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Comparative Study of Intrathecal Bupivacaine with 50 and 75 µg Clonidine in Lower Abdominal Surgeries

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Abstract

Background: Spinal anaesthesia is a safe, reliable, inexpensive technique of providing anaesthesia and blunts autonomic, somatic and endocrine responses. It has many advantages; the limited duration of action appears to be one of its downsides. Clonidine, a partial α2 adrenoceptor agonist, has been shown as an effective and safe drug. It prolongs the action of local anaesthetics and reduces the dosage requirement. *Aims:* To compare the efficacy of intrathecal bupivacaine in combination with 50 µg and 75 µg of clonidine in lower abdominal surgeries. *Materials and Methods:* 60 patients scheduled for lower abdominal surgeries, aged 18-65 years with ASA grade I-II satisfying inclusion criteria were recruited for the study and were randomly divided into two groups of 30 each. Group C50 received Inj. clonidine 50 µg added to 15mg hyperbaric bupivacaine and Group C75 received Inj. clonidine 75 µg added to 15mg hyperbaric bupivacaine. Spinal block characteristics, haemodynamic changes and side effects were recorded. *Results:* Onset of sensory and motor blockade was earlier in group C75 as compared to group C50 but statistically insignificant. Maximum sensory block achieved was T4 in group C75 and T5 in group C50. Two segment regression duration, duration of analgesia, duration of sensory blockade and motor blockade were statistically significantly prolonged in group C75 as compared to group C50. Patients maintained haemodynamic stability. Sedation scoring and side effects were comparable in both the groups. Data was analysed using Chi-square test and Independent t test. *Conclusions:* 75µg Clonidine when added to intrathecal bupivacaine prolongs anaesthesia and postoperative analgesia compared to clonidine 50µg.

Keywords: Clonidine; Hyperbaric Bupivacaine; Spinal Anaesthesia.

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Introduction

Spinal anaesthesia is a commonly used technique for infra-umblical surgeries. It is safe, reliable and inexpensive technique of providing surgical anaesthesia. It offers effective postoperative analgesia and blunts autonomic, somatic and endocrine responses [1].

Hyperbaric bupivacaine 0.5% is three to four times more potent than lignocaine and prolongs duration of action with the disadvantage of slower onset of action [2].

Various drugs like opioids and nonopioids are used as intrathecal adjuvants along with local anaesthetic agents [3]. α2-receptor agonists when used as neuraxial adjuvants improve the quality of perioperative analgesia and alsominimizes the

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anaesthetic dosage requirement, particularly in high-risk patients and in ambulatory procedures [4].

Clonidine, a partial α2 adrenoceptor agonist, has been shown as an effective and safe drug when used intrathecally. It prolongs the duration of action of local anaesthetics and reduces the dosage requirement [5].

In this study, we aimed to evaluate the efficacy of clonidine in two different doses when added to bupivacaine on quality of anaesthesia, time of onset of spinal blockade, intensity of motorblock, duration of analgesia, haemodynamic stability and any side effects.

Objectives

To compare the time taken for the onset, duration of sensory and motor block, two segment regression duration, total duration of analgesia, haemodynamic changes, sedation scoring, any side effects and complications following intrathecal administration of 15 mg of 0.5% hyperbaric bupivacaine with either 50μg or 75μg clonidine in patients undergoing lower abdominal surgeries.

Materials and Methods

After obtaining approval from Institutional Ethics Committee a written informed consent was taken. A prospective randomized double blind study was planned. Patients scheduled for lower abdominal surgeries, aged 18-60 years with American Society of Anaesthesiologists (ASA) physical status class I and II with normal airway (Mallampati grade 1 or 2) were recruited for the study. A total of 60 patients were randomly divided into two groups (30 each). Group C50 received Inj.clonidine 50μg added to 15 mg (3.0ml) hyperbaric bupivacaine intrathecally and group C75 received Inj.clonidine 75μg added to 15 mg (3.0ml) hyperbaric bupivacaine intrathecally.

