

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

A Meta-analysis of Randomized Trials

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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 α_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.

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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)

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 ex-

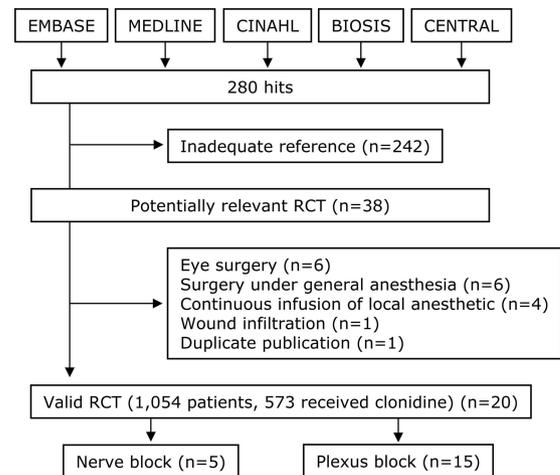


Fig. 1. Flow chart of retrieved, excluded, and eventually analyzed trials. RCT = randomized controlled trial.

plained 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.

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 μ g (13) 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) 2. Ropivacaine 150 mg + clonidine 150 μ g (20) [3. Ropivacaine 150 mg + sufentanil (20)] [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 μ g (20) 2. Ropivacaine 225 mg + no treatment (20)	1/1/0/0
Bernard ¹⁸	1997	Carpal tunnel	Axillary plexus	1. Lidocaine 400 mg + clonidine 30 μ g (14) 2. Lidocaine 400 mg + clonidine 90 μ g (14) 3. Lidocaine 400 mg + clonidine 300 μ g (14) 4. Lidocaine 400 mg + saline (14)	1/0/3/0
Broch ¹⁹	2005	Hand	Axillary plexus	[1. Prilocain 600 mg + tramadol (20)] 2. Prilocain 600 mg + clonidine 1.5 μ g \cdot kg ⁻¹ (20) 3. Prilocain 600 mg + no treatment (20)	1/0/3/0
Büttner ¹¹	1992	Hand	Axillary plexus	1. Mepivacaine 500 mg + saline (30) 2. Mepivacaine 500 mg + clonidine 120 μ g (30) 3. Mepivacaine 500 mg + clonidine 240 μ g (30)	1/0/3/1
Casati ²⁰	2001	Upper extremity	Axillary plexus	All injections with sodium bicarbonate 1. Ropivacaine 150 mg + no treatment (15) 2. Ropivacaine 150 mg + clonidine 1 μ g \cdot kg ⁻¹ (15)	2/1/3/1
Casati ²¹	2000	Hallux valgus	Sciatic-femoral nerves	1. Ropivacaine 225 mg + no treatment (15) 2. Ropivacaine 225 mg + clonidine 1 μ g \cdot kg ⁻¹ (15)	2/1/3/0
Contreras-D ²²	2006	Upper extremity	Axillary plexus	1. Mepivacaine 400 mg + saline (15) 2. Mepivacaine 400 mg + saline (15) 3. Mepivacaine 400 mg + clonidine 150 μ g (15) 4. Mepivacaine 400 mg + clonidine 150 μ g (15) 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) 2. Ropivacaine 150 mg + clonidine 50 μ g (20)	2/1/2/0
