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Original Article

A Protocol to help the Prevent Postoperative Delirium in Cardiac Surgery

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Abstract

Introduction: Postoperative delirium (POD), a highly prevalent syndrome after cardiac surgery, is characterized by a rapid decline in brain function with inattention, disorganized thinking, and an altered level of consciousness. It is clinically important because it is associated with severe negative consequences. This study aimed to develop a protocol to help the prevent postoperative delirium in cardiac surgery.

Methods: This multiphase design study consisted of two phases. The first phase was a scoping review to identify risk factors associated with POD in cardiac surgery. The second phase included three consecutive rounds of expert panels based on a Delphi method to obtain consensus from experts to determine and use these risk factors to develop a protocol. A scoping review was performed using the Arksey and O'Malley framework. Literature searches using PubMed/MEDLINE, Scopus, Web of Science, and ProQuest databases were conducted. Two independent investigators performed the selection of studies and data extraction via checklists. In the second phase, based on two Delphi rounds, risk factors with a significant effect on postoperative delirium in cardiac surgery were identified according to the consensus of experts (≥75% agreement). In the third round of the expert panel, only modifiable factors that could improve based on existing conditions and context were used to develop a protocol.

Results: The final protocol was developed based on 20 pharmacological and non-pharmacological interventions to prevent POD in three stages pre-, intra-, and post-cardiac surgery.

Conclusion: Interventions such as prescribing melatonin instead of benzodiazepines, dexmedetomidine treatment, preoperative education patients that were candidated for cardiac surgery, training nurses, use of arterial filters and pre-bypass filters in the perfusion circuit, prevention of intraoperative hyperglycemia, cerebral oximetry and temperature management during CPB and some interventions in ICU-OH can reduce POD in cardiac surgery.

Keywords: Delirium; Cardiac Surgery; Prevention; Interventions.

Introduction

Cardiac surgery is a medical specialty that deals with the surgical treatment of pathologies related to the heart and thoracic aorta, which play an essential role in cardiovascular health[1]. The prevalence of cardiovascular diseases is continuously increasing due to the epidemiological transition involved in atherosclerosis, hypertension, and lifestyle-related risk factors[2-4]. Despite the advances in surgery and declining incidence of complications following cardiac surgery, postoperative delirium (POD) is a frequent complication, which is still happening[5-8]. POD manifests as an acute brain disorder in 25-52% of post-cardiac surgery cases[9-11]. The underlying pathophysiologic mechanisms of POD in cardiac surgery may include acute inflammation, effects of anesthetics, exposure to artificial circulation or altered perfusion, and gaseous micro-emboli (GMEs). A theory behind the development of delirium is that systemic inflammation causes the dysfunction of the blood-brain barrier (BBB), causing neuro-inflammation processes and leaving neurons vulnerable to damage and

dysfunction[12-14]. Therefore, a condition or exposure which produces an inflammatory response, such as cardiac surgery, may increase the risk for delirium. Delirium has been linked to severe negative consequences, including postoperative cognitive decline, prolonged mechanical ventilation, prolonged hospital, and ICU stay, increased healthcare costs, and a higher risk of morbidity and mortality[15, 16]. Therefore, delirium is one of the significant health problems which imposes a heavy burden on the patient's health and health care system. Knowing the risk factors of POD in cardiac surgery is necessary to design appropriate interventions and prevent delirium. Once delirium has begun, treatments or interventions have little effect on its severity, duration, or likelihood of recurrence[17, 18]. In comparison, it is estimated that 30 to 40% of delirium cases can be prevented before occurrence[19]. Prevention is the most effective strategy to minimize the occurrence of delirium and its adverse consequences. This can be achieved by interventions tackling risk factors, such as including early mobilization, improving Intensive Care Unit (ICU) environment, prophylactic antipsychotic administration, preoperative melatonin use[20], or use of dexmedetomidine instead of propofol for sedation[21-23]. Much research has been conducted on reducing the incidence of POD by using pharmacological and non-pharmacological preventive measures in cardiac surgery patients[24, 25]. These studies' results have shown an independent relationship between POD and significant cardiac side effects[26]. Studies and research about POD and its associated burdens in patients undergoing cardiac surgery would allow healthcare managers to allocate much-needed resources for reducing morbidity and mortality associated with delirium after cardiac surgery[27]. Despite the pharmacological or non-pharmacological interventions proposed to prevent delirium, there is still no undeniable evidence of a successful prevention method. The time has come to develop a practical protocol for this issue with a systematic and focused review. The purpose of this study was to determine the risk factors related to delirium to establish a protocol consisting of pharmacological and non-pharmacological interventions to improve the prevention of POD with the perspective of experts in three stages pre-, intra-, and post-cardiac surgery.

Methods

Study design and Ethical approval

This multiphase design study was conducted to develop a protocol to improve the prevention of POD in cardiac surgery, which includes two phases. The first phase was the scoping review to identify risk factors associated with POD in cardiac surgery. The second phase included three consecutive rounds of expert panels based on a Delphi method to obtain consensus from experts in determining and using these risk factors to develop a protocol. Figure 1 shows the multiphase design of the study. The study protocol was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran (IR.BMSU.BAQ.REC.1400.052). The methodology of this study is fully described in a short video clip, which is available as a related file.

First phase: scoping review

Our protocol in the first phase was developed applying the scope review method of Arksey and O'Malley as a reference[28], as well as the review of Levac et al.[29], and further developed by the Joanna Briggs Institute (JBI)[30]. The review included the following five key steps: (a) identifying the research question; (b) search for relevant studies; (c) selection of studies; (d) data extraction; (e) interpreting, summarizing, and reporting the results and (f) consultation with stakeholders, which is optional.

Identifying the research question

This review was guided by the question, "What are the associated risk factors for POD in cardiac surgery?" According to JBI recommendations, to construct a clear and meaningful research question for scoping review, the "PCC" mnemonic was applied to elaborate the guiding question. The PCC mnemonic represents the population (participants), concept, and context. The study started with a leading question and was divided into more minor questions to provide a great deal of information about the PCC "population, concept, and context." "What are the risk factors associated with POD in cardiac surgery, preoperatively?", "What are the risk factors associated with POD in cardiac surgery, intraoperatively?" and "What are the risk factors associated with POD in cardiac surgery, postoperatively?" In the study, a participatory process that included determining risk factors of POD in cardiac surgery was used to develop the research question defined according to the PCC strategy, among others.

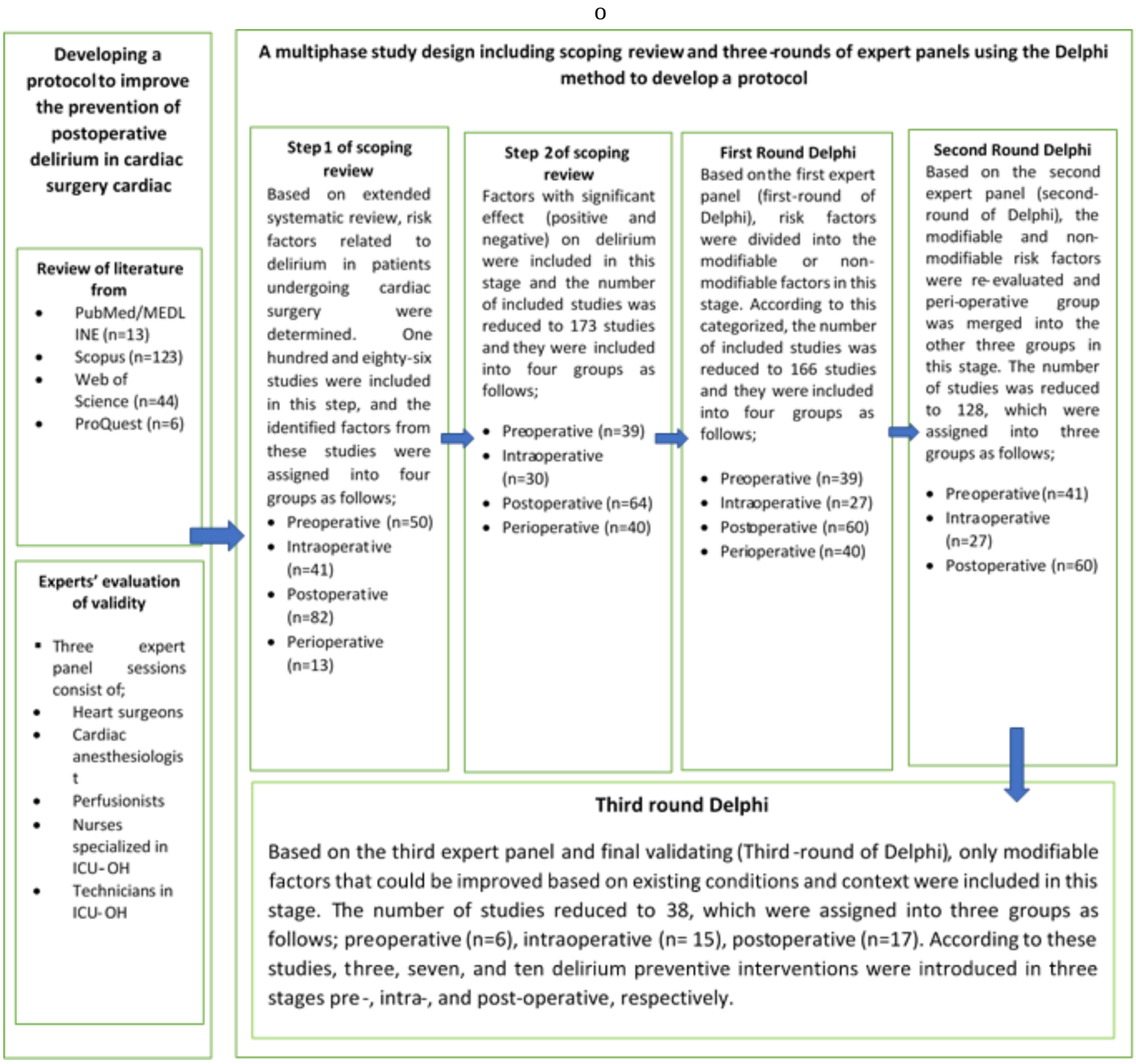

Figure 1: Multiphase study design for developing a protocol to improve the prevention postoperative delirium in cardiac surgery.

