ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 11, pp.41234-41240, November, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

A RANDOMISED CLINICAL TRIAL TO COMPARE THE EFFECTIVENESS BETWEEN BUPIVACAINE AND BUPIVACAINE-CLONIDINE COMBINATION IN BRACHIAL PLEXUS BLOCK BY SUPRACLAVICULAR APPROACH

Dr. Talikoti, D.G., *Dr. Manjunath Shivapujimath, Dr. Shivanand, L.K.

Department of Anaesthesiology, BLDE University's Shri B.M.Patil Medical College, Hospital and Research Centre, Vijayapur, Karnataka

ARTICLE INFO

Article History:
Received 20th August, 2016
Received in revised form
25th September, 2016
Accepted 23rd October, 2016
Published online 30th November, 2016

Key words:

Bupivacaine,
Clonidine,
Motor block,
Sensory block.

ABSTRACT

Background and objectives: Adjuncts to local anaesthetics for brachial plexus block may enhance the quality and duration of analgesia. Clonidine, an Alpha-2 adrenergic agonist, is known to produce antinociception and enhance the effect of local anaesthetics when given epidurally, intrathecally or in various peripheral nerve blocks. The purpose of this study was to assess the effect of Clonidine added to brachial plexus block by supraclavicular approach.

Materials and methods: A prospective, randomized, single blinded study was conducted on 96 ASA I or II adult patients undergoing upper limb surgeries under supraclavicular brachial plexus block. Patients were randomly divided into two groups. Patients in Group B (n = 48) were administered 30mL of 0.375% Bupivacaine and Group BC (n = 48) were given 30mL of 0.375% Bupivacaine with Clonidine 1μg/kg. The onset time and duration of sensory and motor blockade were recorded. Haemodynamic variables (i.e., heart rate, noninvasive blood pressure, oxygen saturation), sedation scores and rescue analgesic requirements were recorded for 24 hrs postoperatively.

Results: The onset of sensory and motor block was significantly faster in Group BC compared to Group B ($P < 0.05$). Rescue analgesic requirements were significantly less in Group BC compared to Group B ($P < 0.05$). Haemodynamics and sedation scores did not differ between groups in the post-operative period.

Conclusion: Clonidine (1μg/kg) in combination with 30mL of Bupivacaine (0.375%) hastened onset of sensory and motor block, and improved postoperative analgesia when used in brachial plexus block, without producing any adverse events.

Citation: Dr. Talikoti, D.G., Dr. Manjunath Shivapujimath, Dr. Shivanand, L.K. 2016. "A randomised clinical trial to compare the effectiveness between bupivacaine and bupivacaine-clonidine combination in brachial plexus block by supraclavicular approach", *International Journal of Current Research*, 8, (11), 41234-41240.

INTRODUCTION

Brachial plexus blocks provide a useful alternative to general anesthesia for upper limb surgeries. They achieve near ideal operating conditions by producing complete muscular relaxation, maintaining sTable intra-operative hemodynamics. The sympathetic block decreases post-operative pain, vasospasm, and edema. Of various local anesthetics, Bupivacaine is used most frequently as it has a longer duration of anesthesia varying from 3 to 8 hours. However, there are many limiting factors like delayed onset, patchy or incomplete analgesia etc. Various drugs like Neostigmine, Opioids, Hyaluronidase, Midazolam (Bazin *et al*., 1997; Bone *et al*., 1999 and Keeler *et al*., 1992). Have been added to local anesthetics in order to modify the block in terms of quick onset, good quality, prolonged duration and post-operative analgesia. Clonidine, an imidazoline alpha-2 adrenergic receptor agonist mainly used as an anti-hypertensive agent. Alpha-2 receptors mediate sedation, analgesia, and sympatholysis. Clonidine has been shown to be of benefit for use in central neuraxial blocks and other regional blocks by increasing the duration and intensity of pain relief (El-Hennawy *et al*., 2009; Bhatnagar *et al*., 2006 and Gabriel *et al*., 2006) as also by decreasing the systemic and local inflammatory stress response (Persec *et al*., 2009 and Romero-Sandoval *et al*., 2007). Neuraxial placement of clonidine inhibits spinal substance P release and nociceptive neuron firing produced by noxious stimulation. So the present study was undertaken in a randomized single blinded manner to evaluate the onset time, duration and analgesic efficacy of clonidine-bupivacaine combination compared to plain bupivacaine (0.375%) for brachial plexus block by supraclavicular approach.

