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Using Magnesium Sulfate to Prevent Atrial Fibrillation after Coronary Artery Bypass Grafting Surgery: A Single Centre Experience in Bangladesh

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Abstract

Background: Atrial fibrillation commonly occurs following cardiac surgery, particularly after coronary artery bypass grafting. Magnesium, known for its stabilizing effect on cell membranes, has shown promise in preventing postoperative atrial fibrillation. This study aimed to assess the impact of intravenous magnesium infusion in preventing atrial fibrillation after off-pump coronary artery bypass grafting, where maintaining stable cell membranes is crucial in averting this complication. **Methods:** A cross-sectional study was conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, from March 2020 to February 2022. Sixty-six patients who underwent off-pump coronary artery bypass grafting were enrolled and divided into two groups. Group A (n = 33) received intravenous magnesium sulfate (10 mmol/2.47gm) for three days after surgery, while Group B (n = 33) did not receive magnesium sulfate. Postoperative atrial fibrillation occurrence in the Intensive Care Unit (ICU) within three days after surgery was evaluated using convenient sampling. Statistical analysis was performed with SPSS version 26.0, utilizing independent Student's t-test for continuous data and Chi-square and Fisher's exact test for categorical data. A p-value of ≤0.05 was considered statistically significant. **Results:** No significant differences in age or gender were observed between the two groups. Group B exhibited significantly lower magnesium levels than Group A on the 0th, 1st, 2nd, and 3rd days post-surgery. Additionally, Group B experienced a higher incidence of postoperative atrial fibrillation, longer ICU stays, and two mortalities. The study did not detect any adverse effects associated with magnesium infusion. **Conclusion:** It has been demonstrated that administering magnesium intravenously after off-pump coronary artery bypass grafting can lower the chances of developing atrial fibrillation. This demonstrates the potential advantages of using magnesium as a preventative measure for postoperative atrial fibrillation in such cases.

Keywords

Atrial Fibrillation (AF), Coronary Artery Bypass Grafting (CABG), Postoperative Atrial Fibrillation (POAF), Magnesium Sulfate, Bangladesh

1. Introduction

Arrhythmia, a common complication after heart surgery, is a major cause of illness and death [1] [2]. The most common arrhythmia after cardiac surgery is atrial arrhythmia [2].

Despite advancements in surgical technique, anesthesia, and intraoperative myocardial protection, the incidence of atrial fibrillation (AF) has not decreased in patients who undergo coronary artery bypass graft (CABG) surgery [3] [4]. The incidence of atrial arrhythmia after cardiac surgeries varies: CABG (31.9%), mitral valve replacement (63.6%), aortic valve replacement (48.8%), and heart transplantation (11.1%) [1]. AF typically manifests within a week after cardiac surgery, with approximately 70% of cases occurring within the first three days post-CABG [5]. AF poses independent risks of mortality, morbidity, and diminished quality of life [6]. The development of postoperative atrial fibrillation (POAF) increases the risk of heart failure, stroke, and hemodynamic deterioration, leading to higher in-hospital mortality [7]. Despite extensive research into its causes, risk factors, and complications, a safe and effective treatment to prevent or manage postoperative AF remains elusive. After CABG, AF can occur due to various factors such as age, gender, hypertension, thyroid dysfunction, withdrawal of β-blockers, impaired cardiac function, chronic lung disease, chronic renal failure, diabetes, cardiopulmonary bypass and cardioplegia, myocardial ischemia and reperfusion, myocardial infarction, right coronary artery disease, local inflammatory reaction, metabolic disorder, excessive catecholamine, electrolyte imbalance, and hypomagnesemia. It is worth noting that hypomagnesemia has been recognized as an independent risk factor for postoperative AF [4].

