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Review Article

NEUROSCIENCE AND NEUROANAESTHESIA

Postoperative delirium: perioperative assessment, risk reduction, and management

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Summary

Postoperative delirium is a relatively common and serious complication. It increases hospital stay by 2–3 days and is associated with a 30-day mortality of 7–10%. It is most prevalent in older patients, those with existing neurocognitive disorders, and those undergoing complex or emergency procedures. Preclinical and clinical research in recent years has uncovered more about the pathophysiology of postoperative delirium and may yield more potential therapeutic options. Using the enhanced recovery pathway framework of risk stratification, risk reduction, and rescue treatment, we have reviewed the current clinical evidence on the validity of delirium prediction scores for the surgical population, the effectiveness of perioperative delirium risk reduction interventions, and management options for established delirium. Effective perioperative interventions include depth of anaesthesia monitoring, intraoperative dexmedetomidine infusion, and multimodal analgesia. Choice of general anaesthetic agent may not be associated with significant difference in delirium risk. Several other factors, such as preoperative fasting, temperature control, and blood pressure management have some association with the risk of postoperative delirium; these will require further studies. Because of the limited treatment options available for established delirium, we propose that risk assessment and perioperative risk reduction may be the most effective approaches in managing postoperative delirium.

Keywords: delirium; neurocognitive dysfunction; pharmacotherapy; postoperative cognitive dysfunction; prevention; risk management

Editor's key points

- Postoperative delirium is a serious problem that is associated with prolonged hospital stay and increased mortality.
- The authors review the pathophysiology of postoperative delirium, identifying risk factors and potentially modifiable factors.

Delirium is a cognitive disturbance characterised by acute and fluctuating impairment in attention and awareness. Postoperative delirium commonly occurs between postoperative days 2–5. Although its incidence in the general surgical population is 2–3%, it has been reported to occur in up to 50–70% of high-risk patient groups.[1,2] In addition, the occurrence of postoperative delirium is associated with considerably raised morbidity and mortality, and increased healthcare resource expenditure.

Animal and human studies have led to the development of several hypotheses regarding the pathophysiology of postoperative delirium; with it, novel treatments are being proposed and developed. However, there are currently limited treatment options available for clinical use. To date, the most effective approach to postoperative delirium management has been the use of risk reduction measures such as reorientation, dexmedetomidine, and melatonin. In addition, there is

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currently limited consensus on the best perioperative practices (such as the fasting time, choice of anaesthesia, perioperative fluids, and BP management) for reducing the risk of delirium.

With the development of enhanced recovery pathways, the framework of risk assessment, risk reduction, and rescue treatment has been applied to several postoperative complications (Fig. 1). Using this framework, we conducted a systematic literature search on EMBASE and Medline, for relevant papers published in English between 2000 and 2019. The search terms were decided based on the American Society for Enhanced Recovery, Perioperative Quality Initiative and European Society of Anaesthesiology guidelines, and other common perioperative considerations[3,4]; the detailed search strategy is listed in the Supplementary Table S1. The search was completed on January 28, 2020, and active literature surveillance continued until March 30, 2020. The findings of the literature are summarised as a narrative review, with discussion on the current clinical evidence for the use of delirium risk prediction scores, perioperative interventions for delirium risk reduction, and treatment options for established delirium.

Epidemiology and healthcare cost

In the general surgical population, the incidence of postoperative delirium is reported to be 2.5–3%.[5,6] In patients aged more than 60–70 yr, the incidence of postoperative delirium is considerably higher at 10–20%.[7–9] Elective extremities surgery is associated with a 2.5–3% risk of postoperative delirium[10]; in comparison, truncal surgery is associated with a 10–20% risk.[11,12] Emergency surgery is associated with a 20–45% risk of postoperative delirium which is 1.5 to three times higher than comparable non-emergency surgery.[13,14] Complex surgeries requiring postoperative critical care management, such as cardiothoracic and hepatic surgeries, are associated with 20–50% risk of postoperative delirium.[15–17] Most notably, neck of femur fracture repair is associated with up to 70% risk of postoperative delirium.[12] There are several explanations: a neck of femur fracture is commonly associated with frail older patients; perioperative pain is a significant issue; and the surgery is usually done in an emergency setting with limited opportunity for preoperative optimisation.

The occurrence of postoperative delirium lengthens hospital stay by 2–3 days and ITU stay by 2 days.[17–19] Postoperative delirium is also associated with a 30-day mortality of 7–10%, compared with 1% in those without delirium.[19,20] In addition, postoperative delirium is associated with significant functional decline and a two to three times higher risk of needing care facilities on discharge.[21,22] The occurrence of postoperative delirium is associated with significantly higher healthcare costs, estimated between £2000 and £8000 additional cost per case.[6,17]

Pathophysiology

There are several theories regarding the pathophysiology of postoperative delirium based on findings from animal models; however, evidence from human studies is currently limited.

