A systematic review of strategies for preventing delirium in patients undergoing vascular surgery

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ABSTRACT

Objectives

Elderly patients undergoing vascular surgery are at risk of developing postoperative delirium, which is associated with a high mortality. Delirium prevention is difficult and is investigated in surgical patients from various specialisms, but little is known about delirium prevention in vascular surgery. For this reason we performed a systematic review on strategies for delirium prevention in patients undergoing elective surgery for peripheral arterial disease or for an aneurysm of the abdominal aorta.

Methods

This systematic review included studies describing strategies for preventing delirium in patients undergoing elective surgery for peripheral arterial disease or for an aneurysm of the abdominal aorta. The search was conducted using the keywords 'vascular surgery', 'prevention' and 'delirium', and was last run on October 21st, 2021 in the electronic databases Pubmed, MEDLINE, Embase, Web of Science, the Cochrane library and Emcare. Risk of bias was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and the ROBINS-1 tool for observational studies.

Results

Four studies including 565 patients were included in the systematic review. A significant decrease in the incidence of delirium was reported by a study investigating the effect of comprehensive geriatric assessments within patients undergoing surgery for an aneurysm of the abdominal aorta or lower limb bypass surgery (24% in the control group versus 11% in the intervention group, $p = 0.018$), and in the total group of a study evaluating the effect of

outpatient clinic multimodal prehabilitation for patients with an aneurysm of the abdominal aorta (11.7% in the control group versus 8.2% in the intervention group, $p = 0.043$, OR = 0.56). A non-significant decrease in delirium incidence was described for patients receiving a multidisciplinary quality improvement at the vascular surgical ward (21.4% in the control group versus 14.6% in the intervention group, $p = 0.17$). The study concerning the impact of the type of anaesthesia on delirium in eleven older vascular surgical patients, of which three developed delirium, did not differentiate between the different types of anaesthesia the patients received.

Conclusion

Despite the high and continuous increasing incidence of delirium in the growing elderly vascular population, little is known about effective preventive strategies. An approach to address multiple risk factors simultaneously seems to be promising in delirium prevention, whether through multimodal prehabilitation or comprehensive geriatric assessments. Several strategies including prehabilitation programs have been proven to be successful in other types of surgery and more research is required to evaluate effective preventive strategies and prehabilitation programs in vascular surgical patients.

1. INTRODUCTION

The incidence of age-related diseases, such as peripheral arterial disease (PAD) and an aneurysm of the abdominal aorta (AAA), will increase in the upcoming decades due to the progressive aging of the population[1]. Age-related postoperative complications, such as a delirium, will therefore be more prevalent[2-4]. Delirium is a common and serious complication, mostly affecting older persons. This neuropsychiatric disorder is characterized by an acute onset and fluctuating course of disturbed consciousness, perceptive function or cognitive function and has a complex, multifactorial aetiology that is still mostly unknown.[5, 6] Delirium rates up to 35% are reported in older hospitalized patients[3, 5, 7, 8]. In fact, Hshieh et al. state that up to 60% of deliriums are undetected[2] and therefore the actual incidence might be higher. A delirium could have a variety of serious consequences such as a prolonged hospital stay, institutionalization after discharge, functional and cognitive decline, significant healthcare costs and eventually death[2, 3, 9-11].

Previous studies reported that older patients, undergoing vascular or endovascular surgery for PAD or AAA, are at risk of developing postoperative delirium[12, 13]. For vascular surgical patients, the known risk factors for delirium are age, intoxications, pre-existing cognitive impairment, a history of delirium and comorbidities[14-18]. Factors related to undergoing surgery, such as physical and mental stress, severe illness, general anaesthesia and an impaired resilience afterwards, will further increase their risk of delirium[3, 5, 12, 19, 20].

