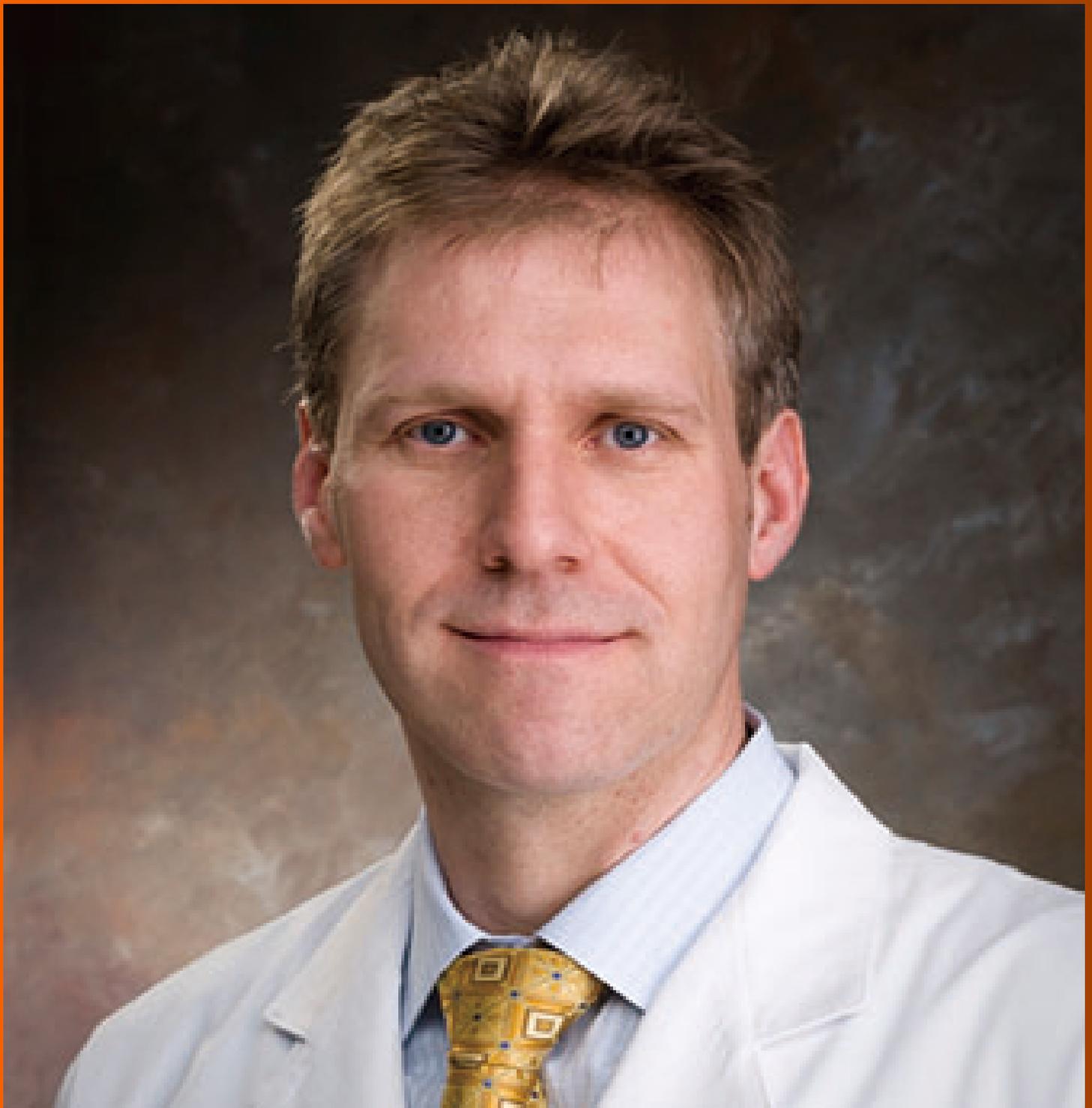


World Journal of *Critical Care Medicine*

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AIMS AND SCOPE

World Journal of Critical Care Medicine (*World J Crit Care Med*, *WJCCM*, online ISSN 2220-3141, DOI: 10.5492) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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INDEXING/ABSTRACTING

The *WJCCM* is now indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yun-Xiaojuan Wu* Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Critical Care Medicine

ISSN

ISSN 2220-3141 (online)

LAUNCH DATE

February 4, 2012

FREQUENCY

Irregular

EDITORS-IN-CHIEF

KLE Hon

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3141/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

June 12, 2019

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<https://www.wjgnet.com/bpg/gerinfo/242>

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<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

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Current controversies and future perspectives on treatment of intensive care unit delirium in adults

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Author contributions: Cascella M, Fiore M, Leone S, Carbone D and Di Napoli R contributed equally to this manuscript.

Conflict-of-interest statement: Authors declare no conflict of interests for this manuscript.

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Manuscript source: Invited manuscript

Received: February 28, 2019

Peer-review started: March 4, 2019

First decision: April 11, 2019

Revised: April 19, 2019

Accepted: May 3, 2019

Article in press: May 5, 2019

Published online: June 12, 2019

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Abstract

Delirium is the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU). Although antipsychotics are widely used to treat this serious complication, recent evidence has emphasized that these agents did not reduce ICU delirium (ICU-D) prevalence and did not improve survival, length of ICU or hospital stay after its occurrence. Of note, no pharmacological strategy to prevent or treat delirium has been identified, so far. In this scenario, new scientific evidences are urgently needed. Investigations on specific ICU-D subgroups, or focused on different clinical settings, and studies on medications other than antipsychotics, such as dexmedetomidine or melatonin, may represent interesting fields of research. In the meantime, because there is some evidence that ICU-D can be effectively prevented, the literature suggests strengthening all the strategies aimed at prevention through no-pharmacological approaches mostly focused on the correction of risk factors. The more appropriate strategy useful to treat established delirium remains the use of antipsychotics managed by choosing the right doses after a careful case-by-case analysis. While the evidence regarding the use of dexmedetomidine is still conflicting and sparse, this drug offers interesting perspectives for both ICU-D prevention and treatment. This paper aims to provide an overview of current pharmacological approaches of

P-Reviewer: Drabek T
S-Editor: Dou Y
L-Editor: A
E-Editor: Wu YXJ



evidence-based medicine practice. The state of the art of the on-going clinical research on the topic and perspectives for future research are also addressed.

Key words: Delirium; Intensive care; Haloperidol; Antipsychotic agents; Major tranquilizers; Cognitive decline; Dexmedetomidine

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Core tip: Delirium represents the most common type of acute brain dysfunction in intensive care unit (ICU). Despite no support from rigorous controlled studies, haloperidol and atypical antipsychotics have been for decades the main class of drugs used for its pharmacological management. Recently, large size studies demonstrated that antipsychotics do not significantly shorten the duration of delirium. However, because ICU delirium has multifactorial pathogenesis it is difficult to postulate that a single agent can be useful for all clinical contexts. In this manuscript we want to provide an overview of most recent pharmacological approaches for the ICU delirium treatment.