The exclusion criteria were patient's refusal, history of allergies to any study medications, gross spinal abnormality, localised skin sepsis, haemorrhagic diathesis, neurological involvement / diseases, with head injury, raised intra cranial pressure, raised intra ocular pressure, psychiatric disorders, asthma, epilepsy and thyroid diseases.

On the previous day of surgery, preoperative assessment was done for each patient and written informed consent was taken. Patients were kept nil per oral for solids for 8 hrs and clear fluids 2 hrs before surgery. All patients were premedicated on the night before surgery with tablet ranitidine 150mg and tablet alprazolam 0.25mg.

On the day of surgery in the preoperative room, an intravenous line was secured with 18 gauge cannula and preloaded with Ringer lactate 15ml/kg half an hour before anaesthesia. Monitoring was done using multiparameter monitor having pulse oximetry, ECG and NIBP.

Spinal anaesthesia was administered in left lateral position. Under aseptic precautions, spinal block was performed at level of L3-L4 through a midline approach using 25G Quincke spinal needle and hyperbaric bupivacaine 3.0 ml (15mg) with clonidine either 50 μg or 75μg. The total volume made up to 3.5 ml was injected with operative table kept horizontal. Patients were turned to supine posture immediately and supplemental oxygen given.The time at which injection completed was considered zero time of study.

The following parameters were noted, onset of sensory blockade (T10 level) and motor blockade, maximum level of sensory blockade attained, time to two segments sensory regression, total duration of analgesia which was determined by time to rescue analgesia (VAS ≥ 4), total duration of sensory blockade(regression to S1dermatome)and motor blockade (recovery to bromage 0), level of sedation and side effects like nausea, vomiting , hypotension and bradycardia were noted.

Sensory blockade was tested using pinprick method with a blunt tipped 27G needle. Quality of analgesia was assessed by visual analogue scale.

Visual analogue scale for pain [6]: 0- No pain, 1-3 Mild pain, 4-6 Moderate pain, 7-10 severe pain.

Motor blockade was assessed using modified Bromage scale [7]. Bromage scale: Grade Definition: 0- Full flexion of knee and feet, 1- Inability to raise extended leg; able to move knee and feet, 2- Inability to raise extended leg and move knee; able to move feet, 3- Complete block of lower limb.

Level of sedation was assessedby Ramsay sedation scale [8].

Scale 1–patient is anxious, agitated or restless, Scale 2 –patient is co-operative, oriented and tranquil alert, Scale 3- patient responds to commands, Scale 4 –patient is asleep but with brisk response to light glabellar tap or loud auditory stimulus, Scale 5 - patient is asleep with sluggish response to light glabellar tap or loud auditory stimulus, Scale 6 – patient is asleep, with no response.

Haemodynamic monitoring was done during the block every 5 mins for first 15 mins and every 10 mins

for next 30 mins and once in 15 mins till the end of surgery and post operatively every hourly.

Hypotension was defined as mean arterial pressure falling more than 20% mm Hg of preoperative value or SBP less than 100 mmHg and was treated by increasing the fluid infusion and with inj. mephenteramine 3-6 mg in bolus doses and bradycardia was defined as heart rate less than 60 beats /min and was treated with 0.6mg of inj.atropine.

Post operative pain was assessed by Visual Analogue Scale (VAS), rescue analgesic inj.diclofenac 75 mg intramuscularly was given if VAS was more than 4 .

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analysed using SPSS 22 version (IBM) software. Categorical data was represented in the form of frequencies and proportions. Chi-square was used as test of significance. Continuous data was represented as mean and standard deviation. Independent t test was used as test of significance to identify the mean difference between two groups. p value <0.05 was considered as statistically significant.

Statistical evaluation of data or parameters was done as follows: Sample size was estimated by using the mean duration of motor block from the study Raj Bahadur Singh et al. [9] with 99% Confidence limit and 90% power, sample size of 17 was obtained in each group. With 10% nonresponse sample size of $17 + 1.7 \approx 20$ cases were included in each group.

Results

In our present study both the groups were comparable with regard to demographic profiles as shown in Table 1.

Spinal block characteristics between the groups are shown in Table 2.

