Original Article

Perioperative systemic magnesium sulfate minimizes the incidence of atrial fibrillation after thoracotomy for lung resection: a prospective observational study

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Background: Postoperative atrial fibrillation (POAF) is the most common complication following general thoracic surgery. POAF significantly increases the risk of adverse cardiovascular events, such as thromboembolism, heart failure, and mortality. Additionally, it also leads to prolonged hospital stays and higher costs. The objective of this observational study was to examine the impact of perioperative administration of magnesium sulphate ($MgSO_4$) on the incidence of POAF.

Methods: A prospective observational study was conducted, enrolling one hundred patients undergoing thoracotomy for lung resection. We compared the incidence of atrial fibrillation (AF) before and after implementing a change in our standard anesthetic management, which involved the addition of $MgSO_4$. $MgSO_4$ was administered during anesthesia induction at a dose of 40 mg/kg over ten minutes, followed by a 24-hour infusion at a rate of 10 mg/kg/h. The primary outcome was the incidence of POAF within the first seven days after surgery.

Results: Within the initial three days following surgery, there was no significant difference in the cumulative incidence of POAF between the $MgSO_4$ group and the control group. However, on postoperative day 7, patients treated with $MgSO_4$ exhibited a reduced incidence of POAF compared to the control group (4% *vs.* 26%; P=0.01). In the subgroup of patients not receiving pre-existing β-blockers, the addition of $MgSO_4$ significantly decreased the occurrence of POAF (14% *vs.* 80%; P<0.001).

Conclusions: Prophylactic administration of $MgSO_4$ is a potentially beneficial approach for reducing the incidence of POAF after non-cardiac surgery, particularly in patients not receiving long-term β-blocker treatment.

Keywords: Atrial fibrillation (AF); magnesium sulphate; lung resection

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Introduction

Lung cancer is one of the most common cancer worldwide and a leading cause of death. Therefore, thousands of patients undergo surgical resection of the lung annually (1). A common complication following thoracic surgical procedures is postoperative atrial fibrillation (POAF) (2,3).

POAF is typically an asymptomatic, self-terminating event that peaks on postoperative days 2 to 4. Approximately 90–98% of the patients revert to sinus rhythm within four to six weeks (4) after surgery. However, the clinical significance of POAF is not solely due to the arrhythmic episode itself, but also its association with increased short- and long-term complications, such as prolonged-hospital stay, stroke, myocardial infarction, hearth failure, and decreased long-term survival (3,5). The mortality risk increases from 3% in patients without POAF to 8–17% in those who develop recurrent or persistent POAF after an operation (6,7). The incidence of POAF ranges from 20% to 42% after cardiac surgery to 10–20% after non-cardiac thoracic operations (8,9). Its occurrence is linked to the intensity of surgical stress (3,4). More invasive procedures such as pneumectomies or lung transplants carry a higher risk of POAF (3). Patients who develop POAF are generally older and have more complex comorbidities, such as hypertension, myocardial infarction, and obesity, compared to those who do not develop arrhythmia (3,4,10). These comorbidities are routinely assessed and reflected in the ASA score (American Society of Anesthesiologists Physical Status Classification System).

The mechanisms that initiate and sustain atrial fibrillation (AF), including POAF, are complex and require both a vulnerable atrial substrate and a trigger to initiate AF (4). To date, the underlying causes remain incompletely understood. The causes of POAF involve complex interactions between several factors, such as inflammation, cardiac overload, hyperadrenergic activity and increased vagal tone (3,11). Based on the multifactorial causes of POAF, various preventive and therapeutic strategies have been proposed and tested, including digoxin, amiodarone, calcium channel blockers, β-blockers and magnesium (12). Since β-blockers have both preventive and therapeutic effects, the influence of long-term β-blocker medication on POAF was also to be assessed in our study. Magnesium sulphate ($MgSO_4$) has been shown to reduce the rate of sinoatrial node impulses and increase the refractory period of the atrioventricular node (13). It may also reduce the afterload of the right heart through vasodilation. $MgSO_4$ has been shown to be effective at reducing the incidence of POAF following coronary artery bypass grafting (CABG) (14).

There is limited data on the effect of $MgSO_4$ on POAF after non-cardiac thoracic surgery. This forms the basis for our study on the prophylactic effect of $MgSO_4$ on POAF after thoracotomy for lung resection. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-506/rc).

Highlight box

Key findings

- Application of prophylactic magnesium sulfate may be beneficial in reducing the incidence of postoperative atrial fibrillation (POAF) in patients without long-term β-blocker treatment.

