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Research Article

Evaluation of Intrathecal Bupivacaine-Clonidine Combination in Lower Abdominal Surgeries: A Double Blind Randomized Control Study

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Abstract: Postoperative pain treatment is unsatisfactory, especially after intermediate and major surgical procedures. Addition of adjuvant drugs to intrathecal local anesthetics improves quality and duration of spinal blockade prolonging postoperative analgesia. The present study was undertaken to assess the efficacy of 150 µg of intrathecal Clonidine added to Bupivacaine on postoperative pain and its side effects in lower abdominal surgeries. Double blind randomized controlled study was conducted on 65 adult patients. Group Control received 3ml Bupivacaine and 1ml normal saline intrathecally, whereas Clonidine (study) Group received 3 ml Bupivacaine and 1ml (150mcg) Clonidine intrathecally. 3 patients were excluded and data from 62 patients was collected and statistically analyzed. Assessment of post operative pain was made on basis of visual analog score (VAS) where 0 cm = "no pain'' and 10 cm = ''worst pain imaginable". Nausea was assessed using 4 point verbal scale. Episodes of vomiting were noted. Onset of sensory block was rapid in Group Clonidine (78 ±1.74) vs Group Control (108 ± 1.54) seconds with $p<0.001$. Motor block was also rapid in Group Clonidine (104 ±3.83) vs Group Control (127 ±2.72) seconds. Regression of block was also slower in Group Clonidine (357 ± 11.2) vs Group Control (176 ± 8.85) minutes. First request for analgesia was late in Group Clonidine (294 ± 10.0) vs Group Control (169 ± 8.52) minutes. VAS (rest) and VAS (movement) scores from $T_{0.5hr}$ to T_{24hr} were less in Group Clonidine. In conclusion intrathecal Clonidine 150µg added to Bupivacaine fasten onset and prolongs duration of sensory and motor block, decreases the rescue analgesic requirement and improves pain score in lower abdominal surgeries.
Keywords: Lower abdominal surgeries, Post operative pain, Intrathecal Clonidine, Intrathecal Bupivacaine.

INTRODUCTION

Despite an acute pain protocols the treatment of postoperative is unsatisfactory, especially after intermediate and major surgical procedures [1]. The hypothesis, that effective analgesia modifies many of the adverse sequlae accompanying acute pain and assists in recovery is supported by sufficient evidences. Though drugs and techniques for effective management are available, postoperative pain remains under treated. The solution to the problem of inadequate pain relief lies not only in the development of new analgesic drugs or technologies but also in the development of an appropriate organization to utilize existing expertise [2]. At the beginning of the last century, Crile was among the first to introduce the concept of preemptive analgesia that is treating pain prior to its onset [3, 5]. He observed that postoperative mortality decreased if pain transmission was blocked prior to the initial surgical incision [3]. Although opioids remained the mainstay of pain therapy, but various drugs are used alone or in combination, via various routes i.e oral, intravenous, epidural or subarachnoid. Nowadays spinal anesthesia is the technique of choice for lower abdominal surgeries. It is safe, effective, easy to perform and inexpensive. Its main limitations are its short duration of action and do not provide prolonged postoperative analgesia when it is performed only with local anesthetics [4-6]. Adding adjuvant drugs to intrathecal local anesthetics improves quality and duration of spinal blockade, and prolongs postoperative analgesia. It is also possible to reduce dose of local anesthetics, as well as total amount of systemic postoperative analgesics.

Various drugs injected intrathecally includes benzodiazepines, opioids, anti cholinestreas, NMDA antagonists, vasoconstrictors, alpha 2 agonists and Baclofen etc. Common adverse effects of opioids are sedation, pruritus, nausea, vomiting, slowing of gastrointestinal function and urinary retention [7]. Efficacy of various regimens is assessed by VAS [8], first request of analgesia and total consumption of analgesic.