Earlier sensory onset was seen in group C75 than in C50 with no statistical significance between the groups. With regard to maximum level of sensory blockade, in C50 group and C75 majority i.e. 83.3% and 46.7% had T6 sensory blockade and 40% in C75 and 10% in C50 group had T5 Sensory blockade. 1 patient (3.3%) in C75 had T4 sensory blockade.This difference in height of sensory blockade was statistically significant (p = 0.021)

Onset of motor block was faster in group C75 as compared to group C50 but there was no statistical significant difference between the groups. Maximum motor blockade attained in both the groups was bromage 3. Duration of two segment regression, duration of analgesia,duration of sensory and motor blockade were statistically significantly prolonged in C75 than C50 (p< 0.001).

Table 1: Demographic profile of the patients

Parameters	Group				P value
	C50 (n=30)		C75 (n=30)		
	Mean	SD	Mean	SD	
Age in years	45.77	17.67	44.07	11.67	0.662
Weight in kgs	62.47	8.30	63.60	7.69	0.585
Sex ratioin % male	13	43.3%	13	43.3%	1.000
Female	17	56.7%	17	56.7%	1.000
Height in cms	174.85	3.5	173.77	6.2	0.354

Table 2: Spinal block characteristics between two groups

Parameters	Group				P value
	C50		C75		
	Mean	SD	Mean	SD	
Onset of sensory blockade in seconds	163.37	40.61	150.00	39.50	0.201
Onset of motor blockade in seconds	213.23	49.07	202.67	48.71	0.406
Two segment regression in minutes	200.0	53.8	234.0	47.8	0.012*
Duration of analgesia in minutes (time to rescue analgesia i.e., when VAS≥4)	248.4	51.5	313.2	73.8	<0.001*
Duration of sensory blockade in minutes (S1segment regression)	302	47.1	378	13.8	<0.001*
Duration of motor blockade in minutes	209.7	20.10	275.3	31.9	<0.001*

Patients were monitored for hemodynamics at varying intervals from baseline to next 24 hours. There were significant changes in mean heart rate and mean arterial blood pressure after spinal anaesthesia at varying intervals as depicted in Table 4,5 and figure 1,2.

With regard to side effects, in group C50, 1 patient (3.3%) had bradycardia and 2 patients (6.7%) had hypotension and in group C75, 9 patients (30.3%) had bradycardia and 12 patients (40.3%) had hypotension. 1patient in group C75 complained of nausea. Bradycardia was treated with inj atropine 0.6mg intravenously and hypotension was treated with oxygen, intra venous fluids and inj. mephentermine as 6mg incremental doses. Hemodynamic changes though clinically significant,

Table 3: Heart rate comparison between two groups at different intervals

	Group				P value
	C50		C75		
	Mean	SD	Mean	SD	
Baseline	83.57	10.93	81.33	7.15	0.353
Immediately	81.43	12.45	74.60	7.19	0.012*
10 Min	75.70	9.13	70.13	8.96	0.02*
30 Min	71.40	7.87	76.77	10.25	0.027*
60 Min	74.37	9.13	78.97	7.30	0.035*
120 Min	75.63	9.69	84.37	7.02	<0.001*
180 Min	76.17	10.08	83.27	7.61	0.003*
240 Min	75.50	9.90	82.97	7.54	0.002*
300 Min	76.10	9.32	82.77	6.88	0.003*
360 Min	76.90	9.65	82.87	5.81	0.005*
420 Min	77.67	9.52	83.43	4.35	0.004*

Table 4: Mean arterial pressure comparison between two groups at different intervals

	Group				P value
	C50		C75		
	Mean	SD	Mean	SD	
Baseline	96.47	8.09	98.87	9.39	0.293
Immediately	92.20	8.46	87.97	7.59	0.046*
10 Min	87.37	9.06	81.83	8.28	0.016*
30 Min	84.40	9.68	78.53	8.71	0.016*
60 Min	87.97	8.42	81.00	7.32	0.001*
120 Min	89.80	7.87	97.93	9.95	0.001*
180 Min	90.73	7.99	97.20	9.30	0.005*
240 Min	91.60	8.02	98.47	8.44	0.002*
300 Min	92.70	7.26	98.23	9.39	0.013*
360 Min	92.70	7.89	98.53	9.08	0.01*
420 Min	93.53	8.05	98.57	8.90	0.025*

