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Research Article

Clonidine as an adjuvant to local anesthetic in supraclavicular brachial plexus block: a randomized, double blinded placebo controlled study

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ABSTRACT

Background: Many drugs have been studied as adjuvants to local anesthetic agents with the aim of improving the quality of anesthesia and to provide profound analgesia. Clonidine has also been used as an adjunct to local anesthetic agents in various regional techniques. The studies regarding clonidine in brachial plexus block have given mixed results. Aim was to determine whether addition of clonidine to the local anesthetic solution for brachial plexus block by supraclavicular approach, prolongs sensory and motor blockade and improves postoperative analgesia. Also to observe side effects if any.
Methods: 60 patients aged 18-60 years, were randomly allocated into two groups. Group A received 2 µg / kg of Clonidine diluted to 1 ml with saline and group B received 1 ml of saline added to bupivacaine (10 ml 0.5%) and lignocaine (20 ml 2 %) solution, in the supraclavicular block. The onset and duration of sensory and motor block was compared along with the duration of analgesia, sedation in both the groups. Patients' pulse rate, blood pressure, saturation was also recorded.
Results: Addition of clonidine had no effect on the onset of the block, but was found to increase the duration of sensory and motor block along with the increase in the duration of analgesia. Visual analogue score for pain was significantly lower in the group receiving clonidine.
Conclusions: Clonidine 2 µg / kg added to 10 ml of 0.5 % Bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200000) is a good option for improving the quality and duration of supraclavicular brachial plexus block.

Keywords: Clonidine, Local anesthetic, Supraclavicular brachial plexus block, Sensory and motor block

INTRODUCTION

Peripheral neural blockade is a well-accepted component of comprehensive anesthetic care. Its role has extended not only intraoperative but also into postoperative period for analgesia and chronic pain management.

Brachial plexus block is one of the most widely used blocks for upper limb surgeries. Local anesthetic drugs have been traditionally used to provide anesthesia and analgesia with any regional block technique. Attempts have been made to prolong intraoperative anesthesia and postoperative analgesia, using various adjuvants.

Certain drugs may be used as adjuvant to local anesthetics to lower doses of each agent and enhance analgesic efficacy while reducing the incidence of adverse reactions. Tramadol and fentanyl had been successfully used as adjuvants to local anesthetic in brachial plexus block.[1,2]

Clonidine has also been used as an adjunct to local anaesthetic agents in various regional techniques. Previous investigators have observed mixed results about usefulness of clonidine on brachial plexus block. While clonidine has been shown to prolong the effects of local anaesthetics, by some, other studies have failed to show any effect of clonidine, independently from the type of

local anaesthetic used (ropivacaine, bupivacaine and mepivacaine).[3-9] Few studies have observed an increased incidence of adverse effects like sedation, hypotension and bradycardia with clonidine.[7,8-11]

The purpose of our study was to determine whether addition of clonidine to the local anaesthetic solution for brachial plexus anaesthesia prolongs sensory and motor blockade and improves postoperative analgesia. Also to observe any side effects associated with addition of clonidine.

Aims and objectives

To assess the effect of Clonidine when added to local anaesthetic solution in a brachial plexus block on 1) The onset and duration of sensory and motor blockade, 2) The duration of analgesia 3) Complications, if any.

METHODS

Approval from Department Review Board and institutional Ethics committee was obtained. After thorough preoperative evaluation and written informed consent, 60 patients aged 18-60 years of ASA physical status II & I, scheduled for upper limb surgeries were included in study. Excluded from the study were patients who were ASA class III and above, patients for whom supraclavicular brachial plexus block or the study medications were contraindicated or those who had a history of significant neurological, psychiatric, neuromuscular, cardiovascular, pulmonary, renal or hepatic disease or alcohol or drug abuse, as well as pregnant or lactating women. Also barred from the study were patients taking medications with psychotropic or adrenergic activities and patients receiving chronic analgesic therapy.

