Med. J. Cairo Univ., Vol. 86, No. 6, September: 3253-3262, 2018
www.medicaljournalofcairouniversity.net

Comparison between 3 Different Doses of Magnesium Sulphate as A Spinal Adjuvant to Bupivacaine and Fentanyl Combination in Lower Limb Orthopedic Surgery

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Abstract

Background: Spinal anesthesia is a simple technique that provides a fast surgical block. It has certain limitations such as limited duration of the blockade and post-operative analgesia. Adjuncts to the Local Anaesthetics (LA) used in spinal anaesthesia can exhibit undesirable side-effects like respiratory depression, urinary retention, pruritis, haemodynamic instability and nausea and vomiting, limiting their use. Magnesium when used in therapeutic doses avoids all of these side-effects.

Objective: Comparing 3 different doses of Magnesium Sulfate as a spinal adjuvant to Bupivacaine-Fentanyl combination in spinal anesthesia on the spread, duration, regression of spinal block, and postoperative analgesia in patients undergoing lower limb orthopedic surgeries.

Patients and Methods: This study was conducted in Assuit University Hospital in period from 1/8/2016 to 31/7/2017. 120 patients aged between 18-60 years, 30 in each group (ASA I or II) scheduled for lower limb orthopedic surgeries were included in our study. The patients were randomly divided into four equal groups of 30 each: Group I (control group) patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 μg) 0.5ml and normal saline 1ml. Group II patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25μg) 0.5ml, $MgSO_4$ (50mg) 0.5ml and normal saline 0.5ml. Group III patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 μg) 0.5ml, $MgSO_4$ (75mg) 0.75ml and normal saline 0.25ml. Group IV patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 μg) 0.5ml and $MgSO_4$ (100mg) 1ml. Onset and duration of sensory & motor block, time to reach the maximum height of the sensory block and incidence of side effects were recorded. Numerical Rating Scale (NRS) was recorded every 6 hours for the next 24 hours.

Results: As regards onset of motor & sensory block, it was delayed in all groups than in control group. As regards duration of motor & sensory block, it was prolonged in all groups than in control group I. The results of our study showed that addition of Magnesium Sulphate to IT Bupivacaine-Fentanyl provides longer duration of analgesia than Bupivacaine-Fentanyl alone. Also total analgesic requirements were more in control group than other groups specially group IV which had the least analgesic requirements. As regards side effects our study showed that there were higher incidence of hypotension, nausea & vomiting in group IV when compared with groups II and III.

Conclusion: Our study shows that the addition of magnesium sulfate to intrathecally bupivacaine-fentanyl in patients undergoing lower limb orthopedic surgery receiving spinal anesthesia prolongs the duration and quality of analgesia better than bupivacaine-fentanyl only but 75mg of this drug was enough to lead a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of sensory and motor blockade, without increasing side effects like hypotension, nasuea & vomiting.

Key Words: *Spinal anesthesia – Bupivacaine – Fentanyl – Magnesium sulfate – Post-operative analgesia.*

Introduction

ORTHOPEDIC procedures have been reported to be among the most painful of surgical procedures [1].

It has been reported that more than half of postoperative patients receive suboptimal pain control [2].

Post-operative pain relief has two practical aims, the first one is the provision of subjective comfort which is desirable for humanitarian reasons.

The second is inhibition of trauma induced nociceptive impulses to blunt autonomic and somatic reflex responses to pain and to enhance subsequent restoration of function by allowing the patient to breath, cough, and move more easily [3].

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Spinal anesthesia is a simple technique that provides a deep and fast surgical block through the injection of small doses of local anesthesitic solution in subarachnoid space, it provides excellent operating conditions for surgery below the umbilicus [4].

Prolongation of spinal anaesthesia is desirable both for long procedures and post-operative pain relief.

Highly lipid soluble opioids like Fentanyl have higher affinity for opioid receptors and improve the quality of intraoperative anesthesia and permit lower doses of local anaesthetics when used intrathecally. They provide faster onset and prolonged duration analgesia and does not cause delayed respiratory depression [5-7].

One of the mechanisms implicated in the persistence of post-operative pain is central sensitization, which is an activity-dependent increase in the excitability of spinal neurons.

Central sensitization has been shown to depend on the activation of dorsal horn N-methyl D-aspartate (NMDA) receptors by excitatory amino acid transmitters such as aspartate and glutamate [8-10].

Magnesium is a non competitive NMDA (N-methyl D-aspartate) receptors antagonist.

Activation of NMDA receptors leads to calcium influx into the cells, the action which can be blocked by magnesium [11].

Calcium influx leads to a series of central sensitization such as windup phenomenon and long term potentiation which are important mechanisms that determine the duration and intensity of post-operative pain, hence the role of magnesium as a NMDA receptors antagonist in the prevention of these cascades of reactions leading to reduced post-operative pain [9].

Patients and Methods

This study was conducted in Assuit University Hospital in period from 8/2016 to 7/2017. After approval by our Local Institutional Ethics Committee of the Faculty of Medicine, Assuit University, written informed consent was obtained from all patients before participation. 120 patients aged between 18-60 years, 30 in each group (ASA I or II) scheduled for lower limb orthopedic surgeries were included in our study.

