

Research Article

Evaluation of Neuraxial Magnesium Sulphate as Adjuvant to Bupivacaine 0.5% for Subarachnoid Block in Orthopedic Surgery.

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Abstract

Aim of work: This randomized, double blinded clinical trial was to compare between two intrathecal adjuvants, magnesium sulphate in two doses 20, and 40 mg and fentanyl when added to hyperbaric bupivacaine 0.5% in lower limb surgeries performed under spinal anesthesia. **Patients and methods:** After ethical committee approval, and obtaining informed written consent, 122 ASA physical status I or II scheduled for lower limb surgery under spinal anesthesia were randomized into four equal groups each of which was thirty three patients: group A received 5ml of hyperbaric bupivacaine 0.5% plus 1ml of normal saline, group B received 5ml of hyperbaric bupivacaine 0.5% plus 0.5 ml (20mg) of magnesium sulphate 10% plus 0.5 ml normal saline, group C received 5 ml of hyperbaric bupivacaine 0.5% plus 0.40 (40mg) magnesium sulphate 10% plus 0.5 ml normal saline, group D received 5ml of hyperbaric bupivacaine 0.5% plus 0.5 ml fentanyl (50µg) plus 0.5ml normal saline. Onset, duration of sensory and motor block, 1st analgesic request, hemodynamic parameters were recorded. **Results:** Intrathecal magnesium sulphate delayed onset of sensory and motor block even more than the control group while fentanyl shortened the onset time. Magnesium, and fentanyl prolonged the duration of spinal anesthesia and this prolongation increased with increased the dose of magnesium. Incidence of side effects such as pruritus, bradycardia, and hypotension was less with magnesium than other two groups. **Conclusion:** Intrathecal magnesium when used as adjuvant to 5 ml of hyperbaric bupivacaine 0.5% in lower limb surgeries delayed onset of both sensory and motor block and prolonged the duration of spinal anesthesia more than fentanyl and control group with less incidence of side effects.

Key words: magnesium sulphate, spinal anesthesia, fentanyl,

Introduction

Subarachnoid block is the first choice of anesthesia in orthopedic surgery in the lower limb because of its multiple advantages such as its fast action, high safety profile, less costs, and less incidence of thromboembolism but it has a weak point which is its short duration and lack of postoperative analgesia⁽¹⁾. A wide variety of drugs were added to the local anesthetic in subarachnoid block such as clonidine, neostigmine, ketamine, and epinephrine to overcome this disadvantage but all of them exhibited many side effects⁽¹⁾.

Opioids such as fentanyl were added to the intrathecal local anesthetic to prolong and potentiate its action but they were associated with significant side effects like

nausea, vomiting, itching, urine retention, and respiratory depression which limit its use as adjuvant to local anesthetic in subarachnoid block⁽¹⁾.

Magnesium is an important body cation and it is essential for many physiological processes and it is defined as physiological calcium antagonist⁽²⁾. Magnesium is a non-competitive antagonist of N-methyl D-aspartate receptors present in the central nervous system which responsible of central sensitization (increased excitability of spinal neurons) and wind up which in turn leads to persistence of postoperative pain⁽³⁾.

Many researchers examined the efficacy of peri-operative intravenous magnesium

sulphate for prevention of postoperative pain and they found conflicting results where many studies showed that subarachnoid administration of magnesium could prolong spinal analgesia⁽¹⁾ while other studies⁽²⁾ reported no direct benefit from subarachnoid administration of magnesium in pain or analgesic requirements and they explained this conflict by the limited passage of magnesium through the blood brain barrier⁽³⁾. It was suggested that direct administration of magnesium in the subarachnoid space with direct contact with dorsal horn N-methyl D- Aspartate receptors would increase its action and this was examined in many researches which found that intrathecal administration of magnesium would prolong the duration of subarachnoid anesthesia⁽⁴⁾. The hypothesis of this study was that addition of magnesium to local anesthetic in the subarachnoid block would prolong the duration of spinal anesthesia in orthopedic surgery in lower limb without significant side effects. This prospective randomized double blind study was designed to compare between the effect of two intrathecal magnesium doses (20 mg and 40mg) and fentanyl 20µg when added to intrathecal bupivacaine 0.5% on the onset and duration of sensory and motor block (primary outcome), highest sensory level, time to two segments regression, duration of spinal anesthesia, hemodynamic parameters, and side effects (secondary outcomes).

