ORIGINAL ARTICLE

Comparison of Drug-Assisted Tracheal Intubation Using Benzodiazepines and Induction Agents for First-Pass Intubation Success in Emergency Airway Management: A Retrospective Cohort Study

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Objective: To determine first-pass intubation success between benzodiazepines and induction agents in adult patients who underwent drug-assisted intubation in the emergency department (ED).

Materials and Methods: A retrospective chart review observational study collected the data of patients who underwent drug-assisted intubation in the ED of a university teaching hospital between January 1, 2021 and August 31, 2022. Two hundred seven patients were enrolled in the present study. The benzodiazepine and induction agent groups were compared in terms of baseline characteristics, and clinical management. Each benzodiazepine and induction agent were compared in first-pass intubation success, time to intubation success, adverse events, and 24-hour mortality.

Results: Of the 207 patients included in the present study, 35 patients used benzodiazepine, and 172 patients used induction agents. The two groups had no differences in baseline characteristics. The first-pass intubation success rate was not significantly different among the medications with 90% in nine diazepam patients, 92% in 23 midazolam patients, 89.8% in 79 etomidate patients, and 94% in 79 propofol patients (p=0.553). Complications associated with intubation included hypotension, desaturation, tachycardia, bradycardia, arrhythmia, cardiac arrest, and pneumonia. No differences in 24-hour survival were observed.

Conclusion: The sedative medications used during drug-assisted intubation should be chosen based on patient comorbidities and characteristics, as well as physician preferences and experiences. There were no differences between the benzodiazepine and induction agent groups in terms of first-pass intubation success, adverse events, or 24-hour survival. The use of benzodiazepines in settings with limited resources may be considered.

Keywords: First-pass intubation success; Emergency department; Etomidate; Propofol; Benzodiazepine; Complication

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Advanced airway management is a crucial skill and a high-risk procedure in patients who require emergency oxygenation and ventilation due to pathologies[1]. Airway management in an emergency setting is an uncontrolled situation compared to an operating room setting. Furthermore, the patient is critically ill[2]. The purpose of critical airway care is to provide efficient breathing and oxygenation while avoiding stomach inflation, regurgitation, aspiration, and prevent comorbidities in critically ill patients[3,4].

An intubation attempt is defined as the insertion of the laryngoscope blade into the mouth of the patient, regardless of whether an attempt is made to insert a tracheal tube. First-pass intubation success is defined as successful tracheal intubation on a single laryngoscope insertion[5]. Evidence suggests that success of the first attempt at intubation is associated with a decrease in adverse events during the procedure[6,7]. One study found that the rate of adverse events was significantly lower in patients who had a successful first-pass intubation compared to those who required multiple attempts[6]. The factors associated with the first-pass success of emergency endotracheal intubation were divided into two categories, operator-related factors, and patient-related factors. Operator characteristics, such

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as clinical experience and working department, and patient features, such as restricted mouth opening, restricted neck extension, and swollen tongue, were independently predictive of first-pass success in emergency endotracheal intubation[8]. However, this association may not necessarily be causal. Other factors may also contribute to the occurrence of adverse events during intubation. Adverse events during peri-intubation occur in almost one third of all intubations in the emergency department (ED), intensive care unit, or medical ward. Adverse events are more common in the intensive care unit and among patients who already have hemodynamic impairment. Prior to intubation, physicians should assess all patients for the possibility of a physiologically difficult airway and plan appropriately for potential hypoxia, hypotension, or cardiac arrest in the peri-intubation phase[9].

One study found that benzodiazepines and induction agents can improve the success rate of tracheal intubation. Furthermore, no differences were observed in the first-pass intubation success rates between midazolam and etomidate in prehospital settings, especially in emergency situations where time is of the essence[10]. In general, both benzodiazepines and induction agents are effective at producing muscle relaxation and improving the success rate of tracheal intubation. However, there may be differences in the specific characteristics and potential side effects of these medications, and the optimal choice may vary depending on the specific patient and the clinical context. Benzodiazepines, such as diazepam and midazolam, are commonly used in the ED to induce sedation and facilitate emergency intubation[11]. However, benzodiazepines have disadvantages that may make them less suitable in certain situations compared to other anesthetic agents, such as etomidate and propofol.

