Original Research Article

Indian Journal of Anesthesia and Analgesia
2018; 5(6): 963-968
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.5618.14

Intrathecal Bupivacaine with Neostigmine versus Clonidine as an Adjuvants in Lower Abdominal Surgeries

Mamta Goda[1], Neelesh Bhatnagar[2]

[1]Senior Resident [2]Assistant Professor, Department of Anesthesiology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan 313001, India.

Abstract

Background: A number of adjuvants to local anesthetics have been used intrathecally to prolong analgesia. So, the present study was planned to study the effect of intrathecal bupivacaine with neostigmine versus clonidine as an adjuvants in lower abdominal surgeries. *Material & Methods:* 128 patients of ASA physical status grade I and II, aged 30-50 years, scheduled for lower abdominal surgeries under spinal anesthesia of a tertiary care teaching hospital were randomly selected in two groups of 64 each; Group BN:12.5 mg (2.5 ml) of 0.5% bupivacaine + 25 µg neostigmine with total volume made up to 3.0 ml with normal saline and Group BC:12.5 mg (2.5 ml) of 0.5% bupivacaine + 50 µg clonidine with total volume made up to 3.0 ml with normal saline. Sensory block characteristics, motor block characteristics, time to first rescue analgesic were recorded. Any adverse effects were also noted. *Results:* Time to reach T_{10} sensory level was 2.53±0.58 min in Group BC and 2.33±0.60 min in Group BN which was statistically comparable (p= 0.06). But time to reach peak sensory level was 8.14±0.77 min in Group BC as compared to 6.38±0.79 min in Group BN (p<0.01). The mean duration of sensory block was 321.72±8.32 min in Group BC and 301.72±27.6 min in Group BN (p<0.01). All patients of both groups achieved Bromage score of 3 signifying complete motor block. Duration of motor block was significantly longer in group BC (223.36±14.39 min) as compared to group BN (204.53±10.64 min) (p<0.01). *Conclusion:* Clonidine as adjuvant to bupivacaine results in significant prolongation of duration of sensory blockade and analgesia as compared to intrathecal neostigmine.

Keywords: Clonidine; Neostigmine; Analgesia; Intrathecal Bupivacaine.

Introduction

Subarachnoid block is one of the most versatile regional anesthesia technique available today. Regional anesthetic techniques may lead to blockade or reduced pain ranged from several hours to several days. Better pain control may result in an earlier hospital discharge and may improve the patient's ability in postoperative period. In addition, it is usually easy to administer and readily available [1]. Local anesthetics are the commonest agents used for spinal anesthesia, but their relatively short duration of action may lead to early analgesic intervention in the postoperative period [2]. Ekblom and Widman were the pioneer workers who employed bupivacaine for spinal analgesia and reported its low toxicity and long duration of action [3].

A number of adjuvants to local anesthetics have been used intrathecally to prolong the intraoperative as well as postoperative analgesia [3,4]. Opioids are commonly used as intrathecal adjuvants to improve the quality of intraoperative analgesia and also prolong analgesia in the postoperative period without significant motor or autonomic blockade [2]. However, side effects such as pruritus, nausea, vomiting, urinary retention, and delayed respiratory depression have prompted further research toward non-opioid analgesics as adjuvants with less serious side effects [5].

Corresponding Author: Neelesh Bhatnagar, Assistant Professor, Department of Anesthesiology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan 313001, India.
E-mail: drneelesh1106@gmail.com

Received on 01.03.2018, **Accepted on** 31.03.2018

Clonidine, a selective partial α_2 -adrenergic agonist, is being extensively evaluated as an adjuvant to intrathecal local anesthetics and has proven to be a potent analgesic free of opioid-related side effects. It is known to increase both sensory and motor blockade of local anesthetics. Intrathecal clonidine has been used as an adjuvant to local anesthetics in various surgical procedures without any clinically significant side effects. Previous studies have described the use of clonidine in a wide range [6,7]. Neostigmine is a reversible cholinestrase inhibitor quaternary ammonium compound used as cholinomimetic analgesic in human. Intrathecal neostigmine prolongs the sensory and motor block induced by bupivacaine spinal anaesthesia and at the same time causes no haemodynamic or respiratory depression in intraoperative and post operative period [8].

