

## Comparative study between magnesium sulphate and fentanyl as an adjuvant to intrathecal bupivacaine for patients undergoing lower limb orthopaedic surgery

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### Abstract

**Background and Aim:** Spinal anaesthesia is widely used for lower limb orthopaedic surgery. A number of adjuvants are added to maximize quality of anaesthesia, effective analgesia and to overcome the side-effects associated with local anaesthetic agents are used. This study has been carried out to evaluate onset of sensory and motor block, duration of block, analgesic efficacy, intraoperative hemodynamic parameters and side-effects of magnesium sulphate and fentanyl when used as an adjuvant to intrathecal bupivacaine in lower limb orthopaedic surgery. **Methods:** This prospective, randomized double blind study was conducted in 100 patients of either sex, ASA I and II, posted for lower limb orthopaedic surgeries. The patients were randomly allocated into two equal groups: Group M-Bupivacaine 15mg (0.5% heavy) with 50 mg magnesium sulphate. Group F-Bupivacaine 15mg (0.5% heavy) with 25µg Fentanyl. The time of onset of sensory and motor blockade, duration of blockade, duration of analgesia, haemodynamic parameters and side-effects were recorded. The data was analysed using chi-square test, paired 't' test and ANOVA test. **Results:** Magnesium caused a significant delay in onset of both sensory and motor blockade as compared to fentanyl ( $p < 0.001$ ). There was insignificant difference in duration of sensory and motor block in both the groups. Mean time of rescue analgesia was comparable among both the groups. In Group M, there was less incidence of intraoperative hemodynamic fluctuation as compared to Group F. **Conclusion:** Addition of magnesium sulphate to intrathecal bupivacaine significantly prolonged the onset of sensory and motor blockade as compared to the fentanyl. Magnesium sulphate provided more stable hemodynamic profile than fentanyl with fewer side-effects.

**Key words:** Spinal anesthesia, Bupivacaine, Magnesium sulphate, Fentanyl, Lower limb orthopaedic surgery.

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### I. Introduction

Spinal anesthesia is commonly used for lower limb orthopedic surgery. Conventional bupivacaine has short duration of action, so adjuvants are being added to improve the outcome of spinal anesthesia.

Fentanyl, a lipophilic agent, binds to dorsal horn receptors to produce rapid onset of analgesia with minimal cephalic spread<sup>[1]</sup> also reduces the dose of local anaesthetic agents. Magnesium is a NMDA-blocker, induces preemptive analgesia, prolongs spinal block and improves postoperative analgesia<sup>[2,3]</sup>.

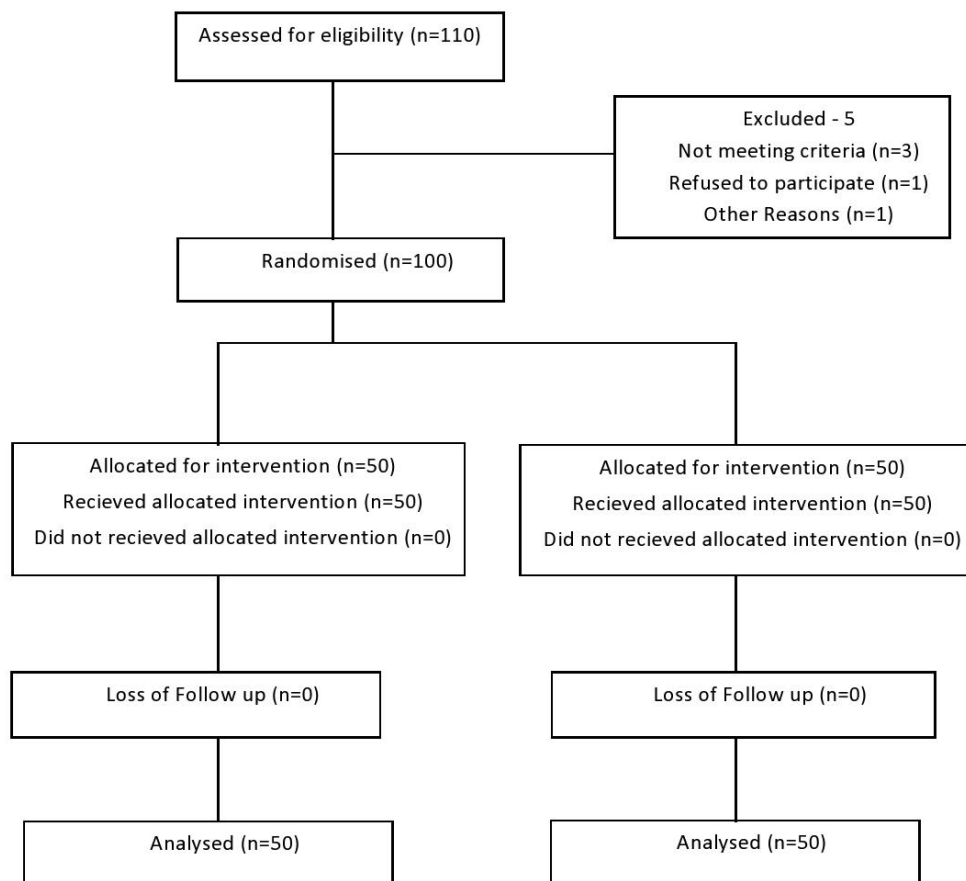
In this study, we have compared the efficacy of magnesium sulphate and fentanyl as an intrathecal adjuvant to bupivacaine in patients undergoing lower limb orthopedic surgery.

