Efficacy of different analgesic or sedative drug therapies in pediatric patients with congenital heart disease undergoing surgery: a network meta-analysis

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Abstract

Background Surgery is an effective therapy for congenital heart disease (CHD) and the management after surgery poses challenges for the clinical workers. We performed this network meta-analysis to enhance the corresponding evidence with respect to the relative efficacy of different drug treatments applied after the CHD surgery.

Methods Embase and PubMed were systematically retrieved to identify all published controlled trials investigating the effectiveness of drugs for patients up to 25 August, 2018. Mean differences (MD), odds ratios and their 95% credible intervals (CrIs) were used to evaluate multi-aspect comparisons. Surface under cumulative ranking curve (SUCRA) was used to analyze the relative ranking of different treatments in each endpoint.

Results Compared to saline, all the drugs achieved better preference under the efficacy endpoints except fentanyl in JET. As for ventilator time, all drugs were more effective than saline while only the difference of dexmedetomidine was statistically obvious (MD = 6.92, 95% CrIs 1.77–12.54). Under the endpoint of ICU time, dexmedetomidine was superior to saline as well (MD = 1.26, 95% CrIs 0.11–2.45). When all the endpoints were taken into consideration and with the help of ranking probabilities and SUCRA values, fentanyl combined with dexmedetomidine was one of the recommended drugs due to its shorter time on ventilator and stay in hospital as well as lower mortality.

Conclusions Overall, based on the comprehensive consideration of all the endpoints, fentanyl combined with dexmedetomidine was considered to be the best-recommended clinical interventions among all the methods.

Keywords Congenital heart disease · Dexmedetomidine · Drug treatments · Fentanyl · Network meta-analysis

Introduction

Congenital heart diseases (CHD) arise from abnormal formation of the heart or major blood vessels [1]. There is 0.4–1 infants born with congenital heart disease in per 100 US infants and approximately 1/4 of these lesions will

require intervention, such as surgery, during infancy [1, 2]. Approximately 10,000 children require anesthesia every year for CHD surgery during their first year of life [3]. Pre- and postoperative treatment of children with CHD poses enormous challenges in the intensive care unit (ICU), especially during the postoperative phase [4, 5].

Intravenous benzodiazepines and opioids are the most commonly used drugs for sedation and analgesia in the pediatric ICU [6]. Fentanyl is the most commonly used opioid for procedural sedation because of its pharmacokinetic profile, analgesic potency, and low cost [7]. The combination of benzodiazepines and opioids often provide satisfactory sedation of children; however, they are associated with adverse reactions such as respiratory depression, prolonged mechanical ventilation, and prolonged ICU stay [8, 9]. Dexmedetomidine (DEX) is a selective alpha-2-adrenergic receptor antagonist that possesses sedative, anxiolytic, and analgesic effects without causing significant respiratory depression

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[10, 11]. Thus, a lot of previous studies have focused on the comparison of fentanyl and dexmedetomidine. In addition, few studies reported the efficacy comparison between dexmedetomidine and other kinds of standard analgesia and sedation medications such as drugs combination consisted of midazolam, propofol, buprenorphine and pentazocine [12].

Junctional ectopic tachycardia (JET) is one type of arrhythmia encountered postoperatively, and is observed almost exclusively after open heart surgery in children with CHD [13]. Patients who developed JET postoperatively tend to have prolonged intensive care unit (ICU) stay. Hemodynamic instability as a result of JET leads to increased mortality [14]. Recently, perioperative administration of dexmedetomidine had been studied as an alternative approach in the treatment of postoperative JET.

Although varieties of the studies focused on the pairwise comparison and improving the precision of estimates results, they cannot fully satisfy the comparison requirement. Besides, a majority of current systematic analyses were restricted to only one medication in terms of a very few endpoints [15–17]. In this study, we conducted a comprehensive search strategy aiming to include all the available drugs and data extracted from the controlled trials to compare and evaluate their relative efficacy at the same time. A total of seven kinds of different therapy methods (saline, dexmedetomidine alone, dexmedetomidine combined with fentanyl, fentanyl alone, analgesic and sedative, etomidate and sufentanil) have been involved in this NMA. Five outcomes have been considered: time on ventilator (VT), time in intensive care unit (ICU), length of stay (LOS), junctional ectopic tachycardia (JET) and mortality. The aim of this NMA is to expand the existing studies and with regard to the results which were obtained from this study, we tried to identify the optimal drugs for the postoperative patients with CHD.

