

Systematic Review

Effects of Anesthetics on Cardiac Repolarization in Adults: A Network Meta-Analysis of Randomized Clinical Trials

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Abstract

Objectives: Prolongation of cardiac repolarization, especially the heart rate-corrected QT (QTc) interval, is associated with life-threatening dysrhythmias. This study aimed to identify the anesthetic with the lowest risk of prolonging cardiac repolarization and provide guidance for anesthesia management in patients with cardiac diseases or long QT syndrome. **Methods:** Randomized controlled trials (RCTs) comparing the effects of anesthetics on cardiac repolarization indices were searched for in multiple databases. The primary outcome was QTc; and the secondary outcomes were other repolarization indices. A network meta-analysis was conducted using a frequentist approach and registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022304970). **Results:** Thirteen RCTs investigating 953 adults with normal QTc interval and without cardiovascular diseases were included. Direct meta-analyses found that propofol had less influence than sevoflurane (95% confidence interval (CI): 16.10, 33.54) and desflurane (95% CI: 4.85, 35.36), and sevoflurane had less influence than desflurane (95% CI: 6.96, 19.39) on QTc prolongation. Network analysis found that propofol had less influence than sevoflurane (95% CI: 17.78, 29.63), halothane (95% CI: 11.29, 41.24), desflurane (95% CI: 23.79, 39.88), and isoflurane (95% CI: 20.11, 46.10), and sevoflurane had less influence than desflurane (95% CI: 0.43, 15.82) on QTc prolongation. The rank order of cumulative ranking curve analysis was propofol (100%), sevoflurane (63.8%), halothane (49.5%), desflurane (21.1%), and isoflurane (15.6%). The direct meta-analysis found that propofol had less influence than sevoflurane on QT prolongation (95% CI: 23.12, 57.86). Other secondary outcomes showed no conclusive findings. **Conclusions:** This meta-analysis found that propofol had a minimal effect on QTc prolongation, followed by sevoflurane and desflurane in adults with normal QTc interval and without cardiovascular diseases. Propofol is the best anesthetic for adult patients with long QT syndrome or cardiac diseases, but still needs more robust evidence.

Keywords

anesthetics; arrhythmia; network meta-analysis; long QT syndrome; propofol

Introduction

Myocardium repolarization is not homogenous, thus producing a physiological transmural dispersion of repolarization. Prolongation of cardiac repolarization or transmural dispersion of repolarization is the substrate for torsades de pointes, a malignant polymorphic ventricular tachycardia responsible for the presenting symptoms of syncope, aborted cardiac arrest, or sudden death, which are characteristic of hereditary long QT syndromes [1]. Cardiac repolarization prolongation can also be drug-induced. Therefore, identifying drugs that have less effect on cardiac repolarization prolongation is essential for medical care.

These following markers can recognize cardiac repolarization: QT interval, QT interval dispersion (QTD), corrected QTD (QTcD), P-wave dispersion (PWD), Tpeak-Tend (Tp-e) interval, and Tp-e/QT ratio [2–4]. Among them, QT interval is usually used to assess myocardium repolarization. QT interval is measured from the beginning of the QRS complex to the end of the T wave of the electrocardiogram [2]. The QT interval varies primarily with heart rate (HR); thus, an HR-corrected QT (QTc) is often applied.

Anesthetics, such as propofol and sevoflurane, possess arrhythmogenic or antiarrhythmic properties owing to their effects on cardiac electrical activity [5]. Therefore, the effects of anesthetics on the prolongation of cardiac repolarization have received considerable attention since the early 1970s. Many studies have found that nearly all anesthetics increase the QTc interval [6]. Propofol appears to have the most minor effect on QTc prolongation [4,7,8]. Moreover, anesthetics can also potentially prolong QTD, QTcD, PWD, Tp-e interval, and Tp-e/QT ratio [2–4]. Identifying the anesthetic with the lowest risk of prolonging cardiac repolarization is vital for anesthesia management in patients with cardiac diseases or long QT syndrome. Therefore, a network meta-analysis was performed to compare the ef-

fects of different anesthetics on the prolongation of cardiac repolarization markers.

Methods

This meta-analysis was conducted following the Preferred Reporting Items for Systematic Review and Network Meta-analyses (PRISMA-NMA) Statement [9] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42022304970).

Search Strategy

Embase, PubMed, Medline, the Cochrane Library, and ClinicalTrials.gov were comprehensively searched from their inception to the date of the literature search (15 July 2023) by two reviewers independently, without restrictions on language, according to the search strategy provided in **Supplementary Data 1**. Any potentially relevant trials were manually searched based on the references of identified trials and systematic reviews.

Eligibility Criteria

Randomized controlled trials (RCTs) comparing the effects of any two of these six anesthetics (propofol, sevoflurane, enflurane, isoflurane, desflurane, halothane) on QT interval, QTc interval, QTD, QTcD, PWD, Tp-e interval, and Tp-e/QT ratio of adults were included. Studies that intravenous anesthetics were not used for anesthesia maintenance, the maintenance concentration of inhalational anesthetics exceeded two minimum alveolar concentrations, and investigated children were excluded. Moreover, these data had to be extractable or calculable as the variation before and after anesthetic treatment. The primary outcome was QTc calculated according to Bazett's or Fridericia's formula [2], and the other indices were secondary outcomes.

Data Extraction

Two reviewers independently screened the retrieved titles and abstracts for potential inclusion, reviewed the full text of potential studies, and extracted the data from the studies that met the inclusion criteria. Discrepancies were resolved through a discussion with a third reviewer where necessary. The following data were extracted: first author, publication date, sample size, age, sex, details of anesthetics, concomitant drug treatment, type of surgery, inclusion and exclusion criteria for patients, timepoints of data collected, cardiac repolarization indices, and the incidence of dysrhythmia.

