ORIGINAL RESEARCH

Effect of Clonidine as an adjuvant to bupivacaine on duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile of patients

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ABSTRACT
Background: Clonidine, a centrally acting selective partial α2 adrenergic agonist (220:1 α2 to α1), is used as an intrathecal adjuvant for quite some time now. Clonidine has been repeatedly demonstrated to prolong sensory and motor block when used intrathecally with local anaesthetics. Clonidine has also been known to affect blood pressure in a complex fashion after intrathecal administration, because of opposing actions at multiple sites. In the view of these facts, this study was planned to compare the effect of clonidine on duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile when used as an adjuvant to bupivacaine. This study also aimed to ascertain the safety of these drugs for use in routine hospital practice.**Methods:** In our study, a total sample size i.e. 60 patients were randomly divided into 2 groups (Group B and C) of 30 patients each using a computer generated random number table.On arrival to the operating theatre, the identity of the patient was confirmed and consent was checked. After spinal injection patients were positioned in supine position and oxygen was provided through a nasal cannula at 2 litres per min. After 2 minutes, every 2 minutes sensory nerve block was assessed bilaterally by using insensitivity to cold (when cotton swab soaked with alcohol was applied) in the midclavicular line. A pretested proforma was used to collect the patients details such demographic clinical parameters, time to achieve sensory and motor block and adverse effects. **Results:** A total of 60 patients (27 were male and 33 were female) were enrolled into study. In group-B 40% were male and 60% were female. In group-C 50% were male and 50% were female. When compared with student t test age, weight, and BMI were comparable between both groups with all insignificant p values. In group-B patients S1 regression time was 195±14.74 minutes and in group-C patients this time was higher (247.5±23.22 minutes. So, it can be said that clonidine is better alternative in prolonging the time for regression to S1 level. Group-B patients took 172.5±12.92 minutes to regain Bromage score 0, and group-C patients took 217.5±23.55 minutes. So, motor blockade was prolonged in clonidine group.**Conclusion:** Our conclusion from the study is that clonidine as intrathecal adjuvant significantly prolongs the sensory and motor blockade of intrathecal hyperbaric bupivacaine without altering the onset of spinal anaesthesia.

Keywords: Clonidine, normal saline, hyperbaric bupivacaine, spinal, infraumbilical

INTRODUCTION

Lower limb and lower abdominal surgeries can be done under general anaesthesia as well as central neuraxial block or local nerve block. However central neuraxial block especially subarachnoid block has gained popularity because of its ease of administration, high success rates, ability to provide good operative conditions, quick onset and better muscle relaxation [1].

Spinal anaesthesia with local anaesthetic alone has a short duration of action. The short duration of action creates lots of difficulties for surgeons, anaesthesiologist and the patient as duration of spinal anaesthesia sometimes falls short than the duration of

surgery. It limits the type of surgeries that can be performed with spinal anaesthesia. Many a time it also warrants conversion to general anaesthesia midway between surgeries due to wearing off of the effect of spinal anaesthesia. Moreover early analgesic intervention is required to manage postoperative pain control after spinal anaesthesia with local anaesthetics alone.

Hence number of adjuvants, such as clonidine, dexmedetomidine, midazolam, opioids, neostigmine and magnesium sulphate has been studied to prolong the effect of spinal anaesthesia [2,3]. Adjuvants are added to increase the duration and density of block but they are not free from side effects. For example, opioids cause pruritus, respiratory depression, urinary retention [4] and neostigmine produces severe nausea & vomiting and pruritus [5]. So, the search goes on for a better intrathecal adjuvant.

Clonidine, a centrally acting selective partial α2 adrenergic agonist (220:1 α2 to α1) [6], is used as an intrathecal adjuvant for quite some time now. Clonidine has been repeatedly demonstrated to prolong sensory and motor block when used intrathecally with local anaesthetics [2,3,7].

Clonidinehas also been known to affect blood pressure in a complex fashion after intrathecal administration, because of opposing actions at multiple sites.