Neuroinflammation

One possible pathophysiological mechanism for postoperative delirium is neuroinflammation. Systemic inflammatory mediators are increased significantly after surgery and remain high during the postoperative period.[23,24] It has been reported that postoperative elevation of peripheral C-reactive protein (CRP) and interleukin 6 concentrations is associated with higher risks of postoperative delirium.[25] Interestingly, the authors also

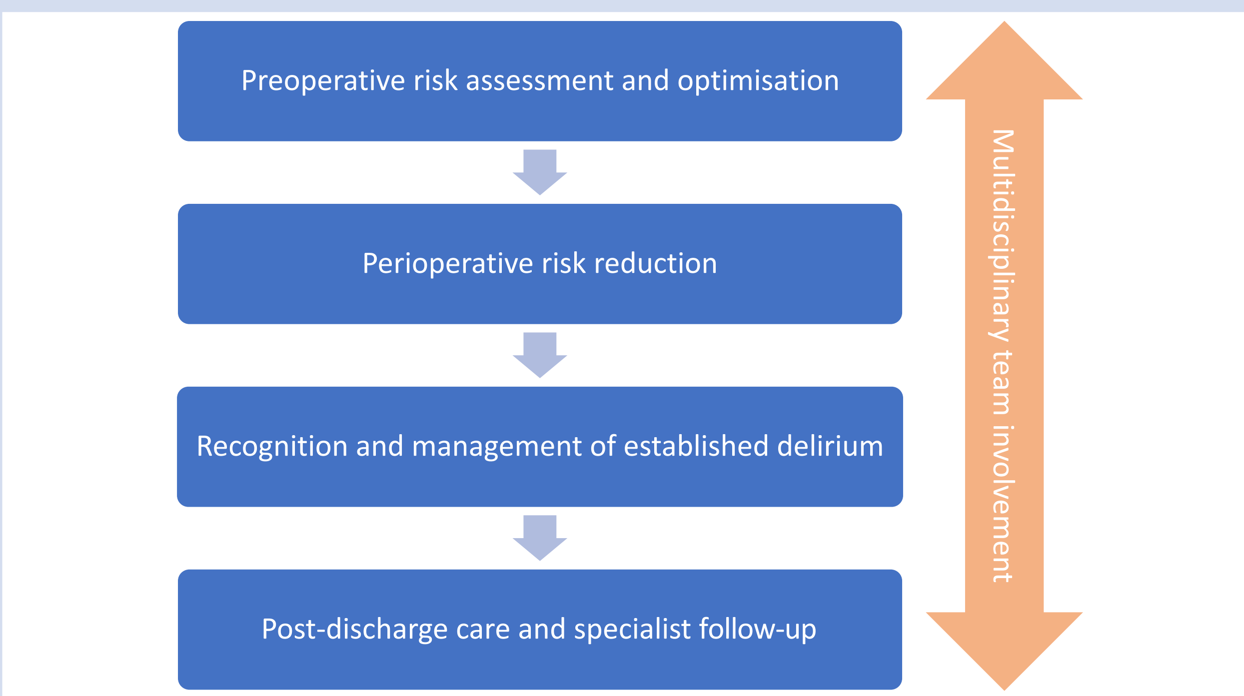

Fig 1. Proposed framework for optimising the management of postoperative delirium (POD).

found that increased preoperative concentrations of CRP and interleukin 6 are also associated with an increased risk of postoperative delirium, thus supporting the hypothesis that preoperative pathologies may also contribute to the risk of subsequent postoperative delirium. Previous studies have shown that preoperative peripheral injuries, such as fractures, are associated with increased inflammatory mediators in the CSF[26,27]; this suggests that peripheral pathology can lead to an increased inflammatory burden in the CNS. Preclinical studies have demonstrated that peripheral inflammation can lead to the loss of structural and functional blood brain barrier integrity[28−30] and subsequently translocation of inflammatory cells and mediators into the CNS.[31] The accumulation of inflammatory mediators then results in the loss of synaptic plasticity,[32] neuro-apoptosis,[33] and impaired neurogenesis.[34] It is thought that amyloid-β deposition may occur as a result of neuroinflammation and anaesthetic exposure; however, a recent study reported that older patients who underwent multiple surgery under general anaesthesia did not demonstrate significantly high amyloid-β. However, the study reported that multiple surgery and anaesthesia is associated with significantly higher risk of abnormal cortical thickening.[35]

