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Effect of addition of intrathecal preservative free magnesium sulfate with 0.5% bupivacaine heavy and fentanyl with 0.5% bupivacaine heavy on post-operative pain relief in patients undergoing hysterectomy

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ABSTRACT

Background: Spinal anesthesia is the most common neuraxial anesthesia for infraumblical surgeries. The use of various adjuvants has become popular in today's scenario to enhance its quality. **Aims and Objectives:** The aim of this study was to evaluate the onset, duration of sensory and motor block, hemodynamic effects (if any), duration of post-operative analgesia, and adverse effects of fentanyl or magnesium given intrathecally with 0.5% bupivacaine heavy in patients undergoing hysterectomy. **Materials and Methods:** This prospective randomized double-blinded study was conducted in total sixty patients undergoing hysterectomy, divided into two groups of 30 patients each. Group F received 25 µg fentanyl with 3 mL 0.5% bupivacaine heavy and Group M received 100 mg magnesium sulfate with 3 mL 0.5% bupivacaine heavy. The onset and duration of sensory and motor blockade, duration of analgesia, hemodyamics, and side effects were assessed. **Results:** The mean time of onset of sensory and motor block was less in fentanyl ($P<0.001$). Duration of sensory, motor block, and duration of analgesia was more in fentanyl group ($P<0.001$), whereas incidence of side effects such as bradycardia, hypotension, and shivering was less in magnesium. **Conclusion:** Our study concluded that addition of fentanyl as adjuvant effectively augmented the quality of spinal anesthesia, but magnesium provided stable hemodynamics and lesser side effects as compared to fentanyl.

Key words: Fentanyl; Magnesium; Hysterectomy; Spinal anesthesia

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INTRODUCTION

Spinal anesthesia is a safe, reliable, and inexpensive technique with the advantage of providing adequate surgical anesthesia and prolonged post-operative pain relief using various local anesthetic agents. It provides a faster onset and effective sensory and motor blockade.[1]

Several intrathecal adjuvants such as opioids, clonidine, neostigmine, ketamine, magnesium, and benzodiazepines are used to prolong analgesia, improve quality of subarachnoid block (SAB), and to reduce the incidence of side effects.[2]

The addition of intrathecal opioids to spinal anesthesia prolongs sensory blockade without prolonging motor recovery.[3,4]

Fentanyl, a synthetic opioid and µ receptor agonist, is a highly lipid soluble drug. On intrathecal administration, it diffuses into the spinal cord and rapidly binds to

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dorsal horn opioid receptors. This causes rapid onset of analgesia with minimal cephalic spread. Although opioids are associated with many side effects such as respiratory depression, nausea and vomiting, pruritus, urinary retention, and hemodynamic instability,[5] they do not delay motor recovery.[6] It has less risk of delayed respiratory depression.[7]

Magnesium is a N methyl D aspartate (NMDA) antagonist. It blocks NMDA channel in a voltage dependent method. It blocks calcium influx by non-competitive inhibition of inositol triphosphate gated calcium channels.[8] It has been suggested that the NMDA receptor antagonists induce preemptive analgesia when administered before tissue injury occurs,[9] because these can prevent the induction of central sensitization from peripheral nociceptive stimulation.

In this prospective randomized controlled study, we compared intrathecal magnesium sulfate versus fentanyl citrate as an adjuvant to 0.5% bupivacaine heavy in spinal anesthesia for hysterectomy.

Aims and Objectives

Aim

The aim of this study was to compare the block characteristics between intrathecal preservative free magnesium sulfate with 0.5% bupivacaine heavy and intrathecal fentanyl with 0.5% bupivacaine heavy.

Primary objective

The primary of this study was to study and compare the efficacy of fentanyl citrate and magnesium sulfate as an adjuvant to intrathecal 0.5% bupivacaine heavy in terms of onset of motor block.

Secondary objective

The primary of this study were as follows:

1. The time of onset of sensory blockade (up to T8)
2. The duration of sensory blockade (regression to L1) and motor blockade (regression to modified Bromage score 0)
3. Duration of analgesia and intra- and post-operative visual analog scale (VAS) scores
4. Incidence of side effects if any.

MATERIALS AND METHODS

After the Institutional Ethics Committee approval, the study was carried out at G.R. Medical College and JAH group of hospitals during 2020–2022. Sixty patients, belonging to age group of 18–60 years and ASA I and II, were included in our study, who were posted for hysterectomy under spinal anesthesia.

