Journal of Bursa
Faculty of Medicine
e-ISSN: 2980-0218

The effects of intravenous magnesium sulfate infusion on perioperative hemodynamics, postoperative recovery, and analgesia in arthroscopic knee surgery during spinal anesthesia.

Murat Ersal[1], Aysel Altan[2]

[1]Department of Anesthesiology and Reanimation, Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Türkiye
[2]Department of Anesthesiology and Reanimation, University of İstanbul Aydın, Vocational School of Health Services, İstanbul, Türkiye

Original Article

Anesthesiology and Reanimatio

Received
May 09, 2023
Accepted
May 15, 2023
Published online
May 29, 2029

J Bursa Med 2023;1(2) 57-64

ABSTRACT

Objectives: Magnesium sulphate infusion after general anesthesia reduces post-operative analgesic consumption. Numerous clinical investigations have demonstrated that magnesium infusion during general anesthesia reduced anesthetic requirement and post-operative analgesic consumption. This study was planned and executed to assess the effects of intravenous magnesium sulfate infusion on perioperative hemodynamics and post-operative analgesic consumption in patients undergoing spinal anesthesia for arthroscopic knee surgery.

Methods: ASA I and II patients, aged 18-65 years, undergoing spinal anesthesia for arthroscopic knee surgery were enrolled in this study. The patients were assigned to two groups according to presence of magnesium sulfate infusion. Patients in the magnesium group (Group M) received magnesium sulphate 40 mg kg-1 for 15 min after spinal anesthesia and then 20 mg kg-1 h-1 by continuous i.v. infusion until the end of surgery. Patients in the saline group (Group I) received the same volume of isotonic saline over the same period. For each case, a patient-controlled analgesia (PCA) device containing tramadol hydrochloride was connected i.v. at the end of surgery. Postoperative pain score, analgesic consumption and hemodynamics were recorded at 4., 8., 12. and 24. h after surgery. The incidences of postoperative nausea, vomiting and headache were recorded. Blood samples for serum Mg concentration were obtained in Group M before surgery, and 30 minutes and 24 hours after surgery.

Results: Fourty patients were included in our study. Postoperative pain score and analgesic consumption in Group M patients were significantly less in comparison with Group I. There was no significant difference in hemodynamic variables and side effects during the intra- or postoperative period. Postoperative serum Mg concentration in Group M was significantly higher than that in Group I at 30. minutes after surgery; however no significant side effect was observed.

Keywords: pain, magnesium, patient controlled analgesia, postoperative, tramadolol

How to cite this article
Ersal M, Altan A. The effects of intravenous magnesium sulfate infusion on perioperative hemodynamics, postoperative recovery, and analgesia in arthroscopic knee surgery during spinal anesthesia. J Bursa Med 2023;1(2):57-64

Address for correspondence
Murat Ersal, MD. Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Mimar sinan Mah. Emniyet Cad. 16310 Yıldırım, Bursa, Turkey.
E-mail: muratersal@hotmail.com

Day care surgery procedures are increasingly gaining ground in anesthesia practice nowadays. In this regard, the role of technological support that ensures less traumatic surgical procedures, as well as drugs with shorter but less side effect profiles entering modern anesthesia practice, is significant. Day surgery procedures are preferred due to their lower cost, shorter hospital stay, reduced expenses, decreased incidence of nosocomial infections, and reduced patient anxiety [1].

Joint arthroscopies are generally day surgery procedures. Spinal anesthesia is an optimal and cost-effective option in arthroscopic surgery. The advantages of spinal anesthesia include minimal nausea and vomiting, patient wakefulness, no airway problems, rapid onset of anesthesia, excellent surgical conditions, no orientation problems for the patient, minimal postoperative care, and a smooth transition to postoperative analgesia [1-3]. However, there are also disadvantages to spinal anesthesia, such as prolonged ambulation time after surgery, increased incidence of headache and back pain after spinal anesthesia, and prolonged urination.

Postoperative pain is an acute type of pain that begins with surgical trauma and ends with tissue healing. This pain not only causes discomfort, depression, and anxiety in the patient but also leads to significant physiopathological changes in the body's organ systems. Eliminating this pain is not only about eliminating an uncomfortable sensation but is also essential for the organism's homeostasis.