Following CABG, nearly 80% of patients experience reduced total and ionized serum magnesium [8]. This decline in magnesium levels can be attributed to hemodilution, elevated catecholamine levels, and increased urinary loss [4]. While the precise link between magnesium deficiency and postoperative AF remains incompletely understood, magnesium's role in stabilizing cellular transmembrane potential, suppressing excessive cellular calcium influx and energy demands, preserving myocardial metabolites, and reducing the severity of reperfusion injuries has been consistently hypothesized [9]. Additionally, magnesium plays a critical role in essential cellular functions, including enzyme regulation, energy metabolism, and aerobic respiration [10]. Furthermore, magnesium has been found to inhibit catecholamine-induced abnormal pacemaker activity, thereby potentially preventing cardiac arrhythmias. The depletion of magnesium levels following CABG may disrupt various cellular processes that rely on magnesium, thereby predisposing patients to unstable cellular activity [11]. Considering the potential significance of magnesium in postoperative AF, administering magnesium supplements following CABG might help prevent the occurrence of AF. While not all studies have reached conclusive results, several have shown that intravenous magnesium therapy can significantly reduce the incidence of AF. Therefore, the aim of this study is to evaluate the effectiveness of intravenous magnesium therapy in preventing postoperative AF in patients undergoing off-pump coronary artery bypass (OPCAB), with the ultimate goal of improving postoperative management.

2. Materials & Method

This research was a cross-sectional study comparing the effects of intravenous magnesium sulfate on preventing atrial fibrillation after OPCAB surgery. The participants were adults who had elected to undergo off-pump coronary artery bypass grafting. The study was conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from March 2020 to February 2022.

The sample size included 66 patients with coronary artery disease who met the inclusion criteria for elective OPCAB. They were divided into two groups: Group A (n = 33) received postoperative intravenous magnesium sulfate, while Group B (n = 33) did not receive magnesium sulfate postoperatively. The inclusion criteria comprised patients willing to provide informed consent, adult patients with normal serum magnesium levels (1.8 - 2.4 mg/dl), and those in sinus rhythm preoperatively. Exclusion criteria involved patients with a history of atrial fibrillation or other supraventricular arrhythmias, those taking anti-arrhythmic drugs, and patients with certain medical conditions, such as recent myocardial infarction, congenital heart disease, hepatic dysfunction, renal dysfunction, and thyroid disorder leading to electrolyte imbalance.

The data was gathered by conducting face-to-face interviews, reviewing medical records, and utilizing a semi-structured questionnaire. Additionally, a checklist was created to document pertinent variables from admission records and history sheets. Before proceeding with data processing, the collected information was thoroughly reviewed for completeness and internal consistency. SPSS version 26 was employed to analyze the data, and descriptive and inferential statistical techniques were utilized. Ethical considerations were considered and informed written consent was obtained from each participant before data collection. This research was carried out on human subjects and followed the guidelines outlined in the Declaration of Helsinki. It has been authorized by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (reference number: BSMMU/2021/7497).

3. Results

A significant number of patients in the study were between the ages of 65 - 75, with 42.4% in Group A and 30.3% in Group B falling within this age range. The mean age and standard deviation for Group A were 55.17 ± 11.64 years, while for Group B, it was 54.50 ± 10.50 years. There was no significant difference in age distribution between the two groups, as shown in **Table 1**. In terms of gender, 93.93% of patients in Group A and 90.9% in Group B were male, with no statistically significant difference between the two groups, as indicated in **Table 2**.

Table 1. Age distribution comparison between group A and group B patients.

[a]Age Group (years)	Age Distribution			p-Value
	Group A (n_1 = 33) f (%)	Group B (n_2 = 33) f (%)	Total (n = 66) f (%)	
35 - 44	5 (15.2)	8 (24.2)	13 (19.7)	0.300^{ns}
45 - 54	6 (18.2)	8 (24.2)	14 (21.2)	
55 - 64	8 (24.2)	7 (21.2)	15 (22.7)	
65 - 75	14 (42.4)	10 (30.3)	24 (36.4)	
[b]Age (Mean, & SD)	55.17 ± 11.64	54.50 ± 10.50		0.300^{ns}

The data was analyzed using [a]Chi-square test, and [b]Students t-test was performed to measure the significance level. The results were presented as mean ± SD. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency.

Table 2. Comparing gender distribution between the two groups of patients.