From the study done by Arora et al.,[8] considering average time for onset of motor block as 5 min with standard deviation 1 min in Bupivacaine + Fentanyl group and average time for onset of motor block as 6 min with standard deviation 1 min in Bupivacaine + Magnesium sulfate at 95% confidence interval and 95% power of test, using the formula

$$\nu = (\Sigma_1^2+\Sigma_2^2)\ (Z\%+Z_{1-\beta})^2/(\mu_1-\mu_2)^2$$

Where S_1 = 1min, S_2 = 1 min
μ_1 = 5 min, μ_2 = 6 min
$Z\%$ = 1.96, $Z_{1-\beta}$ = 1.64

Putting these all values in the formula, we obtained n=26, that is, approximate to 30 So 30–30 patients were assigned under each group, so total sample size required for the study was 60.

Patients were randomized into two groups by sealed envelope method based on adjuvant drug received intrathecally. It was a double blinded study (the drug was prepared by other person, and the characteristics of the drug in a pro forma were observed by someone else).

i. Group F (n=30)-3 mL 0.5% heavy Bupivacaine + Fentanyl 25 μg (0.5 mL)
ii. Group M (n=30)-3 mL 0.5% heavy Bupivacaine + 100 mg MgSO4 (0.5 mL).

Inclusion criteria

Patients giving consent, between age 18 and 60 years and belonging to ASA grade I and II, were included in the study.

Exclusion criteria

The following criteria were excluded from the study:

1. Patients with respiratory, cardiovascular, hepatic and renal diseases, obesity, and pregnancy
2. Any bleeding disorder and patient on anticoagulants or local infection.

Pre-anesthetic assessment was done to screen and evaluate major systemic illnesses, informed consent was obtained from all patients included in study, they were explained about spinal anesthesia procedure and educated about using "VAS." All the patients were examined a day before surgery to do complete general, physical, and systemic examination. All the required routine and special investigations were carried out.

All patients were kept nil orally for at least 8 h before the procedure.

On arrival of the patient in the operation theatre, intravenous access with 18 G cannula was inserted into

the patient's forearm. All routine monitors including Pulse oximeter, B.P. cuff, and E.C.G were connected and observations were recorded by multipara monitor. Preloading was done with approximately 10 ml/kg of Ringer's lactate solution.

Under all aseptic precautions, lumbar puncture was done in the left lateral decubitus position at the L2-L3 interspace through midline approach using 25G Quincke spinal needle. SAB was performed, the study drug was injected, and then, the patient was placed in supine position for the remaining of the study period. Intraoperatively, following spinal anesthesia characteristics and outcomes were recorded and entered into pro forma for statistical analysis.

1. The time of onset of sensory blockade (up to T8) was assessed by pin prick method
2. Time of onset of motor blockade was assessed by Bromage scale (up to modified Bromage score 3)
   - 0 = No motor block
   - 1 = Able to bend the knee (hip blocked)
   - 2 = Able to dorsiflex the foot (hip and knee blocked)
   - 3 = Complete motor block (hip, knee and ankle blocked).
3. The duration of sensory blockade was up to regression to L1 and motor blockade was regression to modified Bromage score 0)
4. Duration of analgesia (from induction to administration of rescue analgesic) and intra- and postoperative VAS scores. VAS score was assessed at 1, 2, 3, 4, 5, and 6 h from induction. If >3, rescue analgesia with inj. Tramadol 2 mg/kg i.v.in 100 mL normal saline was given to relieve post
5. Assessment of hemodynamic parameters (Blood pressure [PR], blood pressure systolic [SBP], blood pressure diastolic [DBP], and mean arterial pressure [MAP]) at 0, 15 30, 45, 60, 90 120, and 150 min from induction. Any fall in MAP below 20% of baseline value was treated with bolus dose of inj. Mephenteramine 6 mg i.v. PR <60 beats/min was treated with inj. Atropine sulfate 0.3–0.6 mg i.v.
6. Observation and recording of side effects and complication of the study drugs and technique.

Statistical methods

Data were composed in suitable spreadsheet, that is, EXCEL and Statistical Package for the Social Sciences (SPSS). After compilation of data, it was analyzed statistically by SPSS software version 20.0.

To compare the two groups for the different characteristics of spinal anesthesia, after checking the assumption for the normality, Chi-square test and unpaired t-test were applied. Significance level was 95% confidence level (P<0.05).

RESULTS

As shown in Table 1, age, height, and weight were comparable between the groups, P>0.05 which was statistically insignificant.

As shown in Table 2, onset of sensory and motor blockade was less in Group F, whereas duration of both the blockade and duration of analgesia was more in Group F, P<0.001 which was statistically highly significant. Furthermore, the time for first rescue analgesia (TRA1) was more in Group F (P<0.001).

