*David S. Warner, M.D., and Mark A. Warner, M.D., Editors*

Anesthesiology 2009; 111:406–15 

# *Clonidine as an Adjuvant to Local Anesthetics for Peripheral Nerve and Plexus Blocks*

## *A Meta-analysis of Randomized Trials*

*Daniel M. Pöpping, M.D.,* Nadia Elia, M.D., M.Sc.,† Emmanuel Marret, M.D.,‡ Manuel Wenk, M.D.,* Martin R. Tramèr, M.D., D.Phil.§*

**The effect of adding clonidine to local anesthetics for nerve or plexus blocks remains unclear. The authors searched for randomized placebo-controlled trials testing the impact of adding clonidine to local anesthetics for peripheral single-injection nerve or plexus blocks in adults undergoing any surgery (except eye) without general anesthesia. Twenty trials (1,054 patients, 573 received clonidine) published 1992–2006 tested plexus (14 brachial, 1 cervical) and nerve blocks (2 sciatic/femoral, 1 midhumeral, 1 ilioinguinal/iliohypogastric, 1 ankle). Clonidine doses ranged from 30 to 300 μg; most patients received 150 μg. Clonidine prolonged the duration of postoperative analgesia (weighted mean difference 122 min; 95% confidence interval [CI] 74–169), sensory block (weighted mean difference 74 min; 95% CI 37–111), and motor block (weighted mean difference 141 min; 95% CI 82–199). In a subgroup of patients receiving an axillary plexus block, these effects were independent of whether clonidine was added to an intermediate or a long-acting local anesthetic. Clonidine increased the risk of arterial hypotension (odds ratio 3.61; 95% CI 1.52–8.55; number-needed-to-harm 11), orthostatic hypotension or fainting (odds ratio 5.07; 95% CI 1.20–21.4; number-needed-to-harm 10), bradycardia (odds ratio 3.09; 95% CI 1.10–8.64; number-needed-to-harm 13), and sedation (odds ratio 2.28; 95% CI 1.15–4.51; number-needed-to-harm 5). There was a lack of evidence of dose-responsiveness for beneficial or harmful effects. Clonidine added to intermediate or long-acting local anesthetics for single-shot peripheral nerve or plexus blocks prolongs duration of analgesia and motor block by about 2 h. The increased risk of hypotension, fainting, and sedation may limit its usefulness. Dose-responsiveness remains unclear.**

CLONIDINE is a frequently used adjuvant to local anesthetics (LA). The analgesic properties of clonidine when administered intrathecally or epidurally have been demonstrated; they seem to be attributable to its $\alpha_2$ agonist properties.[1,2] The benefit of adding clonidine to LAs for peripheral nerve blocks is less clear, although it is widely believed that clonidine improves quality and duration of a LA block. Two reviews have addressed this issue.[3,4] Murphy *et al.* analyzed randomized trials that investigated the usefulness of a variety of adjuvants, including clonidine added to LAs for brachial plexus block.[4] On the basis of data from six trials (349 patients), they concluded that clonidine in doses up to 150 μg increased the duration of postoperative analgesia with minimal adverse effects. McCartney *et al.* reviewed 27 studies (1,385 patients) that all tested clonidine as an adjuvant to LAs for a variety of peripheral nerve blocks.[3] They concluded that clonidine was beneficial only when added to intermediate-acting LAs. These analyses did not provide quantitative estimates of analgesic efficacy (for instance, duration of postoperative analgesia) or adverse effects (for instance, arterial hypotension, sedation, delay of discharge to home). Finally, it remained unclear from these analyses whether there was dose-responsiveness and what the optimal dose of clonidine was. Our meta-analysis was designed to address these issues.

## Materials and Methods

### *Literature Review*

A wide search strategy was used to retrieve relevant reports. We searched in MEDLINE, EMBASE, CENTRAL, BIOSIS, and CINAHL. Key words (nerve, plexus, block, blockade, clonidine) were combined using the Boolean meanings of or and and. The last electronic search was in June 2008. Bibliographies of retrieved articles were checked for additional references. There was no language restriction.

The following inclusion criteria were applied: (1) randomized treatment allocation; (2) comparison of clonidine added to a LA (experimental intervention) with the same LA regimen without clonidine (control intervention); (3)

* Anesthesiologist, Department of Anesthesiology and Intensive Care, University Hospital Münster, Münster, Germany. † Research Associate, Division of Anesthesiology, University Hospitals of Geneva, and Faculty of Medicine, University of Geneva, Geneva, Switzerland. ‡ Consultant Anesthetist, Division of Anesthesiology, University Hospitals of Geneva, Geneva, Switzerland, and Department of Anesthesia and Intensive Care, Tenon University Hospital, Assistance Publique Hôpitaux de Paris, Paris, France. § Professor of Anesthesiology, Division of Anesthesiology, University Hospitals of Geneva, and Faculty of Medicine, University of Geneva.

Received from Department of Anesthesiology and Intensive Care, University Hospital Münster, Münster, Germany, and the Division of Anesthesiology, University Hospitals of Geneva, University of Geneva, Geneva, Switzerland. Submitted for publication January 23, 2009. Accepted for publication March 31, 2009. Dr. Elia's salary was provided by the Evidence-based Critical Care, Anesthesia and Pain Treatment Foundation, Geneva, Switzerland. Presented in part as an abstract at the Annual Scientific Meeting of the European Society of Anaesthesiology, May 31–June 3, 2008, Copenhagen, Denmark. Mark A. Warner, M.D., served as Handling Editor for this article.

Address correspondence to Dr. Pöpping: Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum, Münster, Albert-Schweitzer-Str. 33, D-48149 Münster, Germany. poppind@uni-muenster.de. 

peripheral single-injection nerve or plexus block; (4) adults undergoing surgery without general anesthesia; (5) reporting on intraoperative and/or postoperative pain outcomes and/or drug-related adverse effects. When further adjuvants were used (for instance, epinephrine), the data were considered if the comparison was strictly controlled (*i.e.*, both experimental and control groups received the same regimen except for the clonidine).

Noninclusion criteria were: (1) patients undergoing general anesthesia or having an additional neuraxial block; (2) continuous LA administration or repeated injections; (3) intravenous regional anesthesia (Bier's block); (4) Children (younger than 18 yr); (5) peribulbar block. To overcome random play of chance on estimation of treatment effects, we excluded studies with fewer than 10 participants per group.[5,6] Retrieved articles were reviewed for inclusion by one author (Dr. Pöpping); queries were resolved through discussion with two other authors (Drs. Elia and Marret).