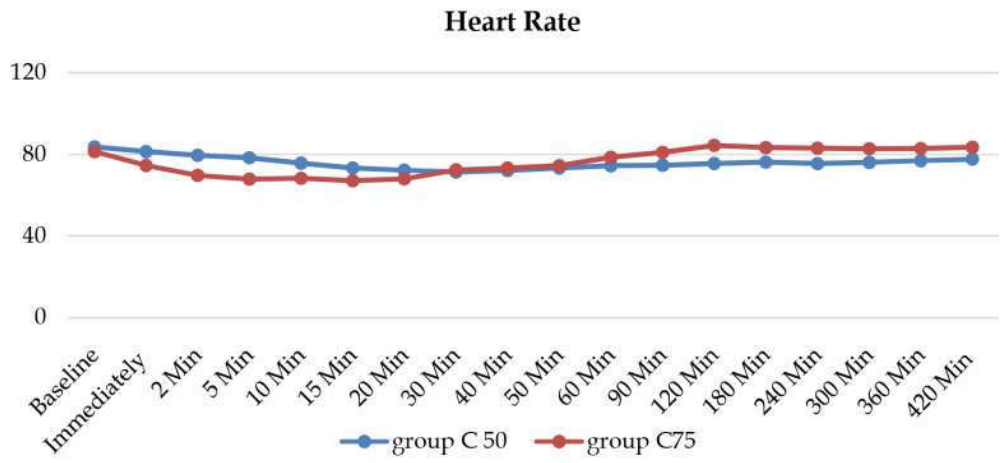

Fig. 1: Line diagram showing heart rate comparison between two groups at different intervals

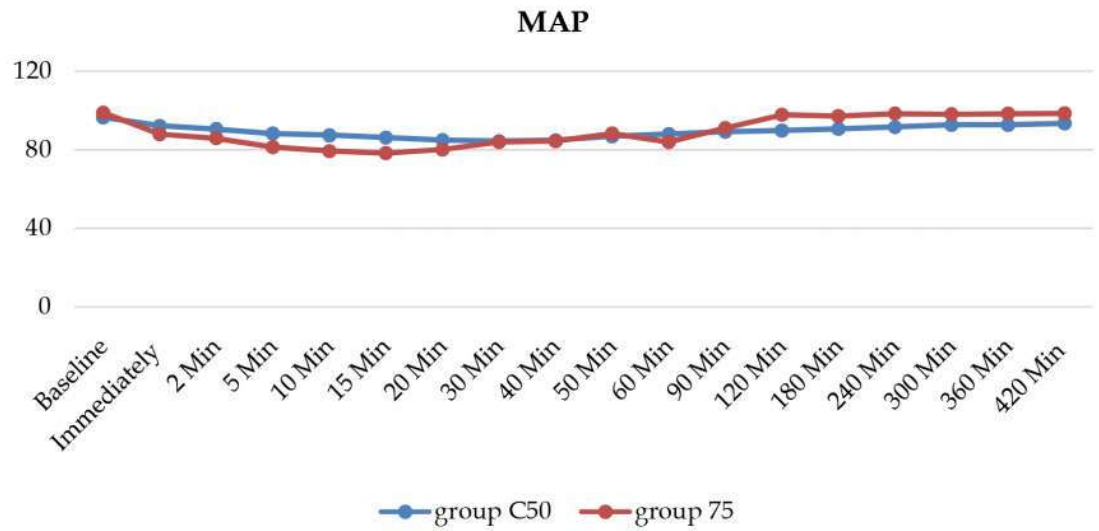

Fig. 2: Line diagram showing MAP comparison between two groups at different intervals

