Comparison of intrathecal clonidine and magnesium sulphate used as an adjuvant with hyperbaric bupivacaine in lower abdominal surgery

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ABSTRACT

Background and Aims: Use of various adjuvants to spinal anaesthesia is a well-known modality to provide intra- and post-operative analgesia. This study was designed to evaluate and compare the analgesic efficacy of clonidine and magnesium when used as an additive to intrathecal 0.5% hyperbaric bupivacaine. **Methods:** Ninety patients of the American Society of Anesthesiologists' physical status grade I or II, scheduled for lower abdominal surgery under spinal anaesthesia, were randomly allocated into three groups. Group B received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL of normal saline, Group C received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL (30 μg) of clonidine and Group M received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL (50 mg) magnesium sulphate. The primary outcome variable was duration of analgesia and secondary outcome variables included onset and duration of sensory and motor block, sedation level and adverse effects. Data were analysed with ANOVA, Kruskal–Wallis and Chi-square tests. **Results:** The time to first rescue analgesia was significantly ($P < 0.01$) longer in the Group C (330.7 ± 47.7 min) than both Groups. Group M (246.3 ± 55.9 min) showed significantly prolonged analgesia than Group B (134.4 ± 17.9 min). Group C and Group M showed significantly prolonged duration of both sensory and motor block compared to Group B. **Conclusion:** Intrathecal clonidine added to bupivacaine prolongs the duration of post-operative analgesia, and hastens the onset and prolongs the duration of sensory and motor block compared to magnesium or controls.

Key words: Bupivacaine, clonidine, magnesium, post-operative analgesia

INTRODUCTION

Intrathecal adjuvants are increasingly used for better post-operative pain management. Intrathecal opioids are used to potentiate post-operative analgesia but their adverse effects have raised the necessity to look for better alternatives.[1] Intrathecal clonidine potentiates post-operative analgesia by hyperpolarising Aδ and C fibre in the substantia gelatinosa of the spinal cord.[2] Low-dose clonidine has good analgesic efficacy with a low incidence of adverse effects.[3] Magnesium prevents the development of central sensitisation of pain by antagonistic action on N-methyl-D-aspartate receptors in the spinal cord. The calcium channel blocking property of magnesium also contributes to its antinociceptive effect.[4]

We designed this study to evaluate and compare the analgesic efficacy of intrathecal clonidine and magnesium sulphate as an adjuvant to hyperbaric bupivacaine in lower abdominal surgeries. We hypothesised that intrathecal clonidine would provide better post-operative analgesia compared to intrathecal magnesium or plain bupivacaine.

METHODS

This prospective, randomised, double-blind, placebo-controlled study was done at a tertiary care centre from November 2015 to May 2016 after the approval of the Institutional Ethical Committee and obtaining written informed consent from all patients.

Ninety patients of either gender, aged between 20 and 60 years with the American Society of Anesthesiologists' (ASA) physical status grade I or II, height between 140 to185cm, weight between 40 to 80 kg, posted for elective lower abdominal surgery under spinal anaesthesia were evaluated for this study.

All the patients underwent a thorough pre-operative examination, including history, general physical examination and necessary blood investigations. Patients with any contraindication to spinal anaesthesia or major neurological, cardiovascular, metabolic, respiratory, renal disease or coagulation abnormalities were excluded from this study. [Figure 1] After taking written informed consent, on the day of surgery, ninety patients were randomised into three groups of thirty patients using computerised randomisation method (Random Allocation Software) and the allocated

Figure 1: CONSORT diagram

group number of each patient was kept concealed in closed envelope. The patients and the anaesthetist who were involved in randomisation and drug preparation were masked about the information regarding further steps of the study (drug administration, data collection and analysis). The visual analogue scale (VAS) scoring system was explained to all the patients. We have used 0-10 VAS scale.