*Data Extraction*

One author (Dr. Pöpping) extracted relevant information from original reports. Quality of data reporting was assessed using a modified three-items, seven-points Oxford scale taking into account method of randomization, concealment of treatment allocation, degree of blinding, and reporting of dropouts.[7] Two authors (Drs. Wenk and Marret) checked all extracted data. Discrepancies were resolved by discussion with two further authors (Drs. Elia and Tramèr). When continuous data were not reported as means with SD, we computed them whenever feasible as previously proposed.[8,9] We contacted the primary investigator of 23 retrieved reports to obtain additional information; seven answered, and additional data could be included in our analyses from three of those.[10–12]

*Analyses*

We first performed analyses that did not distinguish between different nerve and plexus blocks or LAs. For dichotomous data, we calculated Peto-odds ratios (OR) with 95% confidence intervals (CI). When the 95% CI around the OR did not include 1, results were considered statistically significant. To estimate the clinical relevance of a harmful effect, we computed numbers needed to harm (NNH) as numbers needed to treat with 95% CI using OR and control event rate. Confidence intervals around NNH point estimates were computed when the results were statistically significant.[13]

For continuous data, weighted mean differences (WMD) with 95% CI were first calculated. When the data were heterogeneous ($P < 0.1$), we searched for the source of heterogeneity. There was an intention to investigate whether differences in effects could be explained by differences in the doses of clonidine using a linear regression model that was adapted for the analysis of correlated data.[1] We extrapolated variable doses to fixed doses using average body weights of the patient populations as reported in the trials. When no body weight was reported, we assumed that it was 70 kg. When there was no evidence of linear dose-responsiveness, a summary estimate was computed. From dose-finding studies, we selected the group of patients who received a dose of clonidine that was closest to all other doses in that analysis. We were using a random effects model when the test for heterogeneity was significant ($P < 0.1$). Alternatively, a fixed effect model was used.

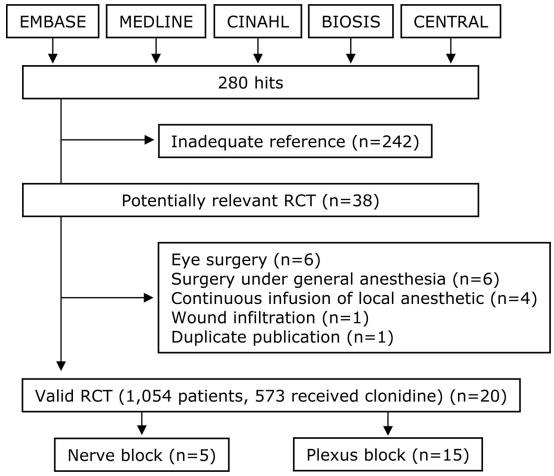


**Fig. 1. Flow chart of retrieved, excluded, and eventually analyzed trials. RCT = randomized controlled trial.**

In sensitivity analyses, we compared the degree of efficacy of clonidine in combination with intermediate and long-acting LAs. To minimize clinical heterogeneity in these sensitivity analyses, we exclusively considered data from trials that tested clonidine in patients receiving an axillary plexus block because this was the largest, clinically homogenous group of studies.

Analyses were performed using RevMan (Computer Program, version 4.3.2; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), Microsoft Excel 11.3. for Mac, Maple 9.5 (University of Geneva, Geneva, Switzerland), and STATA 9 (STATA Corp, College Station, TX).

## Results

*Retrieved and Analyzed Trials*

Of 280 retrieved titles, 38 were potentially relevant (fig. 1). Of those, we excluded 18 for various reasons. Data from one study were published twice[14,15]; we considered the first published report.[14] We eventually analyzed data from 20 randomized controlled trials (1,054 patients, 573 received clonidine) (table 1).[10–12,14,16–31] Fifteen studies tested clonidine for plexus blocks (14

**Table 1. Analyzed Randomized Controlled Trials**

| First Author | Year | Surgery | Nerve or Plexus Block | Comparison (No. of Patients Included) [Group Not Considered] | Quality Score* |
|---|---|---|---|---|---|
| Adnan[16] | 2005 | Arteriovenous fistula | Axillary plexus | 1. Lidocaine 400 mg + clonidine 150 μg (13)<br>2. Lidocaine 400 mg + no treatment (15) | 1/0/3/1 |
| Antonucci[17] | 2001 | Carpal tunnel | Axillary plexus | 1. Ropivacaine 150 mg + no treatment (20)<br>2. Ropivacaine 150 mg + clonidine 150 μg (20)<br>[3. Ropivacaine 150 mg + sufentanil (20)]<br>[4. Ropivacaine 150 mg + tramadol (20)] | 1/0/0/0 |
| Beaussier[10] | 2005 | Inguinal herniorrhaphy | Ilio-inguinal-hypogastric nerves | 1. Ropivacaine 225 mg + clonidine 75 μg (20)<br>2. Ropivacaine 225 mg + no treatment (20) | 1/1/0/0 |
| Bernard[18] | 1997 | Carpal tunnel | Axillary plexus | 1. Lidocaine 400 mg + clonidine 30 μg (14)<br>2. Lidocaine 400 mg + clonidine 90 μg (14)<br>3. Lidocaine 400 mg + clonidine 300 μg (14)<br>4. Lidocaine 400 mg + saline (14) | 1/0/3/0 |
| Broch[19] | 2005 | Hand | Axillary plexus | [1. Prilocain 600 mg + tramadol (20)]<br>2. Prilocain 600 mg + clonidine 1.5 $\mu g \cdot kg^{-1}$ (20)<br>3. Prilocain 600 mg + no treatment (20) | 1/0/3/0 |
| Büttner[11] | 1992 | Hand | Axillary plexus | 1. Mepivacine 500 mg + saline (30)<br>2. Mepivacine 500 mg + clonidine 120 μg (30)<br>3. Mepivacine 500 mg + clonidine 240 μg (30)<br>All injections with sodium bicarbonate | 1/0/3/1 |
| Casati[20] | 2001 | Upper extremity | Axillary plexus | 1. Ropivacaine 150 mg + no treatment (15)<br>2. Ropivacaine 150 mg + clonidine 1 $\mu g \cdot kg^{-1}$ (15) | 2/1/3/1 |
| Casati[21] | 2000 | Hallux valgus | Sciatic-femoral nerves | 1. Ropivacaine 225 mg + no treatment (15)<br>2. Ropivacaine 225 mg + clonidine 1 $\mu g \cdot kg^{-1}$ (15) | 2/1/3/0 |
| Contreras-D[22] | 2006 | Upper extremity | Axillary plexus | 1. Mepivacaine 400 mg + saline (15)<br>2. Mepivacaine 400 mg + saline (15)<br>3. Mepivacaine 400 mg + clonidine 150 μg (15)<br>4. Mepivacaine 400 mg + clonidine 150 μg (15)<br>All injections with epinephrine. Injections in groups 2 and 4 additionally with sodium-bicarbonate | 1/0/0/0 |
| Danelli[23] | 2006 | Carotid endarterectomy | Cervical plexus | 1. Ropivacaine 150 mg + no treatment (20)<br>2. Ropivacaine 150 mg + clonidine 50 μg (20) | 2/1/2/0 |
| Duma[12] | 2005 | Forearm and hand | Axillary plexus | 1. Levo-Bupivacaine 200 mg + saline (20)<br>2. Levo-Bupivacaine 200 mg + clonidine 150 μg (20)<br>3. Bupivacaine 200 mg + saline (18)<br>4. Bupivacaine 200 mg + clonidine 150 μg (20) | 1/0/3/0 |
| El Saied[24] | 2000 | Forearm and hand | Axillary plexus | 1. Ropivavaine 300 mg + saline (23)<br>2. Ropivacaine 300 mg + clonidine 150 μg (23) | 1/0/3/1 |
| Erlacher[25] | 2001 | Forearm and hand | Axillary plexus | 1. Mepivacaine 400 mg + saline (20)<br>2. Ropivacaine 300 mg + saline (20)<br>3. Bupivacaine 200 mg + saline (20)<br>4. Mepivacaine 400 mg + clonidine 150 μg (20)<br>5. Ropivacaine 300 mg + clonidine 150 μg (20)<br>6. Bupivacaine 200 mg + clonidine 150 μg (20) | 1/0/1/0 |
| Fang[26] | 2004 | Arm | Axillary plexus | 1. Lidocaine 400 mg + clonidine 150 μg (15)<br>2. Bupivacaine 100 mg + clonidine 150 μg (15)<br>3. Ropivacaine 160 mg + clonidine 150 μg (15)<br>4. Lidocaine 400 mg + no treatment (15)<br>5. Bupivacaine 100 mg + no treatment (15)<br>6. Ropivacaine 160 mg + no treatment (15) | 1/0/1/0 |
| Helayel[27] | 2005 | Foot or ankle | Sciatic-femoral nerves | 1. Ropivacaine 125 mg + saline (10)<br>[2. Ropivacaine 125 mg + clonidine 2 $\mu g \cdot kg^{-1}$ IM (14)]<br>3. Ropivacaine 125 mg + clonidine 2 $\mu g \cdot kg^{-1}$ (16) | 2/1/0/1 |
| Iohom[28] | 2005 | Paronychia | Axillary plexus | 1. Mepivacaine 400 mg + no treatment (21)<br>2. Mepivacaine 400 mg + clonidine 100 μg (20) | 1/0/3/1 |
| Iskandar[29] | 2001 | Hand | Mid-humeral block | 1. Mepivacaine 600 mg + no treatment (28)<br>2. Mepivacaine 600 mg + clonidine 100 μg (30) | 2/0/3/1 |
| Mjahed[30] | 1996 | Upper extremity | Axillary plexus | 1. Lidocaine 600 mg + saline (30)<br>[2. Lidocaine 600 mg + epinephrine (30)]<br>3. Lidocaine 600 mg + clonidine 150 μg (30) | 1/0/1/0 |

