DOI: 10.14260/jemds/2014/2232

ORIGINAL ARTICLE

A COMPARATIVE STUDY OF ANALGESIC EFFICACY OF INTRATHECAL CLONIDINE WITH BUPIVACAINE & BUPIVACAINE ALONE IN ELECTIVE CAESAREAN SECTION

Chethanananda T. N[1], Sagar G. C[2], Shashank M. R[3], Shilpa Omkarappa[4]

HOW TO CITE THIS ARTICLE:
Chethanananda T. N, Sagar G. C, Shashank M. R, Shilpa Omkarappa. "A Comparative Study of Analgesic Efficacy of Intrathecal Clonidine with Bupivacaine & Bupivacaine alone in Elective Caesarean Section". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 12, March 24; Page: 2973-2982,
DOI: 10.14260/jemds/2014/2232

ABSTRACT: Spinal anaesthesia in caesarean section has many advantages in that it is simpler to perform, provides a more certain endpoint& has a higher degree of success than epidural anaesthesia as it provides more profound block than epidural anaesthesia. As the dose of local anaesthetics used with spinal anaesthesia is small, there is little chance of maternal toxicity & placental transfer of drugs. Bupivacaine 0.5% is the most popular drug used for spinal anaesthesia in caesarean section. Many adjuvant drugs are added intrathecally along with Bupivacaine to increase the duration and intensity of analgesia. Intrathecal Clonidine (an α2 agonist) is being extensively evaluated as an alternative to neuraxial opioid along with local anaesthetic agents. We evaluated the efficacy of clonidine added to 0.5% bupivacaine in prolonging the analgesia produced by intrathecal bupivacaine in parturients undergoing elective lower segment caesarean section (LSCS). 60 parturients between 20-30 years of age weighing 50-70 Kgs belonging to ASA (American Society of Anaesthesiologists) grading I & II were prospectively randomised to two groups. 30 parturients of Group B (control group) received 2.0 ml of 0.5% hyperbaric bupivacaine intrathecally alone and 30 parturients of Group BC received 1.75 ml of 0.5% hyperbaric bupivacaine +0.25 ml (37.5mcg) of preservative free clonidine. The time taken for onset of sensory and motor blockade duration of postoperative analgesia and the duration of motor blockade were noted. The mean time of onset of sensory blockade in Group B was 57.16±9.9 seconds and Group BC was 62.8±6.80 seconds ($p < 0.05$). The meantime taken for onset motor block was 66.00±5.15 seconds in Group B and 81.33±8.89 seconds in Group BC ($p = 0.000$) with the grade of motor blockade was similar in both groups. The mean duration of analgesia was 152.77±11.79 minutes in B group and 288.16±16.73 in BC group ($p = 0.000$). The mean duration of motor blockade was 93.33±8.74 minutes in Group B and 218.00±11.56 minutes in Group BC ($p=0.000$). An α2 agonist like clonidine in a dose of 37.5mcg with 0.5% intrathecal bupivacaine heavy in elective LSCS potentiates bupivacaine spinal analgesia without any side effects.

KEYWORDS: Spinal anaesthesia, Caesarean section, Clonidine, Post-operative analgesia.

INTRODUCTION: "The delivery of the infant into the arms of a conscious and pain free mother is the most exciting and rewarding moments in Medicine"- Moir. Successful anaesthesia for caesarean delivery can be accomplished by a number of ways. Common to all is the need for expert technical skills and understanding of maternal and fetal physiology, pathophysiology and pharmacology.

The two major anaesthetic approaches are regional anaesthesia and general anaesthesia. Regional anaesthesia includes spinal, epidural and combined spinal epidural (CSE).

DOI: 10.14260/jemds/2014/2232

The advantages of spinal anaesthesia in caesarean delivery are simplicity of technique, speed of induction (rapid onset of action), reliability and minimal foetal exposure to drugs, an awake patient and minimization of hazards of aspirations.

