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REVIEW

Prevention of postoperative delirium in elderly patients planned for elective surgery: systematic review and meta-analysis

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Introduction: Vulnerable or "frail" patients are susceptible to the development of delirium when exposed to triggers such as surgical procedures. Once delirium occurs, interventions have little effect on severity or duration, emphasizing the importance of primary prevention. This review provides an overview of interventions to prevent postoperative delirium in elderly patients undergoing elective surgery.

Methods: A literature search was conducted in March 2018. Randomized controlled trials (RCTs) and before-and-after studies on interventions with potential effects on postoperative delirium in elderly surgical patients were included. Acute admission, planned ICU admission, and cardiac patients were excluded. Full texts were reviewed, and quality was assessed by two independent reviewers. Primary outcome was the incidence of delirium. Secondary outcomes were severity and duration of delirium. Pooled risk ratios (RRs) were calculated for incidences of delirium where similar intervention techniques were used.

Results: Thirty-one RCTs and four before-and-after studies were included for analysis. In 19 studies, intervention decreased the incidences of postoperative delirium. Severity was reduced in three out of nine studies which reported severity of delirium. Duration was reduced in three out of six studies. Pooled analysis showed a significant reduction in delirium incidence for dexmedetomidine treatment, and bispectral index (BIS)-guided anaesthesia. Based on sensitivity analyses, by leaving out studies with a high risk of bias, multicomponent interventions and antipsychotics can also significantly reduce the incidence of delirium.

Conclusion: Multicomponent interventions, the use of antipsychotics, BIS-guidance, and dexmedetomidine treatment can successfully reduce the incidence of postoperative delirium in elderly patients undergoing elective, non-cardiac surgery. However, present studies are heterogeneous, and high-quality studies are scarce. Future studies should add these preventive methods to already existing multimodal and multidisciplinary interventions to tackle as many precipitating factors as possible, starting in the pre-admission period.

Keywords: prevention, postoperative delirium, elderly, elective surgery

Introduction

Delirium is a common postoperative complication in the elderly, often caused by multiple factors. It is defined as an acute neuropsychiatric disorder characterized by fluctuating disturbances in attention, awareness, and cognition and can be divided into three different subtypes; hyperactive, hypoactive, or mixed.[1–3] The hypoactive form, present in over 40% of delirium cases, is estimated to be recognized in 20–50% of cases and is often under-diagnosed.[4–6]

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Frail patients are vulnerable due to predisposing risk factors. These risk factors, together with provoking triggers (ie, precipitating risk factors), make patients susceptible to developing delirium.[7,8] Previous studies on delirium pointed out old age, cognitive or functional impairment, number of comorbidities, history of falls, and sensory deprivation as important predisposing factors.[3,8–13] Important precipitating factors are polypharmacy, malnutrition, pain, the use of urinary catheters, ICU admission, length of hospital stay (LOS), blood loss, preoperative anemia, and type of surgery.[8,14–18]

Postoperative delirium occurs in 17–61% of the major surgical procedures.[12,19,20] It may be associated with cognitive decline, prolonged LOS, decreased functional independence, and increased risk of dementia, caregiver burden, health care costs, morbidity and mortality.[3,21–28] Therefore, delirium is a possibly disastrous condition and is both a huge burden on a patient's health and on the health care system in general.

After an initial episode of delirium, post-episode treatment or intervention has little effect on severity, duration, or likelihood of recurrence.[29–32] However, before its onset, delirium is assumed to be preventable in 30–40% of cases,[33] which emphasizes the importance of attention for primary prevention.[29,30] This can be achieved by interventions tackling risk factors, such as adequate pain management, hearing or visual aid, sleep enhancement, exercise training, or dietary advice.[9,34]

Extensive research on reducing the incidence of delirium has been conducted using both pharmacological and non-pharmacological preventive measures in the acute setting and in patients undergoing cardiac surgery.[35–38] Importance of these studies is exemplified by a recent study which showed an independent association between postoperative delirium and major adverse cardiac events.[39]

Several preoperative, perioperative, and postoperative unimodal and multimodal approaches have been tested, trying to alter various components most likely to provoke a delirium.[40] These efforts were heterogeneous and often involved relatively small populations. Irrefutable evidence of a successful preventive method has yet to be found.[41–43] This review provides an overview of interventions in elderly hospitalized patients in need of elective surgery without planned intensive care unit admission.

The aim of this study was to collate, evaluate and pool results of the effectiveness of primary preventive methods on the incidence of delirium in elderly patients (≥65 years), planned for elective surgery.

Methods

Data sources and searches

PubMed (Medline OvidSP), Embase, Cochrane Centre, and Web of Science were systematically searched for relevant studies in March 2018 by a medical information specialist. Our search strategy is shown in the supplementary material. Uniqueness of the individual articles was ensured through deduplication. Reference lists were manually screened for additional eligible articles.

Study selection

Randomized controlled trials (RCTs) and controlled before-and-after studies were selected, with a focus on the prevention of postoperative delirium in elderly surgical patients.

Selected studies were screened for the relevant inclusion criteria: patients undergoing elective surgery, study populations with a mean age ≥65, and studies with the prevention of delirium as a goal. Delirium incidence, duration, and/or severity were used as primary and secondary outcomes. Only articles with their full text available in English were selected. No date limit was set.

Studies concerning postoperative planned ICU admission, cardiac surgery, head or neck surgery, acute surgical intervention, unimodal nurses' training, and pilot studies were excluded.

Data extraction

Two reviewers (TLJ and ARA) independently evaluated titles and abstracts on eligibility for this review. When no decision could be made on bases of title and abstract, full texts were screened. Disagreement was resolved by consensus.

The following study characteristics were independently extracted by two reviewers: number of patients, surgical procedure, incidence, duration and severity of delirium, delirium assessor and type of assessment used, type, timing and effects of intervention, study design, power analysis, inclusion of cognitively impaired patients, inclusion of preoperative delirium, study population, baseline patient characteristics (age, gender, burden of comorbidity), primary and secondary outcomes, blinding of patients and caregivers, and duration of follow-up.

Quality assessment

Risk of bias was scored using the Cochrane Risk of Bias tool[44] and graphically presented using Review Manager

5.3.[45] Studies were scored as to have an unclear, low, or high risk of bias.

Two reviewers (TLJ and ARA) assessed the quality independently. Any disagreements were resolved by consensus, or in case of persistent disagreement via querying the third author.

Statistical analysis

Review Manager[45] was used to present the data from all studies graphically, to perform a meta-analysis when possible and to perform and standardize the risk of bias assessment.

Meta–analysis was performed when two or more articles presented results for the same comparison and similar intervention techniques to prevent delirium (clinically homogeneous groups). Pooled risk ratio (RR) with a 95% confidence interval (CI) was calculated for the incidence of delirium (dichotomous outcome) using random–effects methods. The Mantel-Haenszel test was used. Studies in the pooled analyses were tested for heterogeneity using inconsistency I^2, where a cut-off of 60% was considered methodically relevant.

The *p*-values that are presented in this review are the ones calculated for between-group differences as presented by the authors in the original studies. A *p*-value of <0.05 (two-tailed) was considered statistically significant.

This manuscript was reported using the checklist provided in the PRISMA Statement.[46]

Results

Search

All databases provided a combined total of 1987 articles. A total of 872 studies were removed following deduplication. All titles and abstracts of the remaining articles were screened for relevance, after which 122 studies remained. After screening of full texts, another 95 studies were excluded. Main reasons for exclusion were: acute care patients, ICU patients, study design, non-surgical patients, or delirium were not an outcome. Eight additional articles were handpicked by screening references of systematic reviews on delirium prevention which were found in the initial search.[47–54] In total, 35 studies were included in this systematic review. A complete overview of search results and study selection is presented in Figure 1, which is a flowchart designed in accordance with the PRISMA statement.[46]

Quality assessment – risk of bias

An overview of the "risk of bias" assessment is presented in Figure 2 and in the supplementary table. Figure 2 presents a graphic summary of the assessment, while the table shows our considerations.

Eight studies were considered to have an overall low risk.[55–62] Six of these studies were graded low risk for all types of bias.[55–60] Only the risk of selective reporting was unclear in the study by Kalisvaart et al, since they did not register their research in advance.[61] The same applies to the study by Beaussier et al, with an additional unclear risk of detection bias.[62] All studies with a focus on reducing postoperative pain were among these eight low-risk studies.

All before-and-after studies were rated as high overall risk of bias due to the design of their research, as no blinding of patients, caregivers and outcome assessors, no randomization, and no allocation concealment was possible.[63–66]

The study by McCaffrey et al, was graded high risk of selection bias.[67] They used folded slips of paper, which could be manipulated easily. Two studies were rated as high risk for allocation concealment because the intervention and control groups were treated at different locations.[53,68] Fifteen studies were graded high risk of performance bias,[47,52,54,63–66,69–76] 13 of which because of lack of blinding of caregiver, patient or both due to the nature of their intervention. A total of 15 studies lacked reporting of one of two types of blinding bias in their study; therefore, these studies were rated as having an unclear risk.[47,48,50–52,54,62,67,68,73,77–81]

Fourteen of 35 studies registered their trials and mentioned trial registration number in their paper.[53,55–60,63,70,72,74–76,78] Remaining studies did not register their trial, did not publish their protocol in advance and reported their results as reported in their methods section.

