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TO STUDY AND COMPARE THE ANTI-NOCICEPTIVE PROPERTY OF NMDA RECEPTOR ANTAGONIST: MAGNESIUM

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ABSTRACT

INTRODUCTION – The N-methyl D-aspartate (NMDA) receptor antagonists have garnered increasing attention over the years as an adjunctive/alternative pain treatment modality.

MATERIAL AND METHODS- A prospective, double blind randomized study was conducted in 60 patients with acute closed fracture in one upper limb having ASA grade I or II. Group A received dose of 2g of magnesium sulphate and Group B received dose of 30mg of ketorolac diluted in 100 ml NS slowly over 15 minutes intravenously every 8 hours for 24 hours.

RESULTS - The mean age of all participants was 35.07 ±12.48 years. The consumption of rescue analgesia decreased progressively in group A over the period of 24 hours. No side effects of magnesium were encountered.

CONCLUSION – Magnesium does exhibit analgesic properties but further clinical trials needed for appropriate dosage.

KEYWORDS : Pain, Nmda, Analgesia

INTRODUCTION

The word "PAIN" is rooted in the Latin word 'poena' which means penalty or punishment.[1] As defined by the International Association for the Study of Pain (IASP), it is "an unpleasant sensory and emotional experience which is primarily associated with tissue damage or described in terms of such damage, or both."[2] The N-methyl D-aspartate (NMDA) receptor antagonists have garnered increasing attention over the years as an adjunctive/alternative pain treatment modality.

Magnesium is a physiological antagonist of the NMDA receptor ion channel. The primary mechanism through which magnesium produces analgesia is thought to be NMDA receptor blockade in the spinal cord.[3] Also, magnesium related activation of the nitric oxide pathway is postulated to play a role in the anti-nociceptive effects of systemic magnesium sulfate in somatic, but not visceral, inflammatory pain.[3]

So far, there is no study where magnesium sulphate has been used as a primary drug for the management of acute traumatic pain. We designed the present study to evaluate the analgesic effect of NMDA- receptor antagonist, magnesium in acute traumatic pain of upper limb fracture and compares its analgesic efficacy with ketorolac, a commonly used NSAID.

MATERIAL AND METHODS

After approval from the institutional research/ethical committee, a prospective, double blind randomized study was conducted in 60 patients with acute closed fracture in one upper limb having ASA grade I or II of either sex belonging to age group of 20-60 years. The patients having body mass index > 35kg/m^2, open wounds, head injury, multi-organ injury, opioids/NSAIDs abuse or on chronic treatment, prior treatment with calcium channel blockers or having cardiovascular, hepatic and renal diseases were excluded from the study.

After arrival of patient in Accident and Emergency room, patients were subjected to a detailed clinical history and a general physical and systemic examination. Routine investigations, serum magnesium initially and after 24 hrs, ECG and any other relevant investigation, if needed was carried out and recorded. The purpose and protocol of the study including severity of pain as per numerical rating scale (NRS) score[4] (0-3 mild, 4-6 moderate, and 7-10 severe pain) were explained to the patient. Informed written consent was obtained from the patients.

The patients were randomly assigned to two groups of 30 each using sealed envelope method (containing assigned group). Group A received dose of 2g of magnesium sulphate diluted in 100 ml normal saline (NS) slowly over 15 minutes intravenously every 8 hours for 24 hours. Group B received dose of 30mg of ketorolac diluted in 100 ml NS slowly over 15 minutes intravenously every 8 hours for 24 hours.

All patients were monitored for continuous ECG, oxygen saturation (SpO2) and non-invasive blood pressure. After 30 minutes from the start of infusion of the drug, pain score was re-assessed. If NRS score was > 3, then fentanyl as rescue analgesia was given through a patient controlled analgesia (PCA) pump. The PCA pump was set to deliver 25 µg bolus of fentanyl with a 10 minute lockout interval.

In case of any adverse effects, drug was stopped immediately and necessary actions were taken.

STATISTICAL ANALYSIS

Collected data was entered in the MS Excel spreadsheet, coded appropriately and later cleaned for any possible errors. Analysis was carried out using SPSS (Statistical Package for Social Studies) for Windows version 26.0. Paired and unpaired "t" test was used to calculate difference of means for quantitative variables. Pearson's chi-square test was used to evaluate differences between groups for categorized variables. Normally distributed data were presented as means and standard deviation, or 95% confidence intervals (CI). All tests were performed at a 5% level of significance, thus an association was significant if the p value was less than 0.05.

RESULTS AND OBSERVATION

The mean age of all participants was 35.07 ±12.48 years. Age and sex distribution of the patients in both the groups were comparable (p value ≥ 0.05).

The NRS score declined effectively in group B after giving each dose of ketorolac, however, the NRS score in group A decreased progressively over 24 hours. The mean difference between baseline and 24 hrs in group A was 1.767 (p=0.001) and in group B was 0.067 (p=0.067) i.e the pain score decreased subsequently over the next 24 hrs in group A. (TABLE-1 AND 2)

TABLE 1- Mean of NRS Score at different intervals in A & B groups

Group	Time (hrs)	Mean±SD
Group – A (Magnesium)	Baseline (0)	6.50 ±0.51
	8	6.27±0.79
	16	4.93±0.69
	24	4.73±0.64
Group – B (Ketorolac)	Baseline (0)	5.80±0.61
	8	5.73±0.69
	16	5.73±0.69
	24	5.73±0.69

Table 2- Association between NRS Score at Baseline and after 24 hours of A & B drug administration

Group	Time (hr)	Mean	Mean Difference	Confidence interval	T-Value, degree of freedom	P-Value

Group-A (Magnesium)	Baseline (0)	6.50	1.767	1.513-2.020	14.253, 29	0.001
	24	4.73				
Group-B (Ketorolac)	Baseline (0)	5.80	0.067	-0.028-0.161	1.439, 29	0.161
	24	5.73				

The consumption of rescue analgesia was statistically significant in group A at various time intervals. However, the mean fentanyl consumption decreased progressively over the 24 hrs i.e it was less in T2 as compared to T1 and further less in T3 as compared to T2 and T1 (TABLE-3).