Randomisation and blinding

The study was designed as a prospective, randomized, double blind, placebo-controlled trial. Participants were allocated to two equal groups of 30 each using a computer generated random number list. Group A and group B. Group A received 10 ml of 0.5% bupivacaine with 2 µg / kg of Clonidine (preservative free) diluted to 1ml with saline + 20 ml of 2% lignocaine with adrenaline (1:200000). Group B received 10 ml of 0.5% bupivacaine + 20 ml 2% lignocaine adrenaline (1:200000) + 1 ml saline.

The anesthesiologist administering the injections and observing the effects received serially numbered sealed envelopes indicating the A or B codes for the anesthetic mixture to be administered. The A and B syringes were loaded with drug by another author not involved in administering the injections and in further evaluation of the patients. All observations (hemodynamic variables, oxygen saturation, level of sedation, time required to achieve surgical block in the operation theatre and the time to rescue analgesic in the post anaesthesia care unit) were also recorded in a blinded manner

Patients' pulse rate, electrocardiogram and non- invasive blood pressure were recorded and a wide bore intravenous line was established. The patients were administered a brachial plexus block by supraclavicular approach. The site of injection was shaved and disinfected. The injection site was infiltrated with 1 ml of lignocaine 2% subcutaneously. A nerve stimulator (Stimuplex Dig RC; Braun Melsungen AG, Germany) was used to locate the brachial plexus. The location end point was a distal motor response with an output lower than 0.5 mA. During injection, negative aspiration was performed every 6.5-7.0 ml to avoid intravascular injection.

Both sensory and motor components of block were assessed every 10 minutes for the first hour and thereafter hourly.

Sensory block

Onset of sensory block was defined as time elapsed from injection of drug to complete loss of cold perception of upper limb elicited by using spirit soaked cotton or pinprick. Duration of sensory block was defined as duration between injection of drug and return of pinprick sensation.

Motor block

Onset of motor block was defined as time elapsed from injection of drug to complete motor block elicited by asking the patient to adduct the shoulder, flex the forearm and hand against gravity. Duration of Motor block was defined as duration between drug injections to complete return of motor power with movement of all upper limb joints.

Visual analog scale (VAS) was used for subjective assessment of pain on a scale of 0 to 10, the patient was asked to quantify pain

0- no pain and 10-Worst pain. Rescue analgesic was given with inj diclofenac (IV) if the pain score by VAS >4. Assessment of sedation was done using Ramsay Sedation Scale.[12]

Intraoperative parameters

Pulse rate, blood pressure, peripheral oxygen saturation, and respiratory rate were observed.

Adverse effects like hypotension, bradycardia, nausea, vomiting, respiratory depression, excessive sedation if occurred were noted.

The patient was followed up postoperatively till he recovered completely from sensory and motor block and analgesia

Statistical analysis

Statistical analysis was carried out using SSPS version 12. An unpaired 't' test was used to compare the demographic variables, onset and duration of sensory and motor blocks, sedation scores and pain scores by VAS Intraoperative haemodynamic variables between the 2 groups was compared using unpaired 't' test. Intraoperative haemodynamic variables within group compared using paired 't' test. A 'p' value <0.05 was considered statistically significant.

RESULTS

Table 1 shows demographic variables age, gender, ASA grading and weight were comparable in both the groups. Also there was no statistical difference in the duration of surgery between the two groups.

Table 1: Demographic variables.

	Group A	Group B	p Value
Age	33.13	37.63	0.225
Weight	57.47	56.2	0.565
Sex (M/F)	23/7	22/8	1.0
ASA (I/II)	29/1	27/3	1.0
Duration of surgery (hrs)	2.1± 0.642	2.4 ± 0.764	0.073

Table 2 compares the sensory and motor block between the groups. We observed no difference in the onset of sensory and motor block with the addition of clonidine. The mean time taken from the placement of block and absence of pinprick was comparable in both the groups. Also the time between supraclavicular block and inability of patient to abduct the arm against gravity was comparable in both groups

Table 2: Comparison of sensory and motor block for group A & B.

