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Research article

Perineural versus intravenous clonidine as an adjuvant to Bupivacaine in supraclavicular Brachial plexus block

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ABSTRACT

Background: Clonidine has been used as an adjuvant in Brachial plexus block (BPB) to enhance its quality and duration. However, whether, clonidine in BPB acts perineurally or via systemic absorption is not entirely clear.

Methods: Ninety-three patients of either sex, ASA I and II, aged 18–70 years, undergoing lower end humerus fracture fixation were included in the study. Patients were randomized into 3 groups. All the patients received brachial plexus block using nerve stimulator with 28 ml 0.5% Bupivacaine and 2 ml of NS/NS with clonidine. In the first group (Bc) 2 mcg/kg of clonidine was added to the anaesthesia solution and 10 ml of NS was injected intravenously; second group (Bivc) received clonidine 2 mcg/kg diluted up to 10 ml by intravenous route with 28 ml of 0.5% Bupivacaine and 2 ml of NS in the block; third group (B) received 28 ml of 0.5% Bupivacaine with 2 ml of NS in the block and 10 ml of NS intravenously, as placebo. Onset and duration of sensorimotor block, hemodynamic variables, duration of analgesia, level of sedation and adverse effects were noted.

Results: Onset of sensory blockade was faster in group Bc (7 ± 0.720 min) compared to group B (11.46 ± 1.138 min) and Bivc (11.46 ± 1.170 min) ($p < 0.001$). Onset of motor block was faster in group Bc (16.43 ± 1.136 min) compared to group B (22.75 ± 1.456 min) and Bivc (22.25 ± 1.295 min) ($p < 0.001$). The mean durations of analgesia were recorded as 1160.71 ± 53.259 min in group Bc, 454.64 ± 14.07 min in Group Bivc and 442.50 ± 18.634 min in group B.

Conclusion: Addition of clonidine 2mcg/kg to 28 ml of 0.5% bupivacaine in brachial plexus blocks results in a faster onset, increased duration of block and longer postoperative pain relief when compared to bupivacaine alone. These advantages are not observed when the same dose of clonidine is injected intravenously.

1. Introduction

Brachial plexus block for upper extremity surgery was described by Kulenkampff in 1912 [1], and has only grown in popularity since then. Brachial plexus blocks when used for upper limb surgeries achieve near ideal operating conditions by producing complete muscular relaxation, maintaining stable intra-operative hemodynamics and extending analgesia in post-operative period without systemic side effects.

Longer durations of surgeries have compelled anaesthesiologists to search for adjuvants to regional nerve block with drugs that prolong the duration of anaesthesia with lesser adverse effects.

Clonidine [2] is a selective alpha 2 receptor agonist, initially used as a centrally acting antihypertensive. Over the last few decades, several other effects have come to be known and exploited in anaesthesia.

Since 1980s, Clonidine has been used in a number of studies [3–7] as an adjuvant in local anaesthetic solutions at different doses (1mcg/kg and 2mcg/kg) in brachial plexus block and has convincingly shown to prolong the duration of anaesthesia and post-operative analgesia.

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However, an understanding of the mechanism and site of the action of clonidine used as an adjuvant to brachial plexus block is not entirely clear yet. Moreover, although clonidine has been studied as a preanaesthetic medication and as an adjuvant in a mixture in LA solution in blocks and spinal/epidural anaesthesia, its use as an intravenous adjuvant along with brachial plexus block has not been studied adequately. A literature search on Pubmed, Embase and Scopus gives a limited number of studies till date about clonidine used intravenously with concomitantly administered brachial plexus block.

It continues to be debated topic that whether clonidine added to local anaesthetic in brachial plexus block enhances the block acting perineurally; or it is because of systemic absorption of clonidine administered in the block. An answer to this may be had by comparing the effect of administering the same dose of clonidine perineurally and systemically and finding out the differences, if any.

The primary aims of this study were to study the effects of clonidine as an adjunct to brachial plexus blockade; and to determine its site of action viz perineural or systemic. Therefore, this study was designed with intravenously administered clonidine (systemic control arm) in addition to the study and placebo group.

