REVIEW ARTICLE

The safety of immediate extubation, and factors associated with delayed extubation, in cardiac surgical patients receiving fast-track cardiac anesthesia: An integrative review

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Background: Early extubation (EE), within 8 h of cardiac surgery, is associated with improved resource utilization. Studies have demonstrated that for patients receiving low-dose, fast-track opioid cardiac anesthesia (FTCA) protocols, EE is as safe as conventional care. To date, it is unclear when the earliest timepoints for safe extubation might be. Additionally, some authors pointed out that certain patients receiving FTCA protocols frequently experience delays during extubation attempts. Understanding the factors associated with delayed extubation is crucial for perioperative planning and resource management. This review seeks to 1) determine whether immediate extubation (IE) in the operating room is as safe as EE and 2) identify factors associated with delayed extubation.

Methods: MEDLINE, Cochrane Library, EMBASE and CINAHL (up to March 2022) were searched. Studies pertaining to FTCA, IE, EE or factors associated with delayed extubation were included. All authors extracted, appraised and synthesized data. The primary outcome measures were treatment results and factors associated with delayed extubation.

Results: Six studies investigated treatment outcomes associated with FTCA and IE. One randomized controlled trial reported that outcomes associated with IE were comparable to those with EE. Five observational studies reported incidence for 19 treatment outcomes associated with IE, but no comparisons were made to EE. Six observational studies assessed pre- and intraoperative factors associated with delayed extubation in FTCA patients. In at least one study, 37 factors were investigated and 22 were identified. The most frequently reported factors were pre-existing cardiac insufficiency or renal disease, time on pump and cross-clamp time. Obesity and stroke were investigated but were not associated with delayed extubation. No study examined the influence of race, ethnicity or gender on outcomes.

Discussion and conclusion: Evidence pertaining to treatment outcomes associated with FTCA and IE is weak. Observational studies cannot determine causation. Large multicentre randomized control trials are required to determine the safety of IE. Although numerous factors have been associated with delayed extubation, several studies do not describe how or which factors were selected for examination. Therefore, certain factors may have yet to be evaluated. Future studies should comprehensively define all factors under investigation.

Key Words: *airway extubation; anesthesia; cardiac surgical procedures; coronary artery bypass; early extubation; health resources*

INTRODUCTION

Early extubation following cardiac surgery

Fast-track cardiac care (FTCC) involves the use of low-dose opioid-based general anesthesia and/or time-directed extubation protocols to facilitate safe early extubation (EE) (ie, within 8 h postcardiac surgery). These protocols were developed to address resource demands associated with an increase in the number of cardiac surgeries [1]. The proposed advantages of FTCC include reduced hospital and intensive care unit (ICU) lengths of stay (LOS) and lower hospital costs [1]. Low-dose opioid-based general anesthesia protocols, also called fast-track cardiac anesthesia (FTCA), is an approach to FTCC and typically includes the use of opioids (≤20 μg/kg fentanyl or equivalent) along with sedative-hypnotics such as midazolam with the goal of earlier emergence from anesthesia. Time-directed extubation protocols often accompany FTCA and are generally based on expert consensus and have broad parameters [2]. EE has been arbitrarily defined as occurring within 8 h of cardiac surgery completion (skin closure); however, a rationale for this time parameter has not been provided [3].

The authors of a recent Cochrane review synthesized 19 randomized controlled trials (RCTs) (*n*=2834) comparing FTCA to conventional care in cardiac surgery patients [3]. Conventional care was defined as using high-dose opioid anesthesia (≥20 μg/kg fentanyl or equivalent) and extubation greater than 8 h postsurgery in patients undergoing cardiac surgery (eg, coronary artery bypass graft, aortic valve replacement, mitral valve replacement) [3]. This review, which included studies before May 2015, demonstrated that EE under a FTCA protocol appeared as safe as conventional care regarding the risk of mortality and major postoperative complications such as myocardial infarction, stroke, tracheal reintubation, postoperative renal failure, postoperative risk of major bleeding

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or postoperative mortality. This study demonstrated significantly reduced times to extubation (mean difference –7.40 h, 14 studies) and reduced ICU LOS (mean difference –3.70 h, 12 studies) in the FTCA group. Despite a low level of evidence across studies, these authors concluded that the outcome risks were similar between groups, but the resource demands (eg, shortened ICU LOS) were reduced with FTCA.

Although the review demonstrated the safety of EE with FTCA protocols, identifying the earliest time point for safe extubation may be further advantageous. For example, reductions in ICU LOS or eliminating the need for ICU care may lead to higher patient throughput and shorter surgical wait times. Of the 19 included studies in the Cochrane review, only one described treatment outcomes in patients who were immediately extubated following surgery (following skin closure in the operating room) and reported that treatment outcomes associated with FTCA and immediate extubation (IE) were the same as those associated with conventional care. A synthesis of studies examining the safety of IE may help determine whether it is feasible to do after cardiac surgery.

Factors associated with delayed extubation in patients receiving FTCA protocols

Similarly, FTCA protocols are not always successful in achieving the goal of EE. In two studies, a significant proportion of patients receiving FTCA protocols (11% [4] and 16% [5]) experienced delayed extubation. Patients with delayed extubation have longer LOSs, consume additional resources [4, 6] and have higher mortality rates [7]. Understanding pre-existing and intraoperative factors that may predict delays in extubation are essential to treatment planning and resource management (eg, predicting the need for ICU care) [4].

Although prior studies [4, 5] have sought to establish prediction models for delays in EE, most studies have used data from a wide array of cardiac procedures to construct their model. Furthermore, models to date have primarily been constructed from outcomes measured in single centres and may lack generalizability. As several studies have sought to define factors associated with delayed EE, synthesizing these studies may support the development of more holistic predictive models.

This review aims to address two related questions: 1) What is the evidence regarding the safety of IE in patients receiving a FTCA protocol for cardiac surgery? and 2) In adult patients receiving FTCA protocols for cardiac surgery, which pre-existing and intraoperative factors may be associated with delayed extubation?

METHODS

Data sources and search strategies

This integrative review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8]. We used an integrative review methodology, because we identified diverse methodologies (eg, RCTs and observational studies) used in studies pertaining to the research questions that would not benefit from combining in a systematic review [9, 10]. Four electronic databases (PubMed, CINAHL, Cochrane Library and EMBASE) were searched from inception till March 2022. No restrictions on language, publication date, study location, type or size were applied.