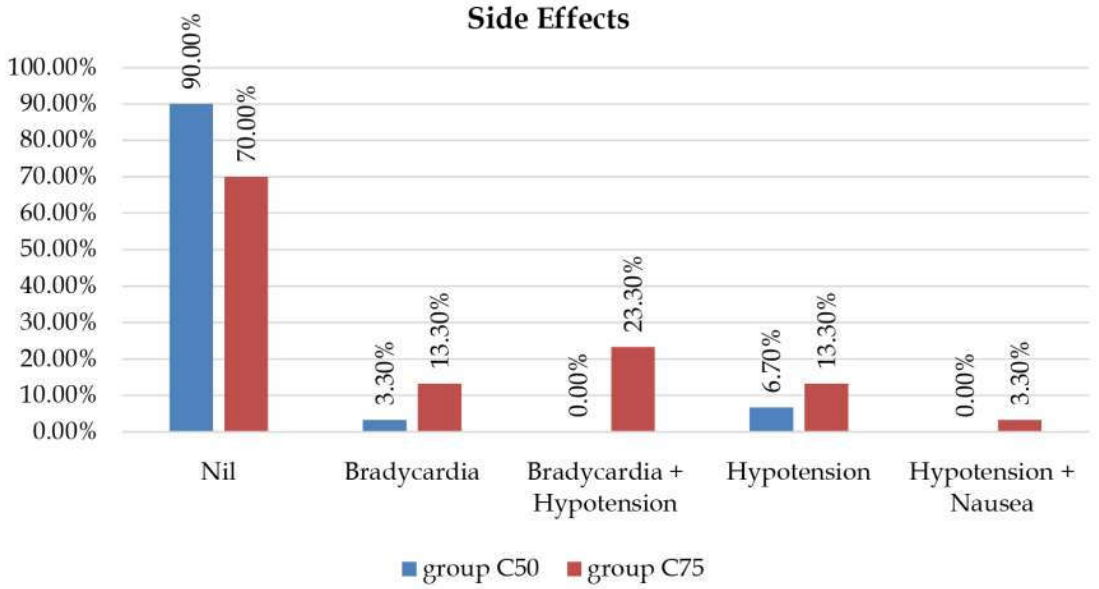

Fig. 3: Bar diagram showing Side effects comparison between two groups

were statistically insignificant. There was no significant difference in side effects between two groups (p = 0.239) as shown in Figure 3.

The sedation scoring was more in group C75 compared to group C50 but clinically insignificant. Patients were easily arousable. Patients were also monitored for other side effects like respiratory depression, dryness of mouth, vomiting and adverse effects, no such incidences were seen.

Discussion

Subarachnoid block has been most extensively used for lower abdominal and lower limb surgeries because of its simplicity, speed, reliability and advantage of avoiding polypharmacy. The aim of it is to provide optimal surgical conditions and offer post op analgesia with minimal side effects. Commonly used local anaesthetics for intrathecal anaesthesia are lignocaine and bupivacaine. Bupivacaine 0.5% heavy single intrathecal injection provides analgesia for about 2-2.5hrs, but the postoperative analgesic duration is limited [9]. Hence, providing intrathecal additive to these local anaesthetics forms a reliable and reproducible method of prolonging post-operative analgesia and to prolong the duration of anaesthesia. As this technique is simple and less cumbersome, it has gained a wide acceptance. Various adjuvant drugs

have been added to local anaesthetics like opioids and non-opioids [3]. α2-receptor agonists like clonidine and dexmedetomidine when used as neuraxial adjuvants improve the quality of perioperative analgesia and also minimize the local anaesthetic dosage requirement [4]. Intrathecal α2-receptor agonists are found to have anti nociceptive action on both somatic and visceral pain [10].

The analgesic effect of clonidine when administered intrathecallyis mediated spinally through the activation of postsynaptic α-2 receptors in substantia gelatinosa of the spinal cord [11-14]. It also activates the descending inhibitory pathway thereby decreasing the release of nociceptive substances from gelatinosa [11].

Various authors have shown that intrathecal clonidine potentiates bupivacaine induced spinal sensory block and motor block and reduces the analgesic requirement in the early postoperative periodwithout the side effects of opioids [5,15-18]. Very low doses of intrathecal clonidine such as 15-30 μg in humans found no hemodynamic instability [17-19]. Studies using 37.5-150 μg reported significant hypotension and bradycardia [17,20]. Intrathecal clonidine at usual doses 1-2 μg/kg is associated with bradycardia, hypotension and sedation [9].