Neurotransmitters

Another possible pathophysiological mechanism for postoperative delirium is the alteration in neurotransmitters. Acetylcholine is thought to be involved in the neuroplasticity, and is present in several neural pathways responsible for attention and memory.[36,37] A recent observational study in cardiac surgery patients indicated that patients with postoperative delirium had lower acetylcholinesterase both preoperatively and up to 2 days postoperatively, and that low acetylcholinesterase activity was an independent risk factor for developing postoperative delirium, as are centrally acting anticholinergic medications (such as amitriptyline).[38] Similarly, another observational study of older patients undergoing noncardiac surgeries also found that patients with delirium had lower postoperative acetylcholinesterase activity.[39] Several dopamine receptors and transporter gene polymorphisms have been found to alter the risk of postoperative delirium,[40] confirmed in a recent meta-analysis.[41] Two small studies have shown that patients with delirium have altered monoamine metabolism, although this is not confirmed to be an independent risk factor through multivariable analysis.[2,42]

Subclinical cerebral vascular events

It was reported that diseases which increase the risk of cerebral vascular events, such as hypertension, atrial fibrillation, and previous stroke, are all risk factors for developing postoperative delirium.[43,44] Although the risk of overt postoperative stroke is rare, radiological evidence of cerebral ischemia can be seen in 7−10% of older surgical patients, and this is associated with more than double the risk of postoperative delirium.[45,46] A small cohort study of lung transplant patient showed that every 10 mm Hg reduction in cerebral perfusion pressure is associated with double the risk of postoperative delirium.[47] Another study retrospectively analysed the association between cerebral perfusion pressure (estimated using cerebral oximetry) and delirium, and found that cerebral perfusion pressure above the autoregulatory limit is an independent risk factor for the development of postoperative delirium.[48]

Preoperative risk prediction

Management of postoperative delirium can be categorised into risk stratification, risk reduction, early diagnosis, and treatment (Fig. 1). With appropriate risk stratification, postoperative delirium could then be managed through risk reduction measures and prophylactic interventions; it would also be possible to monitor high risk patients more closely and implement treatments more promptly. With the development of enhanced recovery pathways, similar frameworks have been proposed and successfully implemented by several international consensus groups for the management of other common postoperative complications.[49,50]

As discussed above, high-risk surgical procedures for postoperative delirium include abdominal and pelvic surgery,[11,12] major emergency surgeries,[13,14] and complex surgeries requiring postoperative intensive care admission.[15−17] In addition, there is a wide range of patient factors strongly associated with increased risk of postoperative delirium. Studies have found that surrogates for comorbidity burden, such as the ASA and Charlson Comorbidity Score,[18,51] and histories of neurological, cardiac, respiratory, and metabolic diseases are risk factors for developing delirium.[43,52−55] Another important aspect of the risk assessment is the patient's functional baseline, such as sensory deficits.[56] In the acute setting, metabolic derangement and pain are also risk factors for developing delirium.[43,55]

In order to further quantify patients' risk for developing postoperative delirium, and to allow efficient healthcare resources allocation, various risk prediction scores have been developed. For example, Inouye and colleagues[57] proposed a delirium risk score based on admission characteristics, which consisted of Mini-Mental State Examination score, Acute Physiological and Chronic Health Evaluation II (APACHE) score, vision score, and blood urea nitrogen/creatinine ratio. This has been validated by Kalisvaart and colleagues[58] in a hip surgery cohort, in which patients with no risk factors had <1% risk of developing postoperative delirium, whereas patients with more than two risk factors had >30% risk of developing delirium. More recently, Kim and colleagues[59] reported a study of more than 6000 patients with hip fractures, and proposed a nine-item scoring system: preoperative delirium, dementia, age, medical comorbidity, ASA grade, functional dependence, smoking, presence of systemic inflammatory response syndrome, and preoperative mobility aid use.

One of the main limitations of using risk scores is that most risk scores are validated using either medical patients, or in one specific surgery type, which weakens the translatability of the score to the general surgical population.[60] The Delirium Prediction Based on Hospital Information (DELPHI) score consists of 10 items with variable weighting. It was internally validated in a cohort of 553 surgical patients (including abdominal, vascular, and trauma surgeries), and was reported to have a positive predictive value of 70% and a negative predictive value of 95%.[61] As it is a single-centre study, it will require external validation to ensure reliability.

Risk-reducing interventions

As we will discuss below, optimal management of postoperative delirium requires the implementation of multicomponent interventions, which are often delivered by different disciplines and specialists. The success of a delirium management program is therefore dependent on the participation and coordination of the multidisciplinary team. Several observational studies and clinical trials have reported that implementation of multidisciplinary delirium care programs can reduce the incidence and severity of postoperative delirium, shorten the duration of delirium, and is also associated with improved mortality and morbidity.[62–64] In this section, we will discuss the evidence base on various delirium risk reducing interventions.

