SciDoc Publishers
Infer, Interpret & Inspire Science

International Journal of Anesthesiology & Research (IJAR)
ISSN 2332-2780

Effect of Magnesium Sulphate on Intra Operative Anesthetic Requirements and Post Operative Analgesia in Plastic Surgery Patients

Research Article

Durga P. Murumu[1], Manjaree Mishra[2*], Atul Kumar Singh3, S. K. Mathur[4]

[1] Junior Resident, Department of Anesthesiology, Ist Floor, O.T. Complex, S. S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.221005. India.
[2] Assistant Professor, Department of Anesthesiology, Ist Floor, O.T. Complex, S. S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.221005. India.
[3] Assistant Professor, Department of Anesthesiology, Ist Floor, O.T. Complex, S. S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.221005. India.
[4] Professor and Head, Department of Anesthesiology, Ist Floor, O.T. Complex, S. S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.221005. India.

Abstract

Background: The management of postoperative pain is one of the most challenging issue for anesthesiologists. The anaesthetic and analgesic-sparing effect of Magnesium sulphate may enable anaesthesiologists to reduce the use of anaesthetics during surgery and the use of analgesics after surgery. To evaluate the effect of preoperative systemic magnesium sulphate on intra-operative vecuronium isoflurane and fentanyl consumption and post-operative analgesia.
Methods: 60 ASA I-II patients of both sex, group M received magnesium sulphate and group S Saline as per study protocol. Patients characteristics, heart rate, systolic, diastolic and mean blood pressure, mean alveolar concentration were noted at definite time intervals. Pain score, dosage and timing of rescue analgesia, episodes of shivering, vomiting or any other significant side effect were recorded till 8th hr. Statistical analysis was performed and P-value below 0.05 was considered significant.
Results: VAS score at 1hr and 4hr, which were significantly lower in Group M and need for rescue analgesia was less ingroup M as compared to group S. None of the patients in group M had shivering and vomiting as compare to group S. Our study demonstrate significant reduction in the consumption of isoflurane and vecuronium magnesium group. Magnesium sulphate was also found having more advantages during the postoperative periods associated with better recovery profiles.
Conclusion: Magnesium has anaesthetic, analgesic and muscle relaxant properties and its intraoperative use lead to significantlyreduces the drug requirements of vecuronium and isoflurane during anaesthesia and post-operative consumption of ketorolac and reduced VAS score.

Keywords: Magnesium Sulphate; Analgesia; VAS, Plastic Surgery.

Introduction

The management of postoperative pain is one of the most challenging issue for anesthesiologists. There have been landmark advances in the clinical pharmacology still the moderate andsevere postoperative pain is reported in 80% and 31–37% of patients, respectively. [1-3]

The pathophysiology of surgical pain is mediated by inflammation of damaged tissues or direct injury to nerve cells. The optimal management of postoperative pain is the key factor for early ambulation after surgery, patient satisfaction and reducing length of hospital stay therefore the cost of treatment.

The various factors associated with post-operative pain may be grouped as; patient-related and surgery-related. The factors like previous pain experiences, social, cultural and psychological status, as well as genetic and sexual factors are major patient-related factors. However, surgical factors include the type of anaesthesia and surgical technique including ability to diagnose and avoid

***Corresponding Author**:
Dr. Manjaree Mishra,
Assistant Professor, Department of Anesthesiology, Ist Floor, O.T. Complex, S. S. Hospital, Institute of Medical Sciences, Banaras Hindu University, Varanasi.221005. India.
Tel: +91-9415352841
E-mail: drmanjareemd@gmail.com

Received: September 06, 2021
Accepted: November 28, 2021
Published: November 29, 2021

Citation: Durga P. Murumu, Manjaree Mishra, Atul Kumar Singh, S. K. Mathur. Effect of Magnesium Sulphate on Intra Operative Anesthetic Requirements and Post Operative Analgesia in Plastic Surgery Patients. *Int J Anesth Res.* 2021;09(03):662-667.

nerve damage if possible.[4]

The plastic surgical procedures are usually associated with moderate to severe pain which makes intra-operative and postoperative analgesia a major concern. The use of opioid analgesics can manage the intra operative pain but the associated side effects are troublesome postoperatively.

