COMPARISON OF INTRATHECAL BUPRENORPHINE VERSUS CLONIDINE AS AN ADJUVANT TO 0.5% HYPERBARIC BUPIVACAINE IN LOWER ABDOMINAL SURGERIES

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Abstract

Introduction: Various adjuvants have been added to bupivacaine to shorten the onset of block and prolong the duration of block. Present study was undertaken to compare the efficacy of intrathecal clonidine or buprenorphine with bupivacaine in lower abdominal surgeries.

Methods: 90 ASA I and II patients undergoing lower abdominal surgeries were randomly allocated into three groups (n=30). Group A received 3ml of 0.5% hyperbaric bupivacaine with 1ml normal saline, Group B received 3ml of 0.5% hyperbaric bupivacaine with 60 mcg buprenorphine (1:5 dilution) and Group C received 3ml of 0.5% hyperbaric bupivacaine with 30mcg clonidine (1:5 dilution) respectively (Total volume 4ml). Onset time and duration of sensory and motor block, duration of analgesia, hemodynamics, VAS score, sedation score and side effect were compared.

Results: The duration of analgesia was significantly longest in Group C (354.50±38.48min), followed by Group B (277.10±25.47min) and Group A (131.50±20.15min) (p<0.001)

Conclusion: Clonidine (30mcg) and buprenorphine (60mcg) when used as adjuvants to 0.5% hyperbaric bupivacaine intrathecally produces significantly longer duration and better quality of postoperative analgesia than bupivacaine alone. On comparing the two drugs, Clonidine appears to be superior in terms of postoperative analgesia.

Keywords: clonidine, buprenorphine, intrathecal, postoperative analgesia.

Introduction

Pain as defined by the International Association for the study of Pain (IASP) is an "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".¹ Lower abdominal surgeries may be performed under regional (spinal or epidural) or general anaesthesia. Spinal block is still the first choice because of its rapid onset, superior blockade, lower risk of infection, lesser failure rates, and cost-effectiveness but has the drawbacks of shorter duration of block and less postoperative analgesia. Local Anaesthetics when used alone is associated with short duration of action. Thus, early analgesic intervention is needed in postoperatively period. Various adjuvants have been used intrathecally to improve the quality and duration of spinal anaesthesia with better postoperative analgesia like epinephrine, neostigmine, midazolam, ketamine, fentanyl, buprenorphine, clonidine and dexmedetomidine.² With this background, this study was designed to compare the efficacy of intrathecal buprenorphine and clonidine with control group for onset

and duration of sensory and motor block, duration of analgesia, sedation and to evaluate the side effects, if any.

Material and Methods

This was a randomized, double blind study, done at a tertiary care centre after the approval of the Institutional Ethical Committee and obtaining written informed consent from all patients after explaining the procedure in detail. 90 ASA I and II, aged 25-55yrs, of either sex, body weight 45-70kgs scheduled for lower abdominal surgeries under spinal anaesthesia were chosen for the study.

Preanaesthetic check-up was done one day prior to the surgery. Patients were evaluated for any systemic diseases and laboratory investigations recorded. The patients with contraindication to spinal anaesthesia (e.g. coagulation defects, infection at puncture site and allergy to drugs used) were excluded from the study.

The patients were educated about the use of visual analog scale (VAS) scoring system. On the day of surgery patients were randomly allocated into three groups (n=30) using sealed envelope technique.

After confirming overnight fasting, patient was taken on the operation table, was connected to monitors and baseline vitals like BP, pulse rate, respiratory rate was recorded. After an 18G intravenous cannula was inserted at the forearm level, lactated Ringer's solution was administered as a bolus of 10ml/kg before subarachnoid block to all patients.