Preoperative interventions

Avoiding perioperative polypharmacy

Polypharmacy is commonly associated with advanced age and presence of multiple comorbidities, both of which increase the risk of postoperative delirium. Polypharmacy itself is also an independent risk factor for the development of delirium in the older population.[65] A large number of medications are thought to directly increase the risk of delirium,[66] while drug-drug interaction is also a significant concern in older patients who take multiple medications.[67]

Avoiding prolonged (>6 h) fluid fasting

Although 2 h of fluid fasting is recommended to allow gastric emptying, patients are often fasted for significantly longer in practice. Prolonged fasting results in dehydration and unnecessary use of i.v. fluids, and other perioperative complications such as nausea and vomiting. A large cohort study found that fluid fasting for more than 6 h is an independent risk factor for developing postoperative delirium, with an odds ratio of 10.6.[68]

Comprehensive geriatric assessment

Comprehensive geriatric assessment (CGA) is a multidisciplinary approach to systematically evaluating and addressing the often complex care needs in older patients. In addition to expert-led medical review, patients' functional, psychological, and social issues are explored before surgery, and individualised plans are made in advance in order to optimise patients for surgery and the postoperative recovery. There is now robust evidence that CGA-based perioperative care improves postoperative outcomes. Several studies have shown that CGA-based care can reduce the risk of postoperative delirium and this is attributed to better identification of delirium risk factors, and proactive initiation of multimodal delirium risk management in higher risk patients.[69,70]

Preoperative pain management

Several observational studies have found that preoperative pain is associated with a 1.5 to three times higher risk of postoperative delirium.[71,72] Pain imposes a direct cognitive burden, triggers an acute stress response, and increases the risk of other postoperative complications, such as atelectasis, which may also cause delirium. Steenberg and Moller[73] conducted a systematic review on preoperative use of the fascia iliaca block for neck of femur fracture; they identified two relevant studies, and the pooled data suggest that fascia iliaca block reduces the risk of delirium. Early repair of femur fractures also reduces pain, which may in turn reduce the risk of delirium, although there is limited evidence available on the topic.

Intraoperative interventions

Depth of anaesthesia monitoring

It is thought that excessively deep anaesthesia in conjunction with patient and surgical risk factors may increase the risk of postoperative delirium,[74] and anaesthetic sensitivity varies significantly between individuals. As a result, several studies have investigated the association between depth of anaesthesia monitoring (using processed EEG) and postoperative delirium. Meta-analyses reported that depth of anaesthesia monitoring is associated with a significantly lower risk of postoperative delirium[75,76]; however, a meta-analysis by Miao and colleagues[77] reported that the pooled results favoured bispectral index (BIS) monitoring, but the difference is not statistically significant (odds ratio 0.69, P=0.05). This difference may likely be attributable to the inclusion of different studies; for example, MacKenzie and colleagues[75] included all depth of anaesthesia monitoring studies, whilst Miao and colleagues[77] only included the use of BIS in patients more than 60 yr old. Further studies are needed to further clarify the benefit of depth of anaesthesia monitoring.

Use of multimodal opioid-sparing analgesia

Pain is the most common complication after surgical procedures. Observational studies have found that a higher postoperative pain score is associated with increased risk of delirium.[54,78,79] Conversely, the use of opioids (particularly longer-acting opioids) has also been associated with increased risk of postoperative delirium.[80] These suggest that the use of a multimodal opioid-sparing analgesia regime is likely to be the optimal management option in minimising postoperative delirium.

One of the main strategies for reducing postoperative opioid requirement after major surgeries is the use of regional and neuraxial anaesthesia. When used appropriately, regional anaesthesia provides effective analgesia, and may also reduce the acute stress response.[81,82] Patel and colleagues[83] conducted a meta-analysis on regional anaesthesia in hip fracture repair and postoperative delirium. They identified 15 prospective and retrospective studies, most of which reported no statistical difference; qualitative analysis was not attempted. However, it is worth noting that most of the included studies are too small to have adequate statistical power. Conversely, there are two larger observational studies which reported that use of regional anaesthesia is independently associated with a 20–40% lower incidence of delirium.[10,80]

Use of paracetamol and NSAIDs

NSAIDs and paracetamol are commonly used as part of multimodal analgesia after surgery; moreover, it has been suggested that these drugs may prevent postoperative delirium by directly alleviating neuroinflammation. NSAIDs are a class of drugs which inhibit the activity of cyclooxygenase enzymes. In animal studies, both ibuprofen and parecoxib have been shown to reduce neuroinflammation secondary to cerebral ischaemia–reperfusion,[84] and neuroinflammation secondary to 'remote' insults.[85,86] An observational study of more than one million surgical patients reported that parecoxib administration is associated with significantly lower risk of delirium (odds ratio=0.85).[10] Mu and colleagues[87] conducted a clinical trial of 600 patients aged 60 yr or more undergoing hip and knee surgeries. They found that intraoperative plus postoperative parecoxib administration reduced the risk of delirium from 11% to 6% (numbers needed to treat [NNT=20]); however, the authors did not report the incidence of acute kidney injury.