Assessment of Methodological Quality

Two reviewers independently assessed the quality of the RCTs based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines. A 'risk of bias' table was created, which included judgments on the method of random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other biases. The quality of RCTs was further quantitatively assessed using a modified Jadad 7-point scale, and a Jadad score ≥ 4 was considered high quality [10]. Therefore, the overall quality of each study was evaluated as 'low' or 'high'. The Grades of Recommendations Assessment Development and Evaluation (GRADE) scale was used to evaluate the strength and level of evidence for recommendations [10].

Statistical Analysis

The mean difference (MD) with 95% confidence intervals (CIs) was used to assess continuous outcomes, and odds ratios with 95% CIs were used to assess dichotomous outcomes. A random-effects model was used throughout the meta-analysis to include the different types of surgery. A direct meta-analysis was performed using Review Manager software version 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The I^2 statistic was used to assess heterogeneity. Generally, I^2 values $\geq 75\%$ indicate considerable heterogeneity, while those $\leq 40\%$ indicate that heterogeneity may not be important [11]. Sensitivity analysis was conducted by omitting one study in turn to investigate the source of the heterogeneity. A network meta-analysis was conducted using frequentist methods with the network package in STATA version 16 (StataCorp LLC, TX, USA). Global inconsistency was assessed using Higgins' model [12]. Local inconsistencies were assessed using the node-splitting method [13]. The rank of anesthetics, which has less effect on the prolongation of QTc, was based on the surface under the cumulative ranking curve (SUCRA). Funnel plots were generated to assess the publication bias. A sensitivity analysis was conducted by excluding studies with ≤ 15 patients in one arm.

Results

Study Selection and Characteristics

A total of 738 studies were identified, of which 696 studies were excluded after reading the titles and abstracts (Fig. 1). Five studies with unavailable full-text and one conference abstract were excluded. After the full text of the remaining 36 articles was read, 23 studies were excluded: two with data unavailable or unextractable, two without relevant outcomes, one that compared the effects of pneu-

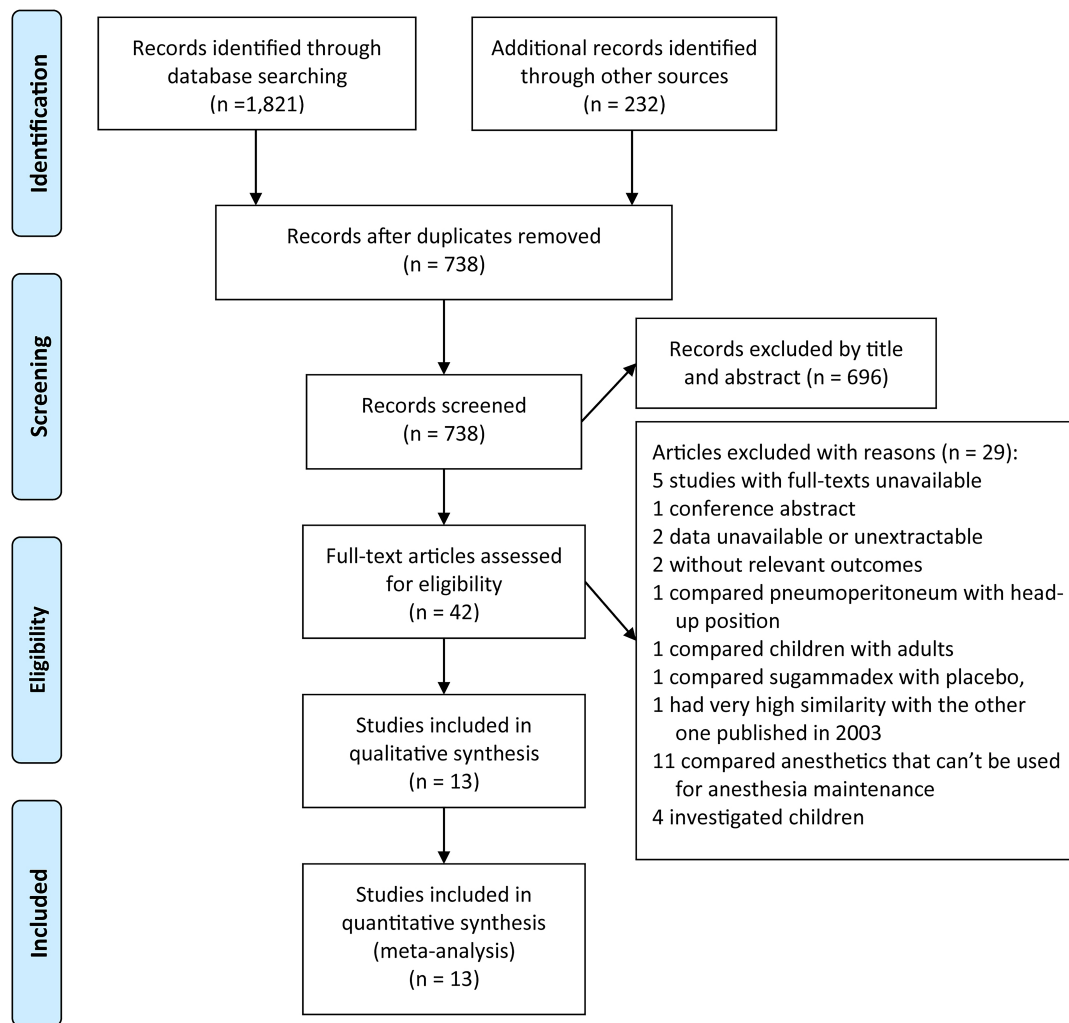


Fig. 1. “PRISMA” flow diagram.

moperitoneum and head-up position on cardiac repolarization, one that compared children with adults, one that compared sugammadex with a placebo, one published in 2010 that was extremely similar to another one published in 2003 [4], 11 compared anesthetics that can’t be used for anesthesia maintenance, and four investigated children. Finally, 13 RCTs [2–4,7,8,14–21] with 953 patients who had no cardiac diseases and long QT syndrome and five anesthetics (propofol, sevoflurane, halothane, desflurane, and isoflurane) were included in the meta-analysis. The basic characteristics of the included studies are summarized in Table 1 (Ref. [2–4,7,8,14–21]).