The addition of clonidine also allows for a reduction in the total dose of the local anaesthetic used, which translates into better hemodynamic stability in the intraoperative period [2,3]. Clonidine has also been shown to have significant analgesic affect in the post-operative period much after the regression of the motor blockade which allows for early and pain free ambulation [8,9].

In the view of these facts, this study was planned to compare the effect of clonidine on duration of analgesia, motor and sensory blockade and the intraoperative hemodynamic profile when used as an adjuvant to bupivacaine. This study also aimed to ascertain the safety of these drugs for use in routine hospital practice.

MATERIALS and METHODS

STUDY DESIGN AND SUBJECTS

This was a unicentric prospective randomized, single blinded, observational study done in Department of Anaesthesiology, Calcutta National Medical College in association with Urology, orthopaedic and gynaecology & obstetrics during February, 2012 to March, 2013. Thepatients (age: 18-65 years) undergoing elective infra-umbilical surgery in supine position having American Society of Anaesthesiology physical status I and II. The patients with allergy to study drugs, contra-indication to spinal anaesthesia, obstetric patients, uncontrolled and labile hypertension, addiction to any substances like opium, alcohol, patients taking sedative drugs, suffering from uncontrolled diabetes, any kind of neurological illness, psychological illness, having spinal deformity, Hepatic or renal disorders or Haematological disorder were excluded from the study. Clearance from the institutional ethics committee is obtained first. Informed consent from patients were also obtained.

SAMPLE SIZE

Sample size was calculated from a similar study done by Kanazi et al., [3] in 2006, taking that as our reference study. Kanazi et al., in 2006 found the mean duration of 2 segment regression in clonidine group was 101 minutes (standard deviation 37 minutes). Using this data, the minimum number of patients required in each group is 25 [taking significant p value <0.05 (i.e. α error 5%), power of study 80% (i.e. β error 0.2) and software used is "computer programmes for epidemiologists (PEPI) by J. H. Abramson and Paul M. Gahlinger version 4.0x"].For convenience 30 patients have been taken in each group. So, total sample size is 30+30 = 60.Total sample size i.e. 60 patients were randomly divided into 2 groups of 30 patients each using a computer generated random number table. Groups were designated according to the study drug received, as follows:Group B- received 2.6 ml of hyperbaric bupivacaine(13 mg) and 0.4 ml of normal saline, and Group C- received 2.6 ml of hyperbaric bupivacaine (13 mg), 37.5 µg of clonidine (0.25ml) and 0.15 ml normal saline.

PROCEDURE

The patients were again checked on the day before surgery and counselled again about the anaesthesia procedure. They were also advised to take a tablet ranitidine 150 mg before supper, light meal and tablet alprazolam 0.25 mg at bed time on the night before surgery and would remain nil by mouth after that. They were asked to take tab ranitidine 150 mg on the morning of surgery with sips of water and also to continue their usual medication, if any. On arrival to the operating theatre, the identity of the patient was confirmed and consent was checked. Then monitors are attached and baseline parameters were noted. ECG, SpO2 and non-invasive blood pressure (NIBP) were monitored before, during and after the surgery. The subarachnoid block was performed with the study drugs with the patient in standard sitting position with a 25G Quinke's needle at L3-L4 intervertebral space using midline approach maintaining strict aseptic condition. After spinal injection patients were positioned in supine position and oxygen was provided through a nasal cannula at 2 litres per min. After 2 minutes, every 2 minutes sensory nerve block was assessed bilaterally by using insensitivity to cold (when cotton swab soaked with alcohol was applied) in the midclavicular line. Motor blockade was assessed by using the modified Bromage scale [10] bilaterally every 2 minutes. The regression for sensory and motor block was checked every 15 minutes in a post anaesthesia care room. Patients were discharged from the post anaesthesia care room after sensory block regresses to S1 dermatome level and motor block to

Bromage 0. No analgesic drug was given in the immediate post-operative period until the patient requested for analgesia and time for first analgesia will be recorded. Any incidence of adverse effects in the intraoperative or immediate postoperative period were noted and again patients were followed up at 24 hours in the ward for incidence of nausea, vomiting or any other adverse reaction.

