Efficacy of clonidine as an adjuvant to ropivacaine in supraclavicular brachial plexus block: A prospective study

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ABSTRACT

Background and Aims: Bupivacaine has been the most frequently used local anaesthetic in brachial plexus block, but ropivacaine has also been successfully tried in the recent past. It is less cardiotoxic, less arrhythmogenic, less toxic to the central nervous system than bupivacaine, and it has intrinsic vasoconstrictor property. The effects of clonidine have been studied in peripheral nerve blockade. The purpose of this study was to evaluate the effects of clonidine on nerve blockade during brachial plexus block with ropivacaine using peripheral nerve stimulator. **Methods:** Sixty patients were randomly divided into two groups, Group A and B. Group A received 30 ml of 0.5% of ropivacaine with 0.5 ml normal saline while Group B received same amount of ropivacaine with 0.5 ml (equivalent to 75 μg) of clonidine for supraclavicular brachial plexus block. The groups were compared regarding quality of sensory and motor blockade, duration of post-operative analgesia and intra and post-operative complications. **Results:** There was a significant increase in duration of motor and sensory block and analgesia in Group B as compared to Group A patients ($P < 0.0001$). There was no significant difference in onset time in either group ($P = 0.304$). No significant side effects were noted. **Conclusion:** The addition of 75 μg of clonidine to ropivacaine for brachial plexus block prolongs motor and sensory block and analgesia without significant side effects.

Key words: Adjuvant, brachial plexus anaesthesia, clonidine, ropivacaine

INTRODUCTION

Regional anaesthesia is a low-cost anaesthetic technique as compared to general anaesthesia and has the benefit of extended post-operative pain relief. Satisfactory surgical conditions are obtained with complete sensory and motor blockade. The brachial plexus block is a safe and useful method for upper limb surgery under regional anaesthesia.[1] The supraclavicular brachial plexus block has been practiced routinely for upper limb surgeries in our institution. Concurrent sympathetic blockade reduces post-operative pain, vasospasm and oedema. Bupivacaine, an amide local anaesthetic, is the most frequently used local anaesthetic but ropivacaine has also been successfully tried recently as ropivacaine is less lipophilic than bupivacaine and is less likely to penetrate large myelinated motor fibres, resulting in

a relatively reduced motor blockade.[2] Ropivacaine is an amino amide local anaesthetic prepared as "S" enantiomer. It is less cardio toxic, less arrhythmogenic, less toxic to central nervous system (CNS) than bupivacaine, and it also has intrinsic vasoconstrictor property.[3] Several adjuncts have been studied to potentiate efficacy of brachial plexus block including opioids, midazolam, neostigmine, bicarbonate, hyaluronidase and α-2 agonists.[4] The results have often been conflicting, but may be useful. Studies continue in search of the ideal adjuvant which could provide further improvements in operative conditions without unwanted short- or long-term side effects.

Clonidine, an imidazoline with selective partial agonist activity at α-2 adrenergic receptors has been used for many years as a centrally acting antihypertensive agent and has also been used as an adjuvant with

ropivacaine for regional anaesthesia including epidural anaesthesia.[5,6] The use of α-2 adrenoceptor agonist for enhancement of peripheral nerve blocks has added a new dimension to their clinical application.[7]

The ability of clonidine to reduce the requirements of traditional anaesthetic and analgesic agents is increasingly being used in the perioperative period. Clonidine, when combined with a local anaesthetic, has been found to extend the duration of nerve block.[8] It has been postulated that this action could be attributed to centrally mediated analgesia, α-2 adrenoceptor-mediated vasoconstrictive effects, attenuation of the inflammatory response and direct action on peripheral nerve.[9]

The purpose of the present study was to evaluate the effects of clonidine in combination with ropivacaine on peripheral nerves during brachial plexus block in term of its onset, duration, degree of sensory/motor blockade, post-operative analgesia and to detect any potential complications.