Various agents and methods are used to provide pain relief after arthroscopic surgery. According to some studies intravenous magnesium sulphate (MgSO4) improves postoperative analgesia without affecting the onset and recovery from spinal anesthesia [4]. Intravenous infusion of either dexmedetomidine or MgSO4 with spinal anesthesia effectively improves the quality of spinal anesthesia and prolongs the duration of postoperative analgesia and decreases the 24-hour postoperative morphine consumption [5]. In our study, the effects of intravenous (i.v.) magnesium sulfate infusion administered during spinal anesthesia on perioperative hemodynamics and postoperative analgesia in arthroscopic knee surgery and the effects of magnesium sulfate on pain relief and tramadol consumption were investigated.

METHODS

This is a prospective controlled study conducted at the Okmeydanı Education and Research Hospital's Orthopedics and Traumatology operating room. The study included 40 patients of both genders, between the ages of 18-65, with ASA class I-II, who under-

Table 1. Comparison of the Clinical and Anesthesia-Related Characteristics of the Groups.

		Group				Test Statistics	Sig. (p)
		Serum Sale (Serum Physiological) Group		Magnesium Group			
		f	%	f	%		
ASA	**ASA1 (No systemic pathology)**	15	75,0	14	70,0	0,125 (χ^2)	0,723
	ASA2 (There is systemic pathology that does not affect daily activity)	5	25,0	6	30,0		
Spinal Block level	**T3**	0	0,0	3	15,0	5,762 (χ^2)	0,450
	T4	4	20,0	3	15,0		
	T5	5	25,0	7	35,0		
	T6	3	15,0	3	15,0		
	T7	5	25,0	2	10,0		
	T8	2	10,0	2	10,0		
	T10	1	5,0	0	0,0		
Motor Block Time (min.)		186,500	2,101	188,950	3,118	-0,652 (t)	0,519
Time to First Analgesic Need (min.)		225,650	3,070	246,250	10,641	-1,860 (t)	0,071

went elective arthroscopic knee surgery. Patients with cardiovascular, hepatic, or renal disorders, neuromuscular diseases, drug addiction, coagulopathy, and psychiatric problems were excluded from the study.

The patients were given premedication with 0.03 mg/kg intravenous midazolam and were then taken to the operating room. Before the operation, a 500 ml ringer lactate solution was administered for 15 minutes. The patients were monitored during the procedure using non-invasive arterial monitoring, pulse oximetry, and electrocardiography (ECG).

The patients were given spinal anesthesia via a 22G spinal needle at the L3-4 or L4-5 intervertebral space with a 0.5% bupivacaine solution (Marcaine® Spinal Heavy) adjusted according to the patient's height. After the procedure, the patients were placed in the supine position.

The patients were randomly divided into two groups: the magnesium group (group M, n: 20) and the saline group (group S, n:20). Patients in the magnesium group received a 15-minute infusion of 40 mg/kg/min magnesium sulfate after spinal anesthesia and then an infusion of 20 mg/kg/h until the end of the surgery. Patients in the saline group were given the same volume of isotonic saline during the same period.

The spinal block level was evaluated 15 minutes after intrathecal bupivacaine injection using a cold sensation test. Efedrin (Efedrin Hidroklorur 0.05 gr/ml Biosel®) was administered when systolic arterial pressure dropped below 80 mmHg or mean arterial pressure dropped below 20%. Atropine was administered when heart rate dropped below 50 bpm. Postoperatively, 10 mg metoclopramide (Metpamid® ampoule 10 mg) was administered intravenously to prevent nausea.

Both groups received 150 ml of serum saline containing 450 mg of tramadol (Contramal® 100 mg/2 ml ampoule) via Patient-Controlled Analgesia (PCA) device (CADD legacy PCA) after surgery. The PCA device was set to administer 10 mg boluses every 10 minutes (lock out time). Systolic blood pressure, diastolic blood pressure, heart rate (HR), tramadol consumption, and pain scores were recorded at postoperative 30 minutes, 4 hours, 8 hours, 12 hours, and 24 hours. If postoperative pain was severe (Visuel analog scala > 7), 75 mg diclofenac sodium was given intramuscular as a rescue analgesic.

