

# Effect of Addition of Magnesium Sulphate to Fentanyl and Hyperbaric Bupivacaine in Spinal Anaesthesia for Abdominal Hysterectomy: A Randomised Clinical Study

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## ABSTRACT

**Introduction:** Subarachnoid block is the most acceptable and popular mode of anaesthesia for gynaecological surgeries. Addition of opioids to intrathecal bupivacaine is routinely practised. Magnesium sulphate ( $MgSO_4$ ), when used intrathecally has an advantage in preventing central sensitisation to peripheral nociceptive pain because it is an N-Methyl-D-Aspartate Receptor (NMDA) antagonist.

**Aim:** To find out the efficacy of  $MgSO_4$  as intrathecal additive to combination of fentanyl and hyperbaric bupivacaine in prolonging duration of analgesia.

**Materials and Methods:** This randomised clinical study was done between June 2022 to November 2022 in women of American Society of Anaesthesiologists (ASA) grade I and II aged 50 to 70 years scheduled for abdominal hysterectomy under spinal anaesthesia. They were randomly divided into two groups of 30 each (group 'S' and group 'M'). Group 'S' received spinal anaesthesia with 3 mL (15 mg) of hyperbaric bupivacaine, 0.5 mL (25 µg) of Fentanyl and 0.1 mL of 0.9% normal saline while group 'M' received 3 mL of hyperbaric

bupivacaine, 0.5 mL (25 µg) of Fentanyl and 0.1 mL (50 mg) of 50%  $MgSO_4$  intrathecally. End points of observation were time for onset of sensory and motor block and duration of analgesia. Data was entered in Microsoft Excel using Statistical Package for Social Sciences (SPSS) version 25.0.

**Results:** Demographic profile was comparable between both the groups. Delay in onset of sensory block was observed in group 'M' ( $9 \pm 0.68$  minutes) compared to group 'S' ( $4.88 \pm 0.47$  minutes) ( $p < 0.001$ ). Similarly, onset of motor blockade too was delayed in group 'M' ( $11.92 \pm 0.71$  minutes) compared to group 'S' ( $6.83 \pm 0.65$  minutes) ( $p < 0.001$ ). Postoperative analgesia was significantly prolonged in group 'M' ( $262 \pm 8.3$  minutes) compared to group 'S' ( $235 \pm 12.3$  minutes) with a p-value of  $< 0.001$ . Haemodynamic profile and side-effects showed no significant difference between both the groups.

**Conclusion:** Addition of  $MgSO_4$  (50 mg) to combination of fentanyl and hyperbaric bupivacaine when given intrathecally prolongs the duration of spinal analgesia significantly in patients undergoing abdominal hysterectomy without significant side-effects.

**Keywords:** Analgesia, Intrathecal additive, Subarachnoid block

## INTRODUCTION

Spinal anaesthesia is the most preferred technique of anaesthesia in patients undergoing gynaecologic surgeries, which provides effective pain relief during intra and early postoperative period. Routinely used intrathecal adjuvants like fentanyl, morphine, clonidine and others have gained popularity for prolonging duration of analgesia [1-5]. Morphine is known for its respiratory depression [5] and clonidine for haemodynamic instability [6] when used as an intrathecal additive. Fentanyl when used as an additive to intrathecal bupivacaine, it was found to have prolonged the duration of analgesia by 20-60 minutes [7]. As there will be a need for dose reduction for intrathecal bupivacaine in older patients undergoing gynaecological surgeries due to anatomical and physiological changes [8,9], the duration of spinal analgesia may be decreased and fentanyl alone as intrathecal additive may not provide adequate prolongation. So, it was thought of using second intrathecal additive.