Systematic literature searches were guided, in part, by the search strategy from the Cochrane review [3]. The following search terms were used across databases for research questions 1 and 2: cardiac surgery, coronary artery bypass, valve replacement, EE, IE and ultrafast-track. The complete search strategy for PubMed is provided in Appendix 1.[1]

Study selection criteria

Research question 1: What is the evidence regarding the safety of IE in patients receiving a FTCA protocol for cardiac surgery?

We included studies that met the following inclusion criteria: 1) study population and intervention: adult patients undergoing cardiac surgery (coronary artery bypass graft, valve replacement or both) with or without cardiopulmonary bypass and irrespective of severity of disease; IE in patients receiving a FTCA protocol (fentanyl ≤20 µg/kg or equivalent) [11] with or without supplemental propofol, etomidate or volatile anesthesia; with a protocol for confirming readiness for IE within the operating room; 2) comparator or control group: no comparison or studies that compared the use of FTCA versus conventional anesthesia (fentanyl >20 µg/kg or equivalent); 3) treatment outcomes: service outcomes and other postoperative complications, including but not limited to mortality, risk of postoperative reintubation, myocardial infarction, stroke, acute renal failure, major bleeding, sepsis, wound infection, extended ICU or hospital LOS; 4) study design: RCT, nonrandomized studies, observational studies; and 5) language: no restrictions.

Research question 2: In patients receiving FTCA protocols for cardiac surgery, which pre-existing and intraoperative factors may be associated with delayed extubation?

We included studies that met the following inclusion criteria: 1) study population and intervention: adult patients undergoing coronary artery bypass graft surgery and/or valve replacement with or without cardiopulmonary bypass and irrespective of the severity of disease; extubation in patients receiving a FTCA protocol (fentanyl ≤20 µg/kg or equivalent) [11] with or without supplemental propofol, etomidate, or volatile anesthesia; with a protocol for confirming readiness for extubation; 2) comparator or control group: no comparison or studies that compared the use of FTCA versus conventional anesthesia (fentanyl>20 µg/kg or equivalent); 3) outcomes: pre-existing or intraoperative factors associated with delayed extubation; 4) study design: observational studies; and 5) language: no restrictions.

Studies that defined EE as greater than 8 h postsurgery were excluded. We also excluded studies with remifentanil for both research questions because of its short half-life and because it does not accumulate with prolonged administration compared to fentanyl [12]. Studies that examined remifentanil or major regional blockades (epidural or intrathecal) or compared hypothermia or normothermia during cardiac surgery have been reviewed previously and were excluded [13, 14].

Because this work was a learning initiative, all steps of the integrative review were done collaboratively. That is, every decision was made through full group consensus. All authors screened titles and abstracts of all identified studies using the selection criteria defined above. For studies that satisfied the selection criteria, full texts were retrieved for review. Reference lists of included studies were hand-searched for relevant papers. All authors contributed to all components of the review and achieved consensus through discussion.

Data extraction

All authors collaboratively extracted the following data from each study using a standardized form: study design; geographic location; year of study; sample size; age and sex of participants; time to extubation; type of surgery; anesthetic protocol; and outcome measures. To ensure that no single voice dominated the discussion, every author participated equally in this process.

Risk of bias assessment

Authors collaboratively assessed the risk of bias in included studies using tools developed by the Joanna Briggs Institute: Checklist for Randomized Controlled Trials [15]; Checklist for Case Series [16]; and Checklist for Case Control Studies [17]. Heterogeneity because of variations in study designs and outcome measures prohibited meta-analysis. As above, all authors contributed equally during analysis and decision-making pertaining to risk of bias.

RESULTS

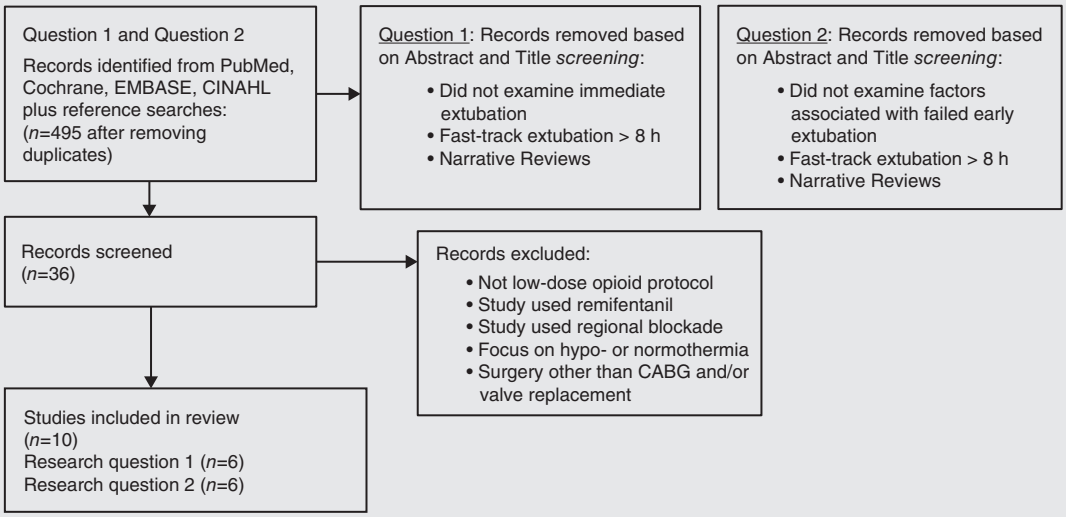
Search results

A total of 495 unique studies pertaining to either question 1 or 2 were identified (Figure 1). Two additional studies were located through hand searching the reference list of the included papers. A total of 485 studies

[1]Supplementary materials are available at https://www.cjrt.ca/wp-content/uploads/Supplement-cjrt-2022-037.docx

FIGURE 1

Systematic literature search. CABG, coronary artery bypass graft.



were excluded following a review of titles, abstracts or full texts. Six studies met the criteria for research question 1 [18–23], and six studies met the criteria for research question 2 [6, 20, 21, 24–26]. Two studies were relevant to both research questions [20, 21].

Characteristics of included studies

Research Question 1: What is the evidence regarding the safety of IE in patients receiving a FTCA protocol for cardiac surgery?

This review included one RCT [22] and five case series [18–21, 23]. Studies were published between 2000 and 2018 (Table 1). There were 2109 subjects across the six studies. In the RCT, there were 52 subjects with 26 subjects in the intervention arm (IE) and 26 subjects in the conventional care arm [22]. A total of 2057 subjects participated in the observational studies [18–21, 23]. The percentage of females in the IE groups was 26.4% (one study [23] did not report sex). The mean age of subjects in the IE group was 56.9±9.4 years (one study [19] did not report age). The single RCT was of low methodological quality [22]. Although observational studies included in this review followed most design expectations, the design was not the most appropriate to the research question. Therefore, all included studies were at high risk of bias and the level of evidence was low (Table 2).