All the patients were fasted for at least 6 h before the procedure. In the operating room, a multiparameter monitor for electrocardiograph (ECG), heart rate (HR), oxygen saturation (SpO_2) and non-invasive blood pressure was attached and the baseline vital parameters were recorded. Intravenous (IV) line was secured with 18-gauge cannula and ranitidine 50 mg IV and metoclopramide10 mg IV were administered. All the patients were pre-loaded with Ringer's lactate 15 mL/kg over 10 min. Under all aseptic precautions, spinal anaesthesia was performed at the L_3–L_4 interspace, with the patient in sitting position. A total of 4 ml study drug was injected over 30 seconds through a 25-gauge spinal needle (BD™ Quincke Spinal Needle). The intrathecal drug compositions depended on the group to which patients were randomised. Patients in Group B received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL of normal saline, those in Group C received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL (30µg) of clonidine (1:5 dilution) and patients in Group M received 3 mL of 0.5% hyperbaric bupivacaine with 1 mL (50mg) magnesium sulphate (1:10 dilution). All the study drugs were prepared in identical volume (4 mL) and in an identical syringe by an anaesthesiologist who was not involved in the anaesthetic management of the patients. The anaesthesiologist who administered the study drugs and anaesthesiologist who recorded the data were blinded to the study drugs.

The patients were placed in supine position with head down tilt immediately after spinal injection to achieve the satisfactory level of the block (up to T_6 spinal level). Then, the patients were kept in horizontal position.

Sensory block was assessed by the pinprick method bilaterally along the mid-clavicular line with a 25-gauge hypodermic needle at 2 min interval till the highest level of block was achieved and the required time was noted. The onset of sensory block was defined as the time from intrathecal injection of the study drug to the time taken to achieve T_6 dermatomal level of sensory block. Regression of sensory block
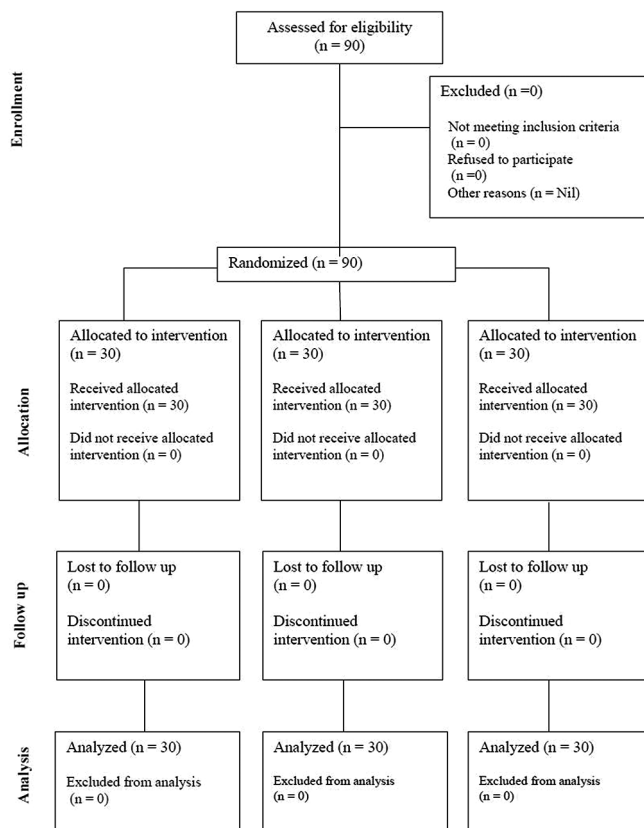
was defined as the time taken for the sensory block to regress by two dermatomal segments from the highest level achieved. Motor block was assessed according to the modified Bromage scale.[2] The onset of motor block was defined as the time from intrathecal injection of the study drug to the time taken to achieve complete motor block (Bromage score-IV). Duration of motor block was the time elapsed from the maximum to the lowest Bromage score I–IV.