Corresponding author: Dr. Manjunath Shivapujimath
Department of Anaesthesiology, BLDE University's ShriB.M.Patil Medical College, Hospital and Research Centre, Vijayapur, Karnataka

MATERIALS AND METHODS

This randomized study was done from December 2014 to June 2016 on patients who were admitted to BLDE UNIVERSITY Shri. B. M. Patil Medical College Hospital and Research Centre, Vijayapur and posted for upper limb surgeries. The study has been conducted after obtaining clearance from ethical committee of the institution. Informed consent was taken from all the patients who participated within the study.
96 patients posted for upper limb surgeries under supraclavicular block would be assigned to 2 groups, each containing 48 patients.

- Control group - Group-B: Received 30 ml Bupivacaine (0.375%)
- Study group - Group BC: Received 30 ml of mixture of Bupivacaine (0.375%) and Clonidine (1µ/kg).

Inclusion criteria

- ASA Class I & II
- Age between 20 to 60 years.

Exclusion criteria

- Patients belonging to ASA Class III & IV.
- Known cause of hypersensitive reaction to Clonidine.
- Patients with medical complications like severe anemia, severe hypovolemia, shock, Septicemia.
- Abnormal BT, CT or on anticoagulant therapy.
- Local infection at the site of proposed puncture for supraclavicular block.

Preanaesthetic evaluation and counseling for surgery will be done on the previous day of surgery and reviewed on the day of surgery. A detailed medical history will be taken and systemic examination will be carried out and relevant investigation will be advised. An informed written consent is taken from all the patients. Patients were informed about known effects and side effects of study drugs and consent is taken for the study.

On arrival to operation theatre

- IV line secured.
- Monitors for Electrocardiogram, Non invasive blood pressure, and Pulse oximeter were connected.

Positioning: Patient was placed in supine position with the head turned away from the side to be blocked. Also, a slight elevation of the head of the bed is often more comforTable for the patient and allows for better drainage and less prominence of the neck veins.

Image Acquisition: With the patient in proper position the supraclavicular area is aseptically prepared and draped and a linear 38-mm, high frequency 10-15 MHz transducer is placed firmly over the supraclavicular fossa in the coronal oblique plane to obtain the best possible transverse view of the subclavian artery and brachial plexus. Nerves in the supraclavicular region appear hypo-echoic and are round or oval. The brachial plexus is located lateral and superficial to the pulsatile subclavian artery and superficial to the first rib.The first rib is identified as a hyper-echoic structure .The brachial plexus is consistently found lateral and superficial to the subclavian artery and above the first rib.

Needle Placement: For the in plane approach (lateral to medial) a 5 cm 22G insulated block needle is inserted under sterile conditions on the outer (lateral) end of the ultrasound transducer (5-12 or 6-13 MHz) after skin local anaesthetic infiltration.The brachial plexus is identified as a compact group of nerves, sometimes compared to a 'bunch of grapes', located over the first rib, lateral and superficial to the subclavain artery. The needle is advanced along the long axis of the transducer in the same plane as the ultrasound beam. This way the needle shaft and tip can be visualized in real time as the needle is advanced towards the target nerves. The identity of the nerves may be confirmed by electrical stimulation if desired. After negative aspiration for blood, 30 ml of respective local anaesthetic drug was injected depending on whether patient is allotted to either of group B or BC so as to cause hydro dissection of the planes around the plexus. Local anaesthetic spread is observed during injection and the needle repositioned to ensure distribution around all the nerve trunks and divisions within the plexus sheath. In plane (medial to lateral) approach may also be used based on user comfort. Inj. Bupivacaine 0.25% 5ml will be given to block intercostobrachial nerve (T2) to avoid tourniquet pain. Onset of sensory blockade, onset of motor blockade, duration of sensory blockade, duration of motor blockade and any adverse effects were noted.

