

The Effect of Intraoperative Magnesium Sulphate Infusion on The Course of Neuromuscular Blockade of Atracurium

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ABSTRACT

Background: Magnesium sulphate (MgSO₄) infusion has been increasingly used during anaesthesia and in intensive care units. The main problem that may arise with the use of MgSO₄, is its interaction with non-depolarizing muscle relaxants.

Aim of the work: The current work was designated to study the effect of Mg²⁺ on neuromuscular blockade by atracurium during the operative period.

Patients and methods: This study was carried out on forty patients scheduled for major abdominal surgery at NCI. All patients had the same premedication and general anaesthesia. Induction of anaesthesia was done with propofol and atracurium to facilitate tracheal intubation, and maintenance was carried on by isoflurane 0.5% and 60% nitrous oxide in oxygen. Patients were, then, randomly divided into two groups, 20 patients (group I) were observed as a control group, while patients of group II (20) had a bolus dose of MgSO₄ (3gm) after induction of anaesthesia. This was followed by a continuous infusion of 0.5 gm.h⁻¹ all through the operative period. Comparison between groups was done as regards the intubating conditions, haemodynamic stability, the effect of MgSO₄ on the course of atracurium neuromuscular blockade (time of onset, clinical duration and recovery index). Side effects after reversal with neostigmine and atropine, and the observed reversal time were demonstrated.

Results: Patients at MgSO₄ group had better intubating conditions and haemodynamic stability. MgSO₄ potentiated the action of atracurium induced neuromuscular blockade, with significant increase in the time of onset, clinical duration and reversal time after neostigmine.

Conclusion: MgSO₄ infusion has many advantageous effects during the course of anaesthesia. However, adequate neuromuscular blockade monitoring is mandatory.

Key Words: Magnesium sulphate - Atracurium - Neuromuscular blockade - Relaxograph.

INTRODUCTION

Recently, the appreciation of the multiple actions of magnesium within the cell, has led to marked increase in its use in clinical practice.

Magnesium (Mg)²⁺ is the second most abundant intracellular cation after potassium (K), and is considered the natural physiologic calcium channel blocker [6].

Mg²⁺ can compete with Ca²⁺ for binding sites on the Ca²⁺ effective proteins, and activate mechanisms involved in the control of Ca²⁺ within the cell. It also influences the Ca²⁺ mediated release of transmitter substances. Moreover, Mg²⁺ is involved in several vital processes which have important implication for anaesthetists e.g. regulation of muscle contraction, neuronal activity, control of vasomotor tone, cardiac excitability and neurotransmitter release [12].

Magnesium infusion has been increasingly used during anaesthesia and in intensive care units for haemodynamic control [29]. Also, the use of Mg²⁺ containing cardioplegia for cardiopulmonary bypass is well established [6].

The vasodilator and antiarrhythmic properties of Mg²⁺ suggest its use during aortic cross-clamping for major vascular surgery. Mg²⁺ has been used in the treatment of serious arrhythmias during anaesthesia. These may include arrhythmias associated with adrenaline administration, bupivacaine induced, hypokalaemia, myocardial infarction and digitalis toxicity [12].

The antiarrhythmic and antihypertensive actions of Mg²⁺ together with its ability to inhibit the release of catecholamines, have been advanced as a rationale for the use of Mg²⁺ infusion in the anaesthetic management of patients undergoing resection of pheochromocytoma [11].

The action of Mg²⁺ as N-methyl - D-aspartate (NMDA) receptor antagonist may provide intra-operative analgesia and may be associated with lower postoperative analgesic requirements [28]. Also, it may play an important role in neural protection during surgical ischaemia of spinal cord or expected global ischemia (21). Furthermore, for its bronchodilator effect, Mg²⁺ may be used for asthmatic patients under going major surgery. (8).

However, Mg²⁺ has been shown to produce dose related inhibition of neuromuscular transmission by competition with Ca²⁺ for membrane channels on the presynaptic terminals leading to a decrease in acetylcholine release [16]. Thus, the potential exists for possible interaction between Mg²⁺ and muscle relaxants used during anaesthesia or for mechanically ventilated patients in intensive care units [9].

This work was designated to study the effect of intraoperative infusion of Mg²⁺ on the course of neuromuscular blockade of Atracurium, as one of the most widely used nondepolarising muscle relaxant during anaesthesia [3].

PATIENTS AND METHODS

This clinical study was done on forty patients scheduled for major abdominal surgery at the National Cancer Institute, Cairo University. Ethics committee approval was granted and all patients gave written informed consent. The selected patients were ASA physical status 1 - 2. Patients with renal or hepatic dysfunction or those receiving drugs known to interact with neuromuscular blocking drugs were excluded.