Risk of Bias Assessment

The quality of each RCT was assessed using the risk of bias and the modified Jadad score (Table 2, Ref. [2–4,7,8,14–21]). Six RCTs [2,4,8,14,16,21] mentioned their randomization procedure using permuted block sizes of 6, a random samples table, or a computer-generated random code generator; the remaining RCTs did not mention how

randomization was performed. Only two [14,16] reported allocation concealment via sealed envelopes. Min *et al.* [16] reported that the vaporizers on the anesthesia machine were covered, and the monitor setting was altered to hide the concentration of the inhalational anesthetic to blind patients and participants. Kim *et al.* [21] described blinding of patients and participants but did not report the details. However, nine studies reported that data analyses were conducted by participants blinded to the groups. Park *et al.* [2] reported one patient each in the sevoflurane and desflurane groups was excluded because necessary data could not be obtained, Min *et al.* [16] reported that seven patients were excluded for incomplete data, and Kim *et al.* [21] reported that no patient was excluded after enrollment. The remaining studies did not report the numbers and reasons for withdrawal and loss of follow-up; thus, we judged that they had an unclear risk of bias of incomplete outcome data. None of the studies had selective outcome reporting or other sources of bias. Finally, only four studies [2,14,16,21] with a modified Jadad score ≥ 4 were considered high-quality.

Table 1. The characteristics of included studies.

ID	Study	Groups	Cases (Male%)	Age (years)	Concomitant drug	Patients	Procedures	Timepoints of data extraction
1	Hanci 2010 [4]	A: propofol 2.5 mg·kg ⁻¹ for induction, 6 mg·kg ⁻¹ ·h ⁻¹ for maintenance B: sevoflurane 7% for induction, 3% for maintenance	36/36 (53/53)	32.9 ± 11/35.4 ± 9.9	Vecuronium 0.1 mg·kg ⁻¹	18–50 years; ASA I–II; without cardiovascular diseases	Elective non-cardiac surgery	T1: before induction T2: 10 after intubation
2	Karagöz 2005 [14]	A: sevoflurane 2% with 66% N ₂ O for maintenance B: halothane 0.8% with 66% N ₂ O for maintenance C: isoflurane 1% with 66% N ₂ O for maintenance	25/25/25 (100/100/100)	33.5 ± 8.2/30.5 ± 8.3/31.1 ± 8.8	Thiopental 5 mg·kg ⁻¹ , fentanyl 1.5 µg·kg ⁻¹ , vecuronium 0.1 mg·kg ⁻¹	Male; ASA I–II; without cardiovascular diseases or QTc >440 ms	Inguinal herniorrhaphy	T1: before induction T2: 10 min after the start of surgery
3	Kim 2022 [21]	A: desflurane 3–7% B: TCI of propofol	60/60 (63/70)	58 ± 10/58 ± 8	Sufentanil 0.1 mg·kg ⁻¹ , rocuronium 0.6 mg·kg ⁻¹	Aged ≥20 years; ASA III–IV; without cardiovascular diseases	Living donor liver transplantation	T1: before induction T2: 30 min after induction
4	Kleinsasser 2000 [7]	A: propofol 2.5 mg·kg ⁻¹ for induction, 6 mg·kg ⁻¹ ·h ⁻¹ for maintenance B: sevoflurane 6% for induction, 2.5% for maintenance	15/15 (0/0)	37.6 ± 3/36.3 ± 2	NM	Female; ASA I–II; without cardiovascular diseases or QTc >440 ms	Elective gynecological surgery	T1: before induction T2: 20 min after induction
5	Kuenszberg 2000 [15]	A: propofol 2.5 mg·kg ⁻¹ for induction, 6 mg·kg ⁻¹ ·h ⁻¹ for maintenance B: sevoflurane 5% for induction, 2% for maintenance	18/18 (0/0)	NM	NM	Female patients; ASA I–II; without cardiovascular diseases or QTc >440 ms	Gynaecological surgery	T1: before induction T2: 10 min after induction
6	Liu 2019 [8]	A: TCI of propofol 4 µg·mL ⁻¹ and was sustained for 5 min B: 8% sevoflurane was applied to reached 1.3 MAC and sustained for 6 min	60/60 (NM)	37 ± 8/37 ± 8	NM	20–50 years; ASA I–II; normal preoperative cardiopulmonary function, ECG, and electrolyte state; QTc <440 ms	Gynaecological laparoscopic operation	T1: before induction T2: 5 or 6 min after the maintenance of anesthesia
7	Min 2016 [16]	A: sevoflurane 1 MAC for maintenance B: desflurane 1 MAC for maintenance	22/21 (68/81)	52 ± 7/52 ± 10	Lidocaine 40 mg, propofol 2 mg·kg ⁻¹ , rocuronium 0.6 mg·kg ⁻¹	18–65 years; without cardiac arrhythmias	Living-donor liver transplantation	T1: before induction T2: 10 min after intubation

Table 1. Continued.

