DISCUSSION

Recent trends of anaesthesia show increased popularity of regional anaesthesia among anaesthetists. General anaesthesia is associated with higher mortality rate in comparison to regional anaesthesia. However, regional anaesthesia is not without risk. Deaths in regional anaesthesia are primarily related to excessive high regional blocks and toxicity of local anaesthetics. Reduction in doses and improvement in technique to avoid higher block levels and heightened awareness to the toxicity of local anaesthetics have contributed to the reduction of complications related to regional anaesthesia.[89]

Intrathecal administration of local anaesthetic and opioid combinations is based on the clinical observation that their combination limits the regression of the sensory block seen with local anaesthetics alone and improves the quality of dynamic pain relief. [90]

Techniques involving the smaller doses of opioid in combination with non-opioid adjuvant drugs are becoming increasingly popular approaches for perioperative pain management.[91]

The optimal non-opioid analgesic technique for postoperative pain management would not only reduce pain scores and enhance patient satisfaction, but also facilitate earlier mobilization and rehabilitation by reducing pain-related complications after surgery. Recent evidence suggests that this goal can be best achieved by using a combination of preemptive techniques involving both central and peripheral-acting analgesic drugs (such as local anaesthetics, non- steroidal anti-inflamatory drugs, kitamine, N-methyl D-aspartate receptor antagonist). [91]

Noxious stimulation leads to the release of glutamate and aspartate neurotransmitters, which bind to various subclasses of excitatory amino acid receptors, including the N-methyl D-aspartate (NMDA) receptor. Activation of NMDA receptors leads to calcium and sodium influx into the cell, with an efflux of potassium and initiation of central sensitization and wind-up.[92,93]

NMDA receptors signalling may be important in determining the duration and intensity of postoperative pain. Magnesium blocks NMDA channels in a voltage-dependent way, and the addition of magnesium produces a reduction of NMDA-induced currents [94]. Magnesium sulfate has been used systemically, and has shown anti-nociceptive effects, but results are not consistent. [95,96]

The aim of this study was to evaluate the effect of I.V. magnesium sulphate infusion in total knee replacement surgery under spinal anaesthesia as regard haemodynamic changes and analgesic effect in postoperative period.

This study was carried out on forty patients scheduled for total knee replacement surgery. They were categorized randomly into 2 groups (20 patients each).

Group I (Magnesium group)

Bupivacaine (heavy) 0.5% 2.5 ml (12.5 mg) with fentanyl 25 µg intrathecally and $MgSo_4$ as a I.V. bolus (50 mg /kg), and then 15mg/kg/hr infusion during the operation intravenously.

Group II (saline group)

Bupivacaine (heavy) 0.5% 2.5 ml (12.5 mg) with fentanyl 25 µg intrathecally and the same volume of isotonic saline I.V. over the same period.

Demographic data

Comparison between the two groups showed no significant difference as regards age, sex, weight and height.

Heart rate

In the present study, there was no statistical significant difference in the heart rate in group I patients during intraoperative period, immediately postoperative and up to 8 hours postoperatively.

Magnesium causes a dose-dependent negative inotropic effect. In humans, haemodynamic studies have shown that it has a peripheral (predominantly arteriolar) vasodilatory effect [120-122]. Prehydration using 500 ml of lactated Ringer's solution can prevent this hypotensive effect of negative inotropism.

Heart rate increased significantly in group I at 12 hours and thereafter. This may be due to the appearance of pain as a result of the offset of magnesium effect which correlated with the VAS changes [121].

Comparing between the two groups showed no statistical significant differences in the heart rate in the most of the period of the study.

Similar results were obtained by Kahraman et al [100] who compared a dose of 65 mg/kg magnesium sulphate in 250 ml 5% dextrose at 3.5 ml/min rate I.V. under spinal anaesthesia and same volume of isotonic saline (the control group) for abdominal hysterectomy. They found no change in heart rate between the 2 groups which could be explained by low serum magnesium concentration (1.7±0.6 mmol/l) which is below the level of minor side effects.

Also similar results were observed by Hwang et al [101] who found that intravenous magnesium (50mg/kg) as a bolus dose and then 15mg/kg/hr $MgSO_4$ as infusion in total hip replacement arthroplasty has no effect on the heart rate.

In contrast to the present study, Seyhan et al [99] compared the effects of three different doses of $MgSO_4$ (group I used 40 mg /kg of magnesium as a bolus before induction of anaesthesia, followed by I.V. infusion of normal saline, group II used 40 mg /kg of magnesium as a bolus followed by magnesium 10 mg /kg/ hr and group III used 40 mg /kg of magnesium as a bolus followed by magnesium 20 mg /kg/hr) on haemodynamic variables and postoperative pain relief in gynaecological surgery. They reported that there

was significant decrease in heart rates in all doses of magnesium which was intensified by increasing magnesium dosing. This difference may be explained by the fact that their procedures were done under general anaesthesia.

