Clonidine prolongs the effect of ropivacaine for axillary brachial plexus blockade

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Purpose: To evaluate the effect of adding clonidine to ropivacaine, for axillary brachial plexus blockade, on the onset and duration of sensory and motor block and duration of analgesia.

Methods: In a prospective randomised double blind placebo controlled study axillary brachial plexus blockade was performed in 50 patients using 40 ml ropivacaine 0.75 %. Group (A) had 150 μg clonidine and Group (B) 1 ml normal saline added to the local anesthetic. Sensory function was tested using pinprick (sharp sensation, blunt sensation or no sensation) and temperature with an ice cube compared with the opposite arm, (cold/not cold). Motor function was assessed using a modified Bromage scale. Postoperative analgesia was standardised. Onset and duration of sensory and motor blockade, duration of analgesia, postoperative pain score, and analgesic requirement were compared.

Results: The clonidine patients showed an increase in duration of sensory loss from 489 min to 628 min with a mean difference of 138 min (95% confidence interval of 90 to 187 min), motor blockade from 552 min to 721 min with a mean difference of 170 min (95% confidence interval of 117 to 222 min), and analgesia from 587 min to 828 min with mean difference of 241 min (95% confidence interval of 188 to 294 min). There was no difference in onset time. No side effects were noted.

Conclusion: The addition of 150 μg of clonidine to ropivacaine, for brachial plexus blockade, prolongs motor and sensory block and analgesia, without an increased incidence of side effects.

Objectif : Évaluer l'effet d'un ajout de clonidine à la ropivacaïne, pour le blocage du plexus brachial axillaire, sur le délai d'installation et la durée du bloc sensitif et moteur et sur la durée de l'analgésie.

Méthode : Il s'agit d'une étude prospective, randomisée et à double insu contre placebo. Un blocage du plexus brachial axillaire a été réalisé chez 50 patients en utilisant 40 ml de ropivacaïne à 0,75 %. On a ajouté à l'anesthésique local, 150 μg de clonidine pour les patients du groupe A et 1 ml de solution salée pour ceux du groupe B. La fonction sensitive a été testée par piqûre d'épingle (sensation vive, légère sensation ou insensibilité) et la température par un cube de glace posé en alternance sur les deux bras (froid, non froid). La fonction motrice a été évaluée avec une échelle de Bromage modifiée. L'analgésie postopératoire a été normalisée. On a comparé le délai d'installation et la durée du blocage sensitif et moteur, la durée de l'analgésie, le score de douleur postopératoire et les besoins analgésiques.

Résultats : Chez les patients qui ont reçu de la clonidine, on a noté une perte sensitive de plus longue durée, de 489 min à 628 min avec une différence moyenne de 138 min (intervalle de confiance de 95 %, de 90 à 187 min), un blocage moteur plus long de 552 min à 721 min avec une différence moyenne de 170 min (IC de 95 %, de 117 à 222 min) et une meilleure analgésie de 587 min à 828 min avec une différence moyenne de 241 min (IC de 95 %, de 188 à 294 min). Il n'y a pas eu de différence de délai d'installation. Aucun effet secondaire n'a été enregistré.

Conclusion : L'ajout de 150 μg de clonidine à la ropivacaïne, pour un blocage du plexus brachial, prolonge le bloc moteur et sensitif et l'analgésie sans augmenter les effets secondaires.

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THE axillary approach to the brachial plexus is a commonly used technique for hand and forearm surgery at our institution. Regional anesthesia provides a safe, low cost technique, with the advantage of prolonged postoperative pain relief. The axillary approach is associated with a lower incidence of side effects than other approaches to the brachial plexus, especially the incidence of pneumothorax. The disadvantages of the axillary approach include slower onset than supraclavicular approach and an increased incidence of tourniquet pain during prolonged procedures.[1,2]

Ropivacaine is an aminoamide local anesthetic prepared as pure "S" enantiomer. This single enantiomer composition and the lower lipid solubility have produced a drug with less cardiotoxicity than bupivacaine.[3] It is prepared as a plain solution without epinephrine due to its unique intrinsic vasoconstrictor activity. Unlike the other amide local anesthetics there appears to be no prolongation of action with the addition of epinephrine.[4,5]

Clonidine, an imidazoline, with selective partial agonist activity at α_2 adrenergic receptors, has been used for many years as a centrally acting anti-hypertensive agent. The ability of clonidine to reduce the requirements for traditional anesthetic and analgesic agents is increasingly being used in the perioperative period.[6] The mechanism of antinociceptive action of clonidine is still obscure with a number of theories being postulated. Several clinical studies have shown that clonidine can prolong the duration of analgesia when used in combination with local anesthetic agents,[7] including when injected into peripheral nerve sheaths.[8] Clonidine appears to be superior to epinephrine in enhancing the duration of plexus blockade with bupivacaine and may offer other advantages while avoiding the potential risks of epinephrine.[9,10] There are no previous reports on the effect of adding clonidine to ropivacaine.