Patient and study characteristics

A complete overview of patient- and study characteristics is shown in Table 1.

Sample sizes varied from 22 patients to 1,155 patients, with nearly 10,000 patients in total. Seven studies included fewer than 100 patients.[50–52,62,67,69,77] Two studies also included general medicine patients or patients undergoing acute surgery.[61,63] Because of a separation in results on delirium incidence in general medicine or surgical patients and acute or elective patients, these were still included in this review. The study by Avidan et al, also included patients undergoing cardiac surgery and did not make a separate analysis, however, due to a large number of patients (466 patients;

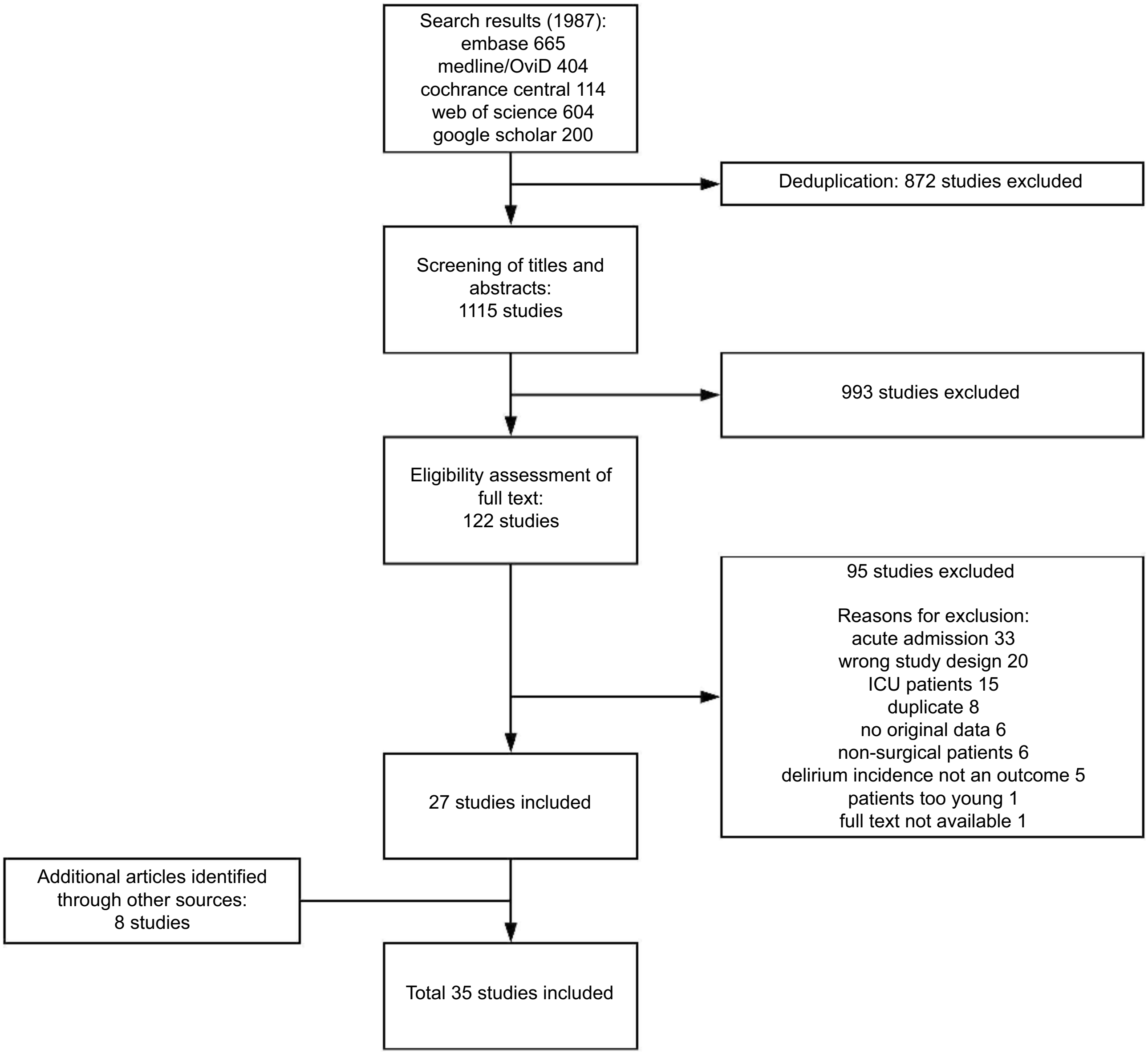

Figure 1 PRISMA flowchart.

70%) undergoing non-cardiac surgery, this study was also included in this review. We did not include the latter in the pooled analysis, since cardiac surgery is pointed out to be a precipitating factor for postoperative delirium and inclusion in the analysis would give a distorted result.

Study designs

Thirty-one out of 35 included studies were RCTs, 13 of which compared an intervention to usual care,[53,56,67–73,75,76,79,80] 10 studies compared an intervention to a placebo,[49,55,57–62,74,77,78] and 7 studies compared different interventions.[47,48,50–52,54,81] Six of these RCTs were multicenter studies.[55,57,60,71,72,79] Four studies were before-and-after studies, all of which compared a multimodal perioperative care plan to usual care in a single center.[63–66]

Comorbidity scoring

APACHE-II,[61] Charlson Comorbidity Index[49,54–56,59,64], and ASA score[47,51,52,57,58,60,62,63,70,74,76,81] were used to score comorbidities in 19 studies. Sixteen studies did not use a comorbidity scoring system.[48,50,53,65–69,71–73,75,77–80] Seven of these did show type or number of comorbidities but did not use an evidence-based scoring system.[50,53,65,66,72,77,79] Four studies showed significant differences in baseline comorbidities.[53,65,66,78] Partridge

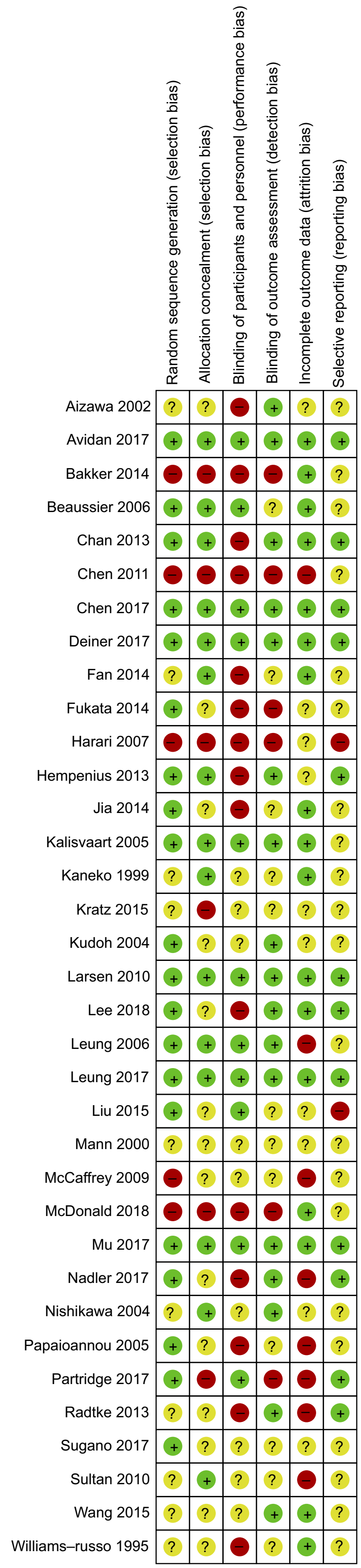

Figure 2 Summary of 'Risk of bias': Review authors' judgements on risk of bias for each study.

Table 1 Complete overview of study characteristics, patient characteristics, interventions, and outcomes

Study	Country	Year	Study type	Single- or multi-centre	Category	Intervention	Timing compared to surgery	Surgical category	Surgical procedure	Number of patients (I/C)	Age	Gender M/F Interven-tion	Gender M/F Control	Comorbidity scoring	Cognitive impairment
Aizawa[69]	Japan	2002	RCT	Single	Sleep-wake cycle	Diazepam 1dd 0.1mg/kg, Flunitrazepam 0,04 mg/kg and Pethidine 1 mg/kg injection vs. usual care	Post	Abdominal	Gastric Colorectal cancer laparotomy	20/20	>70	15/5	11/9	No	Not excluded
Avidan[55]	USA	2017	RCT	Multi	Post-operative pain man-age-ment	Ketamine 0.5 mg injection vs ketamine 1.0 mg injection vs. saline injection	Intra	Combi-nation	All types not differentiated in statistics. thoracic surgery, major vascular surgery, intra-abdominal surgery, open gynaecological surgery, open urological surgery, major orthopaedic or spine surgery, hepatobiliary surgery, and major otolaryngological surgery	227/223/222	>60, Mean = 70	144/83 and 139/84	135/87	CCI[a]	Not excluded
Bakker[63]	Netherlands	2014	BAS[b]	Single	Peri-operative care	CareWell in Hospital program vs. usual care	Peri	Combi-nation	General and surgical patients; differentiation made for statistics. Vascular, trauma, cardiothoracic and oncologic surgery	121/120	>70	Not specified in surgical subgroup	Not specified in surgical subgroup	ASA	Not excluded
Beaussier[61]	France	2006	RCT	Single	Post-operative pain man-age-ment	Intrathecal morphine 300 mcg vs. subcutaneous saline	Intra	Abdominal	Descending colon or rectal cancer	26/26	>70	15/11	12/14	ASA	Mental dysfunction excluded
Chan[70]	China	2013	RCT	Single	Anaes-thesia	BIS-guided anaesthesia vs. usual care	Intra	Combi-nation	Major, non-cardiac, surgery (not further specified)	450/452	>60, Mean = 68	280/170	273/179	ASA	Dementia excluded (MMSE <24)
Chen[64]	Taiwan	2011	BAS	Single	Post-operative care	Modified HELP vs. usual care	Peri	Abdominal	Abdominal surgery for gastric cancer, periampullary cancer, distal pancreatic cancer, and other	102/77	>65	55/47	43/44	CCI	Severe dementia excluded