METHODS

After Institutional Ethical Committee approval and written informed consent, a prospective, randomised, double-blinded study was carried out on 60 American Society of Anesthesiologists physical status I and II patients of either sex, aged 18–60 years undergoing various orthopaedic surgeries on the upper extremities under supraclavicular brachial plexus block. Sixty eight patients were enrolled in the study. Eight patients were excluded as four patients did not meet the inclusion criteria and four refused to participate. So sixty patients were divided into two groups of thirty patients each. None were lost to follow up (Consort flow diagram). The study was conducted in two groups of 30 patients each between May 2011 and September 2012. Patients were randomly chosen by computer-generated random selection to one of the groups. Group A patients received ropivacaine 0.50% (30 ml) and placebo (0.5 ml NS) whereas Group B patients received ropivacaine 0.50% (30 ml) and clonidine 75 µg (0.5 ml). Randomisation was performed by an independent statistician and concealed from patients and investigators until completion of statistical analysis. The exclusion criteria included patient refusal, patients having chronic pain and on analgesic medications, patient with a history of coagulation disorders, history of brachial plexus injury, allergy to the study drugs, patients taking other medications with α-adrenergic blocking effect, hepatic or renal insufficiency, systemic infection or infection at the site of injection, patients with bilateral upper limb fractures and previous shoulder surgery. Patients were instructed pre-operatively about use of numerical rating scale for pain assessment.
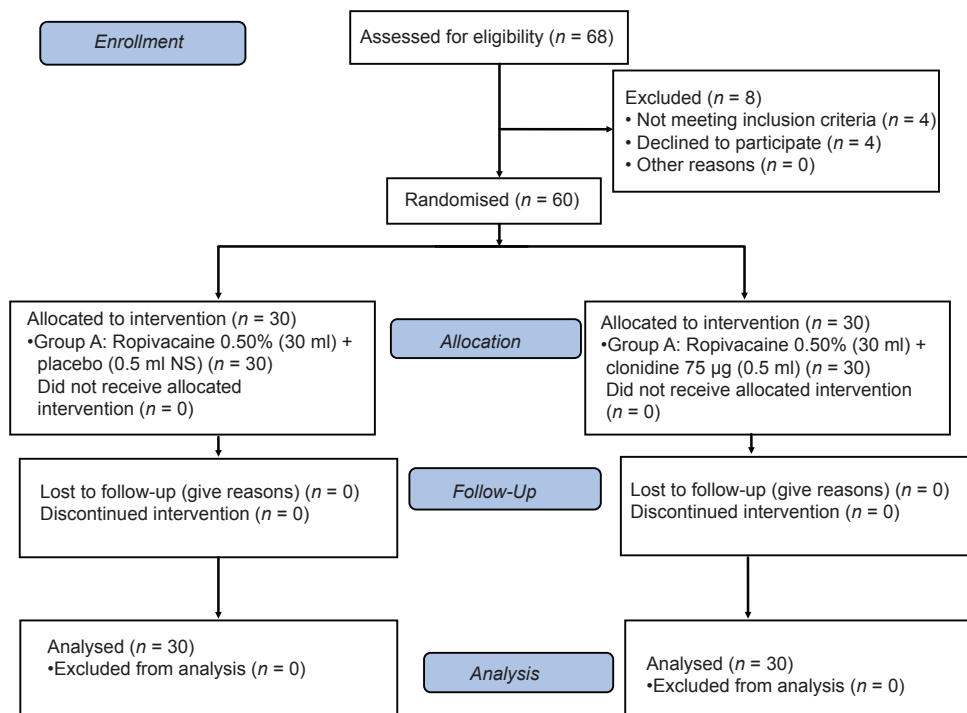

Diagram: Consort flow chart

On arrival in the operation room, baseline heart rate, blood pressure and oxygen saturation were recorded. An intravenous (iv) line was secured in the unaffected limb, and Ringer's lactate was started. Patients were given 0.03 mg/kg of midazolam iv as premedication 15 min before beginning each block technique. Subcutaneous injection with 4 ml of 1% lignocaine was administered at the needle insertion site. All the patients received brachial plexus block through the supraclavicular approach by an experienced anaesthesiologist different from the one assessing the patient intra- and post-operatively. Both were blinded to the treatment groups. The observer was blinded about the nature of the injected drug. The nerve was located using a nerve locator (Stimuplex® Dig RC, B. Braun Melsungen AG, Melsungen, Germany) connected to a 22 G, 50-mm-long stimulating needle (Stimuplex®, Braun, Germany). The end point of the location in median nerve area was a distal motor response with an output lower than 0.5 mA. Following negative aspiration, 30 ml of a solution containing local anaesthetic combined with placebo or clonidine mentioned above was injected. A 5 min compression at the injection site was performed to facilitate an even drug distribution.