On literature research we could find few studies in which intrathecal clonidine versus intrathecal neostigmine was investigated in spinal anesthesia for lower abdominal surgeries [9,10]. No study was investigated efficacy of 50µg clonidine versus 25µg neostigmine in combination with 12.5 mg bupivacaine in spinal anesthesia. This study was planned to study the effect of intrathecal bupivacaine with neostigmine versus clonidine as an adjuvants in lower abdominal surgeries.

Materials and Methods

This hospital based randomized double blind study was conducted in the department of Anesthesiology at tertiary care teaching hospital with due permission from institutional ethical committee after obtaining written informed consent from all patients before participation. One hundred twenty eight patients of ASA physical status grade I and II, aged 30-50 years, scheduled for lower abdominal surgeries under spinal anesthesia were included in the study. Patients not willing to participate in the study, history of chronic disease like hypertension, diabetes mellitus, respiratory disease, epilepsy, cardiac disease, spinal disorders, chronic history of headache and backache, infection in the back, any absolute or relative contraindication to study drug, uncooperative patients were excluded out. After taking written informed consent, patients were randomly allocated into two groups (n=64) using chit in box technique:

Group BN: 12.5 mg (2.5 ml) of 0.5% bupivacaine + 25 µg neostigmine with total volume made up to 3.0 ml with normal saline and *Group BC:* 12.5 mg (2.5 ml) of 0.5% bupivacaine + 50 µg clonidine with total volume made up to 3.0 ml with normal saline intrathecally. Pre-anaesthetic checkup was done a day before the surgery. Patients were connected to monitors and baseline vitals like blood, pulse rate, respiratory rate were recorded. Vitals just before lumbar puncture were noted. Spinal anaesthesia was performed at L3-L4 interspace with the patient in left lateral position by using a 25 Gauge spinal needle under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anesthetic solution, which was administered over 30 seconds according to allocated group. The direction of the needle aperture was cranial during the injection. All patients were immediately placed in a supine position following the injection with a 15^0 head down tilt to achieve level of block of T5-T6. Vitals were checked immediately after block, 2 min, 5 min, 10 min and every 5 min till surgery. The level of sensory block was tested by pin pricking bilaterally at mid-clavicular line which was done every minute till the maximum sensory level was achieved and then after one hour at half an hour interval. Time of onset of motor block was assessed using Bromage scale. Onset of motor block was taken as the time taken to achieve Bromage grade 3 block from the time of subarachnoid injection. Side effects hypotension (SBP < 90 mmHg, bradycardia (Pulse < 50/min), respiratory depression (Arterial oxygen saturation less than 90%), pruritus and nausea and vomiting were also noted.

Postoperatively the pain score was recorded by using Visual Analogue Scale (VAS) between 0 and 10 (0 = no pain , 10 = worst pain). Intramuscular diclofenac (1.5 mg/kg) was given as rescue analgesic. Time from intrathecal injection to the first request of analgesics (i.e. duration of analgesia) was noted. Total analgesic dose in first 24 hours were recorded. Patients were kept under observation for total period of 24 hours to look for any side effects.

Data were entered and analyzed with the help of MS excel, SPSS version 17. Quantitative data were represented as arithmetic mean, (SD), and analyzed by using student t test, qualitative data were presented as number, [proportion (%)] and analyzed by chi square test. P <0.05 was considered as statistically significant.

Results

Both the neostigmine and clonidine groups were statistically comparable regarding mean age, mean weight, height, sex, ASA grading, and duration of surgery (Table 1).

Time to reach T_{10} sensory level was 2.53 ± 0.58 min in Group BC and 2.33±0.60 min in Group BN which was statistically comparable (p= 0.06). But time to reach peak sensory level was 8.14±0.77 min in Group BC which was statistically longer as compared to 6.38 ± 0.79 min in Group BN (p < 0.01). The mean duration of sensory block was 321.72±8.32 min in Group BC and 301.72±27.6 min in Group BN which was significantly longer in Group BC (p<0.01). All patients of both groups achieved Bromage score of 3 signifying complete motor block. Time to reach Bromage score of 3 (motor onset) was significantly shorter in group BN (2.77±0.68 min) as compared to group BC (3.58±0.813 min) (p<0.01). Time to regression to Bromage 0 (duration of motor block) was significantly longer in group BC (223.36±14.39 min) as compared to group BN (204.53±10.64 min) (p<0.01) (Table 2).