In addition to the other issues, sub optimal management of postoperative pain is also associated with impaired wound healing and rehabilitation, delayed gastrointestinal motility, pulmonary complication, higher risk of thromboembolism due to immobilization, and myocardial ischemia.[5-9]

Magnesium sulphatehas been in use as a general anaesthetic. Recent literature has suggested that it bears potentiating effects on peri-operative analgesia by acting as an antagonist to N-methyl-D-aspartate (NMDA) receptors10and muscle relaxation. Thus its anaesthetic and analgesic-sparing effect may enable anaesthesiologists to reduce the use of anaesthetics during surgery and the use of analgesics after surgery.

Magnesium has also a central nervous system (CNS) depressantand itsanaesthetic effects result from cerebral hypoxia after progressive respiratory and cardiac depression. It was suggested that if respiratory support is maintained, patients showed no CNS depression even at very high serum concentrations of magnesium. [11]

The primary objective of the study is to evaluate the effect of preoperative systemic magnesium sulphate on intra-operative vecuronium isoflurane and fentanyl consumption and post-op analgesia .A secondary objective was to examine possible side effects and toxicity associated with the administration of preoperative magnesium.

Methods

The study protocol was approved by institute ethical committee and sample size was decided arbitrarily taking into consideration the time period of the study and average number of patients undergoing plastic surgery. After obtaining informed consent a double blinded randomized control trial was conducted on60 ASA I-II patients of both sex aged between 20-60 year, in the Department of Anaesthesiology, Sir Sunderlal Hospital and Trauma centre, Institute of Medical Sciences, Banaras Hindu University. Patients were randomly assigned to 2 equal groups using sealed envelope method.

Group M- magnesium group (n=30) patients were given intravenous 50 mg/kg of magnesium sulphate in 100 ml of Normal Saline over 20 min immediately before induction and then 10 mg/kg/hr by continuous iv infusion till the end of surgery. Group S- Saline group (n=30) were given the same volume of isotonic saline over same duration.The patients allergic to magnesium sulphate or any other study drugs, with major renal, hepatic or cardiovascular dysfunction, atrioventricular block, neuromuscular disorder such as Myasthenia gravis, Eaton lambert syndrome, neurological disorder, asthma or chronic obstructive pulmonary disease, obesity (BMI>40), pregnancy, opioid or analgesic abuse, Patient taking chronic treatment of calcium channel blocker, magnesium or anticoagulant were excluded.

Oral Tab. Alprazolam 0.25mg, Tab. Ranitidine 150mg was given the evening and in the morning 2 hours before surgery. In the operating room, under aseptic precautions, a 18-gauge peripheralvenouscannula was established on the dorsum of non-dominant or non- operating hand. Pulse oximeter, electro cardiogram, non-invasive arterial blood pressure and BIS electrode were connected to the patients. All patients under the study were preloaded with 500 ml Lactated Ringer solution over 30 minute.

All patients were premedicated with inj. Midazolam 30 mcg/kg intravenously anesthesia was Induced with 1% of inj. Propofol 2 mg/kg. Inj. Vecuronium 0.1 mg/kg was given after conformation of adequate mask ventilation. After mask ventilation for 3 minute a appropriate size endotracheal tube was placed and its position wasconformed. All patients were maintained with 50% oxygen in nitrous oxide, isoflurane andvecuronium. Peri-operative analgesia was maintained with 1 mcg/kg of fentanyl which was given just after inj. Midazolam. Depth of anaesthesia was measured using BIS and was maintained between 40-60 with the help of isoflurane. Vecuronium was administered at its maintenance bolus dose of 0.01mg/kg. The measurements of HR, SBP, DBP, MAP, Oxygen saturation(SpO2) were measured at post induction and intervals of 1, 5, 10, 15, 20, 25, 30, 45, 1 hr, 1 hr 15 min,1 hr 30 min, 2 hr and at the end of surgery. The magnesium sulphate and anaesthetic agents were discontinued at skin closure, and inj. Ondansetron 0.1 mg/kg and paracetamol 1gm were administered. At the end of surgery, neuro-muscular block was reversed by neostigmine 0.05 mg/kgandglycopyrrolate 0.01 mg kg. After termination of anaesthesia, all patients were transferred to the recovery room and assed for any sign of hypermagnesemia and other adverse event and side effects were noted and managed accordingly. The following data were recorded in recovery room and ward:

1. Pain was evaluated using a 0-10 cm visual analogue scale (VAS, starting from 0= no pain, to 10= worst pain imaginable). The VAS score was recorded at emergence from anaesthesia and at 30 min, 1 h, 2 h, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr after the surgery.
2. The dosage and timing of rescue analgesia (ketorolac 30mg Intramuscular) was recorded at 30 min, 1 h, 2 h, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr after operation.
3. Episodes of shivering, vomiting or any other significant side effect were monitored and recorded till 8th hr.

Statistical analysis was performed using SPSS version 16.0 software. For comparison; paired student unpaired t test and chi square test, as appropriate. A P-value below 0.05 was considered significant.

Results

In the present study, a total 60 patients were enrolled. Two study groups were made each consisting 30 patients. Table 1 shows Patient Characteristics and Duration of Surgery in the two Groups. The mean age and duration of surgery was respectively 33.43 ± 12.979 years and 80.9(±23.8) in group S as compared to 34.57 ± 11.334 years and 76.13(±18.57) in group M showed no statistically significance difference. Other parameter like sex, weight and ASA was also comparable.

Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure and

Table 1. Patient Characteristics and Duration of Surgery in Two Groups.

	Group S (n=30)	Group M (n=30)	p-value
Age (yr)	33.43 ± 12.979	34.57 ± 11.334	0.72
sex (m/f)	9/21	10/20	0.781
ASA (I/II)	22/8	22/8	1
Weight (kg)	55.43 ± 7.0	55.97 ± 7.21	0.868
Duration of surgery (min)	80.9(±23.8)	76.13(±18.57)	0.392

Mean Arterial Pressure at various time intervals in two Groups has been shown in Table 2. Mean HR values of both the groups were comparable and not significant ($p>0.05$) except the HR value at 90 minute, which was significantly lower in Group M ($p<0.05$). Mean SBP values of both the groups were comparable and not significant ($p>0.05$) except the SBP value at 5 minute, 10 minute, 60 minute, and at the end of surgery; which was significantly lower in Group M ($p<0.05$). Mean DBP values of both the groups were comparable and not significant ($p>0.05$).Mean MAP values of both the groups were comparable and not significant ($p>0.05$) except the MAP value at 60 minute and at the end of surgery; which was significantly lower in Group M ($p<0.05$). Mean vecuronium consumption was significantly lower in Group M ($p<0.05$) and mean fentanyl consumption was comparable but statistically not significant.

As shown in Table 3, Mean VAS score of both group are comparable and statistically not significant ($p>0.05$) except VAS score at 1hr and 4hr, which were significantly lower in Group M.Table 4 shows the need for rescue analgesia in the two groups and it can been seen to be less in group M as compared to group S. The incidence of shivering and vomiting in two groups are shown in Table 5. None of the patients in group M had shivering and vomiting as compare to group S.

Discussion

Post operative pain control is a major area of concern for anaesthesiologists.In this study we found that with Isoflurane based balanced general anaesthesia, magnesium sulphate produced similar intraoperative conditions and haemodynamics parameter during the surgery as control.