### II. Material And Methods

This prospective, randomized, double blind clinical study was conducted on 100 patients posted for lower limb orthopedic surgery under spinal anesthesia at Indira Gandhi Institute of Medical Sciences, Patna, after obtaining Institutional research and ethical committee approval and registered at www.clinicaltrials.gov, under the number (CTRI/2018/02/012149). After obtaining informed consent, 100 patients of age group 18-60 years of either sex with American Society of Anesthesiologist (ASA) physical status I or II and height 150-180 cm, scheduled for lower limb orthopedic surgery were studied. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting the randomized clinical trial is in figure.1. The patients were randomly allocated into 2 equal groups: Group M (magnesium sulphate) - In this group, 50 patients received intrathecal 3ml=15mg Bupivacaine (0.5% hyperbaric solution) combined with 0.1 ml of 50% (50mg) magnesium sulphate.

Group F (Fentanyl) - In this group, 50 patients received intrathecal 3ml=15mg Bupivacaine (0.5% hyperbaric solution) combined with 0.5 ml (25mcg) fentanyl.

Exclusion criteria - patient's refusal, patients with any contraindication to regional anesthesia such as skin infection, bleeding disorder, neurological disease etc., patients with uncontrolled hypertension, opium addiction or history of any sedative drug consumption on regular basis, any history of allergy to study drugs and patients with any cardiac, pulmonary, hepatic or renal diseases. Each patient was taught how to use Visual Analog Scale (VAS); graded 1-100 mm, from 0 = No pain to 100= worse pain imaginable pre-operatively. All patients fasted overnight and premedication was omitted. Blinding was achieved by random selection of patient by lottery system and preparation of drug with unique code of identification on syringe. On arrival of patient in the operating room, intravenous line was secured and continuous monitoring of non-invasive blood pressure, heart rate, ECG and arterial oxygen saturation was started. All patients were pre-loaded with crystalline solution i.e. Ringer's lactate solution intravenously (15ml/kg), 15 minutes before induction of anesthesia through 18G peripheral IV-cannula. Base line hemodynamic parameters were recorded.



The subarachnoid block was performed under strict aseptic condition with patient in the sitting position at L3-L4 level, by midline approach, using 25G disposable quincke's spinal needle. After ensuring free flow of cerebrospinal fluid, the study drug was slowly instilled into the subarachnoid space according to the group of the patients and time was recorded. After spinal injection, each patient was placed supine with a pillow to support the head and shoulders. The oxygen was delivered at the rate of 4-5 L/min via facemask. Observation and assessment of sensory and motor block, duration of blockade, oxygen saturation, incidence of hypotension, bradycardia, postoperative analgesic requirement and adverse events such as sedation, pruritus, nausea, vomiting, were recorded. Sensory block was assessed by a pin-prick test. The onset of sensory block was defined as the time between the end of injection of the intrathecal anesthetic drug and the absence of pain at the T10 dermatome. The duration of sensory block was defined as the time for regression of two segments from the maximum block height evaluated by pin prick. The maximal level of sensory block was evaluated by pin prick 20 minutes after the completion of injection. Motor block was assessed by the modified Bromage score (0= nomotor loss; 1= inability to flex the hip; 2= inability to flex the knee; and 3=inability to flex the ankle). The onset of motor block was defined as the time from intrathecal injection to Bromage block 1, whereas the duration of motor block was assumed when the modified Bromage score was 0. In this study, the postoperative analgesia in terms of definition was time to first requirement of analgesic supplement from the time of injection. Pain assessment was done by Visual Analogue Scale. No additional analgesic was administered unless requested

