.9%; Group 3 (bupivacaine-clonidine) 40 ml of bupivacaine 0.5% plus 1 ml (0.150 mg) of clonidine; Group 4 (bupivacaine) 40 ml of bupivacaine 0.5% plus 1 ml of NaCl 0.9%. The anaesthetic solution was prepared according to a random-number table by an anaesthetist not otherwise involved in the study. The anaesthetist performing the block was blinded to the treatment group. All observations were carried out by a single investigator who was also blinded to the treatment group.

A standard axillary perivascular block technique was applied in all cases (supine position, arm abducted, forearm flexed, and externally rotated).\(^1\)\(^6\) Surgical dressings that might have compromised examinations of the four major brachial plexus nerves were removed. The axillary pulse was identified and the area shaved and disinfected. The injection site was infiltrated with 1 ml of lidocaine 2% subcutaneously. A 22-gauge, 40-mm, short bevelled, insulated, unipolar cannula (Pajunk, Geisingen, Germany) was connected to a nerve stimulator (Stimuplex HNS11\(^\text{TM}\), B. Braun, Melsungen, Germany) and inserted immediately above the artery until the brachial plexus was located.

Half the study drug was injected at a site at which a motor response was evoked and the remaining 20.5 ml was injected at a second site after relocation of the brachial plexus.\(^1\)\(^7\) The location end point was a distal motor response with an output lower than 0.5 mA (\(t=0.3\) ms; \(f=2\) Hz). During injection, negative aspiration was performed every 6.5–7.0 ml to avoid intravascular injection. Plexus block was considered successful when Vester-Andersen’s criteria—at least two out of four nerve territories (ulnar, radial, median, and musculocutaneous) effectively blocked—were fulfilled.\(^1\)\(^8\)

Sensory and motor block of the musculocutaneous, radial, ulnar, and median nerve were determined immediately and at 5, 10, 30, 60, 120, 180, 240, 360, and 480 min after completion of the injection. Patients were asked to note complete recovery of sensation, which was then verified by an anaesthetist or nurse.

Sensory block was determined by pinprick test. A pin-prick sensation on the contralateral arm was scored as 100 points. Patients were requested to compare pinpricks (27-gauge needle) in the primary innervation areas of the respective nerves in the anaesthetized arm with the contralateral arm as reference. The scale ranged from 100 points (full sensation) to 0 points (no sensation).

Motor block was determined according to a modified Lovett rating scale ranging from 6 (usual muscular force) to 0 (complete paralysis), as follows: thumb abduction for the radial nerve, thumb adduction for the ulnar nerve, thumb opposition for the median nerve and flexion of elbow for the musculocutaneous nerve. Sensory block onset was defined as a reduction in sensibility to 30% or less. Motor block onset was defined as a reduction of muscle force to 3 or less.

The duration of sensory block was defined as the time interval between injection and complete recovery of sensation. If, 30 min after study dose injection, any of the major nerves involved in the planned surgical intervention had a sensibility of more than 30%, they were separately blocked and excluded from further investigation. These nerve blocks were performed with 5 ml of mepivacaine 1.5% on cubital or more distal level for the musculocutaneous, radial, ulnar, or median nerve, and, if a pressure cuff was planned for surgery, also on the s.c. axillary level for the intercostobrachial nerve.

Also measured at the above-mentioned time points were heart rate, non-invasive blood pressure, ventilation rate, oxygen saturation, and sedation and compared with ANOVA across groups and between groups using Levene’s test. Because distribution was heteroscedastic and skewed (Levene’s test: \(P<0.001\)), we used the Kruskal–Wallis test and the Kaplan–Meier method including the Breslow test to compare duration across groups and the Mann–Whitney \(U\)-test to compare duration between individual groups.

Based on the Kaplan–Meier plot and ROC curve, a cut-off level for duration of effect (1500 min) was chosen retrospectively to define responders and non-responders to the effect of clonidine (prolongation or non-prolongation of effect, respectively). We thus split each clonidine-combination group into two subgroups: subgroup responder-levobupivacaine-clonidine, subgroup responder-bupivacaine-clonidine and subgroup non-responder-levobupivacaine-clonidine, subgroup non-responder-bupivacaine-clonidine. The data of the subgroups were parametric and showed no significant differences when analysed by Levene’s test (\(P>0.1\)). Area under the curve and peak were chosen as summary measures for heart rate, non-invasive blood pressure, ventilation rate, oxygen saturation, and sedation and compared with ANOVA across groups and Student’s \(t\)-test between groups during the first hour after injection of the study medication.\(^1\)\(^9\)

All post-hoc tests between groups were corrected by the method of Shaffer. Statistical computation was performed
with SPSS™ v11.0 (SPSS, Inc., Chicago, IL). A two-sided $P$ value $\leq 0.05$ was considered statistically significant.