Hence many authors attempted adding adjuvants to intrathecal bupivacaine to offer prolonged duration of analgesia to the patients. As there were no studies comparing 50μg and 75μg clonidine we have taken up this study.

In our study, we designed this randomized double-blind study to evaluate the postoperative analgesic effect, sensory and motor blockade and hemodynamic effects of two different doses of intrathecal clonidine added to bupivacaine in patients undergoing lower abdominal surgeries.

Our results showed that addition of clonidine in 2 different doses (50 and 75 μg) increases duration of sensory block, motor block, analgesia in patients undergoing spinal block with minimal hemodynamic instability in group using 75 μg of clonidine.

There was no significant difference in onset of sensory block between the groups. Addition of 50 μg of clonidine intrathecally did enhance the onset of sensory block and this finding is similar to that of study conducted by Singh RB et al. [9] and Pal R et al. [21].

Author Yoganarasimha et al. [22], in his study using 75μg of clonidine intrathecally showed addition of clonidine increases bupivacaine induced spinal blockade, providing prolonged post-operative analgesia and better surgical conditions.

Addition of clonidine enhanced onset of motor block but there was no statistically significant differencebetween two groups. Authors Yoganarasimha et al. [22] and Pal R et al. [21] in their studies showed addition of clonidine enhanced onset of motor block.

In our study maximum level ofsensory blockade attained was T4 in one patient in group C75 and T5 in 3 patients in group C50. Majority of patient attained T6 level, 83.3% (25/30 patients) in group C50 and 46.7% (14/30 patients) in group C75. The difference of height was statistically significant. Author Grandhe RP et al. [20] in his study compared combination of 1 μg/kg of clonidine and 1.5 μg/kg clonidine with bupivacaine in lower limb surgery patients and reported that maximum level attained was T6 in group using 1μg/kg and T5 in group using 1.5μg/kg.

With regard to time taken for two segment regression, group using 75μg clonidine had prolonged duration of two segment regression with statistical significance than group with 50 μg clonidine which was similar to study done by Thakur A et al. [23] and Sethi B S. [17] Author Thakur A et al. [23] compared addition of intrathecal clonidine 15 μg and 30 μg to hyperbaric bupivacaine in patients undergoing inguinal herniorraphy and concluded that two segment regression time was prolonged in group using 30 μg than group using 15 μg. In study done by Sethi BS et al. [22] using 1μg/kg clonidine intrathecally two segment regression was 218min similar to our study in group with 50 μg (200±53.8 mins).

Duration of analgesia was prolonged with statistical significance in group C75 compared to group C50 which was similar to studies done by RB Singh et al. [9] Thakur A et al. [23] and Dobrynjov I et al. [19]

Author RB Singh et al. [9] in his study using 50μg clonidine intrathecally reported duration of analgesia as 254.8±84.19 min which is similar to our study in group A (248.8±51.5 min). Author Dobrynjov I et al. [19] reported addition of 15 μg and 30 μg to bupivacaine prolonged time to first analgesic required and reduced post-operative pain.

Total duration of sensory blockade was prolonged significantly in group C75 compared to group C50 which was similar to study done by Strebel. S et al. [12], Dobrynjov I et al. [19] and DeKock M et al. [24] Author Dobrynjov I et al. [19] and Strebel S et al. [12] from their studies concluded duration of sensory was prolonged by addition of intrathecal clonidine in dose dependent manner.

De KockM et al. [24] in his study compared addition of 45 μg and 75 μg clonidine to bupivacaine and concluded addition of 75 μg significantly prolonged sensory and motor blockade.

Total duration of motor block was prolonged with statistical significance in group using 75 μg compared to group using 50 μg similar to study done by Sethi BS et al. [17] and Grandhe RP et al. [20] Author Sethi BS et al. [17] studied the efficacy of addition of intrathecal clonidine 1 μg/kg as adjuvant to bupivacaine and reported that duration of motor block was 205 min where as in our study in group using 50 μg , duration of motor block was 209.7±20 min.