Magnesium is known to induce hypotension, directly by vasodilation and indirectly by sympathetic blockade and inhibition of catecholamine release. In contrary to some studies [12-14] in our study we did not find any episodes of hypotension or bradycardia that warrant the use of vasopressor or atropine. That can be explain by preloading, was done with 500 ml of lactated Ringer's solution. The heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and the mean arterial pressure (MAP) were on the lower side but with statistically insignificant difference in magnesium group. We observed more stable hemodynamic during laryngoscopy and tracheal intubation (LTI) in magnesium group.

Our study demonstrates significant reduction in the consumption of isoflurane and vecuroniumin magnesium group. In comparison to previous animal study shows, increase in magnesium dose was associated with reduction of Halothane MAC in rats,[18] sevoflurane,[15] and desflurane,[16] to our knowledge this is the first study between the interaction of isoflurane and magnesium in human subject.

In accordance to other studies magnesium sulphate in patients undergoing general anesthesia resulted in decrease in the requirement for nondepolarizing muscle relaxants [17, 18] with no delay the recovery from general anaesthesia.[20, 21] Our study shows that in magnesium group mean vecuronium requirement was lower (6.466 ± 1.077mg vs7.37 ± 1.77 mg). As a calcium channel blocker, magnesium decreases acetylcholine release at the presynaptic nerve terminals and diminishes the excitability of muscle fibre thus reduces the amplitude of endplate potential, resulting in the potentiation of neuromuscular blockade by nondepolarizing muscle relaxants.[19] However, our study demonstrated that magnesium sulphate has more advantages during the postoperative periods associated with better recovery profiles.

We observed decreased incidence of postoperative shiveringso decreases discomfort and oxygen consumption, this finding was also confirmed by other studies.[15, 21, 22] Wadhwa et al also demonstrated the effect of magnesium in reducing hypothalamic shivering threshold from 36.6OC to 36.3OC.[23]

Intraoperative use of magnesium sulphate is associated with decreased incidence of vomiting in postoperative period, also found in a study by Ryu JH et al [15] which could be due to lesser consumption of volatile anesthetic rather than any antiemetic property of magnesium. Nevertheless, because nausea and vomiting are one of the common complications encountered in post operative period and is distressing to the patient and the family member.

The study shows that intraoperative use of intravenous magnesium sulphate bolus followed by infusion reduces postoperative pain and analgesic consumption without any notable complication. All patients were pain free at extubation probably because of additional analgesic effect of paracetamol at this period. Pain assessment after plastic surgery shows pain score ranging from 10 to 60 mm on VAS scale.VAS score at 1hr and 4hr were significantly lower in Group M.

Adequate bolus and infusion doses of magnesium sulphate are important for effective analgesia. Pre and intraoperative administration of magnesium sulphate in gynecology patients receiving total intravenous anaesthesia reduced rocuronium requirement and improved the quality of postoperative analgesia without any significant side-effects.[21] Accordingly, in the present study, we administered a 50 mg/kg bolus and a maintenance dose of 10 mg/kg/h.

We found that infusion of magnesium sulphate can provide a clinically important reduction in ketorolac consumption and pain severity in the first 8 hours postoperatively. In consistency with our results, Koglerobserved that intra-operative fentanyl con-

Table 2. Heart Rate, Systolic Blood Pressure, Diastolic Blood Pressure and Mean Arterial Pressure at various time intervals in Two Groups.