DATA COLLECTION

A pretested proforma was used to collect the patients details such demographic (Age, Sex, Body weight and Height, clinical parameters [Heart rate, Blood pressure - systolic, diastolic and mean arterial pressure, O2 saturation (SpO2), Time to achieve sensory block of T10, Time to achieve peak level of sensory block, Peak sensory block level, Time to achieve Bromage score3 motor block, Time to regress 2 segments from peak level, Time taken to regress to S1 segment, Time of 1st analgesic request and Time to regain Bromage score 0] and adverse effects (Bradycardia, Hypotension, Arrhythmia, Sedation, Respiratory depression, Nausea and vomiting, and Post Dural puncture headache).

DATA ANALYSIS

Discrete categorical data are presented as Number and percentage; continuous data are given as mean ± Standard deviation. Differences in demographic, anaesthetic and post-operative data were tested by independent Student's t-test (continuous data) or by Pearson Chi-square test and Fisher's exact test for (categorical data). A p value less than 0.05 is taken as significant.

RESULTS

A total of 60 patients (27 were male and 33 were female) were enrolled into study. In group-B 40% were male and 60% were female. In group-C 50% were male and 50% were female. In group-B 50% were Hindu and 50% were Muslim. In group-C 53.33% were Hindu and 46.67% were Muslim. When compared with student t test age, weight, and BMI were comparable between both groups with all insignificant p values (Table 1).

Table 1: Baseline characteristics of the patients

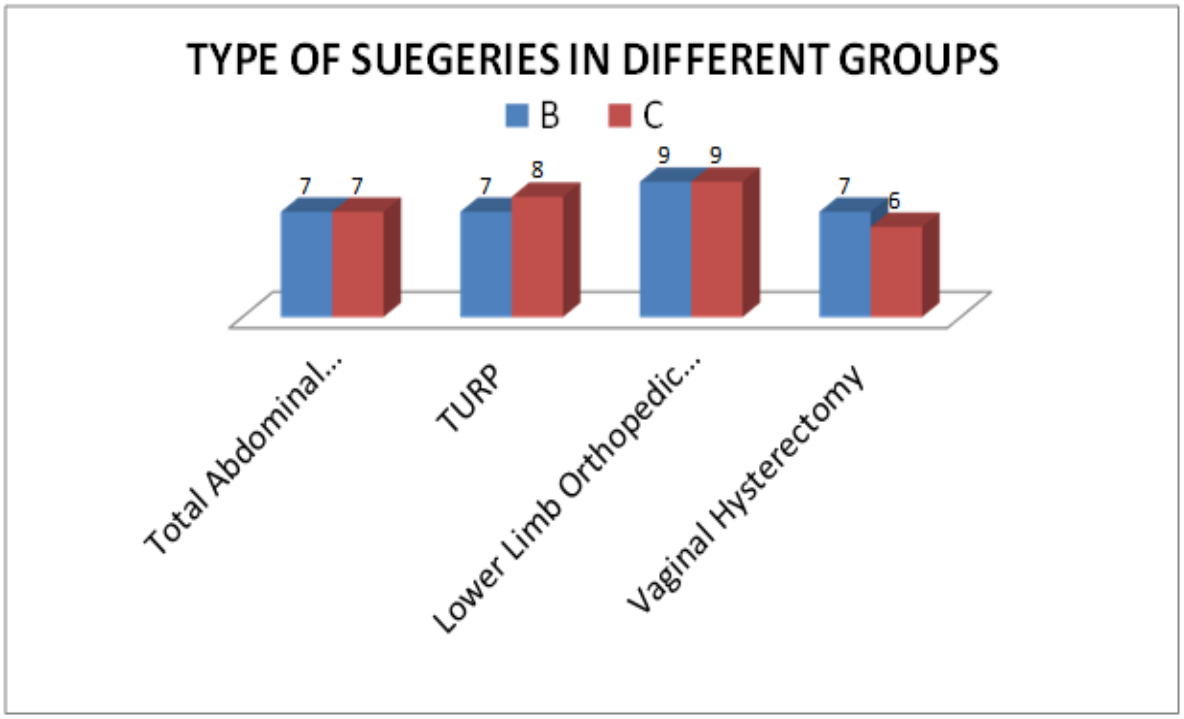
Variables	GROUP-B	GROUP-C	p value
Age (years)	39±10.93	43.4±12.62	0.348
Weight (kgs.)	57.01±4.49	57.15±4.61	0.991
Height (cms.)	161.35±4.42	158.03±4.32	0.008
BMI (kg/m2)	21.95±2.15	22.96±2.52	0.172
Gender			
Female	18	15	0.436
Male	12	15	
Religion			
Hindu	15	16	0.796
Muslim	15	14	