Search for relevant studies

Eligibility criteria, databases, keywords, and search strategies for searching and selecting relevant studies were defined as follows;

- **Eligibility criteria;** All relevant empirical and theoretical full-text studies published in English and Persian from the inception to January 24th, 2022, were included in this study. We left the source of information "open" to have any evidence. Therefore, the "source" of information included any type of study available in this field, which consisted of the following types of documents; original articles (e.g., randomized controlled trials, case-control studies, cross-sectional studies, prospective or retrospective cohort studies, or quasi-experimental studies) and systematic reviews with or without meta-analysis. In addition, the reference lists of selected publications were reviewed for other relevant studies. Eligible studies must be carried out in cohorts containing more than one adult (>18 years old) patient post cardiac surgery, which was defined as any surgery in which an incision is made on the chest and procedure is done on the coronary artery, heart valve,

vessels or myocardium, due to non-congenital heart disease. Postoperative delirium in cardiac surgery as an outcome must be assessed with one of the following tools: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV or DSM-V), Confusion Assessment Method (CAM), Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC) or other well-validated diagnostic standard based on the tools mentioned above.

- Databases and search strategy; On January 24th, 2022, a search was conducted on PubMed/MEDLINE, Scopus, Web of Science, and ProQuest databases in all past publications with MeSH terms using Boolean search (and) for keywords including: ("delirium" OR "acute brain dysfunction" OR "Cognitive Change" OR "cognitive decline" OR "delirious") AND ("cardiac surgery" OR "heart surgery" OR "coronary artery bypass grafting" OR "cardiopulmonary bypass" OR "valve surgery") AND ("risk factors" OR "preoperative risk factors" OR "intraoperative risk factors" OR "postoperative risk factors").

Selection of studies

The search yielded 1,773 results on PubMed/MEDLINE, 1,831 results on Scopus, 1,947 on Web of Science, and 281 on ProQuest. After removing duplicate entries automatically with the software EndNote X7, 2,607 records were screened by title and abstract to identify eligible literature. Two investigators and discrepancies independently performed the screening process were resolved through discussion with a third reviewer. After screening the titles and abstracts, 2,463 articles were excluded due to irrelevance or needing to meet all inclusion criteria. One hundred forty-four studies had eligible criteria, which entered into the three Delphi rounds of expert panels after full-text assessment. During three consecutive rounds of expert panels, 122 articles were excluded, and 22 remaining studies were used to develop the final protocol. In addition, the references of primary articles were also reviewed to identify potentially related studies further. The search through bibliographic review yielded 77 records; after removing duplicate (n=12) and irrelevance articles (n=23), the results of 42 articles entered into the three Delphi rounds of expert panels. In three rounds of an expert panel, 26 out of 39 articles were excluded due to no significant risk factors for POD in cardiac surgery (n=3) and non-modifiable or modifiable factors that could not be improved based on existing conditions and context (n=23), respectively. Totally 38 studies [via databases (n=22) and through bibliographic review (n=16)] were used to develop the protocol. Flowcharts of the review process, which include searches of databases and bibliography review according to PRISMA 2020 statement[31], are presented in Figure 2.

Data extraction and quality assessment

Two researchers independently examined the full text of the remaining selected papers for extracting data. Data were removed from the studies to identify the risk factors of POD in cardiac surgery by a pre-designed checklist that included the following information: the first name of the author, year of publication, types of study, sample size (in clinical trial studies with the number of patients in intervention and control groups), types of intervention for clinical and quasi-experimental studies, objectives for prospective/retrospective cohort studies, case-control studies, cross-sectional studies, a systematic review with or without meta-analysis studies and conclusions. Any ambiguities or disagreements between the evaluators were resolved through discussion and consensus by a third person. The characteristics of the included studies are presented in Table 1.

Two reviewers performed the risk of bias assessment for each included study independently. A third reviewer shall be invited to the discussion to achieve consensus in case of disagreement. The National Institutes of Health (NIH) quality assessment tool was used for observational cohort and cross-sectional studies[32]. All studies (n=16) were assigned a yes, no, or other to each of the 14 criteria outlined in the appraisal tool[20, 33-47]. Then by considering each criterion, we evaluated the overall quality of the study and assigned a generally good, fair, or poor rating to each study (Supplementary file, Table 1). Clinical trial (n=15) and quasi-experimental (n=3) studies were evaluated based on 13 and 9 criteria from the Joanna Briggs Institute (JBI) critical appraisal tool (https://jbi.global/critical-appraisal-tools), respectively[48-63]. All questions were answered as yes, no, unclear, or not applicable and assessed individually. Eligible studies were rated according to the dictionary and guidelines of the tool. After evaluating all the study components, the overall

rating was determined using the criteria set out in the device. Based on the number of "yes" responses, a rating of good = (≥10 yes), medium = (6-9 yes), and poor = (≤5 yes) was assigned to each RCT study. For quasi-experimental studies, a rating of good = (≥7 yes), medium= (4-6), and poor = (≤3 yes) was assigned for nine questions (Supplementary file, Tables 2 and 3). In addition, the Assessment of Multiple Systematic Reviews (AMSTAR-2) measurement tools[64] were used to assess the quality of the included four systematic and meta-analyses studies [65-68].

AMSTAR-2 is a validated tool for evaluating the methodological quality of systematic reviews, with a total of 16 items with simple response categories. These items include an assessment of the protocol's existence, the integrity of the literature search, and the risk of bias in individual studies included in the systematic review (Supplementary file, Table 4).

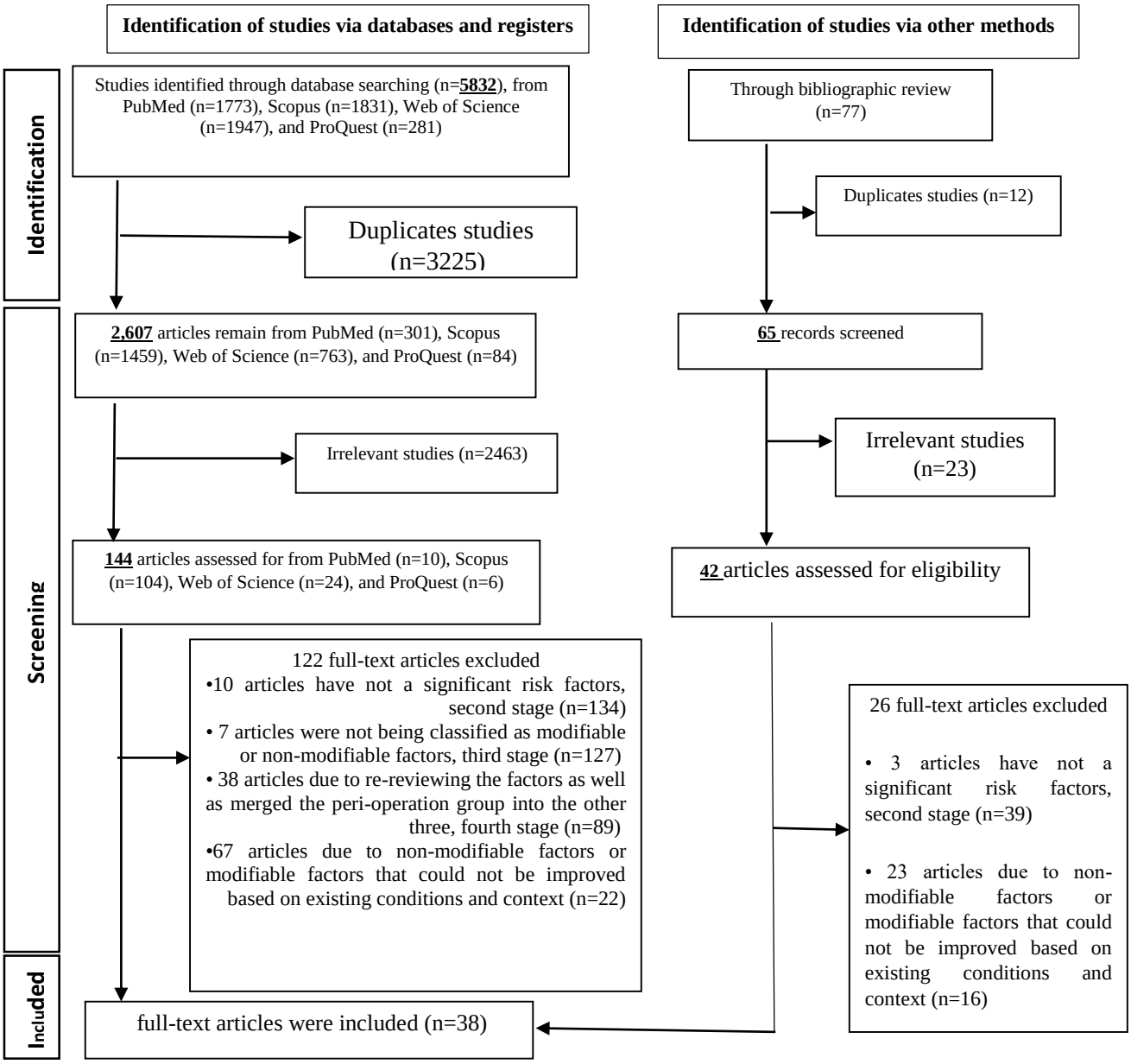

Figure 2: Flowchart of reviews process which include searches of databases and bibliography review according to PRISMA 2020.