Methods

This prospective, randomized, double blinded study was performed in El -Minia university hospital in the period from August 2013 to January 2014. After obtaining approval of the ethics committee of the faculty of medicine and informed written consents from the patients. One hundred thirty two patients ASA I or II aged from 20 to 60 years scheduled for orthopedic surgery in the lower limb under spinal anesthesia. Patients with coagulopathy, infection in the site of the block, allergy to LA used, or sensitivity to prescribed analgesics, and those who refused to participate in the study were excluded.

Patients were allocated randomly into four equal groups each of which is thirty three patients using computer generated randomized numbers, the allocation ratio was 1:1 and the identification cards was put in a sealed envelopes to hide the allocation.

Group A: they received 2 ml of hyperbaric bupivacaine 0.5% plus 1 ml of preservative free normal saline.

Group B: they received 2 ml of hyperbaric bupivacaine 0.5% plus 0.5 ml magnesium sulphate 10% (50 mg) plus 0.5 ml of preservative free normal saline.

Group C: they received 2 ml of ml of hyperbaric bupivacaine 0.5% plus 0.5 ml magnesium sulphate 10% (50 mg) plus 0.5 ml of preservative free normal saline.

Group D: they received 2 ml of ml of hyperbaric bupivacaine 0.5% plus 0.5 ml fentanyl (20 µg) plus 0.5 ml of preservative free normal saline.

Local anesthetic combination was prepared by anesthesiologist not included in the study in syringes of equal volume for the purpose of blindness, each of which was three ml in each. All patients were fasted for 6 h pre-operatively, and they received 10 mg oral diazepam and 100 mg oral ranitidine on the morning of the surgery. At the operation room 18 gauge cannula was inserted in the hand opposite to the fracture side, and patients received fluid preload with 10 ml/kg of lactated Ringer's solution. Patients were attached to a multi-channel monitor (Hewlett Packward, Viridia 24 Germany) to record base line Electrocardiogram (ECG), heart rate (beats/min), systolic, diastolic blood pressure, and oxygen saturation (SpO₂).

Anesthetic technique: with the patients in sitting position and after sterilization of the back of patients with Bovidone-iodine 10%, subarachnoid block was done using 20-gauge Quincke spinal needle (Spinocan, BBraun medical, Melsungen, Germany) at L³-L⁴ interspace through midline approach. After free flow of clear cerebrospinal fluid (CSF), the local anesthetic mixture was injected by the anesthesiologist blinded with type of the solution. Time of complete intrathecal injection was considered as 0

time. Patients lied in supine position with nasal cannula which delivered oxygen at 3 L/minute.

Parameters were recorded:

- Sensory block: It was examined by pinprick at the midclavicular line every 2 minutes after intrathecal injection till 20 minutes and then every 10 minutes. Time of onset of sensory block (time from intrathecal injection to loss of pinprick sensation at T 10 dermatome), height of sensory block (highest dermatome with lost sensation in two sequential times), time to highest sensory block and duration of sensory block (time to two segment regression).
- Motor block was assessed by Bromage scale (I= free movement of legs and feet, II = just capable of knees flexion with free movement of feet, III=incapable of knees flexion, capable of feet's flexion, IV= incapable of feet or knees flexion)⁽¹⁾ every 2 minutes until complete motor block (Bromage scale IV) and then every 10 minutes until complete motor recovery (Bromage scale I). Time to complete motor block and time to complete motor recovery were recorded.
- Hemodynamic parameters such as heart rate (beats/min), and non invasive systolic, diastolic, and mean blood pressure (mmHg) and oxygen saturation were recorded just before intrathecal injection (base line), 1, 5, 10, 15 minute after intrathecal injection and then every 10 minutes till end of surgery. Hypotension was defined as drop of systolic blood pressure more than 20% of the base line value or below 90 mmHg and it was treated by bolus intravenous ephedrine 10 mg and repeated if necessary. Bradycardia was defined when heart rate decreased below 60 beats/minute and it was treated by bolus intravenous atropine 0.5 mg and repeated if necessary. Respiratory depression was recorded when oxygen saturation was below 90 and it was treated by increase oxygen flow or mask ventilation as required.
- Incidence of hypotension, bradycardia, respiratory depression, excessive sedation, pruritus, nausea and vomiting was recorded. At the end of the surgery, patients were transported to the post anesthesia care unit

PACU till complete motor recovery, stable vital signs, and absence of nausea and vomiting then transported to the ward. Time for first analgesic request (time from intrathecal injection to 1st analgesic request) was recorded.

Statistical analysis

Using PASS (Power Analysis and Sample Size System) software (NCSS, East Kaysville, Utah, USA), it was found that the least number of patients required in each group to detect 20 minutes difference in the duration of motor power of spinal anesthesia with 90% power and 0.05% significance level was 20 patients and with 10% dropout ratio, the number increased to 33 patients in each group.

Data were analyzed with Statistical Program SPSS version 21 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean± SD, while qualitative data were expressed as frequency. Data were tested for normal distribution by Kolmogorov- Smirnov test. Analysis of variance ANOVA was used to compare between the means of the groups followed by post-hoc test. Independent T-test was used for comparison of numerical data within the same group. Student's T- test was used to analyze normally distributed continuous data between two groups. Categorical data were analyzed by Fisher's exact test to compare between proportions. All tests are two-tailed and *P* value of <0.05 was considered significant.

Results

One hundred thirty two patients were eligible for the study. They were randomized into four equal groups each of them was thirty three patients, all of them continued the study to be analyzed as shown in the flow chart of the study Fig(1). There was no significant difference between the four groups as regards the demographic data and the duration of the surgery table (1).

As regard the mean blood pressure, there was no significant difference in the baseline values between the four groups. There was a significant decrease in the mean blood

pressure values when compared to the base line values in the four groups started from the five minutes readings and continued till 30 minutes readings, without any significant difference between the four groups table (7).

As regards the heart rate, there was no significant difference in the baseline values between the four groups. There was a significant decrease in the heart rate values when compared to the base line values in the four groups started from the 0 minutes values and continued to 30 minutes values in control group and magnesium groups while it continued to the end of the study in fentanyl group table (7).

As regards the spinal anesthesia characters, there was significant delay in the onset time of sensory and motor block in magnesium groups (B and C) more than the control (A) and fentanyl group (D) which was the

fastest onset. There was significant prolongation of the duration of sensory and motor block in the magnesium groups (B and C) and fentanyl group (D) when compared to control group(A) but no significance between magnesium and fentanyl. As regards time for the 1st analgesic request was significantly prolonged in magnesium (B, C) and fentanyl (D) groups when compared to (A) control group, and significant prolongation of group (C) magnesium 40 mg when compared to group B, and D but there was no significance between magnesium 20 mg(B) and fentanyl group (D) table (8).

As regards the incidence of side effects, all groups did not show excessive sedation or respiratory depression. Fentanyl group (D) showed significant increased incidence of pruritus and bradycardia in comparison to other groups.