The disadvantages of spinal anaesthesia in caesarean delivery are hypotension leading to Intraoperative nausea and vomiting, post dural puncture headache (PDPH), and limited duration of action unless a continuous technique is used or some adjuvant drugs are added to local anaesthetic agents viz. opioids, clonidine, neostigmine & ketamine. One of the main advantages of using α-adrenergic drug like clonidine is the absence of respiratory depression, pruritis, nausea & vomiting.

Recently clonidine a α2 agonist is rapidly gaining popularity as a local anaesthetic adjuvant in regional anaesthesia. Spinal clonidine has been used extensively as an adjuvant in regional anaesthesia. Spinal clonidine has been used extensively as an adjuvant to local anaesthetics as clonidine consistently prolongs sensory and motor blockade of intrathecal anaesthesia.[1]

The primary analgesic mechanism of action of clonidine is believed to be at the level of the spinal cord. These include both pre- & post synaptic sites of action.

Presynaptically α2 receptor activation by clonidine inhibits the release of Substance P from afferent fibres within the dorsal horn. This presynaptic inhibition of Substance P prevent it from further activating neurokinin receptors & ultimately transmitting nociceptive impulses.[2]

Post synaptically α receptor activation by clonidine inhibits the development and subsequent transmission of integrated pain signal within the second order neurons of substantia gelatinosa.

Clonidine may exert its local anaesthetic enhancing effect by vasoconstriction at the site of injection. Clonidine mediated activation of postsynaptic adrenergic receptors may cause localised vasoconstriction thus prolonging sensory and motor blockade by decreasing the systemic absorption of local anaesthetic compound.[3]

Though there are reports of clonidine causing constriction of human uterine arteries in vitro by a mixed α1 and α2 adrenergic mechanism,[4] the effects on uterine blood flow of orally administered clonidine have not been studied, but it has been used safely for many years without apparent adverse maternal, foetal or neonatal effects.

Intrathecal clonidine (150, 300 & 450mcg) has been shown to decrease pain in dose dependant fashion in women undergoing caesarean section.[5] Therefore, this study is designed to study the effect of clonidine as an adjuvant to bupivacaine heavy, given intrathecally for prolonging duration of analgesia.

MATERIALS & METHODS: After obtaining institutional ethical committee approval and informed consent this prospective randomised, controlled, double blinded study was conducted in 60 parturients of ASA status I & II between the age of 20-30 years weighing 50-70 Kgs undergoing elective LSCS under subarachnoid anaesthesia. Parturients unwilling for subarachnoid block, with comorbid diseases, undergoing emergency LSCS, height < 150 cms are excluded from study.

Parturients were randomly allocated in to two groups with 30 in each. Group B (control group) and Group BC (clonidine group). Nil per oral status is maintained. Intravenous (i. v.) access with 18G canula secured i. v. ranitidine 50mg, ondansetron 4mg 2 hours prior to anaesthetic procedure given and connected to multiparameter monitor (ECG, NIBP, pulse oximeter) 30 mins before the scheduled time of surgery, a preloading is done with 1000ml of Lactated Ringers solution.

DOI: 10.14260/jemds/2014/2232

Under aseptic precautions lumbar puncture was done with 27G Quincke Babcock spinal needle in midline approach in lateral decubitus position between L3 & L4 intervertebral space. The patients and the monitoring anaesthesiologist were blinded to the study solutions. When a free flow of CSF was obtained, 2ml of 0.5% hyperbaric bupivacaine was injected in Group B parturients and 1.75ml of 0.5% hyperbaric bupivacaine with 37.5mcg of clonidine (0.25ml) was injected in Group BC. Study drug of 2ml was given in 3 seconds with the operating table kept flat. Immediately after the drug injection, the parturients were turned supine and a wedge was given underneath the parturients right buttock to prevent supine hypotension syndrome and allowed to remain so till the baby was extracted.