Results

Reporting the results and consultation with stakeholders

This scoping study will detail the eminent topics that discuss the target population (patient's post-cardiac surgery), areas of action (pre-, intra-, and post-cardiac surgery), and intervention characteristics (with identified risk factors of POD in cardiac surgery). Risk factors with significant effects on POD in cardiac surgery were determined and assigned into modifiable and non-modifiable categories. According to consultation with stakeholders (here, we used three consecutive Delphi rounds of expert panels, which we will discuss in detail below), modifiable risk factors modifiable factors that could be improved based on existing conditions and context were recognized. Next, according to the identified risk factors, interventions were designed. Finally, the set of interventions was presented as a protocol in three stages pre-, intra-, and post-cardiac surgery (Table 2).

Preoperative intervention is health care or auxiliary intervention before cardiac surgery to prevent POD. It includes when the patient is a candidate for cardiac surgery or is admitted to the hospital for surgery. For this study, the intraoperative period of care includes the care the patient receives from the moment he/she arrives through the cardiac operating theatre doors until they leave the operating theatre post-procedure and are transferred to the recovery and then to intensive care unit open heart (ICU-OH). Postoperative period care includes the care the patient receives from when they arrive at ICU-OH until they leave ICU-OH after cardiac surgery. The aim of postoperative care or intervention in this study is to do whatever is suitable to decrease postoperative delirium.

Second phase: Delphi method

Three consecutive rounds of expert panels using the Delphi method were holed to obtain consensus from experts in determining and using risk factors related to delirium to develop a protocol to improve the prevention of postoperative delirium in three stages pre-, intra-, and post-cardiac surgery. The expert panel includes heart surgeons, cardiac anesthesiologists, perfusionists, nurses specialized in ICU-OH, and technicians in ICU-OH under Professor Mohammad Hassan Kalantar Motamedi (Figure 3).

One hundred and eighty-six studies had eligible criteria. After a full-text review of the articles by two researchers separately, 13 studies were excluded due to the lack of influencing factors (both positive and negative) on delirium in the target population. Therefore, the remaining 173 studies entered three consecutive Delphi rounds of expert panels.

- **Round 1 Delphi:** In the first round of Delphi, identified risk factors from included studies were divided into modifiable or non-modifiable factors. According to this categorization, the number of included studies was reduced to 166. The identified risk factors should be reported as preoperative, intraoperative, and postoperative. But some predisposing and precipitating risk factors cannot be neatly placed into these categories, mainly because of the complexity of identifying the direct cause of POD. Therefore, we chose an additional "perioperative" classification to include the results of these studies. Perioperative care is defined as all care concerning initial diagnosis, from preoperative outpatient clinic visits to postoperative follow-up visits. Although, in the second round, with the consensus of experts, this category of perioperative factors was merged into three other categories. One hundred and sixty-six studies in this round were included in four groups as follows; preoperative (n=39), intraoperative (n=27), postoperative (n=60), and perioperative (n=40). The consensus was defined as experts reporting that they strongly agreed or agreed with every individual statement ≥75%. As consensus (≥75%) was not achieved for all words in round 1, a second Delphi round was pursued to identify any additional key elements that would help to reach consensus.

- **Round 2 Delphi:** In the second round of Delphi, to achieve consensus, the modifiable and non-modifiable risk factors were re-evaluated, and the perioperative group was merged into the other three groups. The number of studies was reduced to 128, which were assigned into three groups as follows; preoperative (n=41), intraoperative (n=27), and postoperative (n=60). Following this second round, all

statements reached a consensus (≥75% agreement).x Following this second round, all reports reached a consensus (≥75% agreement).

- Round 3 Delphi

In the third expert panel and final validating, only modifiable factors that could be improved based on existing conditions and context were included in this stage. The number of studies reduced to 38, which were assigned into three groups as follows; preoperative (n=6), intraoperative (n= 15), and postoperative (n=17). The final protocol was developed based on these 38 articles and consisted of three, seven, and ten pharmacological and non-pharmacological interventions to prevent POD in three stages pre-, intra-, and post-cardiac surgery, respectively. Agreement between panelists in each session was estimated based on Kendall's coefficient of concordance, where the high value of Kendall's [K (range): 0.943–0.976, P-value<0.0001] indicated a strong association between them. During three validation sessions, the content validity ratio (CVR) was 0.56, and the content validity index (CVI) was 0.89. The protocol's reliability was assessed using the inter-rater reliability method with Kohen's Kappa agreement (=0.95) which the principal investigator with all members of the expert panel tested.

Figure 3: Head of the expert panel, Associate Professor Mohammad Hassan Kalantar Motamed.

Table 1: Characteristics of study included.

First Author, Year, Ref	Study type	Sample size	Interventions/objectives	Conclusions	Quality assessment
Owens, 1982,[61]	Semi-experimental	I: 32 C: 32 T: 32	Assess the effect of education pre-operatively about possibility of unusual sensory or cognitive on postoperative delirium experience. Intervention group received some advice and knowledge about this issue before cardiac surgery.	There was no significant difference between two groups in terms of experienced unusual sensory or cognitive after surgery. However, the patients in the intervention group due to the knowledge was significantly more comfortable coped with these unusual situations than the patients in the control group (P<0.05)	Fair
Lee, 2013, [62]	Semi-experimental	I: 49 C: 46 T: 95	Perioperative psycho-educational intervention on patients' candidate for cardiac surgery	Lower incidence of postoperative delirium in the intervention group than that in the control group (12.24% vs. 34.78%, P=0.009)	Good
Zolfaghari, 2012, [63]	Semi-experimental	I: 90 C: 90 T: 180	Staff education, environment changes, and installation of guideline of delirium on ward for treatment of patients' candidate for cardiac surgery	Multifactor intervention was effective in decreasing the prevalence of delirium (11.1% vs. 35.6%, P<0.05)	Good
Demir, 2016,[33]	Descriptive cross-sectional survey	97	Determine the knowledge level of Cardiovascular surgery nurses regarding delirium based on questionnaire	Moderate level of knowledge regarding delirium mean score (41·18±12·50)	Good
Javaherforoosh Zadeh, 2021,[48]	Double-blind randomized clinical trial	I: 30 C: 30 T: 60	Patients candidate for cardiac surgery in intervention group received 3 mg of melatonin and control group received placebo	The lower severity of delirium in intervention group than the control group on the first and second postoperative days (P=0.003)	Good
Billy, 2015,[49]	Interventional clinical study	I: 250 C: 250 T: 500	Patients candidate for cardiac surgery in intervention group received orally 5 mg melatonin the evening before surgery and then every evening until postoperative day 3	Lower incidence of delirium in intervention group compare to control group (8.4% vs. 20.8%, p=0.001)	Fair
Whitaker, 2002,[68]	Review	-	Reviewed the evidence for three main types of intervention include equipment, techniques and drug	Benefit of used membrane oxygenator type membranes and arterial filters and pre-bypass filters in the perfusion circuit	Fair
Puskas, 2007,[34]	Prospective observational study	252	Prevention of intraoperative hyperglycemia in patients underwent coronary artery bypass graft (CABG)	Hyperglycemia was associated with a decrease in cognitive function at 6 weeks (P=0.0351)	Good
Santarpino, 2011,[35]	Retrospective observational study	292	Evaluate the association of Bispectral index with delirium in patients undergoing aortic surgery	Higher incidence of delirium in patients with a Bispectral index reduction of >25% from baseline	Good
Bellido, 2016,[69]	Prospective, before and after, longitudinal study	44	Examine related between cerebral frontal cortex O_2 desaturation with development of delirium symptoms' after cardiac surgery	Reduction of intraoperative cerebral oxygen saturation (rSO_2) higher than 10% at the end of the surgery was related with significantly higher values of delirium symptoms' development during post-surgery staying (rSO2 higher ≥ 10%: 68.8 vs. rSO2 higher<10%: 31.3%, P<0.05)	Good
First Author, Year, Ref	**Study type**	**Sample size**	**Interventions/objectives**	**Conclusions**	**Quality assessment**
Lopez, 2017,[37]	Prospective observational Study	310	Evaluate the association between intraoperative hyperoxic cerebral reperfusion with increased postoperative delirium in cardiac surgery patients	Intraoperative hyperoxic cerebral reperfusion and hyperoxia prior to ischemia were independently associated with a 65% and 10% increase in the odds of delirium	Good
Tse, 2012,[67]	Systematic review	15 studies	Evaluate the literature on medications associated with delirium after	Medications with direct neurological actions have been identified to be	Good