(*continued*)

**Table 1. Continued**

| First Author | Year | Surgery | Nerve or Plexus Block | Comparison (No. of Patients Included) [Group Not Considered] | Quality Score* |
|---|---|---|---|---|---|
| Reinhart[31] | 1996 | Bunionectomy Hammer toe | Ankle block | 1. Lidocaine 260 mg + saline (30)<br>2. Lidocaine 260 mg + clonidine 70 μg (27)<br>3. Lidocaine 260 mg + clonidine 140 μg (25) | 2/0/3/0 |
| Singelyn[14] | 1992 | Hand | Axillary plexus | 1. Mepivacaine 400 mg + saline (10)<br>[2. Mepivacaine 400 mg + clonidine 150 μg SC (10)]<br>3. Mepivacaine 400 mg + clonidine 150 μg (10)<br>All injections with epinephrine | 2/0/1/0 |

* Quality score: randomization (0–2 points)/concealment of treatment allocation (0–1)/blinding (0–3)/descriptions of withdrawals (0–1).
IM = intramuscular; SC = subcutaneous.

axillary, 1 cervical), and five for nerve blocks (2 sciatic-femoral, 1 midhumeral, 1 ilio-inguinal-hypogastric, 1 ankle). All regimens were given as single injections in patients undergoing surgery without general anesthesia.

Clonidine was combined with intermediate-acting LAs (mepivacaine, 6 studies; lidocaine, 5 studies; prilocaine, 1 study) and with long-acting LAs (ropivacaine, 9 studies; bupivacaine, 3 studies; levo-bupivacaine, 1 study) (table 1).

Seventeen trials tested one dose of clonidine, two trials tested two doses,[11,31] and one trial tested three doses.[18] Three trials compared clonidine with other adjuvants.[17,19,30] In three, the effect of clonidine in combination with different LAs was tested.[12,25,26] Two studies had an additional active control group in which patients received clonidine systemically.[14,27] Sixteen trials tested a fixed dose, and four tested a variable dose. Twelve doses, ranging from 30 to 300 μg, were tested (fig. 2); 150 μg was tested in 271 patients (47% of all patients receiving clonidine) in 14 trials (70% of all trials).

The median quality score of data reporting was 4 (range, 1 to 6). Twelve studies (60%) were double-blind, the procedure of randomization was adequately described in seven (35%), and concealment of treatment allocation was described in four (20%).

*Duration of Postoperative Analgesia*

Duration of postoperative analgesia, defined as time until first analgesic request, was reported in 13 trials testing 17 comparisons[11,12,14,18–22,24,26,28,30,31]; 13 comparisons were significant in favor of clonidine.‖ Clonidine doses that were considered for analysis ranged from 90 to 150 μg. In controls, duration of postoperative analgesia was on average 461 min (range, 128 to 1,151 min). Clonidine significantly increased the duration; WMD 123 min (95% CI 74–169; $P < 0.001$). The data were heterogeneous ($P < 0.001$); however, there was a lack of evidence of dose-responsiveness.

*Time to Onset of Sensory Block*

Time to onset of sensory block, determined by pinprick, was reported in 8 trials testing 11 comparisons;[14,16,17,22,23,26,28,30] 5 comparisons were significant in favor of clonidine.# Clonidine doses ranged from 90 to 150 μg. In controls, average time to onset of sensory block was 15 min (range, 4–26). Clonidine significantly shortened that time; WMD −2.2 min (95% CI −4.1 to −0.4; $P = 0.02$). The data were heterogeneous ($P < 0.001$); however, there was a lack of evidence of dose-responsiveness.

*Duration of Sensory Block*

Duration of sensory block, determined by pinprick, was reported in 10 trials that tested 13 comparisons[11,14,16,17,19,22,24,26,28,31]; 10 comparisons were signif-

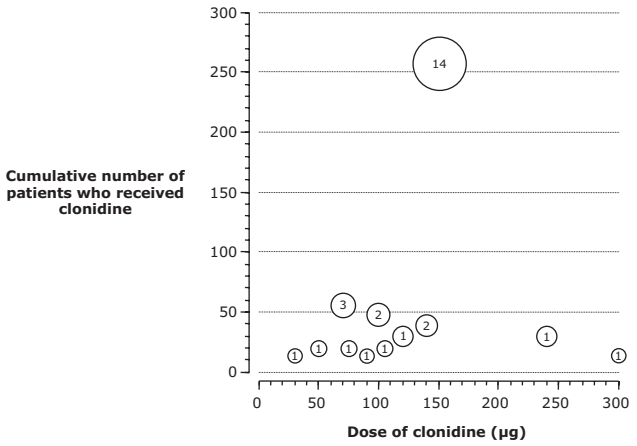


**Fig. 2. Tested doses of clonidine. *Bubble size* corresponds to the cumulative number of patients who received the respective dose of clonidine. *Numbers* within the bubbles indicate the number of comparisons; numbers do not add up because some trials used more than one comparison.**

‖ Figure A, Duration of postoperative analgesia. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