Concept of alfa 2 agonists used as intrathecal adjuvant is recent and among them Clonidine is widely

studied. Clonidine is used preemptively by oral, intrathecal and epidural routes in various surgeries like lower limb orthopedic surgeries [7, 11], colonic surgery [8], radical prostatectomy [14], transurethral resection of prostate [9], cesarean delivery [10,13] arthroscopy [12], and they all had observed that Clonidine significantly reduces post operative pain scores and markedly reduce the post operative analgesic requirements, without any major side effect. Large doses of Clonidine upto 450 µg have been used and found to be safe. On review of literature, we found that number of studies using intrathecal Clonidine in lower abdominal surgeries is limited. The present study was undertaken to assess the efficacy of 150 µg of intrathecal Clonidine on intraoperative hemodynamic and postoperative pain, demand for rescue analgesic and to evaluate side effects of this dose of Clonidine in lower abdominal surgeries.

MATERIAL AND METHODS

After approval from institutional ethical committee and an informed consent, the present double blind randomized controlled study was conducted on 65 adult patients belonging to American society of anesthesiologist (ASA) physical status (ASA 1&2). The patient selected were those from admitted to our hospital and scheduled for lower abdominal surgeries. The Patients with Sinus bradycardia (heart rate less than 60/min), already on oral Clonidine, Hypovolemia, Increased intracranial pressure, allergic to Bupivacaine/Clonidine, bleeding disorders, Infection at the site of lumber puncture, patient who refused spinal were excluded.

The patients were randomized by computer generated numbers to one of two groups .

- Group Control received 3ml (15mg) Bupivacaine 0.5% and 1ml normal saline intrathecally.
- Group Clonidine (Study) received 3 ml (15mg) Bupivacaine 0.5% and 1ml (150mcg) Clonidine intrathecally.

Two blinded anesthesiologists participated in the study. The data collection was done by another investigator who was neither anesthesiologist nor part of the study. Patients were visited the previous evening. Informed consent was taken and relevant investigation was checked. Nil per oral (NPO) instruction were explained. All patients was made familiar with concept of visual analogue scale for pain (VAS), which consisted of 10 cms line, with 0 equaling "no pain" and 10 equaling "worst possible pain." All patients received Diazepam 10 mg HS orally before surgery and Phenargan 50 mg IV about 1 hr prior to surgery. Patients were given 0.05-0.1 mg/kg Midazolam IV in the preanaesthetic room during the waiting period. Hydration for preloading was 10ml/kg Ringer lactate before spinal and infused at 10ml/kg/hr. after spinal anesthesia. Under all aseptic conditions, lumbar puncture was performed at L3&L4 interveretebral space with 26 gauge Quinke's spinal needle and drug consisting of 4ml in volume was injected intrathecally over 30 sec. The intrathecal drug included 3ml (15mg) of hyperbaric Bupivacaine (0.5%) plus 1ml of adjuvant as per allocated in the groups. Patient was placed supine immediately after spinal injection. Sensory loss assessment was done intraoperatively by pin prick test every 5 min for 30 min to assess the highest level of sensory block. Degree of motor block was done by modified Bromage scale as follows:

I. Free movement of legs and feet.
II. Just able to flex knees with free movement of feet.
III. Unable to flex knees, but with free movement of feet.
IV. Unable to move legs or feet.

Motor block was assessed at every 5 min for 30 min to record time to achieve maximum level of block as per Bromage scale. Blood pressure was monitored non invasively every five minutes throughout surgery and a decrease in mean arterial pressure greater than 15% below the pre anesthetic base line value was recorded and treated by incremental dose of Ephedrine 4mg IV. Heart rate, respiratory rate and Oxyhemoglobin saturation (SpO2) was monitored continuously. Any decrease in heart rate <20% from the base line value was noted and treated with incremental atropine 0.25 mg IV.