			cardiac surgery and potential prophylactic agents for preventing it	independently associated with delirium after cardiac surgery	
Siepe, 2011, [50]	Prospective randomized clinical trial	92	Evaluate correlation between systemic perfusion pressure during cardiopulmonary bypass (CPB) with early postoperative delirium	Maintaining perfusion pressure at physiologic levels during normothermic CPB (80—90 mmHg) is associated with less early postoperative delirium	Fair
Hori, 2014, [38]	Prospective observational Study	491	Evaluate the association between the mean arterial pressure (MAP) above the upper limit of autoregulation (ULA) and postoperative delirium	The product of the magnitude and duration of MAP above an ULA was increased the odds ratio of postoperative delirium (OR: 1.09, 95% CI: 1.03 –1.15, P<0.05)	Good
Bagheri, 2017, [39]	Prospective observational Study	100	Investigate the association of postoperative delirium and mean arterial pressure (MAP) during cardiopulmonary pump in patients after coronary artery bypass graft (CABG)	Results showed a significant correlation between incidence of postoperative delirium and mean arterial pressure and O_2 saturation during cardiopulmonary pump	Good
Hori, 2016, [40]	Prospective observational Study	110	Evaluate the association of blood pressure from the optimal mean arterial pressure during and after cardiac surgery with postoperative delirium	Delirium was not associated with perioperative blood pressure excursions; but on secondary exploratory analysis, excursions above the optimal mean arterial pressure were associated with the incidence and severity of delirium on postoperative day 2	Good
Brown, 2014,[20]	Case-control study	87	Evaluate the association between length of storage of transfused red cell units with delirium after cardiac surgery	Transfusion of red cell units that have been stored for less than 14 days is not associated with increased odds of delirium. However, each additional day of storage more than 14 days (OR, 1.07; P=0.03) or 21 days (OR, 1.12; P=0.02) may be associated with increased odds of postoperative delirium	Good
Shin, 2021, [41]	Retrospective propensity-score-matched study	534	Evaluate the incidence of postoperative delirium in patients who underwent cardiac surgery with cardiopulmonary bypass (CPB) according to different primary anesthetic agents: sevoflurane and dexmedetomidine- versus propofol-based anesthesia	The overall incidence of PD after cardiac surgery with CPB did not differ between patients receiving sevoflurane and dexmedetomidine-based versus propofol-based anesthesia. Only hyperactive PD occurred less frequently in patients receiving sevoflurane and dexmedetomidine-based anesthesia	Good
Li, 2021, [65]	Meta-analysis of randomized controlled trials	15 studies including 2813 patients	Examine the role of dexmedetomidine in preventing postoperative delirium (POD) after cardiac surgery	Pooled result showed that dexmedetomidine could reduce the risk of POD in adult population underwent cardiac surgery (OR: 0.56, 95%CI: 0.36–0.89, P=0.0004)	Fair
First Author, Year, Ref	**Study type**	**Sample size**	**Interventions/objectives**	**Conclusions**	**Quality assessment**
Likhvantsev, 2021, [70]	Randomized controlled trial	169	Investigate the effect of perioperative dexmedetomidine on the rate of postoperative delirium after cardiac surgery	Dexmedetomidine administered during and after general anesthesia for cardiac surgery decreased the rate of postoperative delirium (OR: 0.33, 95% CI: 0.12-0.90, P<0.05)	Fair
Billy, 2015, [71]	prospective non-randomized clinical study	250	Evaluate the association between perioperative administration of dexmedetomidine group with the incidence of postoperative delirium in cardiac surgery patients	The incidence of delirium in dexmedetomidine group was significantly lower than control group (5.2% vs. 20.8%, P<0.001)	Fair
Maldonado, 2005, [51]	Prospective randomized clinical study	90	Patients were divided into three equal groups (n=30). Patients in each group received three different postoperative sedation protocol such as dexmedetomidine (0.4 µg/kg followed 0.2-0.7 µg/kg per hour), propofol (25-50 µg/kg per minutes), fentanyl and	The incidence of delirium in the patients received dexmedetomidine was significantly lower than in other patients (3% vs. 50%, P<0.01).	Fair

			midazolam (50-150 µg/h and 0.5-2 mg/h, respectively)		
Andrejaitiene, 2012, [42]	Retrospective observational Study	90	Identify the post-cardiac surgery delirium risk factors and to evaluate clinical outcomes	Increasing the dose of fentanyl administered during surgery over 1.4 mg can increased the possibility of developing a severe delirium (OR:29.4, 95%CI: 4.1-210.3) and longer aortic clamping time could be independently associated with severe postoperative delirium (OR:8.0, 95%CI: 1.7-37.2)	Good
Ottens, 2104, [52]	Randomized, double-blind, placebo-controlled trial	I: 140 C: 138 T: 278	Investigate the effect of high-dose dexamethasone (1 mg/kg) on the incidence of postoperative cognitive decline (POCD) at 1 month and 12 months after cardiac surgery	High-dose dexamethasone did not reduce the risk of POCD at 1 month (RR: 1.87, 95% CI: 0.90 to 3.88, P=0.09) and 12 months (RR: 1.98, 95% CI: 0.61 to 6.40, P=0.24) after cardiac surgery	Good
Taipale, 2012, [44]	Observational study	122	Examine the relationship between nurses' pro re nata administration of midazolam hydrochloride to cardiac surgery patients and the development of post-operative delirium.	Dosage of midazolam hydrochloride administered to cardiac surgery patients were associated with the incidence of delirium independent of age and other risk factors	Good
Taipale, 2011, [43]	Observational study	122	Examine the modifiable risk factors of opiate and benzodiazepine administration given by nurses to determine whether a relationship exists between incident delirium and drug administration	Patients who received midazolam in the first 72-hours post-op were more likely to develop delirium, (OR: 1.079, 95%CI: 1.002 to 1.162, P<0.05).	Fair
Mardani, 2013, [53]	Randomized clinical trial	I: 43 C: 50 T: 93	Evaluate the effect of dexamethasone (DEX) on post-operative delirium after cardiac surgery. DEX group taken 8 mg DEX intra-venous before induction of anesthesia followed by 8 mg every 8 h for 3 day and other group received placebo in same way	Administration of DEX might safely protect brain of the patients who undergone cardiac surgery against post-operative delirium	Fair
First Author, Year, Ref	**Study type**	**Sample size**	**Interventions/objectives**	**Conclusions**	**Quality assessment**
Mardani, 2012, [72]	Randomized clinical trial	I: 43 C: 50 T: 93	Effect of dexamethasone (DEX) prophylaxis on post-operative delirium after cardiac surgery. DEX group taken 8 mg DEX intra-venous before induction of anesthesia followed by 8 mg every 8 h for 3 day and other group received placebo in same way	Results showed that in the first post-operative day delirium, extubation time, and intensive care unit length of stay significantly decreased in the DEX group without increasing serious complications such as infectious diseases. Preoperative administration of dexamethasone might safely protect the brain of patients who undergone cardiac surgery against postoperative delirium	Fair
Tao, 2018, [66]	A meta-analysis of randomized trials	14 studies with 14,139 patients	Determine the effect of pharmacologic agents for the prevention postoperative delirium after cardiac surgery	Pharmacologic agents significantly decrease postoperative delirium (RR: 0.83, 95% CI: 0.75 to 0.91, P<0.00001) and duration of postoperative delirium (RR: 0.37, 95% CI: 0.47 to 0.27, P<0.00001) after cardiac surgery. In addition, dexamethasone was associated with a trend toward a reduction in postoperative delirium (RR: 0.45, 95% CI: 0.30 to0.66, P<0.0001)	Good
Ford, 2016, [55]	Randomized controlled clinical trial	210	Determine if melatonin use reduces the incidence of delirium in individuals undergoing major cardiac surgery	The results of this trial clarify whether melatonin reduces the incidence of delirium following cardiac surgery	Good
Fallahpoor, 2016, [56]	Clinical trial	I: 50 C: 50 T: 100	Study a care program for the management of delirium in patients after coronary artery bypass graft surgery. In the intervention group, the developed	The number and ratio of delirium incidence were significantly lower in the intervention group (P<0.05)	Good