The disadvantage of benzodiazepines is that they have slower onset of action compared to other anesthetic agents[12], which may prolong the time to intubate. Benzodiazepines also have a longer duration of action, which can make it more difficult to titrate the level of sedation and can result in prolonged recovery times. In addition, benzodiazepines can cause respiratory depression, which can be problematic in patients with respiratory compromise or underlying respiratory disease. They can also cause hypotension, which can be harmful in patients with cardiovascular instability or hypotension[13].

Etomidate is a short-acting intravenous medication for anesthetic induction and sedation. Single-dose etomidate is commonly used for emergency airway procedures in critically ill patients. This medication was administered in more than 60% of emergency airway interventions in the United States due to its excellent hemodynamic properties and convenience of administration[14]. However, etomidate is known to result in adrenal suppression, and decreased cortisol level can occur after a single dose of etomidate[15]. Propofol is a highly lipophilic, rapid onset sedative with a faster onset and shorter duration of effect than etomidate. It has anticonvulsant and antiemetic effects, and it may reduce intracranial pressure without causing histamine release. However, propofol has significant adverse effects that include hypotension caused by cardiac depression and vasodilation, thus making it less appealing for trauma patients or patients in shock[16].

Only a few recent studies have explored benzodiazepines for drug-assisted intubation compared with induction agents in a tertiary hospital setting to determine which medication could increase first-pass intubation success. The present study aimed to compare the use of benzodiazepines including diazepam and midazolam with induction agents that include etomidate and propofol for first-pass intubation success and adverse events.

Materials and Methods

A retrospective chart review observational study was conducted in the ED of Songklanagarind Hospital, a teaching hospital and a tertiary care medical center with a capacity of 850 beds. The ED had over 48,000 patient visits per year. The data were collected between January 1, 2021 and August 31, 2022. The inclusion criteria were patients older than 15 years who were sedated and intubated by an emergency physician or emergency resident. Patients with the following criteria were excluded from the study, 1) cardiac arrest prior to drug-assisted intubation, 2) received paralytic agents, 3) intubated by a non-emergency resident or staff physician, 4) referred from other hospitals, 5) received prehospital intubation, and 6) incomplete medical records. Two hundred seven patients were enrolled in the retrospective study (Figure 1).

Operational definitions

Hypotension was defined as systolic blood pressure (SBP) less than 90 mm Hg. Desaturation was characterized as a pulse oximetry saturation below 90% during an intubation attempt[17]. Tachycardia

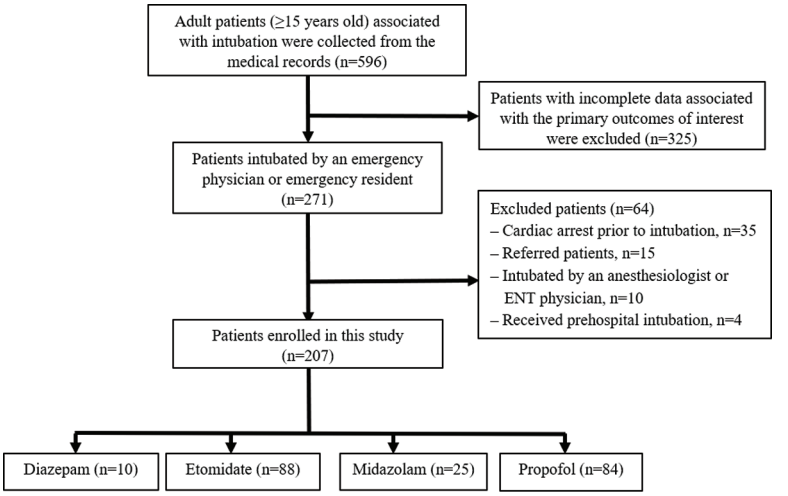

Figure 1. Study flow diagram.

was described as a ventricular rate that exceeds 100 beats per minute (bpm). Bradycardia referred to rhythms with ventricular rates slower than 60 bpm[18]. Arrhythmia was defined as any rhythm other than normal sinus rhythm with normal atrioventricular (AV) conduction[19].