Statistical analysis

The data collected in the study was analyzed using the SPSS 18.0 statistical package program. Variables were described with descriptive statistics (mean, standard error of the mean, minimum, maximum values) for the data. Two independent group t-tests were used to compare the means of the variables between the saline and magnesium groups. χ^2 (Chi-square) independence tests were used to compare data of variables that could not be averaged between the two groups. The significance level in the study was chosen as 0.05.

RESULTS

The study included 40 patients between the ages of 18 and 65, classified as ASA class I-II, undergoing arthroscopic knee surgery under spinal anesthesia. 10 male and 10 female patients were assigned to the saline group, while 9 male and 11 female patients were assigned to the magnesium group. There was no statistically significant difference between the groups in terms of gender, age, height, and weight (*p* values were 0.752, 0.466, 0.642, 0.843, respectively).

The preoperative mean magnesium levels of the patients in the magnesium group were 2.010 ± 0.051 mg/dl (ranging from 1.7 to 2.4 mg/dl). After the operation, the magnesium levels ranged from 2.3 to 4 mg/dl, with an average of 3.055 ± 0.102 mg/dl per patient at 30 minutes post-operation, and ranged from 1.8 to 3 mg/dl, with an average of 2.385 ± 0.060 mg/dl per patient at 24 hours post-operation.

There was no statistically significant difference between the groups in terms of all clinical and anesthe-

Table 2. Comparison of patients' pain scores according to groups.

	Groups		Test Statistic (t)	Sig. (*p*)
	Serum Sale (Serum Physiological) Group	Magnesium Group		
4 Hours After the Operation	5,550 ± 0,276	2,050 ± 0,276	8,966	**0,000***
8 Hours After the Operation	5,500 ± 0,303	2,800 ± 0,268	6,674	**0,000***
12 Hours After the Operation	5,250 ± 0,239	2,600 ± 0,255	7,571	**0,000***
24 Hours After the Operation	1,200 ± 0,296	0,350 ± 0,109	2,697	**0,010***

sia-related characteristics ($p > 0.05$) (Table 1).

The majority of patients in the saline group, accounting for 75%, and also in the magnesium group, accounting for 70%. Meanwhile, 25% of patients in the saline group and 30% of patients in the magnesium group were ASA II patients.

In terms of the spinal block heights achieved by patients in the saline and magnesium groups, it was found that 25% of patients in the saline group were at T5, 25% were at T7, 20% were at T4, 15% were at T6, 10% were at T8, and 5% were at T10. As for the magnesium group, 35% were at T5, 15% were at T4, 15% were at T6, 15% were at T3, 10% were at T7, and 10% were at T8.

The mean motor block duration for patients in the saline group was determined to be 186,500 ± 2,101 minutes, while the mean motor block duration for patients in the magnesium group was 188,950 ± 3,118 minutes.

The average time until the first analgesic requirement for patients in the saline group was found to be 225,650 ± 3,070 minutes, while the average time until the first analgesic requirement for patients in the magnesium group was 246,250 ± 10,641 minutes.

Systolic arterial pressure levels were observed to be higher in the saline group than in the magnesium group at the start of the operation, after spinal anesthesia, 15 minutes after the start of the operation, 30 minutes after the start of the operation, 45 minutes after the start of the operation, at the end of the operation, and 4 hours after the operation. However, at any time, there was no statistically significant difference between the systolic arterial pressure levels measured in the saline and magnesium groups ($p > 0.05$). Therefore, systolic arterial pressure levels did not differ based on whether patients were given saline or magnesium. Findings showed that the diastolic arterial blood pressure levels measured 30 minutes and 12 hours after the operation were statistically significantly different ($p < 0.05$) between the serum physiologic and magnesium groups. In both time periods, the average diastolic arterial blood pressure levels per patient in the magnesium group were statistically significantly higher than those in the serum physiologic group. Although there was no statistically significant difference between the groups, the time periods in which the average diastolic arterial blood pressure levels per patient were higher in the magnesium group than in the serum physiologic group were as follows: 15 minutes after the operation started, 45 minutes after the operation started, at the end of the operation, 4 hours after the operation, 8 hours after the operation, and 24 hours after the operation.