Service and treatment outcomes associated with IE

The purpose of research question 1 was to investigate service and treatment outcomes associated with IE in patients receiving a FTCA protocol for cardiac surgery. Across 6 studies, 20 unique outcomes were reported (Table 3). One study reported no incidence of postoperative complications [23].

Service outcomes

ICU length of stay. Four studies assessed ICU LOS associated with IE [18, 21–23]. The mean LOS reported ranged from 1.5±0.6 [21] to 4.3±0.71 [23] days. One study reported a significant reduction in LOS for the IE group compared to the conventional group (P<0.001) [22].

Hospital length of stay. Hospital LOS was assessed by three studies; however, these studies varied in their definitions [18, 21, 23].

Mortality

Four of the six included studies assessed the mortality rate associated with IE, which was between 0% and 5.8% [18–21]. It is noted that the two more recent studies did not assess for mortality [22, 23]. No studies investigated a comparison between the IE and conventional extubation groups.

Postoperative complications

Myocardial ischemia/infarction. All studies recorded the incidence of myocardial ischemia or infarction. One study reported no incidence [23]. In the five studies that did, the incidence ranged from 0.6% to 7.7% [18–22]. Only one study compared the incidence of myocardial ischemia/infarction between the IE and conventional care groups and demonstrated a significantly lower incidence in the IE group [22].

Reintubation. All studies recorded the incidence of reintubation. One study had no incidence of reintubation [23]. In the five studies, the incidence ranged from 2.5% to 8% [18–22]. Only one study compared the incidence of reintubation between the IE and conventional care group and showed no significant difference [22].

Stroke. Stroke was measured in five studies [18–21, 23]. One study reported no incidence [23], whereas four reported incidences ranging from 0.2% to 2% of cases [18–21]. No study compared the incidence of stroke between the IE and conventional extubation groups.

Renal failure/insufficiency. Five studies recorded the incidence of renal failure and/or need for dialysis [19–23]. One study reported no incidence [23] and four reported incidences ranging from 0.2% to 7.7% [19–22]. One study compared incidence between IE and conventional extubation groups and noted no significant difference [22].

Reoperation because of bleeding or occlusion. Five studies recorded the incidence of reoperation because of bleeding or occlusion, which ranged from 0.4% to 1.5% [19–23]. One study reported no incidence [23]. Only one study compared incidence between IE and conventional groups and noted no significant difference between the two arms [22].

Arrhythmias or blocks. Four studies recorded the incidence of arrhythmia or block [19–21, 23]. One study found no incidence [21]. In the two studies that did, the incidence ranged from 10.3% to 16.3% [19, 20]. No studies investigated comparisons between groups.

Respiratory distress/pneumonia. Three studies recorded the incidence of respiratory distress/pneumonia, which ranged from 0.6% to 2.5% [19–21]. No studies investigated comparisons between groups.

TABLE 1
Characteristics of the included studies for research question 1

Study (year), location	Study design and population size	Time to extubation (hours)	Study details	Anesthetic details	Outcome measures
Salah et al. (2015), Egypt	**Design:** Parallel group randomized control trial **Number of participants:** *n*=52 (immediate extubation group: 26; control group: 26)	**IE group:** 0.23±1.2 h **Conventional group:** 12.94±5.0 h	**Mean age:** IE: 43.8±13.1; conventional: 48.7±12.5 **Sex:** IE: female 42.3% (*n*=11); male 57.7% (*n*=15) conventional: female 15.4% (*n*=4); male 84.6% (*n*=22) **Procedure:** CABG: 50% (*n*=13); MR: 7.7% (*n*=2); MVR 26.9% (*n*=7); ASD closure 7.7% (*n*=2); VSD closure 3.8% (*n*=1)	All patients received the same FTCA protocol **Induction:** midazolam [0.03–0.05 mg/kg], fentanyl [1–2 µg/kg], propofol [1–2 mg/kg], atracurium [0.5 mg/kg] **Maintenance:** sevoflurane (MAC 1–1.5), morphine (10–20 µg/kg/h) with additional doses of fentanyl and atracurium as needed **Reversal:** neostigmine (0.05 mg/kg), atropine (0.02 mg/kg)	**Primary outcome:** ICU length of stay **Secondary outcomes:** Postoperative complications
Montes et al. (2000), Columbia	**Design:** Case Series **Number of participants:** *n*=50	**IE:** 15 min (5–30)	**Mean age:** 60±9 **Sex:** female 28% (*n*=14); male 72% (*n*=36) **Procedure:** elective CABG **Mean number of grafts:** 3 (1–4)	All patients received the same FTCA protocol **Induction:** fentanyl (5–15 µg/kg), thiopental (4–6 mg/kg), pancuronium (0.1 mg/kg) **Maintenance:** isoflurane and oxygen before, during and postcardiopulmonary bypass **Reversal:** atropine (1.0 mg) and neostigmine (2.5 mg)	**Primary outcome:** ICU length of stay **Secondary outcomes:** • Time in OR after surgery • Postoperative length of stay • Postoperative complications
Nagre et al. (2018), India	**Design:** Case Series **Number of participants:** *n*=30	**IE:** Extubated before transfer from OR	**Mean age:** 52.7±4.3 (35–60) **Sex:** Not available **Procedure:** Off pump CABG **Number of grafts:** mean 3.0±0.6 **Additional details:** • Single centre • Single surgeon • Total surgical time: mean: 2.7±0.5 h • Readiness for extubation determined using blood gas results • EF ≥ 30% mean 51 ± 6.6%; • History of prior MI: 13%	All patients received the same FTCA protocol **Induction:** fentanyl (4 µg/kg), propofol (0.5–1 mg/kg), midazolam (0.04 mg/kg), rocuronium (0.6 mg/kg) **Maintenance:** fentanyl (25 µg boluses), propofol (20 mg boluses), atracurium (10 mg boluses) and sevoflurane **Reversal:** neostigmine and glycopyrrolate (doses not provided)	**Primary outcomes:** • Respiratory insufficiency • Reintubation • ICU length of stay **Secondary outcomes:** • Postoperative complications • Hospital length of stay • Also monitored: hypothermia, blood transfusion, inotrope score, atrial fibrillation

TABLE 1 (*Continued...*)
Characteristics of the included studies for research question 1