The treatment of delirium is complex[5, 21, 22]. International guidelines on prevention, diagnosis and treatment of delirium are available[3, 6, 22-26] but further improvements are still urgently needed. Inouye et al. outlined that, even if treatment of delirium is successful, negative

consequences remain existent[3]. Additionally, in 30 to 40% of the cases, delirium is thought to be a preventable condition. Needless to say, the most effective strategy for preventing the negative effects of delirium is to prevent delirium before it develops[2]. With the high incidence rate, preventive strategies for delirium should be a high priority in order to decrease severe adverse health outcomes and high treatment costs[6, 27, 28]. Delirium prevention has already been investigated in surgical patients from various specialisms, such as colorectal surgery, cardiac surgery, neurosurgical and orthopaedic surgery[29-51]. Strategies such as multimodal prehabilitation, nurse interventions, type of anaesthesia and analgesia and the preoperative use of medication such as melatonin, haloperidol, olanzapine, gabapentin and more have been investigated, a few of which have been found to be effective [41, 45-48, 52-54]. However, little has been published about delirium prevention in vascular surgery. Since delirium often occurs in vascular surgical patients, this is an important topic to investigate.

The purpose of this study is to identify strategies for the prevention of delirium in patients undergoing elective treatment for PAD or AAA.

2. MATERIAL AND METHODS

This systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 checklist [55] and included studies describing strategies in preventing delirium in patients undergoing elective surgery for PAD or AAA. The protocol was pre-registered in PROSPERO, the International prospective register of systematic reviews, registration number CRD42021245174.

2.1 Eligibility criteria

Studies were eligible for inclusion if the following criteria were met: 1) original collection of quantitative data, or a systematic review; 2) the study design targeted patients of any age, referred to the hospital for elective treatment of PAD or AAA; 3) the study focused on strategies to prevent delirium; 4) articles available in English or Dutch.

Articles with mixed populations (e.g. inclusion of both elective and urgent patients, non-intensive care unit (ICU) and ICU patients or multiple types of surgery) were considered eligible, on condition that the data for elective, vascular patients was analysed and reported separately. There were no restrictions concerning study date, publication date or publication status. Comment pieces, abstracts or patient surveys were excluded from this review.

2.2 Search and information sources

A search was conducted using the keywords 'vascular surgery', 'prevention' and 'delirium' (Supplemental Table I). The search was last run on October 21st 2021 in the electronic databases Pubmed, MEDLINE, Embase, Web of Science, the Cochrane library and Emcare. All these results were exported into the citation manager tool Endnote[56] to eliminate duplicates. In addition to database searches, reference lists of articles were screened for further eligible papers.

2.3 Study selection

Titles and abstracts were screened for eligibility by two independent researchers (AM and SvM). Remaining studies were read full-text. Disputes were discussed with the other researchers (LvdL and MF) until consensus was reached. The study selection process was performed in Endnote [56].

2.4 Data items and data collection process

Data was manually extracted in Excel[57] by two independent researchers (AM and SvM). Using a standardized data extraction sheet, the following data was collected: study characteristics (year of publication, author, study design, study period, study setting), patient characteristics (inclusion and exclusion criteria, number of patients, vascular pathology, treatment type, control group), strategies used for preventing delirium (including timing and duration of the strategy and compliance), outcome measures (primary and secondary outcomes, incidence rate of delirium, type of score used for diagnosing delirium and length of delirium in days) and risk factors for the development of delirium.

2.5 Summary measures

The principal study measure was 'strategies for preventing postoperative delirium'. Additionally, the incidence, duration and risk factors of delirium were noted.

2.6 Risk of bias in individual studies

Risk of bias was scored for RCTs using the Cochrane Risk of Bias tool and for observational studies using the ROBINS-1 tool [58, 59]. Studies were assessed as low, high or unclear risk of bias for RCTs and low, moderate, serious, critical or unclear risk of bias for observational studies. All the included articles were assessed for quality by two independent researchers

(AM and SvM). Any disagreements were solved by consensus or by soliciting the opinion of the other researchers (LvdL and MF).

