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Effect of Ketamine and Magnesium Sulphate on Anaesthetic Consumption, Haemodynamics and Postoperative Recovery during Propofol-Nitrous Oxide Anaesthesia-A Comparative Study.

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Abstract: *This study was conducted to compare the efficacy of magnesium sulphate and ketamine when used intravenously during propofol-nitrous oxide anaesthesia in terms of, haemodynamics, anaesthetic consumption and postoperative recovery..*

Materials and Methods: *60 patients (20-60 years of both sexes and ASA I and II) who underwent short elective surgery (30 mins to 3 hours) were randomized into 2 groups. Group M patients received 30 mg/kg magnesium sulphate during induction and 8 mg/kg/hr during maintenance and Group K patients received 0.5 mg/kg ketamine during induction and 15 µg/kg/hr during maintenance. Effect of either regimen was assessed on maintenance anaesthesia with propofol infusion along with 50% nitrous oxide in oxygen. Monitoring of intra-operative hemodynamics, propofol consumption, extubation time, recovery time, and postoperative side effect profile was done and results were tabulated and analysed statistically. P value (<0.05) was considered significant.*

Results: *In Group M there was significant fall in both heart rate and blood pressure after induction which returned to baseline values after a few minutes of induction and postoperatively they returned to baseline values in both the groups. Both propofol and vecuronium consumption were found to be significantly lower in Group M. Mean extubation time and mean recovery time were found to be significantly prolonged in the magnesium sulphate group. As far as side effects were concerned the incidence of postoperative pain was more in magnesium sulphate group and postoperative nausea was more in ketamine group.*

Conclusion: *Haemodynamic stability was more with propofol and ketamine combination while anaesthetic consumption was lesser when we use propofol and magnesium sulphate combination.. Side effects like nausea was found to be more when ketamine was used while postoperative pain was found to be more when magnesium sulphate was used.*

Keywords: *Anaesthetic consumption, haemodynamic stability, ketamine, magnesium sulphate, propofol.*

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I. Introduction

Total intravenous anaesthesia using propofol has become popular because of the unique properties of propofol.[1] Some of the adverse effects of propofol can be minimized by using it with some adjuvants. The combination of propofol and ketamine has been shown to provide stable hemodynamics.[2] The analgesic effects of ketamine are present at plasma concentrations significantly lower than those producing hypnosis (0.2µg/ml versus 1.5 to 2.5µg/ml respectively).[3,4] While one study[5] reports that larger doses of ketamine (>24±8µg/kg/min) was associated with increase in psychomimetic side effects and post operative nausea and vomiting, the usual dose of ketamine for maintenance anaesthesia with nitrous oxide[6] is 15-45 µg/kg/min.Recently the role of magnesium in anaesthetic practice has been highlighted.[7-9] Its use has decreased anaesthetic consumption and improved postoperative analgesia. While side effects were more with larger doses[10] , it was milder with lower doses.[9,11]Some form of index is required for monitoring the depth of anaesthesia when we are comparing the regimens to define the same end point. We cannot use BIS (Bispectral Index) monitoring of processed EEG (electroencephelogram) as BIS value is known to increase with ketamine[12] and nitrous oxide.[13] Advanced monitoring systems like symbolic transfer entropy (STE) and trans cranial magnetic stimulation (TMS) are not currently available widely. So we have justification of using monitoring of clinical signs of inadequate antinociception (perspiration, tearing, pupillary dilatation and return of muscle tone and movement).[14] Though these signs are mediated at the level of the nociceptive medullary autonomic

(NMA)[15] circuit, their presence does not necessarily imply regaining of consciousness. Because during loss of consciousness with selective loss of 'feedback' frontoparietal corticocortical connectivity, preserved 'feedforward' parietofrontal connectivity can mediate subliminal (i.e unconscious) sensory processing.[16] Both directions of connectivity are supprssed at the level of surgical anaesthesia and frontoparietal connectivity returned to baseline at recovery.[17]To our knowledge ketamie and magnesium sulphate have not been compared in reducing the dose of propofol, though both are N-methyl-D-aspartate receptor antagonist.[18,19] Hence the following study was conducted to assess the effects of ketamine or magnesium sulphate infusion during maintenance of propofol-nitrous oxide anaesthesia.