Methods

Study design and selection strategy

The database Embase and PubMed were systematically retrieved to identify all published experimental studies, investigating the outcomes of different analgesic or sedative drug therapies in pediatric patients undergoing congenital heart disease surgery up to 25 August, 2018. The medical subject headings, “drug therapy”, “control trial”, “randomized control trial”, “observational study” and their synonyms were combined as search field. The related bibliographies were also searched manually to identify studies that were missed in the electronic search. The search was limited to clinical trials and human studies, age restrictions and language were not implemented.

Inclusion criteria

A large scale of papers and studies selected for our network meta-analysis (NMA) were evaluated if they met the following standards: (1) patients enrolled in this study were infant or child with congenital heart disease and going through surgery; (2) study should at least include two of the eight treatments; (3) study should at least include one of the following outcomes, i.e., time on ventilator (VT), intensive care unit stay (ICU), length of stay in hospital (LOS), and junctional ectopic tachycardia (JET); and (4) original trials should comprise adequate data for NMA.

Exclusion criteria

Studies will be excluded if they satisfy any of the following standards: (1) studies have no primary endpoint; (2) studies focus on other relevant treatments; (3) replicated or incomplete data from the same cohort; (4) the publication type of study are meetings, case reports, and publication reviews.

Outcome measures and data extraction

All relevant data from enrolled studies including references of all retrieved publications were extracted independently by two reviewers using a standardized data collection form. Discrepancies between investigators were resolved by consensus, referring back to eligible study or discussed through a third independent investigator. In this NMA analysis, VT, ICU and LOS were considered as the primary outcomes, and JET and mortality were regarded as secondary outcomes. The following publication information was extracted from each study: (1) the first author’s last name, year of publication and country; (2) study design, blind mode, the specific sort of CHD, anesthetic maintained drug and the therapeutic drugs and dosages after surgery; (3) participants number and several demographic characteristics; and (4) the outcomes contained in the study.

Statistical analysis

The statistical processing was carried out by R (Version 3.5.1) and STATA version 13.0 (Stata Corp, College Station, TX, USA). The first-hand correlation between two interventions, among VT, ICU, LOS, JET and mortality were displayed in the network mapping. The dot sizes illustrated the number of patients receiving corresponding therapy, and the width of lines indicated the number of each comparison. NMA was based on Bayesian framework using a random-effects model. In principle, through NMA, we could randomly allocate any two of the interventions under the specific endpoint. For continuous variables, such as VT, ICU time and LOS, the MD with its 95% CrI was measured while

Fig. 1 Flow diagram summarizing results of study identification and selection

the binary variables, such as morality, were represented as odds ratio (OR) with 95% CrI. Furthermore, surface under cumulative ranking curve (SUCRA) was used to analyze the relative ranking of different treatments in each endpoint. The values of SUCRA are positively correlated with outcomes and the maximum ranking value is 1. Additionally, net heat plots were conducted to exhibit the degree of inconsistency. Finally, comparison-adjusted funnel plots were used to evaluate publication bias. A symmetry plot indicated that there are no small sample sizes affecting the statistical results.

Results

Study selection

Figure 1 showed the process of searching and screening. First, a total of 1830 records were identified through searching methods mentioned early. Another two articles were added by hand searching of related review. After removing 93 duplicates, a total of 1739 articles were taken into next step. By screening on title and abstract, 1714 articles that did not meet the criteria were excluded. Although 22 full-text articles were assessed for eligible, 9 were excluded due to various reasons (Fig. 1). Finally, 13 eligible studies were adopted for further data extraction [7, 12, 18–28].

Characteristics of included studies

The basic characteristics of all 13 eligible studies in this NMA are listed in Table 1. Overall, 1384 patients with congenital heart disease undergoing surgery were involved. In this NMA, 11 studies were two-arm studies and 2 were three-arm studies.

The average age of patients is 21.2 months and the average weight is 9.3 kg. The majority of the eligible trials were based on randomized controlled trial, while only three were retrospective studies and one was unclear. Moreover, the relationship between each two interventions is plotted in Fig. 2.