Citation: Cascella M, Fiore M, Leone S, Carbone D, Di Napoli R. Current controversies and future perspectives on treatment of intensive care unit delirium in adults. *World J Crit Care Med* 2019; 8(3): 18-27

URL: <https://www.wjgnet.com/2220-3141/full/v8/i3/18.htm>

DOI: <https://dx.doi.org/10.5492/wjccm.v8.i3.18>

INTRODUCTION

Delirium is recognised as the most frequent manifestation of acute brain dysfunction in intensive care unit (ICU) as it affects up to 80% patients, especially in the postsurgical or traumatic settings^[1]. This complication is associated with increased duration of mechanical ventilation (MV), prolonged ICU and hospital length to stay (LOS), increased rates of self-extubation, refusal of medications, and overall increased hospital costs^[2]. Of note, it has been also proved that delirium in ICU (ICU-D) represents an independent predictor for increased mortality^[3]. Furthermore, the occurrence of ICU-D and its duration seems to be associated with long-term cognitive impairment in survivors of critical illness^[4], probably due to alterations in brain structure and white-matter disruption^[5].

Clinically, the two recognized subtypes of delirium are the hyperactive type (often called "ICU psychosis") featuring agitation, hallucinations, restlessness, and the hypoactive delirium (also referred as "quiet delirium" or "acute encephalopathy") characterized by apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness. Patients may also exhibit a fluctuation between the hypoactive and hyperactive types (mixed delirium) (Table 1)^[6]. In terms of clinical relevance, hyperactive delirium has generally a low prevalence whereas the hypoactive form is very often underestimated and is associated with a worse prognosis.

Based on these premises, appropriate management of ICU-D through careful prophylaxis, early detection and treatment, is mandatory for improving patient's outcome. However, this target still remains an unmet need. While no-pharmacological interventions focused on the early recognition and correction of risk factors seems to be the more appropriate strategy to prevent delirium^[7], there are numerous controversies concerning pharmacological prophylaxis and treatment of established delirium. Of note, to date there are no United States Food and Drug Administration-approved pharmacologic therapies for ICU-D prevention or treatment. In this complex scenario, this paper aims to offer an overview of current pharmacological approaches and results from evidence based-medicine (EBM) analysis. The state of the art of the clinical research on the topic and perspectives for future research are also addressed.

CURRENT PHARMACOLOGICAL APPROACHES AND CONTROVERSIES

Table 1 Features and pharmacological management of delirium in intensive care unit

| Delirium subtypes | Notes |
|---|---|
| Hypoactive (24.5%-43.5%) ^[6] : Apathy, decreased responsiveness, slowed motor function, withdrawn attitude, lethargy, and drowsiness | Poor response to antipsychotics |
| Hyperactive (1.6%-23%) ^[6] : Agitation, hallucinations, restlessness | May respond to antipsychotics |
| Mixed (52.5%) ^[6] : Fluctuation of hypoactive and hyperactive features | Requires a careful assessment over the time |
| Prevention (Drugs) | |
| Haloperidol | Poor efficacy on ICU-D prevention and related clinical outcomes (<i>e.g.</i> , mortality). Not recommended ^[15] |
| Atypical antipsychotics | Poor efficacy. Not recommended ^[15] |
| Dexmedetomidine | Although not recommended ^[15] , low doses (<i>e.g.</i> , 0.1 µg/kg per hour) may reduce ICU-D occurrence |
| Treatment (Drugs) | |
| Haloperidol | Useful: 2-10 mg (IV every 6 h), but recommended for not routinely using (especially in hyperactive form) ^[15] |
| Atypical antipsychotics | Olanzapine (IM 5-10 mg; max: 30 mg/d), risperidone (0.5-8 mg), quetiapine (orally 50 mg; max 400 mg/d), and ziprasidone (IM 10 mg; max: 40 mg/d) ¹ . Starting regimens may need to be higher than maintenance doses; Recommended for not routinely using ^[15] |
| Dexmedetomidine | Useful, but recommended (with low quality evidence) in adults under MV, especially when hyperactive manifestations preclude weaning ^[15] |
| Short-acting benzodiazepines | Useful in patient experiencing alcohol or sedative withdrawal, or for delirium resulting from seizures; Lorazepam: IM and IV forms; no active metabolites (preferred); Midazolam: IM and IV forms; has active metabolites |
| Drug side effects | |
| Haloperidol | Insomnia, EPSs ² and agitation are the most common side effects. Dose dependent changes of EPSs. Cardiotoxicity occurs at doses > 2 mg IV |
| Atypical antipsychotics | EPSs at high doses. Olanzapine and quetiapine may lead to excessive sedation, ziprasidone is more associated with QTc prolongation |
| Dexmedetomidine | Bradycardia, and hypotension. Hypertension |
| Benzodiazepines | Delirogenic effect |

¹Compared to haloperidol, their efficacy is similar, and with less extrapyramidal side effects;

²EPSs management: dose-escalation; anticholinergic; dopamine agonist; beta blockers or even benzodiazepines for akathisia. ICU-D: Intensive care unit delirium; IV: Intravenous; IM: Intramuscular; MV: Mechanical ventilation; EPSs: Extrapyramidal symptoms; QTc: Corrected QT interval.

About pharmacological interventions (Table 1), despite no support from rigorous randomized controlled trials (RCTs), haloperidol and, subsequently, atypical antipsychotics have been for decades the main class of drugs used for the acute treatment of ICU-D. Haloperidol is a dopamine (D2) receptor antagonist used in 75%-80% of ICU-D cases^[8]. Depending on the severity of the delirium its dose may range from 2 to 10 mg (intravenous every 6 h). Common side effects of haloperidol include agitation, drowsiness, insomnia, headache, restlessness, anxiety, and mood changes. Severe side effects are extrapyramidal symptoms (EPSs) including subacute parkinsonism featuring dystonic reactions or akathisia (*i.e.*, the subjective inner restlessness and feeling to need to move), cardiotoxicity [*e.g.*, corrected QT interval (QTc) prolongation, torsade de pointes, hypotension], and neuroleptic malignant syndrome (NMS). This latter condition represents a rare but serious complication characterized by rigidity, fever, and autonomic dysfunctions (*e.g.*, tachycardia). Among all these complications, insomnia, EPSs, and agitation are the most common side effects. Concerning cardiotoxicity, it usually occurs at high doses, whereas a dosage of 2 mg haloperidol can be safely administered^[9].

Despite its wide use, several controversies regard the efficacy of haloperidol for both prevention and treatment of ICU-D. In critically ill patients, two large size (RCTs), the Hope-ICU and the REDUCE studies, showed that haloperidol administration was of limited efficacy on ICU-D prevention^[10] and compared with placebo did not improve survival at 28 d in patients with a high risk of delirium^[11]. Although there have been a number of criticisms levelled at the REDUCE's study mainly concerning design^[12] and drug regimens used^[13], it seems that this investigation offers more certainties than doubts. Furthermore, it has been demonstrated that low-dose haloperidol did not impact delirium duration and severity even when the antipsychotic was combined with other strategies such as reduced exposure to anticholinergic medications, or the benzodiazepines (BZDs)

use^[14]. Thus, a recent guideline suggests that clinicians should not use antipsychotics, either typical and atypical, to prevent delirium in adult ICU patients^[15].