Also, in contrast to the present study, Manjushree Ray et al [98] assessed the effect of intravenous magnesium sulphate (30 mg/kg as a bolus before induction and 10 mg/kg/hour by infusion) on intraoperative haemodynamics, anaesthetic consumption and postoperative recovery on seventy five patients undergoing elective upper limb orthopaedic surgery. They found that heart rate in magnesium group was significantly lower after induction and in the intraoperative period. This difference may be explained by the fact that their procedures were done under general anaesthesia.

Mean arterial blood pressure:

As regard the mean arterial blood pressure, comparing the two studied groups showed insignificant differences throughout the times of measurement.

Significant increase in the MABP were observed in group I after 120 min, 4, 8, 12, 16, 20 and 24 hrs postoperatively. This may be due to the appearance of pain as a result of the offset of magnesium effect which correlated with VAS changes.

In agreement with the results of the present study, Dabbagh et al [103] studied the effect of 8 mg/kg intravenous magnesium sulfate on postoperative pain started before the incision and continued up to the end of the surgical procedure in 60 patients undergoing lower limb orthopedic surgery using spinal anaesthesia. They found that intravenous magnesium showed no significant hypotension due to prehydration with fluids and the magnesium bolus dose was infused over 15 minutes.

Also Kara et al [104] studied the effect of I.V. magnesium sulphate on perioperative pain (a bolus of 30 mg/ kg then 0.5 g/ h infusion for the next 20 h) on 24 patients undergoing elective hysterectomy under spinal anaesthesia. They found that intravenous magnesium showed no significant hypotension due to prehydration with fluids and the magnesium bolus dose was infused over 15 min. Also, Seyhan et al [99] did not observe hypotensive episodes requiring ephedrine treatment even in the higher rate group.

Disagreement with the results of the present study, Moharari et al [105] added 40 mg/kg magnesium sulphate as a bolus then continuous infusion of 10 mg/kg/hr for the intraoperative hours of laparoscopic gastrointestinal surgeries on 32 patients divided into magnesium and control groups. They reported that MAP of magnesium group decreased during the operation due to decreased both CO (cardiac output) and SVR (systemic vascular resistance) which is measured by Transoesophageal echo. They showed significant decrease in CO in both magnesium and control groups. Intraoperative SVR, showed significant increase in control group, but showed significant decrease in magnesium group. This difference from our study may be due to the use of general anaesthesia in their study.

Arterial oxygen saturation:

As regards the arterial oxygen saturation, there was no significant difference between the two groups all through the measuring intervals which may be due to; first: the spinal anaethesia done in the lateral decubitus position so the local anaesthetic used while

designing the study was kept to minimal possible doses, with non -involvement of the intercostal muscles and/or diaphragm during motor blockade.[106] Second, supplemental oxygen administration through a face-mask throughout the procedure. [107]

In agreement with the present study, Telci et al [108], showed that administration of magnesium sulfate 30 mg/ kg as a bolus dose of magnesium and then 10 mg/kg/hr by continous infusion for 81 patients undergoing elective surgery under spinal anaesthesia, had no significant difference in arterial oxygen saturation between the comparable groups.

Also, Seyhan et al [99] found that none of the patients demonstrated decreased SpO_2% during the magnesium infusion and throughout the procedure.

Respiratory rate:

As regards the respiratory rate, group I was statistically significantly lower than group II at interval time 45, 60 min intraoperatively may be due to the sedative effect of magnesium as expected the magnesium is a CNS depressent.[123]

In the present study, the respiratory rate decreased in some cases of group I to 9 breath /min but it never reach a critical level.

In agreement with the present study, Moharari et al [105] found that postoperative RR, showed significant decrease in magnesium and control groups. The mechanism of action may be due to the effect of magnesium sulphate on the sympathetic system.

Also, Seyhan et al [99] found that none of the patient demonstrated hypoventilation (R.R.<12/min) during the postoperative magnesium infusion and monitored care period in the recovery period.

Efficacy of postoperative analgesia:

Postoperative analgesia was evaluated in the present study using visual analogue scale (VAS) [21], the time for first need for postoperative analgesia and total dose of analgesic consumption in the 24-hour postoperative period.

The VAS was significantly higher in Group II than in group I at 90 min, 12 and 24 hrs respectively.

The time for first need of analgesia was significantly shorter in group II than in group I.

Total dose of analgesic consumption in the 24-hour postoperative period was significantly higher in group II than in group I.