[a]Age Group (years)	Age Distribution			p-Value
	Group A (n_1 = 33) f (%)	Group B (n_2 = 33) f (%)	Total (n = 66) f (%)	
Male	31 (93.93)	30 (90.9)	61 (92.42)	0.671^{ns}
Female	2 (6.07)	3 (9.1)	5 (7.58)	

The data was analyzed using [a]Chi-square test was performed to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency.

Before surgery, there was no noticeable difference in the distribution of New York Heart Association (NYHA) classes between Group A and Group B. Both groups had four patients in Class I, twenty in Class II, seven in Class III, and two in Class IV, as shown in Table 3. Additionally, there were no significant differences (p-value > 0.05) between the two groups regarding preoperative medical risk factors, including smoking history, IHD/MI, hypertension, dyslipidemia, and diabetes mellitus. The results of the drug history evaluation also did not show any significant differences (p-value > 0.05), as displayed in Table 4.

Table 3. Preoperative NYHA classification comparison between study groups.

[a]NYHA Class	Groups		
	Group A (n_1 = 33) f (%)	Group B (n_2 = 33) f (%)	p-Value
I	4 (12.12)	2 (6.6)	0.307 ns
II	20 (60.6)	18 (54.54)	
III	7 (21.2)	7 (21.2)	
IV	2 (6.1)	6 (18.2)	

The data was analyzed using [a] Fisher's exact to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency. NYHA = New York Heart Association

Table 4. Comparing preoperative characteristics between two groups.

Preoperative Variables	Groups		
	Group A (n_1 = 33) f (%)	Group B (n_2 = 33) f (%)	p-Value
[a]Risk factors			
Smoker	27 (81.8)	28 (84.8)	0.741 ns
IHD/MI	29 (87.9)	26 (78.8)	0.322 ns
Dyslipidaemia	18 (54.54)	20 (60.60)	0.798 ns
HTN	17 (51.5)	16 (48.5)	0.806 ns
DM	20 (60.6)	22 (66.7)	0.609 ns
[a]Drug History			
Anti-platelet	31 (93.9)	31 (93.9)	1.0 ns
Statins	28 (84.8)	27 (81.8)	0.741 ns
Diuretics	12 (36.4)	11 (33.3)	0.796 ns
ARB/ACEI	24 (72.7)	25 (75.8)	0.778 ns
OHD	12 (36.4)	19 (57.6)	0.084 ns
Insulin	5 (15.2)	8 (24.2)	0.353 ns

The data was analyzed using [a]Chi-square test to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency. IHD = Ischemic Heart Disease, MI = Myocardial Infarction, HTN = Hypertension, DM = Diabetes Mellitus, ARB = Angiotensin Receptor Blockers, ACEI = Angiotensin Converting Enzyme Inhibitors, OHD = Oral Hypoglycemic Drugs.

There were no significant differences in the mean and standard deviation of Mg^{2+}, Na^{+}, K^{+}, and Ca^{2+} levels before surgery between Group A and Group B, as shown in Table 5. Additionally, the echocardiographic findings before surgery did not reveal any significant differences in RA diameter, LA diameter, and LVEF between the two groups, as shown in Table 5.

Table 5. Comparing preoperative electrolyte levels and echocardiographic attributes between two groups.

Preoperative Variables	Groups		
	Group A (n_1 = 33)	Group B (n_2 = 33)	p-Value
[a]Electrolytes Level (Mean, and SD)			
Mg^{2+} (mg/dl)	2.06 ± 0.131	2.01 ± 0.17	0.133[ns]
Na^{+} (mEq/L)	141.67 ± 5.60	138.65 ± 6.51	0.825[ns]
K^{+} (mmol/l)	3.79 ± 0.17	3.76 ± 0.19	0.906[ns]
Ca^{2+} (mmol/l)	1.11 ± 0.18	1.10 ± 0.12	0.680[ns]
[a]Echocardiographic Attributes (Mean, and SD)			
RA Diameter (mm)	38.87 ± 6.53	41.21 ± 6.35	0.144[ns]
LA Diameter (mm)	34.66 ± 3.11	35.52 ± 3.51	0.296[ns]
LVEF (%)	53.7 ± 10.21	52.33 ± 9.45	0.593[ns]

The data was analyzed using [a]Independent t-test to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency. RA = Right Atrium, LA = Left Atrium, LVEF = Left Ventricular Ejection Fraction.