Heart rate levels were observed to be higher in the serum physiologic group in the measurements taken 4 hours, 12 hours, and 24 hours after the operation, whereas the potassium, magnesium, and calcium (PMC) levels were higher in the magnesium group in the measurements taken at the start of the operation, after spinal anesthesia, 15 minutes after the operation started, 30 minutes after the operation started, 45 minutes after the operation started, at the end of the operation, 30 minutes after the operation ended, and 8 hours after the operation. However, there was no statistically significant difference ($p > 0.05$) in the PMC levels measured at any time between the serum physiologic and magnesium groups.

The study examined whether the evaluation of pain levels based on the Visual Analog Scale (VAS) at specific intervals after the operation differed according to whether the cases in the sample group were in the magnesium or serum physiologic group (Table 2). VAS evaluation scores patients' pain levels from 0-10, with 0 representing no pain and 10 representing severe pain. It was determined that the VAS values of patients were statistically significantly different ($p < 0.05$) between the serum physiologic and magnesium groups in the evaluations performed 4 hours, 8 hours, 12 hours, and 24 hours after the operation. Thus, administering magnesium to patients was more effective

Table 3. Comparison of the painkiller levels given by PCA according to the groups.

	Grup		Test Statistic (t)	Sig. (*p*)
	Serum Sale (Serum Physiological) Group	Magnesium Group		
4 Hours After the Operation	64,000 ± 6,341	16,000 ± 4,554	6,148	**0,000***
8 Hours After the Operation	112,000 ± 10,428	50,000 ± 4,867	5,388	**0,000***
12 Hours After the Operation	160,500 ± 12,407	72,500 ± 4,914	6,594	**0,000***
24 Hours After the Operation	205,000 ± 15,703	85,000 ± 4,730	7,317	**0,000***

in reducing pain compared to administering serum physiologic. In addition, while the perceived average pain level of patients in the serum physiologic group decreased as time passed after the operation, the perceived average pain level in the magnesium group was higher 8 hours after the operation than 4 hours after the operation, and the pain level began to decrease after 8 hours.

Statistically significant differences ($p < 0.05$) were found in the levels of analgesic administered with PCA (patient-controlled analgesia) to patients four hours, eight hours, twelve hours, and twenty-four hours after surgery between the group receiving saline and the group receiving magnesium. This difference may have been caused by the fact that patients in the saline group were administered analgesic at statistically significantly higher doses compared to those in the magnesium group. In both groups, the need for analgesic and the level of analgesic administered to patients increased over time following the surgery.

DISCUSSION

This study demonstrated that intravenous magnesium sulfate infusion during surgery under spinal anesthesia reduced postoperative pain and analgesic consumption without any significant complications. As it is expected that analgesic adjunct drugs will not affect motor block duration and sedation, and will increase the side effect profile while reducing the dose, our findings show that magnesium sulfate infusion meets these.

According to Frassanito *et al*s.' study, they concluded that iv perioperative administration of Mg did not influence postoperative pain control and analgesic consumption after total knee arthroplasty. They adviced that more studies should be performed with different intra and postoperative pain protocols to enhance the potential anti-nociceptive effect of Mg [6]. Developments in understanding pain mechanisms have led to the administration of analgesics before exposure to pain stimuli to prevent central sensitization and postoperative pain amplification. Magnesium sulfate is used in obstetric and cardiac patients. Magnesium reduces the release of acetylcholine from motor nerve terminals and, at lower levels, reduces the sensitivity of motor nerve fibers by lowering the stimulation threshold [7]. Additionally, it has been shown that magnesium ions inhibit postjunctional potentials, reducing muscle fiber excitability [8]. In their study, Akutagawa *et al*. [9] demonstrated that the nerve block of some local anesthetics could be increased by altering the magnesium concentration in the nerve fiber bath depending on its physical properties. However, while the basic mechanism of Mg's analgesic effect is unclear, it is estimated that its NMDA receptor antagonism prevents central sensitization induction due to peripheral nociceptive stimulation and eliminates hypersensitivity. Calcium channel blockers also show antinociceptive effects in animals and enhance the effect of morphine in chronic pain patients.

