General Anesthesia

Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block

[La clonidine comme adjuvant à la mépivacaïne, la ropivacaïne et la bupivacaïne pour une anesthésie par bloc brachial axillaire périvasculaire]

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Purpose: To evaluate the effects of clonidine on three local anesthetics (mepivacaine 1%, ropivacaine 0.75% and bupivacaine 0.5%) with comparable potency and almost the same concentration-response relationship.

Methods: One hundred and twenty trauma-patients were randomly allocated into six groups. In the control-groups (*Mo/Ro/Bo*) brachial plexus was performed using 40 mL of local anesthetic plus 1 mL of NaCL 0.9%. In the clonidine-groups (*Mc/Rc/Bc*) brachial plexus was performed using each 40 mL of drug plus 1 mL (0.150 mg) of clonidine. Onset-time and the duration of the sensory block were recorded. Data are expressed as mean ± SD.

Results: According to the average sensory block determined by a visual analog scale in the median, ulnar and radial nerve distributions and ranging from 100 (no sensory blockade) to 0 (complete sensory blockade), both mepi-groups showed a rapid onset (at 10 min: -*Mo* 20 ± 15 / *Mc* 19 ± 14; at 30 min: -*Mo* 3 ± 4 / *Mc* 5 ± 4). The ropi-and bupi- groups both had a longer onset time (at 10 min: -*Ro* 23 ± 19 / *Rc* 25 ± 22 / *Bo* 24 ± 15; at 30 min -*Ro* 10 ± 6 / *Rc* 11 ± 6 / *Bo* 12 ± 4). The onset time in group-*Bc* was significantly prolonged (at 10 min: -45 ± 21; at 30 min: -20 ± 6).

Duration of motor blockade was prolonged by clonidine only in the mepivacaine and bupivacaine groups; (in minutes: *Mo* 212 ± 47 -*Mc* 468 ± 62; *Ro* 702 ± 52 -*Rc* 712 ± 82; *Bo* 728 ± 36 -*Bc* 972 ± 72).

Conclusion: The present study shows that the addition of clonidine has a different impact on each of the three local anesthetics investigated in terms of onset and duration of block.

Objectif : *Évaluer les effets de la clonidine sur trois anesthésiques locaux à puissance comparable (la mépivacaïne à 1 %, la ropivacaïne à 0,75 % et la bupivacaïne à 0,5 %) qui présentent une relation concentration-réponse presque similaire.*

Méthode : *Cent vingt patients victimes de traumatisme ont été répartis au hasard en six groupes. Dans les groupes témoins (Mo/Ro/Bo), le bloc du plexus brachial comprenait 40 mL d'anesthésique local plus 1 mL de NaCL à 0,9 %. Dans les groupes clonidine (Mc/Rc/Bc), il comprenait 40 mL d'anesthésique local plus 1 mL (0,150 mg) de clonidine. Le délai d'installation et la durée du blocage sensitif ont été notés et exprimés comme la moyenne ± l'écart type.*

Résultats : *D'après le bloc sensitif moyen, déterminé par une échelle visuelle analogique appliquée aux distributions des nerfs médian, cubital et radial et qui s'étend de 100 (aucune anesthésie) à 0 (blocage sensitif complet), les deux groupes de mépivacaïne ont indiqué une installation rapide (à 10 min : -Mo 20 ± 15 / Mc 19 ± 14; à 30 min : -Mo 3 ± 4 / Mc 5 ± 4). Les groupes ropivacaïne et bupivacaïne ont présenté un plus long délai d'installation (à 10 min : -Ro 23 ± 19 / Rc 25 ± 22 / Bo 24 ± 15; à 30 min : -Ro 10 ± 6 / Rc 11 ± 6 / Bo 12 ± 4). Le délai d'installation s'est prolongé de façon significative dans le groupe -Bc (à 10 min : -45 ± 21; à 30 min : -20 ± 6).*

La durée du blocage moteur a été prolongée par la clonidine dans les groupes mépivacaïne et bupivacaïne seulement; (en minutes : Mo 212 ± 47 -Mc 468 ± 62; Ro 702 ± 52 -Rc 712 ± 82; Bo 728 ± 36 -Bc 972 ± 72).