The aim of this study was to evaluate the effect of the addition of clonidine to the onset and duration of anesthesia, analgesia and motor blockade following axillary plexus block with ropivacaine.

Methods

Patient selection

Following approval from the local hospital ethics committee 50 ASA I or II patients with a history of traumatic injury due to undergo hand or forearm surgery lasting more than 30 min, were recruited to a prospective randomised, double blind, placebo controlled study. Exclusion criteria were patients age <18 yr or >60 yr, weight <70 kg or >100 kg, patients receiving anticoagulants, patients with history of hypertension, peripheral neuropathy or hypersensitivity to local anesthetic agents. Details of the anesthetic technique and the study protocol were fully explained at the preoperative visit and informed written consent was obtained from each patient.

Patients were randomised into two groups to receive 40 ml ropivacaine 0.75% with either 1 ml (150 μg) clonidine (group A) or 1 ml normal saline (group B) added to the local anesthetic solution. Identical syringes containing 1 ml of either clonidine or normal saline and labelled only with the study number were prepared by an investigator neither involved in placing the blocks nor following up patients.

Anesthetic technique

On arrival in the anesthetic room all patients had intravenous access secured prior to receiving sedation with 2.5 mg midazolam *iv*. The patient was placed in a supine position with the appropriate arm abducted to 75° and externally rotated. The same investigator (AE), using a sterile aseptic technique, performed an axillary block via a trans-arterial approach with a 23-gauge needle inserted high in the axilla. All solutions were at room temperature prior to injection. A total of 41 ml of solution was slowly injected with 18 ml posterior to the artery and 18 ml anterior. The remaining 5 ml were instilled subcutaneously as the needle was withdrawn to block the intercostobrachial nerve. Compression to the neurovascular sheath was maintained for at least five minutes following performance of the block to avoid haematoma formation and to minimise distal spread of the mixture. The patient's arm was kept elevated on a pillow over their chest for at least 30 min prior to surgery. A 10-cm wide tourniquet was applied to the upper arm, following protection with a layer of orthopedic wool, and inflated to 250 mmHg prior to skin incision.

All patients were monitored before starting until at least one hour after finishing the procedure using automated blood pressure, oxygen saturation, and ECG lead II. Baseline values were taken a few minutes after midazolam premedication. Any episodes of hypotension or bradycardia, defined as a 20% decrease in pressure or heart rate in relation to the baseline value, were noted. Postoperative analgesia treatment was standardised. Mild or moderate pain was treated with acetaminophen 1 g every six hours and/or 50 mg diclofenac every eight hours, severe pain with 5-10 mg morphine every six hours as required.

The time of completion of the injection was taken as the baseline for time interval measurements. Patients were evaluated every five minutes for 40 min from initi-

ation of the block for sensory and motor function as well as sedation score. Sensory function tested by pain and temperature sensation was assessed in five regions corresponding to the nerve distributions in the forearm and hand (ulnar, median, radial, medial cutaneous of forearm and lateral cutaneous of forearm). A two point scale for temperature, ice cube compared with the opposite arm, (cold/not cold) and a 3 point scale for pain using pinprick with a 23G needle (sharp sensation, blunt sensation or no sensation) were used. The patient reported recovery time to 'slight feeling' and then 'full recovery'. Motor function was assessed using a modified Bromage scale (3 = extension of elbow against gravity, 2 = flexion of wrist against gravity, 1 = finger movement, 0 = no movement). The patient reported recovery time to slight movement and then full recovery. Sensory onset was defined as time from injection till disappearance of sharp pain by prick test, while motor onset was defined as time between injection and motor paralysis distal to injection site. Each of the five nerve distributions was assessed separately for sensory function to address the potential problem of differential blockade.