Data collection

The data collected from the electronic medical records and ED data registry included baseline characteristics, triage category, underlying disease, diagnosis, indication for intubation, pre-induction vital signs, sedative agents used prior to intubation, sedative agent dose, first intubator, number of intubation attempts, time to intubation success, ED length of stay, ED disposition, immediate complication, 24-hour mortality, hospital length of stay, and hospital-acquired or ventilator-associated pneumonia. Before intubation, the patients were divided into two groups, the benzodiazepine group, and the inductive agent group.

Outcome measurements

The primary outcome was to determine first-pass intubation success among the two benzodiazepines and two induction agents. The secondary outcome was to determine the associations between each benzodiazepine and induction agent that affected adverse events, 24-hour mortality, and hospital-acquired or ventilator-associated pneumonia.

Statistical analysis

The sample size for the study population to assess two independent proportions was established using the n4Studies tool. The final calculated sample size was 93 patients in each group for a total of 186 patients. After adding a 10% dropout rate, the desired sample size was 102 patients in each group for a total of 204 patients. R software version 4.0.2 was used to conduct the statistical analysis after all data were imported into EpiData version 3.1 (R Foundation, Vienna, Austria). Continuous variables were analyzed and reported as mean and median while categorical variables were reported as percentage. The Student's t-test, Kruskal-Wallis test, and Wilcoxon rank sum test were used for continuous and ordinal variables, and Pearson's chi-square test and Fisher's exact test were used for categorical variables. Analytical results were described as number (percentage) with 95% confidence interval (CI). A p-value of less than 0.05 was considered statistically significant.

Compliance with ethical requirements

The Ethics Committee of Prince of Songkla University approved the present study. The Institutional Review Board of Prince of Songkla University is affiliated with the International Conference on Harmonization in Good Clinical Practice. The informed consent requirement was waived in accordance with our institutional review board's policy because the participants had no greater than minimum risk and the patients received standard medical care. All research information was kept as confidential data in an encrypted file with password and limited data access by only the researcher. The ethics committee approval number was REC. 65-281-20-4. The present study was conducted in accordance with the Declaration of Helsinki.

Table 1. Patient characteristics

Parameters	Total (n=207)	Benzodiazepines (diazepam/midazolam) (n=35)	Induction agents (etomidate/propofol) (n=172)	p-value
Age (years); median (IQR)	72 (60, 81)	70 (60, 78.5)	72 (60, 81.2)	0.424
Sex; n (%)				0.440
Male	127 (61.4)	24 (68.6)	103 (59.9)	
Female	80 (38.6)	11 (31.4)	69 (40.1)	
ESI level; n (%)				0.739
1	132 (63.8)	24 (68.6)	108 (62.8)	
2	74 (35.7)	11 (31.4)	63 (36.6)	
3	1 (0.5)	0 (0.0)	1 (0.6)	
Level of consciousness; n (%)				0.070
Alert	123 (59.4)	15 (42.9)	108 (62.8)	
Responded to voice	38 (18.4)	7 (20.0)	31 (18.0)	
Responded to pain	18 (8.7)	4 (11.4)	14 (8.1)	
Unresponsive	28 (13.5)	9 (25.7)	19 (11.0)	
Underlying disease; n (%)				1.000
Absent	14 (6.8)	2 (5.7)	12 (7.0)	
Present	193 (93.2)	33 (94.3)	160 (93.0)	
• Neoplastic disease	56 (27.1)	11 (31.4)	45 (26.2)	0.667
• Chronic pulmonary disease	43 (20.8)	12 (34.3)	31 (18.0)	0.053
• Cardiovascular disease	67 (32.4)	8 (22.9)	59 (34.3)	0.262
• Chronic renal disease	51 (24.6)	7 (20.0)	44 (25.6)	0.629
• Chronic liver disease	14 (6.8)	2 (5.7)	12 (7.0)	1.000
• Neurological disorder	49 (23.7)	12 (34.3)	37 (21.5)	0.161
• Hypertension	113 (54.6)	17 (48.6)	96 (55.8)	0.550
• Diabetes	71 (34.3)	9 (25.7)	62 (36.0)	0.328
• Others	9 (4.3)	3 (8.6)	6 (3.5)	0.180
Diagnosis; n (%)				
Pneumonia	59 (28.5)	7 (20.0)	52 (30.2)	0.309
Heart failure	51 (24.6)	8 (22.9)	43 (25.0)	0.958
Sepsis	30 (14.5)	4 (11.4)	26 (15.1)	0.763
Traumatic brain injury	4 (1.9)	3 (8.6)	1 (0.6)	0.016
Stroke	18 (8.7)	3 (8.6)	15 (8.7)	1.000
Seizure	7 (3.4)	2 (5.7)	5 (2.9)	0.337
Lower airway disease	18 (8.7)	5 (14.3)	13 (7.6)	0.197
Upper airway disease	3 (1.4)	1 (2.9)	2 (1.2)	0.428
Others	17 (8.2)	2 (5.7)	15 (8.7)	0.743
Indication for intubation; n (%)				0.251
Respiratory failure	146 (70.5)	24 (68.6)	122 (70.9)	
Severe neurological deficit	25 (12.1)	7 (20.0)	18 (10.5)	
Shock	18 (8.7)	1 (2.9)	17 (9.9)	
Airway maintenance	12 (5.8)	3 (8.6)	9 (5.2)	
Severe metabolic acidosis	6 (2.9)	0 (0.0)	6 (3.5)	
Pre-intubation vital signs				
SBP; mean [SD]	146.5 [37.5]	132.1 [44.5]	149.4 [35.3]	0.013
DBP; median (IQR)	87 (68, 102)	70 (60.5, 87.5)	89 (72, 104.2)	0.001
HR; mean [SD]	108.7 [26.5]	105.3 [30.7]	109.4 [25.6]	0.397
RR; median (IQR)	36 (28, 40)	34 (28, 40)	36 (29.5, 40)	0.516
SpO_2; median (IQR)	97 (88.2, 100)	97 (87.5, 100)	97 (90, 100)	0.726