(*Continued*)

Table 1 (Continued)

Study	Country	Year	Study type	Single- or multi-centre	Category	Intervention	Timing compared to surgery	Surgical category	Surgical procedure	Number of patients (I/C)	Age	Gender M/F Interven-tion	Gender M/F Control	Comorbidity scoring	Cognitive impairment
Chen[56]	Taiwan	2017	RCT	Single	Post-operative care	Modified HELP vs. usual care	Peri	Abdominal	Abdominal surgery for gastric cancer, periampullary cancer, distal pancreatic cancer, colorectal cancer and other	197/180	>65	111/86	103/77	CCI	Not excluded
Deiner[57]	USA	2017	RCT	Multi	Anaes-thesia	Dexmedetomidine infusion 0.5 µg/kg/h vs. saline	Intra	Combi-nation	Major non-cardiac surgery; spine, thoracic, orthopaedic, urologic, or general surgery	189/201	>68	92/97	98/103	ASA	Severe dementia (MMSE< 20) excluded
Fan[47]	China	2014	RCT	Single	Trans-fusion manage-ment	Restrictive blood transfusion (Hb < 8 g/dL) vs. liberal blood transfusion (Hb <10 g/dL)	Peri	Ortho-paedic	Unilateral total hip replacement	94/92	>65	30/64	33/59	ASA	Not excluded
Fukata[71]	Japan	2014	RCT	Multi	Anti-psychotics	Haloperidol 1dd 2,5 mg intrave-nously vs. usual care	Post	Combi-nation	Abdominal malignant and benign/Orthopaedic/ Vascular and Others	59/60	>75	32/27	32/30	No	Not excluded
Harari[65]	UK	2007	BAS	Single	Pre-opera-tive assess-ment and peri-operative care	Comprehensive geriatric assess-ment (POPS) vs. usual care	Peri	Ortho-paedic	Orthopaedic surgery	54/54	>65	18/36	25/29	No	Not excluded
Hempen-ius[72]	Netherlands	2013	RCT	Multi	Peri-operative care	Geriatric Liaison Intervention vs. usual care	Peri	Combi-nation	Surgery for solid tumours in breast, skin, vulva, cervix, endometrium, uterus, head/neck, retroperitoneum, gastrointestinal, liver, pancreas, lung, ovary, oropharynx, larynx and intra-abdominal sarcoma	148/149	>65	56/92	51/98	No	Not excluded

(*Continued*)

Table 1 (Continued)

Study	Country	Year	Study type	Single- or multi-centre	Category	Intervention	Timing compared to surgery	Surgical category	Surgical procedure	Number of patients (I/C)	Age	Gender M/F Intervention	Gender M/F Control	Comorbidity scoring	Cognitive impairment
Jia[73]	China	2014	RCT	Single	Peri-operative care	Fast-track vs. usual care	Peri	Abdominal	Colorectal carcinoma	117/116	>70	76/41	70/46	No	Dementia excluded
Kalisvaart[61]	Netherlands	2005	RCT	Single	Anti-psychotics	Haloperidol 3dd 0,5 mg orally vs. placebo	Peri	Ortho-paedic	Hip surgery (elective only)	159/157	>70	Not specified in surgical subgroup	Not specified in surgical subgroup	APACHE-II	Dementia excluded (MMSE <25)
Kaneko[77]	Japan	1999	RCT	Single	Anti-psychotics	Haloperidol 1dd 5 mg intravenously vs. saline	Post	Abdominal	Gastrectomy/Colectomy	38/40	Mean = 73	24/14	26/14	No	Not excluded
Kratz[68]	Germany	2015	RCT	Single	Peri-operative care	Psychogeriatric liaison intervention vs. usual care	Peri	Combination	General, abdominal and trauma surgery; not further specified	61/53	>70	22/39	28/25	No	Advanced dementia excluded
Kudoh[48]	Japan	2004	RCT	Single	Anaesthesia	Bupivacaine spinal and propofol general anaesthesia + LMA vs. propofol and fentanyl anaesthesia + Tracheal intubation	Intra	Ortho-paedic	Total Knee Arthroplasty	75/75	>70	6/69	9/66	No	Dementia excluded
Larsen[58]	USA	2010	RCT	Single	Anti-psychotics	Olanzapine 5 mg orally vs. placebo	Peri	Ortho-paedic	Knee- or hip-replacement	196/204	>65	102/94	81/123	ASA	Dementia excluded
Lee[74]	South Korea	2018	RCT	Single	Anaesthesia	Dexmedetomidine 1 mcg/kg bolus followed by 0.2 to 0.7 mcg/kg/h infusion vs. dexmede-tomidine 1 mcg/kg diluted to a total volume of 10 mL in saline vs. 10 ml saline	Intra	Abdominal	Radical cystectomy, partial or total nephrectomy or colorectal surgery	95/114/109	>65	44/51 and 50/64	47/62	ASA	Cognitive impaired excluded

(*Continued*)

Table 1 (Continued)

Study	Country	Year	Study type	Single- or multi-centre	Category	Intervention	Timing compared to surgery	Surgical category	Surgical procedure	Number of patients (I/C)	Age	Gender M/F Interven-tion	Gender M/F Control	Comorbidity scoring	Cognitive impairment
Leung[49]	USA	2006	RCT	Single	Anaes-thesia	N2O with O2 vs. O2	Intra	Combi-nation	Spine/orthopaedic sur-gery, gynaecological sur-gery and 'others'	105/105	>65	52/62	63/51	CCI + ASA	Not excluded
Leung[59]	USA	2017	RCT	Single	Post-operative pain man-age-ment	Gabapentin 3dd 300 mg vs. placebo	Peri	Ortho-paedic	Spinal surgery, hip and knee arthroplasty	350/347	>65	157/193	189/158	CCI + ASA	Not excluded
Liu[78]	China	2016	RCT	Single	Anaes-thesia	Dexmedetomidine 0.2–0.4 mcg/kg/h continuous infusion vs saline	Intra	Ortho-paedic	Hip, knee or shoulder joint replacement	39/40/60/58	>65	18/21 and 26/34	23/17 and 29/29	No	Not excluded
Mann[50]	France	2000	RCT	Single	Post-operative pain man-age-ment	PCA vs. PCEA	Peri	Abdominal	Major abdominal surgery	33/31	>70	17/18	15/20	No	Abnormal mental status excluded (AMT <8)
McCaffr-ey[67]	USA	2006	RCT	Single	Post-operative care	Music therapy 4dd 1 hour vs. usual care	Post	Ortho-paedic	Hip or knee surgery	11/11	>70	4/7	4/7	No	Not excluded
McDona-ld[66]	USA	2018	BAS	Single	Peri-operative care	POSH program vs. usual care	Peri	Abdominal	Colorectal, general and hepatopancreaticobiliary surgery	183/143	>65	82/98	73/70	No	Not excluded
Mu[60]	China	2017	RCT	Multi	Post-operative pain man-age-ment	Parecoxib 2dd 40 mg dissolved in 5 ml saline vs. 5 ml saline	Post	Ortho-paedic	Total hip and knee replacement	310/310	>60, Mean = 70	81/229	83/227	ASA	Not excluded
Nadler[75]	USA	2017	RCT	Single	Airway manage-ment	Perioperative con-tinuous airway pressure vs. usual care	Peri	Ortho-paedic	Knee or hip arthroplasty	58/56	>50, Mean = 65	22/36	24/32	No	Not excluded
Nishika-wa[51]	Japan	2004	RCT	Single	Anaes-thesia	Propofol vs sevo-flurane anaesthesia	Intra	Abdominal	Laparoscopic choledo-cholithotomy, colectomy and sigmoidectomy	25/25	>65	13/12	12/13	ASA	Cognitive impaired excluded

(*Continued*)

Table 1 (Continued)