ID	Study	Groups	Cases (Male%)	Age (years)	Concomitant drug	Patients	Procedures	Timepoints of data extraction
8	Park 2020 [2]	A: propofol 4.0–4.5 $\mu\text{g}\cdot\text{mL}^{-1}$ and remifentanyl 4.0 $\text{ng}\cdot\text{mL}^{-1}$ for induction, TCI of propofol and remifentanyl for maintenance B: propofol 1.5–2 $\text{mg}\cdot\text{kg}^{-1}$ and TCI of remifentanyl 4.0 $\text{ng}\cdot\text{mL}^{-1}$ for induction, 0.8–1 MAC sevoflurane for maintenance C: propofol 1.5–2 $\text{mg}\cdot\text{kg}^{-1}$ and TCI of remifentanyl 4.0 $\text{ng}\cdot\text{mL}^{-1}$ for induction, 0.8–1 MAC desflurane for maintenance	23/22/22 (NM)	67.3 \pm 5.6/64.0 \pm 6.3/66.1 \pm 6.3	Rocuronium $\text{mg}\cdot\text{kg}^{-1}$	1.2 \geq 19 years, ASA I–III; without cardiovascular diseases or QTc >450 ms	Robot-assisted laparoscopic prostatectomy	T1: before induction T2: 10 min after intubation
9	Paventi 2001 [17]	A: propofol 2.5 $\text{mg}\cdot\text{kg}^{-1}$ for induction, 6 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance B: sevoflurane 6% for induction, 2.2% for maintenance	90/90 (NM)	36.9 \pm 4/35.7 \pm 5	Vecuronium $\text{mg}\cdot\text{kg}^{-1}$	0.1 ASA I–III; without cardiovascular diseases or QTc \geq 440 ms	Elective non cardiac surgery	T1: before induction T2: immediately after intubation
10	Schmeling 1991 [18]	A: halothane inhalation induction and 1–2 MAC for maintenance 25–30 min B: isoflurane inhalation induction and 1–2 MAC for maintenance 25–30 min	6/8/8 (100/100/100)	46.2 \pm 4.7/52.8 \pm 3.6/50.1 \pm 4.9	NM	Male; ASA I–II; no history of cardiac disease; receiving no medications known to affect the cardiovascular system	Elective surgery	T1: before induction T2: 30 min after induction
11	Sen 2004 [19]	A: propofol 2 $\text{mg}\cdot\text{kg}^{-1}$ for induction, 6 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ for maintenance B: sevoflurane 5% for induction, 1–1.5% for maintenance	22/22 (0/0)	31.1 \pm 6.2/31.5 \pm 6.1	Vecuronium 0.1 $\text{mg}\cdot\text{kg}^{-1}$	Female patients; ASA I-II; without cardiovascular diseases or QTc \geq 440 ms	Elective gynaecological laparoscopic surgery	T1: before induction T2: 10 min after the start of surgery
12	Silay 2005 [3]	A: sevoflurane from 0.5% to 5% for induction, 2 MAC for maintenance B: desflurane from 2% to 18% for induction, 2 MAC for maintenance	30/30 (50/53)	33.4 \pm 10.8/32.6 \pm 11.8	NM	16–50 years; ASA I-II; without cardiovascular problems	NM	T1: before induction T2: 3 min after intubation
13	Yildirim 2004 [20]	A: sevoflurane 2% B: isoflurane 1.2% C: desflurane 6%	30/30/ 30 (NM)	NM	Vecuronium 0.1 $\text{mg}\cdot\text{kg}^{-1}$	16–50 years; ASA I; without cardiovascular diseases or QTc \geq 440 ms	Elective non-cardiac surgery	T1: before induction T2: 10 min after reaching steady state end-tidal concentration

N₂O, nitrous oxide; NM, not mentioned; ASA, American Society of Anesthesiologists physical status; QTc, heart rate-corrected QT; ECG, electrocardiogram; MAC, minimum alveolar concentration; BMI, body mass index; TCI, target-controlled infusion.

Table 2. The quality assessment of RCTs was based on the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions and the modified Jadad 7-point scale.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	No selective outcome reporting	Other source of bias	Jadad score	Quality
Hanci 2010 [4]	✓	?	–	✓	–	✓	✓	3	Low
Karagöz 2005 [14]	✓	✓	–	✓	–	✓	✓	5	High
Kim 2022 [21]	✓	?	✓	?	✓	✓	✓	4	High
Kleinsasser 2000 [7]	?	?	–	✓	–	✓	✓	2	Low
Kuenszberg 2000 [15]	?	?	–	✓	–	✓	✓	2	Low
Liu 2019 [8]	✓	?	–	?	–	✓	✓	3	Low
Min 2016 [16]	✓	✓	✓	✓	✓	✓	✓	7	High
Park 2020 [2]	✓	?	–	✓	✓	✓	✓	4	High
Paventi 2001 [17]	?	?	–	✓	–	✓	✓	2	Low
Schmeling 1991 [18]	?	?	–	?	–	✓	✓	2	Low
Sen 2004 [19]	?	?	–	?	–	✓	✓	2	Low
Silay 2005 [3]	?	?	–	✓	–	✓	✓	2	Low
Yildirim 2004 [20]	?	?	–	✓	–	✓	✓	2	Low

✓, low risk of bias; ?, unclear risk of bias; –, high risk of bias. RCT, Randomized controlled trials.