All these results can be explained by the fact that magnesium is a physiologic calcium channel blocker and a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist and these properties appear to play an important role in the prevention and treatment of perioperative pain by preventing central censitization due to peripheral nociceptive stimulation and abolish such hypersensitivity once established. [113]

In agreement with the results of our study, Hwang et al[101] demonstrated the effect of intravenous magnesium (50mg/kg) as a bolus dose for 15 min and then 15mg/kg/hr in total hip replacement arthroplasty under spinal anaesthesia and they reported lower

postoperative pain scores and reduced total analgesic consumption in Mg group in comparsion to the saline group.

Also kara et al [104] and Telci et al [108] stated significant reduction in postoperative analgesic consumption when they used intravenous magnesium in a bolus dose (30mg/kg) and 10 mg/kg as a continuous infusion in comparsion with the saline group under spinal anaesthesia.

Bilir et al [109], added 50 mg magnesium sulphate as a bolus and then continuous infusion 100 mg/kg/hr for 24 hrs during hip replacement under spinal anaesthesia and showed significantly smaller doses of postoperative analgesic requirement and decreased total opiod analgesic consumption.

Also Sedighinejad et al [110] reported a significant decrease in pain scores (VAS) in magnesium sulphate group in the first 24 hrs after magnesium sulphate infusion 5 ml/hr in orthopaedic surgery on 60 patients under spinal anaesthesia.

In contrast to our results, Ko et al [111] studied the effect of administration of magnesium sulphate 50 mg/kg as a bolus followed by 15 mg/kg/hr continuous infusion for 6 hours in abdominal hysterectomy under general anaesthesia. They found that there was no effect on postoperative pain and suggested that perioperative intravenous magnesium infusion may not be useful for preventing postoperative pain when using general anaesthesia.

Also Tramer et al [112] demonstrated that no difference in time to first rescue analgesia or pain intensities after 4 gm $MgSo_4$ administered for ambulatory ilioinguinal hernia repair under general anaesthesia. This difference may be due to the use of general anaesthesia in their study.

Postoperative side effects:

As regarding side-effects, the incidence was comparable in both groups and there were statistical insignificant differences between the studied groups. These side effects possibly related to post spinal anaesthesia side effects [115-118].

Nausea occurred in 6 patients in group I and in 2 patients in group II. Nausea was transient and disappeared spontaneously without treatment.

Vomiting occurred intraoperatively in 1 patient in group I and in 1patient in group II. Vomiting was treated immediately by head down and tilt to the left, followed by administration of dexamethasone 8 mg intraoperatively.

Hypotension occurred in 3 patients in group I and in 1 patient in group II. This hypotension may be explained by the resultant sympathetic blockade due to spinal anaesthesia leading to peripheral vasodilatation, decrease in total peripheral resistance and hence a decrease in arterial blood pressure. [102] After an extra fluid bolus of 4ml/kg administered, mean arterial pressure increased gradually. Despite this, hypotension that occurred was treated with incremental intravenous ephedrine in a dose of 5 mg each time.

Bradycardia occurred in 1patient in group I was treated by atropine 0.5 mg I.V.

Shiviring occurred in 2 patients in group I and in 1 patient in group II may be due to the effect of spinal anaesthesia by inhibiting the body's thermoregulatory capability and cutaneous vasodilation (triggered by post-operative pain) and was treated by active warming .[119]

Flushing occurred in 1 patient in group I and did not occurred in group II may be due to the use of atropine used in treatment of bradycardia and was transient and disappeared spontaneously without treatment.

Similar to our result, Sedighinejad A et al [111] they found fewer side effects on magnesium-sufentanil regimen in terms of nausea, vomiting, and sedation.

Also, Shariat R et al [105] they found minimal side effects of magnesium. So it seems to be beneficial along with routine general anaesthesia in major GI surgeries.

Apan et al. [114] added 5 mg/ kg i.v. bolus of magnesium sulphate followed by a 500 mg /h infusion for 24 hrs on 50 patients under spinal anaesthesia and evaluated the safety of intravenous magnesium sulphate and observed that it had no significant side effects.

SUMMARY

One of the primary aims of anaesthesia is to alleviate the patient's pain and agony, by permitting the performance of surgical procedures without any discomfort. Relief of postoperative pain has gained real importance in recent years considering the central, peripheral and immunological stress response to tissue injury. Any expertise acquired in this field should be extended into the postoperative period, which is the period of severe, intolerable pain requiring attention. So there is a need for extended analgesia without any side effects to achieve this goal.

Understanding pain physiology is very important in countering it. From what is known it is clear that pain recognition involves transduction, transmission, modulation and perception. The signal is modulated at various levels before perceived. Various transmitters, facilitators and inhibitors are involved. Body responds to painful stimuli, which may be helpful or counterproductive. Better knowledge helps not only in artificial modulation of pain but also to suppress the harmful reflex responses.