Network meta-analysis

As presented by Fig. 3 and Table 2, in term of VT, the MD of drug treatments were lower than that of saline, which indicated that the all the drugs therapies showed better efficacy than saline. But the differences were not obvious statistically except dexmedetomidine. What is worth mentioned is that using fentanyl alone performs to be the worst but still superior to saline (MD = 4.84, 95% CrIs − 2.47 to 13.65). The similar outcomes could also be found in terms of intensive care unit time that the dexmedetomidine showed a statistical advantage compared with saline (MD = 1.26, 95% CrIs 0.11–2.45). When it comes to LOS, mortality and JET (Fig. 4), the drug treatments, such as dexmedetomidine, fentanyl combined with dexmedetomidine and fentanyl alone, all achieved better efficacies than saline except fentanyl in JET (OR = 0.93, 95% CrIs 0.016–30), and the differences of dexmedetomidine in JET (OR = 4.1, 95% CrIs 1.3–17), fentanyl combined with dexmedetomidine (OR = 3.3e+07, 95% CrIs 1.8–5.7e+21) and fentanyl alone (OR = 2.7e+07, 95% CrIs 1.7–4.3e+21) in mortality were statistically significant.

Consistency assessments

In this study, net heat plots (Fig. 5) were used to assess the consistency level. And the outcomes indicated that no significant discrepancy was found among all the outcomes.

Table 1 Basic characteristics of included studies

Author, year, country	Design	Blinding	Disease	Anesthetic maintained drug	Treatment	Dosage	Patients			Outcomes
							n	Age (month)	Male (%)	Weight (kg)
Sun, 2017, China	RCT	Double	VSD, or, ASD	Sevoflurane	DEX	Before: 0.5 µg/kg 10 min + peri: 0.5 µg/kg/h	25	28	48	12.2 ②③
El-Amrousy, 2017, Egypt	RCT	Triple	VSD, ASD, VSD + ASD, AVSD, TOF, PS,	–	Saline	Before: volume-matched	25	30.2	54	12.9
					DEX	Before: 0.5 µg/kg 20 min + post: 0.5 µg/kg/h 48 h	60	17	67	12.4 ①②③④⑤
El-Shmaa, 2016, Egypt	RCT	NR	–	–	Saline	Before: volume-matched	30	18	60	12.6
					DEX	Before: 1 µg/kg 20 min + post: 0.5 µg/kg/h 72 h	30	7.2	43	18.4 ①②③④⑤
Kadam, 2015, India	RCT	NR	TOF	–	Saline	Before: 100 ml + post: 100 ml	30	8.3	60	20.6
					DEX + FEN	Peri: (loading) 1 µg/kg 15 min and (continuous) 0.75 µg/kg/h (dex) and NR (fen) + post: 0.75 µg/kg/h 48 h	47	36	62	11.7 ①②④⑤
Jiang, 2015, China	Retro	NA	CHD, with PAH	Isoflurane	FEN	Peri: 2 µg/kg + post: 2 µg/kg	47	28	57	10.2
					DEX + FEN	Post: (dex) 0.25–0.75 µg/kg/h and (fen): 1.0–1.5 µg/kg/h	77	18	57	8.9 ①②③⑤
Gu, 2015, China	–	NA	ASD, VSD, ASD + VSD, TOF	Sevoflurane	FEN	Post: 1.0–1.5 µg/kg/h	97	20	54	9.4
					DEX	Before: 0.5 µg/kg 10 min + peri: 0.5 µg/kg/h	33	16	–	8.9 ①②
Rajput, 2014, India	RCT	Double	TOF	Sevoflurane	Etomidate	Peri: a bolus dose of 0.3 mg/kg	33	20	–	10.2
					Sufentanil	Peri: (sufentanil) 2 g/kg and (midazolam) 0.2 mg/h (rocuronium) 0.6 mg/h	33	18	–	9.2
Naguib, 2013, US	RCT	Double	TOF, ASD, VSD	Isoflurane	DEX	Peri: (loading) 0.5 µg/kg 10 min and (continuous) 0.5 µg/kg/h + post: 0.5 µg/kg/h	110	33.2	78	10 ①②④
					Saline	Peri: volume-matched	110	32.5	69	10.6
Prasad, 2012, India	RCT	Double	ASD + TAPVC, TOF, VSD, PH	Isoflurane	FEN	Before: fentanyl: 10 µg/kg	16	4	75	5.8 ①②③
					FEN + DEX	Before: fentanyl: 10 µg/kg	15	5	73	6.1
Le, 2011, US	Retro	NA	AS, CAVC, TOF, VSD, ASD	Isoflurane	FEN	Post: 1 µg/kg/h	30	68	57	16.8 ①
					DEX	Post: 0.5 µg/kg/h	30	72.8	50	15.8
Chrysostomou, 2011, Spain	Pro-C	NA	VSD, TOF, etc.	Isoflurane	DEX	Post: 0.3–0.7 µg/kg/h	89	14	–	– ①②③
					FEN	–	180	15	–	–
Hosokawa, 2010, Japan	Pro-O	NA	VSD, ASD, TOF, AVSD	Sevoflurane	DEX	Peri: (loading) 1 µg/kg 15 min and (continuous) 0.5 µg/kg/h + post: 0.1–1.5 µg/kg/h 38 ± 4 h	32	4.8	66	5.3 ②③④⑤
					FEN	–	20	2.6	40	3.9
					FEN	Post: 0.2 µg/kg/h	85	12	48	14.9 ①②
					DEX	Post: 0.4–0.6 µg/kg/h	56	12	48	13.7