II. Materials And Methods

After obtaining Research Ethics Board Approval and informed written consent from the patients this prospective, randomised, double blind clinical trial was conducted in the Dept of Anaesthesiology, RIMS, Imphal over a period of 2 years from Sept 2015 to August 2017. 60 patients of both sexes of age 20-60 years belonging to ASA I and II categories undergoing surgery of moderate duration (30 minutes to 3 hours) were included in one of 2 parallel groups. [Magnesium sulphate(M)=30 and Ketamine(K)=30]. The following patients were excluded from the study: patients with hepatic, renal, neurological disorders and neuropathies, known allergy to a particular drug, compromised cardiovascular and respiratory problems and anticipitated difficult airway. Sample size was calculated using web based sample size calculator available at www.stat.ubc.ca/-rollin/stats/ssize/n2.html based on a previous study[9] for α value of 5% and power of 80% assuming a difference of 20% in the mean extubation (of endotracheal tube) time. It came out to be 30 in each group. All the patients fulfilling the inclusion criteria who came within this data collection period were included. The sampling technique that was used was convenience sampling. Computer generated randomization chart was used. Patients were divided into two groups Group M and Group K depending on the randomization. The following variables were studied and compared between the 2 groups like intraoperative haemodynamic parameters like pulse, SBP, DBP, MAP, SpO_2, $ETCO_2$, time reaching TOF $\geq$ 2,any atropine or mephentermine given, total dose of propofol and vecuronium consumed. recovery profile like extubation time, recovery time, time of first complain of pain or nausea/vomiting in the post anaesthetic care unit and side effects like hypotension, bradycardia, shivering, nausea, vomiting, agitation or unpleasant dreams. Group M patients received 30mg/kg magnesium sulphate which was given slowly intravenously (after induction but before endotracheal intubation) followed by 8 mg/kg/hour just after endotracheal intubation. Group K patients received 0.5 mg/kg ketamine (after induction but before endotracheal intubation) followed by 15 µg/kg/min just after endotracheal intubation. This study was double-blinded i.e both the data collector and the patient were blinded. Since both drugs were colourless the primary investigator could be easily blinded. Preparation of the drugs was done by an anaesthetist not involved in the study.

Pre-operative assessment:

Pre-operative visit was done a day before surgery. During this visit good rapport was established with the patient. If all the inclusion criteria were met, written informed consent was taken from the patient.

Pre-Medication:

All patients received tab alprazolam 0.25 mg the night before the surgery. In the morning of surgery tab pantoprazole 40 mg and tab metoclopramide 10 mg were given with a small sip of water 2 hours before induction of anaesthesia. In the pre-operative room intravenous access was established to start the maintenance intravenous fluid. Inj Glyopyrrolate 0.004 mg/kg was given intravenously.

Operation Theatre:

On arrival to the operation theatre baseline monitoring of pulse rate (PR), non-invasive blood pressure (NIBP) and oxygen saturation (SpO_2) and ECG were started. Since we were going to use magnesium in some patients, neuromuscular monitor (TOF-guard) was also attached. Care was taken to maintain normothermia in the operation theatre. Before induction all patients received injection butorphanol 20µg/kg iv slowly and pre-induction blood sample (2 ml) for serum magnesium was collected. After pre-oxygenation for 3 minutes, propofol 1.5 mg/kg iv was given over 60 seconds for induction. Ketamine 0.5 mg/kg or magnesium sulphate 30 mg/kg was given over 30 seconds according to the group assigned. Endotracheal intubation was facilitated by injection vecuronium 0.1 mg/kg iv. Anaesthesia was maintained with propofol infusion-50% nitrous oxide in oxygen. Ventilation was done to maintain end-tidal carbon-dioxide ($ETCO_2$) between 30-35 mm Hg. Propofol infusion was titrated 5-10mg/kg/hour (~80-160 µg/kg/min) to maintain anaesthetic depth on clinical grounds and to keep hemodynamic parameters (pulse,NIBP) within ±15% of baseline. Magnesium sulphate or ketamine infusion were continued according to the group assigned. Top-up dose (1/5th of the intubating dose) of muscle relaxant was given only when the TOF (Train-of-four) count ≥2 on the neuromuscular monitor. Normothermia