Assessment of sensory and motor blockade were done at the end of each minute till the maximum level achieved. Continuous ECG monitoring, measurement of blood pressure, heart rate, respiratory rate and SpO_2 obtained at every 2 minutes for a period of 10 minutes and every 3 minutes till the surgery ends and postoperatively every 1 hour for next 4 hours and all parturients were monitored closely for 1st 24 hours for any complications.

Sensory blockade was assessed using a short bevelled 22G needle and was tested in the midclavicular line over the chest, trunk and legs on either side. Analgesia was defined as loss of sensation to pinprick and anaesthesia as loss of sensation of touch. Motor blockade in the lower limbs was assessed using Bromage scale (1965).

The onset of sensory blockade was taken from the time of injection of spinal anaesthesia till the time the level of sensory block reaches T10 dermatome. Maximum sensory blockade was taken as time required to attain the maximum level of blockade from the time of injection of spinal anaesthesia. The onset of motor block was taken as time required for the development of Bromage grade I motor block from the time of injection of spinal anaesthesia. The maximum motor blockade was taken as time required to attain maximum grade of motor blockade (Bromage grade 3) from the time of spinal drug administration.

Intraoperatively and postoperatively any complications like hypotension, bradycardia, nausea & vomiting were noted, treated & tabulated. Hypotension defined as reduction of systolic BP> 30% from basal or Systolic BP <90mmHg, treated with volume replacement and with Inj. Ephedrine 6mg i.v. in increments. Bradycardia (H. R. < 60/min) was treated with Inj. Atropine 0.6mg i.v.

Postoperatively, the parturients were observed for the duration of analgesia by using visual analogue scale(VAS) scoring system. Parturients were given rescue analgesia once VAS scores were <5. The duration of analgesia was taken from the time of spinal drug administration till the VAS is 5 at the site of surgery. The duration of motor blockade was taken as time required for the recovery of complete power of lower limbs (Bromage 0) from the time of induction of spinal anaesthesia. Time taken for complete recovery of motor blockade was also noted.

The level of sedation was assessed by Ramsay sedation score, and the score was re-evaluated every 10mins. during the surgery & postoperatively up to 120mins.

RESULTS: The mean age of the parturients in the two groups were compared using T-test Group B parturients had a mean age of 25±2.36 years and Group BC parturients had a mean age of 25.13±2.66. There is no significant difference in the age of the parturients between two groups (P>0.05). There was no significant difference in terms of weight (P > 0.05) and height (P > 0.05).

DOI: 10.14260/jemds/2014/2232

Age in years	Group B (control group)		Group BC (clonidine group)	
	Number of parturients	Percent	Number of parturients	Percent
21-25	15	50%	17	56.61%
26-30	15	50%	13	43.29%
Total	30	100	30	100
Mean age in years ± SD	25±2.36		25.13±2.66	
Minimum age in years	21		21	
Maximum age in years	29		29	

Table 1: Age distribution

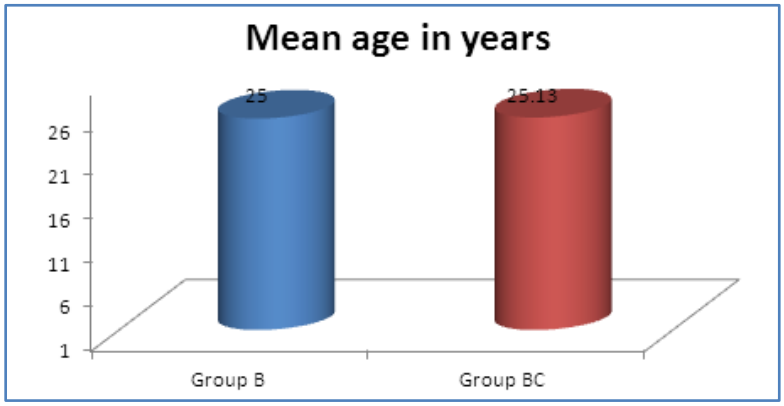

Figure 1: Age Distribution

Table 1 & Figure 1 shows the age distribution of the parturients in both the groups. The minimum age in group B (control group) and group BC (clonidine group) were 21 years. The maximum age in both groups is 29 years. The mean age in group B (control group) is 25.13±2.66 years and group BC (clonidine group) is 25±2.36 years. There is no significant difference in the age of parturients between the groups. Both groups were similar with respect to age distribution (p>0.05).