Upon arrival of patients into the operating room, complete history was taken from the patients and all patients was subjected to thorough examination.

The selected patients were prepared preoperatively in the usual fashion, venous access was obtained in the upper limb with a 18G catheter and patients received 500ml intravenous isotonic NaCl solution 0.9% as a preload over 20 minutes at room temperature.

Intraoperative routine monitoring by ECG, peripheral oxygen saturation (SpO_2) and Non-Invasive Blood Pressure (NIBP) were attached to the patient.

After obtaining the baseline values of hemodynamic variables, The patients were placed on sitting postion with arched back to maximize the "opening" of the vertebral interspaces with the elbows resting on the thighs. Complete sterilization of the back was done by antiseptic solution. The top of the iliac crest was identified. Tuffier"s line (intercristal line) generally corresponds with the 4th lumbar vertebrae or L4-L5 interspace [12].

Lumbar puncture was performed. A25 gauge (pencil point) spinal needle was introduced into the subarachnoid space at the L3-L4 lumber level midline approach with the needle orifice cephalad. Cerebrospinal fluid was aspirated and the ready fluid injected to subarachnoid space over the period of 15s, with no barbotage.

The patients were randomly divided into four equal groups of 30 each:

Group I (control group) patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25μg) 0.5ml and normal saline 1ml.

Group II patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25μg) 0.5ml, $MgSO_4$ (50mg) 0.5ml and normal saline 0.5ml.

Group III patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25μg) 0.5ml, $MgSO_4$ (75mg) 0.75ml and normal saline 0.25ml.

Group IV patients received intrathecal injection hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25μg) 0.5ml and $MgSO_4$ (100mg) 1ml.

Intraoperative episodes of hypotension (define as MBP is >30% below baseline or SBP >90mmHg) was treated with intravenous 6mg ephedrine injection.

Intraoperative episodes of bradycardia (defined as pulse rate <60bpm) was treated with intravenous injection of 0.3mg atropine.

Upon completion of the surgery, the subject was transported to the PACU.

Data monitoring:

A- *Pre-operative:*

Assessment of the demographic patient's profile: To assess the patient's profile as the patient's name, age, sex, type of surgery and the American Society of Anesthesiology (ASA) physical status.

Assessment of Mean Blood Pressure (MBP), Heart Rate (HR), SpO_2, respiratory rate, and Electrocardiogram (ECG).

B- *Intraoperative:*

1- Hemodynamic data (MBP, HR, SpO_2, respiratory rate) were assessed every 5 minutes for the first 15 minutes and every 10 minutes thereafter until the end of surgery.

2- Assessment of motor block after performance of spinal anesthesia. (Modified Bromage Scale) [13] : Bromage 0, the patient is able to move the hip, knee and ankle.

Bromage 1, the patient is unable to move the hip but is able to move the knee and ankle.

Bromage 2, the patient is unable to move the hip and knee but able to move the ankle.

Bromage 3, the patient is unable to move the hip, knee and ankle.

Time for motor block onset was assumed when modified Bromage score became three.

3- Assessment of sensory block level by pin prick test.

Onset of sensory block (time elapsed from the end of intrathecal injection to absence of pinprick sensation at T 10 dermatome).

Maximum level achieved of sensory block, time to reach the maximum level of sensory block (time elapsed from the end of intrathecal injection to attain maximum level of sensory block).

Duration of sensory block (time elapsed from the end of intrathecal injection to regression of sensory block by two dermatomes).

Duration of motor block (time when modified Bromage score became three to the time when modified Bromage score became zero).

Duration of analgesia (time from intrathecal injection to the time of first complain of pain, first request for analgesia, or a reported NRS >4).

C- *Post-operative:*

The data were recorded every 6 hours for the post-operative 24 hours:

1- Post-operative hemodynamic data (MBP, HR, SpO_2, respiratory rate).

2- Numerical Rating Scale (NRS) for post-operative pain.

Supplemental analgesia in the form of (IM) 30 mg ketolac was given if the scale is ≥4. This dose was repeated twice, according to the patient need.

Morphine (0.1mg/kg) was given iv for intractable pain (the dose, and total amount of rescue analgesic drugs will be recorded).

3- Expected side effects of the studied drugs were recorded (nausea, vomiting, hypotension, pruritis, respiratory depression or urine retention) and any other side effect or complication was recorded.

Statistical analysis:

Data were computerized and analyzed using the (SPSS 17.0 software, Chicago, IL, USA) computer program. Parametric data were represented as mean ± standard deviation or numbers and percentages. Comparison between groups was done using One way ANOVA test followed by Post Hoc Test (LSD). Proportions were compared using Chi-squared analysis. p-values <0.05 was considered statistically significant.