IQR=interquartile range; ESI=Emergency Severity Index; SBP=systolic blood pressure; SD=standard deviation; DBP=diastolic blood pressure; HR=heart rate; RR=respiratory rate; SpO_2=oxygen saturation; EM=emergency medicine; ED=emergency department

Table 1. (continued)

Parameters	Total (n=207)	Benzodiazepines (diazepam/midazolam) (n=35)	Induction agents (etomidate/propofol) (n=172)	p-value
First intubator; n (%)				0.282
First-year EM resident	22 (10.7)	1 (2.9)	21 (12.3)	
Second-year EM resident	43 (20.9)	6 (17.1)	37 (21.6)	
Third-year EM resident	125 (60.4)	24 (68.6)	101 (58.7)	
ED staff physician	17 (8.3)	4 (11.4)	13 (7.6)	
Number of attempts; n (%)				0.570
1	190 (91.8)	32 (91.4)	158 (91.9)	
2	14 (6.8)	2 (5.7)	12 (7.0)	
3 or more	3 (1.4)	1 (2.9)	2 (1.2)	
Time to intubation success (minutes); median (IQR)	2 (1, 5)	4 (2, 8.5)	2 (1, 5)	0.068
Immediate complications; n (%)				
Hypotension	21 (10.1)	1 (2.9)	20 (11.6)	0.214
Desaturation	3 (1.4)	0 (0.0)	3 (1.7)	1.000
Tachycardia	9 (4.3)	0 (0.0)	9 (5.2)	0.362
Bradycardia	1 (0.5)	0 (0.0)	1 (0.6)	1.000
Arrhythmia	1 (0.5)	0 (0.0)	1 (0.6)	1.000
Cardiac arrest	3 (1.4)	1 (2.9)	2 (1.2)	0.428
Hospital/ventilator acquired pneumonia; n (%)				1.000
Absent	166 (80.2)	28 (80.0)	138 (80.2)	
Present	41 (19.8)	7 (20.0)	34 (19.8)	
Disposition; n (%)				0.232
Intensive care unit	83 (40.1)	17 (48.6)	66 (38.4)	
General ward	88 (42.5)	12 (34.3)	76 (44.2)	
Dead	4 (1.9)	0 (0.0)	4 (2.3)	
Against advice	1 (0.5)	1 (2.9)	0 (0.0)	
Referred	31 (15.0)	5 (14.3)	26 (15.1)	
24-hour survival; n (%)				1.000
No	12 (5.8)	2 (5.8)	10 (5.8)	
Yes	195 (94.2)	33 (94.2)	162 (94.2)	
ED length of stay (minutes), median (IQR)	225 (171, 310)	220 (149, 300)	225.5 (172.2, 315.8)	0.275
Hospital length of stay (days), median (IQR)	13 (7, 24)	17 (10, 25)	12 (6.8, 24)	0.143