was maintained in the operation theatre.Hemodynamic parameters were monitored every 2 minutes for the first 10 minutes, then every 5 minutes till the end of surgery.Injection Atropine in 0.3 mg increments was given for heart rate ≤ 50/mins and injection mephentermine 3 mg iv increments was given for systolic BP ≤ 90 mm of Hg. All the drug infusions were stopped 15 minutes before the anticipated end of skin closure. Injection Ondansetron 0.1 mg/kg was given towards the end of skin closure. Nitrous oxide was cut 3 minutes before the anticipated reversal of residual neuromuscular blockade, which was down when the T4/T1 ratio in the TOF monitor was ≥ 0.9. Injection Neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg were used for reversal of residual neuromuscular blockade. Extubation time was taken as the time from stopping drug infusion to removal of the endotracheal tube. Recovery time was taken as the time from stopping infusion pumps to opening eye on command. Before shifting the patient to PACU (post anaesthesia care unit) blood sample (2 ml) was taken to measure the serum magnesium level. After shifting in the PACU hemodynamic parameters were recorded every 15 minutes for 2 hours. Time for the first rescue analgesic was noted. Injection diclofenac 75 mg im was given as rescue analgesic. Any episode of nausea and/or vomiting were recorded in the first 4 hours postoperatively, first 2 hours in the post anaesthetic care unit and next 2 hours in the postoperative ward. Other side effects like hypotension, bradycardia, shivering, unpleasant dreams, agitation were noted.

Statistical analysis:

All the data were tabulated and analyzed using SPSS v21 software. Chi-square test was used for categorical data and independent sample- t test was used for continuous data for analysing differences in mean between 2 groups. A p-value of <0.05 was considered significant.

III. Results

The patient characteristics like age, sex and weight were statistically similar in both the groups. The mean duration of surgery was also comparable in both the groups.(Table 1)

Table 1

	Group M	Group K	p value
Mean age (years)	36.567±10.9535	36.167±10.0003	0.883 (<0.05)
Mean weight (kg)	59.067±6.142	59.433±5.794	0.813 (<0.05)
Gender M/F	16/14	15/15	0.796 (<0.05)
ASA Status I/II	23/7	22/8	0.766 (<0.05)
Mean duration of surgery (minutes)	114.533±6.689	112.567±7.7401	0.297 (<0.05)

The heart rates were compared between the groups at 2, 4, 6, 8, 10, 15, 20, 25 and 30 minutes using the independent sample t test and the conclusions were depicted in table 2. Baseline heart rate was found to be similar in both groups statistically as is evident from a p value of 0.336. Following induction heart rate fell significantly in the magnesium sulphate group as is evident from the p values of <0.001 at 2 mins, 4 mins, 6 mins, 8 mins, 10 mins and 15 mins. At 20 mins the p value was found to be 0.004. This showed that the difference in heart rates till around 20 mins was highly significant statistically. But after 20 minutes the heart rate returned to baseline values as is evident from the p values of 0.16 and 0.94 at 25 mins and 30 mins respectively and the difference between the groups was not found to be statistically significant.