Results

120 patients scheduled for lower limb orthopedic surgeries were included in this study receive spinal anesthesia; patients were randomly allocated into four equal groups according to intrathecal injected drugs:

Group I (control group) patients received hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 µg) 0.5ml. Group II patients received hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 µg) 0.5ml, $MgSO_4$ (50mg) 0.5ml. Group III patients received hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 µg) 0.5ml, $MgSO_4$ (75mg) 0.75ml.

Group IV patients received hyperbaric bupivacaine (0.5%) 2.5ml with fentanyl (25 μg) 0.5ml and $MgSO_4$ (100mg) 1ml.

1- *Onset of sensory and motor block:* As regards for onset of sensory block (time elapsed from the end of intrathecal injection to absence of pinprick sensation at T 10 dermatome), it was significantly delayed in all groups than control Group I. Our study shows that Group IV take more duration time for sensory onset as compared with other groups with statistically significant difference when compared with other groups as shown in (Table 1) and Fig. (1).

And as regards onset of motor block (when modified Bromage score became three), it was delayed in all groups than in control Group I.

Our study shows that Group IV take more duration for motor onset as compared with other groups but there is no statistical significance when compared with Group III while there is statistical significance when Group III was compared with Group II and there is statistical significance when Group IV was compared with Group II as shown in (Table 1) and Fig. (1).

2- *Time to reach maximum sensory level:* As regards for maximum sensory level achieved, there was no difference between the groups but there was difference in the time to reach it as shown in (Table 2).

Our study shows that Group IV take more time to reach maximum sensory level as compared with other groups but there is no statistical significance when compared with Group III while there is statistical significance when Group III was compared with Group II and there is statistical significance when Group IV was compared with Group II as shown in as shown in (Table 3) and Fig. (1).

3- *Sensory and motor duration:* As regards for duration of motor and sensory block, it was prolonged in all groups than in control Group I. Our study shows that Group IV take more duration for sensory and motor block as compared with other groups but there is no statistical significance when compared with Group III while there is statistical significance when group III was compared with Group II and there is statistical significance when Group IV was compared with Group II as shown in (Table 4) and Fig. (2).

4- *Duration of analgesia:* As regards for duration analgesia (time from intrathecal injection to the time of first complain of pain, first request for analgesia, or a reported NRS >4), it was prolonged in all groups than in control Group I. Our study shows that Group IV take more duration for sensory and motor block as compared with other groups but there is no statistical significance when compared with Group III while there is statistical significance when Group III was compared with Group II and there is statistical significance when Group IV was compared with Group II as shown in (Table 5).

5- *Total analgesic requirement:* Total analgesic requirement was lower in Group III and IV than in Group I and II. As in Group I 18 patients requested analgesia twice, and 12 patients requested analgesia three times. In group II 28 patients requested analgesia three times and only two patients requested analgesia twice. In Group III 24 patients requested analgesia twice and 6 patients requested analgesia once. In Group IV 19 patients requested analgesia twice and 11 patients requested analgesia once as shown in (Table 6).

6- *Numerical Rating Scale (NRS):* No patient in the four groups complained of pain during surgery. There were Statistically significant difference between four groups after 6 hours as patients from Group I start to demand first analgesia, but patients from Group II, III and IV still had NRS less than 4.

Then, between 6 and 12 hours patients from Group II, III and IV start to demand first analgesia so at 12 hours patients from all groups had low NRS as they already received their analgesia before 12 hours. And also at 18 hours and 24 hours, all groups had NRS less than 4, because they already had received analgesia before time to measure NRS as shown in (Table 7).

7- *Side effects:* The incidence of side effects was compared in the four groups as shown in (Table 8).

The Incidence of nausea & vomiting was 20%, 13.3%, 10% and 23.3% for Group I, II, III and IV respectively. The incidence of hypotension was 33.3%, 16.7%, 10% and 26.6% for Group I, II, III and IV respectively. The incidence of Pruritis was the same in Group I and II and it was 13.3% but no Pruritis occurred in Group III and IV. The Incidence of Shivering was 36.7%, 13.3%, 6.7% and 6.7% for Group I, II, III and IV respectively. No urinary retention or respiratory depression had been observed in the studied groups.

Table (1): Comparison between studied groups according to onset of sensory & motor block.

	Group name								p_1	p_2	p_3
	I (control)		II		III		IV				
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD			
Sensory block onset (min)	1-4	1.7±0.79	2-6	3.53±0.86	3-7	4.63±0.93	4-8	5.8±1.06	0.001 **	0.001 **	0.001 **
Motor onset (min)	2-6	3.23±0.97	3-11	5.83±1.6	4-11	6.63±1.47	5-12	7.67±1.47	0.048 *	0.001 **	0.008

p_1: Comparison between Group II; III. p_2: Comparison between Group II; IV. p_3: Comparison between Group III; IV.

Table (2): Comparison between studied groups according to maximum sensory level.

Maximum level	Group name							
	I		II		III		IV	
	No.	%	No.	%	No.	%	No.	%
T4	7	23.3	6	20	5	16.7	4	13.3
T6	21	70	20	66.7	20	66.7	21	70
T8	2	6.7	4	13.3	5	16.7	5	16.7

Table (3): Comparison between studied groups according to time to reach maximum sensory level.