2. Materials and methods

2.1. Study design

The study was designed as a Prospective Randomized Double Blind Systemic and Placebo Controlled Trial and was conducted at 1000 bed tertiary care teaching hospital from 30/04/2015 to 31/05/15. The study was approved by the Institutional ethical committee. Patients between 18 and 70 years of age of either sex, undergoing fixation of fractures of lower end of humerus under supraclavicular brachial plexus block with ASA PS I or II. Exclusion criteria of study were patient refusal for the procedure, patient with pre-existing significant systemic diseases, allergic to local anaesthetics, infection at local site of block, history of convulsions, pre-existing neurological deficits, coagulopathy or other bleeding disorders, pregnancy and other contraindications to clonidine. Written informed consent was taken from eligible patients to participate in the study. Patient profile, diagnosis, proposed surgery and preanaesthetic remarks were recorded. Patients were randomized using computer generated random numbers into three groups. Allocation concealment was done by opaque, sealed envelopes.

2.2. Sample size calculation

A pilot study done at our hospital showed that the mean duration of analgesia in patients administered Bupivacaine 0.5% 28 ml in brachial plexus block was 150 ± 40 min (mean ± S.D). We aimed for a prolongation of this duration of analgesia to 180 min by the addition of clonidine as the primary outcome measure. For the study to have a two sided confidence interval of 95% and a power of 80%, 28 subjects were required in each group. To compensate for dropouts, we decided to include 31 subjects in each group.

2.3. Groups

- Group Bc (perineural Clonidine):
  - Block solution: bupivacaine 0.5% 28 ml + Clonidine (2 mcg/kg) + NS qs 30 ml.
  - I.V.: Inj NS 10 ml over 15 min.
- Group Bivc (systemic control group: Intravenous Clonidine):
  - Block solution: bupivacaine 0.5% 28 ml + 2 ml NS
  - I.V.: Inj Clonidine 2 mcg/kg + NS qs 10 ml over 15 min
- Group B (placebo):
  - Block solution: bupivacaine 0.5% 28 ml + 2 ml NS
  - I.V.: Inj NS 10 ml over 15 min.

2.4. Technique of anaesthesia

Computer generated random numbers were drawn and the chart was maintained by the head nurse of the operation theatre. She would allocate consecutive eligible patients to groups as per the chart and staple to the case-sheet an opaque sealed envelope containing name of the group allocated. A junior anaesthesia resident aware of the group allocated, prepared the block solution and intravenous drug as per the group. The senior anaesthesia resident and the consultant who were blinded to the group allocation gave anaesthesia and noted down the findings in the proforma that was also attached with the case-sheet. The nursing staff of post-operative ward monitored the patient and filled the rest of the proforma. After 24 h of surgery, the principal investigator collected the proforma and opened the envelope to fill in the group.

Supraclavicular Brachial plexus block was given with nerve stimulator technique using Inmed$^{(R)}$ nerve stimulator using a 50 mm-long stimulating needle (Stimuplex$^{(R)}$ B-Braun$^{(R)}$ Germany or Locoplex$^{(R)}$ Vygon$^{(R)}$, France). Following standard methods, using an insulated needle, muscle twitches were elicited keeping an electric current of 1.5 mA. Electric current was then slowly reduced maintaining muscle contractions. When an acceptable motor response was elicited at current of less than 0.5 mA, LA solution was injected with repeated negative aspirations keeping the needle steady.

Time for the onset of complete sensory and motor block was noted. Sensory function was evaluated by pinprick in the distribution of the nerves (axillary nerve, musculocutaneous nerve, radial nerve, median nerve, ulnar nerve). Assessment of motor block was carried out by the same observer at each minute till complete motor blockade was achieved after drug injection. Onset of motor blockade was considered when there was Grade 1 motor blockade. Motor block was determined according to a modified Bromage scale for upper extremities on 3-point scale [8].

Grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers
Grade 1: Decreased motor strength with ability to move fingers only.
Grade 2: Complete motor blockade with inability to move the fingers.