Olanzapine, risperidone, quetiapine, and ziprasidone are drugs included among the atypical antipsychotics class. These drugs, also indicated as second-generation antipsychotics (SGAs) are prescribed in 35%-40% of patients with ICU-D. Functionally, they have a variety of effects on the dopaminergic, cholinergic, glutamatergic, and serotonergic (5-HT_{2A}) systems. Because SGAs have a higher ratio of 5-HT₂ to D₂ blockade, they induce a low incidence of EPSs. Interestingly, they may decrease neurotoxicity and improve cognitive function^[16]. Compared to haloperidol, the efficacy of SGAs for delirium treatment is similar, although their use was found associated with less EPSs, and lower risk of tardive dyskinesia, or NMS^[7]. However, olanzapine and quetiapine may lead to excessive sedation due to their strong antagonism at H₁ receptors, whereas ziprasidone is more associated with QTc prolongation^[17]. Recent data from the MIND-USA RCT, conducted on a large size of patients ($n = 1183$), demonstrated that compared with placebo haloperidol (maximum dose, 20 mg daily) or ziprasidone (maximum dose, 40 mg daily) did not significantly shorten the duration of delirium or coma. Furthermore, there were no significant differences on other endpoints including mortality (after 30 and 90 d), and duration of MV, or in the ICU and hospital LOS^[18]. Previously, two RCTs designed to evaluate the efficacy of SGAs on ICU-D offered contradictory results^[19,20]. Again, the sample sizes were too small to extrapolate significant data on clinical outcomes (*e.g.*, mortality, or LOS) to be useful for EBM analysis. In one study ($n = 36$), Devlin *et al*^[19] administered quetiapine by increasing its doses every 24 h added to as-needed haloperidol, and obtained good results in terms of faster ICU-D resolution, whereas there was no significant occurrence of side effects compared to placebo ($P = 1.0$). On the contrary, in the other study ($n = 101$), the authors found no significant differences with haloperidol, or ziprasidone, compared to placebo on the duration of ICU-D and MV^[20]. In summary, although the routinely use of haloperidol and SGAs have been not recommended, the short-term use of haloperidol or a SGAs may be helpful, especially in case of hyperactive delirium characterized by excessive agitation^[15]. In case of lack of response to haloperidol/SGAs, other pharmacological strategies could be evaluated in order to avoid serious dose-related side effects.

Short-acting BDZs, such as midazolam and lorazepam, are often used for sedation in ICU. Because, their delirogenic effect especially after continuous infusion^[21] has been well recognized^[22], these drugs are particularly administered for managing delirium only in patient experiencing alcohol withdrawal^[23] whereas there is no evidence to support their use in the treatment of other types of delirium^[24].

Dexmedetomidine is an alpha-2-adrenergic agonist with sedative, analgesic, and anxiolytic properties. Several investigations demonstrated that this agent may reduce the use of other sedatives and the duration of MV. Furthermore, it could be able to promote natural sleep without respiratory depression by inhibiting noradrenergic neurons in the locus coeruleus and, in turn, by inducing rapid eye movement sleep (REM) and non-REM I-III sleep states^[25]. Prophylactic low-dose dexmedetomidine (0.1 µg/kg/h; given only the first postoperative day) significantly decreases the occurrence of delirium (from 23% to 9%) during the first 7 d after non-cardiac surgery. Moreover, there was a reduction in sedative and narcotics agents administration^[26]. Other controlled investigations demonstrated that this alpha-2 agonist medication reduced the incidence and duration of ICU-D when compared with lorazepam^[27] or midazolam^[28] in patients under MV, although with a higher occurrence of bradycardia. About side effects, the administration of dexmedetomidine may induce bradycardia, and hypotension through inhibition of sympathetic activity in the periphery. Moreover, it may lead to withdrawal symptoms if abruptly discontinued, whereas limited data are available on circulatory insufficiency and mortality^[29]. Despite this limitation, a recent guideline recommends - with low quality evidence - the use of dexmedetomidine in the pharmacological management of ICU-D in adults under MV, especially when hyperactive manifestations preclude weaning^[15].

According to the theory of cholinergic deficit in delirium, van Eijk *et al*^[30] tested the cholinesterase inhibitor rivastigmine. Because the intervention did not decrease duration of delirium and, in turn, increased mortality, the RCT was prematurely terminated. The explanation for this negative finding was that plasma cholinesterase activity is impaired in ICU patients^[31], especially in those with sepsis^[32]. However, according to Opdam *et al*^[33] this agent should receive a second chance.

Multiple mechanisms of hippocampal and extra-hippocampal dysfunction due to neuroinflammation are involved in the pathogenesis of delirium^[34]. Thus, based on anti-inflammatory properties of statins, Page *et al*^[35] tested simvastatin in the prevention and treatment of delirium. The results, however, were not encouraging as duration of delirium was not shortened and high creatine kinase concentrations were registered after the statin administration.

Melatonin is a hormone released by the pineal gland with a key role in sleep and circadian rhythm regulation^[36]. In ICU patients, it has been proved a significant alteration in the sleep patterns and these findings are associated with decreased melatonin production and, in turn, with delirium occurrence^[37]. A retrospective analysis demonstrated that the exogenous administration of melatonin for at least 48 hours was associated with a significant reduction in development of ICU-D^[38]. Previously, the administration of melatonin (5 mg preoperatively) has been found to decrease incidence of postoperative delirium (POD)^[39]. Ramelteon is a melatonin receptor agonist prescribed for insomnia due to difficulty with sleep onset. In a RCT this medication (given 8 mg/d every night for 7 d) was associated with a decreased incidence of delirium^[40].

EVIDENCE BASED MEDICINE FINDINGS ON PHARMACOLOGICAL PREVENTIVE AND THERAPEUTIC STRATEGIES

In non-ICU patients, a recent Cochrane analysis found that there is poor evidence about the efficacy of typical or SGAs on the duration of delirium, length of hospital stay, discharge time, or health-related quality of life (HRQoL)^[41]. In the setting of POD, although based on small studies of limited scope, another Cochrane research showed that low dose haloperidol (< 3.0 mg/d) may be effective in decreasing the degree and duration of delirium whereas compared to the SGAs higher doses haloperidol were associated with a greater incidence of side effects^[42]. In contrast with previous EBM analysis that found that prophylactic use of haloperidol, or dexmedetomidine, may be useful for reducing the prevalence of ICU-D^[43], a recent EBM research highlighted and confirmed the poor results demonstrated through the Hope-ICU and REDUCE investigations^[44]. In summary, evidence suggests that there is no benefit from prophylactic treatment with haloperidol, or SGAs, against the development of ICU-D.