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and oxygen saturation (SpO_2) showed no significant change from baseline during intra-operative period in Group BN. Fall in heart and systolic blood pressure was occurred in Group BC at 5, 10, 15 mins interval which was significant as compared to Group BN. (p < 0.05). (Figure 1-3). Hypotension, bradycardia and sedation were more common in group BC as compared to group BN (Table 3).

Table 1: Demographic characteristics of both the groups

	Group-BC (Mean ± SD)	Group-BN (Mean ± SD)	
Age(yrs)	49.78+11.29	49.44+9.59	p>0.05
Height (cms)	156.70±3.26	157.89±4.43	p>0.05
Weight (kgs)	60.84+6.23	59.91+5.54	p>0.05
Sex (M/F)	29/35	33/31	p>0.05
ASA I/II	56/8	58/6	p>0.05
Duration of surgery (min)	59.22±7.16	57.03±7.16	p>0.05

Table 2: Comparison of block characteristics in both the groups

	Group-BC (Mean ± SD)	Group-BN (Mean ± SD)	P value
Time to reach T_{10} (min)	2.53±0.58	2.33±0.60	p>0.05
Time to reach peak sensory level (min)	8.14±0.77	6.38±0.79	p < 0.01
Highest sensory level block	$T_{5.72±0.79}$	$T_{5.73±0.65}$	p>0.05
Time to sensory regression to S1(min)	321.72±8.32	301.72±27.6	p < 0.01
Duration of analgesia (min)	267.84 ± 27.95	219.27 ± 22.65	p < 0.01
Time to reach bromage score 3 (min)	3.58±0.81	2.77±0.68	p < 0.01
Duration of motor blockade (min)	223.36 ± 14.39	204.53± 10.64	p < 0.01

p>0.05 (non-significant), p < 0.01 (significant)