All patients were premeditated with 0.08 mg.kg⁻¹ midazolam IV before induction of anaesthesia. Induction was achieved with Fentanyl 2 (g.kg⁻¹ and propofol (Diprivan) 1.5 - 2.5 mg.kg⁻¹ and maintained with 60 % nitrous oxide in oxygen and isoflurane 0.5 % (end-tidal). Further increments of Fentanyl were given as necessary.

Standard monitoring, consisting of electrocardiography, non invasive blood pressure monitoring, capnography and pulse oximetry, were applied to all patients.

In addition to neuromuscular transmission assessment which was done by electromyogra-

phy EMG (Relaxograph, Datex). The ulnar nerve was stimulated transcutaneously at the wrist with supramaximal stimuli of 0.2 ms duration in a train of four (TOF) mode at 2 Hz every 12 s. The force of contraction of the adductor pollicis was measured and recorded using a force displacement transducer. The first of the four evoked responses was considered the twitch height T1.

To minimize movement induced changes in twitch response, the patient's hand was fixed carefully in a splint, and the arm was covered with a warming blanket to maintain the skin temperature above 32°C [15,27]).

Monitoring started after induction of anaesthesia before giving the muscle relaxant drug to obtain a reference value.

Patients were allocated randomly into one of two groups:

Group I: (Control Group) where 20 patients were given IV saline infusion after induction of general anaesthesia and all through the operative procedure.

Group II: (MgSO₄ Group) where 20 patients were given 30 ml 10% MgSO₄ (3 gm) (EIPi co 100 mg.ml⁻¹ = 0.41 m.Mol.ml⁻¹) by slow bolus dose after induction of general anaesthesia. This was followed by a continuous infusion of 5 ml.h⁻¹ (0.5 gm.h⁻¹) with an infusion pump (MORING) till the end of surgery. Then, Atracurium bolus dose of 0.5 mg.Kg⁻¹ was administered over 5 seconds into a fast flowing infusion.

Patients were intubated 2 min after administration of Atracurium and the intubating conditions were graded as excellent, good or poor, according to the scheme described by Carroll et al, 1998 [3] as shown in table (1).

Adequate relaxation, defined as 0-2 responses of TOF stimulation, was maintained with Atracurium bolus doses until closure of the peritoneum. The following parameters were calculated:

Onset time: time from the end of injection of Atracurium till maximum neuromuscular blockade (complete disappearance of TOF response)

Clinical duration: time from injection of Atracurium until the twitch tension had recovered to 25 % of the control (T1).

The recovery index: time for the twitch tension (T1) to recover from 25 % blockade to 75 % blockade. (The time between T1 = 25 % and T1 = 75 % of the control).

Antagonism of neuromuscular blockade was achieved with 0.01 mg.Kg-1 intravenous atropine and 0.08 mg.Kg-1 neostigmine at 25 % recovery of the first twitch of the TOF (T1) [23]. Measured TOF ratio was above 0.8 before tracheal extubation was performed. The reversal time which is defined as the time from administration of neostigmine to attain a TOF ratio of 0.8 was recorded.

To study the influence of MgSO₄ on the cardiovascular effect of neostigmine induced rever-

sal of neuromuscular blockade, the incidence of bradycardia, tachycardia and arrhythmias was recorded in both groups. Heart rate, immediately before neostigmine administration was taken as baseline, Bradycardia was considered as a decrease in heart rate of at least 20 % and tachycardia as an increase in the heart rate at least 20 % of the baseline value. Other side effects after reversal were recorded.

Statistical analysis was done using SPSS-11. Means and standard deviations were used as a summary of quantitative data. A I-tail t-test was used for comparison of group II with the control group. The threshold of significance was fixed at the % level ($p = 0.05$).

Table (1): Assessment of incubating conditions.

	Excellent	Good	Poor
A. Laryngoscopy			
Jaw relaxation	Relaxed	Relaxed	Poor relaxation
Resistance to blade	No resistance	Slight resistance	Active resistance
B. Vocal cords			
Position	Abductd	Intermediate	Closed
Movement	None	Moving	Closing
C. Reaction to intubation			
Movement of limbs	None	Slight	Vigorous
Coughing	None	Diaphragm	Sustained > 10s

RESULTS

Both groups were comparable for age, weight, and gender distribution. There was no difference between groups as regards the duration of surgery or the type of operation. (Table 2). Premeditation and general anaesthesia were the same in both groups.