variables	Group A	Group B	p value
Onset of sensory block (min)	7.3±1.18	6.9±1.45	0.628
Onset of motor block (min)	13.35±2.13	13.43±1.65	0.866
Duration of sensory block (hr)	6.78±0.7	4.43±0.43	<0.001
Duration of motor block (hr)	5.68±0.5	5.3±0.53	0.006
Duration of analgesia(hrs)	6.85±0.81	5.46±0.68	<0.001

The duration of sensory block was significantly higher in the group receiving clonidine (6.78±0.7) than those receiving placebo (4.43±0.43). Similar was the observation for duration of motor block, which was significantly higher in clonidine group (5.68±0.5) as compared to the placebo group (5.3±0.5).

The duration of analgesia measured as the time between the supraclavicular block administration and onset of pain (i.e. VAS >4) requiring the administration of a rescue analgesic, was also significantly higher when clonidine was added to local anesthetic.

Visual analogue score for pain was recorded. (Table 3) Significant difference (p <0.05) was found 4 hours onwards up to 7 hours. VAS was lower in group A as compared to group B.

Table 3: Comparison of VAS score.

	10min	30min	1hr -3hr	4hr	6hr	8hr
Group A	6.83±1.6	1.83±1.7	0±0.0	0.7±1.5	1.67±1.6	3.8±1.0
Group B	7.23±1.4	2.27±1.9	0±0.0	2.3±1.4	3.8±0.7	4.4±1.0
p value	NS	NS	NS	<0.001	<0.001	0.039

Sedation score was comparable in both groups and addition was clonidine was not found to be associated with more sedation.

Pulse rate and blood pressure were recorded intraoperatively and also postoperatively. Comparison was done with baseline values in each group.

Significantly lower pulse rate was found at 40 min up to 8th hour (p <0.05) in group receiving clonidine while in group B no statistically significant difference was found. Also, significantly lower blood pressure was recorded at 50 min up to 8th hour p<0.05) in group A while in group B no statistically significant difference was found (p>0.05).

DISCUSSION

In Supraclavicular blocks local anesthetic is injected at the level of trunks of brachial plexus, where the entire sensory, motor and sympathetic innervations of the upper extremity are confined to a very small surface area.

Clonidine acts synergistically with local anesthetic. Clonidine enhances both sensory and motor blockade of neuraxial and peripheral nerves after injection of local anaesthetic solution. This is thought to be due to blockage of conduction of delta A and C fibers, increase in the potassium conductance in isolated neurons in vitro and intensification of conduction block achieved by local anaesthetics.[13-15]

We found that the addition of clonidine made no difference to the onset of sensory and motor block and was comparable in both groups. Similar results were observed by various studies. Eledjam J et al studied the effect of 150 µg clonidine and 200 µg adrenaline when added to bupivacaine for axillary brachial plexus block, and found that clonidine did not hasten the onset of block.[16]

Casati A et al added clonidine (1 µg/kg) to 0.75% ropivacaine for foot surgery under sciatic-femoral nerve block. They observed that there was no difference in the time required to achieve surgical anesthesia between patients receiving only 0.75% ropivacaine and those receiving the ropivacaine-clonidine mixture.[17]

This observation was in variance with the study by Singh et al who reported that addition of clonidine hastened the onset of block.[18] Chakraborty S et al did a randomized controlled trial to study effect of clonidine (30 µg) as adjuvant in bupivacaine-induced supraclavicular brachial plexus block. They found that onsets of both sensory (6.2±0.78 min <8.7±1.01 min) and motor block (10.6±1.36 < 18.1±1.35 min) were significantly shorter in the group receiving clonidine.[19]