Sensory block assessment graded as:

Grade 0: Sharp pin felt.
Grade 1: Analgesia (dull sensation felt).
Grade 2: Anaesthesia (no sensation felt).

The block was recorded as fail if at least Grade 1 motor and Grade 2 sensory blocks were not achieved till 30 min from the time of injection or patient needed to be given any supplementation or general anaesthesia. Their post-operative analgesic effect was not recorded and the patient was excluded from the study.

Surgery was allowed to start when motor block was Grade 1 and sensory grading was Grade 2. Vital parameters were monitored as routinely. Heart rate and mean blood pressure (MBP) at 0, 5, 15, 30, 60, 120 and 180 min were noted down. Any incidences of side effects (bradycardia, hypotension and sedation) were noted. Bradycardia was defined as a decrease in HR by 20% from the base-

line value or an absolute HR < 50 bpm and it was treated with Inj. Atropine 0.6 mg IV. Hypotension was defined as decrease in the MBP by 20% from the baseline value or an absolute MBP < 60 mmHg which was managed by boluses of IV crystalloids or increments of mephentermine 6 mg IV.

Intra-operative and post-operative sedation was graded using the 4-point sedation score [4]:

Grade 0: Awake.
Grade 1: Drowsy.
Grade 2: Sleeping but arousable on verbal command.
Grade 3: Sleeping and arousable only on tactile stimulation.

2.5. Outcome assessment

The primary outcome studied was the duration of post-operative analgesia. This was determined by the time interval between the end of local anaesthetic administration to the first dose of rescue analgesic given. Rescue analgesic given was Inj. tramadol 2 mg/kg IV.

Severity of pain was assessed by VAS at 1, 6, 12 and 24 h and opioid consumption. Opioid administered was Inj. tramadol 2 mg/kg IV, given on patients' demand or VAS of 4 or more. Cumulative dose of rescue analgesia given in 24 h was also noted.

The other outcomes studied were,

- Onset of sensory and motor block- Time interval between the end of local anaesthetic administration to Grade 1 motor and Grade 2 sensory block.
- Duration of sensory and motor block- Time interval between the end of local anaesthetic administration to the complete recovery of sensory and motor block. The total duration of block was as reported by the patient.
- Cumulative dose of rescue analgesic given in 24 h.
- Adverse effects, if any.

Statistical analysis: Data were entered using MS Excel and Epi Info 6.The data related to patient distribution according to age, sex, weight, ASA grade, duration of surgery, type of block, VAS score, sedation score and complications were presented as number (percentage) and compared using Pearson Chi square test.

Data related to changes in onset of sensory and motor block, duration of sensory and motor block, duration of analgesia, HR, MBP, were expressed as 'Mean ± SD' and compared using analysis of variance (ANOVA).

3. Results

A total of 93 patients participated in the study with 31 patients allocated in each group. Three patients in each group had failed/incomplete block and hence were dropped from the statistical analysis. Hence we had a total of 84 patients with 28 patients in each group. There were 63 males and 21 females. The patients in each group were comparable with regards to age, weight, ASA grade and duration of surgery (Table A.1).

The duration of sensory block was prolonged in patients who were given perineural clonidine (Group B_C; 939.29 ± 48.069 min) when compared to those who had been given intravenous clonidine (Group B_{IVC}; 398.39 ± 16.780 min) and to controls (Group B; 390 ± 23.766 min).These differences were highly significant (P = 0.000) (Table A.2).

Similarly, the duration of analgesia was greatly prolonged in Group B_C(1160 ± 53.259 min) when compared to group B_{IVC}(454.64 ± 14.072 min) or Group B (442.50 ± 18.634 min).These differences were highly significant (P = 0.000). There was no significant prolongation of analgesia in group B_{IVC} when compared to group B (P = 0.370) (Table A.3).

4. Discussion

The present study was planned to test the hypothesis that clonidine would enhance the duration of bupivacaine induced BPB. In order to do this, two arms were required, one with plain bupivacaine and the other with clonidine added to bupivacaine. To rule out the systemic action of perineurally administered clonidine, we decided to include a third arm of patients in whom the perineural dose of clonidine was administered intravenously.