Vitals were noted just before lumbar puncture. Spinal anaesthesia was performed at L3-L4 interspace with the patient in sitting position by using a 25G Quincke needle under strict aseptic conditions. Free flow of cerebrospinal fluid was verified before injection of the anaesthetic solution 4ml volume, which was administered over 30 seconds. The drug compositions were according to group to which patients were allocated. Group A received 3ml of 0.5% hyperbaric bupivacaine with 1ml normal saline, Group B received 3ml of 0.5% hyperbaric bupivacaine with 1ml (60mcg) of buprenorphine (1:5 dilution) and Group C received 3ml of 0.5% hyperbaric bupivacaine with 1ml (30mcg) clonidine (1:5 dilution). The direction of the needle aperture was cranial during the injection. All patients were immediately placed in supine position. All the patients in three groups received identical volume (4ml) of study drug prepared in an identical syringe by an anaesthesiologist who was not involved in the anaesthetic management of the patients. Monitoring was done using continuous electrocardiography (lead II & V), heart rate, non-invasive blood pressure and continuous pulse oximetry (SpO₂) and patients were given 4.0L/min of oxygen by venti-mask. Vitals were checked every 5 minutes for first 30 minutes then every 10 minutes till the end of the surgery. When adequate spinal block was achieved, the time from the end of intrathecal injection to readiness for surgery was recorded. Then the patient was positioned for planned surgery.

Sensory blockade was assessed every 2 minutes by pinprick test bilaterally in the midclavicular line by using 25G needle. The onset of sensory block defined as the time from the intrathecal injection of the study drug to the time taken to achieve T5-T6 level of sensory block. The highest level of the block and the time to achieve the same was noted. Regression of sensory block was defined as the time taken for the sensory block to regress up to two segments of dermatome from the highest level achieved. Motor blockade was assessed using Modified Bromage Scale. The onset of motor block was defined as the time taken to achieve complete motor block (Bromage Score-3). Duration of motor block was assessed by recording the time elapsed from the maximum to the lowest Bromage score (3-0).

Hypotension was defined as a fall of MAP by more than 30% from baseline or a fall in SBP below 90mmHg and it was treated with incremental doses of mephentermine

6mg IV and IV fluids. Bradycardia, defined as heart rate below 55bpm, was treated with injection atropine 0.3-0.6mg IV.

Postoperatively, the pain was assessed by using visual analogue pain scale (VAS) between 0 and 10 (0- no pain, 10- most severe pain). It was assessed every 30 minutes. Patients were allowed to receive rescue analgesics on VAS score of 3. Intravenous Diclofenac 75mg was given as rescue analgesic. This time from intrathecal injection to first administration of rescue analgesic (total duration of analgesia) was noted. This was the end point of our study. Postoperative sedation level was measured by using FOUR POINT SEDATION SCALE. The incidence of adverse effects such as nausea, vomiting, shivering, respiratory depression, sedation and hypotension were observed for 24 hours and managed.

Statistical Analysis

The sample size was calculated 30 cases for each of the 3 groups at α error 0.05 and power 80% assuming minimal detectable difference in mean time to first analgesic rescue with intrathecal buprenorphine, clonidine and control group to be 20 minutes with SD of 17.93 minutes so for the study purpose 30 cases were taken in each group (total 90 patients).

Statistical analysis was performed with SSPS (Statistical Package for the Social Sciences) software version 21 (SPSS inc., Chicago, IL,USA). Kruskal-Wallis H test was used to assess differences among the three groups with respect to nonparametric variables. If this revealed significant differences, Mann-Whitney U- test was used to analyze differences between the groups in pairs. Parametric testing was done using analysis of variance. The categorical data were compared among groups using Chi square test. Data are presented as mean $\pm$ standard deviation or number of patients (percentage) as per category. Probability was considered to be significant if less than 0.05.

Results

The demographic data, such as age, sex, height, weight, ASA status, type of surgery and duration of surgery were comparable among the groups thereby not having any influence upon the outcomes. There was no statistically significant differences in the demographic variables between the groups ($p>0.05$) (Table 1)

Table 1: DEMOGRAPHIC VARIABLES (Mean $\pm$ SD)

Parameters	Group A (n=30)	Group B (n=30)	Group C (n=30)	P value
Age (years)	43.13 $\pm$ 7.80	44.23 $\pm$ 4.22	41.40 $\pm$ 5.28	0.184
Sex (M/F)	8/22	7/23	8/22	0.943
Weight (kgs)	61.33 $\pm$ 7.26	62.20 $\pm$ 6.72	63.80 $\pm$ 7.37	0.400
Height (cms)	163.70 $\pm$ 7.77	163.53 $\pm$ 7.52	163.23 $\pm$ 7.90	0.972
ASA I/II	24/6	27/3	25/5	0.553
Duration of surgery(min)	63.67 $\pm$ 9.14	60.80 $\pm$ 9.83	65.00 $\pm$ 13.00	0.309

Values presented as mean $\pm$ SD. Statistical test used-ANOVA, Chi-square test. Group A- Control; B-Buprenorphine; C-Clonidine. ASA-American Society of Anaesthesiologist; SD-Standard Deviation.