In our study the duration of both sensory and motor block (Table 2) was prolonged in group receiving clonidine as compared to group B. The difference in duration of sensory and mo block was found to be statistically significant ($p < 0.05$). The total duration of analgesia was also significantly higher in the group receiving clonidine. The time between the supraclavicular block administration and onset of pain (i.e. VAS >4) requiring the administration of a rescue analgesic was measured as the duration of analgesia. Injection diclofenac 75 mg intravenously was given if the VAS was >4. Eledjam JJ et al also observed that total duration of analgesia was significantly longer in clonidine group. They postulated three mechanism by which clonidine prolongs the duration of anaesthesia and analgesia. Firstly, clonidine may interfere with vascular absorption of local anaesthetic due to vasoconstriction by virtue of action of alpha 2 receptor. Secondly clonidine has direct action on pre and postsynaptic alpha 2 adrenergic receptors in substantia gelatinosa of dorsal horn of spinal cord, where agonist effect decreases the release of substance P from primary afferent neuron. Finally clonidine may act on peripheral nerve alpha adrenoreceptor and interfere at the presynaptic level with spinal neurotransmission of pain and/ or through postsynaptic alpha 2 specific effect either direct or via release of endogenous opioids.[16]

Andrea Casati A et al. observed that the mean time from block placement to first request for pain medication was shorter in group Ropivacaine (13.7 h; 25th –75th percentiles: 11.8-14.5 h) than in group Ropivacaine-Clonidine (16.8 h; 25^{th} -75^{th} percentiles: 13.5-17.8 h) ($P = 0.038$).[17]

Jacques T. Ya Deau et al compared addition of clonidine (100 µg) to local anaesthetic, systemic (intramuscular) 100 µg of clonidine and placebo. They found that clonidine resulted in a statistically significant prolongation of analgesia when included with the local anesthetic for popliteal fossa nerve block.[20]

These findings are at variance with the study by Duma et al, which showed no difference in analgesia after addition of clonidine 0.5 µg/kg to levobupivacaine in axillary block.[7]

Probable explanation for this inconsistency may relate to inter-patient variations in the anatomy of the plexus sheath and difference in the spread of local anesthetics in the plexus sheath depending upon the block technique.

Bernard and Macarie, evaluating the effects of adding 30-300 µg clonidine to lignocaine for axillary brachial plexus anesthesia, reported that the addition hastened the onset of the block and improved the efficacy of surgical anesthesia.[21] There are reported differences in the effects of administration of low-dose clonidine on time of onset and efficacy of nerve block, which may be explained by differences in the type of nerve block, exact mixture injected, and technique used to perform the block (single injection versus multiple injections).

We observed hemodynamic parameters in intra operative and postoperative period. Significantly lower pulse rate was found at 40 min up to 8th hour ($p<0.05$) in group A while in group B no statistically significant difference was found ($p>0.05$).

Comparison with baseline blood pressure showed significant fall at 50 min up to 8^{th} hour ($p<0.05$) in group A while in group B no statistically significant difference was found ($p>0.05$).

Though the drop in pulse rate and blood pressure was statistically significant in clonidine group, it was not clinically significant as none of our patients had bradycardia or hypotension nor did they have any hemodynamic instability. But it lays caution that

clonidine does reduce the pulse rate and blood pressure and care should be taken for patient where decrease in pulse rate and blood pressure could be detrimental.

While Singh et al observed that the perioperative and post-operative heart rate was variable at each time interval and was lower in the clonidine group in comparison with the control group; however, the difference was not significant (P>0.05) Chakraborty S et al, found that there was no statistically significant difference in heart rate, blood pressure, and oxygen saturation between the two groups at any time point.[18] However there was incidence of clinically relevant bradycardia and hypotension, which was comparable in both groups.[19]

Clonidine may produce sedation by acting on locus cerulus of brain stem via action on alpha 2 adrenergic receptor but in our study sedation was not significant when clonidine (2 µg/kg) was used in brachial plexus block with local anesthetic.

The patients were monitored postoperatively for any clonidine related side effects namely respiratory depression, bradycardia, hypotension, excessive sedation, confusion, amnesia etc. No complications were noted. There were no neurological and urological side effects either.

CONCLUSION

Clonidine 2 µg/kg (preservative free) when added to 10 ml of 0.5 % Bupivacaine + 20 ml of 2% lignocaine with adrenaline (1:200000) for supraclavicular brachial plexus block, does not hastens the onset of sensory and motor blockade (p>0.05) however, the combination produced prolonged sensory and motor block, improved analgesia, thereby decreasing the need for systemic analgesics. There is also decrease in pulse rate and blood pressure but clinically it was not significant. The clinical benefits of adding clonidine to local anesthetic solutions for upper extremity blocks are convincing.