The effects of magnesium sulfate-induced neuromuscular blockade were investigated in electromyogram and mechanogram in pigs. It was observed that the single stimulation at 0.1 Hz decreased, and the mechanogram was more suppressed than the electromyogram. The absence of fade signs after quadruple stimulation at 2 Hz and the increase in contraction force for 5 seconds after tetanic stimulation at 50 Hz indicate magnesium's presynaptic effects [10]. Magnesium causes dose-dependent desensitization in isolated frog muscle preparations. This effect can be reversed by reducing carbamylcholine concentration or increasing potassium concentration [11]. Our findings are partially consistent with those obtained in a previous study [12]. In this study, after spinal block, patients were given a bolus of 5 mg/kg magnesium sulfate, followed by 500 mg/hour infusion or saline for 24 hours, and significant reduction in postoperative analgesic consumption was observed in the mg group. However, the VAS values of the two groups were similar during the first 24 hours after surgery, except for the first 12 hours, and therefore, it is thought that the magnesium sulfate dosage used was insufficient for postoperative analgesia. Sufficient bolus and infusion doses of magnesium sulfate are important for effective analgesia.

In a recent clinical study, the intravenous infusion of magnesium sulfate did not affect the magnesium concentration in cerebrospinal fluid [13]. On the contrary, when magnesium sulfate was given intrathecally, the magnesium concentration in cerebrospinal fluid increased while plasma levels were unaffected, suggesting that the blood-brain barrier is impermeable to this cation. These results explain why motor block duration did not change after spinal anesthesia in another study [14, 15]. However, the analgesic effect observed in our study is more pronounced.

Activation of small-diameter primary afferent nerves can affect the stimulation of nerves in the spinal cord for a long time, causing the response to

change in different directions and central sensitivity. Woolf *et al*. [16] showed that NMDA antagonists can increase the excitability of the spinal cord while not affecting the reflex response in rats using mustard oil. It has been shown that magnesium sulfate injection reduces nociceptive behavior in experimental peripheral nerve injuries [17]. In this study, it can be considered that the analgesic effects of magnesium sulfate infusion are due to a reduction in sensitivity caused by calcium or the effect of an NMDA antagonist. In the rat postoperative pain model, the antiallodynic effect produced by intrathecal gabapentin is reduced by NMDA antagonists magnesium chloride and ruthenium red. It has been shown that the alpha (2) delta subunit of voltage-gated calcium channels is partly responsible for pain, and magnesium has an affinity for this receptor [18]. Intrathecal injection of isoosmolar magnesium sulfate has been observed to cause long-lasting spinal anesthesia and general sedation in rats and humans [19]. Repeated intrathecal administration has been reported to not cause neurotoxicity in animal studies [20]. The fact that intrathecal magnesium enhances the analgesic effects of spinal opioids (fentanyl) in childbirth analgesia suggests that intrathecal administration of NMDA antagonists may have a role in pain modulation [21].

Magnesium has been shown to significantly reduce the requirements of propofol, remifentanil, and vecuronium in patients undergoing elective spinal surgery with total intravenous anesthesia [22]. Tramer *et al*. [23] have shown in their studies that magnesium sulfate infusion reduces morphine consumption with patient-controlled analgesia (PCA) and provides better sleep scores and comfort in patients undergoing abdominal hysterectomy under general anesthesia. The effects of intravenous drugs such as fentanyl, ketamine, and magnesium sulfate on pain threshold, sensitivity, and opioid consumption were investigated after abdominal hysterectomy surgery. While the effects of the drugs on pain threshold varied, the pain scores and morphine consumption were similar, and all drugs reduced spinal sensitivity after surgery [24]. In addition, in a study conducted in the same surgical group, bolus and infusion administration reduced analgesic requirements without side effects during the perioperative period [25]. However, Zarausa *et al*. [24] reported that the application of oral nifedipine, intravenous nimodipine, and magnesium sulfate during colorectal surgery did not affect perioperative morphine consumption. These unfavorable results can be explained by the number of study groups, the route of administration, the type of calcium channel blocker used, and the mechanism of pain. Recently, Ko *et al*. [13] have shown in their studies that intravenously administered magnesium sulfate infusion during surgery has no positive effect on postoperative pain. The main difference between their study and ours is that the PCA device used to reduce pain was connected to an epidural catheter. Thus, the additive effects of magnesium sulfate and morphine administered by different routes may not have been observed.

In gynecology patients who were administered a bolus dose of 50 mg/kg and maintenance dose of 15 mg/kg/hour of magnesium sulfate before and during surgery, the requirement for rocuronium was reduced and the quality of postoperative analgesia was improved without any significant adverse effects [12,26]. Therefore, in our study, we applied a bolus dose of 40 mg/kg and a maintenance dose of 20 mg/kg/hour.