Heart Rate-Corrected QT (QTc)

Direct meta-analyses found that propofol had less influence than sevoflurane (MD = 24.82, 95% CI: 16.10, 33.54) and desflurane (MD = 20.10, 95% CI: 4.85, 35.36), sevoflurane had less influence than desflurane (MD = 13.17, 95% CI: 6.96, 19.39), sevoflurane (MD = 10.11, 95% CI: –1.01, 21.23) and halothane (MD = 5.92, 95% CI: –1.83, 13.67) had similar effect with isoflurane on QTc prolongation (Fig. 2). No heterogeneity ($I^2 = 0\%$) between sevoflurane and desflurane was detected, but a significant heterogeneity ($I^2 = 89\%$) between propofol and sevoflurane was found, and it greatly reduced to 39% when the study of Paventi *et al.* [17] was omitted (**Supplementary Data 2**), indicating the heterogeneity between propofol and sevoflurane came from the study of Paventi *et al.* [17]. Sensitivity analysis found that significant differences between propofol and sevoflurane and between sevoflurane and desflurane still existed when one study was omitted in turn (**Supplementary Data 2**). Other comparisons could not perform sensitivity analysis due to a lack of studies.

The network geometry (Fig. 3) of the studies revealed the effect of anesthetics on QTc prolongation. Network analysis (Fig. 4) found that propofol had less influence than sevoflurane (MD = 23.71, 95% CI: 17.78, 29.63), halothane (MD = 26.27, 95% CI: 11.29, 41.24), desflurane (MD = 31.84, 95% CI: 23.79, 39.88), and isoflurane (MD = 33.11, 95% CI: 20.11, 46.10), and sevoflurane had less influence than desflurane (MD = 8.13, 95% CI: 0.43, 15.82) on QTc prolongation. Other pairwise comparisons showed no significant differences. Moreover, global inconsistency ($p = 0.38$) and local inconsistency (**Supplementary Data 3**) were insignificant. SUCRA analysis (Fig. 5) showed that propofol had the highest cumulative rank (SUCRA 100%),

followed by sevoflurane (63.8%), halothane (49.5%), desflurane (21.1%), and isoflurane (15.6%), and which means that propofol had the minimal effect on QTc prolongation. However, the asymmetry of the funnel plot indicated a small study effect (Fig. 6).

Sensitivity analysis was conducted by omitting the study of Paventi *et al.* [17], which was the source of heterogeneity between propofol and sevoflurane, or studies that had patients ≤ 15 in one arm. When the study by Paventi *et al.* [17] or Schmeling *et al.* [18] was omitted, the significant differences between propofol and sevoflurane (MD = 19.15, 95% CI: 12.68, 25.62 or MD = 23.67, 95% CI: 17.69, 29.66), between propofol and desflurane (MD = 27.63, 95% CI: 17.22, 38.04 or MD = 31.95, 95% CI: 23.81, 40.08), and between sevoflurane and desflurane (MD = 8.48, 95% CI: 2.42, 14.55 or MD = 8.27, 95% CI: 0.50, 16.05) still existed (data not shown), and the cumulative rank order of SUCRA analysis had no alteration (data not shown).

Other Cardiac Repolarization Indices

The number of studies reporting other cardiac repolarization indices was too little to perform any network meta-analysis, and only some direct meta-analyses were conducted. Four studies [4,7,8,17] compared the effects of sevoflurane with those of propofol on QT, and a direct meta-analysis found that propofol had less influence than sevoflurane on QT prolongation (MD = 40.49, 95% CI: 23.12, 57.86; **Supplementary Data 4**). Moreover, this significant difference existed when one study was omitted from the sensitivity analysis (data not shown). Two studies [2,8] compared the effects of sevoflurane with those of propofol on Tp-e and Tp-e/QT ratio, and direct meta-analyses found that sevoflurane had less effect on Tp-e (MD