3. RESULTS

3.1 Study selection

The database search identified 1588 studies. After removing 845 duplicates and screening of titles and abstracts, 44 studies were selected for full-text screening. Twenty additional articles were identified through backward snowballing. Eventually, 4 studies were included in the review. The most frequent reasons for exclusion were: only describing risk factors of delirium, not describing preventive strategies for delirium, not describing vascular surgical patients, e-comments instead of original articles and exclusively acute admission patients or ICU patients. An overview of the selection process is shown in Figure I (PRISMA flowchart).

3.2 Characteristics of included studies and patients

An overall summary of the results of the studies is shown in Table I. Two studies are randomized controlled trials (RCT)[60, 61]. Partridge et al. studied the effect of a comprehensive geriatric assessment (CGA) on length of hospital stay, cognitive function and complications including delirium in 176 patients aged 65 or older who underwent AAA repair or lower limb bypass surgery[60]. The other RCT was conducted by Papaioannou et al. and investigated the impact of the type of anaesthesia on cognitive status and delirium in 11 older vascular surgical patients[61]. The two remaining studies are before- and after studies, evaluating a particular intervention[62, 63]. Janssen et al. studied the effect of implementing a prehabilitation program in 143 patients undergoing elective repair of AAA and colorectal carcinoma (CRC). Mudge et al. reported their findings of a multidisciplinary quality improvement program in 235 elderly patients admitted to a vascular surgery ward.

Partridge et al. and Mudge et al. exclusively described vascular surgical patients [60, 63], in the other two studies patients of other surgical specialisms were also part of the study

population[61, 62]. In total, 565 patients were investigated. Three studies exclusively included patients undergoing elective surgery, and the study of Mudge et al. did not exclude acutely admitted patients[63]. The type of vascular surgery mainly existed of repair of an AAA and surgery for PAD. Delirium was the primary outcome in two studies[61, 62] and a secondary outcome in the other two studies. For these two studies, main outcome was length of hospital stay (LOS)[60, 63].

3.3 Risk of bias and quality assessment

Table II shows the outcome of the quality assessment. The two before and after studies of Janssen et al. and Mudge et al. were considered to have an overall serious risk of bias, due to the study design[62, 63]. The RCTs of Partridge et al. and Papaioannou et al. were rated as having a high overall risk of bias. Although these studies were considered to have a low risk of bias on multiple domains, there was a high risk of bias by means of the inability of blinding of participants and personnel and blinding of outcome assessment[60, 61].

3.4 Strategies in preventing delirium and individual outcomes

The four included studies investigated different types of strategies to reduce the incidence of delirium. Two studies described a multidisciplinary, multicomponent approach with an emphasis on optimization of nutritional status and physical condition in the preoperative period[62, 63]. Of these two studies, Janssen et. al. assessed patients on basic health, fitness and factors of frailty during the initial visit. Patients would afterwards visit a dietician for analysis and nutritional advice, a physical therapist for assessment and creating a schedule for home-based exercises, a geriatrician for a CGA in case of frailty, and would eventually receive an iron infusion in case of anemia . The other multidisciplinary study, by Mudge et al., set up the 'eat, walk, engage project', with focus on early mobility, nutrition and hydration and

cognitive activities. One study examined the effectiveness of performing a comprehensive geriatric assessment with subsequent delirium preventive interventions[60]. The remaining study focused on the perioperative period by examining the effect of the type of anaesthesia[61].

3.5 Incidence of delirium within different strategies

A significant decrease in the incidence of delirium was reported in the comprehensive geriatric assessment study by Partridge et al. for patients undergoing surgery for AAA or PAD (24% in the control group versus 11% in the intervention group, $p = 0.018$). The total group of AAA and CRC in the multimodal prehabilitation study by Janssen et al. also showed a significant difference in delirium incidence, with an incidence of 11.7% in the control group versus 8.2% in the intervention group (after adjustment for prognostic confounders: $p = 0.043$, OR = 0.56). The subgroup of AAA patients in this study showed a decrease from 9.6 % to 5.7% in the intervention group (OR 0.57, CI 0.16 – 2.04) but should not be interpreted independently since the study was powered on the total group of CRC and AAA and mostly involved patients with CRC in addition to the smaller number of patients with AAA. However, the AAA subgroup still shows a low odds ratio in line with the decrease in the incidence of delirium. Papaioannou et al. reported that 3 out of 11 vascular surgery patients developed delirium, but did not differentiate between the different types of anaesthesia the patients received. Mudge et al. described a decrease in delirium incidence in patients receiving the multidisciplinary quality improvement, although this difference is not significant (21.4% versus 14.6%, $p = 0.17$).