IQR=interquartile range; ESI=Emergency Severity Index; SBP=systolic blood pressure; SD=standard deviation; DBP=diastolic blood pressure; HR=heart rate; RR=respiratory rate; SpO_2=oxygen saturation; EM=emergency medicine; ED=emergency department

Results

Demographic data

Five hundred ninety-six patients associated with intubation in the medical records were registered during the study period. All registered medical records were reviewed, and 207 patients met the enrollment criteria.

Patient characteristics

The enrolled patients were categorized into either the benzodiazepine group, with 35 patients, or induction agent group, with 172 patients. No significant differences in demographic data were observed between the two groups (Table 1).

First-pass intubation and time to success

No differences were observed in the number of intubations attempts or time to intubation success (Table 2). No other factors were associated with first-attempt intubation success (Table 3).

Adverse events

Six immediate complications were recorded as hypotension in 21 patients (10.1%), tachycardia in nine patients (4.3%), desaturation in three patients (1.4%), cardiac arrest in three patients (1.4%), bradycardia in one patient (0.5%), and arrhythmia in one patient (0.5%). During hospitalization, 41 patients (23.6%) were diagnosed as hospital-acquired or ventilator-associated pneumonia (Table 1). All

Table 2. Number of attempts and time to intubation success

Medication	Diazepam (n=10)	Etomidate (n=88)	Midazolam (n=25)	Propofol (n=84)	p-value
Number of attempts; n (%)					0.553
1	9 (90.0)	79 (89.8)	23 (92.0)	79 (94.0)	
2	1 (10.0)	7 (7.9)	1 (4.0)	5 (6.0)	
3 or more	0 (0.0)	2 (2.3)	1 (4.0)	0 (0.0)	
Time to intubation success (minutes); median (IQR)	3 (1.2, 8)	2 (1, 4.2)	4 (2, 8)	2 (1, 5)	0.306

IQR=interquartile range

Table 3. Factors associated with first-attempt intubation success

Parameters	Failed first attempt (n=17)	First-pass success (n=190)	p-value
Age (years); median (IQR)	67 (60, 82)	72 (60, 81)	0.713
Sex; n (%)			1.000
Male	10 (58.8)	117 (61.6)	
Female	7 (41.2)	73 (38.4)	
ESI level; n (%)			0.643
1	10 (58.8)	122 (64.2)	
2	7 (41.2)	67 (35.3)	
3	0 (0.0)	1 (0.5)	
First intubator; n (%)			0.501
First-year EM resident	3 (17.6)	19 (10.0)	
Second-year EM resident	5 (29.4)	39 (20.5)	
Third-year EM resident	8 (47.1)	116 (61.1)	
ED staff physician	1 (5.9)	16 (8.4)	
Medication; n (%)			0.636
Diazepam	1 (5.9)	9 (4.7)	
Etomidate	9 (52.9)	79 (41.6)	
Midazolam	2 (11.8)	23 (12.1)	
Propofol	5 (29.4)	79 (41.6)	
Pre-intubation vital sign			
SBP; mean [SD]	143.4 [46.8]	146.7 [36.7]	0.727
DBP; median (IQR)	88 (64, 106)	87 (69, 101.8)	0.740
HR; mean [SD]	102.8 [21.7]	109.2 [26.8]	0.339
RR; median (IQR)	38 (34, 40)	36 (28, 40)	0.395
SpO_2; median (IQR)	96 (87, 98)	97 (90, 100)	0.453

IQR=interquartile range; ESI=Emergency Severity Index; EM=emergency medicine; ED=emergency department; SBP=systolic blood pressure; DBP=diastolic blood pressure; HR=heart rate; SD=standard deviation; RR=respiratory rate; SpO_2=oxygen saturation

complications and 24-hour survival rates revealed no differences among the medications chosen for intubation during the study period (Table 4).

Discussion

The present study revealed only SBP and DBP differences between the benzodiazepine and induction agents' groups. However, no difference was observed between successful first-pass intubation and adverse outcomes immediately following intubation.