What is known and what is new?

- It is well-known that POAF is a common complication following thoracic surgery and is associated with an increased risk of adverse events.
- Patients without long-term β-blocker treatment are at a higher risk of developing POAF.
- The perioperative application of magnesium sulfate is associated with a reduced risk of POAF without any undesirable effects.

What is the implication, and what should change now?

- The perioperative application of magnesium sulfate may be considered as a preventive option for POAF.
- Further large-scale randomized trials are necessary to confirm the efficacy and safety of POAF.

Methods

This prospective observational study compared 50 consecutive patients scheduled for thoracotomy who received standard care (Standard group) with 50 consecutive patients who received adjunct magnesium sulfate ($MgSO_4$) administration ($MgSO_4$ group) after adjustment of our standard care protocol. The study was conducted between 2013 and 2014. The first 50 patients were included based on their order of appearance and scheduled surgery, while the subsequent 50 patients were included after the implementation of the changed standard operating procedure. Preoperative status, including ASA classification and long-term medication, as well as intraoperative information such as the extent of surgery, were obtained from hospital and operating room records. This prospective observational study was conducted in accordance with the

Declaration of Helsinki (as revised in 2013). The study was approved by local Ethics Committee of University Hospital Mannheim, University of Heidelberg (No. MC 144/2013) and was registered at ClinicalTrials.gov (NCT 02008747). Written informed consent was obtained from all patients participating in this trial.

Control group: anesthetic and surgical standard protocol

All patients received total intravenous anesthesia (TIVA) and double-lumen intubation. Anesthesia was induced with propofol (1–2 mg/kg) and remifentanil (1 µg/kg). The target was to maintain a bispectral index (BIS) value below 60 during anesthesia induction. If this target was not achieved with the induction dose of propofol and remifentanil, additional boluses of 0.3 mg/kg propofol and/or 0.5 µg/kg remifentanil were administered as appropriate.

Anesthesia was maintained with propofol (4–5 mg/kg/h) and remifentanil (0.2–0.5 µg/kg/min). The doses were adjusted for ideal body weight (IBW) using the Broca Index. The depth of anesthesia was monitored using BIS, with a target value between 40 and 60. Hypotension (mean arterial pressure <60 mmHg) was recorded and treated with catecholamines according to hospital standards, with the specific choice and dosage of catecholamines left to the discretion of the responsible anesthesiologist.

Posterolateral thoracotomy was performed with the patient in the lateral decubitus position. All surgeries were performed by the same surgical team. After lung resection, each patient had two 28 French chest tubes placed anteriorly and posteriorly. All patients were extubated at the end of surgery and transferred to the post-anesthesia care unit (PACU).

Analgesic medication was provided according to hospital standards using a systematic opioid-based analgesia regimen, with intravenous piritramide administered via patient-controlled analgesia (PCA) for the first 24 hours. Subsequently, oral opioids (oxycodone), metamizole, paracetamol, and/or ibuprofen were prescribed based on pain intensity. It has been shown that epidural analgesia is not superior to a standardized opioid regimen (15,16) in terms of pain management, bowel function, and length of hospital stay.

Study group: $MgSO_4$ administration

In addition to the standard care described above, $MgSO_4$ was added during anesthesia induction at a dose of 40 mg/kg over ten minutes, followed by a 24-hour infusion at a rate of 10 mg/kg/h.

Assessment of POAF

Cardiac rhythm assessment followed the daily practice of an integrated clinic that included the ICU and ward levels. Patients were continuously monitored by ECG during the first 24 hours postoperatively. As per hospital standards, a 12-lead ECG was performed on the general ward on postoperative day 3 and 7. Additional recordings were obtained if there was clinical suspicion of atrial fibrillation/flutter. The arrhythmia was defined based on physician assessment, using telemetry strips or 12-lead ECG recordings.

Inclusion/exclusion criteria

We included patients aged 18 years or older who were scheduled for posterolateral thoracotomy. Patients who were pregnant, had previous thoracotomy, had presurgical diagnosed neuropathic pain, were hypersensitive to $MgSO_4$, or had pre-existing atrial fibrillation were excluded from the study.

Statistical analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS software version 15.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics included means ± standard deviation (SD) for normally distributed continuous variables or median (interquartile range) with 95% confidence intervals for non-normally distributed continuous variables. The normal distribution of variables was assessed using the one-sample Kolmogorov-Smirnov test. Chi-square and Fisher exact tests were used to compare dichotomous variables. Statistical significance was considered for a P value <0.05.