			care program was implemented in three areas of delirium management before, during, and after the surgery.		
Fraser, 2018, [57]	Pre-post design trial study	30	Assess the effect of a knowledge transfer (KT) intervention on the completion of a delirium detection tool by nurses working with cardiac surgery patients	A tailored intervention based on preidentified barriers and facilitators, using the Determinants of Implementation Behavior Questionnaire, and in collaboration with participants, has the potential to promote evidence-based practice.	Good
Cheraghi, 2016, [45]	Analytical-descriptive study	44	Determine the relationship between sleep and the prevalence of delirium in patients undergoing cardiac surgery	Results showed a significant difference between the sleep disorder and the prevalence of delirium (P=0.007).	Good
Peyer, 2020, [47]	Observational study	NC	Determine the most effective nursing interventions to prevent delirium after cardiac surgery	Positive effect of education programs for health personnel to prevent post-operation delirium and determine the most non-pharmacological effective nursing interventions include cognitive reorientation, adequate environment, sleep improvement, early mobility, pain management, adequate oxygenation	Fair
First Author, Year, Ref	**Study type**	**Sample size**	**Interventions/objectives**	**Conclusions**	**Quality assessment**
Eertmans, 2020,[46]	Prospective, observational study	96	Investigate whether perioperative cerebral desaturations are associated with postoperative delirium in older patients after cardiac surgery	The lowest postoperative cerebral oxygen saturation was lower in patients who became delirious (P<0.001). The absolute and relative postoperative cerebral oxygen saturation decreases were more marked in patients with delirium (6% and 9%, respectively) compared with patients without delirium (4% and 5%; P<0.002 and P<0.001, respectively). Postoperative delirium in older patients undergoing cardiac surgery is associated with absolute decreases in postoperative cerebral oxygen saturation	Good
Shirvani, 2020,[58]	Double-blind randomized clinical trial	I: 46 C: 46 T: 92	Evaluate the effect of early planned mobilization on delirium after coronary artery bypass grafting. A mobilization protocol was applied in the intervention group in the first 2 days after surgery; the control group received routine nursing care only.	The intervention group had significantly higher Neecham scores on postoperative day 2 (22.49 ± 2.03 vs. 26.82 ± 2.10, P=0.001). Early planned mobilization was effective in reducing postoperative delirium in patients undergoing coronary artery bypass grafting.	Fair
Mailhot, 2017,[59]	A randomized pilot study	I: 16 C: 14 T: 30	Assess the feasibility, acceptability and preliminary efficacy of nursing intervention involving family caregivers (FC) in delirium management following cardiac surgery. Patients in intervention group received care based on the Human Caring Theory	Intervention group patients presented better psycho-functional recovery scores when compared with control group patients (p =0·01). Mean delirium severity scores showed similar trajectories on days 1, 2 and 3 in both groups	Good
Eghbali-Babadi, 2017,[60]	Randomized controlled clinical trial	I: 34 C: 34 T: 68	Assess the effect of the relationship between the family and patient on the incidence of delirium in hospitalized patients in cardiovascular surgery intensive care unit. The day after the surgery, one of the family members in the intervention group who had received education the day before was allowed to visit the patient in the morning shift. In the control group, patients received routine care.	Effective communication between the patient and family, as a nonmedical method, can reduce delirium after cardiac surgery, especially, at the end of the day. In the control group, the incidence of delirium in the evening was 32.35%, which was more than that in the morning. A significant difference in the morning and afternoon shifts was observed in the control group (P=0.004)	Good

Table 2: Final protocol to improve the prevention of postoperative delirium in cardiac surgery.

Stages	Interventions
Pre-operation	1. Educate the patients who candidate for cardiac surgery about the process of surgery and answer their questions by the researcher. Researcher-made educational clip (visual media) is also provided to patients [61, 62]. 2. Holding training workshops for nurses to make them more familiar with delirium in patients undergoing cardiac surgery [33, 63]. 3. Prescribed melatonin instead of benzodiazepines to patients who candidate for cardiac surgery [48, 49].
Intra-operation	1. The perfusion group should plan to use membrane oxygenator, arterial filters and prebypass filters in the perfusion circuit[68]. 2. Perform surgery in normothermic conditions (35-37^{0C}) as much as possible and avoid rapid rewarming the patient and use alpha-state strategy during pumping in cases of hypothermia[68]. 3. Prevention of intraoperative hyperglycemia in patients (BS> 200 mg /dl)[34]. 4. Intraoperative cerebral oximetry and avoidance of decrease (cerebral hypoxia) and increase (cerebral hyperoxia) of more than 10% of cerebral oxygen saturation (rso2) compared to baseline[35, 37, 67, 69]. 5. Maintaining systemic perfusion pressure at the physiological level during normothermia (mmhg 80-90) [38-40, 50]. 6. Avoiding transfusion of packed red blood cells with a storage period more than 14 days[20]. 7. Start infusion of Dexmedetomidine at the end of surgery (before transport the patient to the ICU)[41, 65, 70, 71].
Post- operation	1. Using the Dexmedetomidine to sedate the patients in the ICU-OH [42, 51, 52]. 2. Caution in the using of midazolam in 72 hours after surgery to sedate patients [43, 44]. 3. Prescribe the dexamethasone after surgery [53, 66, 72]. 4. Prescribe the melatonin after surgery [55]. 5. Holding training workshops for ICU-OH nurses about delirium in patients undergoing cardiac surgery [33, 63]. 6. Creating environmental changes in the ICU-OH, including: painting the ward (walls and roof), installing a wall clock in direct view of the patients, providing a personal mirror for patients [56, 57]. 7. Programs to preventing sleep deprivation in patients (pain management, calm environment, alarm management of ventilators and monitors, noise reduction and lighting adjustment) [45, 47]. 8. Early mobilization and extubation of patients based on hospital instructions [46, 58]. 9. Managing appointments in the ICU-OH and providing a mobile phone to communication the patients with their families [59, 60]. 10. Strengthen effective communication between nurses and patients in the ICU-OH [47].

This is the first study of a multiphase design that includes scoping review and three Delphi rounds to identify risk factors for delirium to provide a protocol to improve the prevention of POD in cardiac surgery from the experts' perspective. The results of the scoping review and three rounds of Delphi with the consensus of the experts (≥75% agreement) led to the identification of modifiable factors that can be improved based on the existing conditions and contexts and were extracted from 38 final studies. According to these modifiable factors, twenty pharmacological and non-pharmacological interventions were designed and introduced to prevent POD in cardiac surgery and divided into preoperative (n=3)[33, 48, 49, 61-63], intraoperative (n=7)[34, 35, 37, 38, 40, 50, 65, 67-71] and postoperative (n=10)[42-47, 51-56, 58-60].

Preoperative interventions

- Patients' education pre-cardiac surgery: A semi-experimental study by Owens and Hutelmyer[61] assesses the effect of education preoperatively about the possibility of unusual sensory or cognitive on POD experience. Before cardiac surgery, the intervention group received some advice and knowledge about this issue. Their results showed no significant difference between the two groups regarding experienced POD or cognitive after surgery. However, due to their understanding, the patients in the intervention group were significantly more comfortable coping with these unusual situations than those in the control group ($P<0.05$). In addition, a study by Lee et al.[62] showed that the perioperative psycho-educational intervention on patients' candidates for cardiac surgery significantly reduced POD in cardiac surgery ($P=0.009$). According to our findings, one of the most common and effective non-pharmacological preventive measures for POD in cardiac surgery was patients' education preoperative,

which was demonstrated effective in reducing anxiety and complications as well as recovery [73, 74].

-Nurses' education: Raising nurses' knowledge about delirium is necessary to detect any signs or symptoms quickly. Conducting training in the field of POD for the entire ICU staff can increase their knowledge. Therefore, one of the non-pharmacological preventive interventions for POD in cardiac surgery was preoperative nursing education, which was confirmed to have progressed the prevention and treatment of POD [33, 63].

-Prescribed melatonin instead of benzodiazepines: According to evidence, Benzodiazepines are associated with an increased risk of POD[10, 75]. So, melatonin preoperatively was evaluated in a comprehensive search for alternative sedatives mounted. It has shown better results than Benzodiazepines by reducing the incidence of POD in cardiac surgery. An interventional clinical study by Billy et al.[49] was conducted on 500 cardiac surgery candidates to assess melatonin's effect on reducing the incidence of POD. The patients were randomly divided into two equal groups (n=250): a group treated with 5 mg melatonin the evening before surgery and then every evening until postoperative day three. Their results revealed that melatonin significantly reduced the incidence of POD in cardiac surgery. Moreover, in a double-blind, randomized clinical trial study by Javaherforoosh et al.[48], [60] patients undergoing elective on-pump coronary artery bypass graft surgery were randomly divided into groups receiving 3 mg of melatonin and a group receiving a placebo. Their results showed that melatonin significantly reduced the severity of POD in cardiac surgery.

Intraoperative interventions

- Use of membrane oxygenator, arterial line filters, and pre-bypass filters in the perfusion circuit: The most likely cause of delirium is micro-emboli that are transferred to the brain during surgery, which can lead to changes in cerebral perfusion and neuropsychiatric (NP) disorders after cardiac surgery [76]. During cardiac surgery, the oxygenator temporarily replaces the patient's lungs by delivering oxygen to the blood and extracting carbon dioxide. The greatest challenge among perfusionists, medical professionals who work on the heart and lung system, is the possibility of blood clots in the arterial filter that impair oxygenator function. The use of a membrane oxygenator is suggested due to the lower generation of micro-emboli than a bubble oxygenator and the beneficial effect it has on the outcome of NP [68]. Arterial line filters and pre-bypass filters are an integral part of bypass circuitry. An arterial line filter is recommended for its ability to remove both particulate micro-emboli and large air emboli. Also, the pre-bypass filter can reduce micro emboli and other potentially harmful particles during surgery.