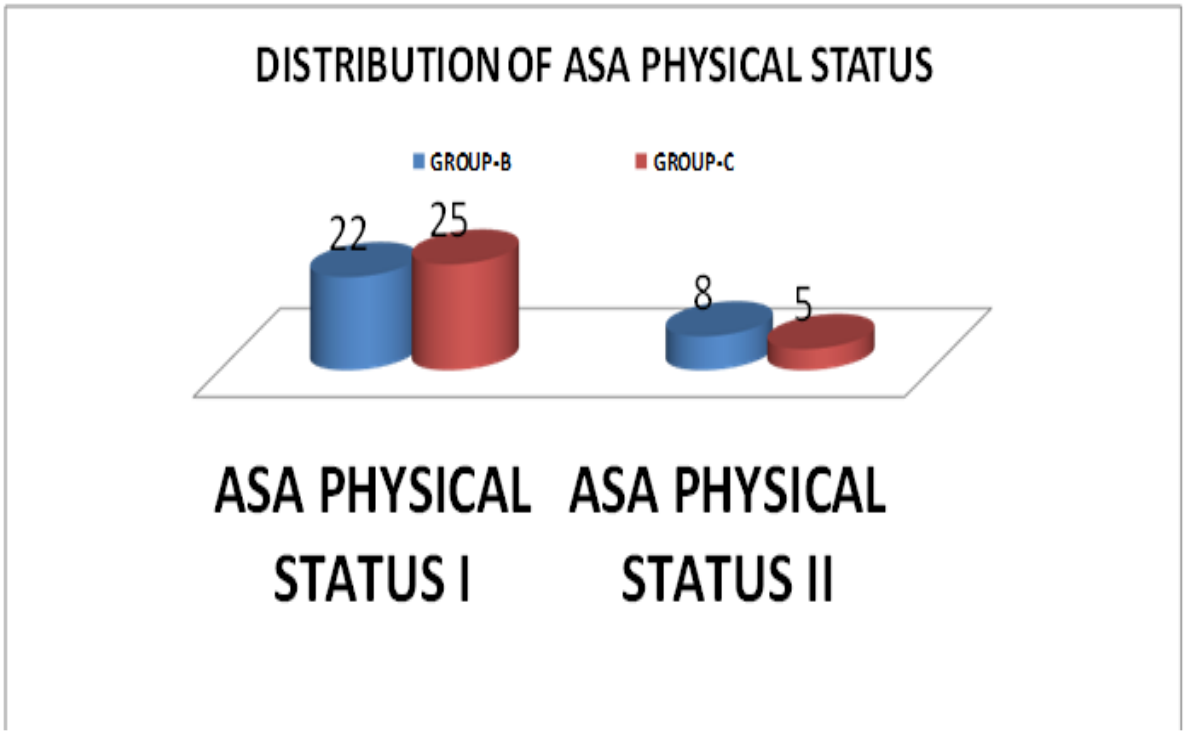
In our study, maximum surgery performed were lower limb orthopaedic surgery (30%), then TURP (25%), then vaginal hysterectomy (21.66%) and total abdominal hysterectomy (23.33%). Type of surgery in different groups were almost identical. Number of ASA physical status I and ASA physical status II patients were comparable in both groups (Table 2 and Figure 1).