Tourniquet discomfort was assessed using a VAS prior to inflation, every 15 min and then just before deflation. Sedation was scored using a four point scale (1 = awake, 2 = drowsy but responsive to command, 3 = very drowsy but responsive to pain, 4 = unresponsive). This postoperative sedation score was performed every two hours until scoring <2 or for 12 hr. All patients stayed in hospital overnight and a printed assessment chart for timing and distribution of return of sensation, movement, pain was given to them to complete with the aid of the ward nurse. Patients were also assessed for total block failure, nerve distributions unblocked, need for supplementation of block, time to first postoperative analgesia and total postoperative analgesia requirements.

To estimate the required sample size, results from previous similar studies were evaluated.[9,11] A 20% increase in duration of postoperative analgesia was considered a clinically relevant difference. For a significance level of 5% and power of 80% the estimated sample size was 44. Results are expressed as mean ± standard error of the mean as well as confidence intervals. Patient characteristics and times were analysed for normality and the two groups compared using unpaired t-tests. Non parametric data was analysed using the Mann-Whitney *U* Test. Statistical significance was considered to be a *P* value of <0.05.

Results

The two groups did not differ in age, weight, sex or duration of surgery (Table I). Fifty patients were studied (25 in each group). Of these four patients were excluded; in two patients the block was incomplete (one from each group). A third patient was discharged without filling in the form, while the fourth patient had no surgery because, after re-examination of his injury he only required manipulation and plaster fixation.

The onset times in each nerve distribution are presented in (Table II). No difference was noted between the groups for onset time.

The mean durations of anesthesia, analgesia, and loss of motor power are shown in Table III. The clonidine group of patients showed an increase in duration of anesthesia (138 min with 95% confidence interval of 90 to 187 min), loss of motor power (170 min with 95% confidence interval of 117 to 222 min) and analgesia (241 min with 95% confidence interval of 188 to 294 min).

No difference in sedation scores was noted between the groups. (1.87 ± 0.17 *vs* 1.47 ± 0.14 $P = 0.082$). Neither hypotension nor bradycardia was noted in any patient and no other early postoperative sequelae (axillary hematoma, parasthesia) were noted.

TABLE I Patient demographics and duration of surgery

	Group 1 (n=23)	*Group 2 (n=23)*	*P*
Sex (Female : Male)	6 : 17	5 : 18	NS
Age (yr)*	24 (17-62)	36 (17-60)	NS
Weight (kg)	75.7 ± 1.5	79.9 ± 3.8	NS
Duration of surgery (min)	85.7 ± 9.5	96.5 ± 13	NS

Values are (mean ± SEM) except *median (range)

TABLE II Onset time (minutes) for sensory block in each nerve distribution and motor blockade

	Group 1 (n=23)	*Group 2 (n=23)*	*P*
Ulnar nerve	18.2 ± 1.2	19.6 ± 1.5	NS
Median nerve	18.9 ± 1.7	20.2 ± 1.2	NS
Radial nerve	22.9 ± 1.9	21.1 ± 1.4	NS
Lateral cutaneous nerve	27.7 ± 2.5	24.6 ± 1.7	NS
Median cutaneous nerve	13.6 ± 1.0	14.1 ± 0.7	NS
Motor power	17.9 ± 1.7	16.3 ± 1.4	NS

(mean ± SEM)

TABLE III Duration of anesthesia, analgesia, and loss of motor power (minutes) in each group

	Group A (n=23)	*Group B (n=23)*	*P*
Duration of anesthesia	628 ± 35	489 ± 34	< 0.01
Duration of analgesia	828 ± 35	587 ±40	< 0.001
Duration of motor power loss	721 ± 38	552 ± 35	< 0.01

(mean ± SEM)

Discussion

The addition of 150 μg clonidine to 40 ml ropivacaine 0.75 % for axillary brachial plexus blockade resulted in an increase in duration of both anesthesia (from 489 min to 628 min) and analgesia (from 587 min to 828 min) while also prolonging duration of motor blockade (from 552 min to 721 min).

Analgesia prolongation has been shown with the addition of clonidine to local anesthetic solutions but opinion differs on the incidence of side effects, particularly the possibility of bradycardia, hypotension and sedation.[12] In this study there was a trend towards an increase level of sedation in the clonidine group but this did not reach statistical significance. Should the number of subjects studied been greater a difference may have been seen. The clonidine dose was arbitrarily chosen based on previous studies.[9–11] Whether lower doses of clonidine can be used with ropivacaine, as with lidocaine,[8] without compromising efficacy of the block is to be determined. This would then reduce the potential for side effects, in particular when used for day-case procedures.