Study (year), location	Study design and population size	Time to extubation (hours)	Study details	Anesthetic details	Outcome measures
Dorsa et al. (2011)*, Argentina	**Design:** Case Series **Number of patients:** *n*=1065	**IE:** Within 15 min, in the OR	**Mean age:** 63.7±9.4 **Sex:** female 12.3% (*n*=131); male 87.7% (*n*=934) **Procedure:** Off-pump CABG **Number of grafts:** 3.1±0.77	All patients received the same FTCA protocol **Induction:** fentanyl (3–5 µg/kg), pancuronium (0.07 mg/kg), propofol (0.5 to 1 mg/kg) **Maintenance:** sevoflurane or isoflurane (MAC 0.6–1.0), fentanyl (5–7 µg/kg bolus, usually before skin incision so the total dose of fentanyl was 8–12 µg/kg). Additional fentanyl was administered (1–2 µg/kg) if necessary. In those cases, the total dose may have reached 14 µg/kg **Reversal:** atropine (15 µg/kg) and neostigmine (40 µg/kg)	***Research question 1*** **Primary outcomes:** • Mortality • ICU length of stay • Hospital length of stay • Postoperative complications
Borracci et al. (2006)*, Argentina	**Design:** Case Series **Number of participants:** *n*=398	**IE:** Extubated in the OR	**Mean age:** 64.1±10.8 **Sex:** female 25.1% (*n*=100); male 74.9% (*n*=298) **Procedure:** coronary, valvular or combined surgery, on pump and off pump	All patients received the same FTCA protocol **Induction:** lorazepam (2 mg), fentanyl (2–3 doses, 100–150 µg throughout the surgery), propofol (1.5–2 mg/kg), atracurium (0.6–0.9 mg/kg) **Maintenance:** sevoflourane (approximately 2%) **Reversal:** atropine (0.5–1 mg) and neostigmine (2–2.5 mg)	***Research question 1*** **Primary outcome:** • Failed immediate extubation **Secondary outcomes:** • Postoperative complications
Horswell et al. (2005), United States	**Design:** Case Series **Number of participants:** *n*=514	**IE:** 5–15 min	**Mean age:** not provided **Sex:** female 24.5% (*n*=126); male 75.5% (*n*=388) **Procedure:** off-pump CABG **Average number of grafts:** 2.84	All patients received the same FTCA protocol **Induction:** sufentanil, 15–20 µg, propofol, 50–100 mg. Orotracheal intubation was facilitated by vecuronium, 0.1 mg/kg **Maintenance:** desflurane titrated to a bispectral Index between 50 and 60 and a continuous infusion of sufentanil at 10–15 µg/h **Reversal:** neostigmine and glycopyrrolate (dosage not provided)	**Primary outcome:** • Reintubation **Secondary outcomes:** • Postoperative complications

*Although these studies are described as case series in this table, they are described as case controls for research question 2 to reflect the nature of the research question being asked.
ASD = atrial septal defect; CABG = coronary artery bypass graft; EF = ejection fraction; FTCA = fast track cardiac anesthesia; ICU = intensive care unit; IE = immediate extubation; MAC = minimum alveolar concentration; MI = myocardial infarction; MR = mitral repair; MVR = mitral valve replacement; OR= operating room; VSD = ventricular septal defect.

TABLE 2

Methodological appraisal of included studies

Randomized Controlled Trial

Study	Research question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13
Salah et al. (2015)	1	✓	✓	×	N/A	×	?	×	N/A	✓	✓	✓	✓	✓

Q1: Was true randomization used for assignment of participants to treatment groups? **Q2**: Was allocation to groups concealed? **Q3**: Were treatment groups similar at the baseline? **Q4**: Were participants blind to treatment assignment? **Q5**: Were those delivering treatment blind to treatment assignment? **Q6**: Were outcomes assessors blind to treatment assignment? **Q7**: Were treatment groups treated identically other than the intervention of interest? **Q8**: Was follow up complete and, if not, were differences between groups in terms of their follow up adequately described and analyzed? **Q9**: Were participants analysed in the groups to which they were randomly assigned? **Q10**: Were outcomes measured in the same way for treatment groups? **Q11**: Were outcomes measured in a reliable way? **Q12**: Was appropriate statistical analysis used? **Q13**: Was the trial design appropriate for the topic, and any deviations from the standard RCT design accounted for in the conduct and analysis?

N/A = not applicable; Q = question; RCT = randomized controlled trial; ✓ = yes; × = no; ? = unclear; Joanna Briggs Institute 2020. Checklist for randomized controlled trials. https://jbi.global/critical-appraisal-tools

Case Series

Study	Research question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Montes et al. (2000)	1	✓	✓	✓	✓	?	✓	✓	✓	×	✓
Horswell et al. (2005)	1	✓	✓	✓	✓	×	×	✓	✓	×	✓
Nagre et al. (2018)	1	✓	✓	✓	?	×	✓	✓	✓	×	✓
Borracci et al. (2006)	1	✓	✓	✓	✓	?	✓	✓	✓	×	✓
Dorsa et al. (2011)	1	✓	✓	✓	✓	✓	✓	✓	✓	×	✓
Wong et al. (1999)	2	✓	✓	✓	✓	✓	✓	✓	✓	×	✓

Q1: Were there clear criteria for inclusion in the case series? **Q2**: Was the condition measured in a standard, reliable way for all participants included in the case series? **Q3**: Were valid methods used for identification of the condition for all participants included in the case series? **Q4**: Did the case series have consecutive inclusion of participants? **Q5**: Did the case series have complete inclusion of participants? **Q6**: Was there clear reporting of the demographics of the participants in the study? **Q7**: Was there clear reporting of clinical information of the participants? **Q8**: Were the outcomes or follow-up results of cases clearly reported? **Q9**: Was there clear reporting of the presenting site(s)/clinic(s) demographic information? **Q10**: Was statistical analysis appropriate?

Q= question; ✓= yes; × = no; ? = unclear; Joanna Briggs Institute 2020. Checklist case series. https://jbi.global/critical-appraisal-tools

Case Control

Study	Research question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Youseffi et al. (2015)	2	✓	✓	✓	✓	✓	✓	✓	✓	N/A	✓
Kandasamy et al. (2013)	2	×	✓	✓	✓	✓	✓	N/A	✓	N/A	✓
Dorsa et al. (2011)	2	×	×	✓	✓	✓	×	×	✓	N/A	✓
Sato et al. (2009)	2	✓	✓	✓	✓	✓	✓	N/A	✓	N/A	✓
Borracci et al. (2006)	2	✓	✓	✓	✓	✓	N/A	N/A	✓	N/A	✓

Q1: Were the groups comparable other than presence of disease in cases or absence of disease in controls? **Q2**: Were cases and controls matched appropriately? **Q3**: Were the same criteria used for identification of cases and controls? **Q4**: Was exposure measured in a standard, valid and reliable way? **Q5**: Was exposure measured in the same way for cases and controls? **Q6**: Were confounding factors identified? **Q7**: Were strategies to deal with confounding factors stated? **Q8**: Were outcomes assessed in a standard, valid and reliable way for cases and controls? **Q9**: Was the exposure period of interest long enough to be meaningful? **Q10**: Was appropriate statistical analysis used?