Postoperative VAS scores and cumulative PCA consumption were significantly lower at 4, 8, 12, and 24 hours. This difference may be due to the fact that the average pain levels perceived by patients in the magnesium group were statistically significantly lower than those in the saline group. Thus, administering magnesium to patients is more effective in reducing pain than administering saline. There was no significant difference in postoperative pain and analgesic use immediately after surgery and at 30 minutes. We attributed this to the residual effect of spinal anesthesia.

However, in previous studies evaluating the effects of Mg on postoperative analgesia, different VAS values were observed between the control and Mg groups, even though PCA was used during the postoperative period [27,28]. Possible explanations include: PCA use can reduce the pain seen after surgery, but cannot eliminate it completely. PCAs are used with or without ketorolac and opioids, which have dose-related side effects such as nausea and vomiting that can limit the use of unlimited PCAs. Additionally, PCA settings include locking times to prevent overdose, and patients may not be able to take as much analgesic as they want.

Magnesium sulfate administration during general anesthesia may have other benefits, such as increasing the strength of neuromuscular blockade [12, 28]. The mechanisms involved include a decrease in the amount of acetylcholine released from motor nerve terminals and a decrease in the depolarization effect of acetylcholine at the endplate or in the excitability of the muscle fiber membrane. Therefore, i.v. magnesium

administration during spinal anesthesia may facilitate muscle relaxation and surgical procedures requiring extensive joint rotation. However, more studies are needed to confirm this hypothesis.

Adjuvant medications such as magnesium sulfate can provide greater pain relief and reduce analgesic consumption in postoperative patients using PCA. Theoretically, mild side effects such as flushing, nausea, and headache are expected at serum Mg levels above 2 mmol/L, and potentially life-threatening complications primarily involving the cardiovascular and neuromuscular systems are observed when serum Mg concentrations exceed 5 mmol/L. In our study, an average magnesium value of 2,010 ± 0.051 mg/dL was obtained in the Magnesium group before surgery. Two patients reported short-lived hot flashes during surgery. The same patients had an average magnesium value of 3,055±0.102 mg/dL 30 minutes after surgery and an average value of 2,385±0.060 mg/dL 24 hours after surgery. None of the patients exceeded 5 mg/dL. Magnesium causes dose-dependent negative inotropic effects, and hemodynamic studies have shown that magnesium has a peripheral (primarily arteriolar) vasodilatory effect in humans [29]. A rapid infusion of 3-4 mg of magnesium sulfate led to a decrease in systemic arterial pressure associated with low systemic vascular resistance [30]. In this study, prehydration was performed with 500 mL of lactated Ringer's solution and magnesium bolus dose infusion was given, likely explaining why significant hypotension was not encountered after the magnesium bolus dose was given and no significant difference was observed between the groups during surgery.

CONCLUSION

Postoperative analgesia is important for the comfort of patients. In today's world where outpatient surgical approaches are becoming more common, the main goal is to minimize the postoperative pain and analgesic consumption during the postoperative period.

In conclusion, it was found that administering intravenous magnesium sulfate during spinal anesthesia reduces postoperative pain and analgesic consumption in knee surgery. Especially in cases where the use of opioids and non-steroidal anti-inflammatory drugs (NSAIDs) needs to be reduced or is contraindicated, this alternative approach can be considered.

Ethics Approval and Consent to Participate

This study titled "The Effects of Intravenous Magnesium Sulfate Infusion on Perioperative Hemodynamics, Postoperative Recovery, and Analgesia in Arthroscopic Knee Surgery During Spinal Anesthesia" was conducted at the Okmeydanı Education and Research Hospital's Orthopedics and Traumatology operating room between 2010 and 2011. Ethics Approval was not required at the time of the study. This study was conducted under the supervision of Associate Professor Aysel Altan at the Okmeydanı Education and Research Hospital.

Authors' Contribution

Study Conception: Study Conception: ME, AA; Study Design: ME, AA; Supervision: AA; Materials: ME, AA; Data Collection and/or Processing: ME, AA; Statistical Analysis and/or Data Interpretation: ME, AA; Literature Review: ME, AA; Manuscript Preparation: ME; and Critical Review: ME, AA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

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