Weight in Kg	Group B (control group)		Group BC (clonidine group)	
	Number of parturients	Percent	Number of parturients	Percent
51-55	7	23.33%	8	26.64%
56-60	14	46.62%	15	49.95%
61-65	8	26.64%	6	19.98%
66-70	1	3.33%	1	3.33%
Total	**30**	**100**	**30**	**100**
Mean weight in Kg±SD	58.4±3.98		58.1±3.46	
Minimum weight in Kg	51		51	
Maximum weight in Kg	69		66	

Table 2: Body weight distribution

DOI: 10.14260/jemds/2014/2232

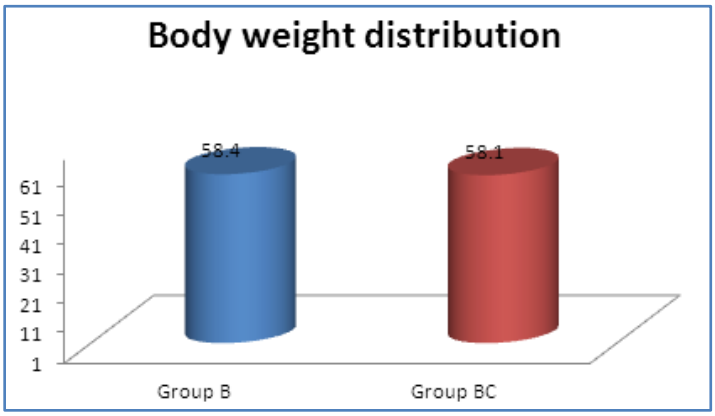

Figure 2: Body weight distribution

Table 2 & Figure 2 shows the body weight distribution of parturients. The mean body weight in group B (control group) is 58.4±3.98kg and group BC (clonidine group) is 58.1±3.46kg. The minimum body weight in both the groups were 51Kg. The maximum body weight in group B was 69Kg and group BC was 66kg. There is no significant difference in the body weight of parturients between the groups (p>0.05).

Height in cm	Group B (control group)	Group BC (clonidine group)
Mean height in cm	155.23±2.93cm	154.66±2.70cm
Minimum height in cm	151cm	150cm
Maximum height in cm	162cm	164cm

Table 3: Height distribution

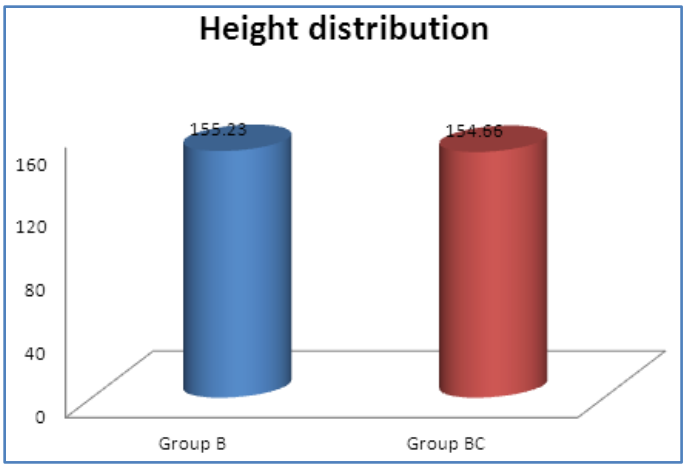

Figure 3: Height distribution

Table 3 & Figure 3 shows the height distribution of parturients. The mean height in group B (control group) is 155.23±2.93cm and group BC (clonidine group) is 154.66±2.70cm. The minimum

DOI: 10.14260/jemds/2014/2232

height is 151cm in control group and 150cm in clonidine group. The maximum height in groupB was 162 and in groupBC was 164cm. There is no significant difference in the height of parturients between the groups(p>0.05).