Table 1 (continued)

Author, year, country	Design	Blinding	Disease	Anesthetic maintained drug	Treatment	Dosage	Patients				Outcomes	
							<i>n</i>	Age (month)	Male (%)	Weight (kg)		
Tokuhira, 2009, Japan	Retro	NA	Pure pulmonary atresia (mainly)	Sevoflurane	DEX	Post: 0.3–0.4 µg/kg/h	9	16	67	8.2	①②	
					A and S	NR	5	1.8	20	9.3		

NR not reported, NA not applicable, JET junctional ectopic tachycardia, VT time on ventilator, LOS length of stay, CHD congenital heart disease, AS arterial stenosis, Retro retrospective study, Pro-C prospective cohort study, Pro-O prospective observational study, DEX dexmedetomidine, FEN fentanyl, A and S, analgesic and sedative = midazolam + propofol + buprenorphine + pentazocine; Outcomes: ① VT; ② ICU; ③ LOS; ④ JET; ⑤ mortality

Ranking with SUCRA value

The ranking probabilities and SUCRA values of each treatment in terms of each endpoint are illustrated in Table 3. As for the efficacy outcomes, fentanyl combined with dexmedetomidine (0.575) and etomidate (0.589) performed better than other treatments in VT. And fentanyl combined with dexmedetomidine seemed to be the most effective one among others treatments under the endpoints of mortality (0.627). In the point of ICU time, analgesic and sedative showed a great potential to rank in the first place (0.615). As for LOS, dexmedetomidine, fentanyl, and dexmedetomidine combined with fentanyl showed similar efficacy (0.459, 0.482 and 0.497, respectively). Surprisingly, the efficacy of saline seemed to be better than fentanyl in JET. And saline is the worst one under the other efficacy outcomes.

Risk of bias

The comparison adjusted funnel plots in Fig. S1. According to the criteria of bias, no obvious publication bias was found in this NMA.

Discussion

Based on our analysis, in terms of the respective efficacy for different drug therapies, all drugs have been demonstrated to be superior clinical effective compared to saline except fentanyl alone in JET. Fentanyl combined with dexmedetomidine, etomidate and sufentanil appeared to be the preferable drugs when the VT was taken at the first consideration. In terms of ICU time and JET, analgesic and sedative and dexmedetomidine achieved at the leading position, respectively. From the point of LOS, dexmedetomidine, fentanyl combined with dexmedetomidine or not performed no statistical differences with each other and all showed better efficacy than saline. As for mortality, fentanyl combined with dexmedetomidine had optimal efficacy.