For decades, induction agents have been used to assist intubation, particularly in university hospitals and tertiary care institutions. Since benzodiazepines can cause hemodynamic complications, longer onset, prolonged time of intubation, and an increased risk of aspiration, the use of benzodiazepines has been reduced in practice[20]. The present study was conducted in a university hospital where drug-assisted intubation was used during the study period. However, the attending physicians were limited in the use of induction agents because of a shortage of etomidate and midazolam between April 9, 2021 and January 16, 2022. Therefore, the application of propofol and benzodiazepines increased but there were no differences in first-pass intubation success or complications.

In general, propofol and etomidate have a faster onset of action compared to benzodiazepines, therefore, a more rapid intubation can be expected[20]. However, the time to intubation success can be influenced by a variety of factors, including the experience and technique of the physician, the presence of any anatomical or physiological challenges, and the overall stability of the patient[21]. It is important to note that the duration of intubation should not be the primary consideration when selecting an anesthetic agent. The goal of intubation is to establish a secure and patent airway as quickly and safely as possible[22]. The present study showed that patients in the induction agent group had more comorbidities than in the benzodiazepine group, which impacted their hemodynamic conditions that included cardiovascular disease, chronic renal illness, chronic liver disease, hypertension, and diabetes. These factors may be considered while deciding for drug-assisted intubation. Etomidate was recognized to have minimal impact on the hemodynamics. Intubated patients with hemodynamic instability received more induction drugs than patients with hemodynamic stability.

While benzodiazepines may have a role in the induction for intubation, they have disadvantages

Table 4. Comparison of adverse events among the medications used

Medication	Diazepam (n=10)	Etomidate (n=88)	Midazolam (n=25)	Propofol (n=84)	p-value
Immediate complication; n (%)					0.493
Absent	10 (100)	71 (80.7)	22 (88.0)	71 (84.5)	
Present	0 (0.0)	17 (19.3)	3 (12.0)	13 (15.5)	
• Hypotension	0 (0.0)	11 (12.5)	1 (4.0)	9 (10.7)	0.585
• Desaturation	0 (0.0)	2 (2.3)	0 (0.0)	1 (1.2)	1.000
• Tachycardia	0 (0.0)	4 (4.5)	0 (0.0)	5 (6.0)	0.773
• Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)	0.575
• Arrhythmia	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	1.000
• Cardiac arrest	0 (0.0)	2 (2.3)	1 (4.0)	0 (0.0)	0.367
Ventilator-/hospital-acquired pneumonia; n (%)	1 (11.1)	18 (23.7)	6 (30.0)	16 (23.2)	0.773
24-hour survivors; n (%)	9 (100)	67 (89.3)	18 (90.0)	68 (97.1)	0.216

compared to other anesthetic agents that may make them less suitable for use in certain situations, such as in patients with respiratory or cardiovascular compromise or in emergency situations[23]. The choice of an anesthetic agent should be guided by the specific needs and characteristics of the patient, as well as the preferences and experience of the physicians[24].

Limitation

There were limitations of this present study. Since the study was retrospective in nature and carried out in a single ED, data might be missing. The emergency conditions that guided the medication selection may have introduced confounders. Due to the short study duration, small sample size, and low occurrence of complications, the authors had insufficient data to draw any conclusions from the use of benzodiazepines.

Conclusion

No differences between the benzodiazepines and induction agents were observed during the present study period regarding success of first-pass intubation, time to intubation success, complications that included hypotension, desaturation, tachycardia, bradycardia, arrhythmia, cardiac arrest, hospital-acquired pneumonia, and 24-hour survival.

What is already known on this topic?

First-pass success in orotracheal intubation in the ED is associated with a low frequency of adverse events. The incidence of adverse events significantly rises as the number of attempts increases.

What does this study add?

This study demonstrates no differences between the benzodiazepines and induction agents in terms of first-pass intubation success, the time to intubation success, complications, and 24-hour survival. Using benzodiazepines in resource limited facilities may be considered.

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Authors' contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analyses, and interpretation. All authors took part in drafting, revising or critically reviewing the article, gave final approval of the version to be published, had agreed on the journal to which the article had been submitted, and agreed to be accountable for all aspects of the work.

Data availability

The retrospective data used to support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

The authors declare no conflicting interests.

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