	Time Interval	Group S(n=30)	Group M (n=30)	p-value
Heart Rate (per minute)	Baseline	88.93 ± 11.965	85.00 ± 15.605	0.278
	Post induction	70.53 ± 10.234	71.90 ± 13.662	0.663
	1 min	67.13 ± 9.537	70.67 ± 13.882	0.255
	5 min	92.80 ± 11.871	87.57 ± 14.670	0.134
	10 min	85.90 ± 12.215	85.00 ± 13.656	0.789
	15 min	83.77 ± 10.112	84.20 ± 10.924	0.874
	20 min	85.10 ± 10.317	84.93 ± 12.720	0.956
	25 min	90.63 ± 14.440	86.33 ± 12.001	0.215
	30 min	93.30 ± 15.043	86.83 ± 15.195	0.103
	45 min	87.87 ± 8.916	87.83 ± 14.345	0.99
	60 min	91.27 ± 9.552	88.38 ± 12.912	0.364
	75 min	89.25 ± 10.031	87.80 ± 10.678	0.683
	90 min	93.92 ± 7.090	78.75 ± 8.302	0.003
	120 min	87.00 ± 7.000	83.50 ± 9.192	0.657
	End of surgery	91.63 ± 9.449	88.23 ± 14.445	0.285
Systolic Blood Pressure (mmHg)	Baseline	129.93 ± 10.596	126.60 ± 11.822	0.255
	Post induction	106.43 ± 8.190	100.10 ± 18.522	0.092
	1min	100.97 ± 8.168	101.57 ± 11.282	0.814
	5min	132.80 ± 13.247	124.30 ± 10.790	0.008
	10min	124.07 ± 10.907	118.77 ± 7.682	0.034
	15min	120.43 ± 8.173	118.17 ± 10.269	0.348
	20min	120.07 ± 8.694	117.77 ± 10.640	0.363
	25min	121.60 ± 10.361	116.47 ± 11.993	0.081
	30min	122.07 ± 8.994	119.57 ± 10.368	0.323
	45min	120.83 ± 10.758	118.62 ± 9.155	0.399
	60min	124.96 ± 9.327	118.37 ± 9.203	0.013
	75min	123.259.596	120.535.914	0.341
	90min	126.098.949	117.504.796	0.095
	120min	122.004.000	119.009.899	0.652
	End of surgery	123.238.877	116.678.612	0.005
Diastolic Blood Pressure (mmHg)	Baseline	77.53 ± 6.073	76.57 ± 7.394	0.582
	Post induction	64.67 ± 6.391	62.87 ± 7.114	0.307
	1min	61.13 ± 5.764	61.97 ± 9.194	0.677
	5min	77.33 ± 8.584	74.87 ± 7.565	0.242
	10min	76.23 ± 7.065	74.00 ± 7.865	0.252
	15min	74.63 ± 4.958	75.13 ± 7.181	0.755
	20min	72.93 ± 4.608	73.10 ± 6.890	0.913
	25min	74.73 ± 6.247	72.07 ± 7.400	0.137
	30min	74.50 ± 6.437	73.20 ± 8.151	0.496
	45min	74.47 ± 7.133	73.59 ± 8.087	0.659
	60min	77.00 ± 5.886	73.52 ± 7.485	0.066
	75min	75.85 ± 6.037	74.88 ± 7.788	0.675
	90min	79.92 ± 7.342	75.00 ± 4.243	0.231
	120min	78.00 ± 3.606	76.00 ± 5.657	0.653
	End of surgery	76.43 ± 6.791	73.93 ± 7.570	0.183
	Baseline	90.60 ± 7.200	89.60 ± 8.508	0.625
	Post induction	78.63 ± 8.327	75.80 ± 8.214	0.19
Mean Arterial Pressure (mmHg)	1min	73.73 ± 7.172	73.20 ± 9.474	0.807
	5min	91.33 ± 8.636	88.43 ± 8.625	0.198
	10min	89.17 ± 8.595	85.07 ± 9.123	0.078
	15min	87.13 ± 6.067	88.07 ± 7.320	0.593
	20min	87.37 ± 6.960	87.07 ± 7.634	0.874
	25min	88.07 ± 6.817	85.90 ± 7.893	0.26
	30min	88.80 ± 7.640	86.30 ± 8.388	0.232
	45min	89.40 ± 6.780	86.14 ± 8.314	0.104
	60min	91.08 ± 6.776	86.00 ± 7.275	0.011
	75min	90.68 ± 7.047	86.81 ± 6.784	0.098
	90min	93.00 ± 7.544	86.75 ± 4.787	0.147
	120min	94.00 ± 6.928	88.50 ± 4.950	0.412
	End of surgery	90.63 ± 7.165	86.03 ± 7.117	0.015

sumption was decreased significantly in magnesium treated group compared to control group in thoracotomy procedure. However, there was no difference in pain intensity at 48 hours after surgery.[25] Albrecht E and colleagues,in a meta-analysis on twentyfive trials comparing magnesium with placebo concluded that perioperative intravenous magnesium reduces opioid consumption and pain scores, in the first 24 hour postoperatively.[26]