Assessment of post operative pain was made on basis of visual analog score (VAS) where 0 cm = "no pain'' and 10 cm = ''worst pain imaginable". All the patients received Diclofenac 75 mg intramuscularly on first request for analgesia in the postoperative period. Nausea was assessed using 4 point verbal scale, where 0= none, 1= mild, 2= moderate and 3= severe nausea. Number of episodes of vomiting was noted and recorded. Ondansetron 4 mg IV was given for moderate and severe nausea or if vomiting occurs. Sedation was assessed using Ramsay sedation score. Other side effects were also recorded.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS).Demographic data were analyzed using Student's t-test or chi- square test as appropriate. Hemodynamic variables, respiratory rate, oxygen saturation were compared using Student s t- test.VAS scores at each time interval, were performed using Mann Whitney test.

RESULTS

65 patients were randomized, where Group Contol was allocated with 31 patients and Group Clonidine with 34 patients. But finally 62 patients participated in the study, as one patient in Group control had patchy anaesthesia, so supplemented with general

anaesthesia and two patients in Group Clonidine had dragging sensation during surgery, so supplemented with general anaesthesia. The data collected from all 62 patients i.e Group Control (n=30) and Group Clonidine (n=32) were tabulated and analyzed (Fig. 1).

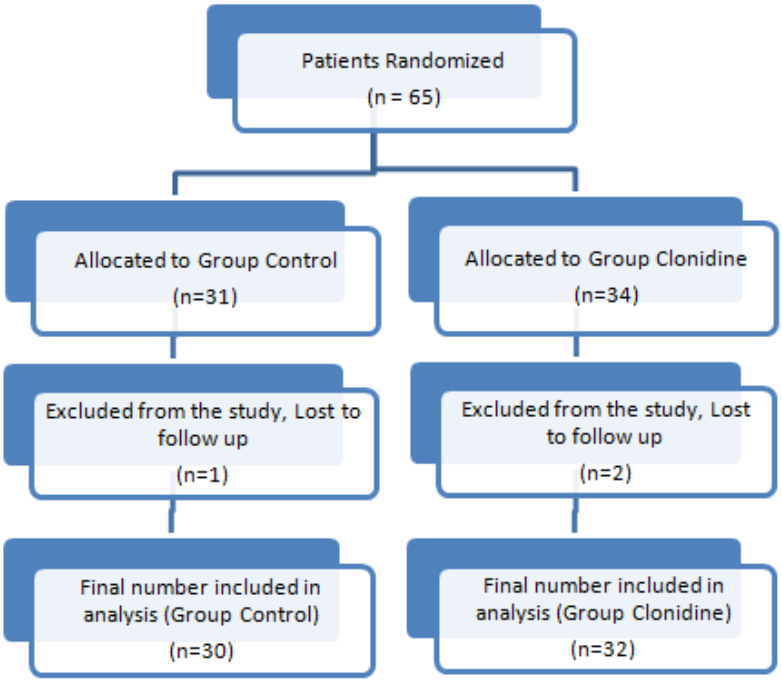

Fig. 1: Consort Chart

Both groups were comparable in terms of age, sex, weight ASA physical status and duration of surgery (Table 1). Intraoperative variables heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate and oxygen saturation were comparable in both the groups. The onset of sensory and motor block was rapid in Group Clonidine ($p < 0.001$).The mean time to two segment regression ,time to first analgesic request and regression to L_3 dermatome was significantly more in Group Clonidine ($p < 0.001$) (Table 2, Fig. 2-4).

There was continuous fall in pulse rate in both groups upto 120 mins, in Group Clonidine there was slight rise at 4 hours but in control there was a marginal fall. The variation in the pulse rate in each group at all observed timings was statistically comparable ($p>0.1$) (Table 3). The percentage fall in systolic blood pressure at each interval time i.e. 10 min, 20 min, 45 min, 60 min, 90 min, 120 min and 4 hr the difference between the groups was statistically not significant ($P>0.1$). Though diastolic blood pressure always remained below the baseline value at all the observed timings, but both groups had comparable variation of diastolic blood pressure at each interval ($p>0.1$) (Table 4).