	Group name								p_1	p_2	p_3
	I (control)		II		III		IV				
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD			
• Time to reach maximum level (min)	2-7	3.87±1.07	4-10	6.43±1.41	5-12	7.47±1.5	6-13	8.23±1.45	0.007**	0.001 **	0.051

p_1: Comparison between Group II; III. p_2: Comparison between Group II; IV. p_3: Comparison between Group III; IV.

Table (4): Comparison between studied groups according to sensory and motor duration.

	Group name								p_1	p_2	p_3
	I (control)		II		III		IV				
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD			
Sensory duration (min)	110-225	176.33±24.03	135-285	222±36.62	160-355	271.67±48.73	175-405	293.67±56.06	0.001**	0.001 **	0.110
Motor duration (min)	150-255	209.17±22.93	195-335	267±31.69	200-400	308.17±48.65	210-465	334.33±58.56	0.003**	0.001 **	0.065

Table (5): Comparison between studied groups according to duration of analgesia.

	Group name								p_1	p_2	p_3
	I		II		III		IV				
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD			
Duration of analgesia	180-410	323.83±52.45	285-615	397.83±76.2	315-665	448.17±81.9	305-695	493.83±92.26	0.016	0.001 **	0.047

Table (6): Comparison between studied groups according to total analgesic requirement.

Total analgesia	Group name								p-value
	I		II		III		IV		
	No.	%	No.	%	No.	%	No.	%	
1	0	0.0	0	0.0	6	20.0	36.7	36.7	<0.001**
2	18	60.0	28	93.3	24	80.0	63.3	63.3	<0.001**
3	12	40.0	2	6.7	0	0	0.0	0.0	<0.001**

Table (7): Comparison between studied groups according to NRS.

	Group name								*p*-value
	I		II		III		IV		
	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	
NRS 6H	2-10	5.27±1.89	1-8	3.87±1.85	0-6	2.7±1.76	0-8	2.2±1.79	<0.001**
NRS 12H	1-7	2.47±1.28	1-4	2.07±0.94	1-3	2.1±0.71	1-6	2.33±1.03	0.364
NRS 18H	1-9	2.97±1.94	1-8	3.27±1.62	1-8	3.6±1.77	1-7	2.9±1.49	0.374
NRS 24H	1-10	2.93±2.26	1-7	2.2±1.47	1-3	1.57±0.63	1-4	1.97±0.89	0.004**

Table (8): Comparison between studied groups according to side effects.

	Group name								*p*-value
	I		II		III		IV		
	No.	%	No.	%	No.	%	No.	%	
Nausea & vomiting	6	20.0	4	13.3	3	10.0	7	23.3	–
Hypotension	10	33.3	5	16.7	3	10.0	8	26.6	–
Pruritis	4	13.3	4	13.3	0	0.0	0	0.0	–
Shivering	11	36.7	4	13.3	2	6.7	2	6.7	–
Urinary retention	0	0.0	0	0.0	0	0.0	0	0.0	–
Respiratory depression	0	0.0	0	0.0	0	0.0	0	0.0	–

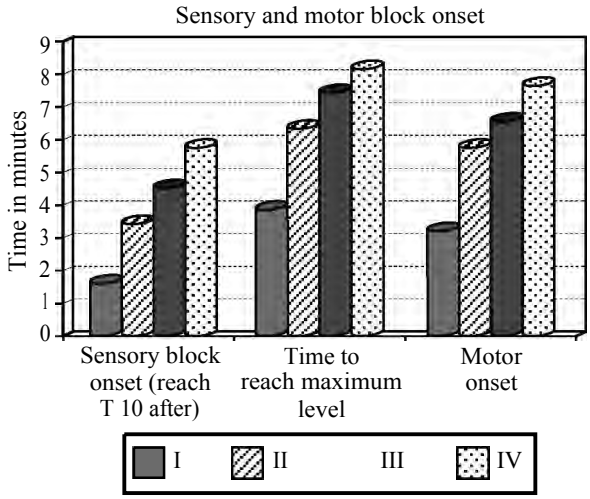

Fig. (1): Comparison between studied groups according to onset of sensory and motor block and time to reach maximum sensory level.

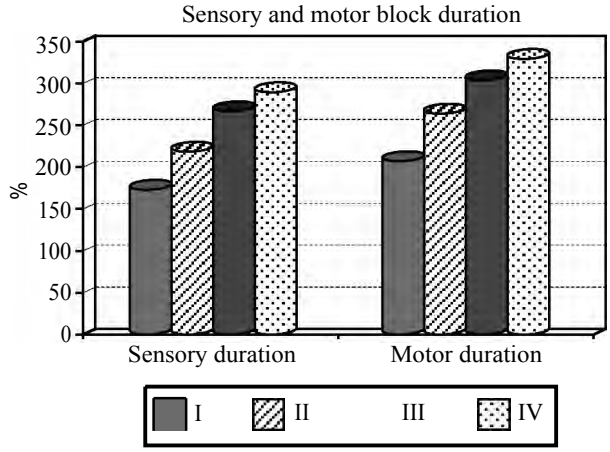

Fig. (2): Comparison between studied groups according to sensory and motor duration.