Duma ¹²	2005	Forearm and hand	Axillary plexus	1. Levo-Bupivacaine 200 mg + saline (20) 2. Levo-Bupivacaine 200 mg + clonidine 150 μ g (20) 3. Bupivacaine 200 mg + saline (18) 4. Bupivacaine 200 mg + clonidine 150 μ g (20)	1/0/3/0
El Saied ²⁴	2000	Forearm and hand	Axillary plexus	1. Ropivacaine 300 mg + saline (23) 2. Ropivacaine 300 mg + clonidine 150 μ g (23)	1/0/3/1
Erlacher ²⁵	2001	Forearm and hand	Axillary plexus	1. Mepivacaine 400 mg + saline (20) 2. Ropivacaine 300 mg + saline (20) 3. Bupivacaine 200 mg + saline (20) 4. Mepivacaine 400 mg + clonidine 150 μ g (20) 5. Ropivacaine 300 mg + clonidine 150 μ g (20) 6. Bupivacaine 200 mg + clonidine 150 μ g (20)	1/0/1/0
Fang ²⁶	2004	Arm	Axillary plexus	1. Lidocaine 400 mg + clonidine 150 μ g (15) 2. Bupivacaine 100 mg + clonidine 150 μ g (15) 3. Ropivacaine 160 mg + clonidine 150 μ g (15) 4. Lidocaine 400 mg + no treatment (15) 5. Bupivacaine 100 mg + no treatment (15) 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) [2. Ropivacaine 125 mg + clonidine 2 μ g \cdot kg ⁻¹ IM (14)] 3. Ropivacaine 125 mg + clonidine 2 μ g \cdot kg ⁻¹ (16)	2/1/0/1
Iohom ²⁸	2005	Paronychia	Axillary plexus	1. Mepivacaine 400 mg + no treatment (21) 2. Mepivacaine 400 mg + clonidine 100 μ g (20)	1/0/3/1
Iskandar ²⁹	2001	Hand	Mid-humeral block	1. Mepivacaine 600 mg + no treatment (28) 2. Mepivacaine 600 mg + clonidine 100 μ g (30)	2/0/3/1
Mjahed ³⁰	1996	Upper extremity	Axillary plexus	1. Lidocaine 600 mg + saline (30) [2. Lidocaine 600 mg + epinephrine (30)] 3. Lidocaine 600 mg + clonidine 150 μ g (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) 2. Lidocaine 260 mg + clonidine 70 μ g (27) 3. Lidocaine 260 mg + clonidine 140 μ g (25)	2/0/3/0
Singelyn ¹⁴	1992	Hand	Axillary plexus	1. Mepivacaine 400 mg + saline (10) [2. Mepivacaine 400 mg + clonidine 150 μ g SC (10)] 3. Mepivacaine 400 mg + clonidine 150 μ g (10) 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 μ g, were tested (fig. 2); 150 μ g 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 μ g. 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 μ g. 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-