# Figure B, Time to onset of sensory block. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

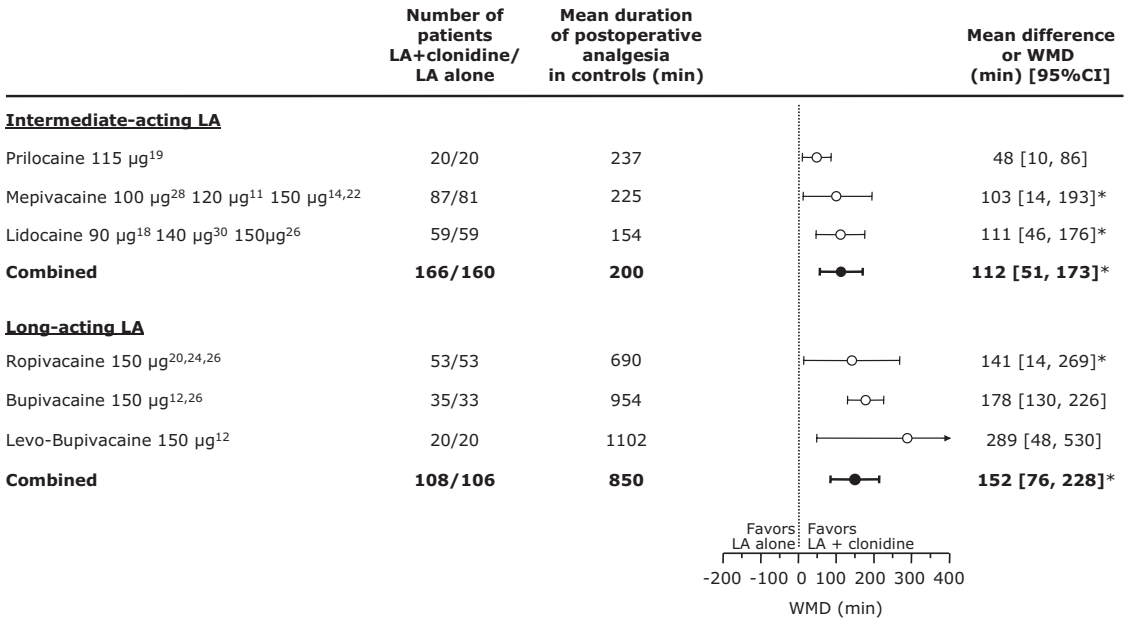


**Fig. 3. Duration of postoperative analgesia. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of postoperative analgesia was defined as time until first analgesic request. Meta-analyses were performed using a fixed effect model, except *random effects model (*P* for heterogeneity < 0.1). *Symbols* and *horizontal lines* are mean differences (single trials) or WMDs (combined data) with 95% CIs. CI = confidence interval; LA = local anesthetic, WMD = weighted mean difference.**

icant in favor of clonidine.** Clonidine doses that were considered for analysis ranged from 90 to 150 μg. In controls, the average duration of sensory block was 269 min (range, 87–596). Clonidine significantly prolonged the duration; WMD 74 min (95% CI 37–111; $P < 0.001$). The data were heterogeneous ($P < 0.001$); however, there was a lack of evidence of dose-responsiveness.

### *Time to Onset of Motor Block*

Time to onset of motor block, quantified using the Bromage scale or defined as a reduction of at least 50% in muscle strength, was reported in four trials that tested seven comparisons[12,16,24,26]; two comparisons were significant in favor of clonidine.†† Clonidine dose was 150 μg in all four trials. In controls, average onset time of motor block was 18.3 min (range, 6.4–25.3). Clonidine had no significant impact on onset time; WMD −0.38 min (95% CI −3.14 to 2.38; $P = 0.79$).

### *Duration of Motor Block*

Duration of motor block, quantified using the Bromage scale or defined as a reduction of at least 50% in muscle strength, was reported in seven trials that tested eleven comparisons[11,16,19,21,24–26]; nine comparisons were significantly longer with clonidine.‡‡ Clonidine doses that were considered for analysis ranged from 115 to 150 μg. In controls, average duration of motor block was 405 min (range, 122–728). Clonidine significantly prolonged the duration; WMD 141 min (95% CI 82–199) ($P < 0.001$). The data were heterogeneous ($P = 0.001$); however, there was a lack of evidence of dose-responsiveness.

### *Incomplete Anesthetic Block*

Incomplete block, or block failure, defined as the need for additional intravenous sedative or analgesic medication, additional nerve block, or wound infiltration during surgery, was reported in 16 trials.[10–12,14,16–21,23,24,27–29,31] Clonidine doses ranged from 30 to 300 μg. In controls, the average incidence of incomplete block was 8%, and with clonidine it was 7.3%, a difference that was not statistically significant; (OR 0.72; 95% CI 0.40–1.30).§§

### *Sensitivity Analyses with Data from Axillary Plexus Block Trials*

Sensitivity analyses were performed to test the impact of adding clonidine to intermediate-acting and long-acting LAs. Duration of analgesia was on average 200 min with intermediate-acting and 850 min with long-acting LAs alone (fig. 3). Clonidine prolonged the duration of analgesia in combination with all tested LAs. All 95% CI overlapped, except when clonidine was added to the intermediate-acting prilocaine (additional duration of analgesia, average 48 min) or the long-acting bupivacaine

** Figure C, Duration of sensory block. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

†† Figure D, Time to onset of motor block. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

‡‡ Figure E, Duration of motor block. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

§§ Figure F, Incomplete anesthetic block. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

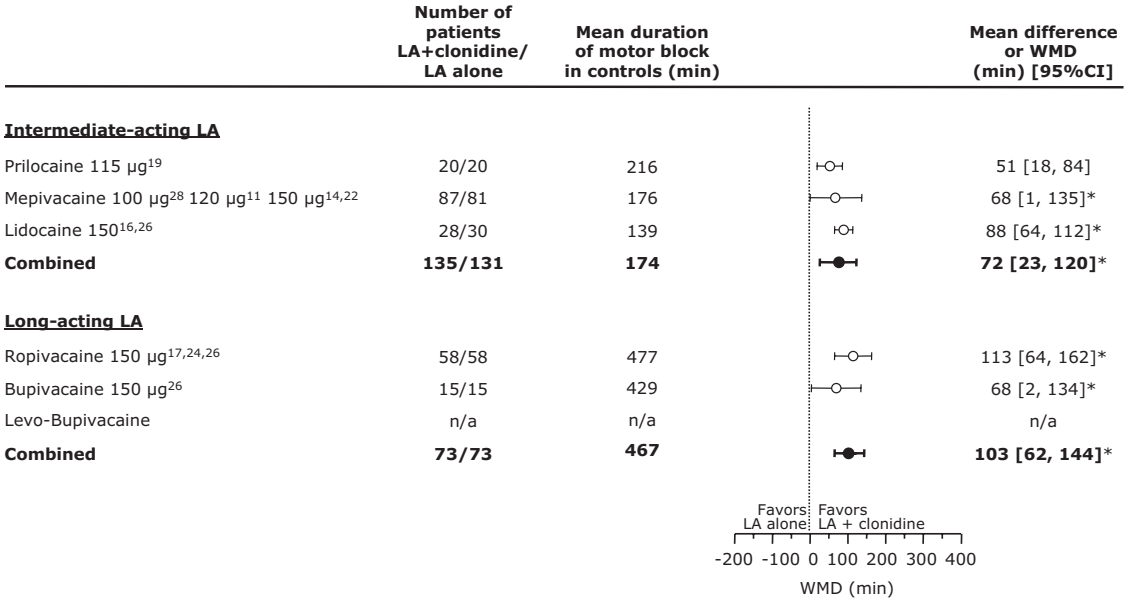


**Fig. 4. Duration of postoperative sensory block. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of sensory block was tested using pinprick. Meta-analyses were performed using a fixed effect model, except *random effects model (*P* for heterogeneity < 0.1). *Symbols* and *horizontal lines* are mean differences (single trials) or WMDs (combined data) with 95% CIs. CI = confidence interval; LA = local anesthetic; n/a = not applicable (no relevant data available); WMD = weighted mean difference.**

(additional duration of analgesia, average 178 min). When combined data of clonidine added to intermediate-acting LAs were compared with combined data of clonidine added to long-acting LAs, there was no evidence of a difference; clonidine prolonged the duration of postoperative analgesia by about 2 to 2.5 h.