Discussion

Post-operative pain is a potent trigger for the stress response that activate the autonomic nervous system and thought affect nearly every organ function and adversely influence post-operative morbidity and mortality. So it was suggested that effective post-operative pain management is not only human but also a very important aspect of post-operative care **[14]**.

Spinal anesthesia has a more rapid onset and is a more reliable analgesia than other regional anesthesia techniques. The disadvantages of spinal anesthesia are a high incidence of cardiovascular instability and a short duration of analgesia. Therefore, adjunctive medications for intrathecal anesthesia have been used to intensify spinal anesthesia with minimal complications **[15]**.

Magnesium exerts its analgesic action as a non-competitive NMDA receptor antagonist, blocking ion channels in a voltage-dependent manner. In the dose range necessary for the effective enhancement of opiate-based analgesia, there is no evidence that magnesium is harmful to neuronal tissue **[16]**.

However, magnesium is ineffective as a primary analgesic and must be used in conjunction with opioids to provide a useful analgesic extension. The combination of magnesium and opioids appears to offer enhanced opioid analgesia, a reduction in the risk of secondary hyperalgesia and possibly a reduction in the risk of the development of post-operative chronic pain syndromes **[17,18]**.

This study was designed to compare between three different doses of Magnesium Sulphate as a spinal adjuvant to Bupivacaine-Fentanyl combination in spinal anesthesia on the spread, duration, regression of spinal block, and post-operative analgesia in patients undergoing lower limb orthopedic surgeries.

The results of our study showed that addition of Magnesium Sulphate to IT Bupivacaine-Fentanyl provides longer duration of analgesia than Bupivacaine-Fentanyl alone as mean ± SD for first analgesic requirement time for patients after surgery was (397.83±76.2min.) for Group II (50mg Magnesium), (448.17±81.9min.) for Group III (75mg Magnesium), (493.83±92.26min.) for Group IV (100mg Magnesium) and (323.83±52.45min.) for control group, and more potent analgesia reflected by NRS pain score but there is no statistical significance when Group IV was compared with Group III as regards of duration of analgesia.

Also total analgesic requirements were more in control group than other groups specially Group IV which had the least analgesic requirements.

As regards onset of sensory & motor block, it was delayed in all groups than control group, our study shows that Group IV take more duration time for sensory onset as compared with other groups but as regards for motor onset Group IV take more duration for motor onset as compared with other groups but there is no statistical significance when compared with Group III.

As regards duration of motor and sensory block, it was prolonged in all groups than in control Group I, Group IV take more duration for sensory and motor block as compared with other groups but there is no statistical significance when compared with Group III while there is statistical significance when Group III was compared with Group II and there is statistical significance when Group IV was compared with Group II.

The results of this study also showed that the incidence of hypotension, nausea & vomiting decreased in Group II and III when compared with control group but increased in Group IV when compared to Groups II and III and that may be due to the dose of $MgSO_4$ (100mg). Also the incidence of shivering decreased in Group II (13.3%) than Group I (36.7%) while Group III and IV was the same (6.7%) and that may be due to Magnesium which causes peripheral vasodilatation which probably improves the cutaneous circulation, thus decreasing the incidence of shivering **[19]**.

Lejuste **[20]** described the inadvertent intrathecal injection of 1000mg of magnesium sulphate, producing a dense motor block followed by complete resolution within 90min, with no neurological deficit at long-term follow-up.

Buvanendran et al., **[21]** in the first human study trial found that intrathecal magnesium 50mg and fentanyl 25 µg, significantly prolonged the median duration of analgesia as compared with plain intrathecal fentanyl when given in laboring parturients and and suggested that the availability of an intrathecal N-methyl-D-aspartate antagonist could be of clinical importance for pain management.

In 2005, Ozalevli M et al., **[22]** demonstrated that in patients undergoing lower extremity surgery under bupivacaine-fentanyl spinal anaesthesia, the addition of 50mg IT $MgSO_4$ led to a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of spinal anaesthesia, without increasing side-effects.

In 2012, Jabalameli et al., **[23]** said that in patients undergoing the caesarean section under hyperbaric bupivacaine spinal anesthesia, the addition of 50, 75, or 100mg magnesium sulfate provides safe and effective anesthesia, but 75mg of this drug was enough to lead a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of sensory and motor blockade, without increasing major side effects. In this study, higher dose (100mg) of magnesium sulfate might result in increasing some of side effects (hypotension, nausea and vomiting). The incidence of hypotension with that dose was 63% and the incidence of nausea & vomiting was 15.2%.

In 2012, Nath et al., **[24]** demonstrated that The addition of 100mg intrathecal magnesium led to prolonged duration of analgesia significantly without increasing the incidence of side effects. Also, there was a significant delay in the onset of both sensory and motor blockade. The incidence of hypotension was 16.66% which is less than our study in the same group (26.6%).