The mean time taken for onset of sensory blockade in Group B is 57.16±4.99secs and in Group BC is 62.8±6.80. The difference is statistically significant (P< 0.05). The mean time taken for the onset of motor blockade was 66.00±5.15secs in Group B and 81.33±8.89secs in Group BC. The difference is statistically significant (P=0.000). The mean duration of analgesia is 157.77±11.77mins. in Group B and 288.16±16.73mins in Group BC. This is statistically significant (P=0.000). The mean duration of motor blockade was 93.33±8.74mins. in Group B and 218.00±11.56mins. in Group BC which is statistically highly significant (P=0.000).

	Group B(control)	Group BC(clonidine)	p-value
Sensory onset in seconds	57.16±4.99	62.8±6.80	<0.005

Table 4: Mean time taken for sensory onset in seconds

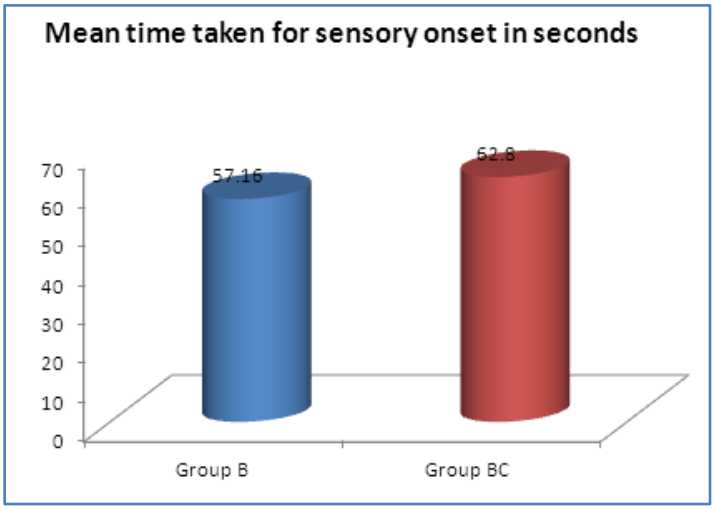

Figure 4: Mean time taken for sensory onset in seconds

The mean time of onset of sensory blockade in group B (control group) is 57.16±4.99 secs and in group BC (clonidine group) is 62.8±6.80secs. There is statistically highly significant difference between the groups (p<0.05).

	Group B (control)	Group BC (clonidine)	p-value
Mean time taken for motor onset in seconds	66.00±5.15	81.33±8.89	<0.005
Grade of motor block(Bromage scale)	1	1	

Table 5: Mean time taken for motor onset in seconds

DOI: 10.14260/jemds/2014/2232

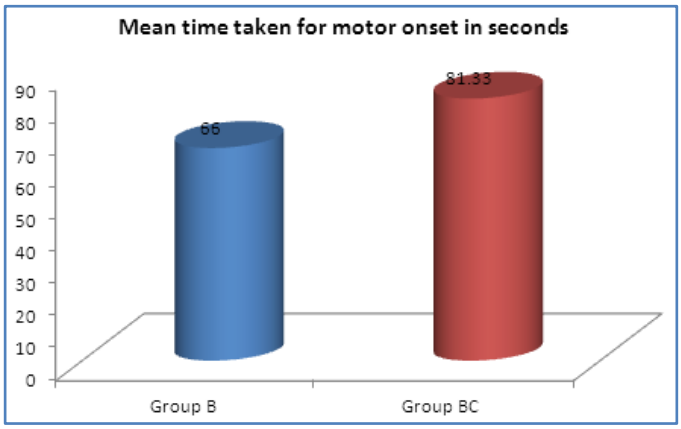

Figure 5: Mean time taken for motor onset in seconds

The mean time taken for the onset of motor blockade is 66.00±5.15secs in group B (control group) and 81.33±8.89secs in group BC (clonidine group). There is statistically highly significant difference between the groups (p=0.000).