Q= question; ✓= yes; × = no; N/A = not applicable; Joanna Briggs Institute 2020. Checklist for case control studies. https://jbi.global/critical-appraisal-tools

Eight postoperative complications were investigated in a few studies. Two of these complications (bleeding not requiring reoperation [18, 22] and vomiting [22]) were found to have lower incidences in the conventional care group (Table 3). Incidence for five postoperative complications (ie, prolonged ventilation [19, 23], mediastinitis [20, 23], need for postoperative transfusion [19, 23], tamponade [19], vasoplegia [20]) was reported, however these were all observational studies and comparisons were not made. Only one study assessed for a reduction in cardiac output, and no reduction was noted [23].

Research Question 2: In patients receiving FTCA protocols for cardiac surgery, which pre-existing and intraoperative factors may be associated with delayed extubation?

Characteristics of included studies. This review included six studies: one case series [24] and five case controls [6, 20, 21, 25, 26] and a total of 3534 patients (Table 4). Two studies investigated factors associated with delayed IE [20, 21], and four investigated factors associated with delayed EE [6, 24–26], although the time frame used to define delayed EE varied between studies.

Studies were published between 1999 and 2015. Across all studies, 78.1% were male (range: 68.0%–87.0%). Mean age was provided in five studies and ranged from 33.8 to 69 years. Although all studies adhered to their design expectations, observational studies are subject to high risk of bias (Table 2).

Three studies predefined potential factors associated with delayed extubation [6, 24, 26], although reasons for those choices were not justified. No study provided a comprehensive description of how preoperative data were collected or defined exclusion criteria.

Information was collected on 37 factors in patients, but no study investigated all 37 factors. Of the 37 factors only 2 (age >60 and pre-existing cardiac insufficiency) were investigated by all six studies. In one or more studies, 22 factors associated with delayed extubation were described. Fifteen pre-existing conditions or intraoperative factors were investigated but were not identified as factors associated with delayed extubation (Appendix 2).[2]

Factors associated with delayed extubation

Pre-existing conditions. Six studies considered preoperative factors that may be associated with delayed immediate [20, 21] or EE [6, 24–26]. Twenty-seven pre-existing conditions were examined, and two were identified as factors that delay EE by three studies *Age (>60).* All six studies considered

[2]Supplementary materials are available at https://www.cjrt.ca/wp-content/uploads/Supplement-cjrt-2022-037.docx

TABLE 3

Detailed outcomes associated with immediate extubation (research question 1)

Study (date) design	Salah et al. (2015) RCT *n*=52	Montes (2000) et al. Case Series *n*=50	Dorsa et al. (2011) Case Series *n*=1065	Nagre et al. (2018) Case Series *n*=30	Horswell et al. (2005) Case Series *n*=514	Borracci et al. (2006) Case Series *n*=398
Mean ICU length of stay (days)	IE: 2.4±0.78; conventional: 4 (P<0.001)	2.06±1.3	1.5±0.6	4.3±0.7	not examined	not examined
Mortality	incidence: not reported	incidence: 0%	incidence: 1.2% (*n*=13)	not examined	incidence: 1.9% (*n*=10)	incidence: 5.8%
Myocardial ischemia/ Infarction	(ischemia) incidence: IE: 7.7%; conventional: 50% (P=0.002)	(ischemia) incidence: 6% (*n*=3)	(infarction) incidence: IE: 1.0% (*n*=11)	no incidence	(infarction) incidence: 0.6% (*n*=3)	(infarction) incidence: 2.5% (*n*=23)
Reintubation	incidence: IE: 7.7% (*n*=2); conventional: 0 (P=0.49)	incidence: 8% (*n*=4)	incidence: 2.5% (*n*=27)	no incidence	incidence: 3.3% (*n*=17)	incidence 4.0% (*n*=12)
Stroke	not examined	incidence: 2% (*n*=1)	incidence: 0.4% (*n*=4)	no incidence	(permanent stroke) incidence: 0.8% (*n*=4); (transient stroke) incidence: 0.2% (*n*=1)	incidence: 2.0% (*n*=8)
Renal failure/ insufficiency	incidence: IE: 7.7% (*n*=2); conventional: 3.8% (*n*=1) (P=1.0)	not examined	incidence: 2.2% (*n*=23)	no incidence	(new onset, acute or worsening): incidence: 1.8% (*n*=9) (new onset requiring dialysis): 0.2% (*n*=1)	incidence: 2.3% (*n*=9)
Reoperation due to bleeding or occlusion	no significant difference	not examined	(bleeding) incidence: 1.2% (*n*=13)	no incidence	(bleeding) Incidence: 2% (*n*=10) (graft occlusion) incidence: 0.4% (*n*=2)	(bleeding) incidence: 1.5% (*n*=6)
Respiratory distress/ pneumonia	not examined	not examined	incidence: 1.9% (*n*=20)	not examined	incidence: 0.6% (*n*=3)	incidence: 2.5% (*n*=10)
Arrhythmias or blocks	not examined	not examined	incidence: 11.3% (*n*=120)	no incidence	(new onset atrial fibrillation) incidence: 10.3% (*n*=53)	incidence: 16.3% (*n*=65)
Bleeding (not requiring reoperation)	incidence: IE 34.6% (*n*=9); conventional: 0% (P=0.002)	incidence: 2% (*n*=1)	not examined	not examined	not examined	not examined
Prolonged ventilation	not examined	not examined	not examined	no incidence	incidence: 2.3% (*n*=12)	not examined
Mediastinitis	not examined	not examined	not examined	no incidence	not examined	incidence: 1.5% (*n*=6)
Requirement for blood transfusion	not examined	not examined	not examined	no incidence	incidence: 27.3% (*n*=128)	not examined

The following complications were investigated and incidence reported by one study: vomiting (Salah, IE: 23.1%, conventional 0% [P=0.023]), tamponade (Horswell, 0.4%), vasoplegia (Boracci, 1.5%). The following complications were evaluated by a single study and no significant incidence was noted: low cardiac output (Nagre), postoperative length of stay (Montes).
Hospital length of stay was investigated in three studies; however, these studies varied in their definition.
ICU = intensive care unit; IE = immediate extubation; RCT = randomized controlled trial.

whether age was a factor associated with delayed immediate [20, 21] or EE [6, 24–26]. Two studies identified age >60 as a factor associated with delayed extubation [6, 24].