Average duration of sensory block was 174 min with intermediate-acting and 467 min with long-acting LAs alone (fig. 4). Clonidine prolonged the duration of sensory block in combination with all tested LAs. Prolongation was shortest when clonidine was added to the intermediate-acting prilocaine (average, 51 min) and was

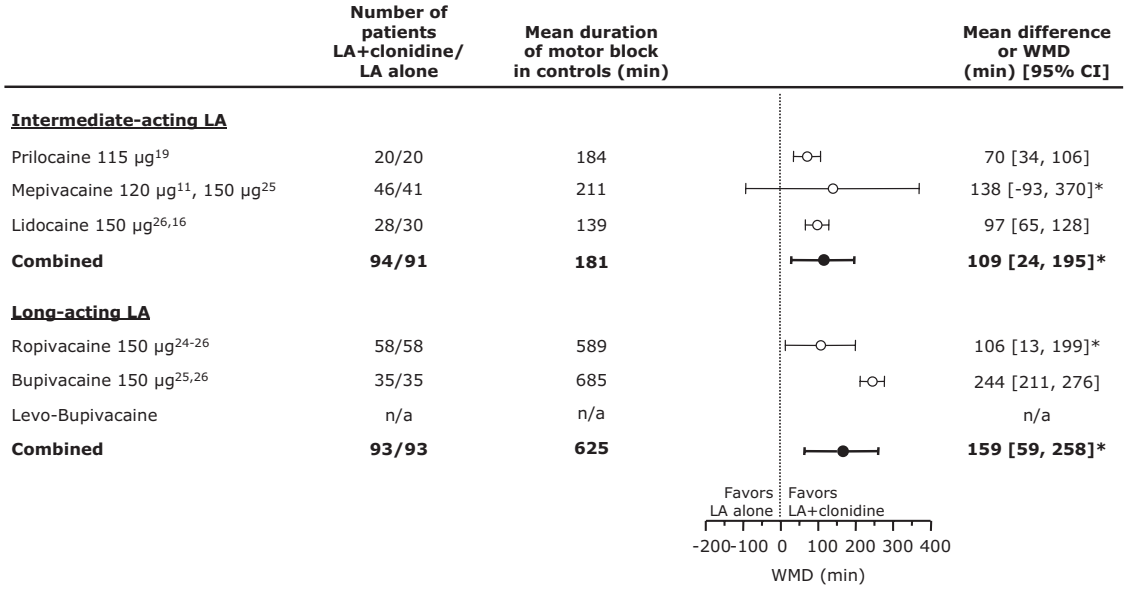


**Fig. 5. Duration of motor block. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of motor block was tested using the Bromage scale or was defined as a reduction of at least 50% in muscle strength. Meta-analyses were performed using a fixed effect model, except *random effects model (*P* for heterogeneity < 0.1). *Symbols* and *horizontal lines* are mean differences (single trials) or WMDs (combined data) with 95% CIs. CI = confidence interval; LA = local anesthetic; n/a = not applicable (no relevant data available); WMD = weighted mean difference.**

**Table 2. Drug-related Adverse Effects**

| Outcome | Definition | Doses of Clonidine ($\mu$g) | N with Outcome/ Total N (%) | | OR (95% CI) | $P_{hetero}$ | NNH (95% CI) |
|---|---|---|---|---|---|---|---|
| | | | LA+Clonidine | LA Alone | | | |
| Arterial hypotension[10,16-18,21,27,30] | Decrease in mean arterial pressure < 55 mmHg, decrease in systolic blood pressure > 20% or > 30%, need for ephedrine | 30, 75, 90, 140, 150, 300 | 20/153 (13.1) | 5/123 (4.1) | 3.61 (1.52–8.55) | 0.88 | 11 (4.4–50) |
| Orthostatic hypotension or fainting[10,18] | Orthostatic hypotension or fainting on mobilization | 30, 75, 90, 300 | 8/62 (12.9) | 1/34 (2.9) | 5.07 (1.20–21.4) | 0.86 | 10 (2.8–177) |
| Bradycardia[10,16-18,21,27,30] | Heart rate < 45 beats/min or < 50 beats/min, > 20% decrease in heart rate, need for atropine | 30, 75, 90, 140, 150, 300 | 13/153 (8.5) | 5/123 (4.1) | 3.09 (1.10–8.64) | 0.9 | 13 (4.4–247) |
| Sedation[10,17-18,21] | ≥ 2 points on a 4- or 5-point scale, ≤ 4 points on a 5-point scale | 30, 75, 90, 150, 300 | 53/95 (55.8) | 22/68 (32.4) | 2.28 (1.15–4.51) | 0.04 | 5 (2.8–32) |

CI = confidence interval; LA = local anesthetic; NNH = number needed to harm; OR = odds ratio. Only data from trials that provided a specific definition of the adverse effects were analyzed.

Forrest plots with individual trial data are freely accessible on http://anesthesiologie.hug-ge.ch/data.htm. See figure G, Arterial hypotension; figure H, Bradycardia; figure I, Sedation; and figure J, Orthostatic hypotension or fainting; accessed April 6, 2009.

longest with the long-acting ropivacaine (average, 113 min). However, 95% CIs of all LAs overlapped. When combined data of clonidine added to intermediate-acting LAs were compared with combined data of clonidine added to long-acting LAs, there was no evidence of a difference; clonidine prolonged the sensory block by about 1.5 h.

Average duration of motor block was 181 min with intermediate-acting and 625 min with long-acting LAs alone (fig. 5). Clonidine prolonged the duration of motor block in combination with all tested LAs, except for mepivacaine (which had a wide 95% CI). All 95% CIs overlapped, except for the long-acting bupivacaine, which prolonged the motor block significantly more than the long-acting ropivacaine or the intermediate-acting prilocaine and lidocaine. With the intermediate-acting LAs and the long-acting ropivacaine, clonidine prolonged the duration of motor block by about 1.5 to 2 h. When clonidine was added to bupivacaine, the motor block was prolonged by about 4 h. The 95% CIs of ropivacaine (WMD, 106 min) and bupivacaine (WMD, 244 min) did not overlap.

### *Drug-related Adverse Effects*

Dichotomous data on arterial hypotension, fainting, bradycardia, or sedation could be analyzed (table 2).

Seven studies reported on presence or absence of episodes of arterial hypotension using specific definitions (*i.e.*, decrease in mean arterial pressure less than 55 mmHg, decrease in systolic blood pressure more than 20% or more than 30%, need for ephedrine).[10,16–18,20,27,30] Of those, five reported on at least one event.|||| Clonidine doses ranged from 30 to 300 $\mu$g. In controls, the average incidence of arterial hypotension was 4.1%, and with clonidine it was 13.1% (OR 3.61; 95% CI 1.52–8.55; NNH 11).