TABLE 3- Mean difference in total consumption of rescue analgesia within group M (T1 = 0-8hr and 8-16 hr, T2= 8-16 hr and 16-24 hr, T3= 0-8 hr and 16-24 hr)

Rescue analgesia (µg)	Mean difference	p value
T1	16.267	.003
T2	30.33	.000
T3	46.600	.000

The magnesium levels were within normal limits. The sedation score in group A was significant (0hr= 2, 24 hr= 3). No adverse effects were noted.

DISCUSSION

Magnesium is the fourth most abundant cation in the body and the second most abundant intracellular cation.[3] Since the early 1990s, the effects of magnesium on postoperative pain and opioid consumption have been studied intensively.[5] Some studies have shown a beneficial effect of magnesium on postoperative pain outcomes, others have not. Differences in dose and onset of magnesium administration; type of magnesium salt and pain scores used, as well as choice of patient population; standard baseline pain medication; and anesthesia may contribute to inconsistencies in the literature.

In our study, group B had better pain relief i.e instantaneous decreased NRS score after administering each dose of ketorolac as compared to group A. Also there was no need of rescue analgesia in group B.

In group A, the NRS score did not decreased immediately after giving each dose of magnesium but subsequently decreased over the next 24 hours when compared to baseline (NRS mean difference between baseline and 24 hrs=1.767, p=0.001). Our results are in accordance with the meta-analysis done by Guo et al which provided similar outcome that perioperative administration of IV magnesium sulfate significantly reduced postoperative pain.[6] Sousa et al (2016) in a randomized double-blind controlled trial showed analogous results.[7]

The mean consumption of rescue analgesia in group A was significantly higher as compared to group B. Fentanyl requirement was more in the first 8 hrs as compared to the last 8 hours i.e. the consumption of rescue analgesia eventually declined till the end of 24 hrs. Even though ketorolac is an established analgesic widely used in clinical practice, our study showed that magnesium has not only reduced the VAS score but has decreased the analgesic consumption of fentanyl (from 168.93 ± 24.64 µg to 152.67 ± 29.15 µg to 122.33 ± 34.23 µg). The meta-analysis compiling 14 RCTs published by Arumugam, Lau, and Chamberlain in 2016 showed a significant decrease in postoperative opioid consumption.[8]

No advere effects were encountered. Our study showed similar results as postulated in the meta-analysis done by De Oliveira et al, Albrecht et al and Murphy et al.[9,10,11] They demonstrated reduced pain scores and decreased opioid consumption. No clinical toxicity related to toxic Mg2+ serum levels was reported. None of the three aforementioned meta-analyses found a difference in the incidence of post-operative nausea and vomiting with the use of systemic Mg2+.

The analgesic effects of magnesium can be attributed to the following reasons: Firstly, magnesium is a NMDA receptor antagonist. The NMDA receptor, an amino acid receptor responsible for excitatory synaptic transmission, has modulatory sites (NMDA binding sites) positive for excitatory amino acids such as glutamate, and modulatory sites (phenylcyclidine binding site) negative for ketamine or magnesium. Furthermore, this receptor is coupled to an ion channel permeable for K+ and Ca+. Magnesium blocks NMDA-induced currents in a voltage-dependent manner by blocking the receptor channel effects.[12] Secondly, magnesium is also a calcium channel antagonist. Calcium channel blockers have shown to have antinociceptive effects. Release of neurotransmitters is coupled with activation of voltage-dependent calcium conductance in synaptic terminal membranes of neurons.[13] The analgesic action of Ca2+ channel blocker could be mediated by an increase in the nociceptive threshold resulting from interference with Ca2+ influx, because Ca2+ influx is critical for the release of neurotransmitters and other substances implicated in nociception and inflammation.[12] Thirdly, NMDA receptors lies at the heart of wind up and central sensitization. Their activation evokes long lasting membrane depolarisation and enhanced membrane excitability. Blocking the NMDA receptor prevents central sensitization due to peripheral nociceptive stimulation and abolishes hypersensitivity.[14]

The serum magnesium levels were within normal range and there was no increase in levels after 24 hrs. No other studies evaluated the serum magnesium levels. There is evidence that the response of the NMDA receptors is greatly enhanced by reducing the extracellular magnesium concentration below the physiological level. Begon et al in 2001 reported that in rat experimental models, magnesium deficiency induces a sensitization of nociceptive pathways in the spinal cord which involves NMDA and non-NMDA receptors.

Hypomagnesaemia induced hyperalgesia is linked to the activation of spinal NMDA receptors.[15]

Even after extensive search in the available literature, our study could not be completely compared to others as all previous studies done were during the intra-operative and post-operative periods, and none of them evaluated the effects pre-operatively in an acute trauma condition.

The limitation of this study is that instead of using a fixed dose, a dose according to the weight could have been more accurate. Secondly, a control group study should have been done to compare the effects.

CONCLUSION

The anti-nociceptive effects of magnesium are conflicting as reflected by the current literature. Further research and clinical trials using optimum dose regimens and pain scores are required to achieve more data on possible analgesic effects.

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