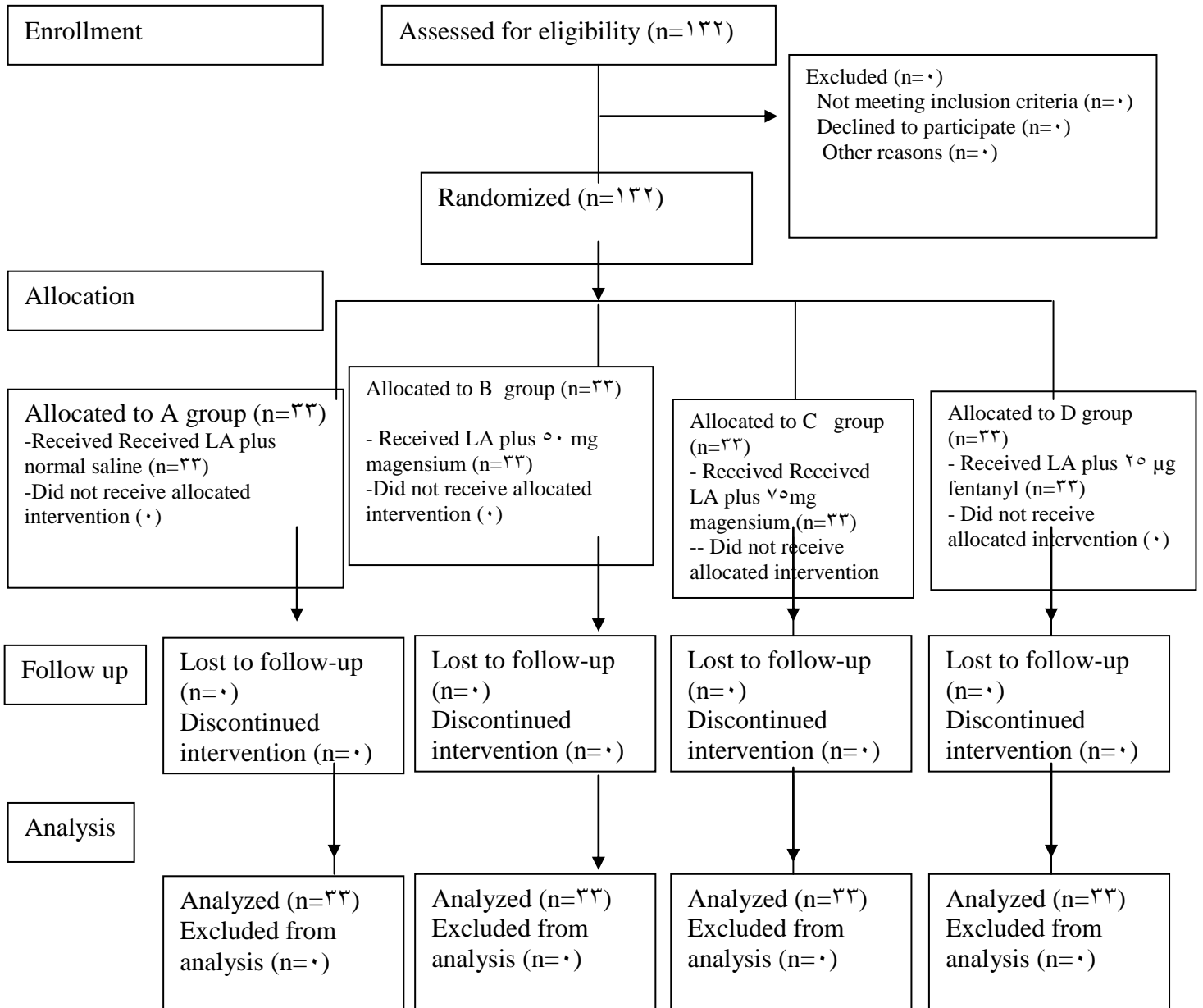


Figure (1) Flow chart in the study.