Results

A total of 100 patients were included in the study, and no patient data was lost during the study period. Patient characteristics are summarized in *Table 1*, and no significant differences were observed between the two groups.

In the first 24 hours after surgery, no cases of POAF occurred in either group. The incidence of POAF on postoperative day 3 was 5%, and on postoperative day 7,

Table 1 Demographic data

Variables	Standard (n=50)	$MgSO_4$ (n=50)	P value
Age (years)	60.0±14.6	57.7±13.5	0.517
Men/women	32/18	31/19	0.5
BMI (kg/m^2)	25.1±4.2	25.6±4.2	0.861
ASA physical status			0.49
I	0	1 [2]	
II	14 [28]	10 [20]	
III	29 [58]	34 [68]	
IV	7 [14]	5 [10]	
Duration of surgery (min)	239.1±88.8	258.0±96.3	0.312
Operation side: left	16 [32]	19 [38]	0.529
Extend of surgery			0.717
Lobectomy	17 [34]	16 [32]	
Wedge resection	27 [54]	24 [48]	
Pneumonectomy	3 [6]	4 [8]	
Sleeve resection	3 [6]	6 [12]	
Preoperative β-blocker	11 [22]	14 [28]	
Preoperative calcium antagonists	5 [10]	4 [8]	

Data are presented as mean ± standard deviation, n, or n [%]. BMI, body mass index; ASA, American Society of Anesthesiologist.

Table 2 Incidence of POAF

Postoperative day	Standard (n=50), n [%]	$MgSO_4$ (n=50), n [%]	Total (n=100), n [%]	P value
POD 1	0	0	0	–
POD 3	3 [6]	2 [4]	5 [5]	0.5
POD 7	13 [26]	2 [4]	15 [15]	0.01

POAF, postoperative atrial fibrillation; POD, postoperative day.

it was 15%. Patients treated with $MgSO_4$ had a lower incidence of POAF on postoperative day 3 (P=0.5), and this difference reached statistical significance on postoperative day 7 (P=0.01) (*Table 2*).

Patients with ASA physical status three had a significantly higher frequency of POAF compared to patients with lower ASA physical status (*Table 3*, P=0.002), and this difference remained significant on postoperative day seven.

The occurrence of POAF was more frequent in patients who underwent multiple wedge resection compared to those undergoing lobectomies, sleeve resection, or pneumonectomy (*Table 4*, P=0.002).

Table 3 Incidence of POAF and ASA status

ASA physical status	Standard (n=50), n [%]	$MgSO_4$ (n=50), n [%]	P value
POD 3			
I	0	0	–
II	1 [2]	0	0.58
III	2 [4]	2 [4]	0.63
IV	0	0	
Total	3 [6]	2 [4]	0.5
POD 7			
I	0	0	
II	1 [2]	0	0.58
III	11 [22]	2 [4]	0.001
IV	1 [2]	0	0.58
Total	13 [26]	2 [4]	0.01

POAF, postoperative atrial fibrllation; ASA, American Society of Anesthesiologist; POD, postoperative day.

Among the patients, 26% were receiving long-term β-blocker treatment prior to surgery. Fifteen patients (30%) in the $MgSO_4$ group and eleven patients (22%) in the Standard group were receiving β-blocker therapy (P=0.362). There was no significant difference in the development of atrial fibrillation on day 7 among patients receiving long-term β-blocker treatment ($MgSO_4$: 0% *vs.* standard: 9.1%; P=0.423). However, patients without long-term β-blocker treatment had significantly lower rates of atrial fibrillation if they received $MgSO_4$ (5.7%) compared to the Standard Care Group (30.8%) (P<0.001) (*Table 5*).

Nine patients (18%) treated with $MgSO_4$ experienced intraoperative hypotension (<20% baseline) compared to fifteen patients (34.1%) without $MgSO_4$ (P=0.061).

Patients in the $MgSO_4$ group had lower magnesium blood levels than patients in the Standard group (P=0.004), although both levels were within the normal range. This difference remained significant postoperatively (P<0.001) (*Table 6*).

Discussion

Our study provides evidence that magnesium sulfate is effective in preventing POAF following non-cardiac

Table 4 Incidence of POAF and extend of surgery

Extend of surgery	POD 3			POD 7		
	Standard (n=50), n [%]	$MgSO_4$ (n=50), n [%]	P value	Standard (n=50), n [%]	$MgSO_4$ (n=50), n [%]	P value
Wedge resection	2 [4]	1 [2]	0.545	9 [18]	0	0.002
Lobectomy	1 [2]	1 [2]	0.742	3 [6]	2 [4]	0.53
Sleeve resection	0	0	–	1 [2]	0	0.33
Pneumonectomy	0	0	–	0	0	–

POAF, postoperative atrial fibrillation; POD, postoperative day.

