|| ISSN(online): 2589-8698 || ISSN(print): 2589-868X ||
International Journal of Medical and Biomedical Studies
Available Online at www.ijmbs.info
NLM (National Library of Medicine ID: 101738825)
Index Copernicus Value 2019: 79.34
Volume 5, Issue 9; September: 2021; Page No.123-129

Original Research Article

BUPRENORPHINE VERSUS MAGNESIUM SULPHATE: ADJUVANTS TO INTRATHECAL HYPERBARIC BUPIVACAINE FOR LOWER ABDOMINAL SURGERIES

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Article Info: Received 28 July 2021; Accepted 04 September 2021
DOI: https://doi.org/10.32553/ijmbs.v5i9.2152
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Conflict of interest: No conflict of interest.

Abstract
Aims: An adjuvant to a local anaesthetic can potentiate spinal anesthesia and provide better postoperative analgesia. Our study has been drafted to evaluate and compare the analgesic potency of the adjuvants, buprenorphine and magnesium, to intrathecal 0.5% hyperbaric bupivacaine.
Methods: One hundred and fifty patients by inclusion criteria posted for an elective lower abdominal surgery were randomised into three groups of 50 each. They received 3ml of 0.5% hyperbaric bupivacaine with either 1ml of 0.9% Saline or 1ml of buprenorphine (60μg) or 1ml of magnesium sulphate (50mg). Time for first rescue analgesia, onset of sensory and motor blocks, time to two-segment regression and duration of motor block, haemodynamic parameters, and side effects were studied. Data was analyzed with ANOVA, Kruskal-Wallis H, Chi-square and Fischer's exact tests. Our Study was carried out from January 2020 to April 2020.
Results: The time for first analgesic request was 248.70> 186.84> 141.44 minutes
(Buprenorphine> magnesium> control), p<0.001. The onset of sensory and motor blocks was faster in buprenorphine group compared to magnesium and control groups. The time to two-segment regression and duration of motor block was significantly prolonged in buprenorphine and magnesium groups compared to control group.
Conclusion: The time to first analgesic request was longer with buprenorphine compared to magnesium sulphate with adequate sedation and negligible complications. Hence, addition of adjuvant buprenorphine (60μg) has a better demonstrable role in postoperative analgesia compared to adjuvant magnesium (50mg) or 0.5% hyperbaric bupivacaine alone.
Keywords: Spinal Anaesthesia; Intrathecal buprenorphine; Intrathecal magnesium; Analgesic efficacy; Intrathecal adjuvants

Introduction

Spinal Anesthesia is simple to perform, economical, highly efficient at less drug doses (1) rapid in onset with complete muscle relaxation, with lesser complications than General Anaesthesia but has shorter duration of action. This necessitates the need for other modes of analgesia postoperatively. By using intrathecal additives to local anesthetics we can attenuate early postoperative analgesic requirements. Semi-synthetic Thebaine derivative, buprenorphine is a mixed agonist-antagonist opioid. It is highly lipophilic with a high molecular weight of 467.64 g/mol. This might be useful in preventing rostral spread and also common side effects associated with intrathecal administration. (2) Naturally occurring mineral, magnesium, blocks NMDA channels in a voltage dependent fashion. (3) Magnesium is not associated with pruritus, respiratory depression, sedation side effects known to be associated with opioids. With this in mind, we fashioned this study to evaluate and compare our primary aim, the time to first rescue analgesia of adjuvants, 60μg buprenorphine and 50mg magnesium sulphate to intrathecal 0.5% hyperbaric bupivacaine. The onset of sensory and motor blocks, time to two-segment regression, duration of motor block, hemodynamic parameters and side effects were also studied. We hypothesized that intrathecal buprenorphine and magnesium would yield superior postoperative analgesia in comparison to plain bupivacaine.

Methods:

Our study is a prospective, randomised, double-blind, placebo-controlled study. It was carried out at a tertiary care centre after the approval of the Institutional Ethical Committee (Number 167 (36)/ MC/ EC/ 2020) and Clinical Trials Registry, India (CTRI/2020/06/025962). The study was conducted from January 2020 to April 2020. Written informed consent was obtained from all patients.

Sample size was calculated to find out difference between the means of three groups from the seed article, (4) in which the duration of total analgesia was 171.63 ± 34.45, 229.43 ± 45.42 and 159.50 ± 31.52 minutes in the magnesium, buprenorphine and control groups, respectively. Using Open-epi sample size calculator for 95% confidence interval and 80% power, sample size was calculated between magnesium and buprenorphine groups to be 16, buprenorphine and control groups to be 5, and that between magnesium and control groups to be 117. Therefore, to bring out the difference between the three groups, ideally the study should be conducted with 117 cases in each group. However, this being a single investigator study and having had to recruit during the time of the pandemic, decision was made to do carry out the study with 50 individuals per group.