Table (1): Characteristics of the patients and duration of surgery

	Group A (n=33)	Group D (n=33)	Group C (n=33)	Group D (n=33)	P value
Age (years)	30±8	31.7±7.4	29.8±0.9	28.7±7.4	0.370
Weight(kg)	77.9±7.4	78.0±6.9	77.7±7	78.1±7.0	0.962
Height(cm)	171.0±8.1	173.7±7.7	170.4±7.4	172.2±7.0	0.319
ASA I/II	20/8	24/9	24/9	22/11	0.870
Sex♂/♀	20/13	18/15	22/11	23/10	0.090
Duration of surgery (min)	90±14	90±13	92±11	94±11	0.370

Data were expressed as mean ± SD or number. P value between the four groups. No significant difference. P value > 0.05.

Table(2): Comparison of mean arterial blood pressure (mmHg) between and within the four groups.

	Group A (n=33)	Group B (n=33)	Group C (n=33)	Group D (n=33)	P value
Base line	92.7±0.8	93.4±4.8	92.1±0.7	94.3±0.1	0.382
1 min AS	80.4±3.1	87.1±3.3	80.7±4.0	80.0±4.3	0.769
5 min AS	83.2±2.0*	83.0±3.7*	81.3±3.7*	82.2±3.2*	0.080
10 min AS	83.0±3.1*	82.7±4.1*	80.0±4.1*	80.2±3.3*	0.222
15 min AS	82.8±2.8*	80.2±2.1*	79.0±3.1*	79.1±3.2*	0.149
30 min AS	80.0±3.0*	80.1±2.3*	87.0±4.0*	84.0±3.8*	0.187
45 min AS	87.3±2.7	87.2±3.4	88.4±3.2	87.0±4.0	0.314
70 min AS	89.0±2.8	89.7±4.1	90.4±3.7	88.0±3.7	0.377

AS, after spinal anesthesia. * Significant between the given time and baseline value in each group. p value between the four groups. P value < 0.05 considered significant.

Table (3): Comparison of the heart rate (beats/min) between the four groups.

	Group A (n=33)	Group B (n=33)	Group C (n=33)	Group D (n=33)	P value
Base line	87.7±7.3	80.3±8.9	84.7±7.4	87.2±7.2	0.404
1 min AS	81.2±0.7	80.2±7.1	78.3±4.1	79.1±4.2	0.109
5 min AS	78.3±4.7*	77.3±4.0*	74.1±3.1*	74.2±3.8*	0.282
10 min AS	77.1±3.2*	74.2±4.1*	72.0±2.4*	71.3±2.7*	0.420
15 min AS	70.7±7.4*	72.1±1.8*	70.7±3.1*	77.2±3.7*	0.380
30 min AS	79.0±7.1*	79.2±2.7*	79.1±2.9*	77.3±4.3*	0.179
45 min AS	80.0±4.0	80.9±3.1	81.1±4.0	70.1±4.7*	0.098
70 min AS	81.0±0.1	82.0±3.0	83.0±3.1	77.4±3.0*	0.102

AS, after spinal anesthesia. * Significant between the given time and baseline value in each group. p value between the four groups. P value < 0.05 considered significant.

Table (4): characters of spinal anesthesia

Item	Group A (n=33)	Group B (n=33)	Group C (n=33)	Group D (n=33)	P value
Onset of sensory block (min)	7.7±1.9	9.4±2.3*†	9.9±2.1*†	5.3±1.2*	0.001
Duration of sensory block (min)	170±23	192±18.1*	199±17.3*	198±10.1*	0.001
Onset of motor block(min)	8.8±2.1	11.3±2.6*†	12.1±2.7*†	7.1±1.9*	0.001
Duration of motor block(min)	122±18.1	100±19.2*	107±20.1*	103±18.6*	0.001
Time to 1 st analgesic request (min)	188±11.2	218±17.1*	240±10.4*†!	230±10.3*!	0.001

* Significant to group A control group. † Significant to group D fentanyl group. ! Significant to group B magnesium 0.0 mg. P value between the four groups.

Table (5): side effects associated with spinal anesthesia in each group

Item	Group A (n=33)	Group B (n=33)	Group C (n=33)	Group D (n=33)	P value
Bradycardia	8/33	9/33	9/33	10/33†	0.226
Hypotension	10/33	10/33	11/33	17/33	0.053
Vomiting	3/33	2/33	3/33	4/33	0.860
Pruritus	0/33	0/33	0/33	9/33†	0.001

†Significant to group D fentanyl group. P value between the four groups.