Concerning ICU-D treatment, the authors of a recent systematic overview of reviews and meta-analyses failed to identify, through their methodology, any EBM study assessing any pharmacological agents^[45]. This lack concerns also dexmedetomidine and confirmed results from the previous analysis. For instance, Chen *et al.*^[46] found no evidence on the prophylactic and therapeutic role of this medication against ICU-D and its clinical outcome when compared with BZDs or propofol. On the contrary, other meta-analysis indicated that dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol^[47], or in patients undergoing non-invasive ventilation in no-cardiac ICU^[48]. According to Maagaard *et al.*^[49], the evidence regarding the use of dexmedetomidine in the treatment of ICU-D is conflicting and sparse. As the authors designed an exhaustive protocol for a systematic review, their results could give us valuable information on the real effectiveness of the drug on delirium management^[49]. Finally, there is more uncertainty on the efficacy of anticholinesterase inhibitors as a systematic review found that these drugs offer no benefit in terms of prophylaxis, or treatment of diagnosed delirium^[50]. Selected evidence-based research on pharmacological management of ICU-D is summarized in [Table 2](#).

ON-GOING TRIALS

Several RCTs focused on pharmacological approaches for prevention and/or treatment of ICU-D are on-going. One study was designed to test haloperidol (2.5 mg haloperidol × 3 daily intravenously with additional doses to a maximum of 20 mg/daily) in a large number of ICU patients with delirium (NCT03392376). Another investigation (NCT02216266) regards the use of physostigmine (24 mg + 25 min a 0.04 mg/kg intravenously) after elective, or emergency, heart surgery. Of note, for assessing the efficacy of their treatment the authors are evaluating changes in the spontaneous EEG and auditory evoked potentials in patients with ICU-D and agitation. Researchers from the Hôpitaux de Paris are evaluating the effect of melatonin *vs* placebo. Through enteral route, low (0.3 mg/d) or high (3 mg/d) doses of the medication will be administered up to Day-14 in patients under MV (NCT03524937). Melatonin is under investigation in another RCT enrolling elderly non-ventilated patients (NCT03013790). Again, a phase II triple blind RCT comparing two doses of melatonin (0.5 mg and 2.0 mg) are currently assessing the feasibility to subsequently design a full-scale RCT (NCT02615340).

Table 2 Selected evidence-based research on pharmacological management of delirium in intensive care unit

| Ref. | Analysis | Findings |
|--|--|--|
| Burry <i>et al</i> ^[41] | Cochrane analysis | In non-ICU patients there is a poor evidence about the efficacy of typical, or SGAs, on the duration of delirium, discharge time, or HRQoL. |
| Lonergan <i>et al</i> ^[42] | Cochrane analysis | Low dose haloperidol may be effective against POD, although with greater incidence of side effects when compared to the SGAs; Limitation: analysis based on small studies of limited scope |
| Serafim <i>et al</i> ^[43] | Systematic review | Prophylactic use of haloperidol, may be useful for reducing the prevalence of ICU-D |
| Herling <i>et al</i> ^[44] | Cochrane analysis | No difference proved between haloperidol and placebo for preventing ICU-D |
| Tao <i>et al</i> ^[53] | Meta-analysis | Administration of dexamethasone was associated with a reduction in delirium after on-pump cardiac surgery; Limitation: studies at a high risk of bias |
| Barbateskovic <i>et al</i> ^[45] | Systematic overview of reviews and meta-analyses | Pharmacological strategies for prevention or management of ICU-D is poor, or sparse |
| Chen <i>et al</i> ^[46] | Cochrane analysis | No evidence on the preventive and therapeutic role of dexmedetomidine against ICU-D and its outcome |
| Liu <i>et al</i> ^[47] | Meta-analysis | Dexmedetomidine may reduce delirium and duration of MV in patients after cardiac surgery when compared with propofol |
| Pasin <i>et al</i> ^[48] | Meta-analysis | Dexmedetomidine may reduce delirium also in patients undergoing non-invasive ventilation |
| Tampi <i>et al</i> ^[50] | Systematic review | Anticholinesterase inhibitors have no benefit against ICU-D prevention, or treatment |
| Lonergan <i>et al</i> ^[24] | Cochrane analysis | There is no evidence to support the use of BDZs in the treatment of non-alcohol withdrawal related delirium |

ICU: Intensive care unit; SGAs: Second generation antipsychotics; LOS: Length of stay; HRQoL: Health-related quality of life; POD: Postoperative delirium; MV: Mechanical ventilation; BDZs: Benzodiazepines.

Based on their protocol adopted for pain control, sedation, and delirium in ICU patients (PAD protocol: Propofol or dexmedetomidine)^[51], researcher from the Duke University are evaluating its feasibility versus midazolam in post cardiac surgery patients under MV (NCT02903407). Apart from the Duke's study, because dexmedetomidine represents an interesting perspective, other RCTs on this drug are on-going. In these studies, dexmedetomidine is used at low dosage continuously (NCT03172897), or during the night of surgery in the ICU unit (NCT03624595). Dexmedetomidine is also investigated compared to propofol in specific delirium types (hyperactive or mixed type) (NCT02807467), in the setting of sepsis (NCT01739933), and with the purpose to reduce incidence and severity of delirium by restoring sleep, in not intubated patients (NCT02856594).

Despite BDZs are commonly used for discomfort, anxiety, agitation, and alcohol withdrawal syndrome in the ICU, their use may induce the so-called BDZ-associated hypoactive delirium. Researchers are testing the hypothesis that the continuous infusion of flumazenil may be able to reverse this hypoactive ICU-D type (NCT02899156).

PERSPECTIVES

In the lack of effective pharmacological strategies for the prevention and management of ICU-D, new scientific evidence is urgently needed. Further large size trials on antipsychotics should be designed, should be conducted in order to evaluate preventive pharmacological strategies. These investigations must necessarily focus on a cohort of patients recognized as at higher risk. For instance, in a no-controlled investigation conducted on high-risk patients, van den Boogaard *et al*^[52] found that prophylactic treatment with haloperidol (3 mg/d) was very effective. Pharmacological prophylactic agents other than antipsychotics should be investigated. For instance, because a meta-analysis suggested that the perioperative use of dexa-

methasone may prevent POD after on-pump cardiac surgery, studies on non-cardiac ICU patients could be encouraged^[53].

Concerning delirium therapy, investigation on different clinical settings (*e.g.*, postsurgical, or sepsis), or focused on sedated or non-sedated patients receiving assessment before and after sedative interruption, could represent an interesting perspective. Moreover, the clinical practice suggests that the hyperactive delirium type seems to respond to antipsychotics whereas the hypoactive form is usually refractory to this therapy. Indeed, because delirium has multifactorial etiology and a complex pathophysiology involving neuroinflammation, microglia activation, surgical stress response (in postsurgical patients), and neurotoxic effects due to systemic infection^[54], it is difficult to suppose that a single drug can be useful for all forms of delirium. Thus, the typology of delirium should be better typed and specific RCTs should be designed on specific ICU-D subgroups or by targeting specific symptoms such as anxiety or apathy.