Study	Country	Year	Study type	Single- or multi-centre	Category	Intervention	Timing compared to surgery	Surgical category	Surgical procedure	Number of patients (I/C)	Age	Gender M/F Interven-tion	Gender M/F Control	Comorbidity scoring	Cognitive impairment
Papaioannou[52]	Greece	2005	RCT	Single	Anaes-thesia	General vs. regional anaesthesia	Intra	Combi-nation	Orthopaedic, urological, vascular and gynaecologic surgery	28/19	>60, Mean = 68	18/10	12/7	ASA	Dementia excluded MMSE <24)
Partridge[53]	United Kingdom	2017	RCT	Single	Pre-operative assess-ment	Comprehensive Geriatric Assessment and optimization vs. usual care	Pre	Vascular	Endovascular/open aortic aneurysm repair or lower-limb arterial bypass surgery	85/91	>65	80/24	79/26	No	Not excluded
Radtke[76]	Germany	2013	RCT	Single	Anaes-thesia	BIS-guided anaesthesia vs. usual care	Intra	Combi-nation	General, abdominal, thoracic, vascular, orthopaedic, otorhinolaryngological, oral and maxillofacial, gynaecological and urologic surgery.	575/580	>60, Mean = 70	318/257	304/276	ASA	Cognitive impaired excluded (MMSE <24)
Sugano[79]	Japan	2017	RCT	Multi	Sleep-wake cycle	Yokukansan 3dd 2.5 mg vs. usual care	Peri	Combi-nation	Gastrointestinal or lung malignancy surgery	93/93	>70	60/33	60/33	No	Not excluded
Sultan[80]	Saudi Arabia	2010	RCT	Single	Sleep-wake cycle	Melatonin 5 mg vs. Midazolam 7.5 mg vs. Clonidine 100 mcg vs. usual care	Pre	Ortho-paedic	Hip arthroplasty	53/50/51/49	>65	24/29, 26/24 and 27/24	22/27	No	Dementia excluded
Wang[81]	China	2015	RCT	Single	Anaes-thesia	Variable ventilation vs. conventional ventilation	Intra	Abdominal	Open gastrointestinal tumour resection	79/83	>60, Mean = 67	33/46	30/53	ASA	Cognitive impaired patients excluded (MMSE <24)
Williams-Russo[54]	USA	1995	RCT	Single	Anaes-thesia	General vs. regional (epidural) anaesthesia	Intra	Ortho-paedic	Total knee replacement	134/128	>40, Mean = 69	63/71	58/70	CCI	Not excluded

Abbreviations: [a]CCI, Charlson Comorbidity Index; [b]BAS, Before-and-After study; [c]N.S., not specified, [d]LOS, length of stay; [e]NS, not significant.

et al, did not provide statistical testing for differences in baseline comorbidities between groups, however cerebrovascular disease and dementia, both important risk factors for the development of delirium, were present more than twice as often in the control group compared with the intervention group.[53]

Cognitive impairment and preoperative delirium

Sixteen studies excluded cognitively impaired patients,[48,50–52,57,58,61,62,64,68,70,73,74,76,80,81] while only seven studies specifically excluded patients with a preoperative diagnosis of delirium.[47,55,60,61,63,68,80] Because of the elective nature of the procedures, it is assumed that unless indicated otherwise, patients of all remaining studies did not have a delirium prior to surgery.

Period of delirium assessment

In 12 studies, assessment for delirium was done during the full extent of the admission,[50,53,56,61–66,68,70,79] while assessment of postoperative delirium was done for 3 days or fewer in nine studies.[47,49,51,52,55,59,67,75,80]

Delirium assessment method

Eighteen studies used the Confusion Assessment Method (CAM), a method for detecting delirium introduced by Inouye et al, in 1990,[1] as a method of diagnosing delirium.[47–49,55–63,66,68,70,74,75,78] Nadler et al, and Larsen et al,[56,75] combined CAM with the DRS-R-98,[82] which also includes delirium severity in the test. Two more studies, by Nishikawa et al, and Jia et al, used the DRS and DRS-R-98 to assess delirium, respectively,.[51,73] Sultan et al, used the Abbreviated Mental Test 10 questions (AMT-10) to score the incidence of postoperative delirium.[80] The NEECHAM Confusion Scale, a screening tool for delirium validated against the DSM-IV criteria,[83,84] was used in two studies.[67,71]

Six studies used the fourth version of the DSM to screen for delirium,[61,69,72,76,79,81] two studies used the DSM-III criteria,[50,52] and two studies used criteria from its successor, the DSM-III-R.[58,77]

Three studies[53,54,65] did not specify the method of delirium assessment, however, Williams-Russo et al,[54] used the same criteria for positive diagnosis as described in the DSM-III-R, making it a reliable diagnosis. The studies by Partridge et al, and Harari et al, did not use a validated tool for diagnosing delirium. To decrease the risk of bias, both were excluded from the pooled analysis.

Delirium preventive interventions and individual outcomes

Interventions to prevent postoperative delirium can be divided into several different categories. Firstly, in pharmacological (n=20)[47,48,50–52,54,55,57–62,69,71,74,77–80] and non-pharmacological interventions (n=15),[49,53,56,63–68,70,72,73,75,76,81] secondly in single-component (n=26)[47–52,54,55,57–62,67,69–71,74–81] and multi-component (n=9)[53,56,63–66,68,72,73]interventions, and thirdly according to timing of intervention. For this review, the third option was chosen. Interventions were divided into preoperative (n=2),[53,80] intraoperative (n=13),[48,49,51,52,54,55,57,62,70,74,76,78,81] postoperative (n=7)[56,60,64,67,69,71,77], or perioperative (n=13),[47,50,58,59,61,63,65,66,68,72,73,75,79] of which the latter is the combination of the first three. Perioperative care is defined as all care concerning initial diagnosis, from preoperative outpatient clinic visit, to postoperative follow-up visits.

Preoperative

A study by Sultan et al, used a single-component approach, by implementing a preoperative pharmacological intervention.[80] Patients received placebo, melatonin 5 mg, midazolam 7.5 mg, or clonidine 100 mcg during the evening before surgery and another dose 90 mins preoperatively. The only intervention able to significantly reduce the incidence of delirium (9.4% vs 32.7%) was administering 5 mg of melatonin (p=0.003).

In a second study using a preoperative approach, Partridge et al, compared preoperative comprehensive geriatric assessment (CGA) of patients by a multidisciplinary team to usual care.[53] The CGA is a tool, performed prior to admission, to identify risk factors of frailty in order to prevent postoperative adverse outcomes and optimize patients' overall health through a multimodal approach.[85,86] Partridge et al, assessed for problems with cognition, tested for anemia, and evaluated cardiac condition. The CGA also included referral to additional caregivers, medication review and advice to patients and ward teams for the postoperative period.[53] Incidence of delirium in this CGA group was significantly less in the intervention group compared with the control group (10.6% vs 24.2%, p=0.018).

Intraoperative

Reducing postoperative pain, one of the precipitating risk factors for delirium, was the main focus of two studies that implemented a single-component pharmacological prevention.[55,62] Beaussier et al, compared the administration of 300 mcg intrathecal morphine immediately prior to surgery combined with postoperative patient-controlled intravenous morphine (PCA) with PCA alone.[62] They were not able to show a significant difference between groups (p-value not specified). Avidan et al, divided patients into three groups: the first group received an injection of 0.5 mg of ketamine after induction of anaesthesia and before surgical incision, the second group received 1.0 mg of ketamine at the same time, and the third group received a saline injection.[55] Neither intervention significantly reduced the incidence, severity or duration of delirium nor found any differences between groups (p=0.80).

Three studies compared the infusion of various amounts of dexmedetomidine with an equal amount of saline infusion.[57,74,78] Dexmedetomidine is a highly selective α2-adrenoceptor agonist, which has sedative, amnestic, sympatholytic, and analgesic effects.[87] Deiner et al, infused 0.5 μg/kg/h of dexmedetomidine during surgery and for up to 2 hrs in the recovery room.[57] By doing so, they were unable to significantly lower the incidence of delirium when compared with the saline group (12.2% vs 11.4%; p=0.94), or to significantly decrease the severity of delirium. Lee et al, compared three groups; dexmedetomidine 1 μg/kg bolus followed by 0.2–0.7 μg/kg/h infusion during surgery, dexmedetomidine 1 μg/kg bolus 15 mins before the end of the surgery, and an equivalent saline bolus 15 mins before the end of surgery.[74] Delirium incidence in the first group was significantly lower compared to the other two groups (9.5% vs 18.4% and 24.8%; p=0.017), and duration of delirium was shorter in both intervention groups (p=0.04). Liu et al, compared infusion of dexmedetomidine to saline infusion in cognitively impaired and in "normal" patients. In both groups, infusion of 0.2–0.4 μg/kg/h dexmedetomidine during surgery significantly decreased the incidence of postoperative delirium (p<0.05).[78]

Another intraoperative approach was tested in two studies, in which they attempted to control the depth of anaesthesia through the use of bispectral index (BIS)-guidance.[70,76] Both studies successfully reduced the incidence of delirium. The study by Radtke et al, terminated early due to limited funding; however, they were still able to show a significant reduction (16.5% vs 21.4%, p=0.036).[76] Chan et al, reduced the incidence of delirium from 24.1% to 15.6% by adding BIS-guidance to their anaesthesia (p=0.01).[70]

Two studies tried to reduce postoperative delirium by changing ventilation.[49,81] Leung et al, mechanically ventilated patients in the intervention group using N_2O and O_2, while the control group only received O_2. They were not able to reduce the incidence of delirium (41.9% vs 43.8%, p=0.78).[49] In contrast, Wang et al, were able to significantly reduce the incidence of delirium through the implementation of mechanical ventilation with varying tidal volumes instead of mechanically ventilating patients conventionally (16.5% vs 28.9%, p=0.036).[81]

Changing method of anaesthesia was hypothesized to decrease the incidence of delirium in four studies.[48,51,52,54] Both groups in the study by Kudoh et al, received intravenous propofol.[48] In the first group, bupivacaine spinal anaesthesia was added and patients breathed spontaneously with a laryngeal mask airway. The second group received additional anaesthesia through intravenous fentanyl and was mechanically ventilated via endotracheal tube. Delirium incidence was reduced in favor of the first group (5.3% vs 16.0%, p=0.03). Nishikawa et al, compared sevoflurane with propofol for induction and maintenance of general anaesthesia.[51] Even though none of the patients in the sevoflurane group developed delirium, compared to 16% in the propofol group, there was no statistically significant difference due to the relatively small sample size of the groups. Severity of delirium was significantly lower in the sevoflurane group compared to the propofol group (p=0.002). Papaioannou et al, and Williams-Russo investigated the effect of general vs regional anaesthesia on postoperative delirium.[52,54] Both studies were not able to show a significant result in favor of either of the two types of anaesthesia (21.4% vs 15.8% and 11.9% vs 9.4%, respectively).