Discussion

Magnesium is non-competitive N-methyl D- aspartate (NMDA) receptor antagonist and inhibits voltage -gated calcium channels⁽¹⁾. Administration of magnesium decreases C- fibers activation through inhibiting slow excitatory post synaptic currents produced by activation of NMDA receptors present in dorsal horn of spinal cord and suppresses nociceptive impulse in neuropathic pain, and increases opioids antinociception⁽¹⁾. Safety of subarachnoid magnesium administration was examined in animal studies such as chanimov et al.,⁽¹⁷⁾ research in which 1.26 mg bolus subarachnoid dose of magnesium was administered in rats on alternate days over a month and they found this dose produced transient motor and sensory block similar to subarachnoid lidocaine with no neurological deficit as shown by clinical examination and histological examination of spinal cord in rats. Simpson et al.,⁽¹³⁾ in their randomized controlled study administered 5mg/kg magnesium in the subarachnoid space of dogs before aortic cross clamping and they found that no dog had neurological deficit as evidenced by histopathological examination, this means

not only the safety of subarachnoid magnesium but also it can protect against ischemic injury. The dos of 5mg/kg (50-60 mg) of subarachnoid magnesium in dogs was extrapolated to 50-60 mg in human with considering the difference in the body weight and cerebrospinal fluid volume between human and dogs.

The dose of subarachnoid magnesium based on clinical finding from rat model of post-operative pain in Kroin et al.,⁽¹⁰⁾ research in which they concluded that 281µg of subarachnoid magnesium potentiated morphine antinociception and based on the difference in cerebrospinal fluid volume in rats and human, this dose was extrapolated to 0.0 mg in human. It was based also on Buvanendran et al.,⁽¹⁷⁾ research which was the first randomized controlled trial investigating the effect of intrathecal magnesium as adjuvant to intrathecal fentanyl in labor analgesia in which they used 0.0 mg of intrathecal magnesium.

Khalili et al.,⁽¹⁹⁾ in their study to evaluate the effects of adding intrathecal magnesium as adjuvant for spinal anesthesia in lower extremity surgery and they used a dose of

100 mg magnesium and they concluded that no more benefits of the dose of 100 mg over 50 mg in its effect in prolongation of sensory, and motor block. Jabalameli et al.,⁽¹⁴⁾ in their study to compare between different doses of intrathecal magnesium for spinal anesthesia in cesarean section and they found that the best dose of intrathecal magnesium was 50 mg to obtain the best benefits with the least side effects. In the current study two doses of magnesium were chosen 50 mg and 100 mg for intrathecal use. As regards the onset and duration of sensory and motor block of spinal anesthesia, this study found magnesium delayed onset of sensory and motor block even more than the control group, the delay was more in the group of 100mg, and it found that magnesium prolonged the duration of spinal anesthesia which was more in the group of 100 mg group but still less than fentanyl group. Buvanendran et al.,⁽¹⁵⁾ in their study found this dose to prolong the analgesia without side effects and they also found that the baricity (measured by refractometer) of local anesthetic solution which contain magnesium significantly affect the onset and duration of spinal anesthesia, They found that hyperbaric solution (compared to cerebrospinal fluid specific gravity) which result from adding magnesium to hyperbaric bupivacaine would increased the duration of spinal anesthesia while when adding magnesium to isobaric bupivacaine would decrease the duration of spinal anesthesia. The current study used hyperbaric bupivacaine 0.5% so it was suspected to have hyperbaric solution and prolonged duration of spinal anesthesia.