Table 5 Incidence of POAF and prior β-blocker treatment

Postoperative day	Long-term β-blocker treatment					
	No			Yes		
	Standard (n=39), n (%)	$MgSO_4$ (n=35), n (%)	P value	Standard (n=11), n (%)	$MgSO_4$ (n=15), n (%)	P value
POD 3	3 (7.7)	2 (5.7)	0.552	0	0	–
POD 7	12 (30.8)	2 (5.7)	<0.001	1 (9.1)	0	0.423

POAF, postoperative atrial fibrillation; POD, postoperative day.

Table 6 Pre- and postoperative ionized magnesium in plasma

Magnesium plasma level	Standard (n=50)	$MgSO_4$ (n=50)	P value
Preoperative ionezed magnesium in plasma (mmol/L)	0.78±0.07	0.74±0.07	0.004
Postoperative ionized magnesium in plasma (mmol/L)	0.76±0.07	1.52±0.19	<0.001

Data are presented as mean ± standard deviation.

thoracic surgery with lung resection. POAF is a well-recognized complication of both non-cardiac and cardiac thoracic surgeries. The etiology of POAF involves a combination of postoperative hyperadrenergic activity and atrial dilation. Other contributing factors may include increased vagal tone, atrial inflammation, pulmonary hypertension, right ventricular dilation, hypoxemia, and infection at the remaining bronchus tip (3,17). POAF typically occurs on the second or third postoperative day, although it can manifest later, as our study findings confirm with the incidence peaking on postoperative day seven. The methods for diagnosing POAF vary among studies, including continuous ECG monitoring for 48 hours, ECG recording when abnormal rhythm is suspected, daily 12-lead ECG during the hospital stay, or telemetry throughout the entire hospital stay (18-20). Since POAF is often asymptomatic and self-limiting, it is possible that we may have missed cases occurring between day three and seven due to the observational design and the use of 12-lead ECG on specific days. More invasive operations such as pneumectomy have a higher risk of POAF, suggesting that the extent of surgical trauma may play a pathogenetic role (3,5). In our study, due to the observational design, we did not randomize specific surgical procedures, resulting in a high proportion of wedge resections (51%), followed by lobectomy (33%), sleeve resection (9%), and pneumectomy (7%). The overall incidence of POAF in our study (15%) falls within the range reported in prior studies (3,8,9), despite the less invasive nature of lung resection. However, it is worth noting that a posterolateral thoracotomy involves greater surgical trauma compared to video-assisted thoracoscopy, which could be an interesting area for future investigations. Patients with underlying health conditions such as obesity, hypertension, diabetes mellitus, structural heart disease, and chronic kidney disease are at a higher risk of developing POAF (21). All these pre-existing

conditions contribute to higher ASA scores. Therefore, we used the ASA score as a surrogate marker and compared the incidence of POAF between the groups. Patients classified as ASA three had a significantly higher incidence of POAF (P<0.002), which is in alignment with previous findings.

The treatment goals for POAF following non-cardiac thoracic surgery are similar to those in other settings. These goals include preventing thromboembolic events, controlling the ventricular response rate, and considering conversion to and maintenance of sinus rhythm. Recommendations for POAF prevention after cardiac surgery involve continuing β-blocker therapy if patients were receiving it before surgery. If β-blockers are contraindicated, prophylactic therapy with amiodarone is recommended. In cases where both β-blockers and amiodarone are contraindicated, intravenous magnesium therapy is suggested (10).

Several approaches have been attempted to prevent POAF. Digoxin is commonly used for rate control in atrial flutter, but its prophylactic use for POAF is not recommended due to studies showing a trend towards increased supraventricular arrhythmias (17,22).

Amiodarone has been demonstrated to be effective in preventing POAF (23). However, its prophylactic use has been limited due to the development of adult respiratory distress syndrome (ARDS) in patients receiving amiodarone (4,24). Another study found that amiodarone prophylaxis was associated with a longer duration of cardiovascular instability and increased need for intensive care (25). In a prospective study comparing the prophylactic effects of amiodarone and magnesium sulfate as antiarrhythmic agents following lobectomy (26), both medications were found to reduce the incidence of atrial fibrillation without significant side effects. Therefore, magnesium sulfate emerges as a potential prophylactic option for preventing POAF, with comparable effectiveness to amiodarone but without the associated adverse effects.