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Heart Rate(HR)(beats/min) comparison between both groups(Table 2)

	Group	**Mean**	**Std Deviation**	**p value**
Baseline HR	MgSO4	83.833	4.9625	**0.336**
	Ketamine	85.033	4.6050	
HR 2 mins	MgSO4	75.867	3.8662	**0.0000**
	Ketamine	84.900	4.9014	
HR 4 mins	MgSO4	78.133	3.3086	**0.0000**
	Ketamine	85.200	5.6593	
HR 6 mins	MgSO4	78.467	4.6885	**0.0000**
	Ketamine	85.200	5.7858	
HR 8 mins	MgSO4	78.467	5.1444	**0.0000**
	Ketamine	85.333	6.3698	
HR 10 mins	MgSO4	78.433	5.2502	**0.0000**
	Ketamine	85.167	4.7640	
HR 15 mins	MgSO4	78.167	5.6084	**0.0000**
	Ketamine	85.367	4.2870	
HR 20 mins	MgSO4	81.300	4.0612	**0.004**
	Ketamine	84.833	5.0520	
HR 25 mins	MgSO4	83.300	4.7861	**0.16**
	Ketamine	85.100	4.9990	
HR 30 mins	MgSO4	85.067	5.4452	**0.94**
	Ketamine	84.967	4.8172	

Similar trends were found in blood pressure values between the groups as well. The systolic blood pressures were compared at 2 mins, 4 mins, 6 mins, 8 mins, 10 mins, 15 mins, 20 mins, 25 mins and 30 mins using independent sample t test and the conclusions were depicted in table 3. The baseline systolic blood pressures in both the groups were found to be statistically similar with a p value of 0.791. Following induction systolic blood pressure fell significantly in the magnesium sulphate group as is evident from the p values of 0.001, 0.031, 0.002 and 0.004 at 2 mins, 4 mins, 6 mins and 8 mins respectively. Thereafter their values returned to baseline parameters and the difference was not found to be statistically significant as is evident from the p values of 0.091, 0.061, 0.792, 0.228 and 0.087 at 10 mins, 15 mins, 20 mins, 25 mins and 30 mins respectively.

Systolic blood pressure(SBP) (mm Hg) comparison between both groups **(Table 3)**

	Group	Mean	Std Deviation	p value
SBP Baseline	MgSO4	124.600	7.4953	**0.791**
	Ketamine	125.167	8.9214	
SBP 2 mins	MgSO4	116.433	10.960	**0.001**
	Ketamine	125.900	8.9495	
SBP 4 mins	MgSO4	121.367	10.206	**0.031**
	Ketamine	127.067	9.780	
SBP 6 mins	MgSO4	117.133	9.153	**0.002**
	Ketamine	125.400	10.653	
SBP 8 mins	MgSO4	122.333	9.364	**0.004**
	Ketamine	130.367	11.050	
SBP 10 mins	MgSO4	124.200	8.294	**0.091**
	Ketamine	128.067	9.108	
SBP 15 mins	MgSO4	125.667	7.880	**0.061**
	Ketamine	130.200	10.327	
SBP 20 mins	MgSO4	125.367	7.228	**0.792**
	Ketamine	126.000	10.942	
SBP 25 mins	MgSO4	125.100	8.845	**0.228**
	Ketamine	127.933	9.169	
SBP 30 mins	MgSO4	125.067	8.090	**0.087**
	Ketamine	128.900	8.938	

The diastolic blood pressures were compared at 2 mins, 4 mins, 6 mins, 8 mins, 10 mins, 15 mins, 20 mins, 25 mins and 30 mins using independent sample t test and the conclusions were depicted in table 4. The baseline diastolic blood pressures also showed no statistically significant difference between the groups as is evident from the p value of 0.766. But the difference was found to be highly statistically significant from 2 mins upto 15 mins as is seen from a p value <0.001 throughout. By 20 mins the diastolic blood pressures returned to baseline and the difference between the groups was not found to be statistically significant as is evident from p values of 0.711, 0.349 and 0.529 at 20 mins, 25 mins and 30 mins respectively.