Onset of sensorimotor block:

Onset of sensory block was significantly earlier in Group Bc when compared to Group Bivc and Group B ($p < 0.005$). Similarly the onset of motor block was also earlier in Group Bc when compared to Group Bivc and Group B. This difference was highly significant ($p < 0.001$). The earlier onset of sensorimotor block in patients who were administered perineural clonidine (Group Bc) suggests an enhancement of neural blockade by clonidine. This might be due to a complex interaction between clonidine and axonal ionotropic, metabolic or structural proteins, which has been demonstrated in several studies [9,10].

Duration of block and analgesia: In the present study, patients who were administered perineural clonidine exhibited a highly significant prolongation of sensorimotor block ($p = 0.000$). There was no statistically significant difference between group Bivc and group B. Similarly, motor block in group Bc lasted for 1060 min which was greater than that in group Bivc and group B with $p = 0.000$.

An offshoot of the prolonged block was a highly significant prolongation of duration of analgesia which lasted for 1160.71 ± 53.25 min in patients in group Bc. This was higher than that with group Bivc and group B with $p < 0.001$ in each.

Ghoshmaulik et al. [11] found that perineurally injected clonidine prolonged the block compared to subcutaneously injected clonidine. Kohli et al. [4] used varying concentrations of clonidine with bupivacaine and found that the duration of analgesia was prolonged in patients receiving higher dose. Erlacher et al. [12] studied clonidine as an adjuvant for mepivacaine, ropivacaine and bupivacaine in BPB and reported a prolongation of motor block when clonidine was used as an adjuvant to bupivacaine for bupivacaine alone. Hutschala [7] reported a prolongation of sensory and motor block in perineurally administered clonidine group compared to both systemic and control group. They also reported plasma clonidine concentration were lower for block as compared to systemically administered clonidine group. The lower plasma clonidine concentration strongly suggests local effect of clonidine.

Therefore, the results of our study and aforementioned studies in the past strongly suggest that:

A. Addition of clonidine to LA significantly prolongs duration of block as well as analgesia in brachial plexus block.
B. This effect is mediated locally rather than systemically as evidenced by the prolongation in the local v/s systemic group.

However, a few other authors have reported findings that contradict with ours. Clubras et al. [13] concluded that the clonidine in BPB does not improve post-op analgesia when mixed with

long-lasting anaesthetic. In a similar study, Gaumann et al. [14] studying effect of adding 150 mcg of clonidine to 40 ml of 1% lignocaine for BPB found that there was no appreciable increase in the duration of analgesia or block in patients who received clonidine when compared to those that did not. Similarly Erlacher et al. [15] failed to show any advantage with addition of clonidine to BPB when compared to pure ropivacaine.

Two independent factors might be responsible for failure of prolongation of block by perineurally administered clonidine in these studies. All these authors used 150 mcg clonidine in 40 ml LA for the block, which gives a concentration of 3.75 mcg/ml of clonidine. One of the proposed mechanisms of clonidine induced prolongation of LA action is vasoconstriction caused by clonidine. This vasoconstriction may be a function of concentration of clonidine. Singelyn et al. [16] demonstrated that although 0.1 mcg/kg clonidine with 40 ml of 1% mepivacaine prolonged analgesia for BPB, it required a dose of 0.5 mcg/kg or more to significantly prolong both anaesthesia and analgesia.

Gaumann et al. [9] examined local anaesthetic effect of clonidine with regard to tonic inhibition of C-fiber action potential on isolated de-sheated rabbit vagus nerve by sucrose–gap method. Clonidine and lidocaine at 500 micromole/L concentration caused a comparebe degree of C-fiber inhibition corresponding to the action potential area under the curve of 75.8% ± 9.4% (mean ± SE) and 82.2% ± 5.9% of control, respectively. Concentration of clonidine less than 500 micromole/L did not inhibit C-fiber action potential. Therefore the lower concentration of clonidine (<5 mcg/ml) used in all these studies might be responsible for the non-enhancement of BPB by clonidine. In addition, the use of ropivacaine which itself has vasoconstrictor property demonstrsted by Erlacher [15] may explain the absence of further augmentation of block by clonidine.