Figure 1 shows that the mean pulse rate was comparable between the groups, P>0.05 which was statistically insignificant.

Figure 2 shows that the mean arterial pressure was comparable between the groups, P>0.05 which was statistically insignificant.

Figure 3 shows that the mean VAS score was less in Group F (P<0.001, statistically highly significant), but since the rescue analgesia was administered early in Group M, at 5th and 6th h Vas score was more in Group F.

Figure 4 shows that the TRA1 was more in Group M, P<0.001 which was statistically highly significant.

Figure 5 shows that the incidence of side effects such as nausea, hypotension, bradycardia, and shivering were more in Group F.

DISCUSSION

In present day practice, anesthesiologists are also involved in effective pain management post-operatively. Spinal

Table 1: Demographic profile (mean±SD) associated with the groups

Demographic parameter	Group F (n=30)	Group M (n=30)	P-value
Age (years)	47.23±9.99	43.9±10.56	0.214
Height (in cm)	152.26±3.33	153.03±3.24	0.370
Weight (in kgs)	65.87±6.5	65.93±9.54	0.975

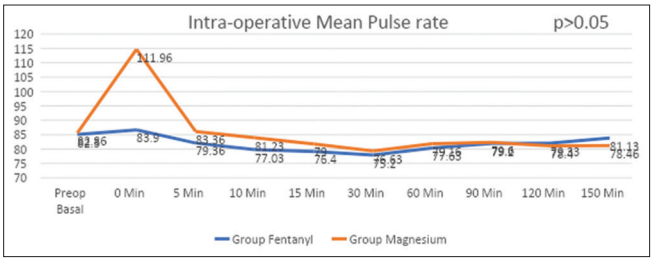

Figure 1: Intraoperative mean pulse rate

Table 2: Parameters of spinal anesthesia

Parameters	Group F (n=30)	Group M (n=30)	P-value
Onset of sensory block (min)	1.96±0.22 min	3.78±0.21 min	<0.001
Onset of motor block (min)	3.03±0.29 min	5.28±0.34 min	<0.001
Duration of sensory block (min)	241.06±23.55 min	184.33±18.26 min	<0.001
Duration of motor block (min)	212.93±20.81 min	137.2±26.95 min	<0.001
Duration of analgesia (min)	317±18.59 min	214.26±11.38 min	<0.001
Time for first rescue analgesia (hour)	5.83±0.37	3.45±0.51	<0.001

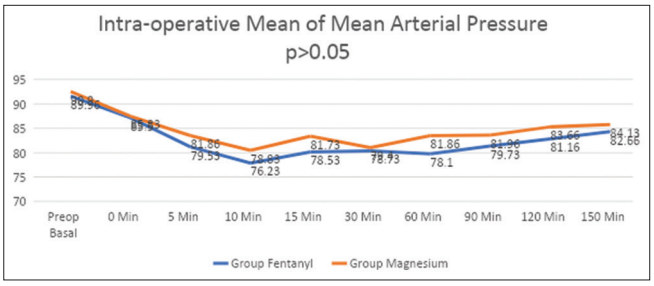

Figure 2: Intraoperative mean arterial pressure

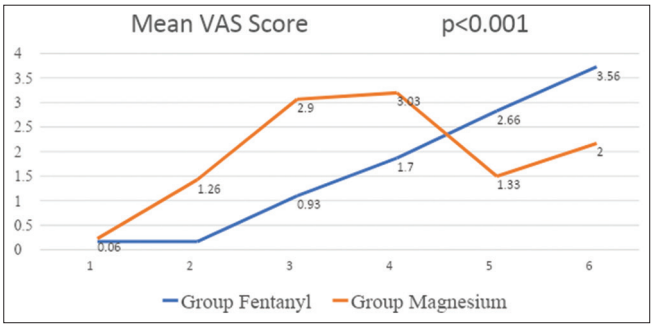

Figure 3: Mean visual analog scale score

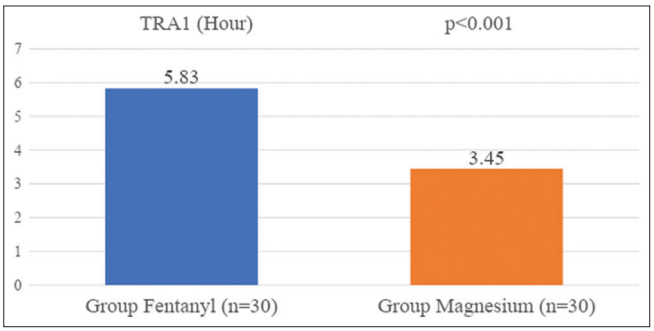

Figure 4: Time for first rescue analgesia (TRA1)

anesthesia is most popular as it is safe, has a rapid onset of action, provides excellent operating conditions, and is also economical.