In contrast to our findings, Bhatia and colleagues reported no significant decrease in the amount of consumed morphine during cholecystectomy.[24] Tramer and Glynn showed that pre treatment with magnesium sulphate no effect on post operative analgesia for first 3 postoperative days.[22] However, unlike our study they did not use fentanyl for intraoperative analgesia. Intense or repeated noxious stimulation causes release of excitatory amino acidsin the dorsal horn. Activation of NMDA receptor leads to Ca2+entry into the cell that initiates a series of central sensitization causes long-term potentiation in the spinal cord in response

Table 3. Mean Visual Analogue Scale(VAS) Score of Group S and Group M at different time intervals starting at 30 minute after the completion of surgery.

Time Interval	Group S (n=30)	Group M (n=30)	p-value
30min	1.63 ± 0.669	1.80 ± 0.887	0.414
1hr	2.87 ± 1.548	2.20 ± 0.761	0.039
2hr	2.97 ± 1.159	2.63 ± 1.066	0.251
3hr	2.53 ± 1.042	2.67 ± 1.124	0.636
4hr	3.37 ± 1.189	2.60 ± 1.133	0.013
5hr	2.63 ± 1.098	2.30 ± 0.952	0.214
6hr	2.73 ± 1.363	2.27 ± 0.980	0.133
7hr	2.33 ± 0.922	2.40 ± 1.102	0.8
8hr	2.87 ± 1.306	2.30 ± 0.877	0.053

Table 4. Mean number of rescue analgesic of Group S and Group M patients at different time intervals starting at 1hr after surgery.

Time Interval	Group S (n=30)	Group M (n=30)
30min	0	0
1hr	9	0
2hr	8	4
3hr	6	5
4hr	11	8
5hr	6	4
6hr	7	3
7hr	3	5
8hr	9	3

Table 5. Postoperative complication.

Complication	Group S (n=30)	Group M (n=30)	p-value
Shivering	4 (13.3)	0	0.112
Vomiting	7 (23.3)	0	0.010

of cells to prolonged stimuli. Central sensitization has an important role for pain perception and the persistence of postoperative pain. Magnesium acts as an antagonist at the same NMDA receptor and its associated ion channels. Therefore, magnesium could modulate postoperative pain via blockade of NMDA-receptor.

Ryu et al demonstrated the effect of intravenous magnesium sulphate in reducing intraoperative anaesthetic requirement and postoperative analgesia in gynecological patients received TIVA, as against the isoflurane based balanced general anaesthesia in our study, and found that IV magnesium sulphate improves quality of postoperative analgesia.[19] Gupta et al also reported that magnesium reduces requirements ofpropofol, rocuronium and fentanyl in spinal surgical patients.[27] It is conceivable that the intraoperative use of magnesium sulphate may mitigate remifentanil-induced hyperalgesia in patients receiving TIVA.

Explanations for these discrepancies in study outcome could be due to the differences in dose, onset of magnesium administration, the type of magnesium salt, pain scores used, choice of patient population, standard baseline pain medication and anesthesia. Besides it, there are many confounding factors, such as age, preoperative pain level and perception, and comedication that are hard to control.

Pain in plastic surgery patient can be multifactorial. Pain perception can be influenced by variety of factors such as gender, psychological, personality, genetic and ethnicity.[28, 29] In both groups of our study, pain score was moderate particularly in early hours (mean VAS of <3) this might be due to the residual effect of paracetamol 1 gm.