Paracetamol is a centrally-acting analgesic and antipyretic drug and is thought to exert its effect through the inhibition of cyclooxygenase enzymes in the CNS. In an animal model, paracetamol alleviated inflammation and oxidative stress in the hippocampus.[88] In a recent clinical trial of cardiac surgery patients, regular postoperative paracetamol administration reduced delirium risk from 28% to 10% (NNT=5.6).[89]

Dexmedetomidine

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist; although it was initially licensed for sedation in intensive care settings, more recent studies have suggested that it may have neuroprotective effects. In animal models, dexmedetomidine administration reduced the expression of inflammatory mediators, microglial activation, and neuroapoptosis.[90,91] Wang and colleagues[92] conducted a meta-analysis of 67 studies, and found that intraoperative dexmedetomidine administration is associated with significantly lower concentrations of stress hormones (cortisol, epinephrine), CRP, and tumour necrosis factor-α after surgery. In addition, sleep disturbance is commonly associated with delirium. A small clinical trial by Wu and colleagues[93] reported that postoperative low dose dexmedetomidine infusion increases the duration of sleep, and the duration of deeper sleep.

Duan and colleagues[94] conducted a meta-analysis of 18 clinical trials and found that intraoperative and postoperative dexmedetomidine administration significantly reduces the risk postoperative delirium (odds ratio 0.35). Most of the earlier research on dexmedetomidine and postoperative delirium was conducted on cardiac surgery patients who received dexmedetomidine infusion as a sedative in the ICU after surgery.[3] This led to concern regarding its applicability in noncardiac surgeries, as its sedative and haemodynamic depressant effects require continuous monitoring in a critical care setting.[95] However, several more recent clinical trials have shown that a shorter course of dexmedetomidine infusion intraoperatively is also effective in preventing delirium.[96–98] Zeng and colleagues[99] conducted a meta-analysis of noncardiac surgery trials and found that dexmedetomidine infusion administered intraoperatively and in the PACU significantly reduced the incidence of postoperative delirium (relative risk 0.61, NNT=10).

Surgical trauma

It is known that surgical trauma can result in both acute stress response and systemic inflammation.[100] In addition, higher incidences of postoperative delirium are mostly reported in association with complex surgeries. Minimally invasive surgery has been shown to reduce postoperative pain, and the stress and inflammatory responses. However, current clinical evidence regarding delirium is conflicting, with some observational studies reporting lower risk of delirium with minimally invasive surgery[101,102] and others reporting no difference[103] (Table 1). More robust clinical evidence is needed.

Perioperative medications and delirium

There are numerous medications that may increase the risk of postoperative delirium, including tricyclic antidepressants and certain antihistamines. In the perioperative period, the most relevant medications are benzodiazepines, gabapentinoids, and scopolamine.

Benzodiazepines are sometimes used as a premedication for anxiolysis and may reduce anaesthetic requirement.[104] However, several large observational studies have reported that perioperative benzodiazepine administration is associated with two to 2.5 times higher risk of postoperative delirium.[10,80]

Gabapentinoids such as pregabalin and gabapentin have been shown to be effective analgesic adjuncts for acute postoperative pain[105] and may reduce postoperative opioid requirement.[106] However, a large observational study has reported that perioperative gabapentinoids are associated with slightly increased risk of delirium (odds ratio=1.26).[10] This needs to be balanced with its opioid-sparing benefits.

Scopolamine is an anticholinergic antiemetic. There have been several case reports of scopolamine-induced delirium in the perioperative setting, and several expert guidelines have recommended avoiding scopolamine in older patients.[67,107]

Ketamine is an *N*-methyl-D-aspartic acid (NMDA) receptor antagonist with hypnotic and analgesic properties. A recent meta-analysis identified six clinical trials which administered sub-hypnotic doses (0.2–0.5 mg kg^{-1}) of ketamine on induction and showed that it did not increase the risk of delirium, however the quality of evidence is low because of the risk of study bias and study heterogeneity.[108]

Choice of general anaesthetics

It is known that volatile and i.v. anaesthesia induces hypnosis through different molecular targets, and there are studies suggesting that volatile anaesthesia, such as with sevoflurane, may induce or exacerbate neuroinflammation.[109] However, observational studies have not demonstrated any significant differences between volatile and i.v. anaesthesia in terms of the incidence of postoperative delirium.[110,111] Miller and colleagues[112] conducted a meta-analysis and identified five relevant studies. They found no significant difference in the risk of delirium between volatile and i.v. anaesthesia, but noted that the quality of current evidence is very low because of the risk of bias and inconsistency.