Diastolic blood pressure(DBP) (mm Hg) comparison between the groups**(Table 4)**

	Group	Mean	Std Deviation	p value
Baseline DBP	**MgSO4**	80.467	2.813	**0.766**
	Ketamine	80.200	4.003	
DBP 2 mins	**MgSO4**	73.100	3.79	**0.000**
	Ketamine	81.033	3.20	
DBP 4 mins	**MgSO4**	74.433	3.692	**0.000**
	Ketamine	82.267	3.982	
DBP 6 mins	**MgSO4**	75.033	3.576	**0.000**
	Ketamine	81.433	4.584	
DBP 8 mins	**MgSO4**	74.800	3.960	**0.000**
	Ketamine	81.967	4.319	
DBP 10 mins	**MgSO4**	77.867	2.874	**0.000**
	Ketamine	81.933	3.912	
DBP 15 mins	**MgSO4**	78.433	3.298	**0.000**
	Ketamine	82.433	4.199	
DBP 20 mins	**MgSO4**	79.400	3.519	**0.711**
	Ketamine	79.733	3.413	
DBP 25 mins	**MgSO4**	79.567	3.213	**0.349**
	Ketamine	80.533	4.592	
DBP 30 mins	**MgSO4**	78.800	3.336	**0.529**
	Ketamine	79.467	4.711	

Mean propofol consumption during the surgery was compared between the two groups using independent standard t test and the results have been depicted in table 5. It was found that the consumption in magnesium sulphate group(8.113±1.867 mg/kg/hr) was significantly lower than the ketamine group

(9.009±0.593 mg/kg/hr) as is evident from the p value of 0.015. Mean vecuronium consumption during the surgery was also compared between the two groups using independent sample t test and the results are depicted in table 5. It was found to be significantly lower in magnesium sulphate group (21.064±2.747 µg/kg/hr) compared to the ketamine group (35.933±6.684 µg/kg/hr) as is seen from the p value of <0.001.

Anaesthetic consumption comparison between the two groups (Table 5)

	Group	Mean	Std deviation	p value
Total dose of propofol consumed(mg/kg/hour)	**MgSO4**	8.113	1.867	**0.015**
	Ketamine	9.009	0.593	
Total dose of vecuronium consumed(µg/kg/hour)	**MgSO4**	21.064	2.747	**0.000**
	Ketamine	35.933	6.684	

Mean extubation time was compared between the groups using independent sample t test and the results were depicted in table 6. The extubation time in the magnesium sulphate group (8.167±1.866 mins) was significantly higher compared to the extubation time in the ketamine group (6.427±1.548 mins) as is seen by the p value of <0.001. The mean recovery time was compared between the groups using independent sample t test and the results were depicted in table 6. It was found that the recovery time was significantly higher in the magnesium sulphate group (10.13±1.821 mins) compared to the ketamine group (8.43±1.511 mins) as is seen by a p value of <0.001.

Recovery profile comparison between the two groups (Table 6**)**

	Group	Mean	Std deviation	p value
Extubation time(minutes)	**MgSO4**	8.167	1.866	**0.000**
	Ketamine	6.427	1.548	
Recovery time(minutes)	**MgSO4**	10.130	1.821	**0.000**
	Ketamine	8.430	1.511	

As far as side effect profile is concerned 1 patient (3.33%) from ketamine group had nausea within the first 30 mins in post anaesthetic care unit and none of the patients in magnesium sulphate group had any symptoms of nausea. None of the patients in either group had any episode of vomiting. 12 patients (40%) in ketamine group and 14 patients (47%) in magnesium sulphate group complained of pain within 2 hours in post anaesthetic care unit and 20 patients (66.66%) in ketamine group and 22 patients (73%) in magnesium sulphate group complained of pain within first 6 hours in post anaesthetic care unit/ward. Preoperative and postoperative serum magnesium are depicted in the table 7 and it was found that their difference was not statistically significant as is seen by a p value of 0.655.