Sensory blockade was assessed every 3 min and motor block was evaluated at 5 min intervals for the initial 30 min following onset of sensory anaesthesia. Sensory block was confirmed by pinprick sensation using a 23-G needle in entire dermatomes innervated by the brachial plexus (C5-T1) that is, median nerve, radial nerve, ulnar nerve and musculocutaneous nerve. Sensory onset was considered when there was a dull sensation to pin prick along the distribution of any of these nerves. Complete sensory block was considered when there was a complete loss of sensation to pin prick. Sensory block was graded as[10] Grade 0 when sharp pin felt, Grade 1 if analgesia and dull sensation felt and Grade 2 when anaesthesia and, no sensation felt.

Assessment of motor blockade was carried out by the same observer. Motor blockade[11] was evaluated by the ability to flex the elbow and hand against gravity as Grade 1 (ability to flex and extend the forearm), Grade 2 (ability to flex or extend only the wrist and fingers), Grade 3 (ability to flex or extend only the fingers) and Grade 4 (inability to move the forearm, wrist, and fingers). The block was considered to be incomplete when any of the segments supplied by median, radial, ulnar and musculocutaneous nerve

did not have analgesia even after 30 min of drug injection. These patients were planned to receive fentanyl (2 µg/kg) iv and midazolam (0.03 mg/kg) iv. When >1 nerve remained unaffected, the block was judged to have failed. In this case, general anaesthesia was administered. Patients were monitored for haemodynamic variables such as heart rate, blood pressure and oxygen saturation every 30 min after the block, intraoperatively and every 60 min post-operatively for 24 h. At the conclusion of the procedure, quality of operative conditions was assessed according to the following scale[12]: Grade 4 (excellent) when there was no complaint from patient, Grade 3 (good) when there was only minor complaint with no need for the supplemental analgesics, Grade 2 (moderate) when patient's complaint that required supplemental analgesia and Grade 1 (unsuccessful) and the patient was administered general anaesthesia. The intra- and post-operative assessment was done by an anaesthesiologist who was unaware of the drug used. Patients were assessed for duration of analgesia as per a numerical rating scale of 0–10. The numerical rating scale was recorded post-operatively every 60 min till the score of 5 and more. The rescue analgesia was given in the form of diclofenac sodium (1.5 mg/kg) intramuscular (i.m.) at the numerical rating scale of 5 and more and the time of administration was noted. All patients were observed for any side-effects like nausea, vomiting, dryness of mouth and complications like pneumothorax, haematoma, local anaesthetic toxicity and post-block neuropathy in the intra- and 24 h post-operative periods. The duration of sensory block was defined as the time interval between the onset of sensory anaesthesia and the complete resolution of anaesthesia on all nerves. The duration of motor block was defined as the time interval between the end of local anaesthetic administration and the recovery of complete motor function of the hand and forearm. Primary outcome measures were duration of analgesia while secondary measures were onset and duration of sensory blockade, pain scores, motor blockade, onset, duration and evidence of any adverse drug reactions. A power analysis was performed to determine the necessary number of patients for each group based on duration of analgesia. With a two-sided type I error of 5% and study power at 80%, it was estimated that 20 patients would be needed in each group in order to detect a difference of 35 min in the duration of analgesia between the two groups. The data was analysed by SPSS for windows (version 17) statistical package (SPSS Inc., Chicago, IL). The data were expressed as mean ± standard deviation (SD).

Unpaired *t*-test was applied for demographic data, onset and duration of sensory and motor blockade and duration of analgesia. Fisher exact test was applied for assessment of quality of block. *P* value was considered significant if < 0.05.

RESULTS

The demographic profiles in both the groups were comparable [Table 1]. The mean time of onset of sensory block in Group A was 8.05 ± 3.21 min (11.13 min–5.82 min), Group B was 9.1 ± 3.16 min (12.24 min–6.27 min) (*P* = 0.304) [Table 2]. The mean duration of sensory block in Group A was 505.5 ± 94.95 min (422.29 min–599.05 min) [Table 2] and in Group B was 726.5 ± 107.47 min (621.53 min–823.44 min) (*P* = 0.0001). The mean time of onset of motor block in Group A was 13 ± 3.69 min (11.12 min–15.90 min) and in Group B was 15.05 ± 4.21 min (11.19 min–18.63 min) (*P* = 0.110) [Table 2]. The mean duration of motor block in Group A was 483.5 ± 85.91 min (402.75 min–557.21 min) and in Group B was 677 ± 86.33 min (632.56 min–764.87 min) (*P* < 0.0001) [Table 2]. None of the patients in the two groups had incomplete or failed block. The mean pain score of patients in both the group at 60 min post-operatively was zero, at 2 h post-operatively mean pain score in Group A and B were 1 and 0 (*P* = 0.1544). 8 h post-operatively it was 4.2 ± 2.3 (6.2–3.5) and 1.6 ± 1.1 (2.6–0.8) (*P* = 0.0001). The number of patients who required rescue analgesia in the form of diclofenac sodium in Group A were 45%, 35%, 20%, respectively, who needed 3, 2, 1 doses of rescue analgesics in 24 h, respectively, whereas in Group B 5%, 15%, 80% needed 3, 2, 1 doses, respectively.