Xenon, a ‘fashionable; anaesthetic gas, is thought to exert its hypnotic effect primarily through inhibition of the NMDA glutamate receptors activity via interaction with its glycine binding site[113,114] and its minimum alveolar concentration is 63–71%.[115,116] In clinical practice, however, it is commonly used in conjunction with an i.v. agent. Animal studies have suggested that xenon may have potent neuroprotective effects through reducing neuroinflammation and neuroapoptosis.[117,118] In addition, xenon anaesthesia is remarkably cardiostable, which may indirectly reduce the risk of delirium as a result of hemodynamic instability.[119,120] There is one clinical trial of 42 patients undergoing off-pump coronary artery bypass, which showed that sevoflurane anaesthesia is associated with significantly higher postoperative delirium than xenon (hazard ratio 4.2).[120] However, several larger trials have reported no difference between xenon and volatile anaesthetics in terms of delirium risk after cardiac surgery or hip fracture repair.[121–123]

Table 1 Summary of the current evidence on intraoperative delirium risk reduction interventions.

Intervention	Level of evidence	Summary of evidence
Effective		
Use of paracetamol	Clinical trial[89]	121-Patient clinical trial, paracetamol 1 g every 6 h for 2 days reduced delirium incidence from 28% to 10%.
Use of NSAIDs	Clinical trial[87]	620-Patient clinical trial, parecoxib 40 mg every 12 h for 3 days reduced delirium incidence from 11% to 6%.
Use of neuraxial anaesthesia	Cohort studies[10,80]	Cohort studies with 40 000 and 1 million patients, respectively; neuraxial anaesthesia is an independent protective factor after multivariable analysis.
Use of dexmedetomidine	Meta-analysis[99]	Included six clinical trials with low risk of bias; intraoperative dexmedetomidine reduced postoperative delirium by 40%.
Preoperative comprehensive geriatric assessment	Clinical trial[69]	176-Patient clinical trial; preoperative comprehensive geriatric assessment and optimisation reduce the incidence of delirium from 24% to 11%.
Avoid prolonged preoperative fluid fasting	Cohort study[68]	One cohort study with 1000 patients; fluid fasting for more than 6 h is an independent risk factor.
Avoidance of intraoperative benzodiazepine and gabapentinoids	Cohort studies[10,80]	Cohort studies with 40 000 and 1 million patients, respectively; intraoperative benzodiazepine and gabapentinoids are independent risk factors for postoperative delirium.
No difference		
Choice of TIVA or volatile anaesthetics	Meta-analysis[112]	Included five clinical trials and showed no significant difference; overall quality of evidence is very low.
Intraoperative use of ketamine	Meta-analysis[108]	Included four clinical trials and showed no significant difference; overall quality of evidence is low.
Equivocal, require further studies		
Depth of anaesthesia monitoring-guided general anaesthetics	Meta-analyses[75–77]	Meta analyses by MacKenzie and colleagues[75] and Bocskai and colleagues[76] reported that depth of anaesthesia monitoring reduced the incidence of delirium; Miao and collleagues[77] reported no significant difference.
Minimally invasive surgical technique	Cohort studies[101–103]	Conflicting evidence from cohort studies.
Strict BP control	Clinical trial[130]	100-Patient pilot study; target MAP >90% of baseline MAP did not result in a significant difference.
Goal-directed fluid therapy	Clinical trial[132]	180-Patient trial; goal-directed fluid therapy did not result in a significant difference.
Restrictive transfusion	Clinical trial[134]	199-Patient trial; haemoglobin target of 8 g dl^{-1} *vs* 10 g dl^{-1} did not result in a significant difference.
Avoiding hypothermia	Cohort study[55]	194-Cardiac surgery patient study; those who developed postoperative delirium had lower intraoperative temperature.

Avoiding hypothermia

Intraoperative heat loss is common and is associated with coagulation dysfunction, and a myriad of cardiovascular and immunological changes.[124] A small observational study reported that in patients undergoing cardiac surgery, those with postoperative delirium were found to have lower minimum intraoperative temperature (34.5°C *vs* 35°C, P=0.035).[55] It is not clear if milder hypothermia is also associated with risk of delirium.

Intraoperative haemodynamic management

Subclinical cerebral vascular events have been implicated in the development of postoperative delirium, and intraoperative haemodynamic fluctuation may result in transient cerebral hypoperfusion, especially in watershed areas. However, several large observational studies and a recent meta-analysis all reported no association between intraoperative hypotension and delirium.[125–127]

Significant intraoperative hypotension often necessitates the use of vasoactive medications and several observational studies have found that postoperative delirium is associated with higher intraoperative vasopressor requirement.[55,128,129] All three studies were done in the context of high-risk surgeries, which may explain the positive results. An alternative explanation is that increased vasopressor requirement represents a greater degree of cardiovascular compromise compared with transient hypotension. Langer and colleagues[130] conducted a small clinical trial in which patients were allocated to either standard practice or an MAP target of >90% the preoperative value that was maintained with vasopressors. They found that the two strategies resulted in a similar incidence of postoperative delirium. Larger clinical trials are needed to further validate this.