The preoperative diagnoses, mainly Tripple Vessel Disease (TVD), showed no significant differences between the groups, as indicated in Table 6. Both groups had the majority of patients receiving three conduits, with no statistical difference in the number of conduits used, also shown in Table 6.

Table 6. Comparing preoperative coronary angiogram findings and number of conduits used during surgery between two groups.

Preoperative and Operative Variables	Groups		
	Group A (n_1 = 33) f (%)	Group B (n_2 = 33) f (%)	p-Value
[a]Vessel Involvement			
DVD	5 (15.2)	4 (12.1)	
TVD	19 (57.6)	21 (63.6)	0.960[ns]
DVD with LMD	3 (9.1)	3 (9.1)	
TVD with LMD	6 (18.2)	5 (15.2)	

Continued

[a]Number of Conduits Used			
Two	3 (9.1)	3 (9.1)	
Three	18 (54.5)	20 (60.6)	0.974[ns]
Four and above	10 (30.30)	9 (27.27)	

The data was analyzed using [a]Chi-square test to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency. DVD = Double Vessel Disease, TVD = Tripple Vessel Disease, LMD = Left Main Disease.

According to Table 7, Group A had a higher mean and SD of magnesium levels compared to Group B on various days after surgery, and the difference was statistically significant (p-value < 0.05). Additionally, Table 8 shows significant differences (p-value < 0.05) in the occurrence of new cases of AF between the two groups on the first and second days after surgery.

Table 7. Comparing post-operative magnesium and other electrolyte levels between the groups.

Postoperative Electrolytes Level (Mean, and SD)	Groups		
	Group A ($n_1 = 33$)	Group B ($n_2 = 33$)	p-Value
O Postoperative Day			
Mg^{2+} (mg/dl)	2.23 ± 0.22	1.79 ± 0.11	0.001[s]
Na^{+} (mEq/L)	143.67 ± 4.6	137.65 ± 6.61	0.674[ns]
K^{+} (mmol/l)	3.8 ± 0.18	3.98 ± 0.16	0.911[ns]
Ca^{2+} (mmol/l)	1.01 ± 0.12	1.1 ± 0.21	0.758[ns]
1st Postoperative Day			
Mg^{2+} (mg/dl)	2.21 ± 0.18	1.8 ± 0.08	0.001[s]
Na^{+} (mEq/L)	140.19 ± 7.21	139 ± 7.51	0.725[ns]
K^{+} (mmol/l)	4.01 ± 0.02	3.88 ± 0.03	0.897[ns]
Ca^{2+} (mmol/l)	0.99 ± 0.11	1.00 ± 0.13	0.875[ns]
2nd Postoperative Day			
Mg^{2+} (mg/dl)	2.1 ± 0.20	1.91 ± 0.17	0.001[s]
Na^{+} (mEq/L)	137.68 ± 6.31	138.65 ± 6.51	0.825[ns]
K^{+} (mmol/l)	3.91 ± 0.03	3.76 ± 0.19	0.641[ns]
Ca^{2+} (mmol/l)	1.1 ± 0.02	1.12 ±0.08	0.728[ns]
3rd Postoperative Day			
Mg^{2+} (mg/dl)	2.16 ± 0.17	1.91 ± 0.12	0.03 [s]
Na^{+} (mEq/L)	145.67 ± 2.61	143.25 ± 2.51	0.741[ns]
K^{+} (mmol/l)	3.91 ± 0.17	3.90 ± 0.19	0.951[ns]
Ca^{2+} (mmol/l)	1.10±0.02	1.10 ± 0.03	0.788 [ns]

The data was analyzed using [a]Independent t-test to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency.

Table 8. Comparing the Incidence of new-onset postoperative atrial fibrillation between the Groups.