3.6 Diagnosis of delirium

242 The Confusion Assessment Method (CAM)[64] and the Diagnostic and Statistical Manual of
243 Mental Disorders (DSM)[65] were the most frequently used diagnostic tools for delirium.
244 Mudge et al. scored the CAM three times a week. In the study of Janssen et al., the Delirium
245 Observation Screening (DOS) scores were taken three times a day by the nurses during the
246 daily ward rounds[66]. When delirium was suspected, the geriatrician was consulted to confirm
247 the diagnosis using the DSM-V criteria or the CAM. Papaioannou et al. used the DSM-III,
248 and Partridge et al. did not report the method to diagnose delirium.

4. DISCUSSION

The findings of this systematic review suggest that little is known about effective preventive strategies for delirium in vascular surgery, despite the high incidence of delirium in the rising elderly vascular population[16, 18, 67]. The majority of all studies on this subject focus on identification of risk factors, but not on development of preventive strategies. Within the limited number of studies that focused on prevention of delirium, multidisciplinary approaches such as prehabilitation might be promising strategies.

Multiple studies have been published about delirium prevention in patients undergoing colorectal surgery, cardiac surgery, neurosurgery and orthopaedic surgery[29-50]. Strategies succeeding in reducing delirium included administration of dexmedetomidine or quetiapine, introduction of screening tools or nursing protocols targeting risk factors or a preventive multicomponent nurse intervention, application of a modified hospital elder life program (mHELP) and the use of BIS-guided anaesthesia[32, 34, 35, 38, 40, 44, 45]. No delirium reduction was found in administration of xenon, nitrous oxide or acetaminophen, a tailored postoperative delirium prevention intervention, preoperative education on delirium, the use of electroencephalography-guided anaesthetic administration, the comparison of intravenous or epidural patient-controlled analgesia and the use of early femoral nerve block intervention on preoperative pain management[30, 31, 36, 37, 42, 46, 48, 50]. Controversial results are published on, among other things, the administration of melatonin[29, 41]. Research studies on strategies are heterogeneous and may show different results for comparable interventions. The various types of surgery as described above, are often performed in an elective setting with time to perform a preventive strategy. This is in contrast to the current assumption that revascularisation in PAD should be performed as soon as possible, and this may account for the lack of research

on preoperative delirium prevention. However, recent studies pointed out that conservative treatment is a fair treatment option for frail patients with a high risk of postoperative complications, with no significant difference in amputation free survival (AFS), quality of life (QoL) or mortality after 1 year[68-72]. This emphasizes that preoperative preventive strategies are also applicable within vascular surgery.

The search revealed a high number of studies that focused on (retrospective) identification of risk factors that contribute to the onset of delirium. Even though certain described risk factors, such as preoperative statin use, elevated cytokines and elevated preoperative plasma levels of C-reactive protein may warrant a preventive strategy, the effect of these factors on prevention was not investigated and therefore the clinical significance of these findings is unclear[73-75]. Although this could be powerful information to identify patients at risk for delirium, it does not automatically mean that a preventive strategy can be directly linked to it[2].

A promising article about delirium prevention in vascular surgical patients was published after our last conducted search. In this pre-post study by Thillainadesan et al., a geriatrician was integrated into the vascular surgery team and provided comprehensive geriatric assessment-based interventions. One of the primary outcomes was the incidence of delirium, which was significantly reduced from 10.0% to 3.3% (p = .02). This emphasizes the importance of multidisciplinary approaches or comanagement and early risk assessment in order to reduce adverse geriatric outcomes, including delirium.