Haemodynamic parameters, as demonstrated in table (3) showed significant increase in systolic blood pressure (SBP), mean blood pressure (MBP) and heart rate (HR), in the control group in response to laryngoscopy and intubation. Maximum increase occurred 2min after intubation and remained high for 3min, then returned gradually to the baseline value 10min after incubation. While in MgSO₄ group, both SBP and MAP decreased steadily after the start of infusion without further increase in response to laryngoscopy and intubation. Heart rate did not change from the pre-induction value. Arrhythmia was observed in 2 patients in the control group, which was transient and did not require medication. While one patient had an

episode of bradycardia which required IV atropine.

Tracheal intubation was considered easy in all patients. There was no significant difference as regard clinically acceptable intubating conditions in both groups i.e. excellent or good condition. Table (4) and Fig. (1) demonstrate that the use of MgSO₄ produced a higher incidence of excellent intubating conditions (70%) than the control group (45%).

The effect of MgSO₄ on the course of atracurium induced neuromuscular blockade, is shown in table (5). The onset time of the block was significantly shorter in group II ($p=0.002$). On the other hand, the clinical duration was significantly longer $p<0.0001$ in group II when compared to the control group. Also, recovery index demonstrated longer duration in MgSO₄ group, however, the difference between both groups was not statistically significant ($p= 0.02$, Table 5). Antagonism of atracurium induced neuromuscular blockade with neostigmine demonstrated significant prolongation of reversal

time in patients pretreated with MgSO₄ (group II). There was statistically significant difference in the reversal time between both groups ($p=0.003$) as shown in table (5).

Observation of side effects after reversal of atracurium induced neuromuscular blockade, demonstrated that, 4 patients in the control group, had episodes of bradycardia, occurred 5-10 min after administration of neostigmine as

reported in table (6). While, in patients pretreated with MgSO₄ (group II) only two patients had bradycardia. In the recovery room, sedation was the most common side effect in MgSO₄ group (6 patients). However, patients were responding to verbal stimuli. While one patient in the control group complained of shivering and 2 patients of nausea. No significant changes in respiratory rate or arterial oxygen saturation was observed in the study.

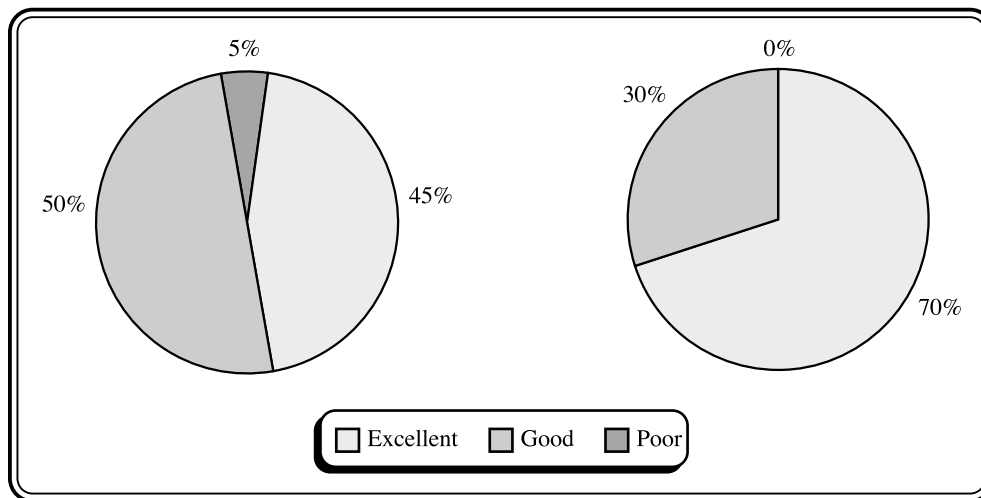


Fig. (1): Intubating conditions in the studied groups (n = 20 Patients/group).

Table (2): Patients characteristics and operative data.

	Group I (Control)	Group II (MgSO ₄)
Number of patients	20	20
Gender M/F	14/6	11/9
Age (Y)	48.3±16.7	52.1±18.2
Weight (Kg)	67.4±14.9	62.7±9.4
Duration of surgery (min)	114.7±12.3	118.6±17.6
<i>Dose of atracurium</i>		
Bolus dose	0.5 mg.Kg ⁻¹	0.5 mg.Kg ⁻¹
Maintenance dose	0.2 mg.Kg ⁻¹	0.2 mg.Kg ⁻¹
<i>Dose of MgSO₄</i>		
Bolus dose	—	3 gm 10% MgSO ₄
Maintenance dose	—	0.5 gm.h ⁻¹
<i>Type of surgery</i>		
Radical cystectomy	8	7
Abd. hysterectomy	4	6
Exploration	2	1
Hemicolectomy	6	6

Table (3): Mean haemodynamic changes before and after tracheal intubation in both studied groups.