Given the significant role of autonomic influences and sympathetic activation in the development of POAF, it is understandable that β-blocker therapy has a protective effect against POAF (3). Prophylactic use of beta-blockers has been shown to significantly reduce the incidence of POAF by more than half following cardiac surgery (23,27). In our study, only one patient with prior long-term beta-blocker medication developed POAF, further supporting the prophylactic potential of beta-blockers. However, the initiation of prophylactic β-blocker therapy prior to non-cardiac surgery is not recommended. While prophylactic β-blocker therapy reduces POAF, non-fatal myocardial infarction, and cardiovascular death, it also increases the risks of hypotension, bradycardia, stroke, and death (28-30). Therefore, withdrawal of long-term β-blocker medication is not recommended (class I recommendation) (4), but the initiation of a new β-blocker therapy seems to be potentially harmful (3).

Prospective studies investigating the preventive effect of magnesium on post-thoracotomy atrial fibrillation are still limited. One study demonstrated a significant reduction in the incidence of POAF in patients who underwent thoracotomy and received prophylactic magnesium sulfate, with the incidence decreasing from 26.7% in the control group to 10.7% in the magnesium group (31). Another prospective trial showed no significant differences in the incidence of POAF between the control group and the magnesium group (25% *vs.* 16.7%), except in high-risk patients undergoing pneumectomy, who had a significant reduction in the frequency of AF (52.9% *vs.* 11.1%) (22). In our study, the incidence of AF was reduced from 24% in the control group (without chronic β-blocker therapy) to 4% in the magnesium sulfate group. There are notable differences between these three trials, particularly in terms of dosing regimens. The first trial used a regimen of 2 g of magnesium sulfate intravenously over 20 minutes at thoracotomy, followed by an additional 2 g intravenously after six hours (31). Saran *et al.* administered three doses of 5 g of magnesium sulfate intravenously during the intraoperative period and on the first and second day after surgery (22). In our study, we administered 40 mg/kg of magnesium sulfate after anesthesia induction, followed by a continuous infusion of 10 mg/kg/h for 24 hours. We did not observe adverse effects such as stinging during peripheral intravenous administration, as reported in the study by Saran *et al.* (22), which resulted in lower compliance and magnesium dosing in the intervention arm of their study. Due to the different doses and dosing regimens used, it is challenging to directly compare and explain the disparate findings of these studies.

Although the findings in our study are encouraging and support our decision to change the standard anesthesia procedure by adding magnesium sulfate, particularly in patients without long-term β-blocker treatment, they reinforce the class IIb recommendation of the AATS Guidelines, where magnesium supplementation may be considered to prevent POAF (4).

Here are several limitations to consider in our study. First and foremost, it is important to note that our study

design was a prospective observational study rather than a randomized controlled trial, which introduces potential risks and biases associated with this type of study. This means that the treatment assignment was not randomized, and there could be confounding factors influencing the results. Therefore, the findings should be interpreted with caution. Another limitation is that we did not conduct a power analysis prior to the trial, which could have helped determine the appropriate sample size for detecting significant differences between the groups. This may have impacted the statistical power of our study and the ability to detect smaller effects.

Furthermore, the intermittent ECG monitoring over the eight-day period may have led to missed cases of POAF, as the arrhythmia could have occurred between the scheduled ECG assessments. Continuous ECG monitoring would have provided more comprehensive data on the occurrence and duration of atrial fibrillation episodes.

The data from our study can serve as a pilot to inform future randomized controlled trials. Conducting such trials with a larger sample size, consistent dosing regimen, and a robust clinical definition of POAF will provide more reliable evidence regarding the efficacy and safety of magnesium sulfate in preventing POAF after non-cardiac thoracic surgery.

Conclusions

In conclusion, our findings suggest that patients undergoing non-cardiac thoracic surgery, particularly those without prior long-term β-blocker treatment, may benefit from the addition of a 24-hour magnesium sulfate infusion to prevent POAF. However, further multicenter randomized controlled trials are needed to validate these findings and establish a standardized dosing regimen. Additionally, investigating the use of magnesium sulfate in a less invasive surgical approach and within an enhanced recovery protocol setting would be valuable areas for future research.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-506/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-506/coif). SB serves as an unpaid editorial board member of *Journal of Thoracic Disease* from February 2023 to January 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This prospective observational study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by local Ethics Committee of University Hospital Mannheim, University of Heidelberg (No. MC 144/2013) and was registered at ClinicalTrials.gov (NCT 02008747). Written informed consent was obtained from all patients participating in this trial.

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