Table 2: Surgical characteristics of the patients

Variables	GROUP-B	GROUP-C	p value
Type of surgery			
Total Abdominal Hysterectomy	7	7	0.986
TURP	7	8	
Lower Limb Orthopaedic Surgery	9	9	
Vaginal Hysterectomy	7	6	
ASA physical status			
ASA physical status I	22	25	0.347
ASA physical status II	8	5	

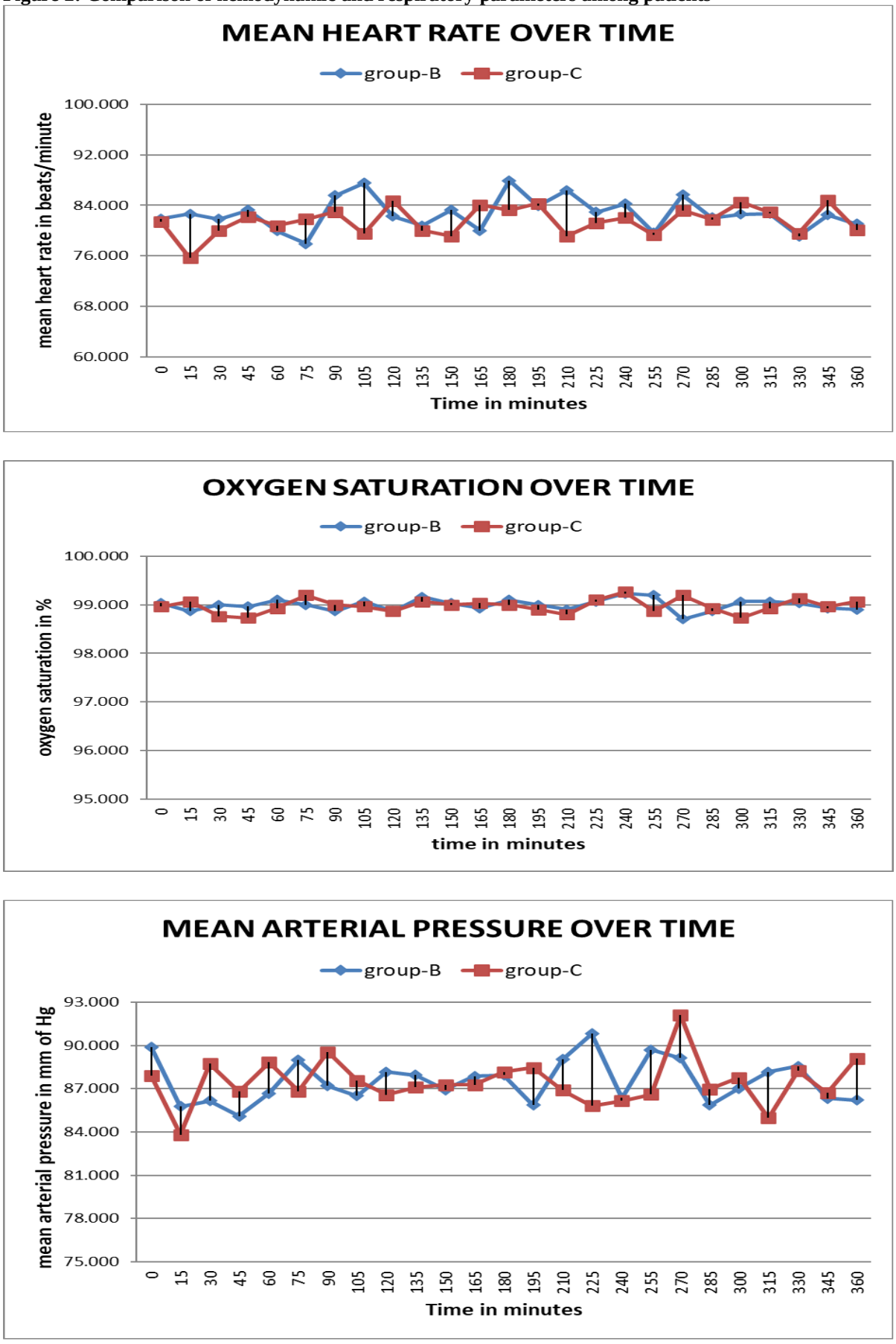
Figure 1: Surgical characteristics of the patients.