Arcioni et al., **[25]** also observed that intrathecal and epidural magnesium sulfate potentiated and prolonged motor block and suggested that the difference in pH and baricity of the solution by addition of magnesium contributed to the delayed onset, which may also be the cause in our study. And he also demonstrated that the use of intrathecal magnesium did not find any signs of systemic toxicity, such as arterial hypotension, cardiac arrhythmias, somnolence, double vision, slurred speech or weakness, either intraoperatively or

during the post-operative course in patients treated with magnesium sulfate who underwent major orthopedic surgery. We too did not find any of the above-mentioned complications during the intra-operative or in the post-operative periods.

The delayed onset could be due to the solution of magnesium sulfate having a different pH, which might explain our findings. However, they cannot offer a satisfactory explanation for this delay and further studies are needed. Also, increase in metabolism of bupivacaine due to the activation of cytochrome P450 (CYP) by magnesium may be responsible for the delayed onset **[26]**. But, it still could not explain the similar motor recovery.

In 2009, Dayio˘ glu H et al., **[27]** clarified that the addition of intrathecal magnesium (50mg) to low-dose bupivacaine-fentanyl in patients undergoing knee arthroscopy prolonged the time for regression of two segments in the maximum block height and time to L2 regression, but did not affect the time to complete recovery of motor function and also did not affect maximum sensory level or the time to reach the highest level of sensory block. They also added even though the time to first analgesic requirement was prolonged significantly by magnesium, the addition of intrathecal magnesium sulfate to spinal anesthesia is not desirable in patients undergoing knee arthroscopy due to the prolonged time to ambulation and the lack of effect of magnesium on postoperative analgesic consumption.

In 2015, Katiyar et al., **[28]** said that addition of magnesium sulphate at 100mg dose or fentanyl 25μg as adjuvants to intrathecal bupivacaine significantly prolongs the duration of analgesia. At these doses, magnesium provides better haemodynamic stability than fentanyl, with fewer side effects. With 100mg of intrathecal magnesium they observed increased duration of analgesia (328.13 min) without increase in adverse effects as observed with intrathecal fentanyl group. This prolongation of analgesia is consistent with the experimental synergistic interaction between spinal local anaesthetic and NMDA antagonists, like magnesium, which causes antinociceptive effects via different mechanisms, hence the rationale for combining the two.

In 2016, Vasure et al., **[29]** showed that magnesium 50mg when added to bupivacaine-fentanyl combination for spinal anesthesia could provide prolonged post-operative analgesia without additional side effects in patients undergoing lower limb orthopedic surgery. Furthermore, it significantly delays the onset of the sensory block as well as time to reach maximum sensory block and also prolongs the duration of sensory blockade. Magnesium 50mg alone when added to bupivacaine too leads to delay in onset of sensory block and prolongation of time to reach maximum sensory block but without prolongation of sensory block duration and duration of post-operative analgesia.

Previous studies are comparable to our study, where there were prolonged duration of both sensory and motor block but with delayed onset of sensory and motor block. There were no side-effects related to the drug used except with the dose 100mg $MgSO_4$. Our study also demonstrates no clinically significant difference in the hemodynamic parameters and adverse effects among the other three groups. In the Group IV with the dose 100mg $MgSO_4$ there were increased incidence of hypotension, nausea and vomiting.

Conclusion:

Our study shows that the addition of magnesium sulfate to intrathecally bupivacaine-fentanyl in patients undergoing lower limb orthopedic surgery receiving spinal anesthesia prolongs the duration and quality of analgesia better than bupivacaine-fentanyl only but 75mg of this drug was enough to lead a significant delay in the onset of both sensory and motor blockade, and prolonged the duration of sensory and motor blockade, without increasing side effects like hypotension, nasuea & vomiting.

References

1- CHUNG F., RITCHIE E. and SU J.: Post-operative pain in ambulatory surgery. Anesth. Analg., 85: 808-16, 1997.

2- RAWAL N., HYLANDER J., NYDAHL P.A., et al.: Survey of post-operative analgesia following ambulatory surgery. Acta. Anaesthesiol. Scand., 41: 1017-22, 1997.

3- KEHLET H.: Post-operative pain and its management. In: Wall and Melzacks Textbook of Pain. 5 th ed., Vol. 5. Philadelphia: Elsevier Churchill Livingstone, p. 635, 2006.

4- BOHANNAN T.W. and ESTER M.D.: Evaluation of subarachnoid fentanyl for post-operative analgesia. Anaesthesiology, 67: A-237, 1987.

5- KOLTKA K., ULUDOG E., SENTURK M., YAVRU A., KARADENIZ M., SENGUL T. and OZYALCIN S.: Comparison of equipotent doses of Ropivacaine-fentanyl and Bupivacaine-fentanyl in spinal anaesthesia for lower Abdominal Surgery. Anaesth Intensive Care Nov., 37 (6): 923-8, 2009.

6- OZGUREL O.: Comparison of fentanyl added to ropivacaine or bupivacaine in spinal anesthesia. Reg. Anesth. Pain. Med., (5 Suppl. 1), 23: Abs 89, 2003.