Seven studies reported on presence or absence of episodes of bradycardia using specific definitions (*i.e.*, heart rate less than 45 beats/min or less than 50 beats/min, more than 20% decrease in heart rate, need for atropine).[10,16–18,20,27,30] Of those, three reported on at least one event.## Clonidine doses ranged from 30 to 300 $\mu$g. In controls, the average incidence of bradycardia was 4.1%, and with clonidine it was 8.5% (OR 3.09; 95% CI 1.10–8.64; NNH 13).

Four studies reported on at least one episode of sedation during surgery using specific definitions (*i.e.*, at least 2 points on a 4- or 5-point scale or no more than 4 points on a 5-point scale).[10,17,18,20] Clonidine doses ranged from 30 to 300 $\mu$g. In controls, the average incidence of sedation was 32.4%, and with clonidine it was 55.8% (OR 2.28; 95% CI 1.15–4.51; NNH 5).***

Two studies reported on orthostatic hypotension or fainting postoperatively.[10,18] Clonidine doses ranged from 30 to 300 $\mu$g. In controls, the average incidence of orthostatic hypotension or fainting was 2.9%, and with clonidine it was 12.9% (OR 5.07; 95% CI, 1.20–21.4; NNH 10).†††

All combined data were homogenous except for sedation ($P = 0.04$). There was a lack of evidence of dose-responsiveness for all drug-related adverse effects.

### *Further Outcomes*

Postoperative pain intensity at 12 and 24 h, incidence of dry mouth, desaturation intraoperatively or postoperatively, postoperative nausea and vomiting, respiratory depression, symptoms of LA toxicity, or tourniquet pain

|||| Figure G, Arterial hypotension. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

## Figure H, Bradycardia. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

*** Figure I, Sedation. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

††† Figure J, Orthostatic hypotension or fainting. Available at: http://anesthesiologie.hug-ge.ch/data.htm; accessed April 6, 2009.

were infrequently reported and were, therefore, not further analyzed.

## Discussion

This meta-analysis of 20 randomized controlled trials suggests that clonidine may be a useful adjuvant to LAs for peripheral nerve and plexus blocks. The duration of the analgesic and sensory block is prolonged by about 2 h. However, clonidine increases the risk of arterial hypotension, fainting, bradycardia, and sedation, and it prolongs the duration of the motor block.

Clonidine, an $\alpha_2$ adrenergic agonist, was initially used for its antihypertensive properties. The large expression of $\alpha_2$ receptors in the central nervous system, *i.e., loecus coeruleus* and dorsal horn of the spinal cord, has eventually focused the interest of that drug on centrally mediated sedation and analgesia. Specific peripheral effects of clonidine appear less obvious because $\alpha_2$ adrenoreceptors are not present on the axon of the normal peripheral nerve.[2] In one study, clonidine without LA given through an interscalene catheter provided better analgesia compared with the systemic administration of the same dose.[32] Similarly, in healthy volunteers, sensory and motor block were significantly prolonged when clonidine alone was administered into the axillary plexus sheath.[33] However, in another clinical study, clonidine alone failed to produce analgesia when injected into the axillary brachial plexus sheath.[34] Thus, data from clinical and experimental trials testing the effect of peripheral clonidine alone have remained inconclusive.

Laboratory and clinical data on clonidine as an adjuvant to LAs for peripheral nerve blocks are more convincing. On the isolated vagus nerve, clonidine intensified the conduction block induced by LAs.[35] When injected concomitantly with lidocaine for intravenous regional anesthesia, clonidine decreased the incidence of tourniquet pain.[36] In our analysis, a majority of comparisons reported on a significantly prolonged duration of postoperative analgesia with clonidine. Perhaps unexpectedly, this well documented analgesic effect did not translate into a decreased risk of block failure. This discrepancy may suggest that clonidine added to LAs primarily enhances the analgesic and less so the anesthetic properties of the peripheral nerve block. However, one major problem with all these studies was their limited size. Small trials are likely to report on results by random chance. For instance, more than 40% of control patients in one study were reported to have an incomplete block.[18] This unusually high baseline risk may have been related to the limited number of patients (n = 14), and it may have led to an overestimation of the rate of successful blocks with clonidine. One strength of meta-analysis is to combine inconclusive data from independent trials.

It has been postulated that clonidine improved the duration of postoperative analgesia only when used as an adjuvant to intermediate-acting LAs and that it was not worthwhile to combine it with long-acting LAs.[3] We performed sensitivity analyses to test this assumption. Interestingly, the beneficial effect of clonidine on the duration of analgesia was observed with all tested LAs. There were individual differences in as much as the benefit was minimal when clonidine was combined with prilocaine (less than 1 h prolongation of analgesia) and was maximal when combined with levo-bupivacaine (more than 4 h prolongation). This indirect comparison should not be overinterpreted because a limited number of patients received these two LAs. Also, 95% CIs of LAs overlapped. The similarity of the combined estimates of intermediate-acting and long-acting LAs suggested that there was actually no substantial differential effect of clonidine on postoperative analgesia that depended on the type of the LA. Those who are using clonidine as an adjuvant to LAs for peripheral nerve or plexus blocks should be aware that the clonidine-related prolongation of postoperative analgesia will last an average of about 2 h and independently of whether an intermediate-acting or long-acting LA is used. In contrast, the relative increase in duration of postoperative analgesia due to clonidine will largely depend on the nature of the LA. For instance, with intermediate-acting LAs alone, average duration of postoperative analgesia was 200 min. When clonidine was added, the duration increased by 112 min, *i.e.*, an increase of 56%. With long-acting LAs alone, average duration of postoperative analgesia was 850 min. When clonidine was added, the duration increased by 152 min, *i.e.*, an increase of 18% only. Thus, although clonidine prolongs duration of postoperative analgesia in association with any LA, the clinical relevance of adding clonidine to a long-acting LA may be questioned because the relative gain will be minimal. The same is true for duration of sensory and motor block.

It cannot be excluded that perineurally injected clonidine has an analgesic effect through systemic reabsorption. Only two studies compared clonidine across routes. In one, patients received 150 $\mu$g of clonidine subcutaneously or added to mepivacaine for brachial plexus block.[14] The duration of postoperative analgesia was longer in patients receiving clonidine into the plexus sheet. In the second, 140 $\mu$g of clonidine was added to ropivacaine for sciatic-femoral nerve block or was injected intramuscularly.[27] In that trial, clonidine had no impact on quality or duration of postoperative analgesia through either route.

Further new knowledge that emerged from our analysis related to the effect of clonidine on the duration of motor block. When added to intermediate-acting LAs, clonidine prolonged motor block by about 1.5 to 2 h. As with postoperative analgesia, the least effect was with prilocaine (average, 70 min). Interestingly, the motor

block prolonging effect that was seen when clonidine was added to ropivacaine (106 min) was very similar to the intermediate-acting LAs. In contrast, when clonidine was added to bupivacaine, prolongation of motor block was more than twice as long (244 min). This may have practical implications, for instance, when an appropriate LA is to be chosen for a patient undergoing ambulatory surgery. Long-lasting postoperative analgesia may be regarded as a beneficial outcome because it implies prolonged pain-free recovery. Prolonged motor block, however, may not always be warranted. For instance, ambulation may be delayed in patients undergoing surgery of a lower extremity.