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REFERENCES

1. Kaabachi O, Ouezini R, Koubaa W, Ghrab B, Zargouni A, Ben Abdelaziz A. Tramadol as an adjuvant to lidocaine for axillary brachial plexus block. Anesth Analg. 2007;23:187-9.
2. Karakaya D, Büyükgöz F, Bariş S, Güldoğuş F, Tür A. Addition of fentanyl to bupivacaine prolongs anesthesia and analgesia in axillary brachial plexus block. Reg Anesth Pain Med. 2001;26:434-8.
3. 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.
4. Erlacher W, Schuschnig C, Koinig H, Marhofer P, Melischek M, Mayer N, et al. Clonidine as adjuvant for mepivacaine, ropivacaine and bupivacaine in axillary, perivascular brachial plexus block. Can J Anaesth. 2001;48:522-5.
5. Iskandar H, Guillaume E, Dixmérias F, Binje B, Rakotondriamihary S, Thiebaut R, et al. The enhancement of sensory blockade by clonidine selectively added to mepivacaine after mid humeral block. Anesth Analg. 2001;93:771-5.
6. 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.
7. 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.
8. Erlacher W, Schuschnig C, Orlicek F, Marhofer P, Koinig H, Kapral S. The effects of clonidine on ropivacaine 0.75% in axillary perivascular brachial plexus block. Acta Anaesthesiol Scand. 2000;44:53-7.
9. Pinto Neto W, Issy AM, Sakata RK. A comparative study between bupivacaine and clonidine associated with bupivacaine in cervical plexus block for carotid endarterectomy. Rev Bras Anestesiol. 2009;59:387-95.
10. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lignocaine solution for epidural anesthesia. Anesthesoilogy. 1990;73:853-9.
11. 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.
12. Ramsay MA, Savage TM, Simpson BR, Godwin R. Controlled sedation with alphaxolone-alphadolone. Br Med J. 1974;2:656-9.
13. El-Hennawy AM, Abd-Elwahab AM, Abd-Elmaksoud AM, El-Ozairy HS, Boulis SR. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. Br J Anaesth 2009;103:268-74.
14. Bhatnagar S, Mishra S, Madhurima S, Gurjar M, Mondal AS. Clonidine as an analgesic adjuvant to continuous paravertebral bupivacaine for post-thoracotomy pain. Anaesth Intensive Care. 2006;34:586-91.
15. Gabriel JS, Gordin V. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol 2001;14:751-3.
16. Eledjam JJ, Deschodt J, Viel EJ. Brachial plexus block with bupivacaine: effects of added alpha-

adrenergic agonists: comparison between clonidine and epinephrine. Can J Anesthesia. 1991;38(7):870-5.
17. Casati A, Magistris L, Fanelli G, Small-dose clonidine prolongs postoperative analgesia after sciatic-femoral nerve block with 0.75% ropivacaine for foot surgery. Anesth Analg. 2000;91(2):388-92.
18. Singh S, Aggarwal A. A randomized controlled double-blinded prospective study of the efficacy of cloni-dine added to bupivacaine as compared with bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries. Indian J Anaesth. 2010;54:552-7.
19. Chakraborty S, Chakrabarti J. Das Effect of clonidine as adjuvant in bupivacaine-induced supraclavicular brachial plexus block: A randomized controlled trials. Indian J Pharmacol. 2010;42(2):74-7.
20. YaDeau JT, LaSala VR, Paroli L. Clonidine and analgesic duration after popliteal fossa nerve blockade: randomized, double-blind, placebo-controlled study. Anesth Analg. 2008;106(6):1916-20
21. Bernard JM, Macarie P. Dose-range effects of clonidine added to lidocaine for brachial plexus block. Anesthesiol. 1997;87:277-84.

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