There is statistically significant reduction in VAS score at rest as well as at movement at 1hr, 4hr, 8hr, 12hr, 16hr, 24hr in group II ($p<0.001$) (Table-5).

In Group Control, 3 (10%) patients had vomiting, and 2 (6.67%) felt somnolence. In Group Clonidine, 2 (6.25%) patients had vomiting, and 2 (6.67%) felt somnolence (Table -6).

Table 1: Demographic data of patients included in study

Patient Characteristics	Group Control (n=30)	Group Clonidine (n=32)	p value
Age (Years)	42.2 + 10.2	42.7 + 9.80	0.85 $^{N.S}$
Weight (Kilograms)	60.70 + 5.28	58.50 + 5.57	0.12 $^{N.S}$
Gender Male Gender Female	8 22	9 23	0.69 $^{N.S}$
ASA Status I ASA Status II	16 14	16 16	0.715 $^{N.S}$
Duration of Surgery	83.6 + 19.80	85.0 + 21.20	0.79 $^{N.S}$

$^{N.S}$ - Non Significant,* - Significant, where Group Control received 3ml (15mg) Bupivacaine 0.5% and 1ml normal saline intrathecally, whereas Group Clonidine (Study) received 3 ml (15mg) Bupivacaine 0.5% and 1ml (150mcg) Clonidine intrathecally.

Table 2: Intraoperative data of patients included in study

Characteristics of Block	Group Control (n=30)	Group Clonidine (n=32)	p value
Onset of sensory block (sec)	108 ± 1.54	78 ±1.74	0.001**
Highest level of block	T_7(T_6- T_8)	T_6 (T_4 _ T_8)	-
Onset of motor block (sec)	127 ±2.72	104 ±3.83	0.001**
Highest Bromage scale	III in 10 IV in 20	III in 2 IV in 30	-
Two segment regression (min)	128 + 8.68	243 + 8.51	0.001**
Time for first request of analgesia (min)	169 + 8.52	294 +10.0	0.001**
Time for complete motor recovery (min)	161 +6.89	270 +6.35	0.001**
Time to regression to L_3 sensory level (min)	176 +8.85	357 + 11.2	0.001**

N.S - Non Significant,* - Significant, where Group Control received 3ml (15mg) Bupivacaine 0.5% and 1ml normal saline intrathecally, whereas Group Clonidine (Study) received 3 ml (15mg) Bupivacaine 0.5% and 1ml (150mcg) Clonidine intrathecally.

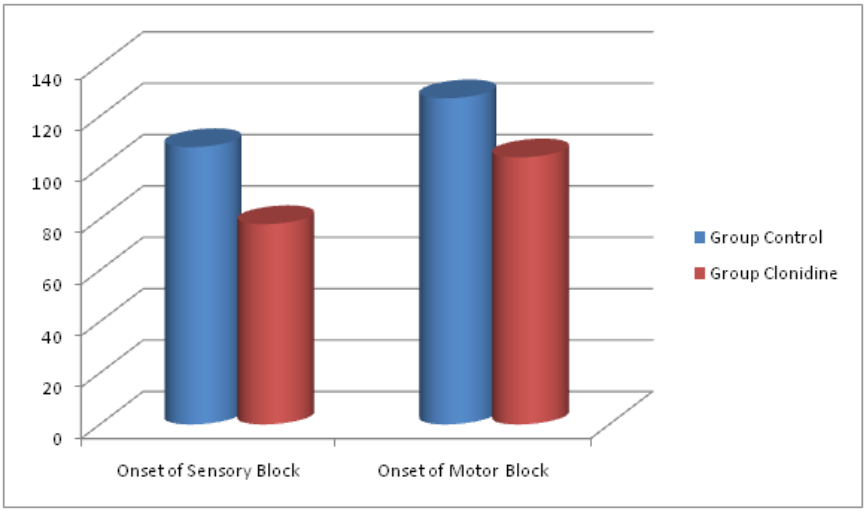

Fig. 2: Onset of block. Significant p- values (<0.001), Group Control vs Group Clonidine