Intravenous fluid and blood products administration

Goal-directed fluid therapy is an approach to administrating i.v. fluids according to specific hemodynamic targets, with the aim of optimising circulating volume and preload. This reduces the risk of excessive fluid administration. Whereas an earlier observational study reported a 75% reduction in postoperative delirium incidence with goal-directed fluid therapy in spinal surgery,[131] a recent clinical trial has reported no significant difference.[132] It is, however, worth noting that both studies have small patient size and likely lack statistical power.

Allogenic blood transfusion is sometimes required in the event of significant anaemia or blood loss. However, it is known that transfusion of processed and stored blood products can trigger significant systemic inflammation.

Observational studies have reported that perioperative transfusion is associated with significantly higher risks of postoperative delirium.[55] More notably, several observational studies found that intraoperative allogenic blood transfusion is an independent risk factor for postoperative delirium, and there is a dose-dependent relationship between volume transfused and the risk of postoperative delirium.[43,133] However, intraoperative transfusion is inherently linked to several factors, such as preoperative haemoglobin, intraoperative blood loss, and haemodynamic stability, which may confound the association. Gruber-Baldini and colleagues[134] conducted a small RCT comparing liberal with restrictive transfusion, and reported no significant difference between the two cohorts; but this may be because of a lack of statistical power of the study.

While i.v. fluid administration can result in metabolic changes,[43,55] there is currently limited clinical evidence regarding the choice of fluids and delirium. Joosten and colleagues[135] conducted a small size clinical trial, which reported no significant difference in the risk of postoperative delirium between intraoperative crystalloid and colloid administration cohorts.

Postoperative interventions

Non-pharmacological delirium prevention

The first-line preventative interventions for postoperative delirium are the non-pharmacological interventions. Reorientation is a strategy to help patients get familiarised with the environment and the people; this is done through minimising staff change and patient transfer, consistent introduction of staff members, access to natural light and time-keeping devices, reminders about the previous events, and future planning. A clinical trial has shown that reorientation alone can reduce the incidence of overt delirium by 40%.[136] Other non-pharmacological interventions include cognitive exercises, vision, and hearing optimisation, sleep optimisation, mobilisation, hydration, and nutrition. These interventions are often instituted as a multicomponent care package. Hshieh and colleagues[137] conducted a meta-analysis of 14 randomised and non-randomised trials, and found that multicomponent interventions reduced the incidence of delirium (odds ratio 0.46, NNT=14.3, Table 2).

Melatonin receptor agonists

Melatonin is a hormone involved in sleep regulation and is used pharmacologically to normalise and consolidate the circadian rhythm. A recent meta-analysis reported that perioperative melatonin administration is associated with a 40% lower risk of developing postoperative delirium.[138] Ramelteon is a synthetic and highly selective melatonin receptor agonist. Similar to melatonin, ramelteon is also effective in reducing the risk of postoperative delirium.[139–141]

Dexamethasone

Dexamethasone is a synthetic corticosteroid which is commonly used intraoperatively for nausea and vomiting prophylaxis. Corticosteroids are often used for the treatment of neuroinflammatory diseases. In animal models of systemic inflammation, dexamethasone administration has been shown to reduce astrocyte and microglial recruitment, and inflammatory mediator expression.[142] In a recent meta-analysis of three cardiac surgery trials, Tao and colleagues[143] reported that high-dose dexamethasone (up to 100 mg) is associated with moderate reduction (20%) in the incidence of postoperative delirium; however, the safety profile of such high-dose dexamethasone used in noncardiac patients is not clear.

Antipsychotics

Antipsychotic drugs are dopamine antagonists and also have varying degrees of affinity to muscarinic, serotonergic, and α-adrenergic receptors.[144] They are divided into first-generation and second-generation agents, with the first generation associated with higher risks of psychomotor complications and the second generation associated with higher risks of cardiovascular and metabolic complications. Several studies and meta-analyses have reported that prophylactic administration of second-generation antipsychotics, such as olanzapine and risperidone, may reduce the incidence of postoperative delirium (odds ratio 0.25).[139] Because of the risk of complications, the clinical value of antipsychotic prophylaxis is not clear.

Management for established postoperative delirium

In the clinical setting, diagnosis of postoperative delirium can be challenging, as delirium may present as agitation (hyperactive) or withdrawal (hypoactive) and tends to fluctuate significantly. Formal neurocognitive assessments are time-consuming and often only used by specialists. Instead, several abbreviated methods have been proposed for the

Table 2 Summary of the current evidence on postoperative delirium risk management.