In our study, there was no fall or excess rise of heart rate in any group at any specific time period and mean heart rate in both groups were comparable over time. As oxygen saturation of different groups were almost identical with each other, it can be concluded that there was no hemodynamic and respiratory problem in any group. There was no fall or rise of mean arterial pressure in any group intraoperatively or postoperatively and the mean arterial pressure of both groups were comparable ($p>0.05$) so, it can be said that clonidine preserves hemodynamic stability when used as intrathecal adjuvant to hyperbaric bupivacaine (Figure 2).

Figure 2: Comparison of hemodynamic and respiratory parameters among patients



In our study the mean time to achieve T10 level sensory block in group-B was 5.73±1.46 minutes, and in group-C was 5.93±1.33 minutes.In group-B patients time for 2 segment regression was 92.5± 13.11 minutes and in group-C patients this time was higher (125.5±13.35 minutes). So, it can be said that clonidine is superior in prolonging 2 segment regression time.In group-B patients S1 regression time was 195±14.74 minutes and in group-C patients this time was higher (247.5±23.22 minutes. So, it can be said that clonidine is better alternative in prolonging the time for regression to S1 level.Group-B patients took 172.5±12.92 minutes to regain Bromage score 0,and group-C patients took 217.5±23.55 minutes. So, motor blockade was prolonged in clonidine group. Group-B patients asked after 156.5±18.76 minutes, and group-C patients asked after 186.5±17.03 minutes for analgesic. So, the inference would be that clonidine increases the time of post-operative analgesia (Table3).

Table 3:Comparison of sensory and motor block anaesthetic features among patients

Variables	GROUP-B	GROUP-C	p value
T10 sensory block time (minutes)	5.73±1.46	5.93±1.33	0.851
Peak level of sensory block			
T4	6	7	0.872
T5	15	13	
T6	9	10	
Peak sensory block time (minutes)	12.93±2.19	12.27±1.80	0.366
BROMAGE 3 motor block time (minutes)	7.73±2.39	7.67±1.97	0.991
2 segment regression from peak level (minutes)	92.5±13.11	125.5±13.35	<0.0001
Time to regress to S1 segment (minutes)	195±14.74	247.5±23.22	<0.0001
Time to regress to BROMAGE 0 motor block (minutes)	172.5±12.92	217.5±23.55	<0.0001
Time to 1st analgesic request (minutes)	156.5±18.76	186.5±17.03	<0.0001

The incidences of different side effects were low in the perioperative period upto a period of 24 hours and they were comparable between both the groups (p>0.05) (Table 4).

Table 4: Side effects of the anaesthesia among patients

Side effects	GROUP-B	GROUP-C	p value
Bradycardia	1	3	0.3
Hypotension	2	2	1
Nausea & Vomiting	3	3	1
Post Dural Puncture Headache	1	2	0.553

DISCUSSION

Clonidine is potent after neuraxial administration, indicating a spinal site of action thus favouring neuraxial administration. Most of the clinical experience gained in the use of intrathecal α2-adrenoceptor agonists have been described with clonidine. The use of intrathecal clonidine has a well-established synergetic effect with local anaesthetics [9].

In our study, group-B patients time for 2 segment regression was 92.5± 13.11 minutes and in group-C patients this time was higher (125.5±13.35 minutes). So, it can be said that clonidine is superior in prolonging 2 segment regression time. Racleet al., [11] reported that the time course required for maximal spread of the sensory blockade did not differ in the bupivacaine spinal anaesthesia with clonidine group and the mean time to two-segment regression from the highest level was significantly longer in bupivacaine spinal anaesthesia with clonidine group and significant prolongation of motor block was also associated with the addition of clonidine.Benhamou et al., [12] in 1998 demonstrated improved intraoperative spinal analgesia by adding 75 µg of clonidine to bupivacaine; side effects were not increased.