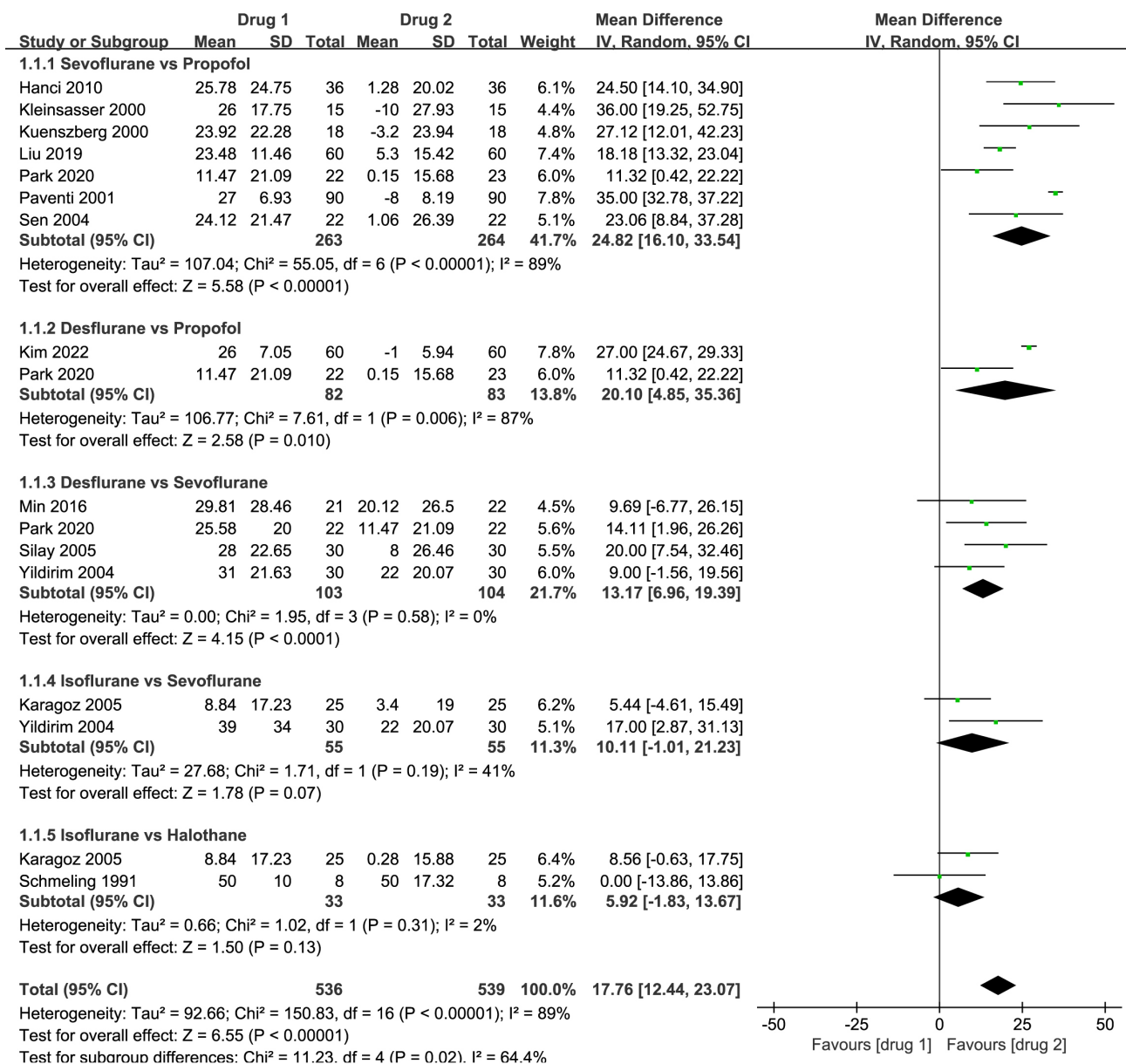


Fig. 2. Forest plots of the direct meta-analysis of the effects of anesthetics on QTc prolongation. QTc, heart rate-corrected QT; SD, standard deviation; CI, confidence interval; IV, inverse variance.

= -3.12, 95% CI: -5.77, -0.48) and Tp-e/QT ratio (MD = -0.02, 95% CI: -0.04, 0.00; **Supplementary Data 4**). The indices of QTD, QTcD, and PWD were unable to perform direct meta-analyses.

Incidence of Dysrhythmia

Three studies investigated the incidence of dysrhythmia: two [3,4] reported no occurrence of dysrhythmia, and the remaining one [17] found that two patients in the propofol group developed a short run of three monomorphic ventricular ectopic contractions. However, no intergroup difference existed between propofol and sevoflurane. Therefore, more data was needed for direct or network meta-analysis.

GRADE Assessment

The GRADE rating results are shown in **Supplementary Data 5**. According to the GRADE system, the strength of the evidence of QTc prolongation was moderate for sevoflurane vs. propofol, desflurane vs. propofol, desflurane vs. sevoflurane; QT prolongation was low for sevoflurane vs. propofol.

Discussion

To our knowledge, this is the first meta-analysis to address anesthetics for cardiac repolarization. Both direct and network meta-analyses found that propofol had less influ-

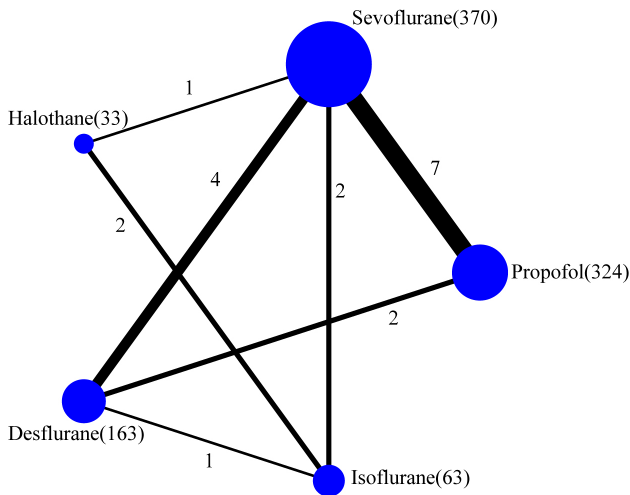


Fig. 3. Network geometry plot of anesthetics based on their effect on QTc prolongation. The size of the nodes is proportional to the number of patients (parentheses). The thickness of the lines connecting the nodes is proportional to the number of trials. QTc, heart rate-corrected QT.

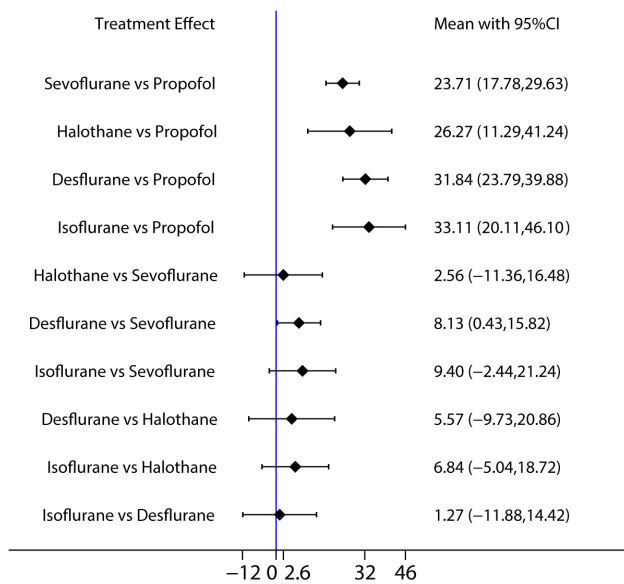


Fig. 4. Forest plots of the network meta-analysis of the effects of anesthetics on QTc prolongation. QTc, heart rate-corrected QT; CI, confidence interval.

ence than sevoflurane and desflurane, and sevoflurane had less influence than desflurane on QTc prolongation. The differences between halothane with other anesthetics and isoflurane with other anesthetics on QTc prolongation were inconclusive for lack of sufficient evidence. In addition, a direct meta-analysis found that propofol had less influence than sevoflurane on QT prolongation. Taken together, our data demonstrated that propofol had a minimal effect on QTc prolongation, followed by sevoflurane and desflurane.