by the patient. If the SBP was 20% below the baseline (measured in the ward) or less than 60 mmHg, Mephentramine 6 mg was administered intravenously. Also, if the HR was less than 60 beats/minute, a dose of 0.5 mg of atropine sulfate was administered intravenously.

The data was analyzed using SPSS package (Stat, version 23.0 SPSS INC, Chicago, IL, USA) for windows. The data were presented as descriptive statistics for continuous variables and percentage for categorical variables and was subjected Chi-square test, paired t test & ANOVA test.

### III. Result

Among 110 patients initially enrolled in this study, 10 patients had to be excluded because of logistical reasons or violations of the study protocol. Total 100 patients were included and randomly assigned for intervention (Fig.1).

The two study groups were comparable with respect to demographic characteristics, presented in Table.1.

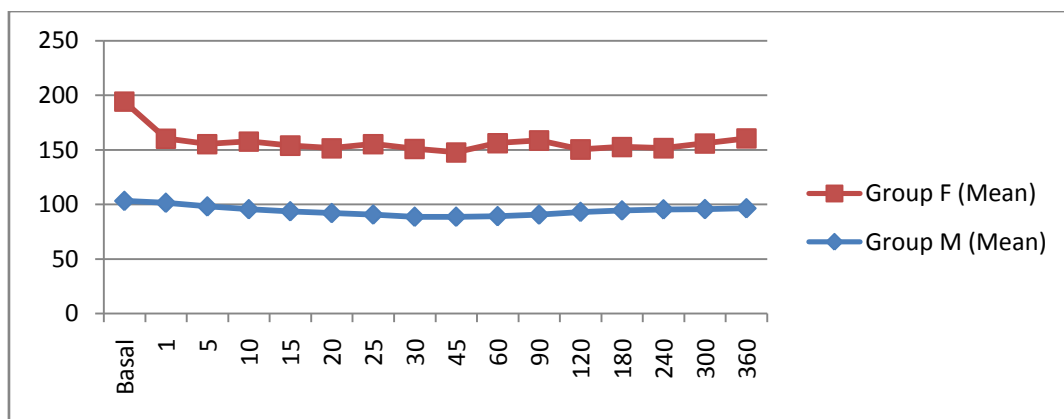
**Table 1:** Demographic data. Values presented as numbers, mean  $\pm$  SD. M = Magnesium group F = Fentanyl group

	Group M (n=50)	Group F (n=50)	p
Mean Age (years)	32.82	37.8	0.61
Sex (F/M)	10/40	14/36	0.35
Mean Height (cm)	159.34	149.2	0.36

**Table 2:** Characteristics of spinal anesthesia, Data are shown as mean  $\pm$  SD.

	Group M (n=50)	Group F (n=50)	p
Onset time of sensory block (min)	4.97 $\pm$ 1.02	1.52 $\pm$ 0.62	< 0.001
Duration of sensory block (hours)	6.27 $\pm$ 0.51	5.29 $\pm$ 0.34	0.235
Onset time of motor block (min)	6.71 $\pm$ 1.53	2.19 $\pm$ 0.48	< 0.001
Duration of motor block (hours)	5.01 $\pm$ 0.67	4.32 $\pm$ 0.39	0.201
Mean time of rescue analgesia (min)	230.4 $\pm$ 28.28	259.4 $\pm$ 34.05	0.121

As shown in Table.2 mean time of onset sensory block in Group M was 4.97  $\pm$  1.02 minutes and Group F was 1.52  $\pm$  0.62 minutes. On comparing these values, significant difference was found (p value = <0.001). Also, there was a significant difference in onset time of motor block between groups M, 6.71  $\pm$  1.53 minutes and F, 2.19  $\pm$  0.48 minutes (P<0.001). The difference in duration of sensory block time (p = 0.235) and motor block time (p = 0.121) between the two groups was insignificant. Moreover, no significant difference was found in mean time of rescue analgesia in both the groups (p = 0.121).



