A comparative evaluation of magnesium sulphate and nitroglycerine as potential adjuncts to lidocaine in intravenous regional anaesthesia

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ABSTRACT

Introduction: This randomized control trial was carried out to evaluate and compare the efficacy of magnesium sulphate and nitroglycerine (NTG) as adjuncts to lidocaine in intravenous regional anaesthesia (IVRA).

Materials and Methods: Seventy-five, ASA grade I and II patients, aged between 20–50 years, scheduled for hand and forearm surgery were selected and entered randomly into three study groups. Patients in group C received 3 mg/kg of preservative free lidocaine 2% diluted with saline to a total volume of 40 ml. Patients in group M received 3 mg/kg of preservative free lidocaine 2% mixed with 6 ml of 25% magnesium sulphate (1.5 g) diluted with saline to a total volume of 40 ml. Patients in group N received 3 mg/kg of preservative free lidocaine 2% mixed with 200 µg of nitroglycerine diluted with saline to a total volume of 40 ml. Sensory and motor block onset and recovery time, tourniquet pain onset time, intraoperative fentanyl requirement, the total number of patients requiring rescue analgesia and the time to first analgesia requirement, intra-operative and postoperative degree of analgesia were evaluated.

Results: The sensory and motor block onset times were shorter in group M and N as compared to group C (P< 0.004, 0.0036 for sensory block, 0.021, 0.038 for motor block. The mean time of onset of sensory block was earliest in group M and the mean time of onset of motor block was earliest in group N. Mean time of onset of tourniquet pain in the three groups was similar in groups M and N. The sensory and motor block recovery time were significantly prolonged in M and N group as compared to group C (P < 0.001). Intraoperative fentanyl requirement (P value= 0.041), the total number of patients requiring rescue analgesia (P value = 0.009) and the time to first analgesia requirement (P value = 0.038) were lower in group M.

Conclusion: The addition of both magnesium sulphate and nitroglycerin (NTG) to lidocaine for intravenous regional anaesthesia (IVRA) leads to early onset of sensory block and prolonged postoperative analgesia, with no side effects.

Key Words: Intraoperative regional anaesthesia, lidocaine, magnesium sulphate, nitroglycerine

INTRODUCTION

Intravenous regional anesthesia (Ivra) was first described in 1908 by August Gustav Bier, a German Surgeon, for anesthesia of hand and forearm.¹ It is easy to administer, reliable, cost-effective and quite safe for operations on limbs. It is also advantageous especially in poor risk patients and in emergency situations. Also, there is very little anesthetic hangover, so that the patient can be discharged the same day. A rapid return to normal function almost immediately after cuff release is highly appealing, as one is able to assess neurological signs after fracture reduction.

Unfortunately, the rapid dissipation of the block with resulting post-operative pain is one of the limitations
of this technique, as is ‘tourniquet pain’. Numerous adjuvants have been tried in an effort to overcome these problems, like opioids, tramadol, nonsteroidal anti-inflammatory drugs, dexmedetomidine, muscle relaxants, potassium, alkalinization with sodium bicarbonate and recently, magnesium and nitroglycerine.\textsuperscript{5,6} Though the efficacy of magnesium sulfate and nitroglycerine in IVRA has been proven, there are no studies to compare the two as adjuncts in IVRA. The present randomized controlled trial was carried out to evaluate and compare the efficacy of magnesium sulphate and nitroglycerine as adjuncts to lidocaine in IVRA, and to note the incidence of side effects, if any.