Cardiac insufficiency (heart failure). All six studies considered whether cardiac insufficiency was a potential factor associated with delayed immediate [20, 21] or early [6, 24–26] extubation. One study identified cardiac insufficiency as a factor associated with delayed IE [20], and two identified it as a factor associated with delayed EE [24, 25].

Renal disease/renal insufficiency. Five studies considered whether renal disease/renal insufficiency was a factor associated with delayed IE [20, 21] or EE [6, 24, 25]. One of these studies identified pre-existing renal disease/renal insufficiency as a factor associated with delayed IE [21], and two studies identified it as a factor associated with delayed EE [6, 24].

Diabetes. Five studies considered whether diabetes was a factor associated with delayed IE [20, 21] or EE [6, 24, 25]. One of these studies identified diabetes as a factor associated with delayed IE [21].

Pulmonary disease. Five studies considered whether the pre-existing pulmonary disease was a factor associated with delayed IE [20, 21] or EE [6, 24, 25]. One study identified pulmonary disease as a factor associated with delayed IE [20].

Sex. Five studies considered whether sex was a factor associated with delayed IE (20, 21) or EE [6, 24, 25]. One study described female sex as a factor associated with delayed EE [24].

Emergency surgery. Four studies considered whether the need for emergency cardiac surgery was a factor associated with delayed IE [20, 21] or EE [6, 24]. One study identified it as a factor associated with delayed EE [24].

TABLE 4

Characteristics of the included studies for research question 2

Study (year), location	Study design and population size	Time to extubation (hours)	Study details	Anesthetic details	Outcome measures
Youssefi et al. (2015), United Kingdom	**Design:** Case Control **Number of participants:** *n*=451 EE: 313; delayed extubation: 138	**Fast-track extubation:** patients extubated within 4 h of transfer out of OR	**Mean age:** EE: 64±12.0; delayed extubation:68±9.2 **Sex:** EE: female: 20.8% (*n*=65); male 79.2% (*n*=248) delayed extubation: female 25.4% (*n*=35); male 74.6% (*n*=103) **Procedure:** CABG, AVR, CABG and ASD repair or minimally invasive direct CABG **Number of Grafts:** EE: 2.9±1.1; delayed extubation: 3.1±1.1	All patients received the same FTCA protocol **Induction:** fentanyl (3–8 µg/kg), propofol (1–2 mg/kg), rocuronium (0.5–1.0 mg/kg); **Maintenance:** isoflurane (MAC 0.5–1), propofol infusion (3–4 mg/kg/h)	Pre-existing conditions and intraoperative factors associated with delayed early extubation (within 4 h)
Kandasamy et al. (2013), India	**Design:** Case Control **Number of participants:** *n*=119 (UFTE: 49; delayed extubation: 70)	UFTE: extubation within 3 h of completion of surgery (2.3±0.9) Delayed extubation defined as: after 3 h of completion of surgery (10.4±12.7)	**Mean age:** EE: 33.8±1.6; delayed extubation: 34.9±11 **Sex:** no difference between groups (specifics not reported) **Procedure:** cardiac valve replacement	All patients received the same FTCA protocol **Induction:** fentanyl (5 µg/kg), midazolam (0.04 mg/kg) and thiopentone (2 mg/kg) **Maintenance:** fentanyl (2 µg/kg/h) and midazolam (0.02 mg/kg/h), isoflurane (0.4–0.8%), vecuronium **Reversal:** neostigmine, glycopyrrolate (doses not provided)	Pre-existing conditions and intraoperative factors associated with delayed ultrafast-track extubation (within 3 h)
Dorsa et al. (2011)*, Argentina	**Design:** Case Control **Number of patients:** *n*=1196 (UFTA=1064; delayed extubation: 132)	IE: Within 15 min, in the OR Time to extubation not provided for the delayed IE group	**Mean age:** 63.9±9.4 **Sex:** female 12.3% (*n*=131); male 87.7% (*n*=934) **Procedure:** off-pump CABG **Number of grafts:** 3.1±0.77	All patients received the same FTCA protocol. **Induction:** fentanyl (3–5 µg/kg), pancuronium (0.07 mg/kg), propofol (0.5 to 1 mg/kg) **Maintenance:** sevoflurane or isoflurane (MAC 0.6–1.0), fentanyl (5–7 µg/kg bolus, usually before skin incision so the total dose of fentanyl was 8–12 µg/kg). Additional fentanyl was administered (1–2 µg/kg) if necessary. In those cases, the total dose may have reached 14 µg/kg **Reversal:** atropine (15 µg/kg) and neostigmine (40 µg/kg)	Pre-existing conditions and intraoperative factors associated with delayed IE
Sato et al. (2009), Japan	**Design:** Case Control **Number of participants:** *n*=479 (EE: 450; delayed extubation: 29)	EE Group: extubation <6 h after admission to ICU Delayed EE group: ≥6 h, after admission to ICU	**Mean age:** EE: 67.9±9.6; prolonged extubation:70.6±8.0 (P=0.11) **Sex:** EE: female 32% (*n*=144); male 68% (*n*=306) Delayed EE: female 38% (*n*=11); male 62% (*n*=18) (P=0.56) **Procedure:** elective isolated on-pump CABG **Number of grafts:** EE: 3.2±1.0; prolonged: 3.5±1.0	All patients received the same FTCA protocol. Fentanyl: 200–500 µg with inhalation anesthetic agents midazolam 0.1 mg/kg (sedative), replaced with propofol 2 mg/kg/h	Pre-existing conditions and intraoperative factors associated with delayed EE (within 6 h)

TABLE 4 (*Continued...*)