In the present study, the demographic variables were comparable between both the groups and were statistically insignificant (P>0.05) similar to the studies of Atallah et al.,[10] and Boucher et al.,[11] (Table 1).

The onset of sensory block with Group F was faster as compared to Group M which was statistically significant

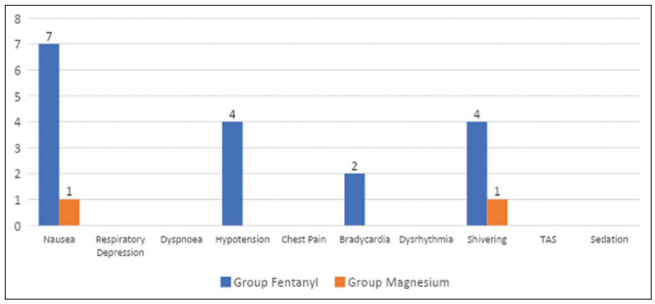

Figure 5: Side effects

with "P"<0.001 (Table 2). The onset of motor block-modified Bromage score 3 in Group F was also rapid as compared to Group M, it was statistically significant with "P"<0.001 (Table 2). Khezri et al.,[12] in their study, also concluded that addition of magnesium sulfate significantly prolonged the onset of sensory and motor blockade, whereas fentanyl had rapid onset. Khalili et al.,[13] also had similar findings in their study. The delayed onset with magnesium is mainly due to change in baricity which leads to slower ascent of the drug. Onset of motor blockade was also delayed with magnesium in study done by Özalevli et al.,[14] and Shashni et al.[15]

The duration of sensory block and motor block in Group F was prolonged as compared to Group M and the difference was highly significant (P<0.001) (Table 2).

Raghu et al.,[16] in their study, also concluded that the duration of sensory and motor block was more in Group F as compared to Group M. Bogra et al.,[17] and Motiani et al.,[18] also have similar increased duration of sensory and motor block with fentanyl in accordance with our study.

Hemodynamic variables (PR, SBP, DBP, and MAP) (Figures 1 and 2) were comparable in our study and the difference was statistically insignificant (P>0.05). In accordance with our study, they were also comparable in studies done by Bharti et al.,[19] and Dobrucali et al.[20]

Duration of analgesia was more in Group F as compared to group M (Table 2), P<0.001 and the difference was highly significant. Singh et al.,[21] Duman et al.,[22] and Techanivate et al.,[23] also had increased duration of analgesia with fentanyl. Magnesium is known to activate P450 isoenzymes

which increase bupivacaine metabolism leading to its shorter duration. The VAS scores (Figure 3) were lower in Group F, and thus, the time for first rescue analgesia (Figure 4) was more than Group M. Due to administration of rescue analgesia, VAS score was lower in Group M at 5th and 6th h as compared to Group F. Similar findings were seen in studies done by Khezri et al.,[12] and Raghu et al.,[16] where lower VAS score was seen with fentanyl as compared to magnesium.

The incidence of side effects (Figure 5) were compared, patients in Group F experienced nausea (n=7.23.3%), bradycardia (n=2.6.7%), hypotension (n=4.13.3%), and shivering (n=4.13.3%), whereas, in magnesium, only 1 patient had nausea and shivering. Magnesium is known to reduce the incidence of shivering and it also has inhibitory effect on nausea and vomiting. The findings of our study were in accordance with the studies of Katiyar et al.,[24] Hemalatha et al.,[25] Singh et al.,[26] and Banihashem et al.,[27] where magnesium had lesser side effects and more hemodynamic stability.

Limitations of our study

The major limitation of our study was that the investigator was unable to objectively quantify and evaluate post-operative pain which being a subjective experience can be a major limiting factor in comparing and estimating the effectiveness of various modalities of treatment.

CONCLUSION

Fentanyl as an adjuvant potentiated the onset and improved the duration of spinal anesthesia,[22,28] but it has some side effects such as nausea, bradycardia, and hypotension. Magnesium, on the other side, delayed the onset and had lesser duration of analgesia, but it provided more hemodynamic stability and had lesser side effects.[29]

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NT- Concept and design of the study, prepared first draft of manuscript; **AG**- Interpreted the results; reviewed the literature and manuscript preparation; **NJ**- Concept, coordination, statistical analysis and interpretation; **MMJ**- Preparation of manuscript and revision of the manuscript.

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