Table 1: Demographic profile of the patients in the two groups

Demographic profile	Group A	Group B	P
Sex (male: female)	10:10	11:9	0.80
Mean age (year)	39±15	33±12	0.64
Mean weight (kg)	62.6±8.64	63.05±8.04	0.78

Table 2: Onset and duration of sensory and motor block in the two groups

Onset and duration of sensory and motor block	Group A	Group B	P
Sensory block			
Onset (min)	8.05±3.21	9.1±3.16	0.304
Duration (min)	505±95	726±107	<0.0001*
Motor block			
Onset (min)	13±3.69	15.05±4.21	0.11
Duration (min)	483.50±86	677±86	<0.0001*

*Statistically significant

Complication in the form of nausea and vomiting was observed in Group A (*P* = 1.00) and sedation in Group B (*P* = 0.11) which were statistically insignificant [Table 3].

DISCUSSION

The addition of 75 μg clonidine to ropivacaine 0.5% for peripheral nerve stimulator (PNS) guided supraclavicular brachial plexus blockade increased the duration of both sensory and motor blockade, and the need for analgesic in post-operative period was also reduced significantly.

Different studies have shown that perineural administration of clonidine is better than subcutaneous or i.m. injections,[13] signifying that the local anaesthetic-enhancing effect of clonidine is possibly mediated at the neuron.[13,14] This explains the difference in response to different types of nerve blocks probably related to the rate and extent to which the injected anaesthetic solutions penetrate into the nerve. It 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 CNS producing its analgesic effect.[15] Researchers are of the opinion that clonidine exerts its local anaesthetic-prolonging effect directly on the nerve fibre, as a result of the complex interaction between clonidine and axonal ion channels or receptors.[16] Clonidine possibly enhances or amplifies the sodium channel blockade action of local anaesthetics by opening up the potassium channels resulting in membrane hyperpolarisation, a state in which the cell is unresponsive to excitatory input.[17] Peripheral antinociception induced by clonidine has also been related to α 2-adrenoceptor-mediated local release of enkephalin-like substances.

The result in our study is in agreement with other studies which showed that sensory block lasts longer than the motor block.[18] Clonidine added to bupivacaine

Table 3: Complications observed in the two groups

Complication	Group A		Group B		P
	Number of patients	Percentage	Number of patients	Percentage	
Nausea/vomiting (intraoperative)	1	5	0	0	1.00*
Sedation (postoperative)	0	0	4	20	0.11*

*Not significant

is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries.[19] These authors explained that large fibres require a higher concentration of local anaesthetic than small fibres. The minimal effective concentration of local anaesthetic for large (motor) fibres is greater than for small (sensory) fibres.

The combination of ropivacaine with clonidine showed a significant difference in the pain scores. At 60 min, the mean scores were zero. After 2 h, the mean score in Group A was 1 and 0 in Group B, the difference being not clinically significant ($P = 0.1544$). At eight 8 h, the mean ± SD is 4.2 ± 2.3 for Group A and 1.6 ± 1.1 for Group B. The difference between the two is statistically significant with a $P < 0.0001$.

Except for hypotension and bradycardia with the use of clonidine,[8] no other untoward effect has been reported. Four patients in Group B were sedated in the post-operative period as has been observed in other studies[8] but the difference being statistically insignificant. The remaining patients in either group had an uneventful course without any major complications except nausea and vomiting which was observed in only one patient in Group A in the intraoperative period.

CONCLUSION

The results of this study support the use of adjunct clonidine with ropivacaine for supraclavicular block anaesthesia as ropivacaine produces good analgesia and motor blockade in PNS guided supraclavicular brachial plexus block and the addition of clonidine to ropivacaine increases the effect of analgesia and motor blockade significantly. Addition of 75 μg of clonidine to ropivacaine, for brachial plexus block, should be considered for a prolonged upper limb surgery and for decreasing the post-operative rescue analgesic requirements.

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