The optimal non-opioid analgesic technique for postoperative pain management would not only reduce pain scores and enhance patient satisfaction, but also facilitate earlier mobilization and rehabilitation by reducing pain-related complications after surgery. Recent evidence suggests that this goal can be best achieved by using a combination of preemptive techniques involving both central and peripheral-acting analgesic drugs.

Neuraxial and other regional anaesthetic techniques play an important role in decreasing the incidence of perioperative thromboembolic complications, providing postoperative analgesia, and facilitating early rehabilitation and hospital discharges.

The aim of this work was to study the effect of intravenous infusion of magnesium sulphate during total knee arthroplasty procedures using spinal anaesthesia on the postoperative pain as regard the analgesic efficacy, and side effects

The study was done on forty patients American Society of Anaesthesiologists (ASA) class I or II aged 40 to 60 years old admitted to Al-Hadara University Hospital in Alexandria. After approval of the medical ethical committee, an informed written consent was taken from all patients.

Patients were randomly categorized into two equal groups (20 each) using closed envelope technique;

Group I (group M, n=20): patients received Bupivacaine (heavy) 0.5% 2.5 ml (12.5 mg) in the subarachnoid space. Magnesium sulphate 50 mg/kg I.V. for 15 min after spinal anaesthesia and then 15 mg /kg/ h by continuous I.V. infusion until the end of surgery.

Group II (group S, n=20): patients received Bupivacaine (heavy) 0.5% 2.5 ml (12.5 mg) in the subarachnoid space. The same volume of isotonic saline over the same period were received.

Preoperative evaluation was done by complete history taking, physical examination and necessary laboratory investigations.

Patients received a volume preload in the form of 500 ml Ringer's solution. Midline-approach spinal anaesthesia was done in the lateral decubitus position at L4-5 intervertebral space by one anaesthesiologist in all patients.

Haemodynamic measurements (heart rate, mean arterial blood pressure, arterial oxygen saturation and respiratory rate) measured before surgery and every 15 min during the procedure, Mean arterial blood pressure and heart rate were recorded every 30 minutes for the first two hours post-operatively, then every 4 hours for the first 24 hours**.** Postoperative pain (visual analogue scale, time to 1st rescue analgesia and total dose of analgesics used), and perioperative side effects or complications (including hypotension, bradycardia, nausea, vomiting...etc.) were all recorded and statistically analyzed.

There was no significant difference between the two groups regarding age, sex, weight and height.

There was significant difference between the two studied groups regarding heat rate, it was significantly higher in group II (saline) than group I ($MgSO_4$) at 90 min and 4 hrs postoperatively.($p=0.025$, $p= 0.026$).

There was no statistically significant difference between the two groups regarding mean arterial blood pressure, arterial oxygen saturation.

As regards R.R., group I was statistically significantly lower than group II at interval time 45, 60 min intraoperatively. ($p= 0.001$ and $p=0.002$)

As regard the visual analogue scale (VAS), The VAS was significant higher in Group II than in group I at 90 min, 2,4,12, 20 and 24 hrs respectively.($p= 0.023$, 0.004, 0.024, 0.012, 0.010, 0.008).

The time for first need of analgesia was significantly shorter in group II than group I in patients who require pethidine supplements. ($P=0.004$)

Total dose of analgesic consumption in the 24-hour postoperative period was significantly higher in group II than in group I. ($P=0.015$)

There was no statistically significant difference between the two studied groups regarding perioperative side effects as nausea, vomiting, hypotension, bradycardia and shivering.

From this study we conclude that:

1. The addition of intravenous magnesium sulphate to the spinal anaesthesia significantly improves pain scores and provide prolonged postoperative analgesia in total knee arthroplasty .
2. Intravenous magnesium together with the spinal anaesthesia produce a significant decrease in postoperative analgesic consumption.
3. The addition of intravenous magnesium sulphate to the spinal anaesthesia provides stable haemodynamics without significant side effects.

From this study, we recommend the following:

1) The use of intravenous magnesium sulphate as a routine for operative anaesthesia and postoperative pain management in all lower limb surgeries.
2) A large randomized controlled study with a prolonged follow-up period would be useful to confirm the clinical safety of intravenous magnesium sulphate .
3) Further study on different comparable intravenous doses of magnesium to reach the ideal intravenous dose with the best postoperative analgesic effect and the least side effects would be useful.

CONCLUSION

From this study, we concluded that:

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2. Intravenous magnesium together with the spinal anaesthesia produces a significant decrease in postoperative analgesic consumption.
3. The addition of intravenous magnesium sulphate to the spinal anaesthesia provides stable haemodynamics without significant side effects.