Assessment of Sensory block

Sensory block was assessed by pin prick with 23 guaze hypodermic needle in skin dermatomes C4-T2 once in every minute for initial 30 minutes and then after every 30 minutes till patient regained normal sensations and graded according to Visual analogue scale (VAS) as

- 0-No Pain
- 2-Annoying (Mild pain)
- 4-UncomforTable (Moderate pain)
- 6-Dreadful (Severe pain)
- 8-Horrible (Very severe pain)
- 10-Agonizing (Worst possible pain)

Assessment of Motor Block

Quality of motor block was assessed at the same intervals and graded according to Modified Lovett's Scoring as

- Grade 6- Normal
- Grade 5 –slightly reduced muscular force
- Grade 4 – pronounced reduction.
- Grade 3 – slightly impaired mobility.
- Grade 2 – pronounced mobility impairment.
- Grade 1 – Almost complete paralysis
- Grade 0– Complete paralysis.

The effect on the following parameters were observed

Onset of motor blockade- time taken from the completion of injection of study drug till the patient develops motor blockade, (Lovett"s Grade 1).

Onset of sensory blockade- time taken from the completion of injection of studydrug till the patient does not feel the pin prick (Visual analogue scale score -0).

Duration of motor blockade- time taken from the onset of motor blockade till complete recovery of motor power, (Lovett's Grade 6).

Duration of sensory blockade – time taken from the onset of sensory blockade till the patient feels pin prick, (visual analogue scale of 2) Patients were watched for bradycardia, convulsions, restlessness, disorientation, drowsiness, nausea, vomiting & any other complications. All the values were expressed as Mean ± Standard deviation, statistical comparison was performed by student's t-test & chi-square test. A two tailed P value of >0.05 was considered to be statistically not significant, < 0.05 as statistically significant, < 0.01 as statistically highly significant. IM injection of Diclofenac sodium would be given as rescue analgesic when patients complains of pain. Number of rescue analgesics in 24 hours of post-operative period would also be recorded.

Sedation score described by University of Michigan Sedation Scale (UMSS)[38] would be used to assess sedation

- Awaked & Alert.
- Minimally Sedated: tired/sleepy, responding to verbal stimulus.
- Moderatly Sedated: somnolent/sleeping, responding to mild physical stimulus.
- Deeply Sedated: deep sleep, responding to moderate to severe physical stimulus.
- Unarousable.

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square ($\chi 2$)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results were considered to be significant. Data were analyzed using SPSS software v.23.0.

RESULTS

Age and sex were comparable in both groups.

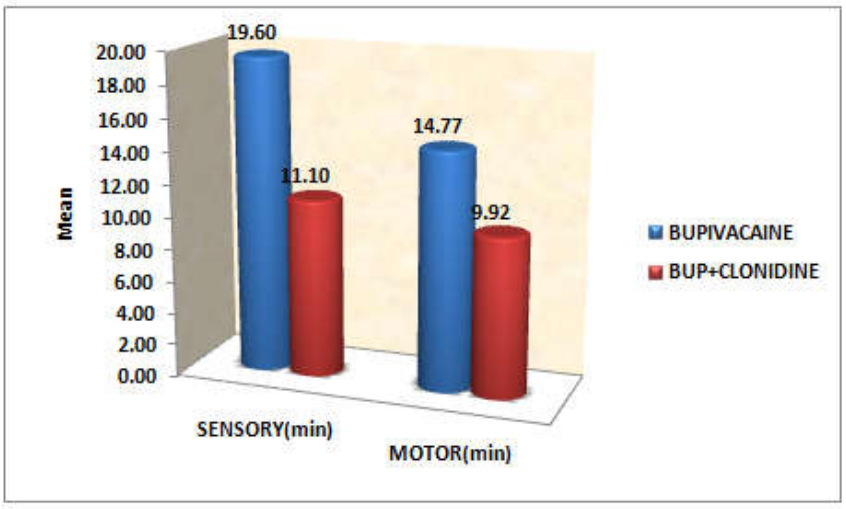
Mean Distribution of Onset of Block among study groups (Tabe1 and Graph 1)

The onset of sensory block in group BC was 11.10 ± 1.26 min and in group B was 19.60 ± 1.62 min. The statistical analysis by student's unpaired 't' test showed that, the time for onset of sensory block in group BC was significantly faster when compared to group B (P< 0.001). The onset of motor block in group BC was 9.92 ± 1.27 min and in group 14.77 ± 1.56 min. The statistical analysis by unpaired student's 't' test showed that, the time for onset of motor block was significantly faster when compared to group B (P< 0.001).