- Temperature management during cardiopulmonary bypass (CPB): Perform cardiac surgery in normothermic conditions (35-37°C) as much as possible and avoid rapid rewarming of the patient and use the alpha-state strategy during pumping in cases of hypothermia. Hypothermia is a protective strategy for the brain and vital organs during CPB for many cardiac surgical procedures. Rewarming to 38°C may directly injure neurons. Also, rapid rewarming can produce micro-emboli, and the rate and extent of rewarming on cerebral outcome have a potential effect [68, 77, 78].

- Prevention of hyperglycemia during CPB: Clinically acute hyperglycemia has conventionally been described as a blood glucose concentration >200 mg/dl. Management of intraoperative hyperglycemia is linked to better cognitive outcomes after cardiac surgery. A prospective observational study by Puskas et al.[34] showed that in nondiabetic patients undergoing coronary artery bypass graft (CABG) operations, intraoperative hyperglycemia is associated with an increased risk of neurocognitive dysfunction (NCD).

-Maintaining cerebral oximetry during CPB: Avoidance of decreased cerebral oxygen saturation (cerebral hypoxia) and increase of cerebral oxygen saturation (cerebral hyperoxia), more than 10% compared to baseline, would protect against POD in cardiac surgery. Neuromonitoring commonly used during cardiac surgery, such as cerebral oximetry and processed electroencephalogram (EEG) monitors (i.e., bispectral index [BIS]), have also proven helpful in predicting POD. In a study by Santarpino et al.[35] concerning the BIS monitor, a longer duration of intraoperative EEG burst suppression along with a BIS value <25% has been shown to correlate with increased odds of developing delirium. A study by Bellido et al. [69] examined the relation between cerebral frontal cortex O2 desaturation and the development of delirium symptoms after cardiac surgery. Their results revealed

that a reduction of intraoperative cerebral oxygen saturation (rSO2) higher than 10% at the end of the surgery was related to significantly higher values of delirium symptoms' development during post-surgery staying. In a prospective observational study, Lopez et al.[37] reported that intraoperative hyperoxic cerebral reperfusion was associated with increased postoperative delirium. Increased oxidative injury following hyperoxic cerebral reperfusion may partially mediate this association.

- Maintaining systemic perfusion pressure during CPB: Keeping perfusion pressure during CPB within physiological ranges would protect against POD in coronary bypass surgery. Siepe et al.[50] reported that maintaining perfusion pressure at physiologic levels during normothermic CPB (80—90 mmHg) is associated with less early POD. In an observational study by Hori et al.[38], the association between the mean arterial pressure (MAP) above the upper limit of autoregulation (ULA) and postoperative delirium was evaluated. Their results showed that optimizing MAP during CPB to remain within the cerebral autoregulation range could reduce the risk of delirium. A study by Bagheri et al.[39] suggested maintaining MAP and O2 saturation of blood at physiologic levels during PBC may be associated with less early POD and cognitive dysfunction. In addition, a study by Hori et al.[40] showed that the POD was not associated with perioperative blood pressure excursions. Still, excursions above the optimal MAP were associated with the incidence and severity of POD.

- Duration of red blood cell unit storage: In retrospective analyses of patients undergoing cardiac surgery, transfusion of red cell units that have been stored for more than 14 days has been associated with postoperative morbidity and mortality, and such poor outcomes also have been reported in other surgical populations. A study by Brown et al.[20] showed that the transfusion of red cell units stored for less than 14 days is not associated with an increased risk of POD. However, each additional day of storage of more than 14 days (OR, 1.07; P=0.03) or 21 days (OR, 1.12; P=0.02) may be associated with increased odds of POD.

- Infusion of Dexmedetomidine immediately at the end of surgery: Dexmedetomidine is a highly selective α2-adrenoceptor agonist, which has soothing, amnestic, sympatholytic, and analgesic effects. In a study by Shin et al.[41], the incidence of POD was evaluated in patients who underwent cardiac surgery with CPB according to different primary anesthetic agents; sevoflurane and Dexmedetomidine vs. propofol-based anesthesia. The overall incidence of POD in cardiac surgery with CPB did not differ between patients receiving sevoflurane and Dexmedetomidine vs. propofol-based anesthesia. Only hyperactive POD occurred less frequently in patients receiving sevoflurane and dexmedetomidine-based anesthesia. A meta-analysis of RCTs showed that Dexmedetomidine could reduce the incidence of POD compared to other sedatives and opioids after cardiac surgery in adult patients [65]. A randomized clinical trial study by Bily et al.[71]. showed a lower incidence of POD after cardiac surgery in patients receiving Dexmedetomidine compared to the control group.

Postoperative interventions

- Using the Dexmedetomidine in the ICU-OH: The effect of postoperatively Dexmedetomidine on POD was assessed in several studies. In a prospective clinical trial study by Maldonado et al.[51], patients who underwent cardiac surgery were divided into three equal groups (n=30). Patients in each group received three different postoperative sedation protocols such as dexmedetomidine (0.4 μg/kg followed by 0.2-0.7 μg/kg per hour), propofol (25-50 μg/kg per minute), fentanyl, and midazolam (50-150 μg/h and 0.5-2 mg/h, respectively). Their results revealed a significantly lower incidence of POD in patients who received dexmedetomidine than in other patients (3% vs. 50%, P<0.01). However, a study by Ottens et al.[52] investigates the effect of high-dose dexamethasone (1 mg/kg) on the incidence of postoperative cognitive decline (POCD) at one month and 12 months after cardiac surgery. Their results showed that the high-dose dexamethasone did not reduce the risk of POCD at one month (RR: 1.87, P=0.09) and 12 months (RR: 1.98, P=0.24) after cardiac surgery.

- Caution in the use of midazolam 72 hours after surgery: Patients are often given sedation immediately after cardiac surgery to minimize anxiety and induce sleep, relaxation, amnesia, analgesia, and tolerance of mechanical ventilation (MV). Midazolam hydrochloride, a benzodiazepine, is often the drug of choice due to its rapid onset and short duration of action.

However, medications administered by nurses to achieve sedation for MV patients have been identified as risk factors for POD[79]. Taipale et al.[44], in an observational study, showed that the dosage of midazolam hydrochloride administered to cardiac surgery patients was associated with the incidence of POD. In addition, another observational study indicated that patients who received midazolam in the first 72 hours' post-op were more likely to develop delirium (OR: 1.079, P<0.05)[43].

- **Postoperative dexamethasone:** Beneficial effect of dexamethasone (DEX) on neurological sequelae after cardiac surgery has been shown by some studies. A randomized clinical trial study by Mardani et al.[53] was conducted on 93 patients who had undergone coronary artery bypass graft to evaluate DEX effects on POD. DEX group (n=43) took 8 mg DEX intra venous before induction of anesthesia, followed by 8 mg every eighth for three days, and the other placebo group (n=50) received PCB in the same way. They found that the administration of DEX would protect the brain of patients who had undergone cardiac surgery against POD. In addition, in the first postoperative day delirium, extubation time, and intensive care unit length of stay significantly decreased in the dexamethasone group without increasing serious complications such as infectious diseases [72].

- **Postoperative melatonin:** Emerging evidence suggests that melatonin may play a biological role in developing delirium. Melatonin supplementation may be beneficial in reducing the incidence of delirium in medical and surgical patients. A randomized clinical trial study by Ford et al.[58] confirmed that melatonin reduces the incidence of delirium after cardiac surgery.

- **Sleep protocol and early mobilization:** Significant relationship between sleep quality and prevalence of POD in cardiac surgery was observed in a study by Cheraghi et al.[45]. Due to the significant relationship between sleep quality and prevalence of delirium, the need to use a program of prevention from sleep deprivation in the clinical nursing instructions in hospitals is essential particularly critical and surgery wards[47]. Environmental interventions such as light adjustment, reducing ambient noise, and using devices such as eye masks and earplugs will help to regulate patients' sleep[80]. Prolonged ICU bed rest contributes to acquired neuromuscular weakness, prolongs hospital stay, and is associated with increased rates of delirium [81]. Early mobilization is defined as interventions that support the patient through passive or active movement exercises to maintain or support patient mobility[82, 83]. A clinical trial study by Shirvani et al.[58] evaluated the effect of early planned mobilization on POD after CABG. A mobilization protocol was applied in the intervention group in the first two days after surgery; the control group received routine nursing care only. According to their results, the intervention group had significantly higher Neecham scores on postoperative day 2.

Conclusion

Delirium remains a frequent manifestation in the cardiac surgical population and contributes to increased morbidity, mortality, and resource utilization. While many studies have identified risk factors and strategies to identify delirium, the ideal treatment strategy has yet to be determined. This multiphase design study includes scoping review. Three Delphi rounds were conducted to identify risk factors for delirium to provide a protocol to improve the prevention of POD in cardiac surgery from the experts' perspective. The study's results identified modifiable factors that can be improved based on the existing conditions and contexts. According to these modifiable factors, twenty pharmacological and non-pharmacological interventions were developed to prevent POD in cardiac surgery in three stages preoperative, intraoperative, and postoperative.

List of Abbreviations:

Postoperative delirium (POD), Cardiopulmonary bypass (CPB), Gaseous micro-emboli (GMEs), Blood-brain barrier (BBB), Intensive Care Unit (ICU), Confusion Assessment Method (CAM), Confusion Assessment Method for the ICU (CAM-ICU), Intensive Care Delirium Screening Checklist (ICDSC), National Institutes of Health (NIH) quality assessment tool, Multiple Systematic Reviews (AMSTAR-2) measurement tool, Intensive care unit open heart (ICU-OH), Content validity ratio (CVR), Content validity index (CVI), Neuropsychiatric (NP) disorders, Coronary artery bypass graft (CABG), Neurocognitive

dysfunction (NCD), Bispectral index (BIS), Mean arterial pressure (MAP).