Seahet al., [13] reported that there was no significant difference in the time required for the highest sensory blockade level and maximal spread of the sensory blockade between the group which received bupivacaine spinal anaesthesia and the group which received bupivacaine spinal anaesthesia with clonidine but the mean time for two segments regression and mean time for regression to L2 were significantly greater in the bupivacaine spinal anaesthesia with clonidine group than in the bupivacaine spinal anaesthesia group.Sia et al., [14] investigated the effect of intrathecal clonidine and found clonidine produced a more rapid onset and a higher quality of analgesia than intrathecal bupivacaine alone. Intrathecal clonidine is also known to significantly prolong the time to regression of the sensory block and recovery of motor block.

Cao et al., [15] did a randomized double-blinded study to evaluate the impact of addition intrathecal clonidine along with bupivacaine in children undergoing orthopaedic surgery. Clonidine significantly prolonged the time for first rescue analgesia and also reduced the requirements of propofol sedation after the surgery.A dose-response study done by Strebel et al., [16] in patients undergoing orthopaedic surgeries examined the dose-response relationship of intrathecal clonidine

at small doses (≤150 μg) with respect to prolonging bupivacaine spinal anaesthesia. The authors reported that duration of pain relief from intrathecal clonidine administration until the first request for supplemental analgesia was significantly prolonged and that small doses of intrathecal clonidine (≤150 μg) significantly prolong the anaesthetic and analgesic effects of bupivacaine in a dose-dependent manner and that (≤150 μg) of clonidine seems to be the preferred dose, in terms of effect versus unwarranted side effects, when prolongation of spinal anaesthesia is desired.

Van Tuijl et al., [17]has shown that addition of clonidine (75 μg) to hyperbaric bupivacaine prolongs spinal anaesthesia after caesarean section and improves early analgesia with no clinically relevant maternal or neonatal side-effects.A prospective, double-blinded study, done by Gecaj-Gashi et al., [18] in patients undergoing Trans Urethral surgeries reported that addition of clonidine with bupivacaine resulted in increased duration of postoperative analgesia, without significant side effects.

In our study, the incidences of different side effects were low in the perioperative period upto a period of 24 hours and they were comparable between both the groups ($p>0.05$). Clonidine prolongs the duration of intrathecally administered local anaesthetics and has potent anti-nociceptive properties. Although such prolongation of the effects of local anaesthetics has been reported for oral [19,20,21] and IV [21] clonidine administration, the intrathecal route is more effective in prolonging bupivacaine spinal anaesthesia [22].

CONCLUSION

Our conclusion from the study is that clonidine as intrathecal adjuvant significantly prolongs the sensory and motor blockade of intrathecal hyperbaric bupivacaine without altering the onset of spinal anaesthesia. In equipotent doses clonidine is more effective as intrathecal adjuvant to hyperbaric bupivacaine than normal saline. Neither clonidine nor normal saline increases side-effects of spinally administered hyperbaric bupivacaine if given in appropriate doses.