Comparison of preoperative and postoperative serum magnesium values(mEq/l) **(Table 7)**

Group	Mean	Std deviation	p value
Preoperative serum magnesium	1.711	0.267	**0.655**
Postoperative serum magnesium	1.742	0.262	

IV. Discussion

The purpose of the current study was to compare the effects of magnesium sulphate and ketamine during maintenance anaesthesia with propofol and nitrous oxide in terms of haemodynamic stability, anaesthetic consumption and postoperative recovery. The rationale for choosing the doses of ketamine and magnesium sulphate in the present study was based on earlier studies.[2-11] There was random allocation of the patients in the two groups and both the groups were statistically comparable (Table1). In our study baseline pulse rate in both the groups were found to be similar(Table 2) as is evident from the values of 83.833 ± 4.9625 beats/min in the M Group and 85.033±4.6050 beats/min in the K group with a p value of 0.336. Following induction pulse rate fell significantly in the M group as is evident from the p values of <0.001 at 2 mins, 4 mins, 6 mins, 8 mins, 10 mins and 15 mins and 0.004 at 20 mins. But after 20 mins the pulse rate returned to baseline values as is evident from the p values of 0.16 and 0.94 at 25 mins and 30 mins respectively and the difference between the groups was not found to be statistically significant.Similar trends were found in blood pressure values between the groups as well. The baseline systolic blood pressures in (table 3) both the groups were found to be similar: 124.6±7.4953 mm Hg in the M group and 125.167±8.9214 mm Hg in the K group with a p value of 0.791. The difference between the groups were statistically significant upto 8 minutes as is evident from the p values of 0.001, 0.031, 0.002, 0.004 at 2 mins, 4 mins, 6 mins and 8 mins respectively. Thereafter their values returned to baseline parameters and was not found to be statistically significant as is evident from the p values of 0.091,