Intervention	Level of evidence	Summary of evidence
Non-pharmacological interventions	Meta-analysis[137]	Included 14 studies (not all RCTs) with variable risk of bias; 45% reduction in delirium risk
Melatonin	Meta-analysis[138]	Included four RCTs and two observational studies with variable risk; 45% reduction in delirium risk
Ramelteon	Meta-analysis[139]	Network meta-analysis; pooled finding favoured ramelteon (odds ratio 0.07)
Antipsychotics	Meta-analysis[139]	Network meta-analysis; pooled finding favoured olanzapine and risperidone (odds ratio 0.25 and 0.27, respectively) but not haloperidol
Use of high dose dexamethasone (in cardiac surgery)	Meta-analysis[143]	Included three cardiac surgery RCTs with low-to-moderate risk of bias; 20% reduction in delirium risk.

diagnosis of delirium. This includes the confusion assessment method, and the delirium observation screening scale,[145,146] and these are used extensively in research and clinical practice. These can be performed by most healthcare professionals after adequate training. Despite the availability of diagnostic tools, delirium is commonly misdiagnosed as depression or dementia.[147] Tabet and colleagues have shown that by creating a focused staff education program, it is possible to improve delirium recognition in clinical settings.[148]

The first-line treatment for postoperative delirium is assessment and management of underlying causes; these may include infection, pain, dehydration, metabolic derangement, constipation, or urinary retention.[149] To date, there are limited pharmacotherapy options for the treatment of delirium. Benzodiazepines were used in the past as symptomatic treatment for agitation in hyperactive delirium; however, it has been increasingly recognised that benzodiazepines may worsen the symptoms of delirium.[139]

Antipsychotics are currently used as first-line treatment for agitation. Some earlier clinical trials have suggested that antipsychotics may reduce the length of delirium symptoms.[150–152] This has, however, been refuted by several recent meta-analyses, which suggested that antipsychotics administration does not reduce the length of delirium symptoms, nor do they reduce the adverse outcomes associated with delirium.[139,153] It is also worth noting that there are concerns regarding the safety of antipsychotics. Several observational studies have reported that both short- and long-term prescription of antipsychotics is associated with a significantly high risk of morbidity and mortality.[154,155] Ralph and Espinet[156] conducted a meta-analysis of more than 350 000 patients with neurocognitive disorders and reported that the patients receiving antipsychotics have double the risk of death. Agar and colleagues[157] conducted a trial comparing haloperidol, risperidone, and placebo in the management of delirium in patients in the palliative care setting. They reported that neither antipsychotic significantly reduced the severity of delirium, and that antipsychotics were associated with significantly shorter survival. The risk profile of short-term antipsychotic use in surgical patients is not clear, but the potential for harm should be considered in the decision-making regarding antipsychotics for delirium management.

It can be surmised that there are, currently, limited treatment options once overt delirium occurs. Although antipsychotics are commonly used to manage the symptoms of agitation, they do not alter the time course of delirium, nor modify its prognosis. As such, risk reduction is the most vital part of postoperative delirium management. As previously discussed by Aldecoa and colleagues,[4] effective implementation of a postoperative delirium management strategy requires active multidisciplinary collaboration and organisation-wide implementation of change. In order to achieve this, enthusiastic leadership, active participation from the stakeholders, and efficient pathway management are needed.

Conclusions

Postoperative delirium is a common complication in the older surgical population, with significant sequelae and associated burden on healthcare. Currently, treatment options for established delirium are limited and do not appear to reduce the risk of mortality and morbidity associated with postoperative delirium. Research in recent years has uncovered more regarding its pathophysiology, although this has not yet yielded effective treatment. We therefore propose that postoperative delirium is best managed by perioperative risk reduction.

Whenever possible, high-risk patients or those undergoing high-risk surgery should be assessed and their delirium risks should be quantified. Effective intraoperative measures for minimising delirium risk include BIS-guided anaesthesia, multimodal opioid-sparing analgesia, and intraoperative use of dexmedetomidine; postoperative measures include non-pharmacological interventions and melatonin. A protocolised perioperative pathway involving risk assessment and risk-stratified management is likely to be the optimal approach in high-risk patient cohorts.

We identified several other potentially effective perioperative interventions, such as the use of regional anaesthesia, paracetamol, and NSAIDs; these need to be evaluated in further larger-scale clinical trials. Most notably, there is still no clear consensus regarding the role of intraoperative haemodynamic changes in delirium. Studies are needed to clarify if cerebral hypoperfusion is associated with postoperative delirium, and how cerebral perfusion may be monitored and managed clinically.

Authors' contributions

Study design/planning: ZJ, DM
Manuscript preparation: all authors.

Declarations of interest

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Appendix A. Supplementary data

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