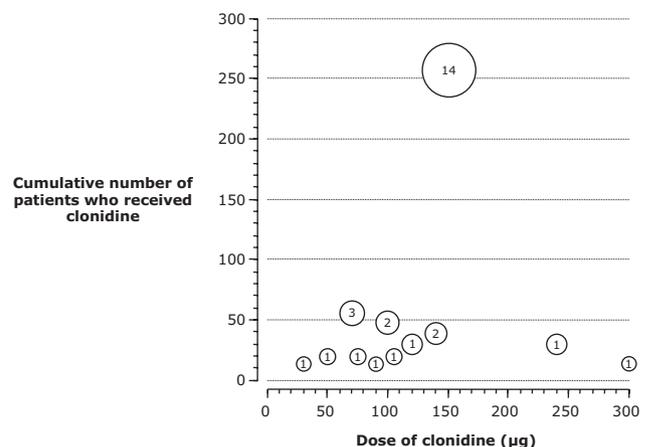


Fig. 2. Tested doses of clonidine. Bubble size corresponds to the cumulative number of patients who received the respective dose of clonidine. Numbers within the bubbles indicate the number of comparisons; numbers do not add up because some trials used more than one comparison.

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

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

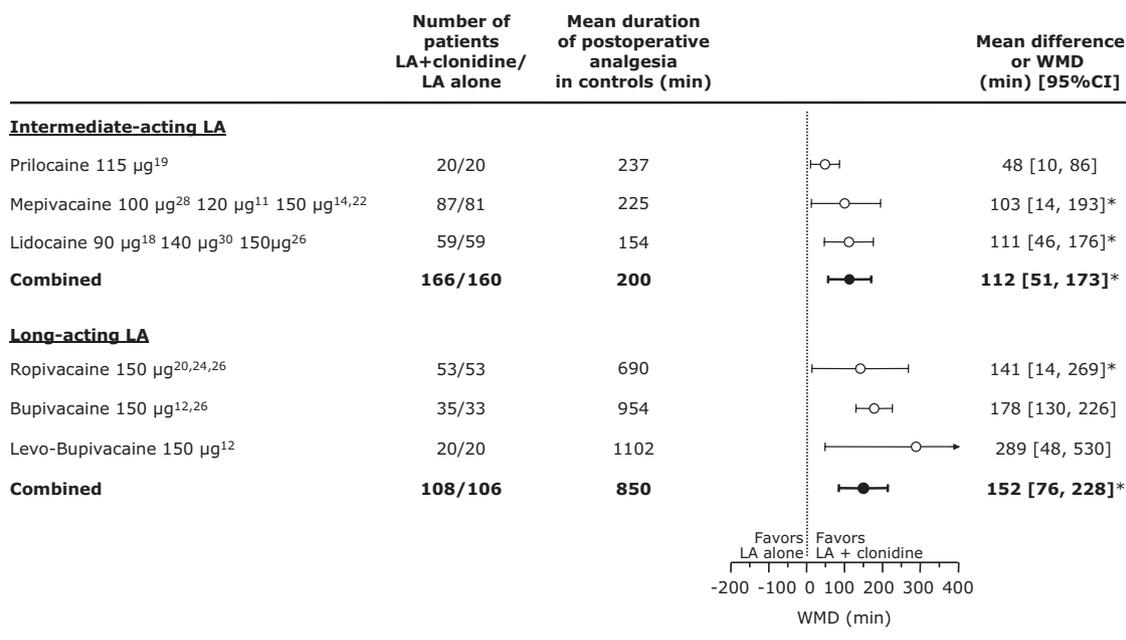


Fig. 3. Duration of postoperative analgesia. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of postoperative analgesia was defined as time until first analgesic request. Meta-analyses 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.