**Fig.2** shows intraoperative and postoperative mean heart rate variation in between Group M and Group F.

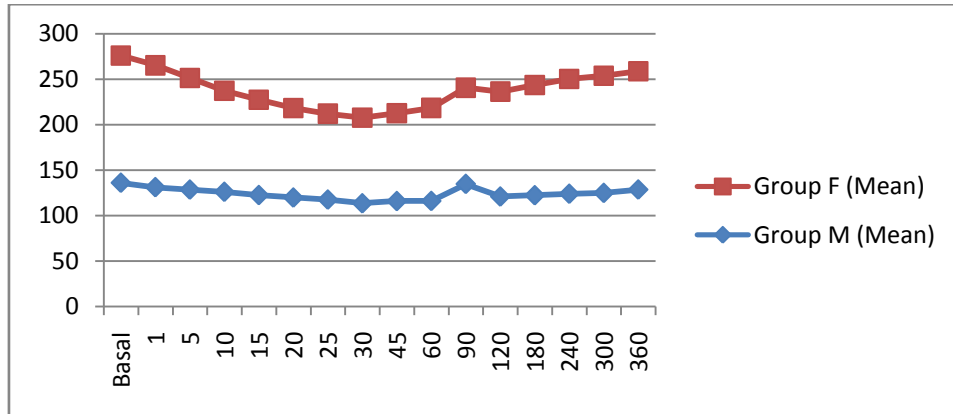


Fig.3 shows mean systolic blood pressure (mm Hg) in study groups at different time interval.

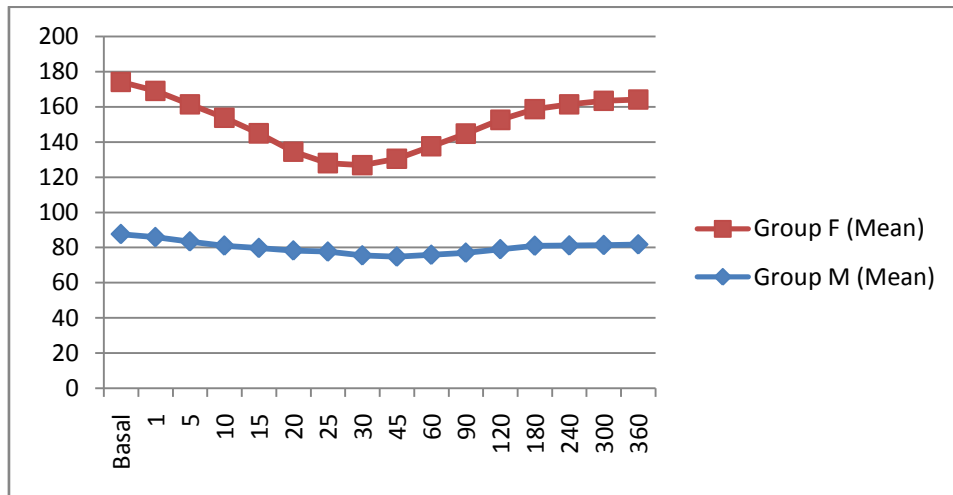


Fig. 4 shows mean diastolic blood pressure (mm Hg) in study groups at different time interval

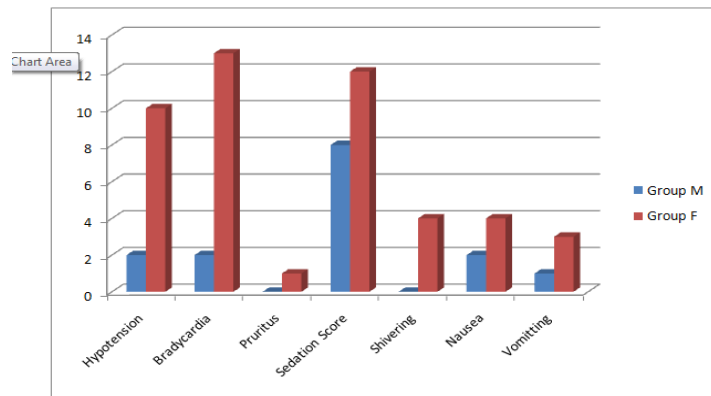


Fig 5 shows different side-effects of Group M and Group F

Table.3 Incidence of Side- effects

Side-effects	Group M		Group F		p- value
	No	percentage	No	Percentage	
Hypotension	2	4%	10	20%	< 0.001
Bradycardia	2	4%	13	26%	<0.001
Pruritus	NIL	0	1	2%	0.25
Sedation score 2	8	16%	12	24%	0.34