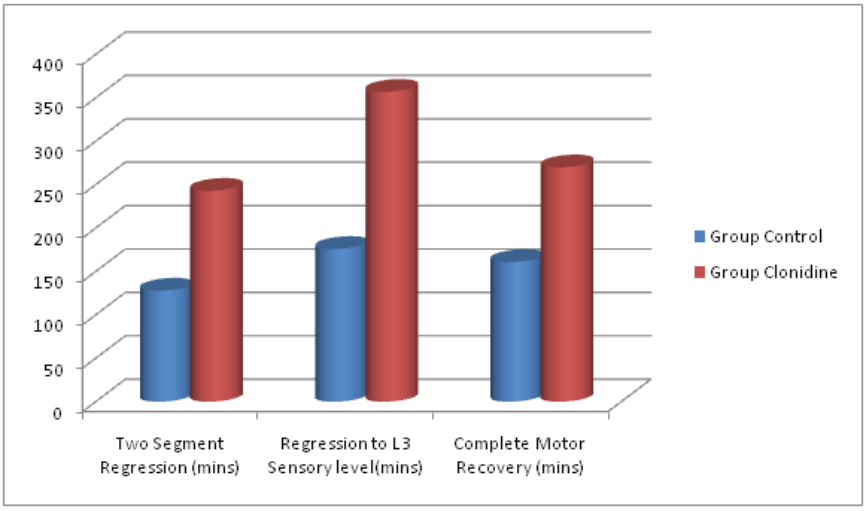

Fig. 3: Regression of block and complete motor recovery, Significant p- values (<0.001), Group Control vs Group Clonidine

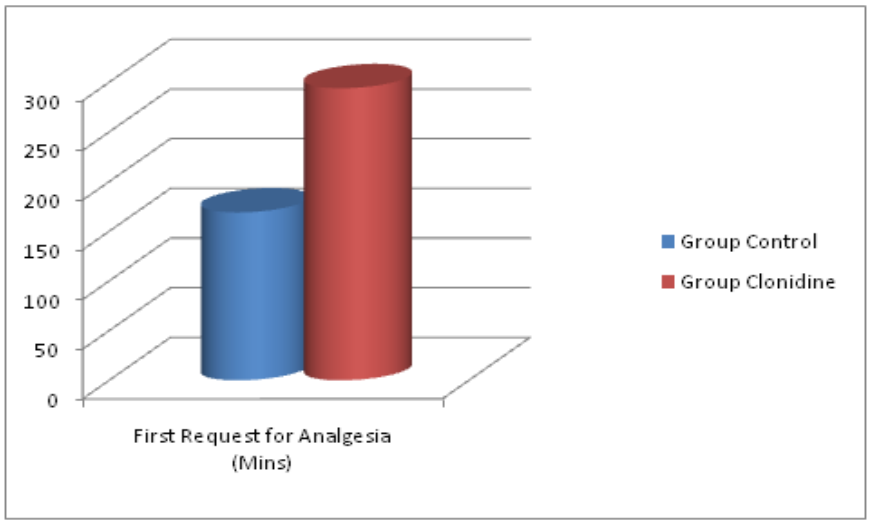

Fig. 4: First reguest for analgesia. Significant p- values (<0.001), Group Control vs Group Clonidine

Table 3: Comparision of pulse rate (per minute) between the Groups

Time	Group Control	Group Clonidine	p Value
0 min	82.46 ± 10.5	82.27 ± 9.77	0.94 $^{N.S}$
10 min	81.20 ± 10.2	81.80 ± 9.12	0.81 $^{N.S}$
20 min	80.60 ± 10.5	79.80 ± 8.44	0.83 $^{N.S}$
45 min	78.00 ± 9.13	78.67 ± 8.64	0.77 $^{N.S}$
60 min	75.66 ± 7.98	75.93 ± 9.34	0.91 $^{N.S}$
90 min	73.86 ± 7.72	74.07 ± 8.97	0.83 $^{N.S}$
120 min	72.86 ± 9.32	71.53 ± 8.80	0.57 $^{N.S}$
4 hour	72.06 ± 7.02	72.20 ± 8.87	0.95 $^{N.S}$