A total of 150 adult patients (25- 60 years) of American Society of Anesthesiologists (ASA) physical status I & II, weighing 45-70kg, of height over 145cm, scheduled for elective lower abdominal surgery at our institute under spinal anaesthesia were recruited. Patients not willing to participate in the study, with allergic history to study drugs, contraindication to spinal anaesthesia or major neurological, cardiovascular, metabolic, respiratory, renal diseases were excluded from the study. Routine Pre-anaesthetic checkup was done a day before the surgery. All the patients were fasted for at least 6 hours before the procedure.

Using a computer-generated random number sheet, serially numbered opaque sealed envelopes (SNOSE) were created by a statistician for allocation concealment. These envelopes were opened on the day of the surgery to allot the patient into one of the three groups. The envelopes were opened by an anaesthesiologist who was not involved in the investigation and all the study drugs were prepared in identical volume (4 mL), in an identical syringe by them and handed over to the investigating anaesthesiologist who administered the spinal block. The patients and the investigating anaesthesiologist were unaware of the drug administered. The same was fed to the system after the analysis, thereby enabling double blinding.

In the operating room, a monitor (UltraviewSL V2.03.13, Spacelabs Healthcare Ltd., Made in USA) with electrocardiograph (ECG), heart rate (HR), pulse oximetry (SpO2) and non-invasive blood pressure (NIBP) was attached and the baseline vital parameters were recorded. Intravenous (IV) line was secured with 18G cannula and patients were pre-loaded with Ringer's lactate 10ml/kg over 10 minutes. Ampoules of 0.5% hyperbaric bupivacaine (Celon Laboratories, Gajularamaram, India), buprenorphine 300µg/cc (Neon laboratories, Thane, India) and magnesium sulphate 50% (Modern laboratories, Indore, India) were used for the study.

Under absolute aseptic precautions, with the patient in sitting position, spinal anaesthesia was performed at the L3-L4 interspace. The total amount of 4 ml of the study drug was injected over 30 seconds through a 25G spinal needle. The intrathecal drug compositions depended on the group to which patients were randomised to. In addition to intrathecal 15mg of 0.5% hyperbaric bupivacaine, Group A received 0.9% Saline, Group B received 60µg buprenorphine at 1:5 dilution, Group C received 50mg magnesium sulphate at 1:10 dilution. The direction of the needle aperture was cranial during the injection. All patients were immediately placed in supine position. The patients were provided Oxygen at the rate of 4.0 L/ minute through Hudson Mask. When adequate spinal block was achieved, the time from the end of intrathecal injection to readiness for surgery was recorded. Vitals were checked every 5 minutes for first 30 minutes then every 10 minutes till the end of the surgical procedure.

The onset of sensory block was defined as the time from the intrathecal injection of the study drug to the time taken to achieve T5-T6 level of sensory block. Sensory blockade was assessed every 2 minutes by pinprick test bilaterally in the midclavicular line with a 25G needle. 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. The onset of motor block was defined as the time taken to achieve complete motor block and was assessed using Modified Bromage Scale. Duration of motor block was assessed by recording the time elapsed from the maximum to the lowest Bromage score (3- 0).

Hypotension, defined as fall of MAP by more than 30% from baseline or fall in SBP below 90mmHg, was treated with incremental doses of IV Mephentermine and IV fluids. Bradycardia, defined as heart rate below 55bpm, was treated with IV Atropine 0.3- 0.6mg.

Postoperatively, pain was assessed by using visual analogue scale for pain (VAS) between 0 and 10 (0- no pain, 10- most severe pain). It was assessed every 30 minutes. Patients were allowed to receive rescue analgesic (IV Diclofenac 75mg) on VAS score of 3. This time, i.e., 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 occurrence of adverse effects such as nausea, vomiting, shivering, sedation, respiratory depression and pruritus was observed for and managed appropriately.

Statistical analysis was performed with SSPS (Statistical Package for the Social Sciences) software version 21 (SPSS Inc., Chicago, IL, USA). The quantitative variables were checked for normality using Kolmogorov-Smirnov test. For the quantitative variables following normality, Analysis of Variance (ANOVA) test was used for comparing the groups. Intergroup comparisons were done with Tukey's post hoc test. Kruskal-Wallis H test was used to assess differences among the three groups for the variables not satisfying the assumption of normality and qualitative data as appropriate. Chi-square and Fischer's exact tests were used to check the association between two categorical data. The results were considered as statistically significant for p value <0.05.