Since cardiac repolarization is developmentally changed with growth and heart rate in children is very different from that in adults; thus, this study only included RCTs that investigated adults. However, our results were the same as those data in children that propofol had less influence than sevoflurane and sevoflurane had less influence than desflurane on QTc prolongation [1,22,23], indicating these results are also applicable in children.

Furthermore, we assessed the effects of anesthetics on other cardiac repolarization indices that predispose patients to cardiac dysrhythmias. Tp-e index, the interval from the peak of the T wave to the end of the T wave, is an indicator of transmural dispersion of repolarization. Thus, some studies reported its prolongation could better predict ventricular arrhythmias, such as torsades de pointes [24,25]. HR influences Tp-e; therefore, the Tp-e/QT ratio, which is less dependent on HR, has been utilized to assess cardiac repolarization [25]. Tp-e interval >117 ms or Tp-e/QT ratio >0.28 are strongly associated with the risk of torsades de pointes [24,25]. Although our direct meta-analyses found that sevoflurane had less effect on Tp-e and Tp-e/QT ratio than propofol, which was contrary to the result of QTc or QT prolongation, the 95% CIs of Tp-e and Tp-e/QT ratio were close to zero and had no clinical significance, and the sample size was too small. Moreover, two studies [1,23] found no differences in children's Tp-e intervals and Tp-e/QT ratio detected between sevoflurane and propofol. Therefore, these data indicate that propofol and sevoflurane had no difference in the prolongation of Tp-e intervals and Tp-e/QT ratio.

QTD, the difference between the maximum and minimum QT intervals, is considered an index of left ventricular repolarization inhomogeneity [26]. Increased QTD or QTcD is a sign of heterogeneous repolarization and possible arrhythmogenic re-entry [27]. Yildirim *et al.* [20] found that sevoflurane, isoflurane, and desflurane significantly increased QTD and QTcD, while Silay *et al.* [3] found that sevoflurane and desflurane did not influence QTD prolongation. PWD is the difference between the maximum and minimum P-wave duration, and prolongation is accepted as an independent predictor of atrial arrhythmias, such as atrial flutter or fibrillation [28,29]. Hanci *et al.* [4] found that sevoflurane significantly increased PWD compared to propofol. Owczuk *et al.* [5] found that desflurane had no influence on PWD, but propofol decreased it. However, the effects of anesthetics on QTD and PWD could not be defined by this meta-analysis due to a lack of studies.

Although inhalational anesthetics significantly increased the QTc interval, no dysrhythmia was reported during anesthesia with inhalational anesthetics in the studies included this meta-analysis. Some RCTs [17,26,30–33] reported that transient dysrhythmias, such as supraventricular arrhythmia, ventricular arrhythmias, and idioventricular rhythm, were detected in the treatment of anesthetics including propofol, thiamylal, thiopentone, sevoflurane,

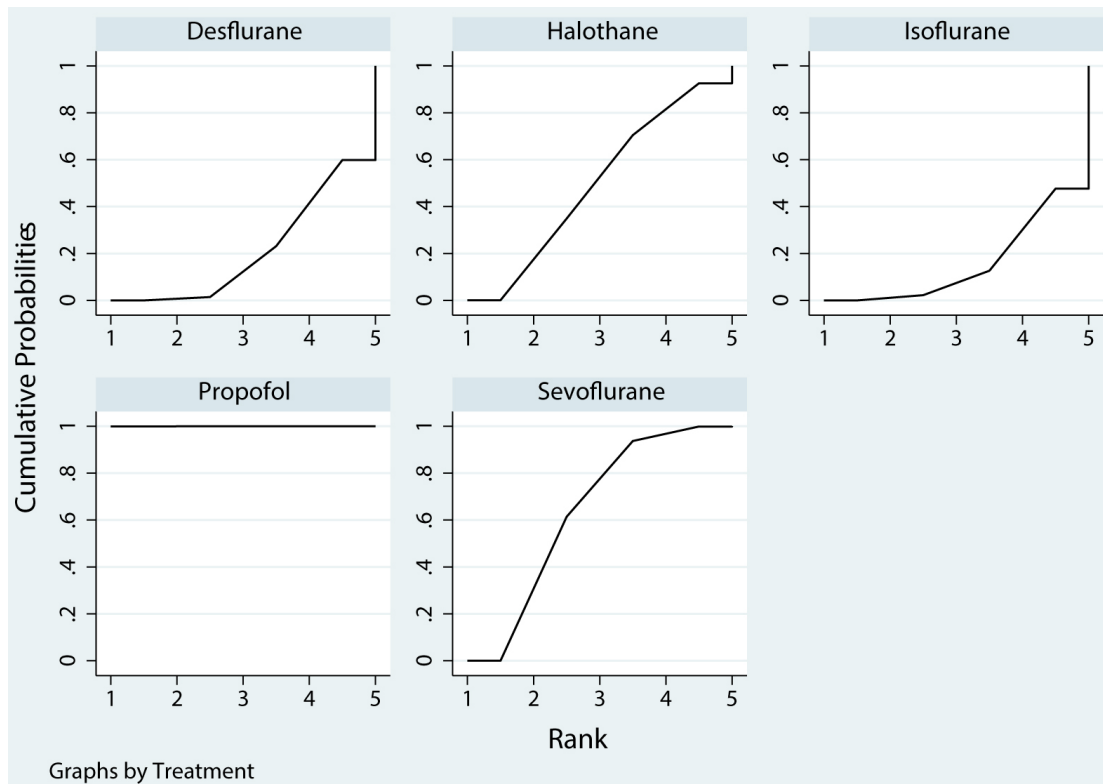


Fig. 5. Surface under the cumulative ranking curve analysis (SUCRA) graphs for the effects of anesthetics on QTc prolongation. QTc, heart rate-corrected QT.