Shivering	0	0	4	8%	0.22
Nausea	2	4%	4	8%	0.65
Vomiting	1	2%	3	6%	0.54

Table. 3 shows, the various side-effects found in study groups. The incidence of hypotension and bradycardia are more in Fentanyl group as compared to the magnesium group and p-value < 0.001 ie found highly statistically significant.

In addition, no statistically significant difference in Spo2 values between two groups was demonstrated.

There was no report of postdural puncture headache after surgery and also no patient in either group with any sensory or motor complications was identified.

#### IV. Discussion

In lower limb orthopedic surgery, postoperative pain is moderate to severe and is associated with neuroendocrine responses, catecholamine release and increase morbidity<sup>[4,5]</sup>. Neuraxial blocks are most commonly accepted technique for lower limb orthopedic surgery. It is safer than general anesthesia by avoiding problems, like polypharmacy, airway manipulations and pulmonary complications. It gives both intra and post-operative pain relief with full preservation of mental status and normal reflexes. Subarachnoid block is preferred over epidural route, because of its rapid onset, good density block, lower failure rates in experienced hands, no catheter related complications and cost-effectiveness<sup>[6]</sup>. But, spinal anesthesia have some limitations like; shorter duration of action and inability to extend the analgesia postoperatively because conventional spinal anesthesia using hyperbaric bupivacaine alone is relatively shorter duration of action. A number of Intrathecal adjuvants have been added to prolong the duration and quality of block, increase postoperative analgesia and helps early recovery and rehabilitation<sup>[7,8]</sup>.

Fentanyl,  $\mu$ -opioid receptor agonist, is a lipophilic and rapidly diffuses into the spinal cord and binds to dorsal horn receptors rapidly, when administered intrathecally. This produces a rapid onset of analgesia with minimal cephalic spread .The profound segmental antinociception produced by neuraxial opioids in doses is much smaller than that would be required for comparable antinociception, if administered systemically. They improve the quality of intraoperative anesthesia, reduces doses of local anesthetic agents, provide faster onset of surgical block and prolong the duration of postoperative analgesia. But, co-administration of opioid with bupivacaine is associated with significant side effects such as pruritus, hemodynamic instability, respiratory depression, urinary retention, nausea and vomiting.

Central sensitization depends upon the activation of dorsal horn N-methyl-D-aspartate (NMDA) receptors by excitatory amino acid neurotransmitters such as aspartate and glutamate<sup>[9,10]</sup>. Magnesium blocks NMDA-channels in a voltage-dependent manner. It induces preemptive analgesia, because these can prevent the induction of central sensitization from peripheral nociceptive stimulation<sup>[11,12]</sup>. Additionally, magnesium sulphate have anti-inflammatory property<sup>[13]</sup> and physiological calcium channel blocker. Its anti-nociceptive effects seen in rats<sup>[14,15]</sup>.Magnesium sulphate when administered intrathecally in low doses prolong spinal block, less hemodynamic instability and improve postoperative analgesia<sup>[16,17]</sup>.

The results of our study showed that the addition of 50 mg Magnesium sulphate to 15 mg spinal bupivacaine (0.5%) hyperbaric prolonged the onset time of sensory and motor blockade without prolonging the duration of spinal anesthesia. This finding is in agreement with the previous report by **Khezri et al**<sup>[16]</sup>, they evaluated that magnesium sulphate delays onset of sensory & motor block, when given intrathecally as an adjuvant to bupivacaine for lower limb orthopedic. They found that onset of sensory block in Group M was (5.86±1.25) minute and Group F was (1.46±0.57) minute. p-value <0.001, ie highly significant. Onset of motor block in Group M was (8.10±1.90) minutes, in Group F was (2.46±0.57) minutes, p-value < 0.001 ie highly significant. Our result is also supported by **Rajesh Vasure et al**<sup>[17]</sup>. **Rajmala Jaiswal et al**<sup>[18]</sup> concluded that intrathecal magnesium along with bupivacaine for spinal anaesthesia modifies the quality of sensory block. **Arcioni et al**<sup>[19]</sup> also observed that intrathecal and epidural magnesium sulfate potentiated and prolonged motor block. The authors suggested that the difference in pH and baricity of solution by addition of magnesium contribute to delayed onset. Also, increase in metabolism of bupivacaine due to the activation of Cytochrome P450 by magnesium may be responsible for delayed onset. Other possible cause may be magnesium sulphate vasodilates the tissue around the injection site, will eventually accelerate the systemic uptake of local anesthetic, thereby prolonging the onset time of block.