Disclosure statement

None to declare.

Authors' contributions

AM, A.VA, ST.M and H.M are contributors responsible for study design, overseeing study implementation, and providing methodological support to coordinators. SMR.A, A.VA and H.M drafted the manuscript and participated in the recruitment, organizing the intervention materials, and intervention sessions. All authors read and approved this final manuscript.

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Ethical Statement

The study protocol was approved by the Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran (IR.BMSU.BAQ.REC.1400.052). The study was performed in accordance with the Declaration of Helsinki of the World Medical Association. Informed consent was obtained from all participants.

References

1. Weisse AB. Cardiac surgery: a century of progress. Texas Heart Institute Journal. 2011;38(5):486.
2. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.
3. Fakhri M, Sarokhani D, Ghiasi B, Dehkordi AH. Prevalence of hypertension in cardiovascular disease in Iran: Systematic review and meta-analysis. Int J Prev Med. 2020;11.
4. Kim HC. Epidemiology of cardiovascular disease and its risk factors in Korea. Global Health & Medicine. 2021.
5. O'Neal JB, Billings FTI, Liu X, Shotwell MS, Liang Y, Shah AS, et al. Risk factors for delirium after cardiac surgery: a historical cohort study outlining the influence of cardiopulmonary bypass. Can J Anesth. 2017;64(11):1129-37.
6. Labaste F, Porterie J, Bousquet P, Marcheix B, Sanchez-Verlaan P, Frances B, et al. Postoperative delirium is a risk factor of poor evolution three years after cardiac surgery: an observational cohort study. Clin Interventions Aging. 2020; 15:2375.
7. Vlisides P, Avidan M. Recent advances in preventing and managing postoperative delirium. F1000 Res. 2019;8.
8. Brown CH, Max L, Laflam A, Kirk L, Gross A, Arora R, et al. The Association between Preoperative Frailty and Postoperative Delirium after Cardiac Surgery. ANESTH ANALG. 2016;123(2):430-5.
9. Ibrahim K, McCarthy CP, McCarthy KJ, Brown CH, Needham DM, Januzzi Jr JL, et al. Delirium in the cardiac intensive care unit. Journal of the American Heart Association. 2018;7(4): e008568.
10. Pagad S, Somagutta MR, May V, Arnold AA, Nanthakumaran S, Sridharan S, et al. Delirium in cardiac intensive care unit. Cureus. 2020;12(8).
11. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB, Shotwell MS, et al. Intraoperative Oxidative Damage and Delirium after Cardiac Surgery. ANESTHESIOLOGY. 2020;132(3):551-61.
12. Rudolph JL, Ramlawi B, Kuchel GA, McElhaney JE, Xie D, Sellke FW, et al. Chemokines are associated with delirium after cardiac surgery. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2008;63(2):184-9.
13. Mietani K, Sumitani M, Ogata T, Shimojo N, Inoue R, Abe H, et al. Dysfunction of the blood-brain barrier in postoperative delirium patients, referring to the axonal damage biomarker phosphorylated neurofilament heavy subunit. PLoS ONE. 2019;14(10): e0222721.
14. van Munster BC, Aronica E, Zwinderman AH, Eikelenboom P, Cunningham C, de Rooij SE. Neuroinflammation in delirium: a postmortem case-control study. Rejuvenation research. 2011;14(6):615-22.
15. Rahimi-Bashar F, Abolhasani G, Manouchehrian N, Jiryaee N, Vahedian-Azimi A, Sahebkar A. Incidence and risk factors of delirium in the intensive care unit: a prospective cohort. BioMed Res Int. 2021;2021.
16. Rahimibashar F, Miller AC, Salesi M, Bagheri M, Vahedian-Azimi A, Ashtari S, et al. Risk factors, time to onset and recurrence of delirium in a mixed medical-surgical ICU population: A secondary analysis using Cox and CHAID decision tree modeling. EXCLI journal. 2022; 21:30.
17. Tehranineshat B, Hosseinpour N, Mani A, Rakhshan M. The effect of multi-component interventions on the incidence rate, severity, and duration of post open heart surgery delirium among hospitalized patients. J Cardiothoracic Surg. 2021;16(1):1-8.
18. Burry L, Mehta S, Perreault MM, Luxenberg JS, Siddiqi N, Hutton B, et al. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. Cochrane Database Syst Rev. 2018(6).
19. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. Nature Reviews Neurology. 2009;5(4):210-20.
20. Brown CH, Grega M, Selnes OA, McKhann GM, Shah AS, Laflam A, et al. Length of red cell unit storage and risk for delirium after cardiac surgery. ANESTH ANALG. 2014;119(2):242-50.

21. O'Neal JB, Liu X, Shotwell MS, Liang Y, Shaw A, Shah A, et al. IMPACT OF PREOPERATIVE STATIN OR BETA BLOCKER USE AND DELIRIUM FOLLOWING CARDIAC SURGERY. ANESTH ANALG. 2016;122.
22. Chen HY, Mo L, Hu HJ, Ou YL, Luo J. Risk factors of postoperative delirium after cardiac surgery: a meta-analysis. J Cardiothoracic Surg. 2021;16(1).
23. Liu X, Xie GH, Zhang K, Song SW, Song F, Jin Y, et al. Dexmedetomidine vs propofol sedation reduces delirium in patients after cardiac surgery: A meta-analysis with trial sequential analysis of randomized controlled trials. J Crit Care. 2017; 38:190-6.
24. Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, et al. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. Intensive Care Med. 2021;47(9):943-60.
25. Liu Y, Li X-J, Liang Y, Kang Y. Pharmacological prevention of postoperative delirium: a systematic review and meta-analysis of randomized controlled trials. Evid-Based Complement Altern Med. 2019;2019.
26. Ogawa M, Izawa KP, Satomi-Kobayashi S, Tsuboi Y, Komaki K, Gotake Y, et al. Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery. PLoS ONE. 2017;12(12): e0190359.
27. Lin L, Zhang X, Xu S, Peng Y, Li S, Huang X, et al. Outcomes of postoperative delirium in patients undergoing cardiac surgery: A systematic review and meta-analysis. Front Cardiovasc Med. 2022;9.
28. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International journal of social research methodology. 2005;8(1):19-32.
29. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation science. 2010;5(1):1-9.
30. Peters M, Godfrey C, McInerney P, Soares CB, Khalil H, Parker D. Methodology for JBI scoping reviews. The Joanna Briggs Institute Reviewers Manual 2015: Joanna Briggs Institute; 2015. p. 3-24.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev. 2021;10(1):1-11.
32. Alturkistani A, Greenfield G, Greaves F, Aliabadi S, Jenkins RH, Costelloe C. Patient portal functionalities and uptake: systematic review protocol. JMIR Res Prot. 2020;9(7): e14975.
33. Demir Korkmaz F, Gok F, Yavuz Karamanoglu A. Cardiovascular surgery nurses' level of knowledge regarding delirium. Nurs Crit Care. 2016;21(5):279-86.
34. Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar-Yosef S. Intraoperative Hyperglycemia and Cognitive Decline After CABG. Ann Thorac Surg. 2007;84(5):1467-73.
35. Santarpino G, Fasol R, Sirch J, Ackermann B, Pfeiffer S, Fischlein T. Impact of bispectral index monitoring on postoperative delirium in patients undergoing aortic surgery. HSR proceedings in intensive care & cardiovascular anesthesia. 2011;3(1):47-58.
36. Bellido I, Aldana E, Valverde J, Medina S, Green C, Campos V, et al. Delirium symptoms' development during the intensive care unit post-surgery staying is related with reduced intraoperative cerebral oxygen saturation in the elderly subjected to cardiac surgery. European Psychiatry. 2016;33(S1): S169-S70.
37. Lopez MG, Pandharipande P, Morse J, Shotwell MS, Milne GL, Pretorius M, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. Free Radic Biol Med. 2017; 103:192-8.
38. Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, et al. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. BR J ANAESTH. 2014;113(6):1009-17.
39. Bagheri K, Honarmand A, Hosseini-Moosa SJ. Association of mean arterial pressure during cardiopulmonary pump and incidence of delirium after coronary artery bypass graft surgery. J Isfahan Med Sch. 2017;35(449):1358-63.
40. Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H, et al. Blood Pressure Deviations from Optimal Mean Arterial Pressure during Cardiac Surgery Measured with a Novel Monitor of Cerebral Blood Flow and Risk for Perioperative Delirium: A Pilot Study. J Cardiothorac Vasc Anesth. 2016;30(3):606-12.
41. Shin HJ, Choi SL, Na HS. Prevalence of postoperative delirium with different combinations of intraoperative general anesthetic agents in patients undergoing cardiac surgery: A retrospective propensity-score-matched study. Medicine. 2021;100(33).
42. Andrejaitiene J, Sirvinskas E. Early post-cardiac surgery delirium risk factors. Perfusion. 2012;27(2):105-12.
43. Taipale P, Ratner P, Galdas P, Jillings C, Manning D, Fernandes C, et al. ANALGESIA, AND SEDATION FOLLOWING CARDIAC SURGERY: AN ASSOCIATION WITH DELIRIUM? Can J Cardiol. 2011;27(5): S348-S.
44. Taipale PG, Ratner PA, Galdas PM, Jillings C, Manning D, Fernandes C, et al. The association between nurse-administered midazolam following cardiac surgery and incident delirium: An observational study. Int J Nurs Stud. 2012;49(9):1064-73.
45. Cheraghi MA, Hazaryan M, Bahramnezhad F, Mirzaeipour F, Haghani H. Study of the relationship between sleep quality and prevalence of delirium in patients undergoing cardiac surgery. International Journal of Medical Research & Health Sciences. 2016;5(9):38-43.
46. Eertmans W, De Deyne C, Genbrugge C, Marcus B, Bouneb S, Beran M, et al. Association between postoperative delirium and postoperative cerebral oxygen desaturation in older patients after cardiac surgery. BR J ANAESTH. 2020;124(2):146-53.
47. Peyer M. THE MANAGEMENTOF POSTOPERATIVE DELIRIUM IN CARDIAC SURGERY. European Heart Journal Supplements. 2020;22(G): G121-G.
48. Javaherforoosh Zadeh F, Janatmakan F, Shafaeebejestan E, Jorairahmadi S. Effect of Melatonin on Delirium After On-Pump Coronary Artery Bypass Graft Surgery: A Randomized Clinical Trial. Iran J Med Sci. 2021;46(2):120-7.
49. Bily B, Sabol F, Turuk P, Artemiou P, Bilecova-Rabajdova M, Kolarcik P. Influence of prophylactic melatonin administration on the incidence of early postoperative delirium in cardiac surgery patients. Anesteziol Intenzivni Med. 2015;26(6):319-27.
50. Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, et al. Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium. Eur J Cardiothorac Surg. 2011;40(1):200-7.
51. Maldonado JR, Wysong A, van der Starre PJ, Block T, Reitz B. Postoperative sedation can dramatically alter the development of delirium after cardiac surgery. Psychosomatics. 2005;46(2):185-6.
52. Ottens TH, Dieleman JM, Sauer AC, Nierich AP, Nathoe HM, Van Dijk D, et al. The effect of dexamethasone on cognitive decline after cardiac surgery: a randomized clinical trial. Eur J Anaesthesiol. 2014; 31:119-.
53. Mardani D, Bigdelian H. Prophylaxis of dexamethasone protects patients from further post-operative