Clonidine increased the risk of bradycardia, arterial hypotension, and sedation. This was not unexpected, and it is most likely the result of systemic reabsorption. For rational decision-making it is important to know how often these adverse effects happen, whether they depend on the dose of clonidine, and whether they are clinically relevant. The NNH for sedation was about 5, and it was about 10 for hypotension and bradycardia. These typical, clonidine-related, adverse effects may be considered as minor harm. However, they all have the potential to interfere with early mobilization. There was limited evidence that the risk of orthostatic hypotension and fainting was significantly associated with clonidine. Although rare, these adverse effects cannot be classified as minor harm. In one study, two patients who had received 300 $\mu$g of clonidine could not be discharged after day case surgery because they fainted on ambulation or because systolic blood pressure was less than 80 mmHg.[18] In another study, one patient who had received 300 $\mu$g of clonidine developed severe hypotension for several hours and needed to be monitored.[31] These observations indicate that 300 $\mu$g of clonidine is too high a dose. Today, this dose is likely to be obsolete. However, we were unable to find evidence of dose-responsiveness for harm. Consequently, the safe dose that still has adequate analgesic properties remains unknown.

Our meta-analysis has limitations. First, all patients underwent surgery without general anesthesia. Drugs used for general anesthesia, such as opioids, may have effects that last into the postoperative period and may interfere with, for instance, the delay until first analgesic request. In patients undergoing surgery with a nerve block alone, the duration of analgesia will exclusively be the consequence of the drugs that were used for the block. Strictly speaking, our results are applicable only to awake patients who receive a peripheral nerve or plexus block. In patients undergoing surgery with a combination of general anesthesia and interscalene plexus block with bupivacaine, the additional perineural injection of clonidine did not prolong postoperative analgesia.[37] Second, we were unable to demonstrate dose-responsiveness for either benefit or harm, which does not imply that there was none. One reason for that failure may have been that the majority of patients received the same dose, *i.e.*, 150 $\mu$g. Data from randomized dose-finding studies are largely inconclusive. In one, the authors claimed that 30, 90, and 300 $\mu$g of clonidine produced dose-dependent prolongation of analgesia when added to lidocaine for axillary plexus block.[18] However, ranges of duration of postoperative analgesia were very wide (with the largest dose, duration ranged from 190 to 1,440 min), need for rescue analgesia was not different between the three groups, and the lowest dose (30 $\mu$g) was more efficacious in producing sensory block than the medium dose (90 $\mu$g). In another dose-finding study, patients who had received 70 $\mu$g of clonidine added to lidocaine for ankle or metatarsal block reported less pain and needed less rescue analgesia postoperatively compared with controls who had received the lidocaine alone; however, those who had received 140 $\mu$g of clonidine were not different from controls.[31] Thus, data from these dose-finding studies do not help us further in deciding whether or not there is dose-responsiveness within the tested dose-range. A similar dilemma was described with clonidine added to LAs for intrathecal anesthesia.[1] Finally, data on postoperative pain intensity, at 12 and 24 h for instance, could not be analyzed because these data were only inconsistently reported in the original trials. Time to first analgesic request may be regarded as a surrogate for pain intensity; patients with moderate to severe pain are expected to request rescue analgesia earlier.

Our systematic review may be used as a rational basis for future research. There is an argument in favor of further investigations of very small doses of perineural clonidine. Very small doses are less likely to trigger systemic adverse effects. The benefit of other $\alpha_2$ agonists should be elaborated. For instance, dexmedetomidine added to lidocaine for intravenous regional anesthesia improved the quality of anesthesia and decreased analgesic requirements.[38,39] Also, the observation that the additional, clonidine-related duration of analgesia or motor block does not depend on the nature of the LA begs the question as to whether and why the efficacy of perineural clonidine depended on the duration of effect of the LA itself. Finally, none of these studies was performed with ultrasound guidance, and this may have an effect on the results.[40] The performance of clonidine when used as an adjuvant to LAs in the setting of peripheral nerve or plexus blocks that are performed with ultrasound guidance remains unknown and should be included in the research agenda.

In conclusion, in patients undergoing surgery without general anesthesia, clonidine, when added to a LA for peripheral nerve or plexus block, prolongs the duration of postoperative analgesia by about 2 h. This beneficial, albeit limited, effect can be observed with both intermediate-acting and long-acting LAs. The relative benefit, however, will be more pronounced with intermediate-

acting LAs. When clonidine is added to ropivacaine, prolongation of motor block will be shorter than when added to bupivacaine. Clonidine is associated with typical, systemic, adverse effects such as arterial hypotension and sedation that are most often minor. Orthostatic hypotension and fainting are more serious adverse effects; they may delay ambulation. The current literature does not allow establishing dose-responsiveness for either beneficial or harmful effects; thus, the optimal dose remains unknown.

Special thanks go to Marc Beaussier, M.D., Associate Professor, Department of Intensive Care, Hôpital St. Antoine, Université Pierre and Marie Curie, Paris, France; Sushma Bhatnagar, M.D., Professor, Department of Anaesthesiology, Institute Rotary Cancer Hospital, All India Institute of Medical Science, New Delhi, India; Johannes Buttner, M.D., Department Head, Department of Anaesthesiology and Intensive Care, Unfallklinik Murnau, Murnau, Germany; Darren J. Couture, M.D., Department of Anesthesiology, Naval Hospital Twentynine Palms, Twentynine Palms, California; Andreas Duma, M.D., Department of Anaesthesiology and Intensive Care, Medical University of Vienna, Vienna, Austria; Sandra Esteves, M.D., Servicio de Anestesia, Hospital Geral de Santo Antonio, Porto, Portugal; and Stephen Mannion, M.D., Department of Anaesthesia and Intensive Care, Cork University Hospital, Cork, Ireland, who responded to our inquiries. Ching-Hei Yeung, M.D., Ph.D., Institute of Reproductive Medicine, University Hospital of Münster, Münster, Germany, translated a Chinese paper into English.

## References

1. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR: Clonidine as an adjuvant to intrathecal local anesthetics for surgery: Systematic review of randomized trials. Reg Anesth Pain Med 2008; 33:159–67

2. Eisenach JC, De Kock M, Klimscha W: Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). ANESTHESIOLOGY 1996; 85:655–74

3. McCartney CJ, Duggan E, Apatu E: Should we add clonidine to local anesthetic for peripheral nerve blockade? A qualitative systematic review of the literature. Reg Anesth Pain Med 2007; 32:330–8

4. Murphy DB, McCartney CJ, Chan VW: Novel analgesic adjuncts for brachial plexus block: A systematic review. Anesth Analg 2000; 90:1122–8

5. L'Abbé KA, Detsky AS, O'Rourke K: Meta-analysis in clinical research. Ann Intern Med 1987; 107:224–33

6. Moore RA, Gavaghan D, Tramèr MR, Collins SL, McQuay HJ: Size is everything–large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. Pain 1998; 78:209–16

7. Elia N, Tramèr MR: Ketamine and postoperative pain–a quantitative systematic review of randomised trials. Pain 2005; 113:61–70