**MATERIALS AND METHODS**

This study was conducted after obtaining approval from hospital ethical committee and written informed consent from the patients. Seventy-five ASA grade I and II patients, aged between 20–50 years, of either sex, scheduled for hand or forearm surgery (that is carpal tunnel release, tendon repair, trigger finger) were randomly chosen. Patients with sickle cell anemia, history of drug allergy, Raynaud’s disease, scleroderma, myasthenia gravis, cardiac disease, diabetes mellitus, peptic ulcer, gastritis, liver or renal insufficiency and history of convulsions were excluded from the study. All patients were kept fasting for 6 hours before surgery. Intradermal test for lidocaine sensitivity was done in all patients. The patients were divided randomly into three groups of 25 each, according to computer generated table of random numbers. All patients were premedicated with 0.1 mg/kg midazolam and atropine 0.01 mg/kg, administered intramuscularly 45 minutes prior to surgery. In the operation theatre, noninvasive arterial blood pressure, electrocardiogram and peripheral oxygen saturation monitoring was started. Two intravenous cannulae were placed; one in a vein on the dorsum of the hand to be operated (22 gauge) and the other in the opposite hand. A double tourniquet was positioned on the upper arm of the hand to be operated. Arm was elevated for 2 min and Esmarch bandage applied for exsanguination of the arm. Circulatory isolation of arm was confirmed by inspection of the color of the limb, absence of radial pulse and loss of pulse oximetry tracing in the ipsilateral index finger. The upper (proximal) tourniquet was then inflated to a pressure of 100 mmHg above the systolic blood pressure of the patient and Esmarch bandage was removed. The anesthetic solution was prepared by an observer unaware of the study and was given over a period of 90 seconds.

- Patients in group C received 3 mg/kg of preservative free lidocaine 2% diluted with saline to a total volume of 40 ml
- Patients in group M received 3 mg/kg of preservative free lidocaine 2% mixed with 6 ml of 25% magnesium sulphate (1.5 g) diluted with saline to a total volume of 40 ml
- Patients in group N received 3 mg/kg of preservative free lidocaine 2% mixed with 200 microgram of nitroglycerine diluted with saline to a total volume of 40 ml.

When patient felt discomfort at the proximal tourniquet site, the distal tourniquet was inflated to the same pressure and proximal one was deflated. Onset of sensory block was assessed by a pin prick performed at 1 minute interval in the dermatomal sensory distribution of the medial and lateral ante brachial cutaneous, ulnar, median and radial nerves. Sensory block onset time was noted as time elapsed from injection of drug to sensory block achieved in all dermatomes. Onset of motor block was assessed by asking the subject to flex and extend his/her wrist and fingers. Complete motor block was noted when no voluntary movement was possible. Time of onset of tourniquet pain was recorded. Assessment of tourniquet pain and Intra-operative degree of analgesia was evaluated by Visual Analogue Scale (vas) of 0–10 every 10 minutes (0 = “no pain” and 10 = “worst pain imaginable”). When pain was > 3 on the VAS scale, patients were given intravenous fentanyl 1 μg/kg. Times and total dose of intraoperative fentanyl were recorded. Sensory block recovery time was noted as the time elapsed from release of tourniquet to sensory block recovery in all dermatomes. Motor block recovery time was noted as the time elapsed from release of tourniquet to complete motor block recovery. The tourniquet was not deflated before 30 min and was not kept inflated for > 2 h. At the end of surgery, the tourniquet was deflated by a cyclic deflation technique. Mean arterial pressure (MAP), heart rate (HR) and visual analogue scale (VAS) were recorded at 1, 2, 4, 6, 12, and 24 h. The time to first analgesic requirement was noted (the time elapsed from tourniquet release until first patient request for analgesic). Patients were given 75 mg of diclofenac intramuscularly when VAS was > 4. Complications, if any, were looked for in the perioperative period.

**Statistical analysis**

The statistical analysis was done using SPSS (statistical package for the social sciences) software version 12.0 for windows. The sample size was determined using Altman’s normograph with power of 80% and deducing a standardized difference as the ratio between smallest clinically worthwhile difference and standard deviation. Quantitative variables were analyzed and reported as mean and standard deviation. Statistical significance among the groups was evaluated using one-way analysis of variance (ANOVA) followed by application of Bonferroni’s \textit{t} test to look for intergroup comparisons.

**RESULTS**

Seventy-five patients were enrolled in the study. All the three groups were comparable in age, sex, weight, ASA grading, duration of surgery and duration of
tourniquet [Table 1]. Sensory block was achieved earliest in group M (2.60 ± 0.50 min in group M, 3.44 ± 0.278 min. in group N, 5.10 ± 1.00 min. in group C) and motor block in group N (5.00 ± 0.677 min. in group N, 6.46 ± 0.627 min. in group M, 8.92 ± 0.886 min. in group C) [Table 2]. Mean time of onset of tourniquet pain was comparable in the three groups [Table 2]. The mean sensory and motor block recovery time was significantly prolonged in test groups as compared to control group (P value < 0.001) but there was no significant difference between the two test groups [Table 2]. The quality of intraoperative analgesia as assessed by VAS was comparable in the three groups. Intraoperative fentanyl requirement and the total number of patients requiring rescue analgesia were significantly lower in group M [Table 3]. The time to first request for postoperative analgesia was significantly prolonged and the total analgesic requirement was significantly lowest in group M [Table 3]. Nausea was reported in 3 patients in Group C.