Intraoperatively, monitoring of blood pressure, pulse rate, saturation and respiratory rate were done at 5 min interval. Hypotension was defined as a fall of mean arterial pressure (MAP) by more than 20% from baseline or a fall of systolic blood pressure below 90 mmHg and it was treated with incremental IV doses of mephentermine 5 mg and IV fluid as required. Bradycardia, defined as HR <50 bpm, was treated with injection atropine 0.6 mg IV.

The post-operative pain and sedation level were assessed according to the VAS (0-10) and the 'four point sedation scale' (score 1 = spontaneous eye opening [awake and alert]; score 2 = drowsy, responsive to verbal stimuli; score 3 = drowsy, arousable to physical stimuli; score 4 = unresponsive), respectively, at 30-min interval up to 4 h and hourly thereafter till the request for first rescue analgesia.[5] Every patient received injection diclofenac 75 mg IV as rescue analgesic on VAS of 3. The time from intrathecal injection to first rescue analgesia (total duration of analgesia) was recorded and this was the end point of our study. We observed all patients for next 24 h regarding any complications such as nausea, vomiting, hypotension, bradycardia, respiratory depression and managed them accordingly.

Statistical analysis was done with the statistical programming software – Statistical Package for the Social Science version 20.0.0 (SPSS Inc., Chicago, Illinois, USA) and Primer of Biostatistics (version-6.0) by Stanton A. Glantz, McGraw-Hill, 2005. The sample size was calculated using online software StatsToDo (www.statstodo.com). Calculated sample size was 27 participants in each of the three groups with an expected standard deviation of 30 (based on the pilot study with ten participants in each of the three groups), assuming clinically significant difference of time to first rescue analgesia of 30 min, power of 90% and considering $P < 0.017$ as significant (after Bonferroni correction for three arm study). For the study purpose, thirty patients were recruited in each of the three groups (total ninety patients)

with 25% safety margin. The data of continuous variables (quantitative data) such as age, weight, height, blood pressure, HR and time were tested for normality by Kolmogorov–Smirnov test. The normally distributed data (presented as a mean ± standard deviation) were analysed by applying one-way ANOVA test and Tukey's honesty significant difference *post hoc* multicomparison test for the intergroup comparison. The categorical variables (qualitative data) such as ASA grade, sex, grade and sedation level were expressed in frequency or number and percentage. Chi-square test, Kruskal–Wallis test and Mann–Whitney test were used for the analysis of qualitative and non-normally distributed data as appropriate. A $P < 0.05$ was considered statistically significant.

RESULTS

All the groups were comparable with respect to age, weight, ASA status, type of surgery and duration of surgery [Table 1].

The duration of analgesia (time to first rescue analgesia) was significantly ($P < 0.01$) prolonged in Group C (330.7 ± 47.7 min) compared to both Group M (246.2 ± 55.9 min) and Group B (134.4 ± 17.9 min), and Group M showed a significantly ($P < 0.01$) longer duration of analgesia compared to Group B [Table 2 and Figure 2].

The onset of both sensory and motor block was significantly ($P < 0.01$) faster in Group C (4 ± 0.8 min and 4 ± 0.7 min) compared to both Group M (7.1 ± 2.5 min and 8.5 ± 3.6 min) and Group B (6 ± 1.2 min and

Table 1: Distribution of demographic variables				
Variables	**Group B (*n*=30)**	**Group C (*n*=30)**	**Group M (*n*=30)**	***P***
Age (years)	42.87±8.58	39.9±8.83	43.73±8.86	0.212#
Weight (kg)	58.67±12.18	59.6±13.72	58.97±10.92	0.956#
Height (cm)	165.17±8.28	164.77±9.86	162.77±8.6	0.54#
Sex (male/female)	4/26	3/27	3/27	0.894*
ASA (I/II)	26/4	25/5	25/5	0.92*
BMI	21.6±4.9	22.3±6.3	22.5±5.1	0.8#
Duration of surgery (min)	66.67±5.84	68.07±7.6	67.8±6.96	0.703#
Type of surgery				
TAH±BSO	22 (73.33)	23 (76.67)	25 (83.33)	0.878*
Appendicectomy	4 (13.33)	3 (10)	3 (10)	
Laparotomy (for ovarian cysts)	4 (13.33)	4 (13.33)	2 (6.67)	