Magnesium being an NMDA antagonist, blocks NMDA channels and has antinociceptive effects. Magnesium sulphate acts by blocking NMDA channels in voltage dependant fashion and thereby preventing influx of sodium and calcium into the cell, efflux of potassium and initiation of central sensitisation and wind up phenomenon [10,11]. Magnesium sulphate prevents the induction of central sensitisation to peripheral nociceptive pain and blocks the activity of excitatory amino acids such as glutamate and aspartate in the posterior horn of spinal cord by blocking NMDA receptors. The safety of intrathecal

administration has been evaluated and established as effective adjuvant in gynaecological surgeries [12]. A study by Jabalameli M and Pakzadmoghadam SH found no increase in duration of analgesia with 50 mg of  $MgSO_4$  when used as an additive to bupivacaine intrathecally whereas concluded to have increased duration of analgesia when used 100 mg as additive but with side-effects like hypotension, nausea and vomiting [13]. Fentanyl is a highly lipophilic, potent, short acting and synthetic opioid. So, fentanyl is added to local anaesthetics as adjuvant for postoperative analgesia in neuraxial block [14]. In this study, it was hypothesised that by adding 50 mg of  $MgSO_4$  to the combination of fentanyl and hyperbaric bupivacaine intrathecally may prolong duration of analgesia as compared to adding fentanyl or  $MgSO_4$  alone.

## MATERIALS AND METHODS

A randomised, single blinded clinical study was done in a tertiary care centre, Davangere, Karnataka for a period of six months from June 2022 to November 2022 after obtaining Institutional Ethical Committee Clearance (IEC) (ECR/731/Inst/KA/RR-18).

**Inclusion criteria:** A total of 60 women of ASA grade I and II aged between 50 to 70 years scheduled for abdominal hysterectomy under spinal anaesthesia were included in the study.

**Exclusion criteria:** Patients with co-existing neuromuscular disease, having contraindications for neuraxial blockade, mentally challenged, history of allergy to study drugs were excluded from the study.

**Sample size:** Sample size of 60 was estimated considering the prevalence of hysterectomy in India to be 3.2% [15]. Formula used for sample size calculation.

$$n = \frac{Z^2 pq}{d^2}$$

where,

Z: Standard normal deviation equal to 1.96 at 5% level of significance with 95% confidence level.

p: prevalence=3.2% [15]

q=100-p=100-3.2=96.8%

d=allowable error=5%

Computing using above values in the formula, the calculated sample size was 48. Considering the non response rate as 20%, the sample size was 57.6 which was rounded off to 60. These 60 cases were divided into two groups of size 30 each [Table/Fig-1].

After thorough preanaesthetic evaluation, patient who met inclusion criteria were explained about the study procedure, then written informed consent was obtained. Nil per oral guidelines were followed.

On the day of surgery, patients were shifted to Operation Theatre (OT) Table, i.v. access was obtained at proper site and i.v. fluid was initiated. Baseline vitals like Blood Pressure (BP), Pulse Rate (PR), Pulse Oximeter (SPO<sub>2</sub>), Electrocardiogram (ECG) were recorded. In left lateral position using midline approach with aseptic precautions, lumbar puncture was done at L<sub>3-4</sub> intervertebral space by using Quincke spinal needle (25 G) and subarachnoid block was instituted with 3 mL (15 mg) 0.5% hyperbaric bupivacaine plus 0.5 mL (25 µg) of Fentanyl and one of the adjuvants of 0.1 mL as per designated group using computer generated randomisation table [13].

Group S: 0.1 mL containing normal saline was added.

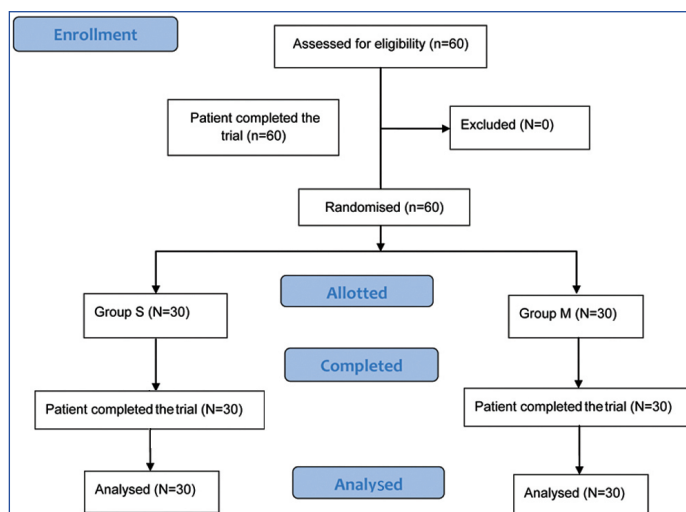
Group M: 0.1 mL (50 mg) of 50% magnesium sulphate was added [13].