Postoperative delirium is a trending topic as this complication becomes more prevalent with the ageing population. Nonetheless, the postoperative period is not the only period of time during which delirium can develop. Chronic limb threatening ischaemia patients are often frail and cognitive impaired[68]. They are already at high risk of delirium prior to intervention and in some cases delirium might already be present during hospital admission. Hence,

patients who receive conservative treatment should also be subjected to delirium prevention programmes. Further research should be performed on delirium prevention prior to hospital admission and in patients that are treated conservatively in addition to surgically treated patients.

As mentioned in the introduction, delirium has both short- and long-term consequences[3, 76-79]. A recently published meta-analysis showed that delirium was significantly associated with long-term cognitive decline in both surgical and nonsurgical patients[80] and a cohort study showed that delirium in aged populations was associated with an eightfold increased risk of subsequent dementia[81]. If delirium prevention is successful, we expect it to prevent above severe events from happening. However, the long-term effects of delirium prevention on overall mortality has not yet been investigated.

Strengths of this study are the narrow focus of the main question, applied in a wide-ranging search that was performed within a high number of databases. Relevant evidence was selected using formulated inclusion criteria and all articles were assessed for risk of bias. A limitation of the study is the fact that this review only focused on elective patients. This was chosen since the pathophysiology and treatment of acute and elective vascular surgical patients is very different and report different numbers of delirium incidence[63, 67, 82]. Added to this, since little research is performed on this specific topic, too little comparable data was available to perform a meta-analysis. The outcomes of the current review are more of a descriptive character, but they do give insight in the few preventive strategies known to date.

In conclusion, little research is published about prevention of delirium in vascular surgical patients, even though it is highly necessary to devote attention to this issue. A multimodal approach to address multiple risk factors seems to be promising in delirium prevention, whether through multimodal prehabilitation or comprehensive geriatric assessments. Further research on the prevention and preventive strategies of delirium is needed and more

awareness needs to be created. With this in mind, our study group is currently investigating the effect of a multimodal, multidisciplinary prehabilitation program on the occurrence of delirium in elderly patients with chronic limb threatening ischaemia.

5. CONCLUSION

Despite the high and continuous increasing incidence of delirium in vascular surgical patients, little is known about effective preventive strategies. Strategies that focus on multiple possible risk factors simultaneously seem to have added value. Many additional strategies, including multimodal prehabilitation programs, have been proven to be successful in other types of surgery and more research is required to evaluate effective preventive strategies and prehabilitation programs in vascular surgical patients.

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Table I. Overview of study characteristics, interventions and outcomes (part 1)								
Author	**Title**	**Study design**	**Study period**	**Study setting**	**Inclusion criteria**	**Exclusion criteria**	**Pathology**	**No. Patients (I/C)[d]**
Janssen[61], 2019	Multimodal prehabilitation to reduce the incidence of delirium and other adverse events in elderly patients undergoing elective major abdominal surgery: An uncontrolled before-and-after study	Single-center, uncontrolled before-and-after study	2013 - 2018	Large teaching hospital, the Netherlands	Patients ≥ 70 with elective surgery for CRC[a] or AAA[b]	Acute hospitalisation or surgery, previous surgery six months prior to diagnosis, surgery planned within 2 weeks of the MDM[c]	AAA and CRC	Total: 267/360 AAA: 70/73
Partridge[59], 2017	Randomized clinical trial of comprehensive geriatric assessment and optimization in vascular surgery	Single-center RCT	2012 - 2014	Inner-city teaching hospital, United Kingdom	Patients ≥ 65 elective EVAR[e] or open AAA or lower limb bypass surgery	Emergency surgery or admission	AAA and PAD[f]	Total: 85/91
Papaioannou[60] 2005	The impact of the type of anaesthesia on cognitive status and delirium during the first postoperative days in elderly patients	Randomized controlled trial	Not mentioned	University Hospital, Greece	Patients ≥ 60 undergoing elective surgery	Illiteracy, auditory or visual disturbances, alcoholism or drug dependence, central nervous system disorder, antidepressants, parkinson, MMSE[g] <23, dementia	Orthopedic (16), urological (15), vascular (11) and gynaecologic (5) surgery	Total: 19 /28. Vascular surgery; 5/6
Mudge[62], 2019	Multidisciplinary quality improvement programme for older patients admitted to a vascular surgery ward	Prospective pre-post evaluation of an intervention	2012-2014	Metropolitan teaching hospital, Brisbane	Patients ≥ 65 admitted to the vascular surgical ward with LoS[h] of 3 days or more	Palliative patients, previously enrolled, discharged within 3 days or unable to be assessed within 7 days.	Vascular surgical pathology	Total: 112/123