Different outcomes such as delirium duration, ICU length of stay, mortality, duration of MV as well as the correlation between the severity of delirium and these clinical outcomes must be better highlighted. The issue of safety endpoints included excessive sedation and drug-related side effects could be exceeded through studies designed with defined drug regimens.

In addition, clinical studies on medications other than antipsychotics as a potential alternative or adjunct treatment could offer useful data. For instance, it seems that melatonin, and melatonin agonists (*e.g.*, L-tryptophan, and ramelteon) may offer some benefit, although clinical data are inconclusive^[55]. Positive results from studies on valproic acid^[56], or suvorexant^[57], a potent and selective orexin receptor antagonist, should encourage further attempts focused on these interesting substances. More research should be also conducted on dexmedetomidine in order to investigate its overall safety profile, and efficacy in different clinical settings. Finally, systematic reviews with low risk of bias, or addressing serious adverse events, and clinical outcomes such as those related to the HRQoL and cognitive function are urgently warranted.

CONCLUSION

Despite the huge number of clinical investigations conducted on the topic, to date results from EBM analysis highlighted that there are no effective pharmacological strategies in both prevention and management of established ICU-D. Thus, for these purposes no-pharmacological approaches must be preferred. The identification of specific risk factors and their prompt correction is certainly a winning strategy; however, given the significant clinical impact of this complication, it is necessary to offer clinicians effective and safe therapeutic opportunities. Results from several ongoing RCTs could provide useful information. Furthermore, a careful analysis of the unsatisfactory results obtained from previous research is necessary to identify possible lines of research.

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Prospective Study

Implementation of a nurse-led protocol for early extubation after cardiac surgery: A pilot study

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Author contributions: Sanfilippo F designed the research and proposed the clinical audit; Serena G, Sanfilippo F, Fletcher N designed the protocol; Sanfilippo F, Serena G, Corredor C and Fletcher N collected and analysed the data; Sanfilippo F, Corredor C wrote the paper; Fletcher N reviewed the paper.

Institutional review board

statement: As part of a clinical audit, this study received a waiver from the institutional review board.

Clinical trial registration statement:

This audit has not been registered as a clinical trial.

Informed consent statement:

Informed consent was not required, as data were collected as part of a clinical audit.

Conflict-of-interest statement:

Authors declared no conflict-of-interest.

Data sharing statement: Authors will provide full data declared in this manuscript on request.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative

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Abstract**BACKGROUND**

Protocols for nurse-led extubation are as safe as a physician-guided weaning in general intensive care unit (ICU). Early extubation is a cornerstone of fast-track cardiac surgery, and it has been mainly implemented in post-anaesthesia care units. Introducing a nurse-led extubation protocol may lead to reduced extubation time.

AIM

To investigate results of the implementation of a nurse-led protocol for early extubation after elective cardiac surgery, aiming at higher extubation rates by the third postoperative hour.

METHODS

A single centre prospective study in an 18-bed, consultant-led Cardiothoracic ICU, with a 1:1 nurse-to-patient ratio. During a 3-wk period, the protocol was implemented with: (1) Structured teaching sessions at nurse handover and at bed-space (all staff received teaching, over 90% were exposed at least twice; (2) Email; and (3) Laminated sheets at bed-space. We compared “standard practice” and “intervention” periods before and after the protocol implementation, measuring extubation rates at several time-points from the third until the 24th postoperative hour.

RESULTS

Of 122 cardiac surgery patients admitted to ICU, 13 were excluded as early weaning was considered unsafe. Therefore, 109 patients were included, 54 in the standard and 55 in the intervention period. Types of surgical interventions and baseline left ventricular function were similar between groups. From the third to the 12th post-operative hour, the intervention group displayed a higher

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Manuscript source: Unsolicited manuscript

Received: February 14, 2019

Peer-review started: February 15, 2019

First decision: March 14, 2019

Revised: March 31, 2019

Accepted: May 21, 2019

Article in press: May 22, 2019

Published online: June 12, 2019

P-Reviewer: Drabek T

S-Editor: Wang JL

L-Editor: Filipodia

E-Editor: Wu YXJ



proportion of patients extubated compared to the standard group. However, results were significant only at the sixth hour (58% *vs* 37%, $P = 0.04$), and not different at the third hour (13% *vs* 6%, $P = 0.33$). From the 12th post-operative hour time-point onward, extubation rates became almost identical between groups (83% in standard *vs* 83% in intervention period).

CONCLUSION

The implementation of a nurse-led protocol for early extubation after cardiac surgery in ICU may gradually lead to higher rates of early extubation.

Key words: Fast-track; Extubation protocol; Intensive care; Mechanical ventilation; Implementation strategies

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Core tip: Fast-track is emerging in cardiac surgery, and early extubation is a cornerstone for fast-track. Nurse-led extubation protocols may be introduced in clinical practice with different teaching techniques, aiming for early extubation.

Citation: Serena G, Corredor C, Fletcher N, Sanfilippo F. Implementation of a nurse-led protocol for early extubation after cardiac surgery: A pilot study. *World J Crit Care Med* 2019; 8(3): 28-35

URL: <https://www.wjgnet.com/2220-3141/full/v8/i3/28.htm>

DOI: <https://dx.doi.org/10.5492/wjccm.v8.i3.28>

INTRODUCTION

Close monitoring of patients is required during the early postoperative period after cardiac surgery, particularly the first few hours, in order to identify and treat potentially life-threatening complications such as bleeding and cardiovascular instability. Traditionally, patients are managed in the intensive care unit (ICU) during the initial perioperative period. Nonetheless, the evolution of surgical perfusion techniques and anaesthetic management have allowed the successful implementation of fast-track care protocols after cardiac surgery. Patients with lower levels of complexity can be safely managed in post-anaesthesia care units (PACUs) with a decreased time to extubation, shorter ICU and hospital length of stay (LOS), and possible cost reduction^[1-3]. These results have been confirmed by a Cochrane meta-analysis, which found no difference in complication rates, and outcomes between conventional care *vs* fast-track approach in low and moderate risk cardiac surgery patients. Moreover, the fast-track approach shortened time to extubation and LOS in ICU compared to conventional care^[4]. Early extubation is a cornerstone for fast-track cardiac care and is associated with shorter duration of mechanical ventilation (MV), decreased ICU and hospital LOS, and fewer postoperative respiratory complications^[5]. Conversely, prolonged MV in ICU is associated with higher incidence of pulmonary complications, increased ICU and hospital LOS and associated cost in both general ICU^[6] and in the post-cardiac surgery populations^[2,7,8].