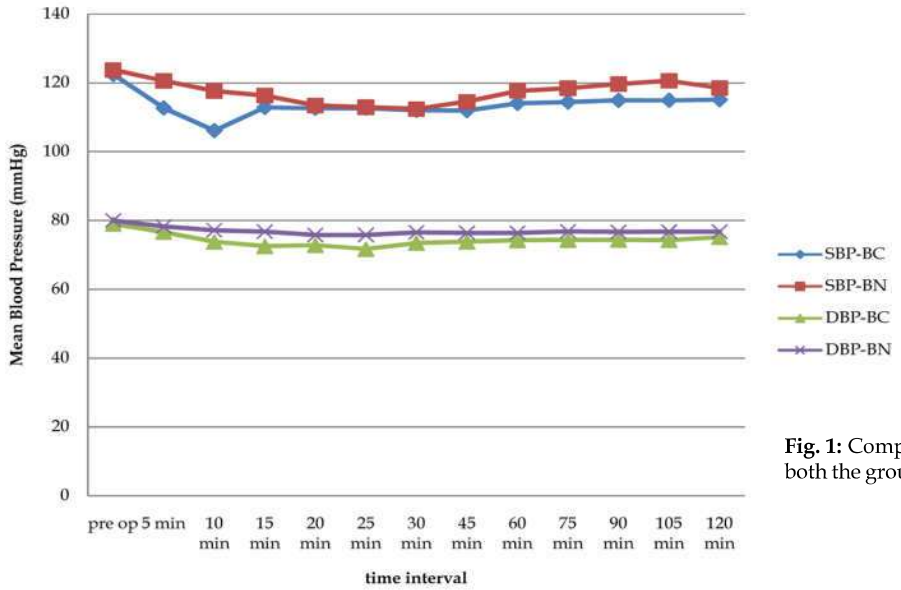

Fig. 1: Comparison of blood pressure in both the groups

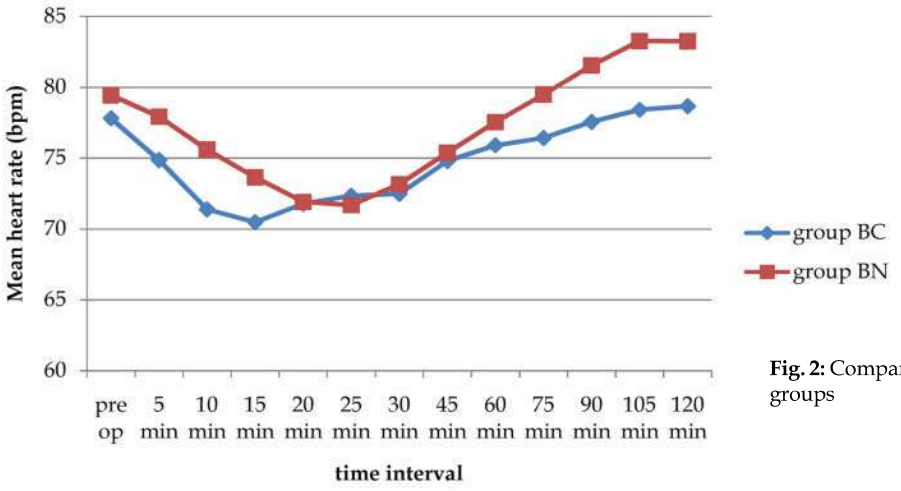

Fig. 2: Comparison of Heart rate in both the groups

Table 3: Adverse effects in both the groups

	Group-BC n (%)	Group-BN n (%)
Hypotension	18 (28.1%)	2(3.1%)
Bradycardia	13(20.3%)	2(3.1%)
Nausea	5(7.8%)	9(14.1%)
Vomiting	0	3(4.7%)
Sedation	14(21.9%)	0
Respiratory Depression	0	0
Others	0	0

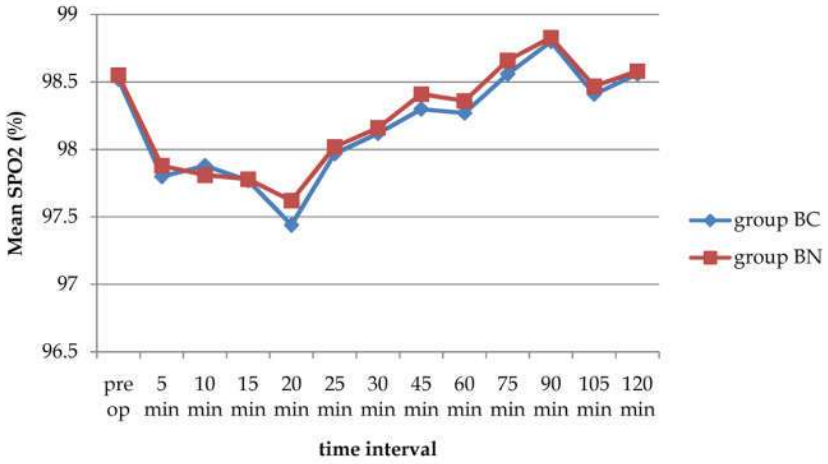

Fig. 3: Comparison of SpO_2 in both the groups

Discussion

Local anesthetics are the commonest agents used for spinal anesthesia. A number of adjuvants to local anesthetics have been used in pain management [3,4]. In present study clonidine and neostigmine were compared for its effects as adjuvant to bupivacaine. In present study both the groups were comparable demographically.

In present study time to reach T_{10} sensory level was 2.53±0.58 min in Group BC and 2.33±.60 min in Group BN which was statistically comparable. But time to reach peak sensory level was 8.14±0.77 min in Group BC which was statistically longer as compared to 6.38±0.787 min in Group BN. Similar results were obtained by Yoganarasimha et al study which has used 75 µg of clonidine [9]. Adhikari et al. conducted study using bupivacaine 0.5% -3 ml (hyperbaric) with 0.1ml of normal saline intrathecally in Group A and bupivacaine 0.5% -3 ml (hyperbaric) with 50 µg neostigmine methylsulfate (0.1 ml)) in group B and reported onset time for sensory block was 136.80± 13.45 sec in group A and 136.6±12 .87