7- LEE Y.Y., NGAN KEE W.D., MUCHHAL K. and CHAN C.K.: Randomised double blind comparison of Ropivacaine-fentanyl and Bupivacaine-fentanyl for spinal Anaesthesia for urological surgery. Acta Anaesthesiol. Scand., 49: 1477-82, 2005.

8- ROSEAG O.P., LUI C.P., CICUTTI N.J. and BRAGG P.R.: Perioperative multimodal pain therapy for caesarean section: Analgesia and fitness for discharge. Can. J. Anesth., 44: 803e9, 1997.

9- WOOLF C.J. and THOMPSON S.W.: The induction and maintenance of central sensitization is dependent on N-methyl-D aspartic acid receptor activation; implications for the treatment of post-injury pain and hypersensitivity states. Pain, 44: 293e9, 1991.

10- WOOLF C.J. and CHONG M.S.: Preemptive analgesia: Treating postoperative pain by preventing the establishment of central sensitization. Anesth. Analg., 77: 362e79, 1993.

11- V.Y. FAWCETT, E.J. HAXBY and D.A. MALE: Magnesium; physiology and pharmacology. Br. J. Anaesth., 83: pp. 302-20, 1999.

12- SNIDER K.T., KRIBS J.W., SNIDER E.J., DEGENHARDT B.F., BUKOWSKI A. and JOHNSON J.C.: Reliability of Tuffier's line as an anatomic landmark. Spine (Phila Pa 1976). Mar. 15; 33 (6): E161-5. doi:10, 2008.

13- BROMAGE P.R.: A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. Acta Anesthesiol. Scand. Suppl., 16: 55-69, 1965.

14- MORGAN G.E., MIKHAIL M.S. and MURRAY M.J.: Local anesthetics: In Clinical anesthiology. A Lang Medical Book, pp. 233-42, 2002.

15- ALEBOUYEH M.R., IMANI F., RAHIMZADEH P. and FAIZ S.H.: Evaluation of the efficacy of intrathecal injection of amitriptyline and doxepin in spinal anesthesia in comparison with bupivacaine in rats. Anesth. Pain Med., 1 (1): 159, 2011.

16- KROIN J.S., McCARTHY R.J., VON ROENN N., SCHWAB B., TUMAN K.J. and IVANKOVICH A.D.: Magnesium sulfate potentiates morphine antinociception at the spinal level. Anesth. Analg., 90: 913-7, 2000.

17- TAKANO Y., SATO E., KANEKO T. and SATO I.: Antihyperalgesic effects of intrathecally administered magnesium sulfate in rats. Pain, 84: 175-9, 2000.

18- TRAMER M.R., SCHNEIDER J., MARTI R.A. and RIFAT K.: Role of magnesium sulfate in post-operative analgesia. Anesthesiology, 84: 340-7, 1996.

19- NATH M.P., GARG R., TALUKDAR T., CHOUDHARY D. and CHAKRABARTY A.: To evaluate the efficacy of intrathecal magnesium sulphate for hysterectomy under subarachnoid block with bupivacaine and fentanyl: A prospective randomized double blind clinical trial. Saudi J. Anaesth., 6: 254-8, 2012.

20- LEJUSTE M.J.: Inadvertent intrathecal administration of magnesium sulfate. S. Afr. Med. J., 68: 367-68, 1985.

21- BUVANENDRAN A., McCARTHY R.J., KROIN J.S., LEONG W., PERRY P. and TUMAN K.J.: Intrathecal magnesium prolongs fentanyl analgesia: A prospective, randomized, controlled trial. Anesth. Analg., 95: 661-6, 2002.

22- M. OZALEVLI, T.O. CETIN, H. UNLUGENC, T. GULER and G. ISIK: The effect of adding intrathecal magnesium sulphate to bupivacaine-fentanyl spinal anaesthesia. Acta Anaesthesiol. Scand, 49 (10): 1514-19, 2005.

23- JABALAMELI M. and PAKZADMOGHADAM S.H.: Adding different doses of intrathecal magnesium sulfate for spinal anesthesia in the cesarean section: A prospective double blind randomized trial. Adv. Biomed. Res., 1: 7, 2012.

24- NATH M.P., GARG R., TALUKDAR T., CHOUDHARY D. and CHAKRABARTY A.: To evaluate the efficacy of intrathecal magnesium sulphate for hysterectomy under subarachnoid block with bupivacaine and fentanyl: A prospective randomized double blind clinical trial. Saudi J. Anaesth., Jul. Sep., 6 (3): 254-8, 2012.

25- ARCIONI R., PALMISANI S., TIGANO S., SANTORSOLA C., SAULI V., ROMANO S., et al.: Combined intrathecal and epidural magnesium sulphate supplementation of spinal anaesthesia to reduce postoperative analgesic requirements: A prospective, randomized, double-blind, controlled trial in patients undergoing major orthopedic surgery. Acta Anaesthesiol. Scand., 51: 482-9, 2007.