Direct comparisons are the best way to evaluate the effectiveness among different drugs. However, due to scare of these head-to-head comparisons, one of the strength way is to enforce the method of NMA. Although various treatments have been assessed in previous MA, many of them just involve few of the treatments. Prasad et al., Le et al., Chrysostomou et al. and Tokuhira et al. all compared the efficacy between fentanyl and dexmedetomidine [18, 22, 24, 26]. However, the endpoints reported in these four studies varied. Prasad et al. only reported VT while Chrysostomou et al. studied the ICU time, LOS, JET and mortality but no VT [18, 26]. Such problem would make it difficult for us to compare the therapeutic effect between fentanyl and

Fig. 2 Evidence network. The width of the lines represents the cumulative number of trials for each comparison; the area of circles stands for the cumulative number of patients for each intervention *VT* time on ventilator (h), *ICU* time in intensive care unit (d), *LOS* length of stay (d), *JET* junctional ectopic tachycardia

dexmedetomidine comprehensively. On the other hand, limited by the design and feasibility, one study tend to investigate only one or two drugs during one period. Sun et al., El-Amrousy et al. and Rajput et al. investigated the efficacy of dexmedetomidine in contrast to saline [19, 27, 28]. Kadam et al., Jiang et al. and Naguib et al. studied the outcomes after using fentanyl alone or fentanyl combined with dexmedetomidine [7, 23, 25]. In this NMA, we combined and analyzed the efficacy of all the frequently used drugs

which were mentioned in previous studies for pediatric patients with congenital heart disease undergoing surgery. All common drugs used to manage postoperative patients with CHD from previous control studies were analyzed in current NMA and the efficacy of them was ranked under the five endpoints (VY, ICU time, LOS, JET and mortality). Through this NMA, it is helpful for us to determine the appropriate choice of drugs for postoperative pediatric patients with CHD from multiple points of view. Thus, this

Fig. 3 Forest plot. Mean differences with 95% CrI showing the relative efficacy of medications under outcome of VT and ICU. VT time on ventilator, ICU Intensive Care Unit

study can be a guideline for the clinical workers when making decision.

However, when it comes to recommending one optimal drug, integrated factors also need to be considered. With respect to the different outcomes, fentanyl combined with dexmedetomidine was one of the recommended drugs due to its shorter time on ventilator and stay in hospital as well as lower mortality. Analgesic and sedative also showed an outstanding performance in terms of decreasing ICU time reducing the incidence of junctional ectopic tachycardia, and even seems better than fentanyl combined with dexmedetomidine. Besides, the investigation about etomidate and sufentanil was also in scarcity. Gu et al. compared dexmedetomidine, etomidate and sufentanil in a study with 3 contrasts included 33 in each group but the design of his study was not reported [21]. Given the decent outcomes of etomidate and sufentanil in this network meta-analysis, more research about these two drugs could be taken into consideration to provide more evidence for the use of etomidate and sufentanil.

However, despite the improvements achieved in this NMA, there are still some limitations in our study. Our study is limited to using VT, ICU time, LOS, JET and mortality as the endpoints. While, not all the studies included in

this NMA have reported all these five results. The lack of specific outcomes values in some original studies makes it difficult to compare all drugs under those endpoints. For example, etomidate and sufentanil and analgesic and sedative were missing under the endpoints of LOS, JET and mortality. Another potential limitation is the doses of the treatments which do not considered in this study. Given small sample size and lack of sufficient raw data, the dosing and timing have not included to analysis. Therefore, the optimal dosing, timing, and duration of different drugs was not available from this NMA. In addition, as for the reliability of NMA, between-study heterogeneity, such as average age, MRI, male ratio, history treatments were also influential. Moreover, since different outcomes were chosen by eligible trials and multiple treatments involved in this NMA, it is hard to compare all treatments under one endpoints and this would increase the consistency. However, according to our analysis, inconsistency was not found in this NMA. All in all, to resolve all the restrictions mentioned above, better-designed RCTs need be conducted.

Overall, based on the comprehensive consideration of efficacy, fentanyl combined with dexmedetomidine was considered the best-recommended clinical interventions among integrated endpoints. Even though this study provides some

Table 2 Mean difference with 95% CrI of VT, ICU and LOS and odds ratio with 95% CrI of JET and mortality according to the network meta-analysis