DISCUSSION

The addition of both magnesium sulphate and nitroglycerine (NTG) to lidocaine for IVRA leads to early onset of sensory block and prolonged postoperative analgesia when given in Bier’s block, with no side effects. Bier’s block is a safe, easy and effective technique wherein local anesthetic is administered into a region where venous return is mechanically impeded. Since its first use in 1908, several studies have been performed to improve the quality of this method by adding different additives. Our study compared the effects of addition of 25% magnesium sulphate and 200 µg NTG to lidocaine for IVRA. We found that both magnesium and NTG improved the speed of onset and the quality of anesthesia; prolonged the sensory and motor block recovery time and increased the duration of postoperative analgesia without any significant side effects.

IVRA is reported to be acting on major nerve trunks, reaching to the nerve trunk via small venules within the nerve core.[6] Other workers have reported its site of action being the peripheral nerve endings.[7] The mechanism of action of magnesium as an adjunct to lidocaine in IVRA is multifactorial. Magnesium has been proven to have an endothelium-derived nitric oxide induced vasodilatory effect.[8,9] Nitric oxide causes an activation of guanyl cyclase and an increase in cyclic guanine monophosphate, which mediates the relaxation of vascular smooth muscles.[10] It may also block peripheral calcium channels or peripheral NMDA receptors.[12] With IVRA, drug is injected close to the site of surgery. Tourniquet causes ischemia distorting nerve penetration by oxidative stress and affecting the blood nerve barrier.[13] Nitric oxide donors protect the vascular endothelium from ischemia and reperfusion mediated endothelial dysfunction.[10] Glutamate, the excitatory amino acid transmitter for the NMDA receptor, can be found in peripheral sensory fibers.[14] It may, therefore, be speculated that there are peripheral NMDA receptors and associated magnesium channels.[13] Alternatively, magnesium may have a direct peripheral analgesic effect.[12] All these mechanisms or their combination may have played a role in our results.

| Table 1: Patient characteristics |
| Variables | Group C | n = 25 | Group M | Group N |
| Age (years)* | 32.88 ± 5.00 | 32.55 ± 6.21 | 32.44 ± 6.94 |
| Sex (female/male)* | 5/20 | 6/19 | 6/19 |
| Weight (kg)* | 55.92 ± 3.52 | 57.36 ± 3.92 | 56.68 ± 3.97 |
| ASA grade (II)* | 20/5 | 21/4 | 20/5 |
| Duration of tourniquet (min)* | 67.3 ± 2.7 | 66.2 ± 1.9 | 66.2 ± 2.4 |
| Duration of surgery (min)* | 65.1 ± 4.3 | 63.3 ± 3.1 | 64.1 ± 3.3 |

Group C received 3 mg/kg of preservative free lidocaine 2% diluted with saline to a total volume of 40 ml. Group M received 3 mg/kg of preservative free lidocaine 2% mixed with 6 ml of 25% magnesium sulfate diluted with saline to a total volume of 40 ml. Group N received 3 mg/kg of preservative free lidocaine 2% mixed with 200 µg of nitroglycerine diluted with saline to a total volume of 40 ml. *P value is not significant. ASA: American society of Anaesthesiology

| Table 2: Intraoperative patient variables |
| Variable (mins) | Group C | n = 25 | Group M | Group N | Group C and M | Group C and N | Group M and N |
| Sensory block onset time | 5.10 ± 1.00 | 2.60 ± 0.50 | 3.44 ± 0.278 | 0.004 | 0.00360.036 | 0.61 |
| Motor block onset time | 8.92 ± 0.886 | 6.46 ± 0.627 | 5.00 ± 0.677 | 0.021 | 0.038 | 0.713 |
| Onset of Tourniquet pain | 17.12 ± 2.43 | 17.04 ± 1.98 | 16.68 ± 2.59 | 0.98 | 0.816 | 0.79 |
| Sensory block recovery time | 3.28 ± 1.33 | 6.48 ± 1.15 | 6.00 ± 0.92 | 0.00021 | 0.00087 | 0.87 |
| Motor block recovery time | 4.40 ± 1.44 | 6.60 ± 1.11 | 6.96 ± 0.840 | 0.00065 | 0.00075 | 0.00610.0 |