This was in agree with the results of Sunil et al.,⁽¹⁶⁾ in their study to compare between multiple adjuvants to local anesthetics in subarachnoid block and they noticed delay in the onset of sensory and motor block in magnesium group more than fentanyl group. Also this was in agree with Malleeswaran et al.,⁽¹⁷⁾ who examined 50 mg of intrathecal magnesium as adjuvant to intrathecal bupivacaine 10 mg and fentanyl 20 µg in mild preeclampsia and they noticed that intrathecal magnesium delayed the onset of spinal anesthesia and they prolong duration of spinal anesthesia.

Ozalveli et al.,⁽¹⁸⁾ in their clinical trial on 100 patients scheduled for lower limb surgery under spinal anesthesia and they found that 50 mg of intrathecal magnesium would delay onset of sensory and motor block and prolong duration of spinal anesthesia produced by 10 mg bupivacaine and 20 µg fentanyl and they explained this by the difference in baricity and pH of the magnesium containing solution.

Nath et al.,⁽¹⁹⁾ in their study to evaluate efficacy and safety of intrathecal 100 mg of magnesium as adjuvant to bupivacaine 0.5% in subarachnoid block for hysterectomy found that there was a delay in the onset of sensory and motor block and they referred this results to the changes of pH of local anesthetic solution and they concluded that magnesium had a good safety profile.

Dayioglu⁽²⁰⁾ in their study to evaluate the effects of 50 mg of intrathecal magnesium as adjuvant to bupivacaine 0.5% and fentanyl in knee arthroscopy and they found that there was prolongation of time to two segments regression without affecting the time of complete motor recovery.

Kherzi et al.,⁽²¹⁾ in their study in which they compared between intrathecal 50 mg magnesium and 20 µg fentanyl as adjuvant to hyperbaric bupivacaine 10 mg in subarachnoid block for lumbar lower limb orthopedic surgery and they found that magnesium delayed onset of both sensory and motor block compared to fentanyl and prolonged the duration of spinal analgesia with subsequent decrease in the analgesic consumption.

Jabalameli et al.,⁽¹⁴⁾ in their study to compare between different doses of intrathecal magnesium for spinal anesthesia for cesarean section and they found that addition of magnesium would delay onset of sensory and motor block but prolonged the duration of spinal analgesia. These effects increased with increase in the dose of magnesium but side effects like nausea, vomiting, and hypotension began to appear at a dose of 100 mg intrathecal magnesium. On the other hand Unlugenc and colleagues⁽²²⁾ concluded that magnesium had no effects on the onset of spinal

anesthesia while fentanyl produce high level of sensory block with rapid onset more than magnesium and they explained this by the supraspinal action of fentanyl beside its spinal action at opioid receptors in the dorsal horn while magnesium had spinal action only and cannot pass the blood brain barrier, also they reported that magnesium decreased the duration of spinal analgesia by 19 minutes which could be explained rapid removal of magnesium from cerebrospinal fluid. Otukomi et al.,⁽¹⁷⁾ explained the delayed onset of local anesthetic mixture containing magnesium by the stimulation of cytochrom P450 enzyme which responsible of hydroxylation and metabolism of bupivacaine. As regards safety and side effects of intrathecal magnesium the current study found that intrathecal magnesium was not associated with serious side effects as respiratory depression, excessive sedation, nausea, and vomiting. This was in agree with Arcioni et al.,⁽¹⁸⁾ in their study for evaluation the effect of combined intrathecal and epidural magnesium sulphate on postoperative analgesic requirements, they reported that intrathecal use of magnesium was not associated with serious side effects such as systemic toxicity, hypotension, arrhythmia, somnolence, slurred speech neither intra-operative nor postoperative.

Conclusion

This study concluded that intrathecal magnesium sulphate when used as adjuvant to hyperbaric bupivacaine 0.5% in lower limb surgeries delayed the onset of spinal anesthesia (both sensory and motor block) and prolonged the duration of spinal anesthesia. These effects increased with increase the dose of intrathecal magnesium from 0.5mg to 1.0mg. Intrathecal magnesium was associated with less incidence of side effects than fentanyl and control groups.

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