The mechanism whereby clonidine prolongs the duration of local anesthetic blockade when injected into a nerve sheath remains speculative. Clonidine is highly lipid soluble, easily crosses the blood brain barrier to interact with alpha$_2$ adrenergic receptors at both spinal and supraspinal sites within the central nervous system producing its analgesic effect.[13,14] Epidural and intrathecal clonidine does produce analgesia when used as the sole analgesic agent.[15] Clonidine injected into peripheral nerve sheath may act by translocation via nerves (axonal transport) or blood stream to the spinal cord as has become evident with opiate analgesics.[16,17] However, it is unlikely that this mechanism is the main mechanism of action in enhancement of peripheral nerve blockade. This is supported by the failure of clonidine to increase the duration of brachial plexus blockade when injected subcutanuously and when injected into the nerve sheath without local anesthetic.[11,18]

The mechanism is more likely to be at the site of injection around peripheral nerves. The "vasoconstriction theory" whereby stimulation of the adrenergic receptors results in the reduction of systemic absorption of local anesthetics,[19] is unlikely because the intrinsic vasoconstrictive effect of ropivacaine is not enhanced by epinephrine.[4]

The effect may occur by direct action of clonidine on nerve fibre conduction, specifically C and A delta fibres.[20,21] However, this would require high local concentrations and would not explain why clonidine alone injected into the nerve sheath failed to produce prolonged analgesia.[18] The action of clonidine would then more likely be via a synergistic mechanism of action in combination with the local anesthetic resulting in the prolonged effect. This is probably the only mechanism that would explain the extended duration of both the sensory and motor blockade.

What is certain is that clonidine has mixed α_1 and α_2 agonist effects at both pre and postsynaptic receptors as well as effects on a number of other specific receptors. Its mechanism of action and effects, therefore, are likely to be compound and complex.

Both the concentration and the volume of local anesthetic are likely to affect the onset and efficacy of plexus blockade.[22] Ropivacaine 0.75% was comparable with bupivacaine 0.5% when used for supraclavicular brachial plexus block.[23] We elected to use ropivacaine 0.75% in the same volume as we had previously used for bupivacaine (40 ml). This dose of ropivacaine is the maximum dose of ropivacaine recommended by the manufacturer for brachial plexus blockade in adults.[24] It provides a high quality dense block, prolonged duration with minimal failure rate or incomplete block.[22] Patients weighing < 60 kg were excluded to avoid the potential risks of administering excessive doses.

Epinephrine has traditionally been added to local anesthetic solutions to prolong the duration of analgesia and reduce the systemic absorption. The addition of epinephrine to ropivacaine does not provide any prolongation of the duration of sensory or motor block,[4] nor does it reduce the systemic absorption of local anesthetic.[5] This may be partially explained by the unique intrinsic vasoconstrictor activity of ropivacaine. Prolongation of analgesia and anesthesia with the addition of clonidine that was observed in this study has been seen in previous studies combining clonidine with other local anesthetics.[9]

In some cases we may have underestimated the onset time for loss of motor power, as movement was restricted at the wrist or fingers because of pain and/or physical injury. Nevertheless, we noted that the motor block was profound, and the onset and duration was comparable with that of the sensory block. The relative sparing of motor block, as seen with epidural ropivacaine,[25] was not seen in this study. This may partially be explained by the higher doses used but may also reflect a differential effect on central and peripheral nerves. The prolongation of motor blockade with the addition of clonidine has not previously been observed.

Clonidine has been shown to prevent tourniquet pain when used with lidocaine for intravenous regional anesthesia.[26] Despite prolonged periods of surgery, in some

cases, no tourniquet pain was seen in any group and thus we are unable to evaluate the effect of clonidine on tourniquet pain following axillary plexus blockade.

The extended effect of adding clonidine to ropivacaine may prove valuable in cases requiring prolonged surgery, as in reimplantation surgery. The four hours of additional analgesia with the low incidence of side effects makes the addition of clonidine an attractive option to prolong analgesia routinely in the postoperative period. These findings are in agreement with previous studies examining the effect of combining clonidine with local anesthetic agents injected into nerve sheaths. In conclusion, this study shows that clonidine added to ropivacaine is an appropriate technique for clinical practice with a low side effect profile and considerable therapeutic benefit.

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