0.061, 0.792, 0.228, 0.087 at 10 mins, 15 mins, 20 mins,25 mins and 30 mins respectively.The baseline diastolic blood pressures (table 4) also showed no statistically significant difference as is evident from the p value of 0.766 with diastolic pressures of 80.467±2.8129 mm Hg in the M Group and 80.2±4.0034 mm Hg in the K group. The diastolic pressures showed highly statistically significant differences upto 15 mins with a p value <0.001throughout. By 20 mins the values returned to baseline and the difference between the groups was not found to be statistically significant as is evident from p values of 0.711, 0.349, 0.529 at 20 mins, 25 mins and 30 mins respectively.The variation in hemodynamic parameters between the groups could be explained by the properties of the study drugs employed. Ketamine stimulates cardiovascular system and is usually associated with increases in heart rate, blood pressure and increase in cardiac output.[27] It has a direct cardiodepressant, negative inotropic effect next to an indirect stimulatory effect secondary to activation of the sympathetic system.[28] Ketamine causes the systemic release of catecholamines, inhibition of the vagal nerve, inhibition of norepinephrine reuptake at peripheral nerves and nonneuronal tissues such as the myocardium, and norepinephrine release from sympathetic ganglia.[28] The most prominent effect of propofol is a decrease in arterial blood pressure during induction of anesthesia.[28] Whereas heart rate does not change significantly after an induction dose of propofol.[29] Propofol either may reset or may inhibit the baroreflex, thus reducing the tachycardic response to hypotension.[28] The stress response of laryngoscopy and intubation further adds upto the hemodynamic response produced by ketamine. Thus the elevated heart rate and systolic and diastolic blood pressures in the ketamine group after induction could be the sum total of cardiovascular stimulation and stress response to laryngoscopy and intubation as well as surgical stimulus. Elsharnouby and Elsharnouby[10] used magnesium sulphate 40 mg/kg intravenously over a period of 15 minutes before induction and 15 mg/kg/hour by continuous infusion intraoperatively. They noticed more episodes of severe hypotension using the dose of magnesium sulphate. In our study we reduced the dose of magnesium sulphate to 30 mg/kg before induction and 8 mg/kg/hour by continuous infusion intraoperatively. The dose selected by us resulted in a steady and smooth reduction of blood pressure and heart rate with no episodes of severe hypotension and bradycardia. Our finding was supported by a study conducted by Telci and Esen[11] who used similar dose of magnesium sulphate as ours. Honarmand A et al[30] and colleagues found that magnesium sulphate attenuated the hemodynamic response to endotracheal intubation. Magnesium inhibits release of catecholamines and might blunt the haemodynamic responses to inadequate analgesia. These anti-adrenergic actions have led to the use of magnesium during surgery for pheochromocytoma[31] and to evaluation of its efficacy in attenuating the response to endotracheal intubation.[32] The anti-adrenergic actions of magnesium sulphate along with the hypotensive effect of propofol could explain the fall in heart rate and blood pressure at induction and blunting of stress responses to laryngoscopy and intubation. So the opposing effects of ketamine and magnesium sulphate on the sympathetic nervous system could be the possible explanation for the difference in intraoperative hemodynamics that was noticed in this study.We also compared the consumption of anaesthetic drugs (table 5) in our study namely propofol and vecuronium. Propofol consumption was seen as 8.1127±1.86699 mg/kg/hour in the magnesium sulphate group and 9.0087±0.59254 mg/kg/hour in the ketamine group. This was statistically significant as is seen by a p value of 0.015. It is hard to speculate on the exact mechanism of magnesium's contribution to anaesthesia in our study. Magnesium sulphate has been reported to produce general anaesthesia and enhance the activity of local anaesthetic agents.[7] Depressant effects of magnesium sulphate on the central nervous system of animals has been reported too.[33] A narcotic state in human beings undergoing surgical operations was achieved in a study by Peck and Meltzer[34] who reported three patients undergoing herniorrhaphy under attempted anaesthesia by magnesium sulphate infusion. However Aldrete[35] and colleagues suggested that this anaesthetic state was actually a sleep-like state caused by cerebral hypoxia from progressive respiratory and cardiac depression. So it is not clear if magnesium sulphate decreased the propofol requirements by virtue of its general anaesthetic properties. One shortcoming in our study was the lack of monitoring of intraoperative awareness with a suitable device like the BIS monitor. The propofol infusion was titrated basically with the sole aim of keeping hemodynamic parameters within 15% of the baseline and not by an actual assessment of awareness. Ketamine group because of its higher hemodynamic variables like pulse, blood pressure would have required more propofol dose to keep the variables within acceptable limits. So in this study the decreased propofol requirement in magnesium sulphate group could have been because of the lesser requirement in that group to maintain the hemodynamic parameters. Clearly further studies of the interaction between magnesium sulphate and propofol as a sole agent are needed.

As far as total dose of vecuronium that was consumed in the two groups it was seen that the Group M required less vecuronium compared to Group K. Vecuronium consumption in Group M was 21.0640±2.74695 μg/kg/hr and in Group K it was 35.9333±6.68370 μg/kg/hr and the difference was highly statistically significant with p value of <0.001. It was observed that magnesium sulphate given for treatment of preeclampsia and eclamptic toxaemia potentiates the neuromuscular blockade induced by non-depolarizing neuromuscular blocking drugs.[36,37] After a dose of 40 mg/kg of magnesium sulphate the ED_{50} of vecuronium was reduced by 25%, the onset time was nearly halved, and the recovery time nearly doubled.[37] Neostigmine

induced recovery is also attenuated in patients treated with magnesium.[36] The mechanisms underlying the enhancement of nondepolarizing block by magnesium probably involve both prejunctional and postjunctional effects. High magnesium concentrations inhibit Ca^{2+} channels at the presynaptic nerve terminals that trigger the release of acetylcholine.[38] Further magnesium ions have an inhibitory effect on postjunctional potentials and cause decreased excitability of muscle fibre membranes. In patients receiving magnesium, the dose of nondepolarizing neuromuscular blocking drugs must be reduced and carefully titrated using a nerve stimulator to ensure adequate recovery of neuromuscular function at the end of surgery.[39] The findings of our study regarding vecuronium consumption is consistent with the available evidence in various literatures. Thus magnesium sulphate prolongs neuromuscular blockade while being used with non depolarizing neuromuscular blocking drugs.