In the general ICU setting, Kollef *et al*^[9] showed that a nurse-led extubation protocol was as safe as physician-guided extubation, showing similar complications and mortality rates, significantly reducing MV time and possibly being effective in cost reduction. In the cardiac surgery setting, the largest amount of studies evaluating the safety and advantages of early extubation are based in the PACU, where staff are usually more experienced in rapid extubation than ICU personnel, and often have a higher physician-to-patient ratio.

Early extubation following cardiac surgery can be also used as a performance indicator in cardiac surgical centres^[10]. Achieving safe early extubation depends on many contributing factors comprising the pre, intra and postoperative periods. Early extubation also relies on the successful coordination of efforts from multiple disciplines, *i.e.*, nursing, surgery, anaesthesia and critical care.

In our study, we aimed to evaluate the results of the implementation of a nurse-led protocol for early extubation after cardiac surgery in ICU as part of a quality improvement initiative. Research Ethics committee authorization and informed consent were not required to perform this study.

MATERIALS AND METHODS

This was a single centre prospective study in an 18-bed Cardiothoracic ICU across an 11-week period (11.08.2014 – 21.12.2014). Our Cardiothoracic ICU is a closed critical care consultant-led ICU admitting patients after cardiac, thoracic and vascular procedures. During the period of study, the Cardiothoracic ICU was staffed with a team of two consultants from 8:00 to 18:00 and one consultant during the night hours with junior doctor support. Patients mechanically ventilated after cardiac surgery received nursing care in a one-to-one ratio.

In the two years preceding this study, almost 1000 cardiac surgical cases per year were performed at our institution with an average of 80% being admitted to the Cardiothoracic ICU. The remaining 20% was managed in the fast-track PACU. In this study, we aimed to evaluate the results of the introduction of a nurse-led protocol for early extubation after cardiac surgery. Before the implementation of the nurse-led protocol, patients after cardiac surgery were extubated according to the decision of the treating physician. A simplified nurse-led protocol for extubation after cardiac surgery was introduced as part of a quality improvement initiative. A small steering group wrote a draft of the nurse-led protocol, which was reviewed, modified and approved by all of the Cardiothoracic ICU consultants and senior nurses. The final version of the protocol is shown in [Figure 1](#). The protocol did not involve any changes in the anaesthetic or surgical intraoperative management.

The study was divided into two periods of eight weeks each. The “standard practice” period, 11/08/2014 to 05/10/2014 and the “intervention” period, 27/10/2014 to 21/12/2014 ([Figure 2](#)). We anticipated approximately 100 patients per period. The overall data collection included the following time-points: admission, 1st - 2nd - 3rd - 4th - 5th - 6th - 9th - 12th - 15th - 18th - 24th postoperative hour. Data were collected in a pre-defined sheet by the bed-space nurse and entered into spread-sheet software (Microsoft Office Excel 2011). Patients admitted to the ICU were included in the nurse led protocol, unless a consultant anaesthetist/intensivist or cardiac surgeon stated it would have not been safe to extubate the patient early, based on both pre-morbid status and/or intraoperative course. Therefore, for this pilot study, we followed a pragmatic approach for the inclusion of patients in the nurse-led extubation pathway.

Implementation strategy

The two study periods were separated by a three-week period (06/10/2014 – 26/10/2014) dedicated to teaching the new protocol to all nursing and medical staff using short small group sessions held by the members of the steering group. Additionally, we delivered one to one bed-side teaching to the nursing staff. An attendance form was kept to ensure that all staff received frontal teaching. This resulted in over 90% of the staff exposed to this teaching at least twice. The protocol was disseminated *via* email to the entire staff, and laminated sheets containing the protocol were printed and distributed at each bed-space with additional copies available in the staff room.

Characteristics of the new protocol

As shown in [Figure 1](#), the new protocol set a target of extubation from operating theatre arrival by the third postoperative hour, if conditions specified by the protocol were met. The bedside nurse was in charge of implementing the protocol from arrival with setting of pre-specified parameters for titration of sedation and analgesia. Mechanical ventilation settings following a “lung protective strategy” were also outlined in the protocol. Within one hour from arrival, the bedside nurse confirmed the absence of several exclusion criteria (excessive bleeding and/or tamponade, metabolic and hemodynamic derangements, hypoxia and or hypercarbia, hypothermia) against a checklist, before decreasing sedation levels and attempting to start pressure support ventilation mode. From the second postoperative hour, or whenever criteria for extubation were met, nurses were asked to wean sedation and mechanical ventilation in order to extubate by the third postoperative hour, after confirming the clinical decision with the senior nurse in charge or with the doctor on duty. Bedside nurses informed the senior nurse in charge and/or the doctor on duty in case of clinical issues or uncertainty.

Outcomes

The primary outcome of our study was that a proportion of patients extubated at different pre-defined time-points (from the third until the 12th postoperative hour). Secondary outcomes were re-intubation rates within 12 hours from extubation and adherence to a lung protective ventilation strategy. Lung protective was defined as a tidal volume of 6-8 mL/kg ideal body weight.

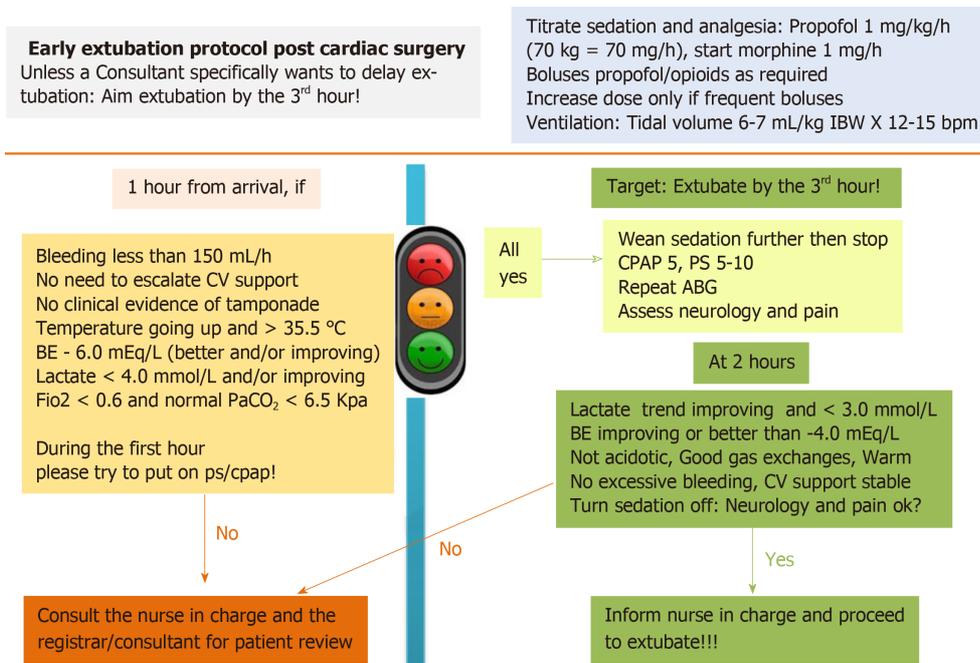


Figure 1 Protocol for the management of patients after cardiac surgery. ABG: Arterial blood gas; BE: Base excess; CPAP: Continuous positive airway pressure; CV: Cardiovascular; IBW: Ideal body weight; PS: Pressure support.