Table 1. Mean Distribution of Onset of Block among study groups

	Bupivacaine		Bup+Clonidine		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
SENSORY(min)	19.60	1.62	11.10	1.26	28.70	8.50	<0.001*	7.91	9.09
MOTOR(min)	14.77	1.56	9.92	1.27	16.72	4.85	<0.001*	4.28	5.43

*Statistically significant at 5% level of significance



Graph 1. Mean Distribution of Onset of Block among study groups

Table 2. Mean Distribution of Duration of Block among study groups

	Bupivacaine		Bup+Clonidine		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
Sensory(hr)	5.82	0.49	12.88	0.95	-45.76	7.06	<0.001*	-7.36	-6.75
Motor(hr)	5.13	0.44	7.86	0.44	-30.17	2.73	<0.001*	-2.91	-2.55

*Statistically significant at 5% level of significance

Mean Distribution of Duration of Block among study groups (Table 2 and Graph 2)

Patients of both groups were observed for 24 hours. Time was noted when the patient asked for rescue analgesics. The mean duration of sensory block in group BC was 12.88 ± 0.95 hours and in group B was 5.82 ± 0.49 hours. The statistical analysis by students unpaired 't' test showed that the duration of sensory block in group BC was significantly longer when compared to group B ($P < 0.001$). The mean duration of motor block in group BC was 7.86 ± 0.44 hours and in group B was 5.13 ± 0.44 hours. The statistical analysis by students unpaired 't' test showed that the difference between duration of motor block in group BC was significantly longer when compared to group B ($P < 0.001$).

Number of rescue analgesic among study groups (Table 3 and Graph 3)

The mean of number of rescue analgesic required in post – operative period for 24 hrs in group BC was 1.27 ± 0.45 and in group B was 2.33 ± 0.48. The statistical analysis by students unpaired 't' test showed that the difference between number of rescue analgesics in post-op 24hr in group BC was lesser when compared to group B ($P < 0.001$).

Sedation Score among study groups (Table 4 and Graph 4)

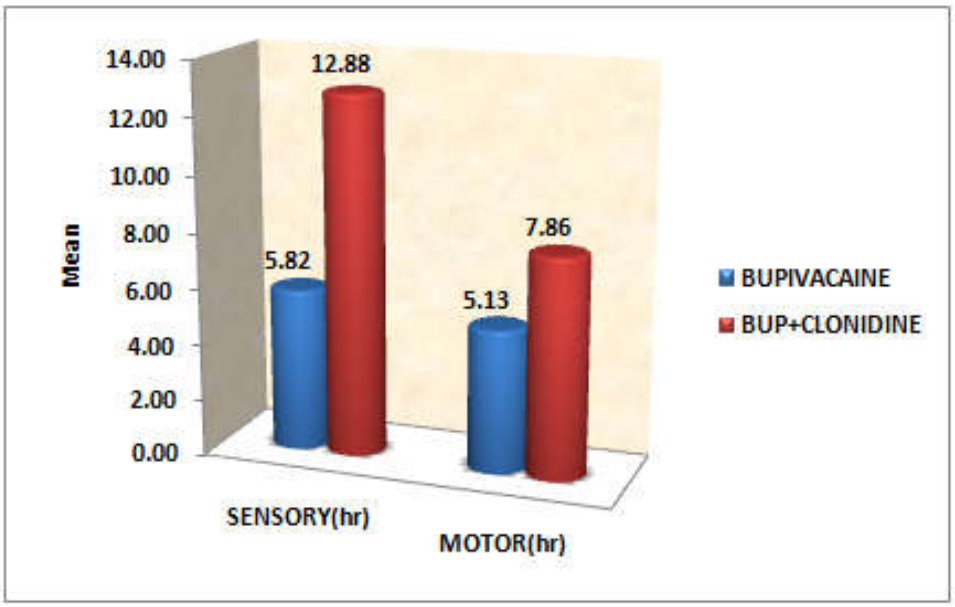
In group B, all patients were awake and alert and had sedation score of 1. In group BC, sedation corresponding to score 2 was observed in some patients between 15 min from time of injection and 60 min. 20.80% of patients at 15 min, 33.30% of patients at 30 min and 27.10% of patients at 60 min had sedation score of 2. None of the patients had sedation score of 3 and above during the study period. Statistical analysis of sedation score by Chi-square test showed that the difference in sedation score was significant ($P < 0.05$).