$^{N.S}$ - Non Significant, * - Significant

Table 4: Comparision of Blood pressure (mm of Hg) between the Groups

Time	Systolic blood pressure			Diastolic Blood Pressure		
	Group control	Group Clonidine	p value	Group Control	Group Clonidine	p Value
0 min	128.20 ± 9.65	128.47 ± 9.09	0.91 $^{N.S}$	82.80 ± 4.19	81.80 ± 2.89	0.29 $^{N.S}$
10 min	126.00 ± 9.13	125.67 ± 9.08	0.89 $^{N.S}$	80.27 ± 4.89	80.13 ± 3.96	0.91 $^{N.S}$
20 min	124.13 ± 8.47	123.60 ± 7.17	0.79 $^{N.S}$	77.20 ± 4.89	78.87 ± 4.92	0.19 $^{N.S}$
45 min	122.67 ± 8.14	121.80 ± 8.02	0.68 $^{N.S}$	76.60 ± 4.30	75.13 ± 4.75	0.21 $^{N.S}$
60 min	120.47 ± 7.77	120.73 ± 6.82	0.89 $^{N.S}$	73.80 ± 4.77	72.20 ± 4.47	0.18 $^{N.S}$
90 min	118.33 ± 8.12	118.40 ± 8.13	0.95 $^{N.S}$	72.67 ± 3.91	72.60 ± 4.55	0.95 $^{N.S}$
120 min	118.60 ± 9.13	118.40 ± 7.64	0.93 $^{N.S}$	72.93 ± 4.69	72.60 ± 4.01	0.77 $^{N.S}$
4 hour	118.73 ± 7.90	118.07 ± 7.97	0.75 $^{N.S}$	71.27 ± 4.12	71.07 ± 4.29	0.85 $^{N.S}$

$^{N.S}$ - Non Significant, * - Significant

Table 5: Comparison of VAS scores

Time	VAS (Rest), Group Control vs Clonidine p-Value	VAS (Movement) Group Control vs Clonidine p- Value
$T_{0\ hr}$	0.103	0.034
$T_{0.5hr}$	0.070*	0.0007*
T_{1hr}	0.005*	0.0004*
T_{4hr}	0.004*	0.0007*
T_{8hr}	0.002*	0.0001*
T_{12hr}	0.0001*	0.0001*
T_{16hr}	0.0001*	0.0001*
T_{24hr}	0.0001*	0.0001*

$^{N.S}$ - Non Significant, * - Significant

Table 6: Side effects and complications

	Group Control (n=30)		Group Clonidine (n=32)		p value
	N	%	n	%	-
Vomiting	3	10%	2	6.25%	>0.05 $^{N.S}$
Respiratory depression	0	0%	0	0%	-
Somnolence	2	6.67%	2	6.25%	>0.05 $^{N.S}$
Headache	0	0%	0	0%	-

$^{N.S}$ - Non Significant, * - Significant

DISCUSSION

Spinal anaesthesia with hyperbaric Bupivacaine hydrochloride is popular for longer procedure as it has prolonged duration but there is need to intensify and increased duration of sensory blockage without increasing the intensity and duration of motor blockage and thereby prolongs the duration of post operative analgesia [15]. Discovery of adrenergic pain modulating system in the spinal cord has led to the usage of adrenergic agonists neuraxially for perioperative analgesia. Clonidine prolongs the duration of intrathecally administered local anesthetics and has potent antinociceptive properties [16]. Our study compared the characteristics of subarchnoid block and time to first analgesia request and quality of postoperative analgesia using VAS scores.