26- HUNG Y.C., CHEN C.Y., LIRK P., WANG C.F., CHENG J.K., CHEN C.C., et al.: Magnesium sulfate diminishes the effects of amide local anesthetics in rat sciaticnerve block. Reg. Anesth. Pain. Med., 32: 288-95, 2007.

27- DAYIOGLU H., BAYKARA Z.N., SALBES A., SOLAK M. and TOKER K.: Effects of adding magnesium to bupivacaine and fentanyl for spinal anesthesia in knee arthroscopy. J. Anesth., 23: 19-25, 2009.

28- KATIYAR S., DWIVEDI C., TIPU S. and JAIN R.K.: Comparison of different doses of magnesium sulphate and fentanyl as adjuvants to bupivacaine for infraumbilical surgeries under subarachnoid block. Indian J. Anaesth., Aug., 59 (8): 471-5, 2015.

29- VASURE R., ASHAHIYA I.D., MAHENDRA R., NARANG N. and BANSAL R.K.: Comparison of Effect of Adding Intrathecal Magnesium Sulfate to Bupivacaine Alone and Bupivacaine-Fentanyl Combination during Lower Limb Orthopedic Surgery. Saudi J. Anaesth., Jul-Sep., 6 (3): 254-8, 2012.

مقارنة بين ٣ جرعات مختلفة من عقار سلفات الماغنسيوم كمساعد داخل القراب لمزيج عقارى البيوبيفكين والفنتانيل فى عمليات جراحة العظام للطرف السفلى

التخدير الشوكى هو تقنية بسيطة توفر تخدير عصبى سريع للجراحة. لديها قيود معينة مثل مدة محدودة من التخدير العصبى والتسكين بعد العمليات الجراحية. يمكن أن تؤدى المساعدات للتخدير الموضعى المستخدم فى تخدير العمود الفقرى إلى ظهور آثار جانبية غير مرغوب فيها مثل التثبيط التنفسى وإحتباس البول والحكة وعدم الإستقرار فى ضغط الدم والغثيان والقئ مما يحد من إستخدامها. وقد أجريت هذه الدراسة لمقارنة ٣ جرعات مختلفة من سلفات الماغنسيوم بإعتباره مساعد العمود الفقرى لمجموعة بوبيفاكين–فنتانيل فى التخدير الشوكى على الإنتشار والمدة، وتراجع التخدير الشوكى، وتسكين بعد العملية الجراحية فى المرضى الذين يخضعون لجراحات العظام بالطرف السفلى.

طريقة الدراسة: أجريت هذه الدراسة فى مستشفى أسيوط الجامعى فى الفترة من ٢٠١٦/٨/١ إلى ٢٠١٧/٧/٣١. ١٢٠ مريضا تتراوح أعمارهم بين ١٨–٦٠ سنة، ٣٠ فى كل مجموعة المقرر لجراحات العظام بالطرف السفلى كانت المدرجة فى دراستنا. تم تقسيم المرضى عشوائيا إلى أربع مجموعات متساوية من ٣٠ لكل منهم: تلقى مرضى المجموعة الأولى حقن بوبيفاكايين داخل القراب (٠.٥٪) ٢.٥مل مع الفنتانيل (٢٥ ميكروغرام) ٠.٥مل والمالحة العادية ١مل. تلقى مرضى المجموعة الثانية حقن داخل القراب بوبيفاكايين (٠.٥٪) ٢.٥مل مع الفنتانيل (٢٥ ميكروغرام) ٠.٥مل، (٥٠ملغ $MgSO_4$) ٠.٥مل والملح الطبيعى ٠.٥مل. تلقى مرضى المجموعة الثالثة حقن داخل القراب حقن بوبيفاكين (٠.٥٪) ٢.٥مل مع الفنتانيل (٢٥ميكروغرام) ٠.٥مل، (٧٥ملغ $MgSO_4$) ٠.٧٥مل والمالحة العادية ٠.٢٥مل. تلقى مرضى المجموعة الرابعة حقن داخل القراب بوبيفاكايين (٠.٥٪) ٢.٥مل مع الفنتانيل (٢٥ ميكروغرام) ٠.٥مل و (١٠٠ملغ $MgSO_4$) ١مل. بداية ومدة التخدير النصفى الحسى والحركى، تم تسجيل الوقت للوصول إلى أقصى إرتفاع للكتلة الحسية وحدوث آثار جانبية. تم تسجيل مقياس التصنيف العددى (NRS) كل ٦ ساعات لل٢٤ ساعة القادمة.

نتائج الدراسة: تبين دراستنا أن إضافة سلفات الماغنسيوم إلى بو بيفاكايين–فنتانيل داخل القراب فى المرضى الذين يخضعون لجراحة العظام للطرف السفلى تلقى التخدير الشوكى يطيل مدة ونوعية تسكين أفضل من بوبيفاكين–فنتانيل فقط ولكن ٧٥ملغ من هذا الدواء كان كافيا لتأخير كبير فى بداية التخدير الحسى والحركى، وإطالة مدة التخدير الحسى والحركى، دون زيادة الآثار الجانبية مثل إنخفاض ضغط الدم، الغثيان والقئ.