Early POAF	Groups		
	Group A n = 33 f (%)	Group B n = 33 f (%)	p-Value
0 POD			
Yes	2 (6.1)	4 (12.1)	0.392[ns]
No	31 (93.9)	29 (87.9)	
1st POD			
Yes	2 (6.1)	9 (27.3)	0.02[S]
No	31 (93.9)	24 (72.7)	
2nd POD			
Yes	3 (9.1)	12(36.4)	0.008[s]
No	30 (90.9)	21 (63.6)	
3rd POD			
Yes	2 (6.1)	6 (18.2)	0.131[ns]
No	31 (93.9)	27 (81.8)	

The data was analyzed using [a]Chi-square test to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency.

In **Table 9**, postoperative parameters were compared, and it was found that the length of stay in the ICU had a significant difference (p-value = 0.001). However, there were no significant differences in the use of ventilators or length of hospital stays between the two groups (p-value > 0.05).

Table 9. Comparing post-operative outcomes between two groups.

Post-Operative Outcomes	Groups		
	Group A f (%) n = 33	Group B f (%) n = 33	p-Value
[a]Mean Duration of Ventilator Used (Hours) Mean, & SD	6.45 ± 1.61	6.63 ± 1.03	0.399[ns]
[a]Mean Duration of ICU Stay (Hours)	60.45 ± 9.26	80.23 ± 8.45	0.001[s]
[a]Mean Hospital Stays (Days)	9.41 ± 2.22	10.56 ± 2.34	0.06[ns]
[b]Mortality	0 (0)	2 (6.06)	0.151[ns]

The data was analyzed using [a]Independent t-test, and [b]Fisher's exact to measure the significance level. A p-value of ≤0.05 was considered significant, while "ns" means not significant, and "f" indicates frequency.

4. Discussion

Electrolyte abnormalities, particularly hypomagnesemia, have been identified as significant contributors to cardiac rhythm disturbances [12] [13] [14]. This study compares the effectiveness of intravenous magnesium sulfate in preventing atrial fibrillation (AF) after off-pump coronary artery bypass grafting (CABG). Sixty-six patients with coronary artery disease underwent off-pump CABG and were divided into two groups. Group A (n = 33) received daily doses of intravenous magnesium sulfate (10 mmol or 2.47 gm) for three days after surgery, while Group B (n = 33) did not receive magnesium sulfate. The mean age of both groups was 55.17 ± 11.74 and 54.50 ± 10.50 years, respectively, with the majority being in the advanced age group (>65 years). However, the mean difference was insignificant ($p > 0.05$). Similar studies conducted by Kohno and colleagues also identified advanced age as an independent predictor of postoperative AF, alongside magnesium levels [4]. The study had a similar distribution of genders in both groups, with 92% of patients being male and 8% female. In Group A, which received treatment, 94% were male, and 6% were female. In Group B, which did not receive treatment, 91% were male, and 9% were female. These results are consistent with previous studies conducted by Zangrillo, *et al.* and Kohno, *et al.*, which also found a higher proportion of male patients in their respective studies [4] [15]. This suggests that males are more likely to suffer from coronary artery disease. Regarding the NYHA class, our study observed almost 60.6% and 54.54% of patients in NYHA class II in the study and control groups, respectively. This finding deviates from a study by Toraman, *et al.*, which reported 34% of patients in both study groups to be within NYHA class II [11]. Echocardiographic parameters, including RA size, LA size, and LVEF, were compared between the two groups, but no statistically significant differences were observed ($p = 0.144$, $p = 0.296$, $p = 0.593$, respectively). These results are consistent with a study by Toraman, *et al.*, which also did not find significant differences in preoperative LVEF between the study and control groups [11]. The number of patients receiving three conduits for the bypass was 54.5% in Group A, and 60.6% in Group B. Kohno, *et al.* also reported a mean number of bypass grafts of 2.7 ± 0.9 and 2.6 ± 1.1 in their study and control groups, respectively, which is consistent with our findings [4]. Overall preoperative mean magnesium levels were similar between the two groups ($p = 0.133$), and no statistically significant differences were observed in serum electrolytes other than magnesium, both preoperatively and postoperatively, between the two groups. However, relevant data on this aspect from the literature were not found. Postoperative atrial fibrillation was observed in 18%, 33%, 46%, and 24% of cases on the 0^{th}, 1^{st}, 2^{nd}, and third postoperative days, respectively. The occurrence of postoperative atrial fibrillation was significantly higher in the untreated group than in the treated group on the first and second postoperative days ($p = 0.02$ and 0.008, respectively). Furthermore, 94% of patients in the untreated group experienced postoperative atrial fibrillation, compared to 27% in the treated group. These findings align with studies by Kohno, *et al.* and Toraman, *et al.*, which also demonstrated a positive association between postoperative atrial fibrillation and hypomagnesemia following off-pump CABG [4] [11]. Despite several studies, it has not been determined that magnesium supplementation can effectively protect against postoperative atrial fibrillation. [16] [17] [18]. Duration of mechanical ventilation and hospital stay were similar between the two groups ($p > 0.05$). However, the time of ICU stay was significantly higher in Group B, mainly due to postoperative atrial fibrillation. This finding aligns with the research of Zangrillo, *et al.* [15] as well as studies carried out by Weintraub, *et al.* [19]. Two mortalities were recorded in this study but were not statistically significant ($p > 0.05$). A pilot study determined that ten mmol (2.47 gm) of magnesium sulfate was necessary to achieve normal or supernormal magnesium levels in the postoperative period. Kohno, *et al.* and Toraman, *et al.* also found that 2 grams of magnesium sulfate were required to attain normal magnesium levels postoperatively [4] [11]. In conclusion, the high frequency of hypomagnesemia after off-pump CABG underscores its importance as a risk factor for postoperative AF. Lower serum magnesium levels were associated with an increased incidence of AF in this study. Intravenous magnesium sulfate therapy following off-pump CABG shows promising results in preventing postoperative atrial fibrillation, with the study dosages posing a minimal risk of adverse effects in patients with normal renal function. Therefore, intravenous magnesium sulfate may be considered a routine preventive measure for postoperative atrial fibrillation.