sec which was comparable in both groups [11]. Jamliya et al. studied 3ml of 15 mg hyperbaric bupivacaine 0.5% plus 0.2 ml saline in group A and 15 mg (3ml) of hyperbaric bupivacaine 0.5% plus 30 µg clonidine in group B and reported that time of onset of adequate level of sensory block (T10) was longer for group B (126±14sec.) than group A (95±10sec.) [12]. It was observed that adding neostigmine to bupivacaine resulted in significant shortening of peak sensory onset time as compared to intrathecal clonidine with bupivacaine. It might be due to that intrathecal administration of cholinergic receptor agonist or cholinesterase inhibitors produces antinociceptive effect which is mediated by spinal muscarinic receptors in animals and human beings [13].

In present study, Group BC achieved peak sensory level of $T_{5.72 \pm 0.79}$ [median T8 range (T6-T8)] which was statistically comparable with $T_{5.73 \pm 0.65}$ in Group BN. Similar comparable results were also found in Yoganarsimha et al. and Klamt et al. study [9,14]. It might be concluded that addition of neostigmine or clonidine as an adjuvants do not affect peak level of sensory block.

The mean duration of sensory block was 321.72±8.32 min in Group BC and 301.72 ± 27.6 min in Group BN which was significantly longer in Group BC. Yoganarasimha et al also reported the total duration of analgesia was significantly prolonged in (362 ± 32 min) Group BC as compared to (300 ± 25 min) Group BN but not mentioned the duration of sensory block [9]. Similar significant results were also found in other studies [2,11,12,15]. It can be concluded that clonidine enhances the duration of sensory block more as compared to neostigmine.

All patients in both groups achieved Bromage score of 3 signifying complete motor blockade. Yoganarasimha et al and jamliya et al also reported complete motor block in lower abdominal surgeries [9,12]. Time to reach Bromage score of 3 (motor onset) is significantly shorter in group BN (2.77±0.68 min) as compared to group BC (3.58±0.813 min). Yoganarasimha et al also reported that 110±15 secs in group BN compared to 210±20 secs in group BC. In addition to the potential direct inhibition of motor activity by administration of neostigmine, it was speculated that increased spinal levels of acetylcholine may augment motor block as a result of axonal conduction block from spinal bupivacaine [9]. That might be the reason in present study in which there was hastened onset of motor block with neostigmine.

In present study duration of motor block was defined as return of Bromage score 0. Time to regression to Bromage 0 (duration of motor block) was significantly longer in group BC (223.36±14.39 min) as compared to group BN (204.53±10.64 min). Similarly, Yoganarasimha et al reported significantly shorter motor block duration 185 ± 40 mins in group BN compared to 210±50 mins in group B [9]. Jamliya et al and kayalha et al also showed similar results [11,15]. Clonidine has more prolonged duration of motor block as compared to neostigmine. Intrathecal clonidine when combined with local anaesthetic significantly potentiates the intensity and duration of motor blockade possibly due to the fact that $\alpha 2$ adrenoreceptor agonists induce cellular modification in the ventral horn of the spinal cord and facilitate the local anaesthetic action and prolongation in sensory block can be due to vasoconstrictive effect of clonidine [2].

In present study, time of requirement of first rescue analgesic dose (duration of analgesia) was significantly longer in group BC as compared to group BN. Similar results were obtained in other studies [9,11,12]. Potency of intrathecal neostigmine is increased in post operative period, because descending noradrenergic or cholinergic antinociceptive spinal system is activated by ongoing pain causing an increase in release of acetylcholine which in presence of neostigmine results in augmented selective analgesia [11].

In our study, HR, SBP, DBP, and SpO_2 showed no significant change from baseline during intraoperative period in Group BN. Fall in systolic blood pressure and heart rate was seen in Group BC which was significant as compared to Group BN just after spinal anaesthesia at 5 ,10 ,15 mins interval. In Group BC 28.1% patients had developed hypotension and 20.3% patients bradycardia. In previous study by Yoganarasimha et al. intraoperative blood pressure was well maintained in the neostigmine group and clonidine group. None of the patient in both groups developed pruritus, tremors, arrhythmia, and respiratory depression. In Yoganarasimha et al. study also, no patients of either groups had sedation, nausea and vomiting, pruritus, post dural puncture headache or transient neurological symptoms at intraoperative period or during post operative follow up [9]. This showed that intrathecal clonidine and neostigimne can be used safely in spinal anesthesia without affecting hemodynamic variables significantly.