Results:

All the groups were comparable with respect to age, weight, sex, ASA status, type and duration of Surgery. (Table. 1)

The duration of analgesia, i.e., time for first rescue analgesia was significantly ($p<0.001$) highest in Group B followed by Group C, and Group A (Figure. 1)

The onset of sensory and motor block was statistically significant among the three groups ($p<0.001$). It was faster in Group B compared to both Group A and Group C but the difference between Group A and Group C is proved to be statistically insignificant ($p>0.05$).

The time to two segment regression was longest in Group C followed by Group B, and

Group A denoting statistically significant difference amongst all the groups ($p<0.001$). The duration of motor block was significantly longer in Group B when compared to Group C, and Group A denoting statistically significant difference among the three groups ($p<0.001$). (Table. 2)

The hemodynamic parameters such as hear rate (HR), mean systolic blood pressure (SBP), mean diastolic blood pressure (DBP) and mean arterial pressure (MAP) were not statistically significant at different time intervals intraoperatively or postoperatively ($p>0.05$). VAS score was statistically significant in the three groups from 30 to 150 minutes. It was highest in Group A followed by Group C and lowest in Group B ($p<0.05$) from 30 minutes postoperatively up to first request for rescue analgesic. The sedation score between the three groups was observed to be statistically insignificant ($p>0.05$) and only two cases in Group B had a four-point sedation score of 2 at 0 and 60 minutes postoperatively.

On comparing the three groups in regards to adverse effects such as nausea, vomiting, hypotension, bradycardia, shivering, respiratory depression and pruritus, the difference was found to be statistically insignificant ($p>0.05$). (Figure. 2)