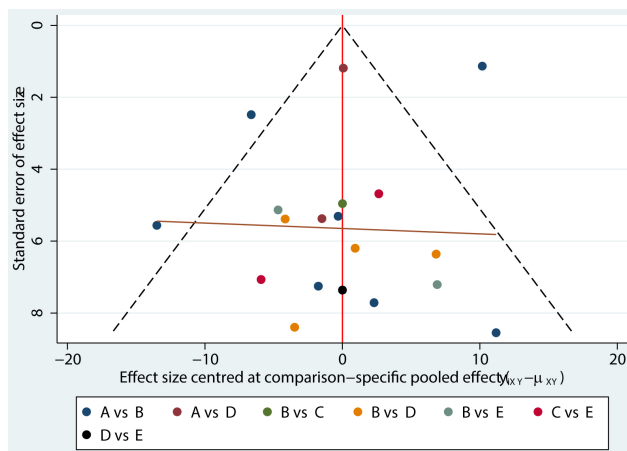


Fig. 6. Comparison-adjusted funnel plot of the effects of anesthetics on QTc prolongation. A, B, C, D, and E correspond to propofol, sevoflurane, halothane, desflurane, and isoflurane, respectively. QTc, heart rate-corrected QT.

isoflurane, and halothane, but no intergroup differences were reported. This might have occurred because all the RCTs investigated adult patients with normal QTc interval and no cardiovascular diseases. However, torsade de pointes and the need for defibrillation did occur in a patient with no relevant medical history [34] and usually occurred in patients with long QT syndrome when receiving sevoflu-

rane [35–37]. In addition, torsade de pointes also occurred in a patient with chronic atrial flutter/fibrillation and normal QT interval during sevoflurane anesthesia [38]. Taken together, these results indicate that the effects of inhalational anesthetics on QTc prolongation may trigger lethal dysrhythmia, especially in patients with long QTc intervals or cardiac diseases. Therefore, we recommend the avoidance of volatile agents and the use of propofol for anesthetic management in patients with long QT syndrome or cardiac diseases.

Cardiac repolarization is affected by the efflux of potassium (K^+) ions through slowly activating (iK_s) and rapidly activating (iK_r) delayed rectifier K^+ channels during phases 2 and 3 of the electrical cardiac cycle [1]. Small inward fluxes of sodium ions partially counter the outward flow of current through late-activating sodium channels and the activity of the sodium-calcium exchanger pump. The outward and inward flow balance through these ion channels determines the repolarization duration. Volatile anesthetics are known to inhibit iK current. However, each volatile anesthetic affects the iK_r and iK_s channels differently, resulting in varying degrees of QT prolongation. Suzuki *et al.* [39] found that isoflurane at clinical concentration inhibited iK_s by approximately 80% while iK_r by 20%, and Park *et al.* [40] found that 5.3% desflurane depressed the iK_s current by about 70% in guinea pig ventricular muscles. In contrast, the propofol concentrations re-

quired for iK suppression were higher than those currently used in clinical scenarios [41]. Therefore, volatile agents at clinic concentrations can prolong QT interval compared with propofol.

However, this study had some limitations. First, the sample size is small and a publication bias might have been present in this network meta-analysis. To minimize this risk, we attempted to search systematically and include unpublished studies, but no additional trials were available for data extraction. Second, most of the included RCTs did not mention how to perform randomization, allocation concealment, and blind patients and participants, and did not report the numbers and reasons for withdrawal and loss of follow-up, which led to a high risk of bias in this meta-analysis. The third limitation was some unaccountable confounding factors, such as different doses or concentrations of anesthetics, observational times after anesthetic treatment, adjuvants, genders, and a great range of ages due to a lack of data. These limitations decreased the overall validity of this meta-analysis.

Conclusions

Overall, our meta-analysis found that propofol had a minimal effect on QTc prolongation, followed by sevoflurane and desflurane in adult patients with normal QTc intervals and without cardiovascular diseases. Propofol is currently the best anesthetic for patients with long QT syndrome currently but still needs more robust evidence considering the confounding factors, publication bias, and small sample size in this study.

Abbreviations

RCT, randomized controlled trials; HR, heart rate; QTc, HR-corrected QT; QTD, QT interval dispersion; QTcD, corrected QTD; PWD, P-wave dispersion; Tp-e, Tpeak–Tend; GRADE, the Grades of Recommendations Assessment Development and Evaluation; MD, mean difference; CI, confidence interval; SUCRA, the surface under the cumulative ranking curve.

Availability of Data and Materials

The data and materials used to support the findings of this study are included in the article.

Author Contributions

BC designed the trial. BC, YC and ZY were responsible for the data extraction, data analysis and writing of the

manuscript. HO and YD are responsible for the production of pictures and tables. HH provides methodological support and read the full text and provided comments. HO, YD and HH also designed the work and interpreted the data. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at <https://doi.org/10.59958/hsf.6969>.

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