Extubation time(table 6) was also found to be significantly higher in the M group at 8.167±1.8663 minutes while it was 6.427±1.5476 minutes in the K group with a p value <0.001. This is expected as the effect of magnesium sulphate in potentiating the blockade of vecuronium has already been discussed above.[36-39]

Recovery time(table 6) was also found to be significantly higher in the M group at 10.130±1.8212 minutes while it was 8.43±1.5107 minutes in the K group with a p value of <0.001. The delay in recovery may be attributed to the central nervous system depressant effect of magnesium sulphate which was discussed earlier.[33-35]

As far as side effects are concerned 1 patient (3.33%) from Group K had nausea within the first 30 mins in PACU and none of the patients in Group M had any symptoms of nausea. And it was also observed that there is no incidence of any vomiting in any of the groups. As a whole, low incidence of nausea and no incidence of vomiting can be attributed to the antiemetic effect of propofol and possible antiemetic effect of magnesium sulphate which have been explained in a few studies. Propofol possesses significant antiemetic activity with small (subhypnotic) doses (i.e 10 mg in adults). The median concentration of propofol with an antiemetic effect was 343 ng/ml which also causes mild sedative effect.[28] This concentration can be achieved by an initial dose of propofol infusion of 10 to 20 mg followed by 10 µg/kg/min which is much less than the doses employed by us in our study. Ryu JH and colleagues[40] report on a randomized controlled trial comparing infusions of remifentanil with infusions of magnesium sulphate for the maintenance of hypotension during middle ear surgery. Of particular interest in this study was the fact that magnesium was associated with a substantially decreased incidence of nausea and vomiting and a lower requirement for rescue antiemetics in a procedure in which nausea and vomiting is a common complication. So the finding of nausea in Group K (3.33 %) and none in Group M could be because of the antiemetic properties of magnesium sulphate used. Regarding pain 12 patients (40%) in Group K and 14 patients (47%) in Group M complained of pain within first 2 hours in PACU and while 20 patients (66.66%) in Group K and 22 (73%) in Group M complained within first 6 hours in PACU/Ward. Ketamine administered in small doses decreased post-operative analgesic consumption by 33%.[28] Magnesium has antinociceptive effects, probably because of its antagonistic action on the NMDA receptor.[41] Intravenous administration of magnesium sulphate (50 mg/kg preoperatively and 8 mg/kg/hour intraoperatively) significantly reduced intraoperative and postoperative fentanyl requirement.[42] Thus both drugs are reasonably effective in providing postoperative analgesia.

As part of the study we had taken serum magnesium samples preoperatively and postoperatively and it was found that the serum magnesium levels preoperatively and postoperatively did not show any statistically significant difference (table 7) as is seen by a p value of 0.655. Thus it can be concluded that the magnesium sulphate doses employed by us in this study did not alter the serum magnesium levels of the patients significantly

Limitations of the study and future direction

One of the limitations in this study was that the monitoring of the depth of anaesthesia was based on haemodynamic parameters and clinical findings, and is not satisfactory. While continuous EEG based parameters like BIS has been widely used for monitoring the depth of anaesthesia, choice of study drugs (ketamine, nitrous oxide) does not permit its use. More advanced monitors like fMRI, symbolic transfer entropy or transcranial magnetic stimulation may become widely available in the future.

V. Conclusion

It can be concluded from the present study that

1. Haemodynamic stability is more with propofol and ketamine combination.
2. Propofol and vecuronium consumption is less in the magnesium group.
3. Side effects like nausea is more in ketamine group.
4. The number of patients asking for rescue analgesia in the first and second hour in post anaesthetic care unit is more in magnesium group.

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