Time (min)	Before induction	Start of induction	2 min after intubation	4 min after intubation	10 min after intubation
<i>Changes in SBP (mm Hg)</i>					
Group I (control)	123.3±4.9	121.6±6.2	154.4±9.4	136.2±11.6	120.3±8.7
Group II (MgSO ₄)	121.8±3.4	120.6±5.3	110.0±07.4	108.5±9.2	28.7±4.1
<i>Changes in MBP (mm Hg)</i>					
Group I (control)	91.6±6.4	93.2±9.2	102.9±8.6	98.7±7.3	94.9±9.6
Group II (MgSO ₄)	92.0±4.3	90.3±6.1	86.4±5.7	84.8±4.1	82.2±3.9
<i>Changes in HR (beat. Min⁻¹)</i>					
Group I (control)	178.6±9.6	76.9±7.2	104.7±9.1	98.4±8.7	103.5±6.2
Group II (MgSO ₄)	77.8±4.3	76.7±6.4	80.9±4.9	78.1±5.7	77.9±4.6

SBP: Systolic blood pressure MBP: Mean blood pressure HR: Heart rate Figures are mean ±SD

Table (4): Intubating conditions.

	Group I (Control)	Group II (MgSO ₄)
Excellent	9	14
Good	10	6
Poor	1	0

Figures are number of patients.

Table (6): Side effect after reversal of Atracurium induced neuromuscular blockade.

	Group I (Control)	Group II (MgSO ₄)
Bradycardia	4	2
Tachycardia	-	-
Arrhythmia	2	-
Sedation	-	6
Shivering	1	-
Nausea	2	-

Figures are number of patients.

DISCUSSION

MgSO₄ is increasingly used as an adjuvant to general anaesthesia, mainly for haemodynamic control and nociception modulation [28]. Two major problems may arise with the use of MgSO₄ in patients undergoing general anaesthesia. First, MgSO₄ may enhance the action of non-depolarizing neuromuscular blockers by reducing endplate sensitivity and decreasing muscle fibers excitability. Second, Mg²⁺ may interact with calcium at vascular membranes and decrease peripheral vascular resistance [6].

The increasing interest in therapeutic uses of MgSO₄ in anaesthesia and intensive care unit

Table (5): Effect of MgSO₄ on the course of Atracurium induced neuromuscular blockade.

	Group I (Control)	Group II (MgSO ₄)	t-value	p-value
Onset time (min)	2.14±0.42	1.76±0.36*	3.07	0.002
Clinical duration (min)	27.32±3.74	34.7±5.91*	4.71	<0.0001
Recovery index (min)	12.6±3.8	14.8±2.3	2.21	0.02
Reversal time (min)	3.58±1.79	5.26±1.9*	2.87	0.003

Figures are mean ±SD

* Significant (p<0.05)

mandate an independent study for its neuromuscular effect and its possible interactions with non-depolarizing muscle relaxants.

The current study was carried out to demonstrate the effect of MgSO₄ infusion on atracurium induced neuromuscular blockade.

The first part of the study focused on the intubating conditions after MgSO₄ infusion as compared to the control group. A subject of interest to the anaesthetist is how to create favorable conditions conducive to ease of laryngoscopy and atraumatic placement of a tracheal tube.

The topic still fascinates clinicians, as several independent factors must be controlled, mainly the depth of hypnosis induced, the onset profile of the muscle relaxant and the interval between administration of muscle relaxants and laryngoscopy [15].

Several authors suggested that laryngoscopy and tracheal intubation elicited potentially harmful cardiovascular responses [4,5,18]. This was explained by sympathetic stimulation demonstrated by the rise of norepinephrine level ob-

served by Derbyshire et al., 1983 [4] in their clinical study. Their results were in agreement with the current results, as the control group demonstrated significant changes in SBP, DBP and HR after intubation. Prior administration of MgSO₄ (group II), resulted in prevention of haemodynamic stimulation observed in group I (Table 3).

The ability of Mg²⁺ to inhibit the release of catecholamines from adrenergic nerve terminals and from the adrenal medulla, supports its use to control the hypertensive response to intubation and surgical stimulation [12]. Beside haemodynamic stability, MgSO₄ affords favorable intubating conditions, because Mg²⁺ speeds the onset of atracurium and has direct effect on muscle fibers, besides its analgesic and sedative properties.