Conclusion : *La présente étude montre que l'addition de clonidine provoque des effets différents sur chacun des trois anesthésiques locaux expérimentés quant au délai d'installation et à la durée de l'anesthésie.*

T he three amino amid local anesthetics mepivacaine, bupivacaine and ropivacaine show differences in terms of onset, duration and quality of block, due to differences in their lipophilic side-chains. In the concentrations used, mepivacaine 1%, bupivacaine 0.5% and ropivacaine 0,75%, are almost equipotent with a very similar concentration-response relationship.[1,2] Clonidine,[3,4] an imidazole compound, has a history as a block prolonging adjuvant in regional anesthesia. The aim of the present study was to evaluate the effects of clonidine on these three substances on onset-time and duration of axillary perivascular brachial plexus block.

Methods
After institutional approval and written informed consent, we consecutively investigated 120 patients (ASA I–III) undergoing surgery of the forearm or hand after trauma, under axillary perivascular brachial plexus block. A standard block technique for a perivascular approach according to Winnie was applied in all cases. To locate the plexus sheath, a nerve stimulator (Alphaplex™, Sterimed, Germany) with a 24-gauge, 4 cm Sprotte needle was used. Patients were allocated in six groups in a controlled, randomised double-blinded design using a computer-generated randomisation list. Table I shows how groups were assigned.

Injection time was chosen as the beginning of all time intervals. Sensory block and motor block of musculocutaneous, radial, ulnar and median nerve were recorded after five, 15, 30, 60, 120, 180, 360 and 480 min. Sensory block was determined by a visual analogue-scale in comparison to the contra lateral arm from 100 (no sign of sensory blockade) to 0 (complete sensory blockade). Sensory onset of each nerve was assessed by pinprick and compared to the same stimulation on the contra lateral arm. Motor block was evaluated by thumb abduction (radial nerve), thumb adduction (ulnar nerve), thumb opposition (median nerve) and flexion of the elbow in supination and pronation of the forearm (musculocutaneous nerve). Measurements were performed by using a

modification of the Lovett rating scale, from 6 (normal muscular force) to 0 (complete paralysis).[5] The duration of sensory block was considered as the time interval between the administration of the local anesthetic and the first postoperative pain. Heart rate, non-invasive blood pressure, oxygen saturation, were measured at the same time points.

The necessary sample size was estimated by data of previous studies using Machin and Campbell tables. Data were expressed as mean ± SD. For statistical analysis of demographic data and for comparison of groups paired t test and for the comparison of difference of data the analysis of variance was performed. A *P* value <0.05 was considered significant.

TABLE I Group-assignment

Group Mo	40 mL of mepivacaine 1% plus 1 mL of NaCL 0.9%
Group Mc	40 mL of mepivacaine plus 1 mL (0.150 mg) of clonidine
Group Ro	40 mL of ropivacaine 0.75% plus 1 mL of NaCL 0.9%
Group Rc	40 mL of ropivacaine 0.75% plus 1 mL (0.150 mg) of clonidine
Group Bo	40 mL of bupivacaine 0.5% plus 1 mL of NaCL 0.9%
Group Bc	40 mL of bupivacaine 0.5% plus 1 mL (0.150 mg) of clonidine

TABLE II Clinical characteristics

	Group Mo	*Group Mc*	*Group Ro*	*Group Rc*	*Group Bo*	*Group Bc*
Sex (m/f)	11/9	10/10	7/13	9/11	11/9	9/11
Age (yr)	44 ± 21	46 ± 19	40 ± 13	46 ± 20	46 ± 14	48 ± 20
Weight (kg)	70 ± 13	74 ± 8	76 ± 13	74 ± 13	77 ± 12	73 ± 9
Height (cm)	169 ± 6	172 ± 8	170 ± 16	170 ± 11	173 ± 8	170 ± 7

TABLE III Onset time of sensory blockade

	5 min	*10 min*	*20 min*	*30 min*
Group Mo	35 ± 22	20 ± 15	10 ± 7	4 ± 3
Group Mc	38 ± 24	19 ± 14	12 ± 6	5 ± 4
Group Ro	68 ± 24	23 ± 19	16 ± 10	10 ± 6
Group Rc	64 ± 26	25 ± 22	17 ± 10	11 ± 6
Group Bo	68 ± 26	24 ± 15	16 ± 6	12 ± 4
Group Bc	63 ± 25	45 ± 21*	26 ± 9*	20 ± 6*