Postoperative

Kaneko et al, administered 2.5 mg intravenous haloperidol daily for three consecutive days to the intervention group, through which they showed a significant decrease in postoperative delirium incidence (10.5% vs 32.5%, p<0.05), severity and duration (no numbers given) compared to a group receiving a placebo.[77] Fukata et al, administered twice this dose, 5 mg intravenous haloperidol, daily for five consecutive days to their intervention group and compared this to usual care.[71] More people in the intervention group developed postoperative delirium, although this result was deemed not to be significant (42.4% vs 33.3%, p=0.309). No significant effect was found on severity (no *p*-value) and duration of delirium (p=0.356). Both studies involved small populations.

Mu et al, successfully decreased delirium incidence by reducing postoperative pain (6.2% vs 11%, p=0.031).[60]

They provided patients in the intervention group with 40 mg of parecoxib (a COX-inhibitor) dissolved in saline every 12 hrs for 3 days and compared this to the control group who received regular saline.

In another postoperative intervention study, Aizawa et al, successfully lowered delirium incidence from 35% to 5% (p=0.023) by influencing the sleep-wake cycle and providing patients with injections of diazepam (1dd 0.1 mg/kg), flunitrazepam (0.04 mg/kg), and pethidine (1 mg/kg) for three nights following surgery.[69] In both groups, only 20 patients were included.

Music therapy for four times a day for an hour significantly increased NEECHAM scores and reduced postoperative confusion rates in a study by McCaffrey et al (p=0.014).[67]

The final two postoperative studies, both performed by Chen et al, modified the Hospital Elder Life Program (HELP)[88] by adding a postoperative component to improve the perioperative care program.[56,64] They added three standardized protocols in patient care on immediate postoperative return to the surgical ward. They focused on orientation, oral and nutritional assistance and early mobilization, integrating this into their perioperative patient management. In their first study in 2011,[64] they managed to reduce the incidence of delirium to zero in their intervention group. In both studies, Chen et al, were able to significantly reduce the incidence of delirium (0% vs 16.7%; p<0.001 and 6.6% vs 15.1%; p=0.008).

Perioperative

Kalisvaart et al, provided the intervention group with 0.5 mg oral haloperidol three times a day, starting preoperatively and continuing until the third postoperative day.[61] By doing so, they were not able to reduce the incidence of delirium (p=0.435), however, severity and duration decreased significantly (p<0.001 for both outcomes). In contrast, Larsen et al, were able to significantly reduce the incidence of delirium by administering 5 mg of oral olanzapine right before and after surgery to their intervention group (14.3% vs 40.2%, p<0.0001).[58] In their intervention group however, delirium was more severe (p=0.02) and lasted longer (p=0.02).

Leung et al, and Mann et al, were unable to significantly lower incidence of delirium by reducing postoperative pain. Leung et al. compared the use of 3dd 300 mg gabapentin (an anti-epileptic) the day before surgery until 3 days after surgery with a placebo (24.0% vs 20.8%, p=0.30).[59] Mann et al, compared combined epidural analgesia and general anaesthesia followed by postoperative patient-controlled epidural analgesia, with general anaesthesia followed by patient-controlled analgesia with intravenous morphine (24% vs 26%, no p-value was given).[50]

Presence of obstructive sleep apnea is independently associated with the occurrence of delirium.[89] Therefore, Nadler et al, studied the effects of obstructive sleep apnea on delirium and compared perioperative continuous positive airway pressure with routine care.[75] They did not show a decrease in postoperative delirium (21% vs 16%, p=0.53) or its severity.

In a study by Fan et al, restrictive blood transfusion (Hb<8 g/dL) was compared with liberal blood transfusion (Hb<10 g/dL).[47] They found no significant difference between the two protocols (21.3% vs 23.9%, p=0.727).

The focus of the study by Sugano et al, was trying to influence the sleep-wake cycle by providing the intervention group with 2.5 mg yokukansan (a traditional Japanese herbal medicine), three times a day from 7 days prior to surgery to 4 days post-surgery.[79] They were also unable to show a significant decrease in delirium (6.5% vs 9.7%, p=0.471).

Six studies investigated a non-pharmacological approach to decrease the incidence of postoperative delirium by implementing a multimodal intervention program, or perioperative care pathway.[63,65,66,68,72,73] They tried to alter multiple components during both preoperative and postoperative care to prevent postoperative delirium. The number of components influenced varied in each study. These are discussed in detail below.

Perioperative multicomponent interventions

The CareWell in Hospital program (CWH) was designed by Bakker et al,[63] and developed in line with HELP,[88] and consists of two main concepts which were applied during admission: improving patient-centered care by proactive and intensive support and increasing awareness and competency of personnel providing geriatric care. A first screening by a nurse, a second screening by a geriatric nurse, medication review, a CareWell plan, follow-up during admission, collateral history assessment, a CGA, a multidisciplinary meeting, stimulation of cognitive and physical activities by trained volunteers, and education of nurses and physicians were the components of this program. In this before-and-after study, there was no significant difference in delirium incidence in the group receiving the CWH program and the control group (12.4% vs 13.3%; p=0.983).

Results may, however, be influenced by the significantly bigger number of ASA III and IV patients in the intervention group.

The team of McDonald et al, developed The Perioperative Optimization of Senior Health (POSH) program.[66] They involved patients and their families and focused specifically on cognition, medication, comorbidities, mobility, functional status, nutrition, hydration, pain, and advanced care planning. Patients were assessed before admission in a Geriatric Evaluation and Treatment Clinic for multidisciplinary preoperative evaluation and care coordination. Due to this increased attention and focus, instead of reducing the incidence of delirium, they found a much larger percentage of patients with delirium in the intervention group (28.4% vs 5.6%; p<0.001).

Hempenius et al, designed the Liaison Intervention in Frail Elderly (LIFE) consisting of preoperative assessment and planning of preventive measures by a geriatric team (CGA) and monitoring during hospital stay using several checklists, focusing on orientation, medication, comorbidities, sensory impairment, nutrition, mobility, anxiety, pain, sleep, defecation, incontinence, infection, depression, and cognitive, social, and instrumental functioning.[72] LIFE was not able to significantly reduce incidence (9.4% vs 14.3%, OR 0.29–1.35) or severity of delirium (p=0.23).

Kratz et al, focused their intervention, implemented by a geriatric liaison nurse during admission, on six components: early mobilization, improvement of sensory stimulation, fluid and nutritional intake and sleep, cognitive activation, and validation therapy.[68] Through the optimization of these components, Kratz et al, successfully reduced the incidence of delirium (4.9% vs 20.8%, p=0.01) compared to usual care.

The perioperative care pathway developed by Jia et al, significantly reduced the incidence of delirium by implementing a fast-track protocol during admission, focusing on preoperative preparation, anaesthesia, postoperative pain control, and postoperative management of diet, urinary catheter and mobilization (3.4% vs 12.9%; p=0.008).[73]

Harari et al, developed the "POPS" intervention, which can be divided into three categories: Preoperative assessment and education of patients before admission, education of staff on postoperative interventions and follow-up home-based therapy. Patients were preoperatively assessed by a geriatrician, geriatric nurse, occupational therapist, physiotherapist, and social worker. Patients were educated in optimizing postoperative recovery by giving them preoperative home exercises, good nutrition, relaxation techniques, and advice on pain management. Staff were educated in early detection and treatment of medical complications, early mobilization, pain management, bowel-bladder function, nutrition, and discharge planning. After discharge, follow-up home-based therapy was offered to those in need.[65] The implementation of this intervention successfully reduced the incidence of delirium (5.6% vs 18.5%; p=0.036).

Overall outcomes and pooled analysis

Delirium incidence

A total of 19 out of the 35 included studies showed a significantly lower incidence of delirium in the intervention group compared to the control group.[48,53,56,58,60,64–70,73,74,76–78,80,81] In the study by Sultan et al,[80] the postoperative delirium incidence was significantly reduced in the melatonin group compared to the usual care group.