Haemodynamic parameters

The statistical analysis that there was no significant difference in Pulse rate, Systolic BP, Diastolic BP and Oxygen saturation between the two groups ($P > 0.05$).

DISCUSSION

Brachial plexus block provides postoperative analgesia of short duration, even when a long-acting local anaesthetic like Bupivacaine is used alone. Various adjuvant drugs like Opioids, Midazolam, Neostigmine and Hyaluronidase have been evaluated in conjunction with local anaesthetics to



Graph 2. Mean Distribution of Duration of Block among study groups

Table 3. Mean Distribution of Number of rescue analgesic among study groups

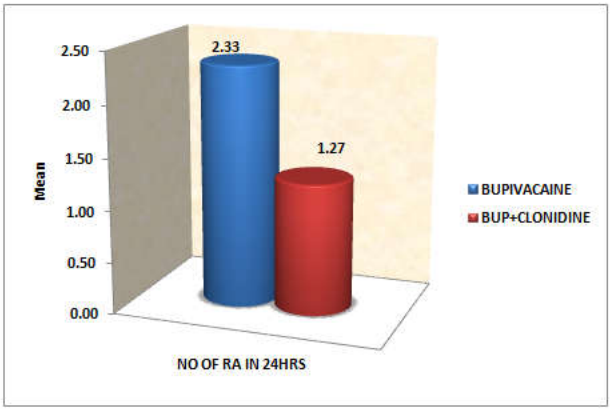
	BUPIVACAINE		BUP+CLONIDINE		t value	Mean Difference	p value	95% CI	
	Mean	SD	Mean	SD				Lower	Upper
NO OF RA IN 24HRS	2.33	0.48	1.27	0.45	11.24	1.06	<0.001*	0.87	1.25

*Statistically significant at 5% level of significance

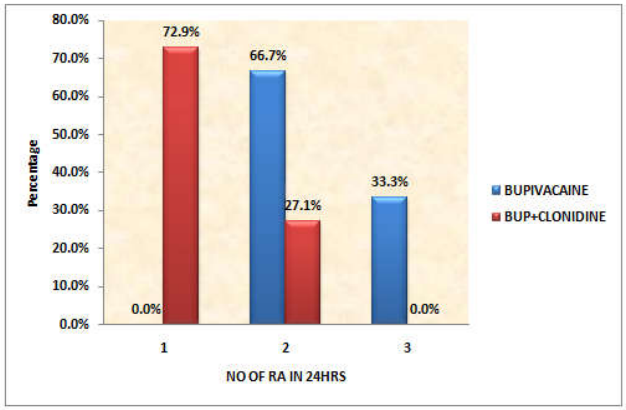
Table 4. Percent Distribution of Number of rescue analgesic among study groups

NO OF RA IN 24HRS	BUPIVACAINE		BUP+CLONIDINE		Total		Chi square p value
	N	%	N	%	N	%	
1	0	0.00%	35	72.90%	35	36.50%	<0.001*
2	32	66.70%	13	27.10%	45	46.90%	
3	16	33.30%	0	0.00%	16	16.70%	
Total	48	100.00%	48	100.00%	96	100.00%	