REFERENCES

1. David J Birnbach and Ingrid M Browne. Anaesthesia for obstetrics. In: Miller R D, Lars I. Eriksson, Lee A. Fleisher, Jeanine P. Wiener-Kronish, William L. Young editors. Miller's Anaesthesia. Philadelphia; Churchill Livingstone Elsevier Inc.;2010, 7th edition, chapter 69,page 2219
2. Elia N, Culebras X, Mazza C, Schiffer E, Tramèr MR. Clonidine as an adjuvant to intrathecal local anaesthetics for surgery: Systematic review of randomized trials. RegAnesth Pain Med. 2008; 33:159–67.
3. Kanazi GE, Aouad MT, Jabbour-Khoury SI, Al Jazzar MD, Alameddine MM, Al-Yaman R, Bulbul M, Baraka AS. Effect of low-dose Dexmedetomidine or Clonidine on the characteristics of Bupivacaine spinal block. ActaAnaesthesiol Scand. 2006 Feb; 50(2):222-7.
4. Stoelting R K, Hillier Simon C; Pharmacology & Physiology in Anaesthetic Practice. Philadelphia. Lippincott Williams & Wilkins.2006,4th edition chapter 3, page 90-91
5. Stoelting R K, Hillier Simon C; Pharmacology & Physiology in Anaesthetic Practice. Philadelphia. Lippincott Williams & Wilkins.2006,4th edition chapter 9, page 262
6. Stoelting R K, Hillier Simon C; Pharmacology & Physiology in Anaesthetic Practice. Philadelphia. Lippincott Williams & Wilkins.2006,4th edition page 340
7. Axelsson K, Gupta A. Local anaesthetic adjuvants: Neuraxial versus peripheral nerve block. CurrOpinAnaesthesiol. 2009 Oct; 22(5):649-54.
8. Rajni Gupta, JaishriBogra, ReetuVerma, Monica Kohli, Jitendra Kumar Kushwaha, Sanjiv Kumar. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. Indian J Anaesth. 2011; 55(4): 347–351.
9. Niemi L. Effects of intrathecal Clonidine on duration of Bupivacaine spinal anaesthesia, haemodynamics, and postoperative analgesia in patients undergoing knee arthroscopy. ActaAnaesthesiolScand 1994; 38:724–8.
10. Bromage PR: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. ActaAnaesthScand 1965; 16:555-69.
11. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric Bupivacaine spinal anaesthesia with Epinephrine and Clonidine for hip surgery in the elderly. AnesthAnalg. 1987; 66(5):442-6.
12. Benhamou D, Thorin D, Brichant JF, Dailland P, Milon D, Schneider M., Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. AnesthAnalg. 1998 Sep; 87(3):609-13.
13. Seah YS, Chen C, Chung KD, Wong CH, Tan PP. Prolongation of hyperbaric Bupivacaine spinal anaesthesia with Clonidine. Ma ZuiXueZaZhi. 1999; 29(1):533-7.
14. Sia AT Optimal dose of intrathecal Clonidine added to Sufentanil plus Bupivacaine for labour analgesia. Can J Anaesth. 2000; 47(9):875-80.
15. Cao JP, Miao XY, Liu J, Shi XY. An evaluation of intrathecal Bupivacaine combined with intrathecal or intravenous Clonidine in children undergoing orthopedic surgery: a randomized double-blinded study. PaediatrAnaesth. 2001; 21(4):399-405.
16. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small-dose intrathecal Clonidine and isobaric Bupivacaine for orthopedic surgery: a dose-response study. AnesthAnalg. 2004;99(4):1231-8.
17. van Tuijl I, van Klei WA, van der Werff DB, Kalkman CJ., The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: a randomized controlled trial., Br J Anaesth. 2006 Sep; 97(3):365-70. Epub 2006 Jul 21.
18. Gecaj-Gashi A, Terziqi H, Pervorfi T, Kryeziu A. Intrathecal Clonidine added to small dose Bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery. Can UrolAssoc J. 2012; 6(1):25-9.
19. Liu S, Chiu AA, Neal JM, et al. Oral Clonidine prolongs Lidocaine spinal anaesthesia in human volunteers. Anaesthesiology 1995; 82:1353–9.

20. Ota K, Namiki A, Iwasaki H, Takahashi I. Dose-related prolongation of Tetracaine spinal anaesthesia by oral Clonidine in humans. AnesthAnalg 1994; 79:1121–5.
21. Rhee K, Kang K, Kim J, Jeon Y. Intravenous Clonidine prolongs Bupivacaine spinal anaesthesia. ActaAnaesthesiolScand 2003; 47:1001–5.
22. Bonnet F, Buisson VB, Francois Y, et al. Effects of oral and subarachnoid Clonidine on spinal anaesthesia with Bupivacaine. RegAnesth 1990; 15:211–4.