Heart rate and BP remained relatively stable intra operatively and post operatively. In our study at baseline there was no significant difference in mean heart rate between 2 groups. Significant difference in heart rate was observed at various interval after spinal anaesthesia. Bradycardia was observed in 1 patient (3.3%) in group C50 and 9 patients in group C75 (30.3%). Bajwa BS et al. [25] in his study using 50 μg clonidine reported 1 patient had bradycardia which is similar to our study. Author Sethi BS et al. [17] observed few incidences of hypotension and bradycardia with 1 μg/kg clonidine used intrathecally.

Significant difference in MAP was observed between 2 groups at various intervals after spinal anaesthesia with increased incidence of hypotension in group C75, 2 patients (6.7%) in group C50 and 12 patients (40.3%) in group C75 had hypotension. Author Grandhe RP et al. [20] in his study reported significant decrease in MAP in clonidine group. There was significant incidences of hypotension requiring fluid or vasopressors as shown by Thakur A et al. [23] Hypotension was more in clonidine group with 30 μg than 15μg. Increasein doses increased incidencesof hypotension as shown by authors Dobrynjov I et al. [19] and Grandhe RP et al. [20] Author Yoganarasimha et al. [22] in his study using 75 μg of clonidine observed hypotension in 40% patients (10/25) and 6 patients had hypotension and bradycardia requiring atropine. Author RB Singh et al. [9] reported gradual decrease in MAP in 6% patients (3/50) requiring vasopressor in clonidine group similar to our study.

In our study there was no significant difference observed in sedation scores with patients in both groups. Author Pal R et al. [21] observed high sedation score with clonidine group compared with fentanyl and buprenorphine groups. Bajwa BS et al. [25] observed more sedation in clonidine group, 8 patients (16%) were drowsy and difficult to arouse. Author Sethi BS et al. [17] observed high sedation score in clonidine group using 1 μg/kg of clonidine intrathecally. Author Bhar S et al. [26] in his study reported that sedation was more in clonidine group when compared to neostigmine and dextrose groups.

Nausea was seen in 1 patient in group C75. Author Dobrynjov I et al. [19] reported nausea and vomiting in 1 patient in clonidine group using 15μg and 2 patients in group using 30 μg. Fewer incidences of nausea and vomiting was seen in the study done by Yoganarasimha et al. [22]. There was no incidence of respiratory depression and other adverse effects observed in both groups.

Conclusion

Addition of 75 μg of clonidine to intrathecal bupivacaine provides dose dependent prolonged sensory and motor block and effectively prolongs duration of postoperative analgesia than 50μg with minimal hemodynamic instability which requires constant vigilant monitoring.

Acknowledgement

I sincerely thank Dr. Ravi. M, our Professor for his support and guidance while conducting the study.

Key Messages

Spinal anaesthesia is safe technique for lower abdominal surgeries, local anaesthetics along with adjuvants shortens the onset and prolongs the duration of action and postoperative analgesia. Alpha 2 agonists are considered to improve the quality of anaesthesia better compared to other adjuvants. Clonidine in lower dosage maintained better haemodynamic stability.

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Conflicting Interest: None

References

1. David LB. Spinal, Epidural and Caudal Anaesthesia. In Miller's Anesthesia 7th Edition. Philadelphia: Churchill Livingstone Elsevier: 2010.