*P<0.05

Table III shows the average sensory block by visual analog scale of the median, radial and ulnar nerves for measurements after 5/10/20 and 30 min. The visual analog scale ranges from 100 (no sensory blockade) to 0 (complete sensory blockade) and was determined selectively for each nerve distribution.
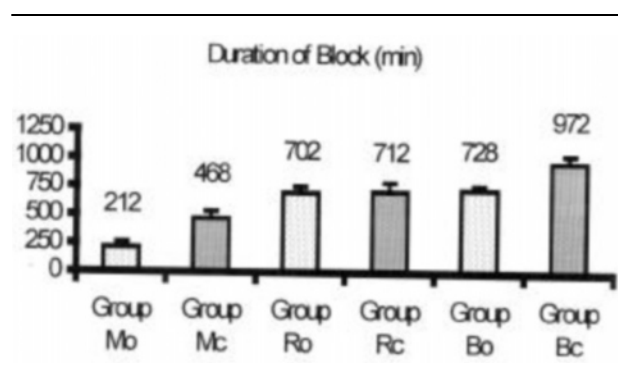
FIGURE Duration of motor blockade with mepivacaine 1%, bupivacaine 0.5%, ropivacaine 0.75% with and without clonidine 0.150 mg. The duration of blockade (in minutes) is prolonged by the addition of clonidine in the mepivacaine and the bupivacaine-groups. Block was not prolonged by clonidine in the ropivacaine-group.

Results

Clinical characteristics were not different between groups (Table II). The addition of clonidine resulted in a block-prolonging effect, both in the mepivacaine 1%-group, and in the bupivacaine 0.5%-group. As adjuvant for ropivacaine 0.75%, clonidine failed to prolong the block (Figure). Onset of sensory block was significantly shorter in both mepivacaine-groups. The bupivacaine-and ropivacaine-groups all had a longer onset-time, in the bupivacaine/clonidine-group the onset was even significantly prolonged (Table III). Hemodynamic parameters (data not shown) were stable in all groups throughout the entire study period. Side effects, such as hypotension, nausea and vomiting were not recorded in any of the cases.

Discussion

The major finding of the present study is that the addition of clonidine has a different impact on each of the three investigated local anesthetics in terms of onset and block prolonging activity.

Alpha 2-adrenoceptors are located on primary afferent terminals, on neurons in the superficial laminae of the spinal cord, and within several brainstem nuclei implicated in analgesia, supporting the possibility of analgetic action at peripheral, spinal, and brainstem sites. Clonidine enhances both sensory and motor blockade from epidural or peripheral nerve injection of local anesthetics. Clonidine blocks conduction of C and A gamma fibres and increases potassium conductance in isolated neurons and intensifies conduction block of local anesthetics. Local vasoconstriction resulting in reduced absorption from the injection site was an other point of discussion, but compared with epinephrine as adjuvant it failed to influence plasma levels, indicating a direct action on the nerve.

The addition of clonidine to mepivacaine 1% and to bupivacaine 0.5% resulted in a very impressive block prolongation but did not lead to an additional block prolonging effect in the ropivacaine group.[6] A possible explanation for these negative findings may be the conditions permitting a synergistic effect of clonidine and the local anesthetic chosen. Studies have been performed in volunteers to determine the effect of ropivacaine compared with bupivacaine and lidocaine on cutaneous blood flow after injection of 0.1 mL. Both, bupivacaine and lidocaine produced vasodilatation in human skin, but ropivacaine decreased skin blood flow.[7] In dogs, a significant constriction of the pial arteries could be shown after the local application of ropivacaine.[8] As ropivacaine had intrinsic vasoconstricting properties not mediated by an activation of alpha 2-adrenoceptors, this could have explained why the addition of clonidine did not result in any benefit.

Ropivacaine and bupivacaine resulted in comparable duration of peripheral blockade. In the isolated rat vagus nerve, ropivacaine was less potent than bupivacaine in blocking A beta fibres, but it was more effective than bupivacaine in the blockade of A gamma and C-fibres. The two agents have almost identical dissociation constants with a pKa of 8.0 and 8.1 and similar apparent protein-binding capacity, but ropivacaine is less lipid soluble than bupivacaine. It would be reasonable to expect that a weaker binding to extra neural fat and tissues with ropivacaine might also contribute to greater availability of ropivacaine for transfer to the site of action in the nerves. These factors could have explained the tendency towards a more rapid block onset obtained with ropivacaine.[9,10]

It might be speculated that stereospecific factors are involved in the mechanism of action of clonidine on the sodium-channels.

Clonidine is associated with specific side effects, specially cardiovascular (e.g., bradycardia, hypotension), and bupivacaine is known for its potential cardiotoxicity and cerebral convulsant activity. Ropivacaine appears well suited to achieve long lasting nerve blockade without having to resort to adjuvant medications.

References

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