*Statistically significant at 5% level of significance



Graph 3. Mean Distribution of Number of rescue analgesics among study group



Graph 4.Percent Distribution of Number of rescue analgesics among study group

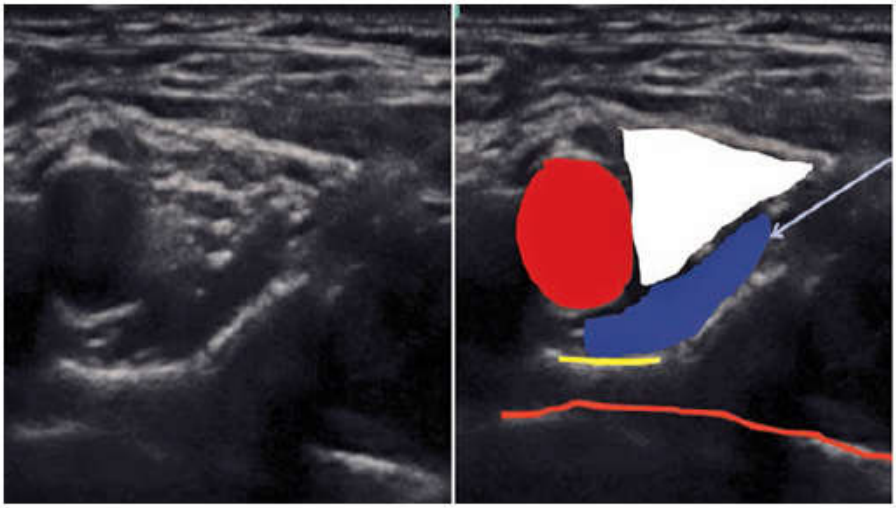


Fig: Spread of local anaesthetic solution deep to the plexus. Red area: subclavian artery, white area: brachial plexus, yellow line: periostium of first rib, red line: pleura, blue arrow: needle, navy area: local anaesthetic

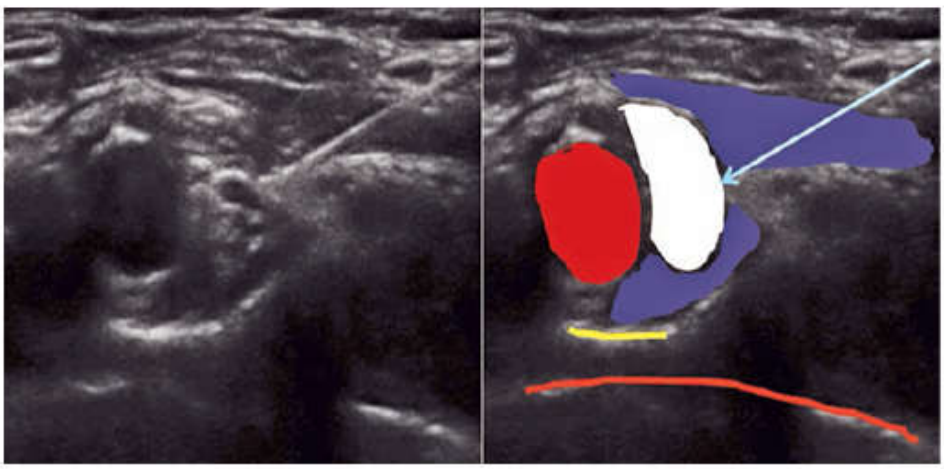


Fig.: Spread of local anaesthetic solution superficial to the plexus. Red area: subclavian artery, white area: brachial plexus, yellow line: periostium of first rib, red line: pleura, blue arrow: needle, navy area: local anaesthetic

prolong the period of analgesia, but they were found to be either ineffective or to produce an unacceptably high incidence of adverse effects. Clonidine is known to produce antinociception and to enhance the effect of local anaesthetic when administered intrathecally and epidurally. Clonidine produces this effect by its action on Alpha 2 adrenergic receptors found in peripheral nerves. Hence an attempt has been made to assess the efficacy of Clonidine as an adjuvant to Bupivacaine (0.375%) in brachial plexus block (supraclavicular approach) in terms onset time, duration of analgesia and sedation. Haemodynamic variables and rescue analgesic requirements in first 24 hours was also studied. In our study we found that the onset of sensory and motor blocks was significantly faster in patients who received a combination of Clonidine and Bupivacaine. Onset of sensory block (group BC, 11.10 ± 1.26 min; group B, 19.60 ± 1.62 min). Onset of