8. Casas JP, Chua W, Loukogeorgakis S, Vallance P, Smeeth L, Hingorani AD, MacAllister RJ: Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: Systematic review and meta-analysis. Lancet 2005; 366:2026–33

9. Hozo SP, Djulbegovic B, Hozo I: Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5:13

10. Beaussier M, Weickmans H, Abdelhalim Z, Lienhart A: Inguinal herniorrhaphy under monitored anesthesia care with ilioinguinal-iliohypogastric block: The impact of adding clonidine to ropivacaine. Anesth Analg 2005; 101:1659–62

11. Büttner J, Ott B, Klose R: The effect of adding clonidine to mepivacaine. Axillary brachial plexus blockade. Anaesthesist 1992; 41:548–54

12. Duma A, Urbanek B, Sitzwohl C, Kreiger A, Zimpfer M, Kapral S: Clonidine as an adjuvant to local anaesthetic axillary brachial plexus block: A randomized, controlled study. Br J Anaesth 2005; 94:112–6

13. Tramèr MR, Walder B: Number needed to treat (or harm). World J Surg 2005; 29:576–81

14. Singelyn FJ, Dangoisse M, Bartholomee S, Gouverneur JM: Adding clonidine to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Reg Anesth 1992; 17:148–50

15. Singelyn FJ, Gouverneur JM, Robert A: A minimum dose of clonidine added to mepivacaine prolongs the duration of anesthesia and analgesia after axillary brachial plexus block. Anesth Analg 1996; 83:1046–50

16. Adnan T, Elif AA, Ayse K, Gulnaz A: Clonidine as an adjuvant for lidocaine in axillary brachial plexus block in patients with chronic renal failure. Acta Anaesthesiol Scand 2005; 49:563–8

17. Antonucci S: Adiuvants in the axillary brachial plexus blockade. Comparison between clonidine, sufentanil and tramadol. Minerva Anestesiol 2001; 67:23–7

18. Bernard JM, Macaire P: Dose-range effects of clonidine added to lidocaine for brachial plexus block. ANESTHESIOLOGY 1997; 87:277–84

19. Broch O, Breucking E: Comparison of clonidine and tramadol added to prilocaine brachial plexus block - Analgesia, sensory and motor block. Anasthesiol Intensivmed Notfallmed Schmerzther 2005; 40:526–31

20. Casati A, Magistris L, Beccaria P, Cappelleri G, Aldegheri G, Fanelli G: Improving postoperative analgesia after axillary brachial plexus anesthesia with 0.75% ropivacaine. A double-blind evaluation of adding clonidine. Minerva Anestesiol 2001; 67:407–12

21. Casati A, Magistris L, Fanelli G, Beccaria P, Cappelleri G, Aldegheri G, Torri G: Small-dose clonidine prolongs postoperative analgesia after sciatic-femoral nerve block with 0.75% ropivacaine for foot surgery. Anesth Analg 2000; 91:388–92

22. Contreras-Dominguez V, Carbonell-Bellolio P, Sanzana Salamanca E, Ojeda-Grecie A: Addition of sodium bicarbonate and/or clonidine to mepivacaine: Influence on axillary brachial plexus block characteristics. Rev Esp Anestesiol Reanim 2006; 53:532–7

23. Danelli G, Nuzzi M, Salcuni PF, Caberti L, Berti M, Rossini E, Casati A, Fanelli G: Does clonidine 50 microg improve cervical plexus block obtained with ropivacaine 150 mg for carotid endarterectomy? A randomized, double-blinded study. J Clin Anesth 2006; 18:585–8

24. El Saied AH, Steyn MP, Ansermino JM: Clonidine prolongs the effect of ropivacaine for axillary brachial plexus blockade. Can J Anaesth 2000; 47:962–7

25. Erlacher W, Schuschnig C, Koinig H, Marhofer P, Melischek M, Mayer N, Kapral S: Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block. Can J Anaesth 2001; 48:522–5

26. Fang L, Liu F, Li L, Wang TJ, Yang LS, Sun XX: Effects of clonidine combined with various local anesthetics in brachial plexus block. Zhonghua Yi Xue Za Zhi 2004; 84:1712–3

27. Helayel PE, Kroth L, Boos GL, Jahns MT, Filho GRO: Effects of intramuscular and perineural clonidine on sciatic nerve block with 0.5% ropivacaine. Rev Bras Anestesiol 2005; 55:483–90

28. Iohom G, Machmachi A, Diarra DP, Khatouf M, Boileau S, Dap F, Boini S, Mertes PM, Bouaziz H: The effects of clonidine added to mepivacaine for paronychia surgery under axillary brachial plexus block. Anesth Analg 2005; 100:1179–83

29. Iskandar H, Guillaume E, Dixmerias F, Binje B, Rakotondriamihary S, Thiebaut R, Maurette P: The enhancement of sensory blockade by clonidine selectively added to mepivacaine after midhumeral block. Anesth Analg 2001; 93:771–5

30. Mjahed K, Jabri L, Benslama A, El Mouknia M, Barrou L, Benaguida M: Lidocaine-clonidine *versus* lidocaine-epinephrine in supraclavicular nerve block. Cahier d'Anesthesiol 1996; 44:507–11

31. Reinhart DJ, Wang W, Stagg KS, Walker KG, Bailey PL, Walker EB, Zaugg SE: Postoperative analgesia after peripheral nerve block for podiatric surgery: Clinical efficacy and chemical stability of lidocaine alone *versus* lidocaine plus clonidine. Anesth Analg 1996; 83:760–5

32. Iskandar H, Benard A, Ruel-Raymond J, Cochard G, Manaud B: The analgesic effect of interscalene block using clonidine as an analgesic for shoulder arthroscopy. Anesth Analg 2003; 96:260–2

33. Hutschala D, Mascher H, Schmetterer L, Klimscha W, Fleck T, Eichler HG, Tschernko EM: Clonidine added to bupivacaine enhances and prolongs analgesia after brachial plexus block *via* a local mechanism in healthy volunteers. Eur J Anaesthesiol 2004; 21:198–204

34. Sia S, Lepri A: Clonidine administered as an axillary block does not affect postoperative pain when given as the sole analgesic. Anesth Analg 1999; 88:1109–12

35. Gaumann DM, Brunet PC, Jirounek P: Clonidine enhances the effects of lidocaine on C-fiber action potential. Anesth Analg 1992; 74:719–25

36. Gentili M, Bernard JM, Bonnet F: Adding clonidine to lidocaine for intravenous regional anesthesia prevents tourniquet pain. Anesth Analg 1999; 88:1327–30

37. Culebras X, Van Gessel E, Hoffmeyer P, Gamulin Z: Clonidine combined with a long acting local anesthetic does not prolong postoperative analgesia after brachial plexus block but does induce hemodynamic changes. Anesth Analg 2001; 92:199–204

38. Esmaoglu A, Mizrak A, Akin A, Turk Y, Boyaci A: Addition of dexmedetomidine to lidocaine for intravenous regional anaesthesia. Eur J Anaesthesiol 2005; 22:447–51

39. Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I: Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004; 98:835–40

40. Abrahams MS, Aziz MF, Fu RF, Horn JL: Ultrasound guidance compared with electrical neurostimulation for peripheral nerve block: A systematic review and meta-analysis of randomized controlled trials. Br J Anaesth 2009; 102:408–17