Delirium severity

Nine studies investigated the effect of their interventions on the severity of postoperative delirium.[51,55,57,58,61,71,72,75,77] Three studies showed a significant reduction in the severity of delirium following the implementation of their intervention,[51,61,77] although Kaneko et al,[77] did not support this claim with numbers. In the study of Larsen et al,[58] on the other hand, a significantly higher severity of delirium was observed in the intervention group. The five remaining studies were not able to show any differences between the two groups.[55,57,71,72,75]

Delirium duration

Six studies examined the effect of their interventions on the duration of postoperative delirium.[55,58,61,71,74,77] In three of these studies a significantly reduced length of delirium was observed in the intervention group, although Kaneko et al, again did not support this claim with numbers.[61,74,77] Olanzapine administration significantly increased the observed length of delirium.[58] The remaining two studies did not show significant differences between either of the groups.[55,71]

A complete overview of numbers on delirium incidence, severity, and duration is shown in Table 1.

Pooled analysis of preventive methods to reduce the incidence of delirium

Pooled analyses were performed on seven categories of interventions: multicomponent interventions (n=7),[56,63,64,66,68,72,73] antipsychotics (n=4),[58,61,71,77] postoperative pain management (n=3),[59,60,62] sleep-wake cycle (n=3),[69,79,80] dexmedetomidine (n=3),[57,74,78] general vs regional anaesthesia (n=2),[52,54], and BIS-guidance (n=2).[70,76] The study by Mann et al, was excluded from the pooled analysis, since they did not compare their intervention to usual care.[50] Pooled analysis, in-study comparisons and the results of these comparisons are shown in Figures 3–9.

Analyses showed significant results for dexmedetomidine treatment (RR 0.58 [0.45–0.76]; 95% CI) and BIS-guided anaesthesia (RR 0.71 [0.60–0.85]; 95% CI) Pooled analyses did not show a significant reduction in the incidence of delirium for multicomponent interventions (RR 0.57 [0.24–1.38]; 95% confidence interval), the use of antipsychotics (RR 0.60 [0.29–1.24]; 95% confidence interval), postoperative pain management (RR 0.87 [0.54–1.40]; 95% confidence interval), sleep-wake cycle improvement (RR 0.69 [0.36–1.35]; 95% confidence interval), or in favor of regional or general anaesthesia (RR 1.12 [0.60–2.07]; 95% confidence interval.

Results of these pooled analyses should be interpreted with caution, due to the heterogeneity of the included studies. Sensitivity analyses were therefore performed.

Sensitivity analysis

Sensitivity analyses were performed to check whether a change in significance occurred. Different outcomes in favor of the interventions were then observed for multicomponent interventions and the use of antipsychotics. For multicomponent interventions, when leaving out the before-and-after studies with a high risk of bias (Bakker, Chen 2011, McDonald and Kratz), a significant decrease in the incidence of delirium was observed for these interventions when compared to usual care (RR 0.47 [0.31–0.74]; 95% confidence interval). For antipsychotics, when leaving out the study with a relatively high risk of bias (Fukata), results shift to a significant decrease of delirium incidence in favor of the use of antipsychotics (RR 0.45 [0.26–0.77]; 95% confidence interval). For all other pooled analyses, sensitivity analyses did not alter outcomes.

Discussion

Prevention of delirium in the elderly surgical patient is essential as postoperative delirium is an important health care issue. This study aimed to describe and pool results of interventions with a focus on preventing postoperative delirium in elderly surgical patients, electively planned for non-cardiac surgery without planned postoperative ICU admission.

Summary and interpretation of results

Pooled analysis of all studies implementing multicomponent interventions shows that these are unable to successfully lower the incidence of delirium. However, McDonald et al, started the POSH program in order to improve perioperative care and prevent adverse postsurgical outcomes.[66] Contrary to their desired effect, their program led to a significant increase in delirium. They concluded that their results were an expected consequence of improved screening. None of the

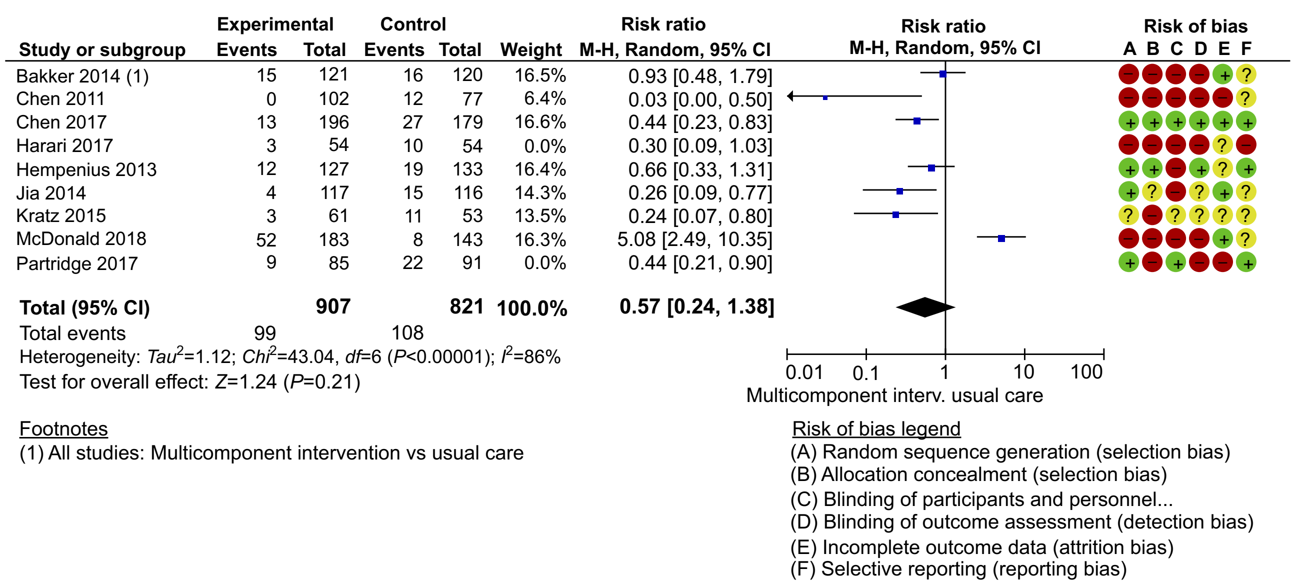

Figure 3 Forest plot 1. Multicomponent interventions.

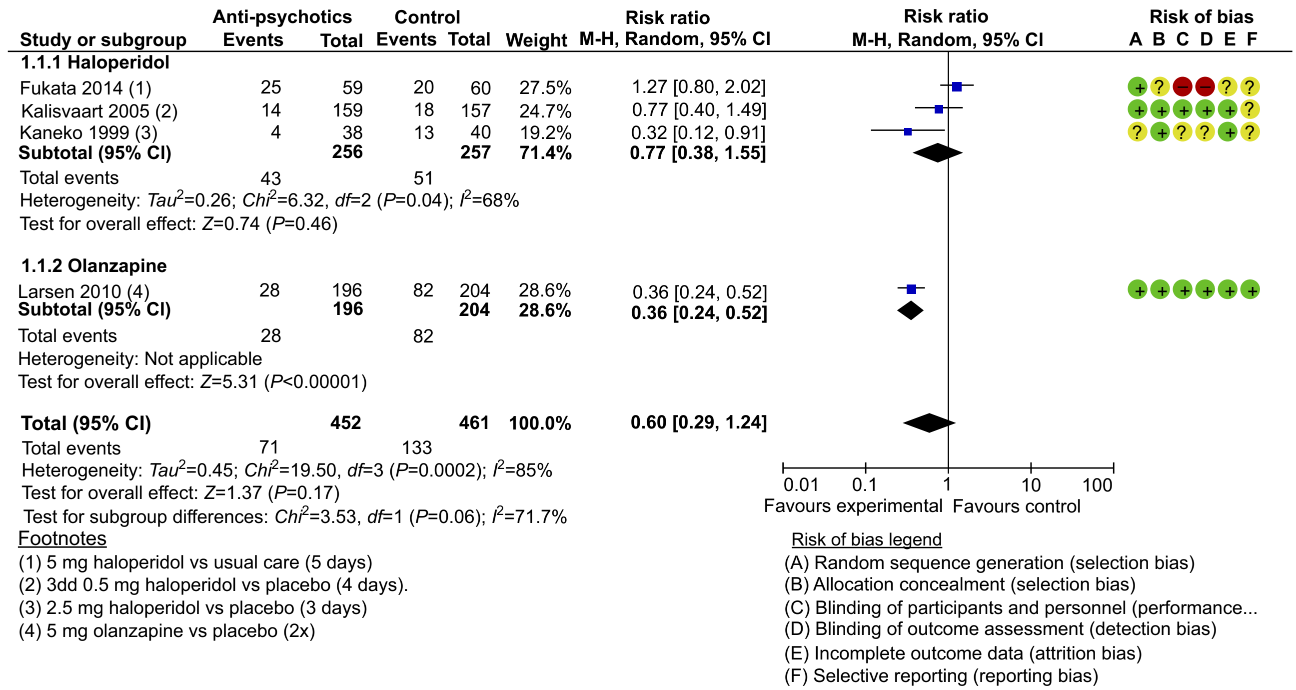

Figure 4 Forest plot 2. Antipsychotics.