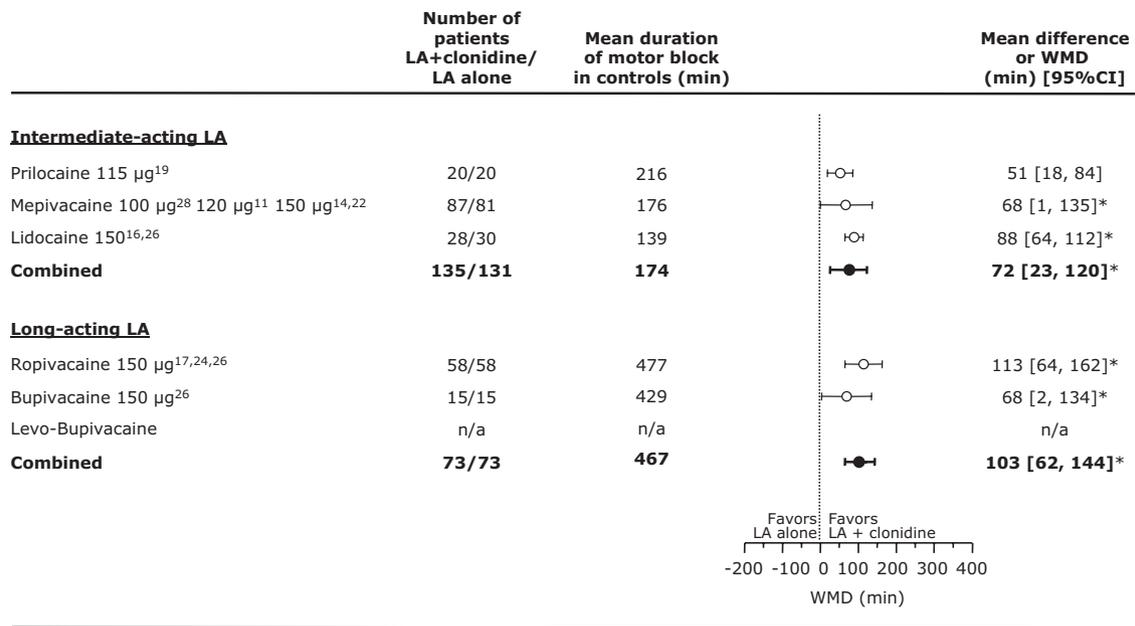


Fig. 4. Duration of postoperative sensory block. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of sensory block was tested using pinprick. Meta-analyses were performed using 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

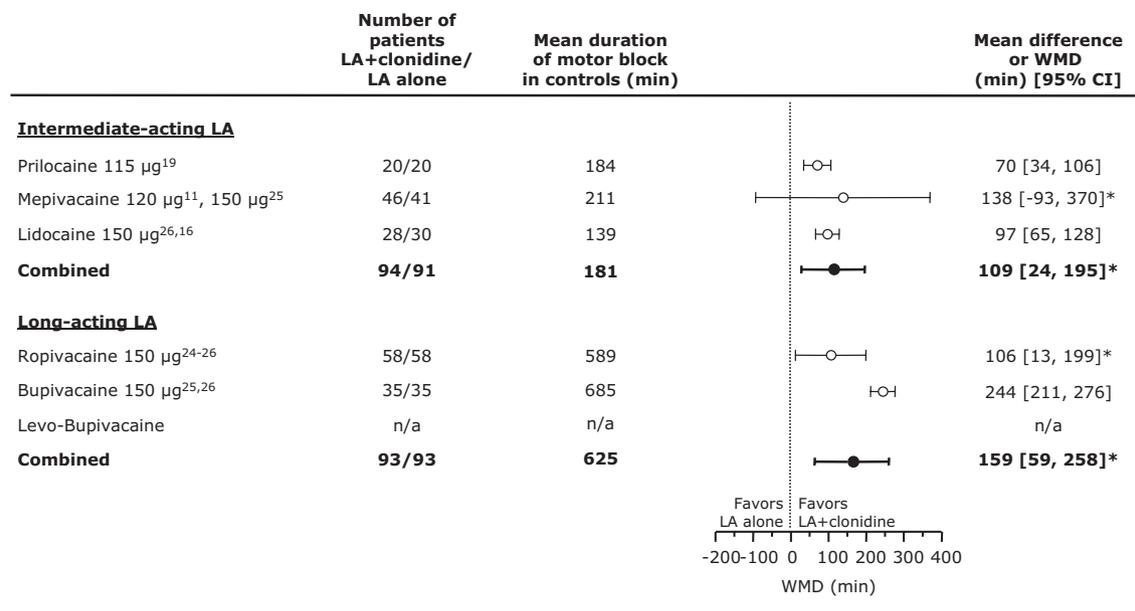


Fig. 5. Duration of motor block. Sensitivity analysis comparing the efficacy of clonidine added to intermediate-acting and long-acting local anesthetics in patients receiving an axillary plexus block. Duration of motor block was tested using the Bromage scale or was defined as a reduction of at least 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 (μg)	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 μg . 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 μg . 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 μg . 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 μg . 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 α_2 adrenergic agonist, was initially used for its antihypertensive properties. The large expression of α_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 α_2 adrenoceptors 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 μg 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 μg 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 μg 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 μg of clonidine developed severe hypotension for several hours and needed to be monitored.³¹ These observations indicate that 300 μg 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 μg . Data from randomized dose-finding studies are largely inconclusive. In one, the authors claimed that 30, 90, and 300 μg 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 μg) was more efficacious in producing sensory block than the medium dose (90 μg). In another dose-finding study, patients who had received 70 μg 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 μg 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 α_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 IAs. 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.

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