Group: C, Control, Group M: Magnesium sulphate, Group N: Nitroglycerine

| Table 3: Patient variables |
| Intraoperative fentanyl requirement (in µg) | Group C | 59.87 ± 12.23 | Group M | 28.56 ± 9.78 | Group N | 35.73 ± 17.10 | P | 0.031 | 0.033 | 0.012 |
| Number of patients req. rescue analgesia | 18/25 | 6/25 | 10/25 | 0.412 | 0.055 | 0.043 |
| Time to first request for postoperative analgesia (in min.) | 21.20 ± 3.78 | 81.44 ± 7.10 | 52.56 ± 4.48 | 0.0167 | 0.041 | 0.032 |
| Total diclofenac consumption (in mg) | 148.4 ± 18.23 | 88.47 ± 9.32 | 136.38 ± 15.76 | 0.028 | 0.038 | 0.0118 |
There have been many studies to demonstrate the peripheral anesthetic activity of magnesium in Bier’s block. Similar to our findings, various workers have shown that magnesium leads to decreased intraoperative fentanyl consumption, tourniquet pain, improved the quality of anesthesia and prolonged sensory and motor blockade with no side effects.[12,16] Addition to magnesium also led to a faster onset as well as duration of sensory and motor blockade similar to the works of Mirkheshti et al.[17]

Intravenous magnesium as a supplementary analgesic has been shown to suppress postoperative pain and less analgesic consumption in the postoperative period in patients undergoing lower limb orthopedic surgery.[18]

Magnesium should be used cautiously in patients with compromised renal function, bradycardia, and atrioventricular conduction abnormalities.[16] Side effect seen with using magnesium in IVRA is injection pain, however we didn’t encounter this problem probably because it was diminished with the lidocaine dose and the concentration we used, similar to the findings of Turan et al.[16]

The beneficial effects of NTG, which we showed in this study, might depend on a direct strong vasodilatory effect that promotes distribution of lidocaine to nerves. This would explain the rapid onset of sensory and motor block. NTG is metabolized to nitric oxide (NO) in the cell.[11,19] NO causes an increase in the intracellular concentration of cyclic guanosine monophosphate, which produces pain modulation in the central and peripheral nervous system.[11,20] NO generators also induce anti-inflammatory effects and analgesia by blocking hyperalgesia and the neurogenic component of inflammatory edema by topical application.[21] Another possible mechanism includes an analgesic effect through the direct stimulation of peripheral fibers mimicking the actions of locally applied acetylcholine.[11,22] Nitroglycerine with lidocaine for intravenous regional anesthesia has been used and seen to improve the speed of onset and quality of anesthesia, decreased tourniquet pain and intraoperative and postoperative analgesic consumption and caused no side effects.[23]

NTG has a very short half-life.[18] In our study, the tourniquet was not deflated before 30 minutes and the tourniquet deflation was performed by the cyclic deflation technique at the end of surgery. These techniques, combined with the short half-life of NTG, may reduce the frequency and severity of unwanted side effects. In our study also, no significant side effect was seen with the use of NTG.

Though there have been studies to prove the efficacy of NTG and magnesium sulfate in IVRA, on reviewing literature, we found no study comparing these two in IVRA. We found that though both magnesium sulfate and NTG prolonged the sensory and motor block recovery time and increased the duration of postoperative analgesia without any significant side effects, the onset of sensory block was earlier and the duration of postoperative analgesia was also prolonged in magnesium sulphate group as compared to other groups. No side effects were noted in test groups. Three patients in the control group complained of nausea.

To conclude, magnesium when compared with NTG in IVRA provides a longer duration of analgesia without any significant side effects.

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