Conclusion

Clonidine as adjuvant to bupivacaine results in significant prolongation of duration of sensory

blockade and analgesia as compared to intrathecal neostigmine. Both clonidine and neostigmine in lower doses can be used as an adjuvant to local anesthetic alternative to commonly used opioids in spinal anesthesia for lower abdominal surgeris without serious adverse effects. Intrathecal clonidine has better clinical profile than intrathecal neostigmine in terms of analgesia.

References

1. Ramsay MAE. Acute postoperative pain management. Proc (Bayl Univ Med Cent) 2000;13(3):244-7.
2. Thakur A, Bhardwaj M, Kaur K, Dureja J, Hooda S, Taxak S. Intrathecal clonidine as an adjuvant to hyperbaric bupivacaine in patients undergoing inguinal herniorrhaphy: A randomized double-blinded study. J Anaesthesiol Clin Pharmacol 2013;29:66-70.
3. Solaiappan B, Jeevarathnam R. Comparative study of intrathecal neostigmine and clonidine. J. Evolution Med. Dent. Sci. 2016;5(57):3917-25.
4. Bhar D, RoyBasunia S, Das A, Kundu SB, Mondal RC, Halder PS et al. A comparison between intrathecal clonidine and neostigmine as an adjuvant to bupivacaine in the subarachnoid block for elective abdominal hysterectomy operations A prospective, double blind and randomied controlled study. Saudi J Anaesth 2016;10:121 6.
5. Chaney MA. Side effects of intrathecal and epidural opioids. Can J Anaesth 1995;42:891-903.
6. Biswas BN, Rudra A, Bose BK, Nath S, Chakrabarty S, Bhattacharjee S. Intrathecal fentanyl with hyperbaric bupivacaine improves analgesia during caesarean delivery and in early postoperative period. Ind J Anaesthe 2002;46(6):469-72.
7. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Ind J Anaesthe 2007;51(5): 415-9.
8. Faiz SHR, Rahimzadeh P, Sakhaei M, Imani F, Derakhshan P. Anesthetic effects of adding intrathecal neostigmine or magnesium sulphate to bupivacaine in patients under lower extremities surgeries. J Res Med Sci 2012;17(10):918–22.
9. Yoganarasimha N, Raghavendra TR, Amitha S, Shridhar K, Radha MK. A comparative study between intrathecal clonidine and neostigmine with intrathecal bupivacaine for lower abdominal surgeries. Indian J Anaesth 2014;58:43-7.
10. Pan PM, Huang CT, Wei TT, Mok MS. Enhancement of analgesic effect of intrathecal neostigmine and clonidine on bupivacaine spinal anaesthesia. Reg Anaesth Pain Med 1998;23(1):49-56.
11. Adhikari D, Sinha S, Choudhuri R, Mitra M, Bhattacharyya S. A study to compare intrathecal bupivacaine and bupivacaine with neostigmine for post operative analgesia in patients undergoing vaginal hysterectomy. International journal of basic and applied medical sciences 2014:4(3)123-9.
12. Jamliya RH, Vansola R, Shah BJ, Chauhan DL. Effect of clonidine addition to hyperbaric 0.5% bupivacaine for spinal anaesthesia in lower limb surgery: a comparative study. NJIRM 2012;3(1):101-7.
13. Lograsso M, Nadeson R, Goodchild CS. The spinal antinociceptive effects of cholinergic drugs in rats: receptor subtype specificity in different nociceptive tests. BMC Pharmacol 2002;2:20.
14. Klamt JG, Slullitel A, Garcia IV, Prado WA. Post operative analgesic effect of intrathecal Neostigmine and its influence on spinal anaesthesia. Anaesthesia 1997;52:547-51.
15. Kayalha H, Mousavi ZS, Barikani A, Yaghoobi S, Khezri MB. The effects of intrathecal neostigmine added to bupivacaine on postoperative analgesic requirement in Patients undergoing lower limb orthopedic surgery. MEJA 2015;23(2):199-204.