**Results**

Analysis of patient characteristics demonstrated no significant differences between groups (Table 1).

Eighty patients were studied. A successful block was achieved in 79 cases.

Motor onset time and sensory onset time, as shown in Table 2, were not significantly different between groups. Duration of sensory block is shown in Table 2. There was a significantly greater variance ($P<0.001$) in the two groups with clonidine compared with those without.

As seen in Figure 1, the levobupivacaine-clonidine group appeared to have a significantly longer duration of block than the other groups. We tested for the clinical implication of this outcome, using a Kaplan–Meier plot (Fig. 2) and Breslow test. According to this analysis, the median duration of block, measured when still in effect in 50% of the patients, was as follows: (median [95% confidence interval; CI]) 1340 (606–2074) min in the levobupivacaine-clonidine group, 1065 (912–1218) min in the levobupivacaine group, 1035 (1002–1068) min in the bupivacaine-clonidine group, and 1060 (1029–1091) min in the bupivacaine group. Ranges and confidence intervals of all four groups overlap each other for the most part. Therefore, the Breslow test for equality of survival distributions was not significant ($P=0.29$). Comparison of the responder and non-responder subgroups of the levobupivacaine-clonidine group and bupivacaine-clonidine group shows parametric data with similar scattering in the subgroups (Table 3).

**Vital parameters and sedation score**

Heart rate, non-invasive blood pressure, ventilatory frequency, peripheral oxygen saturation as well as sedation score showed no significant inter-group differences.

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### Table 1 Patient characteristics (absolute numbers or mean (SD) [range]).

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<tr>
<th></th>
<th>Lc*</th>
<th>L†</th>
<th>Bc†</th>
<th>B‡</th>
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<td>[21–84]</td>
<td>[18–79]</td>
<td>[19–80]</td>
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<td>75 (16)</td>
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<td>(bone/soft tissue)</td>
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### Table 2 Median (minimum – maximum) of onset time and duration of block.

Motor onset time, sensory onset time, and duration were not significantly different between groups. *Levobupivacaine-clonidine group. †Levobupivacaine group. ‡Bupivacaine-clonidine group.

<table>
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<th>Motor onset time (min)</th>
<th>Duration (min)</th>
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<tr>
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<tr>
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<td>10 (5–120)</td>
<td>1083 (785–1680)</td>
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<tr>
<td>Bc†</td>
<td>10 (5–60)</td>
<td>30 (5–60)</td>
<td>1040 (520–2380)</td>
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<td>B‡</td>
<td>10 (5–60)</td>
<td>10 (5–60)</td>
<td>1063 (600–1310)</td>
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</tbody>
</table>

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**Fig 1** Boxplot of the duration of block. Ranges of all four groups overlap each other for the most part. Lc, levobupivacaine-clonidine group; L, levobupivacaine group; Bc, bupivacaine-clonidine group; B, bupivacaine group; X, mean; O, outlier.

**Fig 2** Kaplan–Meier plot of duration of block. Percentage of patients with sensory block (vertical axis) plotted against time after injection of study dose (horizontal axis). The test for equality of survival distributions was not significant ($P=0.29$).
Table 3 Responders and non-responders. Based on the Kaplan–Meier plot and ROC curve, a cut-off level for duration of effect (1500 min) was chosen to define responders and non-responders to the effect of clonidine (prolongation or non-prolongation of effect, respectively). We thus split each clonidine-combination group into two subgroups: subgroup responder-levobupivacaine-clonidine, subgroup non-responder-levobupivacaine-clonidine, and subgroup non-responder-bupivacaine-clonidine. Comparison of the responder and non-responder subgroups of the levobupivacaine-clonidine group and bupivacaine-clonidine group results in parametric data with similar scattering in the subgroups. *Subgroup responder-levobupivacaine-clonidine. #Subgroup non-responder-levobupivacaine-clonidine.

patient showed any signs of local anaesthetic toxicity, inflammation of puncture site, or nerve lesion.