We observed that onset of sensory block was early in Group Clonidine as compared to plain Bupivacaine (78sec vs 108sec). Similarly onset of motor block was rapid in Group Clonidine (104sec vs 127sec). This is similar to study by Kanazi GE *et al*. who used 30 mcg of Clonidine intrathecally .They observed a significant shorter onset of motor block and significantly long sensory and motor regression times in Group Clonidine [9]. The highest sensory level was comparable in both the groups as observed by Strebel S *et al*. examined the dose-response relationship of intrathecal Clonidine at small doses (≤150 μg). He used increasing doses of Clonidine 37.5 μg, 75 μg, and 150 μg with 18mg of isobaric Bupivacaine.in orthopedic surgery. Duration of sensory block (regression below L_1) and pain relief until the first request for supplemental analgesia was increased in a dose dependent manner longest being in 150 μg group (337±78 min)(+17%), (445±136min)(+51%) [7]. In our study, time for two segment regression, time for first request for analgesia and time to regression to L_3 sensory level and complete motor recovery was significantly increased in Group Clonidine. The mechanism of Clonidine-induced potentiation of sensory block in spinal anesthesia is reported to be mediated by presynaptic (inhibition of transmitter release) [17] and postsynaptic (enhancing hyperpolarization) [18, 19] effects. Intrathecal Clonidine alone, even in doses of up to 450 μg, does not induce motor block or weakness [20]. In contrast, intrathecal Clonidine combined with local anesthetic significantly potentiates the intensity and duration of motor blockade [21- 23]. The explanation for this could be that the α_2-adrenoceptor agonists induce cellular modification in the ventral horn of the spinal cord (motoneuron hyperpolarization) and facilitate the local anesthetic action. However, these effects seem to be dose related, because 30 μg, but not 15 μg, of Clonidine added to bupivacaine potentiated motor block.

Though there is fall in pulse rate, systolic and diastolic blood pressure below baseline in both the groups but variation in hemodynamic parameters was not statistically significant on comparing both groups. These observations are similar to study by Strebal S *et al*. where he observed relative hemodynamic stability among groups with 150 mcg Clonidine intrathecally [7]. Racle *et al*. used isobaric Bupivacaine spinal anaesthesia with Epinephrine and Clonidine for hip surgery in elderly and found that intrathecal Clonidine (150 μg) for patients aged 75years or more resulted in a decrease in systolic blood pressure of only 15% from resting values [21].

In our study, in postoperative period, there was better and prolonged pain relief in Group Clonidine as compared to Group Control. Chiari *et al*. in a dose response study using intrathecal Clonidine as sole analgesic during first stage of labour found that 50 - 200μg of intrathecal Clonidine produces dose dependent analgesia [24]. De Kock M *et al*. concluded that both intraoperative spinal Clonidine and Bupivacaine improve immediate postoperative analgesia [8]. Andrieu G *et al*. found that addition of Clonidine to intrathecal morphine reduced intraoperative Sufentanil use, prolonged time until first request for PCA rescue, and further prolonged analgesia at rest and with coughing [14]. Nishiyama *et al*. had shown that intrathecally administered combinations of Bupivacaine and Clonidine produced synergistic analgesic effects on both acute thermal and inflammation-induced pain with decreased side effects. The synergistic potency was higher for inflammatory-induced pain than for thermal-induced pain [25].

In our study, total 5 patients had episode of vomiting (3 in Group Control group and 2 in Group clonidine). This is consistent with observation made by Dobryndjov *et al*. [26]. In their study, four patients had nausea and vomiting (one in each Group B and BC30 and two patients in BC 30). Total 4 patients had somnolance in our study (2 in each group) that is statistically insignificant.

CONCLUSION

We concluded that, intrathecal Clonidine 150µg added to Bupivacaine not only fasten onset of sensory and motor block but also prolongs duration of the same, therefore decreasing the rescue analgesic requirement and hence improve pain score in postoperative period in lower abdominal surgeries.

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