Patient's vitals were monitored continuously using Non Invasive Blood Pressure (NIBP), SPO<sub>2</sub> and ECG. These parameters were observed and recorded every five minutes for first 15 minutes and every 15 minutes till the end of surgery and every 30 minutes in postoperative period till complete recovery from sensory and motor block. Assessment of sensory block was done by pinprick test. The onset of sensory blockade (as defined by time from intrathecal injection to absence of pain at T8 dermatome) was recorded. The highest level of sensory block was noted [13].

Assessment of motor blockade was done using Modified Bromage scale (0=able to lift legs against gravity, 1=able to flex knee but unable to flex leg, 2=able to move feet but unable to flex knee, 3=unable to move any joint) [16]. The onset of motor blockade was defined as time from intrathecal injection to modified bromage scale score 3 [17]. Duration of analgesia was defined as the time from the intrathecal injection to request of rescue analgesia (injection diclofenac 75 mg I.M). Rescue analgesic was avoided until demanded by the patient. Pain intensity was assessed using Visual Analogue Scale (VAS). VAS was recorded after the end of surgery and at 3, 4 and 5 hours thereafter. (0-2=No pain, 2-4=mild pain, 4-6=severe pain, 6-8=very severe pain, 8-10=worst pain possible). Side-effects like hypotension, bradycardia, vomiting, pruritis was attended as and when required.

## STATISTICAL ANALYSIS

The ASA physical status was analysed by Chi-square test, demographic data using unpaired t-test. Analysis of quantitative data was done using Student's t-test and qualitative data like side-effects was analysed using unpaired t-test using SPSS software version 25.0 A p-value <0.05 was considered significant.



[Table/Fig-1]: Consort flow diagram.

## RESULTS

Sixty subjects were enrolled in the study, with 30 patients in each group. ASA physical status is represented in [Table/Fig-2] and there was no significant difference between both the groups. The demographic data is depicted in [Table/Fig-3] and there was no significant difference between groups.

ASA	Group S, n (%)	Group M, n (%)	$\chi^2$	p-value
ASA-I	21 (70)	23 (76.67)	0.3409	0.5593
ASA-II	9 (30)	7 (23.33)		

[Table/Fig-2]: ASA physical status.

Parameter	Group S	Group M	t	p-value
	Mean±SD	Mean±SD		
Age (years)	46.4±9.8	45.8±7.5	0.25	0.80, NS
Height (cm)	154.40±5.25	155.33±5.01	-0.70	0.48, NS
Weight (Kg)	54.20±8.49	55.60±8.16	-0.65	0.52, NS

[Table/Fig-3]: Demographic profile.

The mean time for onset of sensory block, motor block and the duration of analgesia is depicted [Table/Fig-4]. The onset of motor blockade was also delayed in group 'M' (11.92±0.71 minutes) compared to group 'S' (6.83±0.65 minutes) (p-value <0.001). The mean time for sensory block, motor block was significantly higher in the group with magnesium sulphate (p-value <0.001).

Parameter	Group S	Group M	t	p-value
	Mean±SD	Mean±SD		
Sensory block (min)	4.88±0.47	9.00±0.68	-27.26	<0.001, HS
Motor block (min)	6.83±0.65	11.92±0.71	-29.01	<0.001, HS
Duration of analgesia (in mins)	235.20±12.30	262.8±8.3	-10.21	<0.001, HS

[Table/Fig-4]: Onset of sensory block, motor block and duration of analgesia. Unpaired t-test, p<0.05: significant, p<0.001: HS: Highly significant

At five hours, the mean VAS scores were not significant between the groups. However, at four hours, VAS score was significantly lower in the magnesium sulphate group (p-value=0.0001). The mean VAS scores at different intervals is depicted in [Table/Fig-5]. Side-effects between both the groups is presented in [Table/Fig-6].