Schenk et al. [26] demonstrated that MgSO₄ infusion suppress airway hyper-reactivity through inhibition of intracellular calcium release from the sarcoplasmic reticulum, in addition to inhibition of calcium channels at bronchial smooth muscle. Sato et al. [25] also demonstrated that MgSO₄ can suppress airway reflexes and hyperreactivity. Mg²⁺ blocks the N-methyl-D-aspartic acid (NMDA) receptors existing in the airway. NMDA receptor activation seems to be linked to the release of sensory neuropeptide resulting in increased airway tone [22].

The results of the current study demonstrated earlier onset time of atracurium in MgSO₄ group as compared to the control group. This clinically interesting phenomenon, may contribute to improvement in intubating conditions. These results were in accordance with the study of Lampl and Dandoy [18], where speed of onset of atracurium was increased markedly when patients were pretreated with MgSO₄.

Taking into consideration that the onset of neuromuscular block is faster for the larynx than peripheral muscles [5]. As there is ample evidence that onset of block at the adductor pollicis lags considerably behind the neuromuscular effects seen at muscles that have greater relevance to ease of intubation such as the laryngeal adductors, diaphragm and masseter [7]. The indirectly evoked muscular response at the hand is not a very useful measure for evaluating readiness for tracheal intubation.

However, marked peripheral vasodilatation observed after induction of general anaesthesia, together with warming of the hand by warm blanket to more than 32°C, resulted in increase in muscle perfusion, as well as skin blood flow. Then drug delivery to the muscles of the hand will be enhanced and results in larger drug level at the myoneural junction [14].

Furthermore, MgSO₄ was demonstrated to produce significant potentiation of atracurium induced neuromuscular blockade with significant prolongation of its clinical duration (from 27.32±3.74 min in the control group, to 34.7±5.91 min in MgSO₄ group ($p < 0.0001$)). Several studies supported the current results and proved the effect of MgSO₄ in prolongation of clinical duration of different neuromuscular blocking drugs [1,9,13,17].

Non-depolarizing neuromuscular blockers have both presynaptic and postsynaptic activity at the neuromuscular junction. Presynaptic action is thought to occur at nicotinic receptors on the nerve terminals that mediate autofacilitation of acetylcholine release, while the postsynaptic action inhibits end-plate depolarization. MgSO₄ has mainly presynaptic effects by inhibiting acetylcholine release at motor nerve terminals, an effect which may be responsible for the interaction with atracurium. Postsynaptically Mg²⁺ inhibits end-plate depolarization by competing with Ca²⁺ for activation sites on the myosin ATPase necessary for excitation contraction coupling. In the presence of high concentrations of Mg²⁺, fewer Ca²⁺ bind to acetylcholine containing vesicles, thus decreasing acetylcholine release from the nerve endings. [19].

In this clinical situation, calcium may be useful, as Mg²⁺ competitively blocks its entry into the presynaptic nerve terminals [20]. The rapid recovery of atracurium contributes to its safety in clinical practice. MgSO₄ considerably prolongs its clinical duration. One may speculate that, a longer clinical duration of action together with slower recovery, may increase the risk for relaxant induced curarization. In this condition, increasing the dose of neostigmine may not be useful. Besides, it may increase its potential cardiovascular side effects [2].

In the current study reversal with neostigmine started at 25 % recovery of the first twitch of TOF (T1) to standardize the degree of block.

It is well documented that the potency of anticholinesterase drugs is inversely related to the degree of neuromuscular block. Neostigmine is more efficacious when the intensity of neuromuscular block is less [10].

In the present study, the reversal time, measured from administration of neostigmine to attain a TOF ratio of 0.8 was significantly longer in patients pretreated with MgSO₄. However, recovery was adequate in all patients, with stable postoperative haemodynamic parameters and arterial oxygen saturation. No signs of re-urazation was observed in any patient in both groups.

Adjusting the dose of MgSO₄ to get desirable clinical response without adverse effects is mandatory. The dose of MgSO₄ used in the current study was considered safe by Tramer et al. [28]. Continuous infusion was used to provide stable plasma concentration, where Mg²⁺ is eliminated rapidly in the presence of normal renal function [24].

In conclusion, MgSO₄ administered before intubation improves intubating conditions and provides adequate intraoperative haemodynamic stability. MgSO₄ produced significant potentiation of atracurium induced neuromuscular blockade with significant prolongation of the clinical duration and reversal time after neostigmine administration. Adequate neuromuscular blockade monitoring is mandatory in patients pretreated with MgSO₄.

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