The duration of analgesia was statistically significant among the three groups ($p<0.001$). Group C (354.50 ± 38.48 min) had the longest duration of analgesia when compared to Group A (131.50 ± 20.15 min) and Group B (277.10 ± 25.47 min). (Table 2 and Figure 1). The onset of sensory and motor block was statistically insignificant between Group B and Group C ($p>0.05$). The time to two segment regression was longer in Group C (166.50 ± 23.34 min) and shortest in Group A (94.00 ± 24.41 min) and there was statistically significant difference among all the groups ($p<0.001$). The duration of motor block was significantly longer in clonidine group (235.50 ± 38.82 min) as compared to buprenorphine (204.13 ± 46.53 min) and control group (116.27 ± 16.37 min) and there was significant difference among the three groups ($p<0.001$).

The hemodynamic parameters such as pulse rate, mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP) and mean arterial pressure (MAP) were not statistically significant at different time intervals intraoperatively and postoperatively ($p>0.05$).

VAS score was statistically significant throughout the postoperative period and it was highest in Group A (control group) and lowest in Group C (clonidine group) ($p<0.05$) from 90 minutes postoperatively up to first request for rescue analgesic. (Figure 2)

Postoperative Sedation score was significantly more in patients of Group C and Group B as compared to control group (Figure 3). On comparing the three groups with regards to the adverse effects such as nausea, vomiting, hypotension, bradycardia, shivering and respiratory depression, the difference was found to be statistically insignificant ($p>0.05$) intraoperatively as well as early postoperatively. (Table 3)

Table 2: Characteristics of motor and sensory block

Parameters	Group A		Group B		Group C		P value		
	Mean	SD	Mean	SD	Mean	SD	A v/s B	A v/s C	B v/s C
Duration of analgesia (min)	131.50	20.15	277.10	25.47	354.50	38.48	$P<0.001$	$P<0.001$	$P<0.001$
2 segment regression(min)	94.00	24.41	121.60	12.28	166.50	23.34	$P<0.001$	$P<0.001$	$P<0.001$
Duration of motor block (min)	116.27	16.37	204.13	46.53	235.50	38.82	$P<0.001$	$P<0.001$	$P<0.001$
Onset of sensory block (min)	5.10	1.17	3.37	0.79	3.07	0.80	$P<0.001$	$P<0.001$	0.147
Onset of motor block(min)	5.68	1.44	4.15	0.82	4.03	0.59	$P<0.001$	$P<0.001$	0.529

Data presented as mean $\pm$ SD. SD-Standard deviation, $p<0.001$ suggests statistically significant difference. Group A- Control; B-Buprenorphine; C-Clonidine. Statistical test-ANOVA test, Post Hoc turkey test.

Figure 1: Comparison of duration of analgesia (time to first rescue analgesia)

Figure 2: Mean visual analog score scale versus time. Values significantly different from 90 min upto 360 min by Kruskal-Wallis H test.

Figure 3: Mean Postoperative Sedation score versus time. Values were significantly different upto 60min by Kruskal-Wallis H test.

Table 3: Incidence of intraoperative and early postoperative adverse effects

Variables	Group A		Group B		Group C		P value
	No.	%	No.	%	No.	%	
Hypotension	6	20.00	4	13.33	8	26.67	0.355
Bradycardia	2	6.67	0	0	3	10.00	
Nausea & Vomiting	4	13.33	4	13.33	4	13.33	
None	18	60.00	24	80.00	15	50.00	
Total	30	100.0	30	100.0	30	100.0	

Values are presented as number. Statistical test- Chi-square test. Group A- Control; B-Buprenorphine; C- Clonidine.