Values presented as mean±SD, *n* (%). #Statistical test used – ANOVA, *Chi-square test. Group B – Control; C – Clonidine; M – Magnesium. BMI – Body mass index; ASA – American Society of Anesthesiologists; SD – Standard deviation; TAH – Total Abdominal Hystrectom; BSO – Bilateral Salpingooophorectomy

Table 2: Characteristics of spinal block							
Variables	Group B (*n*=30)	Group C (*n*=30)	Group M (*n*=30)	*P* (ANOVA)	*P* (*post hoc* test)		
					B versus C	B versus M	C versus M
Onset of sensory block (min)	6±1.2	4±0.8	7.1±2.5	<0.01	<0.01	0.033	<0.01
Duration of sensory block (min)	94±24.4	166.5±23.3	123±16.6	<0.01	<0.01	<0.01	<0.01
Onset of motor block (min)	6.7±1.4	4±0.7	8.5±3.6	<0.01	<0.01	0.007	<0.01
Duration of motor block (min)	116.3±16.4	218.5±52.7	138.3±25.7	<0.01	<0.01	0.043	<0.01

Values are presented as mean±SD. Statistical test – ANOVA and *post hoc* test – Tukey's HSD. Group B – Control; C – Clonidine; M – Magnesium. Intergroup comparison showed *P*<0.05 in regards to all the parameters of spinal block. SD – Standard deviation

P<0.01 among three groups; Group-B vs. Group-C= P<0.01[★]; Group-C vs. Group-M= P<0.01[✚]; Group-M vs. Group-B= P<0.01[▲]; Group-B= control, C= clonidine, M= magnesium sulphate.
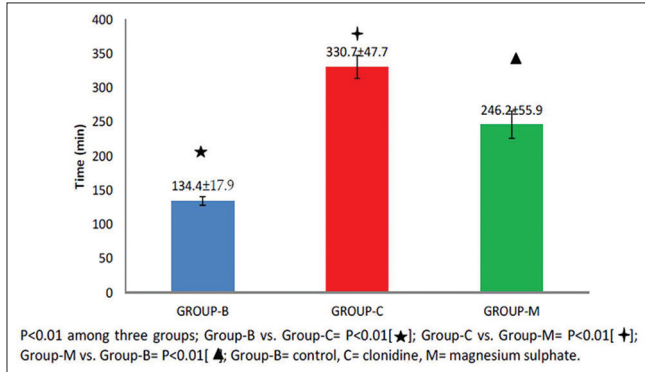
Figure 2: Comparison of time to first rescue analgesia

6.7 ± 1.4 min), whereas Group M showed the significantly delayed onset of both sensory ($P = 0.033$) and motor ($P = 0.007$) blockade compared to Group B. The duration of both sensory and motor block was significantly ($P < 0.01$) prolonged in Group C (166.5 ± 23.3 min and 218.5 ± 52.7 min) compared to Group M (123 ± 16.6 min and 138.3 ± 25.7 min) and Group B (94 ± 24.4 min and 116.3 ± 16.4 min) and Group M also showed the significantly longer duration of both sensory ($P < 0.01$) and motor ($P = 0.043$) block compared to Group B [Table 2].