VT	Analgesic + sedative	0.57 (−2.44, 3.55)	1.26 (−2.38, 4.86)	0.72 (−3.14, 4.6)	0.85 (−2.49, 4.16)	1.83 (−1.38, 5.06)	0.75 (−3.13, 4.6)
	Dexmedetomidine	0.73 (−11.26, 12.5)	0.69 (−1.35, 2.71)	0.14 (−2.33, 2.62)	0.28 (−1.21, 1.74)	1.26 (0.11, 2.45)	0.19 (−2.28, 2.62)
	1.88 (−12.12, 16.93)	1.12 (−6.75, 10.31)	Dexmedetomidine + fentanyl	−0.54 (−3.7, 2.65)	−0.41 (−1.81, 0.99)	0.58 (−1.77, 2.96)	−0.5 (−3.68, 2.7)
	2.31 (−12.54, 17.25)	1.6 (−7.47, 10.65)	0.48 (−12.64, 12.21)	Etomidate	0.13 (−2.76, 3)	1.11 (−1.6, 3.86)	0.04 (−2.37, 2.44)
	−1.31 (−14.24, 12.34)	−2.07 (−7.53, 4.41)	−3.18 (−9.42, 2.67)	−3.66 (−14.05, 7.7)	Fentanyl	0.99 (−0.89, 2.9)	−0.1 (−2.95, 2.79)
LOS	−6.22 (−19.43, 6.62)	−6.92 (−12.54, −1.77)	−8.03 (−19.09, 1.14)	−8.51 (−19.26, 1.82)	−4.84 (−13.65, 2.47)	Saline	−1.07 (−3.83, 1.62)
	1.98 (−13.01, 16.87)	1.27 (−7.84, 10.27)	0.15 (−12.95, 12.03)	−0.34 (−9.43, 8.7)	3.34 (−8.07, 13.76)	8.17 (−2.13, 18.9)	Sufentanil
	Dexmedetomidine	0.23 (−3.56, 4.69)	1.49 (−1.64, 5.41)	1.42 (0.25, 2.85)	JET		
	0.3 (−4.41, 5.13)	Dexmedetomidine + fentanyl	1.26 (−0.92, 3.52)	1.18 (−3.34, 5.29)			
	0.3 (−3.23, 3.99)	0 (−3.18, 3.19)	Fentanyl	−0.07 (−4.11, 3.4)			
Mortality	−2.46 (−5.01, 0.12)	−2.76 (−8.21, 2.57)	−2.76 (−7.27, 1.62)	Saline			
	Dexmedetomidine						
	16 (−0.35, 48.73)	Dexmedetomidine + fentanyl					
	15.8 (−0.37, 48.43)	−0.13 (−2.11, 1.76)	Fentanyl				
	−1.23 (−3.51, 0.79)	−17.3 (−50.09, −0.61)	−17.1 (−49.81, −0.55)	Saline			

The bolded number showed statistically significant results. *Analgesic + sedative*, midazolam + propofol + buprenorphine + pentazocine, *VT* time on ventilator, *ICU* time in ICU, *LOS* length of stay, *JET* junctional ectopic tachycardia

Fig. 4 Forest plot. Mean differences with 95% CrI showing the relative efficacy of medications under outcome of LOS and odd ratios with 95% CrI of mortality and JET. *JET* junctional ectopic tachycardia, *LOS* length of stay

Fig. 5 Heat plot. Net heat plots for different study designs revealing inconsistency between direct and indirect evidence. A sufentanil, B saline, C fentanyl, D etomidate, E dexmedetomidine + fentanyl, F dexmedetomidine, G analgesic + sedative

Table 3 SUCRA values of 7 treatments

Treatments	VT	ICU	LOS	JET	Mortality
Analgesic + sedative	0.431	0.615	–	–	–
Dexmedetomidine	0.485	0.553	0.459	0.593	0.238
Dexmedetomidine + fentanyl	0.575	0.307	0.482	0.517	0.627
Etomidate	0.589	0.473	–	–	–
Fentanyl	0.304	0.455	0.497	0.188	0.598
Saline	0.053	0.135	0.062	0.202	0.036
Sufentanil	0.563	0.463	–	–	–

Top two SUCRA under each endpoint were bolded. *Analgesic + sedative* midazolam + propofol + buprenorphine + pentazocine, *VT* time on ventilator, *ICU* time in ICU, *LOS* length of stay, *JET* junctional ectopic tachycardia

comparison for the efficacy and effectiveness of various drugs, clinicians still need to consider the side effects and safety of the therapy, clinical preference, patients' feature, and disease history to choose the suitable treatments.

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Compliance with ethical standards

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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