Statistical analysis

Formal sample size calculation was not performed in this study, but assumption on the length of each period was made based on average number of cardiac surgery intervention admitted to the Cardiothoracic ICU.

The Kolmogorov-Smirnoff test, histograms and normal quartile plots were examined to test for the normality assumption of continuous variables. Continuous variables are presented as mean (SD) with 95% confidence interval (95%CI) or median [(interquartile range) (IQR)] and categorical variables as number and percentage (%). A Wilcoxon signed rank test was then used to detected differences among pairs of samples. Categorical variables were compared through the Chi-square test with Yates correction. All tests were two-sided, and a result of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using IBM® SPSS® Statistics 17 for Windows.

RESULTS

During the two study periods, a total of 122 postoperative cardiac surgical patients were admitted to the cardiothoracic ICU, 60 in the standard practice and 62 during the intervention period. Thirteen patients (six in the standard practice period and seven in the intervention period) were excluded from the early extubation protocol at the discretion of the attending consultant due to complex surgery, comorbidities or intraoperative issues. Therefore, data from a total of 109 patients were collected, 54 in the standard practice and 55 in the intervention period.

Patients in the “standard period”, as compared to the “intervention period”, had similar height (168.3 ± 9.7 cm *vs* 170.8 ± 8.8 cm respectively, $P = 0.11$) and age (66.5 ± 11.7 *vs* 65.7 ± 10.9 , respectively, $P = 0.74$) and body weight (76.8 ± 13.4 kg *vs* 82.3 ± 14.8 kg, respectively, $P = 0.07$). In both periods, male patients represented 76% of the population ($P = 0.96$).

The types of interventions were similar between groups. The two most common surgical intervention were isolated elective coronary artery surgery ($n = 31/54$, 57% of all surgeries during the “standard period” *vs* $n = 27/55$, 49% in the “intervention period”, $P = 0.50$) and coronary surgery associated to aortic valve replacement ($n = 7/54$, 13% “standard period” *vs* $n = 5/55$, 9% “intervention period”, $P = 0.73$). The groups were also comparable with regards to their baseline LV function (Table 1).

Extubation rates

Extubation rates did not differ between the two study groups at the third post-operative hour. However, from the third to the 12th post-operative hour, the inter-

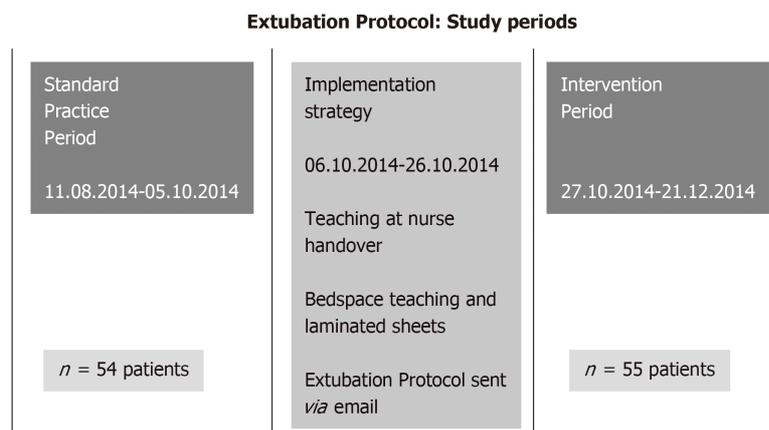


Figure 2 Study periods. Three study periods were identified: "standard practice", "implementation" and "intervention". The duration of each period is indicated in the figure.

vention group displayed a higher proportion of patients extubated compared to the standard group. The difference was only statistically significant at the sixth postoperative hour (37% in the standard *vs* 58% in the intervention period, $P = 0.04$). A non-significant trend towards higher extubation rates in the intervention period was found from the fourth until the ninth postoperative hour (fourth hour: $P = 0.12$; 5th h: $P = 0.13$; ninth hour: $P = 0.10$). From the 12th post-operative hour time-point onward, extubation rates became almost identical between the groups (Figure 3). Only one patient in the standard group and two patients in the intervention group were re-intubated within 12 h after extubation. All cases were due to respiratory failure, and the difference between periods was not statistically significant ($P = 0.99$).

Lung protection

Patients were ventilated with similar positive end-expiratory pressure (PEEP) levels throughout the postoperative period between groups. More than 99% of PEEP values recorded were 5 cmH₂O or above in both groups. There was an acceptable degree of adherence to the indication regarding the TV, with less than 7% of patients in both groups ventilated with 8 mL/kg or higher, and in most cases, such TV were achieved in pressure support ventilation mode.

DISCUSSION

Early extubation is a cornerstone in fast-track care protocols after cardiac surgery, and it has been repeatedly investigated in dedicated PACU settings. Our study found that early extubation following the introduction of a nurse-led protocol can be implemented in a cardiovascular ICU setting, possibly resulting in a greater number of early extubations.

The early extubation project constitutes the initial stages of a quality cycle aimed to streamline and standardize patient flow in our cardiovascular ICU to improve patient outcomes. We observed statistically significantly higher rates of extubation in the intervention group at the sixth postoperative hour ($P = 0.04$). Although non-significant, we saw also a trend towards higher extubation rates from the fourth until the ninth postoperative hour. We believe that our study was underpowered to detect significant differences in extubation rates between the study groups. Indeed, there was a lower-than-expected number of patients included in the study due to unplanned reduction in our case-load. Therefore, it remains speculative that collecting a higher number of cases would have resulted in an earlier and larger separation of the extubation rate curves. From the 12th postoperative hour, the curves of patients extubated did not differ between the two investigated periods, likely because patients mechanically ventilated beyond this stage were not suitable for early extubation and that the reduced number of cases had no impact after the 12th postoperative hour. We found similar compliance with TV and PEEP levels compatible with a lung protective strategy in both groups, which probably reflects the widespread practice of lung protective ventilation in modern ICUs.

We acknowledge that our protocol failed to boost the target set by our protocol of increasing extubation rates as early as two hours after cardiac surgery. This is not unexpected, since adopting a new and faster protocol may take time. Resistance to

Table 1 Distribution of left ventricular function between the pre- and post-implementation of extubation protocol

| | Before the implementation of extubation protocol (<i>n</i> of patients) | After the implementation of extubation protocol (<i>n</i> of patients) |
|--------------------------------|--|---|
| Normal LV function | 41 | 40 |
| Mild-to-moderate LV impairment | 11 | 14 |
| Severe LV impairment | 2 | 1 |
| Total | 54 | 55 |

LV: Left ventricular.

sudden changes in clinical practice is not uncommon. Nevertheless, studies in other scenarios have shown that improvements in clinical practice can be obtained when new interventions are introduced using a continuous education program leading to improving outcomes in critically ill patients^[11]. The need for a learning curve based on experience is likely, and this should be taken into account as well. Moreover, the lower-than-expected number of cases included in our study probably reduced staff exposure to the new strategy on early extubation, which in turn may have slowed the learning curve process. We believe our strategy for implementing the new protocol was well-designed and had the advantage of making the personnel more comfortable with the new approach.