Limitations

We did not measure serum and cerebrospinal fluid magnesium concentration however it has been studied that most of the body magnesium is intracellular and estimation of plasma magnesium

does not represent magnesium content of body tissue.[30] Performing lumber puncture could have given us further information in normal human subject. Furthermore, the study population was not large; however the sample size was based on predefined effect size and power. We did not assess patient satisfaction, therefore we cannot comment on future use of same analgesia again after similar operation. Movement-related pain during forced expiration might be more sensitive to altered sensory processing; which was not assessed in our study. However, the role of hyperalgesia in postoperative pain is not fully understood.

Conclusion

The reason for failure to provide adequate postoperative analgesia is multifactorial, for Postoperative pain management to be effective it should beproperly planned, delivered in a consistent, evidence based manner and based on patients' assessment of their own pain whenever possible.We conclude that magnesium has anaesthetic, analgesic and muscle relaxant properties and its intraoperative use lead to significantlyreduces the drug requirements of vecuronium and isoflurane during anaesthesia and post-operative consumption of ketorolac and reduced VAS score.

The current literature of analgesic effects of magnesium is conflicting, and additional major clinical trials using well-defined dose regimens and pain scores are required to achieve more data on possible anti-nociceptive effects.

The high therapeutic index and cost-effectiveness of magnesium could makes it's a potent adjuvant drug for anaesthesia and with appropriate use it can improve surgical outcome and patients' satisfaction.

References

[1]. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. Local RegAnesth. 2014 May 29;7:17-22. PubMed PMID: 24872720.

[2]. Carr DB, Goudas LC. Acute pain. Lancet. 1999 Jun 12;353(9169):2051-8. PubMed PMID: 10376632.

[3]. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. AnesthAnalg. 2003 Aug;97(2):534-540. PubMed PMID: 12873949.

[4]. Voscopoulos C, Lema M. When does acute pain become chronic? Br J Anaesth. 2010 Dec;105Suppl 1:i69-85. PubMed PMID: 21148657.

[5]. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet. 2003 Dec 6;362(9399):1921-8. PubMed PMID: 14667752.

[6]. Holte K, Kehlet H. Postoperative ileus: a preventable event. Br J Surg. 2000 Nov;87(11):1480-93. PubMed PMID: 11091234.

[7]. Gandhi K, Heitz JW, Viscusi ER. Challenges in acute pain management. AnesthesiolClin. 2011 Jun;29(2):291-309. PubMed PMID: 21620344.

[8]. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012 Feb;116(2):248-73. PubMed PMID: 22227789.

[9]. Lucas CE, Vlahos AL, Ledgerwood AM. Kindness kills: the negative impact of pain as the fifth vital sign. J Am Coll Surg. 2007 Jul;205(1):101-7. PubMed PMID: 17617339.

[10]. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain. 1991 Mar;44(3):293-299. PubMed PMID: 1828878.

[11]. Somjen G, Hilmy M, Stephen CR. Failure to anesthetize human subjects by intravenous administration of magnesium sulfate. J PharmacolExpTher. 1966 Dec;154(3):652-9. PubMed PMID: 5928261.

[12]. Tramer MR, Schneider J, Marti RA, Rifat K. Role of magnesium sulfate in postoperative analgesia. Anesthesiology. 1996 Feb;84(2):340-7. PubMed PMID: 8602664.

[13]. Koinig H, Wallner T, Marhofer P, Andel H, Hörauf K, Mayer N. Magnesium sulfate reduces intra- and postoperative analgesic requirements. AnesthAnalg. 1998 Jul;87(1):206-10. PubMed PMID: 9661575.

[14]. Kara H, Sahin N, Ulusan V, Aydogdu T. Magnesium infusion reduces perioperative pain. Eur J Anaesthesiol. 2002 Jan;19(1):52-6. PubMed PMID: 11913804.

[15]. Ryu JH, Sohn IS, Do SH. Controlled hypotension for middle ear surgery: a comparison between remifentanil and magnesium sulphate. Br J Anaesth. 2009 Oct;103(4):490-5. PubMed PMID: 19687032.