Characteristics of the included studies for research question 2

Study (year), location	Study design and population size	Time to extubation (hours)	Study details	Anesthetic details	Outcome measures
Borracci et al. (2006)*, Argentina	**Design:** Case Control **Number of participants:** *n*=398 (IE: 87% (*n*=346); delayed extubation: 13% (*n*=52)	IE: extubated in the OR Delayed IE group: Mean time to extubation not provided	**Mean age:** 64.1±10.8 **Sex:** female 25.1% (*n*=100); male 74.9% (*n*=298) **Procedure:** coronary, valvular or combined surgery, on pump and off pump on pump and off pump	All patients received the same FTCA protocol **Induction:** lorazepam (2 mg), fentanyl (2–3 doses, 100–150 µg throughout the surgery), propofol (1.5–2 mg/kg), atracurium (0.6–0.9 mg/kg) **Maintenance:** sevoflourane (approximately 2%) **Reversal:** atropine (0.5–1 mg) and neostigmine (2–2.5 mg)	Pre-existing conditions and intraoperative factors associated with delayed IE
Wong et al. (1999), Canada	**Design:** Case Series **Number of participants:** *n*=885 all underwent fast track protocol	EE group: extubation: ≤6 h	**Mean age:** 60.8±11.3 **Sex:** female 24% (*n*=212); male 76% (*n*=673) **Procedure:** on-pump CABG	All patients received the same FTCA protocol. **Induction:** midazolam 1–3 mg, fentanyl-10–15 µg/kg with or without propofol 50–100 mg, pancuronium 0.15 mg/kg **Maintenance:** isoflurane 0%–2% before CPB, propofol infusion during CPB 2–6 mg/kg/h	Pre-existing conditions and intraoperative factors associated with delayed extubation (within >10 h)

*Although these studies are described as case control studies in this table, they are described as case series for research question 1 to reflect the nature of the research question being asked.
ASD = atrial septal defect; AVR = aortic valve replacement; CABG = coronary artery bypass graft; EE = early extubation; FTCA = fast track cardiac anesthesia; ICU = intensive care unit; IE = immediate extubation; MAC = minimum alveolar concentration; OR = operating room; UFTE = ultrafast-track extubation.

Obesity. Four studies considered whether obesity was a factor associated with delayed IE [20] or EE [6, 24, 25]. None of these studies identified it as a factor.

History of stroke. Four studies considered whether a history of stroke was a factor associated with delayed IE [20] or EE [6, 24, 25]. None of these studies identified it as a factor.

Lower EuroSCORE. Three studies considered whether the European System for Cardiac Operative Risk Evaluation (EuroSCORE) was a factor associated with delayed IE [21] or EE [6, 25]. Two studies identified a higher EuroSCORE as a factor associated with delayed EE [6, 25].

Hypertension. Three studies considered whether hypertension was a factor associated with delayed IE [21] or EE [6, 24]. One study identified it as a factor associated with delayed EE [6].

Recent myocardial infarction. Three studies considered whether a recent myocardial infarction was a factor associated with delayed EE [6, 24, 25]. Each study defined recent MI differently (eg, one study defined recent MI as within 2 weeks [25], whereas another defined it as within 1 week [24]). One study identified MI before surgery as a factor associated with delayed EE [24].

Intra-aortic balloon pump. Two studies considered whether the need for a preoperative intra-aortic balloon pump was a factor associated with delayed IE [21] or EE [24]. Each study identified a preoperative intra-aortic balloon pump as a factor associated with delayed extubation.

Fourteen pre-existing factors were investigated only once. Of these, only two, prior cardiac surgery [21] and number of diseased vessels [25], were identified as factors associated with delayed extubation (Appendix 2).

Intraoperative factors. Six studies considered intraoperative factors that may be associated with delayed IE [20, 21] or EE [6, 24–26]. Eleven intraoperative conditions were examined, and two were identified as intraoperative factors associated with delayed IE or EE by three studies (Appendix 2).

Cross-clamp time. Four studies considered whether a longer cross-clamp time was a factor associated with delayed IE [20] or EE [6, 24, 26]. One study identified a longer cross-clamp time as a factor associated with delayed IE [20], and two studies identified it as a factor associated with delayed EE [6, 26].

Time on pump. Four studies considered whether time on pump was a factor associated with delayed EE [6, 24–26]. Three studies identified time on pump as a factor associated with delayed EE [6, 24, 26].

Difficulty discontinuing cardiopulmonary bypass. Two studies considered whether difficulty discontinuing cardiopulmonary bypass was a factor associated with delayed IE [20] or EE [24]. Each study identified it as a factor.

Requirement for intraoperative cardiac pacing. Two studies considered whether the need for intraoperative cardiac pacing was a factor associated with delayed IE [20] or EE [26]. Each study identified the need for intraoperative pacing as a factor.

Requirement for transfusion. Two studies considered whether the requirement for transfusion was a factor associated with delayed EE [25, 26]. Each study identified it as a factor.

Four intraoperative conditions were investigated only once (see Appendix 2). Of these, two, total surgical time [21] and first lactate or acid-base deficit after surgery [6], were identified as factors associated with delayed extubation. Two conditions, intraoperative hemofiltration and peak intraoperative CK-MB, were only investigated by a single study and were not identified as factors associated with delayed extubation [20, 26].

Pre-existing cardiac disease [20, 24, 25], pre-existing renal disease [6, 21, 24], time on pump [6, 24, 26] and cross-clamp time [6, 20, 26] were

each identified as risk factors for delayed extubation in three studies and many others were identified but less consistently. Diabetes, pre-existing pulmonary disease, stroke, sex and obesity were rarely associated with delayed EE.

Risk of bias in included studies

Research question 1: Of the six studies, one used a design with the potential to provide the highest level of evidence; however, it had critical methodological weaknesses [22]. The other observation studies, while meeting most expectations of their designs, have inherent noncontrollable biases, and at best provide low levels of evidence. [Table 2; 18–21, 23]. A further challenge with included studies was that they used a variety of extubation protocols (Appendix 3[3]). Consequently, evidence for question 1 was low.

Research question 2: All studies used observational designs and met most methodological expectations of their designs [6, 20, 21, 24–26; Table 2]. The potential for bias is high with observational studies, so the level of evidence must be considered low. Specific limitations of these included studies were that observational studies cannot determine cause and that no study provided a rationale for identifying factors for investigation. Finally, studies employed a variety of extubation protocols (Appendix 3).

DISCUSSION

Research Question 1: What is the evidence regarding the safety of IE in patients receiving a FTCA protocol for cardiac surgery?

In the early 1990s, FTCA was introduced to reduce resource demand in patients undergoing cardiac surgery. EE with FTCA has been shown to reduce ICU LOS and hospital costs [1]. Authors from the previous Cochrane review of 19 studies [3] identified that EE under a FTCA protocol appeared safe, regarding the risk of mortality and major postoperative complications, as conventional care. That study included a single study that suggested IE with FTCA may be equally safe as EE [3]. A synthesis of studies evaluating the safety of IE might ultimately support change in practice that reduces resource waste.