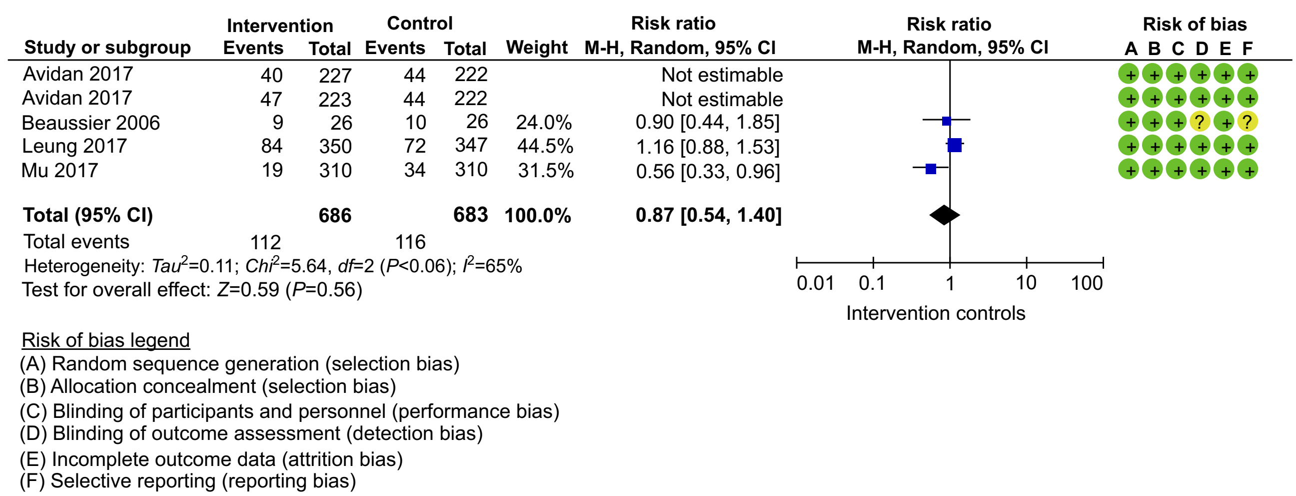

Figure 5 Forest plot 3. Postoperative pain management.

other studies showed a similar effect of improved screening for delirium; therefore, diagnostics and screening before intervention may have been inadequate prior to the implementation of this program. Their program did extremely well in increasing awareness, and with that, in diagnosing delirium. However, as a preventive method, it was proven unsuccessful. McDonald et al, also reported the lowest percentage of delirium incidence in their control group, which also supports this theory. The authors believe that this deviant result causes a distorted outcome. Without this study, multicomponent intervention would have given a significant reduction of delirium (RR 0.44 [0.25–0.78]; 95% CI, not shown in a figure). Risk of bias was relatively high due to the number of before-and-after studies that implemented multicomponent interventions. On the basis of sensitivity analysis, by removing these high risk studies from the pooled analysis, significant results in favor of multicomponent interventions compared to usual care were observed.

Pooled results do not support the use of antipsychotics in the prevention of delirium, however, based on the sensitivity analysis antipsychotics can successfully prevent delirium. Larsen et al,[58] the only study investigating the

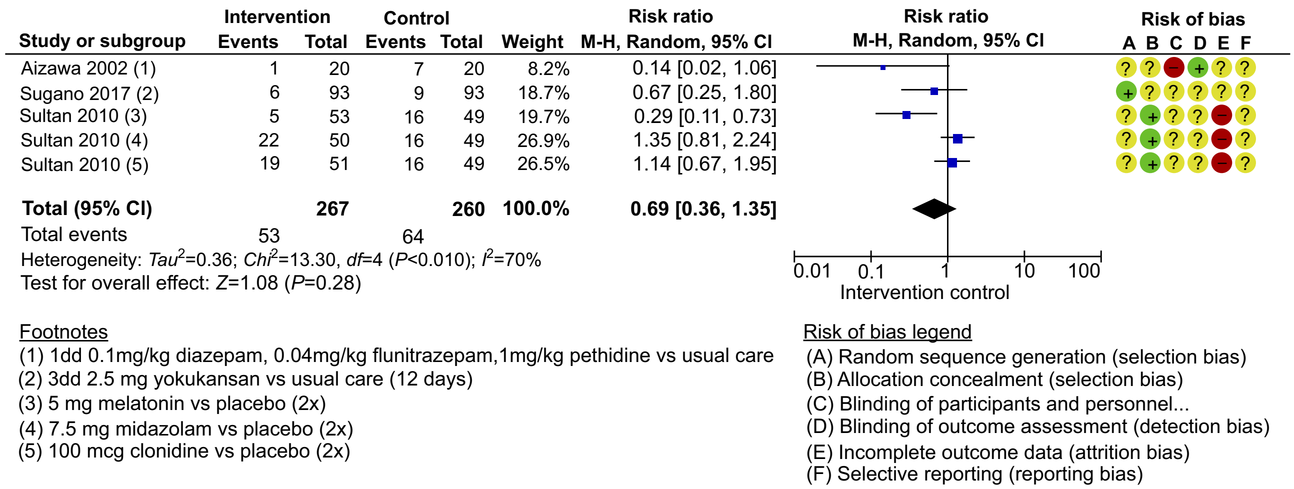

Figure 6 Forest plot 4. Sleep-wake cycle.

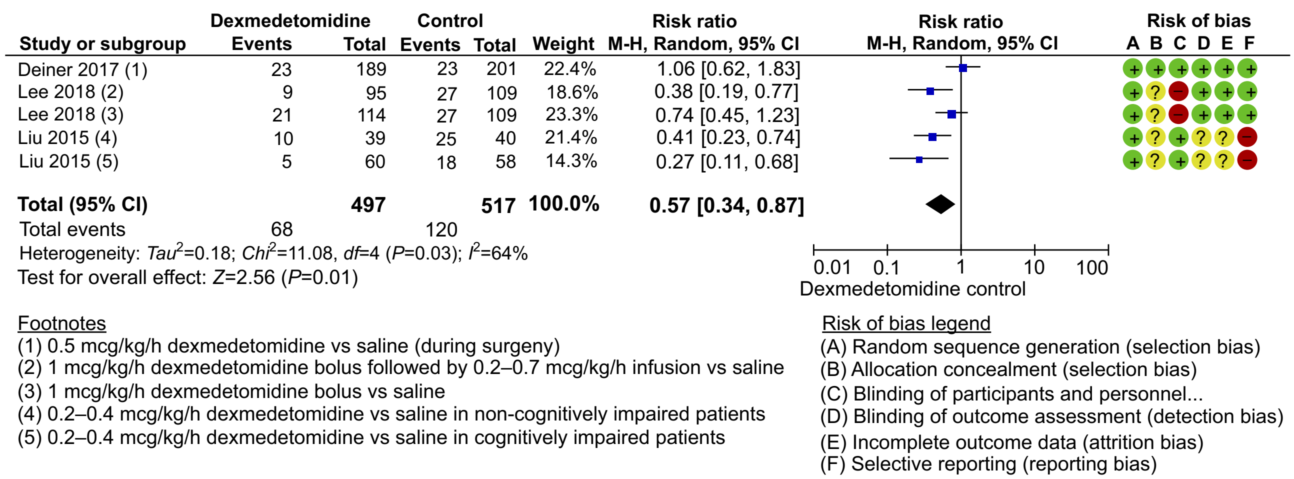

Figure 7 Forest plot 5. Dexmedetomidine treatment

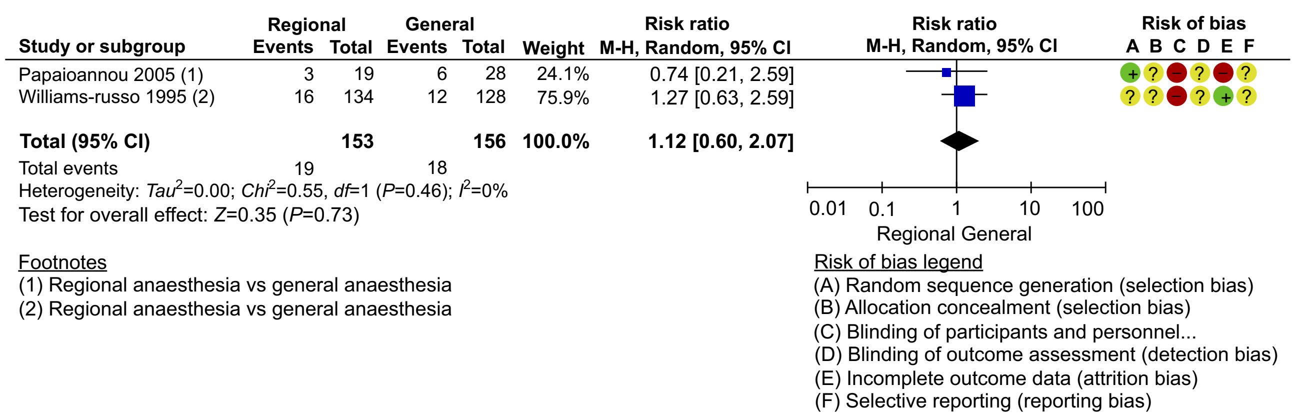

Figure 8 Forest plot 6. Regional vs. general anaesthesia

effect of olanzapine, showed a significant reduction in the incidence of delirium. However, they reported negative effects on duration and severity of delirium. In contrast, the administration of haloperidol did not significantly reduce the incidence of delirium but did have advantageous effects on both severity and duration. These contradictory effects might best be explained by the bigger anticholinergic effects of olanzapine, caused by its high