Please note that the current study has some limitations that should be considered. Firstly, it is important to acknowledge that the sample size used in this study was small, which means that the findings may not represent the broader population of patients undergoing cardiac surgery. This could limit the generalizability of the findings. Secondly, this study was not designed as a randomized clinical trial, which may introduce potential bias in treatment assignment and limit the ability to establish a cause-and-effect relationship between intravenous magnesium sulfate and the prevention of postoperative atrial fibrillation. Additionally, the lack of follow-up after patient discharge prevents the assessment of adverse outcomes during the postoperative period, such as heart failure, myocardial infarction, the need for revascularization, and stroke. Consequently, the long-term impact of intravenous magnesium therapy on patient outcomes remains unknown. Lastly, it is important to note that continuous electrocardiogram (ECG) monitoring was not conducted after shifting patients to the postoperative ward from the ICU. This may lead to an underestimation of the true incidence of arrhythmias in this study, potentially missing some cases of postoperative atrial fibrillation or other arrhythmias.

After conducting our study, we have some recommendations:

1) To prevent postoperative atrial fibrillation, it is advisable to maintain optimal magnesium levels after off-pump coronary artery bypass grafting by regularly monitoring them. This can be done as a routine measure for prophylaxis.

2) It is essential to conduct a more comprehensive study with a more significant number of participants to confirm and strengthen the results of this study. This will provide more conclusive evidence of the effectiveness of intravenous

magnesium therapy in preventing postoperative atrial fibrillation after off-pump coronary artery bypass grafting.

5. Conclusion

This research indicates that after off-pump coronary artery bypass grafting, there is a significant decrease in average serum magnesium levels, which may be linked to atrial fibrillation after surgery. Notably, the group that did not receive magnesium treatment had a much higher incidence of postoperative atrial fibrillation than the treated group. Therefore, administering intravenous magnesium sulfate after surgery helps maintain normal serum magnesium levels and plays a critical role in preventing atrial fibrillation after off-pump coronary artery bypass grafting.

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Authors' Contributions

The first author who initiated this study had a crucial role in creating and planning the research, collecting data from the hospital, analyzing the data, and writing the manuscript. All authors worked together to interpret the results and agreed upon the final version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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