Intraoperatively, both HR and MAP were significantly ($P < 0.05$) different among three groups from 5 min to 50 min and from 5 min to 30 min, respectively. HR was significantly ($P < 0.001$) lower in Group C (from 5 min to 50 min) and Group M (from 10 min to 50 min) in comparison to Group B. On the other hand, significant ($P < 0.05$) differences in HR were observed between Group C and Group M at 5 min, 10 min and 30 min, respectively. Intraoperatively, MAP was found to be significantly ($P < 0.05$) lower in Group C compared to Group B (from 5 min to 30 min) and Group M (from 5 min to 25 min) whereas Group M showed significantly ($P < 0.05$) lower MAP compared to Group B at 20 min. The post-operative haemodynamic data failed to show any significant differences among these three groups.

Among these three groups, VAS was significantly different ($P < 0.001$) from 30 min to 120 min whereas Group B showed significantly ($P < 0.05$) higher values of VAS compared to other two groups. The patients of Group M showed a significantly ($P < 0.05$) higher level of VAS compared to Group C at 60 min, 90 min and 120 min [Table 3].

Regarding the postoperative sedation score, no significant differences ($P > 0.05$) were observed among the three groups throughout the post-operative period.

The incidences of adverse effects such as nausea and vomiting, shivering, hypotension and bradycardia were also comparable ($P > 0.05$) among all the three study groups [Table 4].

DISCUSSION

Use of intrathecal adjuvants with local anaesthetics has become a very popular practise in recent years for the better post-operative analgesia as well as to improve the quality of spinal block to facilitate functional recovery of patients.[6] Although various studies established analgesic efficacy of both intrathecal clonidine and magnesium, none of them compared simultaneously. Prolonged duration of analgesia, as well as the earlier onset and prolonged duration of both sensory and motor block, were observed with intrathecal clonidine compared to intrathecal magnesium sulphate in our study. The synergistic action of both clonidine (on alpha-2 receptors) and local anaesthetic (on the neural sodium channels) is responsible for the profound analgesia and better quality of both sensory and motor block.[7] Various studies have established these properties of clonidine without significant morbidity and mortality. Intrathecal clonidine in diferrent doses such as 50 mcg and 75 mcg showed enhanced post-operative analgesia with clonidine compared to intrathecal bupivacaine in lower abdominal surgery.[8,9] Instead of high doses, lower doses of clonidine (15 mcg, 30 mcg) were also found to be effective in prolonging the post-operative

Table 3: Comparison of post operative VAS			
Time	Group B (*n*=30)	Group C (*n*=30)	Group M (*n*=30)	P
0 min	0	0	0	
30 min	1 (1-2)	0	0	<0.001
60 min	2 (2-3)	0	0 (0-1)*	<0.001
90 min	3 (2-4)	0	1 (0-2)*	<0.001
120 min	2 (1-2)	0	1 (1-2)*	<0.001
150 min	2 (1-2)	0 (0-1)	2 (1-2)	0.095
180 min	2 (1-2)	1 (1-1)	2 (2-2)	0.487
210 min	2 (1-2)	2 (1-2)	2 (2-3)	0.134
240 min	2 (1-2)	2 (2-2)	2 (2-2)	0.169
300 min	2 (1-2)	3 (2-4)	2 (2-3)	0.586
360 min	1.5 (1-2)	2 (1-2)	1 (1-2)	0.462

Values are presented as Median (IQR); Group B – control; C – Clonidine; M – Magnesium sulphate. *$P<0.05$ between Group C and group-M

Table 4: Incidence of adverse effects				
Variables	Group B	Group C	Group M	P
Nausea and vomiting	4	2	2	0.578
Shivering	4	0	2	0.117
Hypotension	1	2	0	0.355
Bradycardia	1	3	0	0.16

Values are presented as number; Statistical test – Chi-square test. Group B – Control; C – Clonidine; M – Magnesium sulphate

analgesia compared to intrathecal bupivacaine in spinal anaesthesia.[3,10] In our study, intrathecal clonidine (30 mcg) prolonged the post-operative analgesic duration significantly compared to both magnesium sulphate and control.