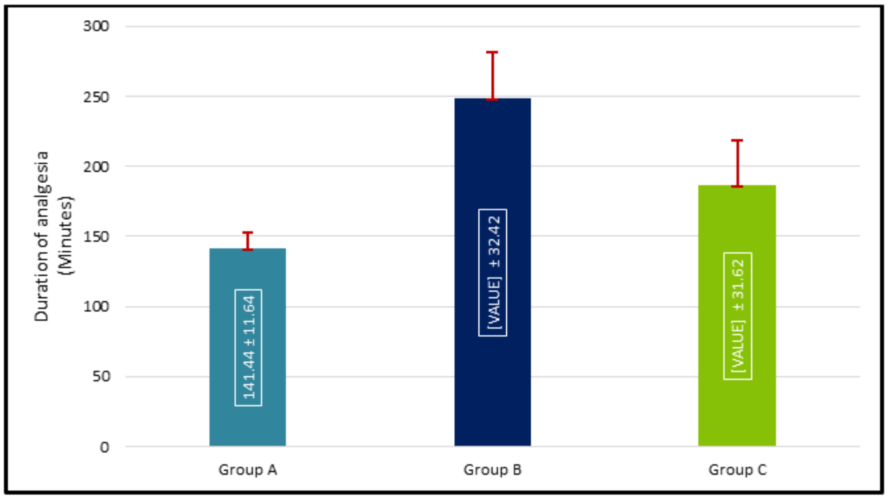

Figure 1: Duration of Analgesia

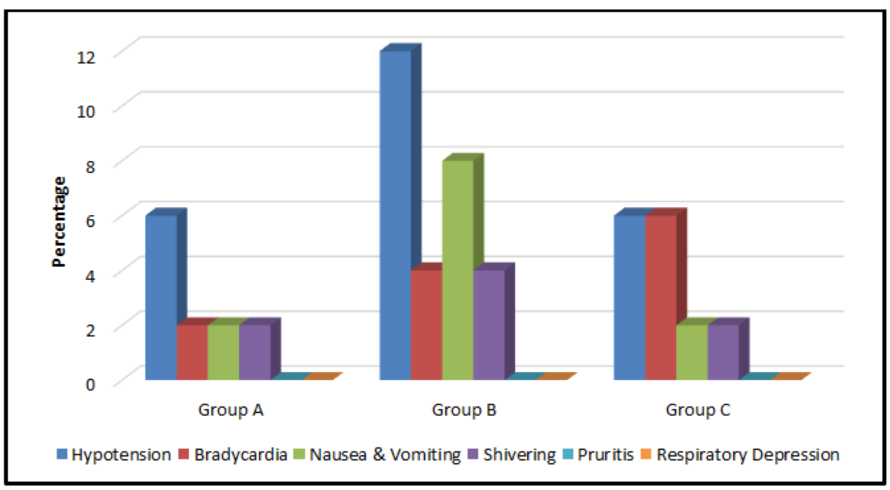

Figure 2: Side effects

Values presented in percentage. Statistical test used: Fisher exact test

Table 1

Variables	Group A	Group B	Group C	p value
Number of cases	50	50	50	-
Age (Years)	41.62 ± 12.77	41.70 ± 10.86	44.82 ± 9.15	0.487* (N.S)
Weight (Kg)	58.36 ± 6.07	58.76 ± 6.03	56.4 ± 6.09	0.069* (N.S)
Height (Cm)	155.68 ± 6.29	155.54 ± 5.19	155.42 ± 4.78	0.972ǁ (N.S)
Sex (No. Male/ Female)	17/ 33	16/ 34	17/ 33	.970** (N.S)
ASA Status (I/ II)	36/ 14	41/ 9	42/ 8	.335** (N.S)
Duration of Surgery (Min)	90.5 ± 0.71	90.08 ± 0.27	90.28 ± 0.70	0.958 ǁ (N.S)
Type of Surgery				
Abdominal Hysterectomy	15 (30%)	20 (40%)	21 (42%)	.614** (N.S)
Myomectomy/ Laparotomy	13 (26%)	14 (28%)	12 (24%)	
Herniorrhaphy	12 (24%)	10 (20%)	13 (26%)	
Appendectomy	10 (20%)	6 (12%)	4 (8%)	

Values presented as Mean ± SD. Statistical test used *Kruskal Wallis H ǁANOVA, **Chi-square test.
Group A: Control, Control B: buprenorphine, Group C: magnesium.
ASA - American Society of Anaesthesiologists; SD - Standard deviation; S - Significant (p <0.05); N.S - Non-Significant (p > 0.05)

Table 2: Characteristics of Spinal Block

Variables	Group A	Group B	Group C	p value (S/ N.S)	Inter- group p value**		
					Group A v/s Group B	Group A v/s Group C	Group B v/s Group C
Mean Duration of Analgesia (Min)	141.44 ± 11.64	248.70 ± 32.42	186.84 ± 31.62	<0.001* (S)	<0.001	<0.001	<0.001
Mean Onset Time of Sensory Block (Min)	4.52 ± 0.99	3.19 ± 1.57	4.54 ± 0.98	<0.001* (S)	<0.001	<0.001	<0.001
Mean Onset Time of Motor Block (Min)	5.03 ± 0.96	4.26 ± 1.46	5.56 ± 0.93	<0.001* (S)	<0.001	<0.001	<0.001
Time to Two Segment Regression (Min)	115.94 ± 14.49	134.82 ± 12.66	146.96 ± 24.89	<0.001* (S)	<0.001	<0.001	<0.001
Mean Duration of Motor Block (Min)	133.06 ± 11.44	195.58 ± 22.76	153.26 ± 25.70	<0.001* (S)	<0.001	<0.001	<0.001

Values presented as Mean ± SD. Statistical test used *ANOVA, **Post hoc tukey test.
Group A: Control, Group B: buprenorphine, Group C: magnesium.
S - Significant (p <0.05); N.S - Non-Significant (p > 0.05)

Discussion:

Pain being a noxious stimulation, should be effectively controlled and is essential to the care of a surgical patient. By doing so, the patient is comfortable, satisfied, mobilizes early, has fewer cardiovascular, haematological and pulmonary complications thus enabling faster recovery and lesser health care cost. [5] When inadequate, it is inhuman, and may result in increased morbidity or mortality. Pain causes release of glutamate and aspartate neurotransmitters, that additionally bind to NMDA receptors and activate it. This leads to calcium and sodium influx into the cell with an efflux of potassium resulting in initiation of central sensitization and wind-up. Our study adjuvant drugs, buprenorphine and magnesium have their own unique properties of countering pain to provide analgesia. Buprenorphine is a centrally acting lipid soluble, partial μ agonist opioid with slow dissociation from the receptors being responsible for its long duration of action. It has both spinal and supraspinal component of analgesia. [6] Magnesium is a non-competitive antagonist to NMDA receptor and produces analgesia by preventing the induction of central sensitization, one of the mechanisms implicated in the persistence of postoperative pain, from peripheral nociceptive stimulation [7]