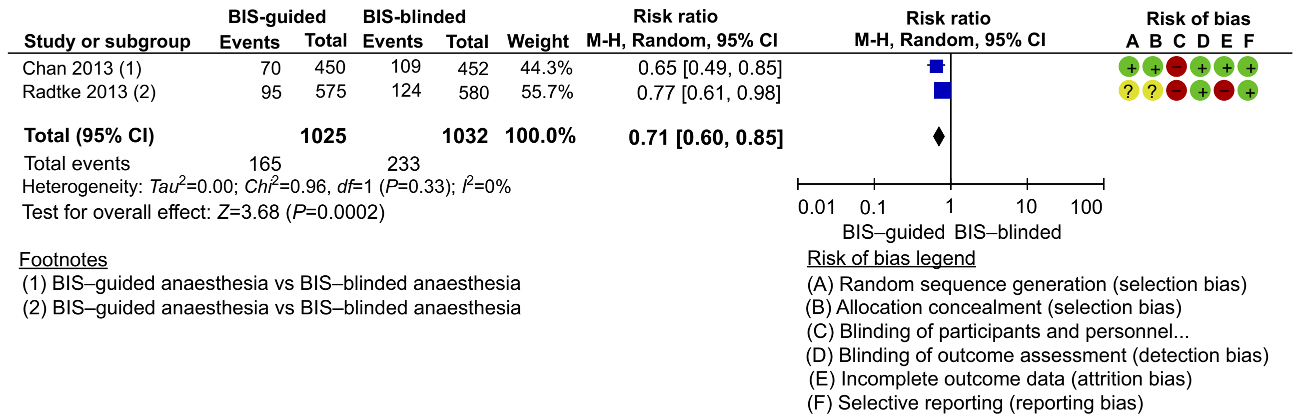

Figure 9 Forest plot 7. BIS-guidance.

affinity to the muscarinic cholinergic receptor. In contrast, haloperidol has a negligible affinity for this receptor. All studies investigating the effects of antipsychotics were heterogeneous in terms of the type of antipsychotic, route of administration and dosage. Overall, the risk of bias in these studies was deemed to be relatively low.

Studies on the prevention of postoperative pain are well set-up, all of them scoring low in our quality assessment. Unfortunately, they were not able to show a significant effect on the incidence of delirium. All of these studies used different analgesic medication, of which only the use of parecoxib seemed to lower the incidence of delirium.[60] A similar effect of parecoxib use was seen in patients with femoral head fractures in a study by Li et al, in 2013.[90]

The three studies investigating interventions to improve the sleep-wake cycle lacked clear reporting of their methods, which made the risk of bias unclear. Pooled analysis did not show a significant decrease of delirium. Sultan et al, investigated three types of medication, of which only melatonin seemed to have a favorable effect on delirium incidence.[80] This is in line with an earlier published report by Al-Aama et al,[91] which supports the use of melatonin in non-surgical patients. In elderly patients with hip fractures however, melatonin was not able to reduce the incidence of delirium.[92]

Pooled analysis of studies using dexmedetomidine to prevent delirium showed a significant reduction in favor of this intervention. The study by Deiner et al, was rated low risk, but was the only study that did not show a statistically significant result.[57] A 2015 review concluded that dexmedetomidine was an effective method to prevent delirium when compared to propofol or benzodiazepines in surgical patients.[93] Two studies in cardiac patients showed promising results of the drug's effects on postoperative delirium,[94,95] however opposing results were published by a further study.[96] Yet another study was able to show a significant reduction of delirium incidence in non-cardiac ICU patients.[97] Dexmedetomidine is a drug with potential beneficial effects; however, more extensive research using a larger sample is needed to identify patients who might benefit most from this treatment.

Two of the studies included in this review compared regional with general anaesthesia, but neither study was able to show a significant outcome in favor of any of the two. These results are in accordance with a study on vascular surgical patients by Ellard et al,[98] and two systematic reviews, performed by Mason et al,[99] in 2013 and O'Donnel et al,[100] in 2018.

Controlling the depth of anaesthesia using BIS-guided anaesthesia seems to have an advantage over BIS-blinded anaesthesia. Both studies and pooled analysis showed a significant reduction in postoperative delirium incidence after BIS-guided anaesthesia. They both included approximately a thousand patients, which strengthens their results, although only the study by Chan et al,[70] was rated as having a low risk of bias.

The seven other studies identified for this review could not be used for meta-analysis, since the interventions used in these studies have only been done in a single trial.[47–51,67,75] Sample sizes are small, and the quality of the evidence is often poor. The studies by Kudoh et al, and McCaffrey et al, showed a significant result in favor of their interventions, although the quality of the latter was poor and scored a high risk of bias.[48,67]

An extensive review by Siddiqi et al, in 2016 showed similar results in favor of multicomponent interventions and BIS-guided anaesthesia.[101] They did not include studies examining the effects of dexmedetomidine on delirium incidence. Another review by Zhang et al, in 2013 did examine the effects of dexmedetomidine and concluded that dexmedetomidine sedation, the use of antipsychotics and implementation of multicomponent interventions could potentially prevent postoperative delirium.[102] These findings are in line with this systematic review and meta-analysis. Contrary to this study, however, pilot studies and studies involving non-surgical patients, cardiac patients, and patients acutely admitted to the hospital were all included in both systematic reviews.

Recommendations

The authors believe that due to the multifactorial etiology of delirium, multicomponent, perioperative and multidisciplinary interventions should be implemented to prevent patients from developing delirium. In the United Kingdom, implementation of multimodal approaches is already recommended in the existing NICE guidelines on how to recognize, prevent, and treat delirium.[103] Most of these interventions are performed during admission, focusing on improvement of orientation, mobilization, nutritional status, senses, and sleep, on decreased medication use, pain, and anxiety, and on stimulation of activities. By adding new components to these efforts and combining them with prophylactic antipsychotics, fast-track protocols, BIS-guided anaesthesia and the use of dexmedetomidine, even more successful multicomponent perioperative care pathways could possibly be created to ensure an additional decrease postoperative delirium and other complications.

Using these methods, both the preoperative and postoperative period are covered. This leaves open a possibility for interventions during the pre-admission period to further optimize patients prior to surgery, especially since incidence rates of up to 25% are still observed in the intervention groups. These interventions should be customized and tailor-made to tackle specific (precipitating) factors of frailty for each patient individually. Especially in elective surgery, integration of preoperative optimization into the perioperative management of patients may be able to further reduce delirium in elderly surgical patients, a theory also suggested by a recent study on elective cardiac surgery.[104] In addition, this "prehabilitation"[105] might be able to reduce other adverse postoperative outcomes.

Since previous studies are heterogeneous and lack high-quality results, special attention should be paid to improve these factors. Severity and duration of delirium and quality of life should be considered as additional outcome factors, because although implementation of an intervention might not necessarily reduce the incidence of delirium, it might reduce the burden on the patient as well as the burden on the health care system of this still often encountered and significant condition.

Limitations

Studies on the prevention of delirium have been conducted for almost 20 years, with an increase in attention in recent years. These studies show little uniformity, which leads to the conclusion that a successful preventive method has yet to be found. Studies on prevention are heterogeneous, have varying (often small) sample sizes or have an unclear or high risk of bias. On exploring heterogeneity using χ^2 and inconsistency (I^2), as shown in Figures 3–9, considerable heterogeneity was found for pooled analyses on multicomponent interventions, antipsychotics, postoperative pain management, sleep-wake cycle, and dexmedetomidine. As a consequence of the heterogeneity in the investigated studies included in this review, a great variance in incidence rates of delirium was found (5.6–62.5%).

Twenty-eight studies did not exclude patients with preoperative delirium, which is a significant weakness of these studies. Since prevention of delirium, and not treatment, was the focus of these studies, these patients should have been excluded from analyses in the included studies. However, as mentioned earlier, because of the elective nature of the procedures, it is likely that patients in these studies did not have a delirium prior to surgery.

Another limitation in several of our reviewed studies was that the number of days over which delirium was assessed was less than one week in half of the studies, some of which only assessed for delirium in the first 2 days after surgery. The average time to onset of postoperative delirium is 2.1 ±0.9 days,[106] which is why a two-day follow-up is considered insufficient to assess for postoperative delirium fairly.

Conclusion

Multicomponent interventions, the use of antipsychotics, BIS-guided anaesthesia, and administration of dexmedetomidine during anaesthesia can successfully reduce the incidence of delirium. By adding these interventions to already existing multicomponent and multidisciplinary approaches, the incidence of delirium might be reduced even further. Additionally, other adverse postoperative outcomes could potentially be prevented by combining these approaches. In order to obtain possible additional benefits, interventions to tackle precipitating risk factors should be supplemented to interventions that are proven successful. In elective surgical patients, a potential for reducing the incidence of postoperative delirium lies in the pre-admission phase. Multimodal prehabilitation pathways should therefore be considered for investigation.

Abbreviations list

AMT, Abbreviated Mental Test; BIS, Bispectral index; CAM, Confusion Assessment Method; CCI, Charlson Comorbidity Index; CGA, Comprehensive Geriatric Assessment; CI, Confidence interval; CPAP, Continuous positive airway pressure; HELP, Hospital Elder Life Program; LOS, Length of hospital stay; PCA, Patient-controlled analgesia; RCT, Randomized controlled trials; RR, Risk ratio.

Authors' contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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