Table I. Overview of study characteristics, interventions and outcomes (part 2)

Author	Preventive strategy	Timing of strategy	Primary and secondary outcomes	Incidence rate of delirium (I/C)	Score for delirium	Length of delirium (I/C)
Janssen[61], 2019	Multimodal prehabilitation: assessment of basic health, fitness and factors of frailty. Risk assessment, home-based exercise, dietary instructions, CGA[i], iron infusion in case of anemia.	5 weeks prior to surgery (pre-admission)	Primary; incidence of delirium	Total: 22 (8.2%) /42 (11.7 %). OR[j] 0.56 (p = 0.043)*. AAA: 9.6%, / 5.7% . OR 0.57, 95% CI[k]: 0.16 - 2.04	Dos score, DSM-V[l], CAM[m].	3 days /3 days
Partridge[59], 2017	Comprehensive geriatric assessment and optimization in outpatient clinic	Preoperative, in outpatient clinic setting	Primary: length of hospital stay. Secondary; new co-morbid diagnosis made, cognitive impairment, complications including delirium, discharge to a higher level of care dependency, readmission within 30 days	9 (11%) / 22 (24%), p = 0.018	Not mentioned	Not mentioned
Papaioannou[60] 2005	Regional anesthesia	Peroperative	Extracted from the study title: primary outcome: cognitive status and delirium	Vascular patients: 3/11, but not reported which patients received general and regional anesthesia	DSM III criteria	Not mentioned
Mudge[62], 2019	Comanagement with a senior general medical register, and the eat walk engage project (multisciplinary work group ; small improvement cycles. Focus on early mobility, nutrition and hydration and cognitive activities.)	During admission	Primary; LoS, delirium, functional outcome. Secondary: complications, discharge location, total hospital LoS	Total: 18 (14.6%) / 24 (21.4%) p = 0.17. Non-elective: 11 (16.2%) / 21 (35.6%). Elective: 7 (12.7%) / 3 (5,7%)	CAM, three times a week	Not mentioned

a CRC = colorectal carcinoma, b AAA = abdominal aneurysm of the aorta, c MDM = multidisciplinary meeting, d I/C = intervention/control, e EVAR = endovascular aneurysm repair, f PAD = peripheral arterial disease, g MMSE = mini-mental state examination, h LoS = length of hospital stay, I CGA = comprehensive geriatric assessment, j OR = odds ratio, k CI = confidence interval, l DSM = diagnostic and statistical manual of mental disorders, m CAM = confusion assessment method, * = after adjustment for prognostic confounders

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TABLE II: Summary of Risk of bias for each study

RANDOMISED CONTROLLED TRIALS*	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selection of the reported result (reporting bias)	Overall bias
Partridge[59]	Low	Unclear	High	High	Low	Low	High
Papaioannou[60]	Low	Unclear	High	High	Low	High	High

OBSERVATIONAL STUDIES*	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
Mudge[62]	Low	Low	Low	Low	NI	Serious	Low	Serious
Janssen[61]	Moderate	Low	Low	Low	Low	Serious	Low	Serious

* *Risk of bias was assessed using the Cochrane Risk of Bias tool for randomized controlled trials and using the ROBINS-1 tool for observational studies*