We observed that the onset of sensory and motor block was directly related to the dose of magnesium sulfate used and with an increase in dose, the onset was delayed. These results were also reported by **Ozalevli et al**<sup>[20]</sup> when adding intrathecal magnesium to fentanyl and isobaric bupivacaine and **Malleeswaran et al**<sup>[21]</sup> who used hyperbaric bupivacaine as in the present study and both explained this delay by the difference in pH and

baricity of the solution containing magnesium. Our study is in contrast to the study conducted by **Olanrewaju N, Akanmu et al**<sup>[22]</sup> who found that by adding magnesium sulphate, there was no effect of onset of motor block.

Duration of sensory and motor block was prolonged in Group M as compare to the Group F, it was statistically insignificant. Our finding is concordance with study conducted by **Mridu Paban Nath et al**<sup>[23]</sup> and **Ali E. Rashad and Emad El-Hefnawy**<sup>[24]</sup>.

The mean time of rescue analgesia in Group M was (230±28.28) minutes & Group F, was (259.4±35.05); (Table 9), p-value=0.121. Hence, although, time of first analgesic requirement was more in Fentanyl group but it is insignificant. Some study suggested that intrathecal magnesium failed to reduce the severity of postoperative pain and the cumulative analgesic consumption. **Khezri et al**<sup>[16]</sup>, demonstrated that the addition of MgSO<sub>4</sub> (50 mg) to 15 mg of spinal bupivacaine (0.5%) failed to prolong the time to first analgesic requirement, as seen with fentanyl and bupivacaine combination. **Dayioglu et al**<sup>[25]</sup>, also concluded that addition of magnesium sulfate(50mg) to spinal anesthesia prolonged the time to first analgesic requirement, but postoperative analgesic consumption was not reduced. Our finding is also supported by **Unlugenc et al**<sup>[26]</sup>.

The mean oxygen saturation remained stable at all time interval among the study group ranges between 98-100%.

Analysis of intraoperative hemodynamic showed that the incidence of hypotension and bradycardia was more in fentanyl group as compared to magnesium group p-value was <0.001 ie highly significant. Our study is consistence with result of study conducted by **Khezri et al**<sup>[16]</sup>. They found significant difference in occurrence of hypotension episodes between groups F and M (p = 0.001). **katiyar et al**<sup>[27]</sup>, showed magnesium provides better hemodynamic stability than fentanyl with fewer side effects. They found that haemodynamic parameters (HR, SBP, DBP) decreased by more than 20% in fentanyl group. **Maridu Paban Nath et al**<sup>[23]</sup>, also found addition of 100mg intrathecal magnesium reduces incidence of side effects. **Rajesh Vasure et al**<sup>[17]</sup>, found addition of magnesium sulfate provide, a more stable hemodynamic profile and causes less side effects.

Although, there was less incidence of other adverse events; like Pruritus, Sedation, Urinary retention, Nausea, Vomiting, shivering; in Group M as compared to Group F, there was no significant difference found.

Moreover, intravenous magnesium has been shown to suppress postoperative shivering. The drug not only exerts a central effect but is also a mild muscle relaxant.

## V. Conclusion

Based on the data found in our study, it could be concluded that addition of magnesium sulphate (50mg) intrathecal to 15 mg hyperbaric bupivacaine (0.5%) in spinal anesthesia prolonged the onset time of sensory and motor blockade without prolonging the duration of spinal anesthesia. Furthermore, magnesium administration could provide a more stable hemodynamic profile, lower the ambulation time and cause less side effects as compared to fentanyl.

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