In our study, there was a definite highly significant increase in the duration of block and analgesia in group Bc when compared to group B. The fact that this is not because of systemic absorption of clonidine is supported by persistence of a longer and better block in group Bc as compared to group Bivc.

The mean VAS scores at 12 h in group Bc was zero, while that in group Bivc was 3.29 ± 0.85 and in group B was 3.36 ± 0.73. This difference was statistically highly significant (p 0.000). This difference also reflects on the superior quality of sensory block and resultant analgesia obtained by adding clonidine to LA. However, there was no significant difference in the VAS scores of group Bc, group Bivc and group B (3.54 ± 0.64, 3.39 ± 0.57 and 3.57 ± 0.57 respectively) at 24 h. This may be because of the fact that all patients received rescue analgesic latest by the 20th hour and hence the VAS scores at 24 h were not a measure of the quality of block.

Hemodynamics and adverse effects: Heart rate in group Bivc was significantly less than in group Bc (p = 0.01) and that in group B (p = 0.006 and 0.026) at 120 and 180 min respectively. The heart rate in group Bivc was also less than in group B at 30 min (p = 0.04). It has to be emphasized however, that at no point in time, did the heart rate reach levels for it to be labeled as bradycardia (lowest HR = 75 ± 10 beats/min). Since bradycardia is an idiosyncratic reaction to systemic clonidine administration, the decrease in heart rate in group Bc when compared to group Bivc suggests that systemic absorption of clonidine was minimal in group Bc. Hence the enhancement of sensorimotor block would have been due to a local rather than a central mechanism. Hence, the enhancement of sensorimotor block would have been due to a local rather than a central mechanism. Eleven patients in group Bivc and two patients in group Bc showed sedation scores of two (sleeping but arousable) at 30 min. The occurrence of sedation in more than one third of patients in group Bivc can be easily explained as an adverse effect of systemic clonidine administration. The fact that only two patients in group Bc were sedated suggests once again that absorption of clonidine from the injection site was minimal.

5. Limitations of our study

The primary limitation of the present study is that we did not use USG to place our nerve blocks, as this modality is not yet available at our hospital. The use of USG guidance would have improved the quality of our study.

6. Conclusion

The present study concludes that addition of clonidine 2mcg/kg to 28 ml of 0.5% bupivacaine in brachial plexus block results in a faster onset and increased duration of block when compared to bupivacaine alone. It also results in significantly longer pain relief. These advantages are not observed when the same dose of clonidine is injected intravenously along with the brachial plexus block suggesting a local action of clonidine.

We, therefore recommend that clonidine in a dose of 2 mcg/kg can safely and effectively be used as an adjuvant tosupraclavicular brachial plexus block for fixation of fractures of lower end of humerus.

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Appendix A

Table A.1
Demographic characteristics and duration of surgery.

Parameter		Group Bc	Group Bivc	Group B
Mean age		40.36 ± 15.08	39.71 ± 12.69	38.07 ± 15.63
Mean weight (kg)		66 ± 7.88	65.79 ± 5.97	63.43 ± 4.98
ASA grade (mean)	1	18	24	19
	2	10	4	9
Mean duration of surgery (min)		91.25 ± 12.14	84.82 ± 14.68	86.61 ± 16.21

Table A.2
Duration of sensory block.

	Duration (min)	P-value	
Group Bc	939.29 ± 48.069	Group Bc/Bivc	0.000
Group Bivc	398.39 ± 16.780	Group Bc/B	0.000
Group B	390 ± 23.766	Group Bivc/B	0.599

Table A.3
Duration of analgesia.

	Duration (min)	P-value	
Group Bc	1160.71 ± 53.259	Group Bc/Bivc	0.000
Group Bivc	454.64 ± 14.072	Group Bc/B	0.000
Group B	442.50 ± 18.634	Group Bivc/B	0.370

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