The grade of motor blockade is similar in both the groups (Bromage grade1).

	Group B (control)	Group BC (clonidine)	p-value
Mean duration of analgesia in minutes	152.77±11.79	288.16±16.73	<0.005
Mean duration of motor blockade	93.33±8.74	218.00±11.56	<0.005

Table 6: Mean duration of analgesia and motor blockade

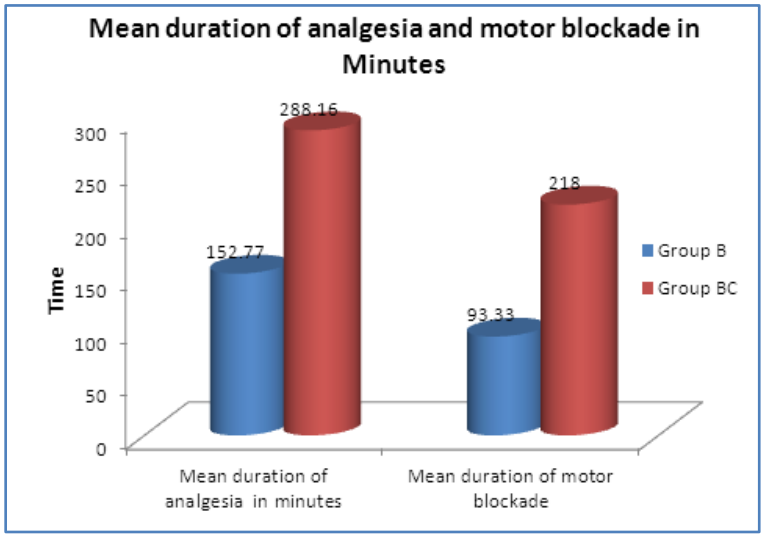

Figure 6: Mean duration of analgesia and motor blockade

DOI: 10.14260/jemds/2014/2232

The mean duration of analgesia is 152.77±11.79 mins in group B (control group) and 288.16±16.73 mins in group BC (clonidine group). There is statistically highly significant difference between the groups (p=0.000).

The mean duration of motor blockade is 93.33±8.74mins in group B (control group) and 218.00±11.56 mins in group BC (clonidine group). There is statistically highly significant difference between the group (p=0.000).

DISCUSSION: Our study indicates that addition of clonidine 37.5 mcg to intrathecal bupivacaine 0.5% in parturients undergoing elective LSCS significantly prolongs the duration of analgesia as compared to bupivacaine alone. Our findings are consistent with those reported by several studies.[6, 7]

Several adjuvant have been used to prolong the duration of analgesia of bupivacaine for intrathecal analgesia even in parturients undergoing caesarean section. Use of opioids is associated with an increased incidence of pruritis & postoperative nausea & vomiting[8]. The advantage of clonidine is that it prolongs the duration of analgesia without an increase in the incidence of respiratory depression, pruritis & urinary retention which are commonly seen with neuraxial opioids.

Clonidine acts both supraspinally & spinally. Supraspinally it acts on the Nucleus Ceruleus & decreases nor-epinephrine & epinephrine release spinally it acts on the spinal receptors. The rationale behind the intrathecal administration of clonidine is to achieve a high drug concentration in the vincity of α 2 adrenoceptor in the spinal cord and it work by blocking the conduction of C and A δ fibres, increases K^+ conductance and intensifies conduction block of local anaesthetics.[7]

In our study a study a block up to L_1 was considered for the onset of sensory block. The mean time for the onset of sensory block was 57.16±4.99secs. in Group B & 62.8±6.80 secs. in Group BC. This delay in Group BC may be because of the reduced dose of bupivacaine used in this group compared to Group B. The mean time for the onset of surgical anaesthesia at L_1 was 72.03±6.82 secs in Group B and 86.86±9.13secs in Group BC. The reason of observed difference between our result and other studies is not apparent,[9] but it could be attributed to methodological difference such as difference in dosage or population studied.