## DISCUSSION

In this study, it was found out that addition of MgSO<sub>4</sub> to combination of intrathecal local anaesthetic and opioid was efficient in prolonging duration of analgesia. This result was comparable with a study by Ozalevi M et al., who studied efficacy of MgSO<sub>4</sub> as an intrathecal additive in lower extremity surgeries [17]. Inadequate management of acute postoperative pain was found to have negative impact

VAS	Group S		Group M		p-value
	Mean±SD		Mean	SD	
Intraoperative	0.03±0.18		0.03±0.18		1.00, NS
3 h	0.1±0.25		0.73±1.05		0.001*, HS
4 h	4.62±0.68		3.65±0.9		0.0001, HS
5 h	6.47±0.86		6.70±0.70		0.25, NS

**[Table/Fig-5]:** Visual Analogue Scale (VAS Score).

Unpaired t-test, p≤0.05: significant, p≤0.001: HS: Highly significant

Side-effects	Group S n (%)		Group M n (%)		Z	p-value
Nausea	4	(13.3)	3	(10)	0.39	0.6891
Vomiting	4	(13.3)	3	(10)	0.39	0.6891
Pruritus	7	(23.3)	5	(16.7)	0.66	0.5157
Hypertension	6	(20)	9	(30)	-0.89	0.3734
Bradycardia	7	(23.3)	5	(16.7)	0.66	0.5157
Shivering	4	(13.3)	2	(6.7)	0.85	0.3897
Nil	10	(33.3)	11	(36.7)	-0.28	0.7871

**[Table/Fig-6]:** Side-effects.

Z-test of proportionality, p ≤0.05=significant

characterised by longer duration of hospital stay, chronic postoperative pain development, poor recovery after surgery, increased requirement and consumption of opioid in postoperative period and economical burden to the patient [18].

Addition of MgSO<sub>4</sub> to combination of opioid and local anaesthetic intrathecally is known to increase analgesic effect of opioid [19]. Analgesic effect of local anaesthetics can be enhanced with addition of adjuvant like MgSO<sub>4</sub> [20]. NMDA receptor activation produces slow excitatory post synaptic currents by activating pain sensitive C fibres and this effect can be inhibited by adding MgSO<sub>4</sub> intrathecally [21]. By acting on NMDA receptors it abolishes central sensitisation and wind up phenomenon which was the cause for pain sensation. Excitatory amino acids like aspartate and glutamate act on dorsal horn and produce hypersensitisation through NMDA receptors and this effect can be blocked using MgSO<sub>4</sub> [10,11].

Intrathecal MgSO<sub>4</sub> as an adjuvant is studied in doses varying from 50 to 100 mg [13]. A study by Jabalameli M and Pakzadmoghadam SH did not find increase in postoperative analgesia by adding 50 mg of MgSO<sub>4</sub> alone to intrathecal bupivacaine and suggested that there were increased side-effects with 100 mg of MgSO<sub>4</sub> as an additive [13]. Fentanyl has faster onset of action as it is lipophilic and 10-20 times more potent when administered intrathecally compared to the i.v. route [22]. In a study by Ahmed F et al., intrathecal addition of fentanyl to bupivacaine have found increase duration of analgesia as compared to intrathecal bupivacaine alone [23]. To know the efficacy of MgSO<sub>4</sub> as second additive drug intrathecally, dose of 50 mg (MgSO<sub>4</sub>) was added to combination of fentanyl and bupivacaine and evaluate its efficacy in prolonging duration of analgesia. The anaesthetic effect was compared between two groups. Side-effects like hypotension, bradycardia, nausea and vomiting were also compared between both the groups and did not show any statistically significant difference.

In a similar study by Nath MP et al., onset of sensory block was delayed by five minutes and motor block by two minutes in MgSO<sub>4</sub> group who underwent hysterectomy and this result was comparable with present study [12]. The change in pH and baricity of the solution containing MgSO<sub>4</sub> as an additive might be the reason for delay in onset of sensory blockade as quoted in various other studies, who also quoted that in patients undergoing caesarean section under hyperbaric bupivacaine spinal anaesthesia, the addition of 50 mg MgSO<sub>4</sub> led to a significant delay in the onset of sensory blockade [12,17,24,25]. The mean duration of analgesia

was increased by 27.6 minutes in group 'M' which was statistically significant and was comparable with studies by Nath MP et al., and Malleeswaran S et. al., [12,24].

### Limitation(s)

The limitation of present study was that double blinding was not done and it was a single blinded study.

### CONCLUSION(S)

Magnesium sulphate when added to combination of opioid like fentanyl and bupivacaine intrathecally proved to be efficacious in prolonging analgesic duration. Studies can be done in paediatric population to know the efficacy of MgSO<sub>4</sub> as an adjuvant in prolonging duration of analgesia through caudal route for infraumbilical surgeries.

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