Intrathecally used clonidine was not only found to potentiate post-operative analgesia but also facilitate other characteristics of spinal anaesthesia such as onset and duration of both sensory and motor blockade. It is mainly due to the pre-synaptic inhibition of transmitter release and post-synaptic hyperpolarisation of dorsal horn neurons.[10] Though different studies with intrathecal clonidine in higher doses such as 50 mcg, 75 mcg have already established earlier onset as well as protracted duration of both sensory and motor blockade,[8,9,11] there are studies which have shown similar results even with lower doses of intrathecal clonidine (such as 15 mcg, 30 mcg, 25 mcg).[3,10,12] Similar results were also found in our study with intrathecal clonidine at the dose of 30 mcg.

The incidence of hypotension, bradycardia and sedation vary with the dose of intrathecal clonidine. It is mainly due to the central alpha-2 agonistic activity.[10] Various studies reported significant hypotension, bradycardia and sedation with intrathecal clonidine in higher doses (37.5–50 mcg, 75 mcg).[9,13] Contrastingly, lower doses of intrathecal clonidine were found to be devoid

of these untowards effects without compromising the analgesic and anaesthetic efficacy.[3,10,12] In this study, we chose intrathecal clonidine at a low dose (30 mcg) which showed superior anaesthetic and analgesic efficacy without significantly high incidence of adverse effects.

Intrathecally used magnesium also known to prolong not only the duration of both sensory and motor block but also the post-operative analgesia. When used with fentanyl, magnesium sulphate was found to prolong the mean duration of analgesia.[14,15] This augmentation of opioid analgesia due to blockade of spinally mediated facilitatory component evoked by repetitive C-fibre stimulation.[4] Similar observations have been found in different studies where intrathecal magnesium (50 mg) effectively prolonged the duration of the pain-free period as well as the duration of motor block compared to control.[16,17] Intrathecal magnesium (50 mg) was also found to be superior to the intrathecal midazolam with regard to post-operative analgesic effect.[18] We observed significantly prolonged post-operative analgesic duration with magnesium sulphate compared to control but it was lesser than the clonidine.

The delayed onset of both sensory and motor block could be an important issue regarding the use of intrathecal magnesium. Various theories such as differences in baricity and pH between the solution containing magnesium sulphate and cerebrospinal fluid,[19] hydrolysis of intrathecal bupivacaine by magnesium-induced activated cytochrome P450 and alteration of the pharmacokinetics of intrathecal bupivacaine have been postulated to explain magnesium-induced delayed onset of spinal anaesthesia.[16] Various studies have also established protracted onset of both sensory and motor block with intrathecal magnesium with respect to control.[6,18,20] The delay in onset of both sensory and motor block was found to be more pronounced in higher doses of intrathecal magnesium compared to low doses (75 mg, 100 mg vs. 50 mg).[21] Although in our study, while intrathecal magnesium (50 mg) was associated with delayed onset of both sensory and motor block compared to both control and clonidine, it prolonged the duration of these blocks compared to control.

Various animal and human studies have established the safety of intrathecal magnesium sulphate and a recent study not only established the safety but also showed the beneficial effects of intrathecal

magnesium.[22] Although studies with higher doses of intrathecal magnesium reported better analgesic efficacy, they also encountered high incidence of adverse effects such as hypotension, nausea and shivering.[21] Different studies with intrathecal magnesium in low doses such as 50 mg showed prolonged post-operative analgesia without any significant adverse effect.[16,18] It provides the rationale for choosing the dose of intrathecal magnesium in our study where the incidences of adverse effects were also not significant compared to other groups.

CONCLUSION

Intrathecal clonidine (30 mcg) prolonged post-operative analgesia along with earlier onset and prolonged duration of sensory and motor blockade compared to both magnesium (50 mg) and control without any significant adverse effects or haemodynamic perturbation. Intrathecal magnesium (50 mg) also increased the analgesic duration compared to control but it was associated with delayed onset of both sensory and motor blockade compared to both clonidine and control.

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Conflicts of interest
There are no conflicts of interest.

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