The mean duration of analgesia in our study is 152.77±11.79mins. in Group B and 288.16±16.73mins. in Group BC and is statistically highly significant. Our study concurs with the study conducted by Braga et.al[9] who observed that mean duration of analgesia to be 163.55±22.67 mins when using bupivacaine 8mg (1.6ml) + clonidine 0.75mcg (0.5ml) + morphine 100mcg (1ml) in Group 1 and 191.18±41.99mins when using bupivacaine 10mg(1.6ml) + clonidine 0.75mcg (0.5ml) + morphine 100 mcg (1 ml) in Group 2 and Grandhe P.R et al.[10] observed the mean duration of analgesia of 6.3±0.8hrs when using clonidine of 1mcg/kg with mean weight of 60.6±19.4kgs.

In our study Motor blockade was checked by using Bromage scale and the onset was taken when the parturient developed Grade I motor blockade. The mean time for the onset of motor block was 66.00±5.15secs. in Group B and 81.33±8.89secs in Group BC which is statistically highly significant but in a study conducted by Shah Bhavani Bhushan et al.[11] the onset of motor block was 1.7±0.51mins in Group BC (60), 1.59±0.52mins in Group BC and 1.48±71mins in Group BC(15) in clonidine group (60mcg, 30mcg, 15mcg respectively) which is higher than in our study & this may be due to the less mass of clonidine used.

The duration of motor blockade was taken as the time required for recovery of complete power of lower limbs (Bromage scale 0) from the time of induction of spinal anaesthesia. The mean duration of motor blockade in our study was 93.33±8.74mins in Group B and 218.00±11.56mins in Group BC which is statistically significant. Our study does not concur with the study conducted by Braga et al.[9] who observed the mean duration of motor blockade to be 198.48±47.63mins when using bupivacaine 8.0mg (1.6ml)+clonidine 75mcg (0.5ml)+morphine 100mcg (1ml) in group 1 and 232.84±63.66 mins when using bupivacaine 10mg (1.6ml)+clonidine 0.75mcg (0.5ml)+morphine 100mcg (1ml) most probably because we used only a low dose of clonidine with 1.75ml of bupivacaine without an opioid drug.

We chose a low dose of clonidine (37.5mcg) in our study as there were studies showing that increasing the dose from 1 to 2mcg/kg epidurally, did not enhance the analgesic efficacy of clonidine[12] and the adverse effects like respiratory depression, bradycardia & hypotension increases with the dose[13] and also considering the overall reductions in the dose requirement of drugs during pregnancy.

The side effects of neuraxial clonidine administration includes hypotension, bradycardia. The antihypertensive effects results from stimulation of α2 inhibitory neurons in the medullary vasomotor centre of brainstem which leads to a reduction in norepinephrine turnover & sympathetic nerve outflow from CNS to the peripheral tissues. Bradycardia is caused by an increase in vagal tone resulting from stimulation of parasympathetic outflow, as well as reduced sympathetic drive[14]. But none of the parturients in our study, who received clonidine developed hypotension or bradycardia.

CONCLUSION: We conclude that clonidine in a dose of 37.5mcg added to 0.5% of 1.75ml of hyperbaric bupivacaine intrathecally in elective caesarean section cases significantly prolongs the duration of postoperative analgesia when compared to 0.5% of 2ml of hyperbaric intrathecal bupivacaine alone without any side effects.