Discussion

Effective postoperative pain control is an essential component of the care of the surgical patient. Inadequate pain control, apart from being inhuman, may result in increased morbidity or mortality.^{9,10} Evidence suggests that surgery suppresses the immune system and that this suppression is proportionate to the invasiveness of the surgery. Good analgesia can reduce this deleterious effect.^{11,12}

Regional analgesia have shown to improve surgical outcomes by decreasing intraoperative blood loss, postoperative catabolism, the incidence of thromboembolic events and by improving vascular graft blood flow and postoperative pulmonary function.¹³ Spinal anaesthesia is a commonly used regional anaesthesia technique for lower limb and lower abdominal surgeries owing to its well-known advantages like quick onset, excellent sensory and motor block and avoidance of complications of general anaesthesia.⁹ Various studies in the past have established the role of clonidine and buprenorphine as an adjuvant to local anaesthetic.

The antinociceptive properties of clonidine indicate that it might be useful as an alternative to intrathecal opioids for postoperative analgesia.¹⁴ The growing interest in alpha 2 agonist for intrathecal use has motivated innumerable research due to its ability to improve anaesthesia and neuraxial analgesia without the side effects of opioids such as respiratory depression, pruritis and urinary retention.

With this background a comparative study was performed to know the effectiveness of intrathecal buprenorphine versus clonidine as adjuvants to 0.5% hyperbaric bupivacaine in patients undergoing lower abdominal surgeries in relation to time of onset and duration of motor and sensory block and duration of analgesia. Incidence of side effects were also noted and compared. Our study showed that patients receiving 0.5% Bupivacaine had least duration of analgesia (131.50 minutes) whereas addition of 60 µg buprenorphine to 0.5% bupivacaine, the duration increased to 277.10minutes but when 30µg clonidine was used as an adjuvant, the duration was

maximally prolonged upto 354.50 minutes. Our results have been strengthened by findings of Rashmi Pal et al⁶ who demonstrated prolonged analgesia with 50mcg clonidine(353.19±7.69min) and 75mcg buprenorphine (294.00±17.93min). When clonidine used intrathecally prolongs the analgesic action by acting spinally through the activation of postsynaptic alpha2 receptors in substantia gelatinosa of spinal cord^{15,16} and block the conduction of C and A delta fibres.³

Our results were further strengthened by findings of Negi AS et al⁵ who showed duration of analgesia was more with 37.5mcg clonidine (355.80±63.85 min) as compared to 75mcg buprenorphine (283.20±51.84 min). Similarly, Srinivasagam K et al⁷ also found addition of 50 mcg clonidine to hyperbaric bupivacaine increases the duration to first time of rescue analgesia. Similar results were shown by Lomate P et al⁸ who used 30mcg clonidine. We also used 30 mcg clonidine in our study which showed similar results to all above studies.

The onset of sensory and motor block was not prolonged in clonidine and buprenorphine. Our results were supported by the study done by Lomate P et al⁸, Rashmi Pal et al⁶ and Srinivasagam K et al⁷. The duration of sensory block and motor block was more with clonidine as compared to buprenorphine and control group. Lomate P et al⁸ observed similar results which used 30mcg clonidine in their study.

In our study hemodynamic parameters were comparable at different time intervals intraoperatively and postoperatively. Many studies who have used very low doses of intrathecal clonidine such as 15-30 mcg^{2,4} in humans found no hemodynamic instability which is proven in our study as we have used low dose clonidine (30mcg). Our findings are similar to study done by Negi AS et al⁵ who had used 37.5mcg clonidine in patients undergoing lower limb surgeries showed no hemodynamic instability.

In our study, postoperative sedation score was highest with clonidine group. Patients developed sedation as assessed by sedation scores but were easily arousable.

On comparing the three groups with regards to adverse effects like hypotension, bradycardia, nausea, vomiting, respiratory depression and shivering the difference was statistically insignificant. Srinivasagam K et al⁷ reported increased incidence of hypotension and bradycardia with 50mcg of clonidine. This difference could be due to the use of lower doses (30mcg) in our study. One limitation of our study was that a therapeutic end point of VAS score 3 or request for analgesic was used. 24 hours total analgesic requirements were not recorded which would have better demonstrated the analgesic qualities of the studied drugs. However, our study found buprenorphine and clonidine

both prolonged analgesia and decreased postoperative VAS scores.