2. Colin VJ. Spinal anaesthesia-principles. 3rded. In: Principles of anaesthesiology. Philadelphia:Lea and Febiger; 1993.pp.1445-52.
3. Burlacu CL, Buggy DJ. Update on local anesthetics: focus on levobupivacaine. Ther. Clin. Risk Manag. 2008;4:381-92.
4. Axelsson, Kjell; Gupta, Anil . Local anaesthetic adjuvants: neuraxialversus peripheral nerve block. Current Opinion in Anaesthesiology 2009;22:649-54.
5. Sapate M, Sahu S, Shah B, Suryawanshi C, Kulkarni A. Evaluation of bupivacaine-clonidine combination for unilateral spinal anesthesia in lower limb below-knee orthopedic surgery. Saudi J Anaesth 2014;8: 384-87.
6. Breivik H, Borchgrevink PC, Allen SM, Rosseland LA, Romundstat L, Hals B et al. Assessment of pain. Br J Anaesth 2008;101:17-24.
7. Bromage PR. Epidural Anesthesia. Philadelphia, WB Saunders, 1978.p.144.
8. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J. 1974;222(5920):656-9.
9. Singh RB, Chopra N, Choubey S, Tripathi RK, Prabhakar. Role of clonidine as adjuvant to intrathecal bupivacaine in patients undergoing lower abdominal surgery. Anesth Essays Res 2014;8:307-12.
10. Eisenach James C, De Kock Marc, Klimscha, Walter. Alpha sub 2- adrenergic agonist for regional anaesthesia. A clinical review of clonidine. Anesthesiology: 1996; 85(3):655-674.
11. 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;6:25–29.
12. Strebel S, Gurzeler JA, Schneider MC, Aeschbach A, Kindler CH. Small dose intrathecal Clonidine and isobaric bupivacaine for orthopedic surgery: a dose-response study. AnaesthAnalg 2004;99:1231-8
13. ChiariA, Eisenach JC. Spinal anaesthesia: Mechanisms, agents, methods, and safety. RegAnesth Pain Med 1998;23:357-62.
14. Van Tuijl I, I, Giezeman MJ, Braithwaite SA, Hennis PJ, Kalkman CJ, van Klei WA. Intrathecal low dose hyperbaric bupivacaine- clonidine combination in outpatient knee arthroscopy: A randomized controlled trial. ActaAnaesthesiolScand 2008;52: 343-9.
15. 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;87: 609-13.
16. Bajwa SJ, Bajwa SK, Kaur J, Singh A, Parmar SS. Prevention of hypotension and prolongation of postoperative analgesia in emergency cesarean sections: A randomized study with intrathecal clonidine. Int J CritIllnInjSci 2012;2:63-9.
17. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anaesth 2007;51: 415-9.
18. Shah BB, Shidhaye RV, Divekar DS, Panditrao M, Panditrao MM, Suryawanshi C. Effect of addition of clonidine to bupivacaine used for patients undergoing spinal anaesthesia: A randomized, double blind, controlled study. Sri Lankan J Anaesthesiol 2011;19:17-21.
19. Dobrydnjov I, Axelsson K, Thorn SE, et al. Clonidine combined with small-dose bupivacaine during spinal anaesthesia for inguinal herniorrhaphy: a randomized double-blinded study. AnesthAnalg 2003;96:1496503.
20. Grandhe RP, Wig J, Yaddanapudi LN. Evaluation of bupivacaine-Clonidine combination for unilateral spinal anaesthesia in lower limb orthopedic surgery. J AnaesthesiolClinPharmacol 2008;24(2):155-8.
21. Pal R, Arora KK, Doneria NS. Intrathecal buprenorphine, clonidine and fentanylas adjuvant to 0.5% hyperbaric bupivacaine in lower abdominal and lower limb surgeries. Jof evolution of med and Dent Sci 2015;4: 8009-17.
22. Yoganarasimha N, Raghavendra TR, Amitha S, Shridhar K, Radha MK. A Comparitive study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries. Indian J. Anaesth 2014;58:43-47.
23. Thakur A, Bhardwaj M, Kaur K, Dureja J, Hooda S. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy. J AnaesthesiolClinPharmacol 2013;29: 66-70.
24. De kock M, Gautler P, Fanard L, Hody JL, Lavand'homme P. Intrathecal Ropivacaine and Clonidine for ambulatory knee arthroscopy. A dose response study. Anesthesiology 2001;94:574-8.
25. Bajwa BS, Singh AP, Rekhi AK. Comparison of intrathecal clonidine and fentanyl in hyperbaric bupivacaine for spinal anaesthesia and post-operative analgesia in patients undergoing lower abdominal surgeries.Saudi J Anaesth 2017;11:37-40.
26. Bhar S, Basunia SR, Kundu SB, Mondal RC, Halder PS. A Comparison between intrathecal clonidine and neostigmine as an adjuvant to bupivacaine in the subarachnoid block for elective abdominal hysterectomy operations. Saudi J Anaesth 2016;10: 121-26.