REFERENCES:

1. Eisenach JC, DeKock M, Klimscha W: α2-Adrenergic agonists for regional anesthesia. Anesthesiology 1996, 85:655-674.
2. Eisenach JC: Overview: First international symposium on α2-adrenergic mechanisms of spinal anesthesia. Reg Anesth 1993, 18:207-212.
3. Langer SZ, Duval N, Massingham R: Pharmacologic and therapeutic significance of alpha-adrenoreceptor subtypes. J Cardiovasc Pharmacol 1985, 7 (Suppl. 8):S1-S8
4. Rebeiro CAF, Macedo TA: Pharmocological characterisation of the post-synaptic alpha-adrenoceptor in human uterine artery. J Phram Phramocol 1986, 38:600-605.
5. Filos K, Goudas LC, Patroni O, et al. Hemodynamic and analgesic profile after intrathecal clonidine: A dose response study. Anesthesiology 1994, 81:591-601.
6. Dobrydnjov I, Axelsson K, Samarutel J, Holmstrom B. Postoperative pain relief following intrathecal bupivacaine combined with intrathecal or oral clonidine. Acta Anaesthesiol Scand 2002;46:806-14.
7. Filos KS, Goudas LC, Patroni O, Polyzou V. Hemodynamic and analgesic profile after intrathecal clonidine in humans: A dose-response study. Anesthesiology 1994; 81:591-601.

8. Vetter TR, Carvallo D, Johnson JL, Mazurek MS, Preson RG Jr. Comparison of single dose caudal clonidine, morphine, or hydromorphone combined with ropivacaine in paediatric patient undergoing ureteral reimplantation. Anaesth Analg 2007; 104:1356-63.
9. Braga Assuncao, Frias Fachini, Braga Franklin Silva et.al. Use of different doses of hyperbaric bupivacaine associated with morphine and clonidine. Acta Cir. Bras. vol.28 no.1 Sao Paulo Jan. 2013.
10. Grandhe PR, Wig J, Yaddanapudi LN. Evaluation of bupivacaine-clonidine combination for unilateral spinal anesthesia in lower limb orthopedic surgery. J Anaesth Clin Pharmacol 2008;24:155-8.
11. Shah BB, Joshi SS, Shidhaye RV, Lakhe JN. Comparison of different doses of clonidine as an adjuvant to intrathecal bupivacaine for spinal anesthesia and postoperative analgesia in patients undergoing caesarian section. Anaesth Pain & Intensive Care 2012;16:266-272.
12. Klimscha W, Chiari A, Michalek-Sauberer A, Wildling E, Lerche A, Lorber C. The efficacy and safety of clonidine/bupivacaine combination in caudal blockade for paediatric hernia repair. Anaesth Analg 1998;86:54-61.
13. Breschan C, Krumpholz R, Likar R, Kraschl R, Schalk HV. Can a dose of 2mcg/kg caudal clonidine causes respiratory depression in neonates? Paediatr Anaesth 1999; 9:81-3.
14. De Beer DA, Thomas ML. Caudal additives in children solutions problems? Br J Anaesthe 2003; 90:487-98.

AUTHORS:

1. Chethanananda T. N.
2. Sagar G. C.
3. Shashank M. R.
4. Shilpa Omkarappa

PARTICULARS OF CONTRIBUTORS:

1. Associate Professor, Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar, Bellur.
2. Post Graduate, Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar, Bellur.
3. Post Graduate, Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar, Bellur.
4. Post Graduate, Department of Anaesthesiology, Adichunchanagiri Institute of Medical Sciences, B. G. Nagar, Bellur.

NAME ADDRESS EMAIL ID OF THE CORRESPONDING AUTHOR:

Dr. Chethanananda. T. N,
P. B. 21, AIMS Staff Quarters,
B. G. Nagar, Nagamangala Taluk,
Mandya District – 571448.
E-mail: drchethananand@gmail.com

Date of Submission: 19/02/2014.
Date of Peer Review: 20/02/2014.
Date of Acceptance: 05/03/2014.
Date of Publishing: 18/03/2014.