motor block (group BC, 9.92 ± 1.27 min; group B, 14.77 ± 1.56 min). This could be due to a local direct action of Clonidine and its synergistic action with that of local anaesthetics. The onset of motor block was found to be faster than the onset of sensory block in both groups. Winnie *et al*.[9], observed the same and attributed this to the somatotrophic arrangement of fibres in a nerve bundle at the level of the trunks in which motor fibres are located more peripherally than sensory fibres. Hence, a local anaesthetic injected perineurally will begin to block motor fibres before it arrives at the centrally located sensory fibres. Our results showed that sensory block tended to last longer as compared to motor block which agrees with the observation by de Jong *et al*.[10] These authors explained that large fibres require a higher concentration of local anaesthetic than small fibres. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block. In our study duration of motor block was prolonged when clonidine was added to bupivacaine. (Group BC, 7.86 ± 0.44 hrs; group B, 5.13 ± 0.44 hrs). In our study, the mean duration of sensory block (i.e. time elapsed from time of injection to appearance of pain requiring analgesia) was significantly higher ($P < 0.05$) in group BC than in group B. (Group BC, 12.88 ± 0.95 hrs; group B, 5.82 ± 0.49 hrs).

Various studies in which Clonidine was used in peripheral nerve block found that Clonidine with Bupivacaine improves analgesic characteristics compared to Bupivacaine alone. K Sri Hyndavi, *et al* (2016). conducted prospective, randomized double-blind placebo controlled study to evaluate the effect of Bupivacaine and Clonidine combination of drugs with respect to the onset, duration of sensory and motor blockade and duration of analgesia in infra-clavicular brachial plexus block for elective upper limb orthopedic surgeries. It was concluded that addition of small dose of clonidine (60µg) to bupivacaine shortens the onset time and prolongs the duration of sensory and motor blockade and duration of post operative analgesia significantly without any major side effects. Sirohiya P. *et al* (2016), conducted study which evaluated the effect of Bupivacaine Clonidine combination in supraclavicular brachial plexus block for upper limb surgeries and they found that duration of post operative analgesia was prolonged when Clonidine is added to Bupivacaine. Audichya PC, Goyal S. (2016) conducted study to compare the effect of Clonidine v/s placebo as adjuvant to lignocaine for brachial plexus block, by supraclavicular approach, for different upper limb surgeries. They concluded that when Clonidine is added to local anesthetic solution in supraclavicular brachial plexus block, it provides rapid onset of block, better analgesia, good hemodynamic stability and profound & longer analgesia without any adverse effects. Sumanta Ghoshmaulik, *et al.* (2012), conducted study on Clonidine as an adjuvant in axillary brachial plexus block for below elbow orthopedic surgeries and they concluded that clonidine as an adjuvant in axillary block resulted in significant prolongation of duration of sensory and motor blockade, and analgesia without any hemodynamic alteration, probably by locally mediated mechanism of action. Shivinder Singh, Amitabh Aggarwal (2010) conducted A randomized controlled double-blinded prospective study of the efficacy of Clonidine added to Bupivacaine as compared with Bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries and they found that Clonidine added to Bupivacaine is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries. Sumitha Chakraborty, *et al.* (2010) conducted study on the effect of Bupivacaine-Clonidine combination in supraclavicular brachial plexus block for upper limb orthopedic procedures and it was concluded that addition of a small dose of Clonidine to 0.5% Bupivacaine significantly prolonged the duration of analgesia without producing any clinically important adverse reactions other than sedation. In our study, the number of patients who required rescue analgesia and the mean number of supplemental analgesic boluses required were also significantly lower in patients in Group BC. Similar observation was made in the above mentioned study by Chakraborty *et al*. (2010), The prolonged analgesia in Group BC could be due to the action of Clonidine by inhibiting action potential of A & C fibers in peripheral nerves as demonstrated by Gaumann *et al*. (1992). In our study, sedation scores were higher in patients in Group BC compared to Group B, 15 min after injecting the drug until 60 min after injection. Similar observation was made in the above mentioned study by Chakraborty *et al*. (2010). This may have been due to partial vascular uptake of Clonidine, and its transport to the central nervous system where it acts and produces sedation.Though mean sedation score in group BC was higher as compared to group B ($P < 0.05$), we did not observe clinically significant sedation in patients in group BC. No patient experienced airway compromise or required airway assistance. This mild sedation was actually desirable during that period.

Conclusion

From our study, we conclude that, the addition of Clonidine (1µg / kg) as an adjuvant to bupivacaine (0.375%) has following effects:

- Faster onset of sensory block.
- Faster onset of motor block.
- Longer duration of sensory block.
- Longer duration of motor block.
- Less number of rescue analgesics in post-op 24 hours.
- ComforTable sedation intraoperatively without any need for airway assistance.