Our research team reviewed the evidence regarding the safety of IE in patients receiving a FTCA protocol. Although most included studies used designs that did not permit comparison of treatment outcomes in patients undergoing IE versus EE, they do allow the identification of frequently reported postoperative complications in patients undergoing IE.

The studies included in this review were conducted in countries with diverse resources, so treatment outcomes reported may reflect variations in system capacities. Participants represented in this review were predominantly male (79%). Although women may be proportionally represented in some studies [27], the authors failed to conduct gender- or sex-based analysis. Furthermore, none of the studies investigated associations between race and treatment outcomes. Such analyses are important as prior studies demonstrate that 20% of the recently approved drugs exhibit racial and/or ethnic differences in disposition and response [28], whereas other studies have shown associations between sex and cardiac surgery outcomes [27].

Currently, the evidence to support IE under an FTCA protocol is low, demonstrating the need for adequately powered multicentre RCTs that examine the service and treatment outcomes in patients receiving IE with a FTCA protocol. These studies should seek to control variables that may introduce bias (eg, variations in extubation protocols across studies, resource and skill capacities of investigating centres). This review also establishes a list of treatment outcomes that should be considered in these future trials. Future studies should consider the influence of race, sex, gender and ethnicity on treatment outcomes associated with IE.

As with EE, adopting IE in practice may support additional reductions in resource demands making further primary research in this area important. Evidence that supports safe IE protocols would enable and encourage anesthesia care teams to consider IE.

[3]Supplementary materials are available at https://www.cjrt.ca/wp-content/uploads/Supplement-cjrt-2022-037.docx

Research Question 2: In patients receiving FTCA protocols for cardiac surgery, which pre-existing and intraoperative factors may be associated with delayed extubation?

In a small percentage of patients undergoing cardiac surgery with an FTCA protocol, extubation within a desired time frame (eg, within 8 h) is not appropriate and therefore delayed [4, 5]. These patients often experience longer LOS, use more medical resources and experience higher mortality rates. Understanding pre-existing and intraoperative factors that may predict delayed extubation is essential for ensuring the best quality of care and pre- and postoperative planning. This review synthesized studies that investigated pre- and intraoperative factors that may predict delayed extubation in cardiac surgery patients on a FTCA protocol. Six studies [6, 20, 21, 24–26] totalling 3534 patients were included. As this synthesis aimed to determine factors associated with delayed extubation, the designs employed in the included studies were appropriate for this research question. Furthermore, all six studies met most expectations of their methodological designs.

Studies included in this synthesis evaluated 37 unique factors; however, no single study investigated all 37. Pre-existing cardiac insufficiency, pre-existing renal disease, time on pump and cross-clamp time were each investigated in four or more of the included studies and identified as risk factors for delayed extubation in three. Factors that were associated with delayed extubation in multiple studies may warrant consideration as important potential predictors for future research on this topic.

The EuroSCORE predicts in-hospital mortality risk following major cardiac surgery [29]. Three studies investigated EuroSCORE as a predictor of delayed extubation, and two studies identified it as a predictor. It is interesting to note that five components that are used in the calculation of the EuroSCORE (age, diabetes, pulmonary disease, emergency surgery and sex) were not identified as possible predictors of failed extubation when concurrently examined in these studies. This indicates that further consideration should be given regarding using the EuroSCORE as a predictor of delayed extubation.

The total collective sample size addressing research question 2 is low and few factors were investigated by all studies. A significant limitation of the included studies is the lack of justification by authors regarding how these factors were identified and/or selected. Future studies could be more deliberate in selecting and researching outcomes related to delayed extubation. Furthermore, other important factors such as race, ethnicity and gender have not been investigated, and other possibly important factors (eg, sleep apnea [30]) have yet to be evaluated. Finally, there were numerous variables across studies that were difficult to account for. Potential jurisdictional variations in resource and equipment availability, practice guidelines, extubation protocols and skill capacity may have influenced study outcomes.

Future studies should include prospective comparative designs that incorporate a more judicious list of outcome measures and analyses that define combinations of factors most associated with delayed extubation. Adequately powered prospective multicentred observational studies will provide a higher level of evidence. Such evidence will support the development of algorithms that predict those at risk for delayed extubation and support resource allocation.

As with research question 1, future studies should seek to control variables that may introduce bias (eg, race, ethnicity, gender, variations in extubation protocols across sites, resource and skill capacities of investigating centres).

Strengths and limitations

Although the present study has strengths, the results should be interpreted relative to its limitations.

Strengths: This is the first review that synthesized the studies examining the outcomes of IE. To our knowledge, this is also the first review to synthesize the studies of pre- and intraoperative factors associated with delayed extubation in patients receiving FTCA protocols. This review also included studies published in multiple languages. All authors worked collaboratively to conduct a comprehensive search, review citations, synthesize data and assess study quality, thereby minimizing the likelihood of bias [31].

Limitations: Our searches were limited to studies published in peer-reviewed journals. There were few studies for each research question and relatively low sample sizes in most studies. Although the studies were generally of high quality for their chosen design, most were observational designs; thus, they produced a low level of evidence. In research question 2, there was heterogeneity across studies regarding the time to extubation. Furthermore, the four most frequently reported risk factors (ie, pre-existing cardiac disease, pre-existing renal disease, time on pump and cross-clamp time) lacked consistent definitions in the papers. For example, the amount of time on pump considered to be a risk for failed extubation was not quantified. Because of the significant heterogeneity and the absence of control in most studies, meta-analysis was not possible. It is also important to note that the studies included in this review are all single-centred. Single-centre studies typically lack the external validity required to draw widespread conclusions about a given practice or population, and their incorporation into universal guidelines and policies may be inappropriate.

Finally, studies including remifentanil, an opioid often used in FTCA, were excluded from this review because its pharmacokinetic properties differ significantly from those of fentanyl and sufentanil (12). This prohibits the applicability of our findings from settings where remifentanil is used as part of the FTCA protocol.

CONCLUSION

Our review highlights the paucity of high-quality studies examining the safety of IE in patients receiving FTCA. Although the included studies were of insufficient quality or design to enable comparisons of treatment outcomes in patients undergoing IE versus EE, they have allowed the development of a comprehensive list of common treatment outcomes.

This review reveals factors associated with delayed extubation, but the results are lacking in that not all studies looked for the same pre- and intraoperative factors, and the most frequently reported factors were inconsistently defined.

DISCLOSURES

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Contributors

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Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Ethical Requirement of Research Ethics Board approval for this project was not required.

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