delirium after cardiac surgery: A randomized trial. J Res Med Sci. 2013;18(2):137-43.
54. Mardani D, Bigdelian H. Predictors and clinical outcomes of postoperative delirium after administration of dexamethasone in patients undergoing coronary artery bypass surgery. Int J Prev Med. 2012;3(6):420-7.
55. Ford AH, Flicker L, Passage J, Wibrow B, Anstey M, Edwards M, et al. The Healthy Heart-Mind trial: Melatonin for prevention of delirium following cardiac surgery: Study protocol for a randomized controlled trial. Trials. 2016;17(1).
56. Fallahpoor S, Abedi H, Mansouri M. Development and Evaluation of Care Programs for the Delirium Management in Patients after Coronary Artery Bypass Graft Surgery (CABG). International Journal of Medical Research & Health Sciences. 2016;5(7):547-53.
57. Fraser V, Cossette S, Mailhot T, Brisebois A, Dubй V. Evaluation of an Intervention with Nurses for Delirium Detection After Cardiac Surgery. Worldviews Evid-Based Nurs. 2018;15(1):38-44.
58. Shirvani F, Naji SA, Davari E, Sedighi M. Early mobilization reduces delirium after coronary artery bypass graft surgery. Asian Cardiovasc Thorac Ann. 2020;28(9):566-71.
59. Mailhot T, Cossette S, Сфтй J, Bourbonnais A, Сфтй MC, Lamarche Y, et al. A post cardiac surgery intervention to manage delirium involving families: a randomized pilot study. Nurs Crit Care. 2017;22(4):221-8.
60. Eghbali-Babadi M, Shokrollahi N, Mehrabi T. Effect of family–patient communication on the incidence of delirium in hospitalized patients in cardiovascular surgery ICU. Iran J Nurs Midwifery Res. 2017;22(4):327-31.
61. Owens JF, Hutelmyer CM. The effect of preoperative intervention on delirium in cardiac surgical patients. Nurs Res. 1982;31(1):60-2.
62. Lee J, Jung J, Noh JS, Yoo S, Hong YS. Perioperative psycho-educational intervention can reduce postoperative delirium in patients after cardiac surgery: a pilot study. Int J Psychiatry Med. 2013;45(2):143-58.
63. Zolfaghari M, Arbabi M, Razi SP, Biat K, Bavi A. Effectiveness of a multifactor educational intervention on delirium incidence and length of stay in patients with cardiac surgery. Hayat. 2012;18(1):52-66.
64. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358.
65. Li P, Lu-xi L, Zhen-zhen Z, Xie J, Cheng-long Z, Xiao-ming D, et al. Dexmedetomidine reduces the incidence of postoperative delirium after cardiac surgery: a meta-analysis of randomized controlled trials. BMC Anesthesiol. 2021; 21:1-13.
66. Tao R, Wang XW, Pang LJ, Cheng J, Wang YM, Gao GQ, et al. Pharmacologic prevention of postoperative delirium after on-pump cardiac surgery: A meta-analysis of randomized trials. Medicine. 2018;97(43).
67. Tse L, Schwarz SKW, Bowering JB, Moore RL, Burns KD, Richford CM, et al. Pharmacological risk factors for delirium after cardiac surgery: A review. Curr Top Med Chem. 2012;12(15):181-96.
68. Whitaker DC, Stygall J, Newman SP. Neuroprotection during cardiac surgery: Strategies to reduce cognitive decline. Perfusion. 2002;17(SUPPL.):69-75.
69. Bellido I, Aldana E, Valverde JL, Medina S, Green C, Campos V, et al. Delirium symptoms' development during the intensive care unit post-surgery staying is related with reduced intraoperative cerebral oxygen saturation in the elderly subjected to cardiac surgery. European Psychiatry. 2016;33: S169-S70.
70. Likhvantsev VV, Landoni G, Grebenchikov OA, Ovezov AM, Skripkin YV, Lembo R, et al. Perioperative Dexmedetomidine Supplement Decreases Delirium Incidence After Adult Cardiac Surgery: A Randomized, Double-Blind, Controlled Study. J Cardiothorac Vasc Anesth. 2021;35(2):449-57.
71. Bily B, Artemiou P, Sabol F, Bilecova-Rabajdova M, Kolarcik P, Torok P. The role of dexmedetomidine in the prevention of postoperative delirium in cardiac surgery patients. Cardiol Lett. 2015;24(6):435-44.
72. Mardani D, Bigdelian H. The effect of dexamethasone prophylaxis on postoperative delirium after cardiac surgery: A randomized trial. J Res Med Sci. 2012;17(1 SPL.1): S113-S9.
73. Xue XF, Wang P, Wang JJ, Li X, Peng F, Wang ZN. Preoperative individualized education intervention reduces delirium after cardiac surgery: a randomized controlled study. J Thorac Dis. 2020;12(5):2188-96.
74. Chevillon C, Hellyar M, Madani C, Kerr K, Kim SC. Preoperative education on postoperative delirium, anxiety, and knowledge in pulmonary thromboendarterectomy patients. Am J Crit Care. 2015;24(2):164-71.
75. Clegg A, Young J, Siddiqi N. Delirium in cardiac patients: A clinical review. British Journal of Cardiac Nursing. 2012;7(3):111-5.
76. Whitaker DC, Stygall J, Hope-Wynne C, Walesby RK, Harrison MJ, Newman SP. A prospective clinical study of cerebral microemboli and neuropsychological outcome comparing vent-line and auto-venting arterial line filters: Both filters are equally safe. Perfusion. 2006;21(2):83-6.
77. Saad H, Aladawy M. Temperature management in cardiac surgery. Global Cardiology science and practice. 2013;2013(1):7.
78. Thompson HJ, Kirkness CJ, Mitchell PH. Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury. Journal of trauma nursing: the official journal of the Society of Trauma Nurses. 2010;17(4):173.
79. Hughes CG, McGrane S, Pandharipande PP. Sedation in the intensive care setting. Clinical pharmacology: advances and applications. 2012; 4:53.
80. Polat E, Зavdar İ, Şengur K. The Effect of Earplugs and Eye Masks Usage in the Intensive Care Unit on Sleep Quality: Systematic Review. Dubai Medical Journal. 2022:1-8.
81. Reston JT, Schoelles KM. In-facility delirium prevention programs as a patient safety strategy: a systematic review. Ann Intern Med. 2013;158(5_Part_2):375-80.
82. Banerjee A, Girard TD, Pandharipande P. The complex interplay between delirium, sedation, and early mobility during critical illness: applications in the trauma unit. Curr Opin Anaesthesiol. 2011;24(2):195.
83. Nydahl P, McWilliams D, Weiler N, Borzikowsky C, Howroyd F, Brobeil A, et al. Mobilization in the evening to prevent delirium: A pilot randomized trial. Nurs Crit Care. 2022;27(4):519-27.