Discussion

We found no difference between levobupivacaine and bupivacaine in onset or duration of axillary plexus block. These findings are consistent with those of other trials comparing racemic bupivacaine with levobupivacaine.12 13

The results of our study showed no significant difference in onset of motor or sensory block when plain local anaesthetic was compared with anaesthetic plus clonidine in axillary brachial plexus. These findings are in accord with those of previous trials.3–5, 10–12, 21, 22

With regard to prolongation of block, it is interesting to note that clonidine is widely recommended to prolong duration of axillary plexus block.1–5 However, there is ample evidence to dispute this recommendation. Some trials have, in fact, showed benefit from the use of clonidine.2–5 But, as in other previous studies,6–9 no difference in duration with or without the use of clonidine could be found in our trial. At the same time, a marked variability of duration of block in the groups containing clonidine can be seen (Fig. 1).

In previous peripheral block studies that reported a significant effect with clonidine, a similar tendency to variability of duration of block in the groups containing clonidine exists.3–5 Edeljam and colleagues5 had an overlap of ranges between groups of about 50%. Others described dose-dependent effects of clonidine added to lidocaine or mepivacaine for brachial plexus block.4, 5

When the standard deviations are examined, they are seen to increase from 50 min to nearly 600 min at increasing concentrations of clonidine. Singhelyn and others showed a significant disparity in variance with Levene’s test, paralleling our findings.5

Clonidine prolonged the duration of peripheral nerve block in some of our patients, resulting in skewed distribution with two peaks and a wide range. That clonidine does not prolong the duration of block consistently is supported by the finding that data of both the responder and the non-responder subgroups are parametric. Considering our and earlier data, it may be concluded that clonidine is not able to prolong duration of block consistently.

Several explanations are possible for the strongly scattered distribution duration of block in the groups containing clonidine.

(i) Inter-patient variations in the anatomy of the plexus sheath or plexus nerves.16 This could include fat content or the structure of the epineurium, perineurium, endoneurium, or of the Schwann cells. However, there was no striking correlation of patient characteristics (i.e. BMI, body surface area, sex) with duration of block in the groups containing clonidine, suggesting that differences in these characteristics are not responsible for the broad scattering.

(ii) The chosen plexus block technique. Local anaesthetics spread differently in the plexus sheath depending on the block technique, resulting in different concentrations of clonidine at the nerve.16 Among other studies using a multiple injection technique,8, 22 only one reported a consistently prolonging effect with clonidine.22 To examine this fact further, the ultrasound-guided deposition of a precise volume of local anaesthetic in precise distance from the nerve could be a reliable aid in evaluating the impact of the technique factor.

(iii) The unclear mechanism of action of clonidine in peripheral nerve blocks. Clonidine in neuroaxial techniques (epidural, intrathecal) has an established mechanism of action that affects mainly synaptic adrenergic receptors.1 These studies cannot, however, be compared with peripheral nerve block studies (e.g. brachial plexus block, femoral nerve block) or with studies on the intra-articular application of clonidine.

Spinal effects of clonidine deposited in the axillary brachial plexus sheath (e.g. via retrograde axonal active transport, retrograde axonal passive flow, or simple diffusion) can be excluded by the low velocity of these mechanisms,20 or by X-ray.16

Local vasoconstriction under the influence of clonidine, which would result in higher concentrations at the nerve and lower plasma levels of local anaesthetic, can be excluded by the trials showing no differences in plasma levels.7, 21

Concerning peripheral nerve blocks, we favour the hypothesis that clonidine exerts an effect directly on the nerve fibre, as a result of a complex interaction between clonidine and axonal ionotropic, metabolic, or structure proteins (α-receptors), that was shown in different laboratory studies.1, 20, 23, 24

Finally, as long as we (i) do not know the relevant factors about the actions and failures of clonidine at peripheral nerves, and (ii) observe inconsistent, unpredictable variations in duration of block without reliable benefit, we cannot
recommend the use of clonidine in conjunction with bupivacaine or levobupivacaine for peripheral nerve blocks.

Clonidine as an adjuvant to the long-acting local anaesthetics bupivacaine and levobupivacaine in axillary brachial plexus block exerts an uncertain and inconsistent effect, resulting in a lack of predictability and no significant prolongation of duration.

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