We have demonstrated that the duration of analgesia, i.e., time to first rescue analgesic postoperatively, was significantly prolonged in buprenorphine and magnesium group compared to control group at 248.70, 186.84 and 141.44 minutes, respectively thus confirming our hypothesis. Kaushik Theerth et al. compared both the adjuvants in the same study and concluded that intrathecal 50mg magnesium sulphate significantly prolonged the time for first analgesic request though to a lesser extent than 150µg buprenorphine, akin to our studies. The probable reason for greater duration of analgesia of buprenorphine compared to other adjuvants, even other lipophilic opiates is due to its high opiate receptor affinity and dose dependent action. (4,8) Rashmi Ravindran et al., Dalai et al., Khandelwal et al. also obtained similar results. (9,10,11)

In our study, onset time of sensory and motor blocks in buprenorphine group were significantly shorter when compared with magnesium or control groups. On comparing magnesium and control groups, there was not a significant difference. This finding is in contrast to Khezri et al., Khalili et al., (12,13) but supported by Hemalatha et al. who demonstrated that post-hoc analysis of onset of sensory and motor blockade showed no statistical difference between control and 50mg magnesium group and concluded that 50mg of magnesium had no effect on onset of sensory block but only 100mg of magnesium resulted in a significant delay in onset of sensory and motor blockade.(14) This difference among the groups can be attributed to buprenorphine's high lipid solubility and higher affinity for opiate receptors(2) and magnesium not particularly being the strongest NMDA receptor blocker, it activates CYP450 hydroxylation of bupivacaine, changes bupivacaine pharmacokinetics due to local vasodilation at injection site. (12,15,16) The mean time to two segment regression in buprenorphine group was only slightly lesser when compared to magnesium group but both groups had a greater difference when compared control group. This result was in contrast to the study carried out by Kaushik Theerth et al., (4) where 50mg magnesium had a lesser time to two segment regressions at 132.17 minutes compared to 150µg buprenorphine at 138.33 minutes, but their results on comparison of the adjuvants to control group were similar to ours. The difference in the results of the two studies could be due to the difference in doses of the drugs and local anesthetic. The mean duration of motor block in both buprenorphine and magnesium groups were significantly longer when compared to control group. This observation in relation to the adjuvant groups and control group is supported by studies done by Hemalatha et al., Kaur et al., Shukla et al., (14,17,18) These findings can be attributed to buprenorphine's nonspecific local anesthetic effect (19) and magnesium ions' ability interfere with normal electrophysiological properties of nerve fibres (15,20) resulting in more pronounced motor blockade than plain bupivacaine.

The hemodynamic parameters namely HR, SBP, DBP and MABP were statically indifferent and comparable in all the groups. The number of cases with complications (Figure.2) was minimal and statistically insignificant among the groups in our study like other studies. (21,22,23) Nausea, vomiting and pruritus of a mild nature was observed to be slightly higher only with 300µg subarachnoid buprenorphine by Ipe et al. (24) and even though higher doses of intrathecal magnesium reported better analgesic efficacy it was at the cost of higher occurrence of adverse effects such as hypotension, nausea and shivering.(25) Ozgodam et al. (26) observed by electron microscopic examination, that intrathecal magnesium sulphate administration induced neurodegeneration in rats but recently intrathecal magnesium has been studied to be safe and with beneficial effects. (27)

The limitation of our study was at VAS score of 3, i.e., time to first rescue analgesic being the therapeutic end point. Twenty-Four hours total analgesic requirements including opioid consumption in the postoperative period could not be documented vigilantly as documented by Khezri et al., (12) who demonstrated that magnesium reduced postoperative opioid consumption. Long term follow-up was not feasible to record possible neurological or other grave deficits.

Studies on comparing the effects intrathecal buprenorphine and magnesium simultaneously are limited. Hence, we wanted to compare and elicit the various above discussed effects of the adjuvant study drugs at lower range doses, from previous other studies, that has proved to potentiate postoperative analgesia without significant hemodynamic changes or complications.

Conclusion:

Even though buprenorphine (60µg) and magnesium sulphate (50mg) proved to be efficient as adjuvants to intrathecal 0.5% hyperbaric bupivacaine in terms of anaesthesia and analgesia with minimal complications intraoperatively and postoperatively, the time to first analgesic request was longer with buprenorphine compared to magnesium sulphate with negligible complications. Hence, we conclude that addition of adjuvant buprenorphine(60µg) has a better demonstrable role in postoperative analgesia compared to adjuvant magnesium (50mg) or 0.5% hyperbaric bupivacaine alone.

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