No significant difference in haemodynamic variables i.e., pulse rate, systolic BP, diastolic BP and O_2 saturation.

REFERENCES

Audichya, P.C., Goyal, S. 2016. Utilization of clonidine in supraclavicular brachial block in upper limb surgery at Udaipur, Rajasthan. *J Adv Med Dent Scie Res.,* 4(3):108-112.

Bazin, J.E., Massoni, C., Bruelle, P., Fenies, V., Groslier, D., Schoeffler, P. 1997. The addition of local anaesthetics in brachial plexus block: The comparative effects of morphine, buprenorphine and sufentanil. *Anaesthesia,* 52:858-62.

Bhatnagar, S., Mishra, S., Madhurima, S., Gurjar, M., Mondal, A.S. 2006. Clonidine as an analgesic adjuvant to continuous paravertebral bupivacaine for post-thoracotomy pain. Anaesth Intensive Care, 34:586-91.

Bone, H.G., van Aken, H., Brooke, M., Burkle, H., Brooke, M., Burkle, H. 1999. Enhancement of axillary brachial plexus block anaesthesia by coadministration of neostigmine. *Reg Anesth Pain Med.,* 24:405-10.

Chakraborty, S., Chakrabarti, J., Madal, C.M., Das, S. 2010. Effect of clonidine as adjuvant in bupivacaine-induced supraclavicular brachial plexus block : A randomized controlled trial. *Indian J of Pharmacology,* 42(2):74-7.

De Jong, R.H., Wagman, I.H. 1963. Physiological mechanism of peripheral nerve block by local anaesthetics. Anesthesiology, 24:684-727.

Dorothee, M. Gaumann, M.D., Pascale, C. Brunet. 1992. PHD and Petr Jirounek, Clonidine Enhances the Effects of Lidocaine on C Fiber Action Potential. A & A May, vol. 74 no. 5 719-725.

El-Hennawy, A.M., Abd-Elwahab, A.M., Abd-Elmaksoud, A.M., El-Ozairy, H.S., Boulis, S.R. 2009. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. *Br J Anaesth*,103:268-74.

Gabriel, J.S., Gordin, V. 2001. Alpha 2 agonists in regional anesthesia and analgesia. Curr Opin Anaesthesiol, 14: 751-3.

Ghoshmaulik, S. 2012. Clonidine as an adjuvant in axillary brachial plexus block for below elbow orthopedic surgeries: A comparison between local and systemic administration. Anesthesia: *Essays and Researches,* 6: 184-8.

Sri Hyndavi, K., Divakar Patil, Abhijit Mohite, Rajesh Navale, 2016. Jyotsna Paranjpe bupivacaine in infraclavicular brachial plexus block for prolongation of post operative analgesia.International Journal of *of Recent Trendsin Science and Technology*. March. 18(2):368-372.

Keeler, J.F., Simpson, K.H., Ellis, F.R., Kay, S.P. 1992. Effect of addition of hyaluronidase to bupivacaine during axillary brachial plexus block. *Br J Anaesth*., 68 :68-71.

Persec, J., Persec, Z., Husedzinovic, I. 2009. Postoperative pain and systemic inflammatory stress response after preoperative analgesia with clonidine or levobupivacaine: a randomized controlled trial. *Wien KlinWochenschr* 121:558-63.

Romero-Sandoval, A., Eisenach, J.C. 2007. Clonidine reduces hypersensitivity and alters the balance of pro and anti-inflammatory leukocytes after local injection at the site of inflammatory neuritis. *Brain Behav Immun.,* 21:569-80.

Singh, S., Aggarwal, A. 2010. A randomized controlled double-blinded prospective study of the efficacy of clonidine added to bupivacaine as compared with bupivacaine alone used in supraclavicular brachial plexus block for upper limb surgeries. *Indian J Anaesth*., 54: 552-7.

Sirohiya, P., Mantan, K., Rehman, H., Kumari, M., Devra, V., Singh, R. 2016. Effect of bupivacaine and bupivacaine-clonidine combination in supraclavicular brachial plexus block – A comparative study. IAIM, 3(5): 29-37

Winnie, A.P. 1984. Plexus anesthesia vol.1, 1st ed., p. 83

****