Conclusion

Both buprenorphine (60mcg) and clonidine (30mcg) were effective and safe as adjuvants to 0.5% hyperbaric bupivacaine when given intrathecally in patients undergoing lower abdominal surgeries. Clonidine appeared to be better in terms of prolongation of the duration of analgesia as compared to buprenorphine. Clonidine provide adequate sedation in postoperative period without significant postoperative complications.

References

1. Merskey H, Bogduk N. Part III: Pain Terms, A Current List with Definitions and Notes on Usage Recommended by the IASP Subcommittee on Taxonomy. *Pain*. 2012;6:209-214.
2. Devendra V, Ankush G, Udit N, Smita B, Pradeep B, Vikas S Clinical efficacy of isobaric ropivacaine alone with fentanyl in spinal anaesthesia for vaginal hysterectomy: a prospective, randomized, comparative study. *Ejpmr*, 2016, 3 (9), 223-228.
3. Sethi BS, Samuel M, Sreevastava D. Efficacy of Analgesia Effects of Low Dose Intrathecal Clonidine as Adjuvant to Bupivacaine. *Indian J Anaesth* 2007;51:415.
4. Dobrydnjov I, Axelsson K, Thorn SE, Matthiesen P, Klockhoff H, Holmstrom B, et al. Clonidine combined with small dose bupivacaine during spinal anaesthesia for inguinal herniorrhaphy: A randomized double-blind study. *Anaesth Analg*. 2003;96:1496-503.
5. Negi AS, Gupts M, Singh A. Comparison of effect of intrathecal buprenorphine vs clonidine as an adjuvant to hyperbaric bupivacaine on subarachnoid block characteristics. *J Recent Adv Pain* 2015;1(2):67-72.
6. Rashmi Pal, K.K Arora, N.S. Doneria comparison of buprenorphine, clonidine and fentanyl adjuvants to hyperbaric bupivacaine in lower abdominal surgeries. *Journal of evolution of medical and dental sciences* 2015;Vol 4, issue 46, June 08; page:8009-8017, 2015
7. Srinivasagam K, Ayyavu Chandrasekaran, Nanthaprabu. M. Comparison of buprenorphine, clonidine and fentanyl as adjuvant to hyperbaric bupivacaine in lower abdominal surgeries. *IOSR-JDMS, VOLUME 15, Issue 7 Ver. VII (July, 2016), PP 25-30*
8. Lomate P, Jyotsna Parajpe, Shilpa Gaikwad. Comparison of the efficacy of intrathecal buprenorphine and clonidine as adjuvant to bupivacaine in abdominal hysterectomy. *FMIJOANS* 2019;9(3):201-207.
9. Sharrock NE, Cazan MG, Hargett MJ, Williams-Russo P, Wilson PD. Jr changes in mortality after total hip and knee arthroplasty over a ten-year period. *Anaesth Analg*. 1995;80:242-248.
10. Katz J, Jackson M, Kavanagh BP, Sandler AN. Acute pain after thoracic surgery predicts long term post-thoracotomy pain. *Clin J Pain*. 1996;12:50-55.
11. Pollack RE, Lotzova E, Stanford SD. Mechanism of surgical stress impairment of human perioperative natural killer cell cytotoxicity. *Arch Surg*. 1991;126:338-342.
12. Lennard TW, Shenton BK, Borzotta A, Donnelly PK, White M, Gerrie LM, Proud G, Taylor RM. The influence of surgical operations on components of the human immune system. *Br J Surg*. 1985;72:771-776.
13. Yeager MP, Glass DD, Neff RK, Brinck-Johnsen T. Epidural anaesthesia and analgesia in high risk surgical patients. *Anaesthesiology*. 1987;66:729-736.
14. Yaksh TL, Reddy SV. Studies in the primates on the analgetic effects associated with intrathecal action of opiates, alpha-adrenergic agonists and baclofen. *Anaesthesiology*. 1981;54:451-67.
15. Reddy SVR, Yaksh TL. Spinal noradrenergic terminal system mediates antinociception. *Brain Res*. 1980;189:391-401.
16. Brandt SA, Livingston A. Receptor changes in spinal cord of sheep associated with exposure to chronic pain. *Pain*. 1990;42:323-9