Extubation remains a challenging perioperative stage with a higher number of perioperative respiratory complications occurring at the extubation rather than during the intubation process (12.6% *vs* 4.6%)^[12]. Furthermore, extubation may expose fragile cardiac patients to significant shifts in intrathoracic pressures, which can lead to a number of cardiac complications such as pulmonary oedema due to left ventricular dysfunction. Therefore, safe extubation demands a systematic approach, especially in the setting of complex surgery in patients with significant comorbidities. Early extubation of patients after cardiac surgery involves multiple tasks, such as appropriate sedation and analgesia titration, frequent neurological assessment, continuous evaluation of haemodynamic stability, progressive respiratory weaning, careful temperature control and assessment of bleeding. Our protocol covered all of the aspects mentioned above. We believe that these tasks can be satisfactorily accomplished by trained and motivated nurses, with the back-up support of experienced medical staff. In the general ICU, a large study showed that a nurse-led extubation protocol had similar complications and mortality rates than physician-guided extubation and significantly reduced MV time, possibly having positive effects on cost saving^[9].

Our study has the value of investigating the implementation of a structured nurse-led protocol for early extubation after cardiac surgery in a Cardiothoracic ICU with a 1:1 nurse-to-patient ratio for ventilated patients. However, in the cardiac surgery setting, the largest amount of studies evaluating safety and advantages of early extubation are based in the PACU, where staff have more experience in extubation than the ICU personnel. Moreover, PACU usually has a higher consultant-to-patient ratio compared to ICU. For instance, Probst *et al*^[13] recently compared post-cardiac surgery management in PACU *vs* cardiac ICU and found a significant shorter extubation time and a higher rate of extubation within the first six postoperative hours in hemodynamically stable, normo-thermic, non-bleeding patients admitted to PACU as compared to a similar group of patients admitted to ICU. Moreover, PACU patients had shorter LOS before step-down and less arrhythmic complication, with no difference in other complication rates. When looking at such results, it is worthwhile noting some of the structural differences between PACU and ICU in this study: (1) 3-bed PACU *vs* 21-bed ICU; (2) Dedicated post-cardiac surgery PACU *vs* mixed ICU; and (3) 1:3 consultant-to-patient ratio in PACU and 1:12 in ICU. Considering these structural differences together with the usually higher airway skills of PACU staff, the observed differences are not surprising.

The most important limitation of our study is the lower than expected number of cases collected in the study period. We were able to analyse data from only 105 patients rather than the estimated target of 200. A second limitation is the lack of standardisation of anaesthetic management that likely influenced the neurological appropriateness for extubation. A third limitation of this study is that safety could not be fully evaluated with such small numbers; although only three patients were reintubated after extubation, this is not an infrequent event after cardiac surgery, and larger numbers are required to fully evaluate the safety of early extubation in Cardiothoracic ICU after cardiac surgery. Finally, protocols implementing nurse-led

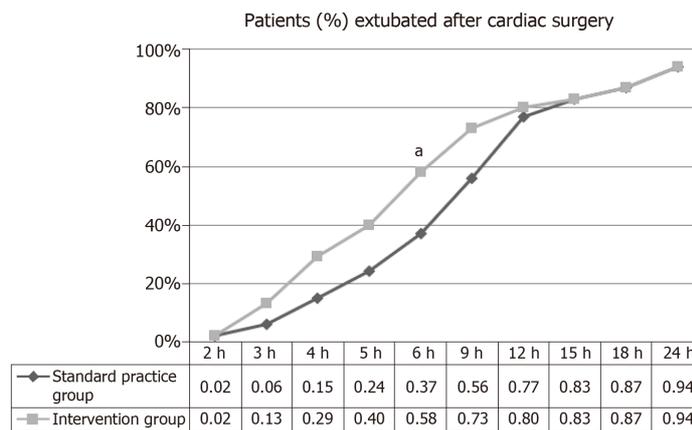


Figure 3 Rates of patients extubated at different time-points. The analysis starts at the third postoperative hour. Standard practice group is shown in black colour (series 1) and intervention group in grey (series 2). * $P < 0.05$, standard practice group vs intervention group.

extubation should take into account the staff skills and knowledge. Our results should be interpreted, considering that in the United Kingdom, there is a very high level of training and continuous re-training for nurses. Other countries and Healthcare Systems with lower resources may struggle in providing such level of training and therefore the practice of nurse-led extubation after cardiac surgery may not be practical.

The study covered the data acquisition, pattern analysis, interpretation and change in action stages necessary to initiate a quality cycle^[14]. Our intention is to complete the quality cycle by acquiring further data for a larger cohort of patients and periodical evaluation of outcomes.

In conclusion, we implemented a nurse-led protocol for early extubation in the Cardiothoracic ICU with structured teaching and training. Although the extubation rates were similar by the third postoperative hour, a higher rate of patients in the intervention group was extubated by the sixth postoperative hour. We did not have enough data to establish the safety of our early extubation protocol.

ARTICLE HIGHLIGHTS

Research background

Nurse led-extubation is safe in the general intensive care unit (ICU) setting, but data in field of cardiac surgery are scarce and limited to post-anaesthesia care units.

Research motivation

Nurse-led extubation protocols may help in shortening postoperative mechanical ventilation, thus expediting patient recovery after cardiac surgery.

Research objectives

To evaluate the results of the implementation of a nurse-led extubation protocol.

Research methods

In a single centre prospective study during a 3-wk period, we implemented a nurse-led extubation protocol in patients admitted after cardiac surgery. The protocol was implemented with structured teaching sessions at nurse handover, teaching at bed-space, information provided *via* email and apposition of laminated sheets with the protocol at each bed-space. We performed a comparison of before and after protocol implementation (“standard practice” and “intervention” periods, respectively), measuring extubation rates at several time-points from the third until the 24th postoperative hour.

Research results

We included 109 patients, 54 in the standard and 55 in the intervention period. Although the intervention group displayed a higher proportion of patients extubated from the third to the 12th post-operative hour compared to the standard group, results were significant only at the sixth hour (58% *vs* 37%, $P = 0.04$) and not different at the third hour (13% *vs* 6%, $P = 0.33$). After the 12th post-operative hour time-point onward, extubation rates become almost identical between groups.

Research conclusions

The implementation of a nurse-led protocol for early extubation after cardiac surgery in the cardiac ICU may gradually lead to higher rates of early extubation.

Research perspectives

The present study adds information regarding a growing body of literature of fast-track extubation and identifies a nurse-led protocol as a possible intervention that shortens the length of mechanical ventilation in patients recovering after cardiac surgery. The study findings should be interpreted in the context of the level of training and the nurse-to-patient ratio.

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