[16]. Tomak Y, Tekin M, Kati I, Belenli C, Aydogmus M. Analysis of the effect of perioperative magnesium sulphate on minimal alveolar concentration of desflurane using bispectral index monitoring. Magnes Res. 2011 Dec;24(4):181-8. PubMed PMID: 22064369.

[17]. Na HS, Lee JH, Hwang JY, Ryu JH, Han SH, Jeon YT, Do SH. Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy. Br J Anaesth. 2010 Mar;104(3):344-50. PubMed PMID: 20042475.

[18]. Ryu JH, Koo BW, Kim BG, Oh AY, Kim HH, Park DJ, Lee CM, Kim ST, Do SH. Prospective, randomized and controlled trial on magnesium sulfate administration during laparoscopic gastrectomy: effects on surgical space conditions and recovery profiles. SurgEndosc. 2016 Nov;30(11):4976-4984. PubMed PMID: 26969660.

[19]. Fisher DM. Clinical pharmacology of neuromuscular blocking agents. Am J Health Syst Pharm. 1999 Jun 1;56(11 Suppl 1):S4-9. PubMed PMID: 10437710.

[20]. Ozcan PE, Tugrul S, Senturk NM, Uludag E, Cakar N, Telci L, Esen F. Role of magnesium sulfate in postoperative pain management for patients undergoing thoracotomy. J CardiothoracVascAnesth. 2007 Dec;21(6):827-31. PubMed PMID: 18068060.

[21]. Ryu JH, Kang MH, Park KS, Do SH. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. Br J Anaesth. 2008 Mar;100(3):397-403. PubMed PMID: 18276652.

[22]. Tramèr MR, Glynn CJ. An evaluation of a single dose of magnesium to supplement analgesia after ambulatory surgery: randomized controlled trial. AnesthAnalg. 2007 Jun;104(6):1374-9, table of contents. PubMed PMID: 17513629.

[23]. Wadhwa A, Sengupta P, Durrani J, Akça O, Lenhardt R, Sessler DI, Doufas AG. Magnesium sulphate only slightly reduces the shivering threshold in humans. Br J Anaesth. 2005 Jun;94(6):756-62. PubMed PMID: 15749735.

[24]. Bhatia A, Kashyap L, Pawar DK, Trikha A. Effect of intraoperative magnesium infusion on perioperative analgesia in open cholecystectomy. J ClinAnesth. 2004 Jun;16(4):262-5. PubMed PMID: 15261316.

[25]. Kogler J. The analgesic effect of magnesium sulfate in patients undergoing thoracotomy. ActaClin Croat. 2009 Mar;48(1):19-26. PubMed PMID: 19623867.

[26]. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013 Jan;68(1):79-90. PubMed PMID: 23121612.

[27]. Gupta K, Vohra V, Sood J. The role of magnesium as an adjuvant during general anaesthesia. Anaesthesia. 2006 Nov;61(11):1058-63. PubMed PMID: 17042843.

[28]. Al-Hashimi M, Scott S, Griffin-Teall N, Thompson J. Influence of ethnicity on the perception and treatment of early post-operative pain. Br J Pain. 2015 Aug;9(3):167-72. PubMed PMID: 26516573.

[29]. Kim H, Neubert JK, San Miguel A, Xu K, Krishnaraju RK, Iadarola MJ, Goldman D, Dionne RA. Genetic influence on variability in human acute experimental pain sensitivity associated with gender, ethnicity and psychological temperament. Pain. 2004 Jun;109(3):488-496. PubMed PMID: 15157710.

[30]. Hwang JY, Na HS, Jeon YT, Ro YJ, Kim CS, Do SH. I.V. infusion of magnesium sulphate during spinal anaesthesia improves postoperative analgesia. Br J Anaesth. 2010 Jan;104(1):89-93. PubMed PMID: 19933175.