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Preoperative intervention to prevent delirium in patients with hip fracture – a systematic review

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ABSTRACT

INTRODUCTION. Delirium is a syndrome characterised by disturbance of consciousness and is a common complication to hip fractures. This systematic review was conducted to investigate the effect of simple preoperative interventions for the prevention of delirium in patients with hip fractures. The aim was to establish an easily implementable and resource-sparring treatment for the initial admission phase of hip fracture patients aimed at reducing the incidence of delirium.

MEHODS. Five databases were searched to identify randomised controlled trials comparing preoperative interventions other than geriatric assessment to placebo or usual care. Our primary outcome was incidence of delirium using a well-defined delirium-screening tool. Secondary outcomes included need for pharmacological treatment, duration of delirium and mortality.

RESULTS. A total of 13 RCTs provided data on 2,222 patients who had been exposed to 11 different interventions. Four interventions significantly reduced of the incidence of delirium: methylprednisolone (odds ratio (OR) = 0.42; 95% confidence interval (CI): 0.17-1.00; p = 0.048), fascia iliaca block (OR = 0.39; 95% CI: 0.18-0.84; p = 0.02), hypertonic saline (OR = 0.21; 95% CI: 0.08-0.55; p = 0.001) and rivastigmine patches (OR = 0.23; 95% CI: 0.07-0.77; p = 0.013). All studies were rated as having a high risk of overall bias.

CONCLUSIONS. Robust conclusions are precluded by study heterogeneity and high risk of bias in the included studies. However, this systematic review provides an indication of treatments that should be investigated further to establish any effect on delirium in the preoperative setting in hip fracture patients.

KEY POINTS

- Few studies have investigated prevention of preoperative delirium.
- The current gold standard, geriatric assessment, is resource heavy and difficult to implement.
- Four simple pharmacological treatments have shown a potential to reduce preoperative delirium specifically in hip surgery patients.
- Knowledge of effective prophylaxis is based on heterogenous data with a high risk of bias.

Delirium is a neuropsychiatric syndrome characterised by disturbance of consciousness and change of cognition [1]. Delirium is often fluctuating and develops rapidly [2]. The condition occurs in response to underlying organic causes including infection, trauma, surgery, pain and pharmaceutical agents [2].

Delirium is a common complication to hip fractures with an incidence of delirium in patients with hip fractures ranging from 4% to 53% [3]. In the year 2000, an estimated 1.6 million hip fractures occurred worldwide [4], potentially making delirium in patients with hip fractures a major burden to patients and healthcare systems. By 2050, the estimated number of hip fractures is 6.26 million [5].

Hip fracture in patients with delirium has been associated with a higher mortality and morbidity than in patients with no delirium [6]. Likewise, hip fracture patients with delirium carry a higher risk for cognitive decline beyond the acute hospitalisation [7]. Pharmacological treatment of established delirium has poorly documented effect and prevention may therefore be the most effective management strategy [7, 8].

The majority of research into delirium in patients with hip fractures has focused on post-operative delirium [9-11]. However, some studies indicate that up to 92% of delirium cases have a preoperative onset [3]. This makes it relevant to study preoperative delirium and interventions initiated preoperatively.

Studies on preoperative prevention of delirium have mainly focused on multicomponent geriatric care, but an overall view of preoperative interventions other than geriatric assessment is still needed because the involvement of the geriatric assessment requires considerable resources, which may be unavailable and show only a limited effect [11-13]. Consequently, identification of an easily implementable treatment for hip fractures upon arrival to the emergency department should be highly beneficial, widely available and would possibly reduce mortality and morbidity.

The purpose of this review was to identify potential preventive interventions to limit delirium in patients with hip fractures in addition to geriatric assessment.

METHODS

A protocol for this review was registered with PROSPERO International Prospective Register of Systematic Reviews (Reg. No. CRD42019131221).

Eligible studies were limited to randomised controlled trials (RCTs), quasi-RCT and cluster RCTs. We included studies with patients who were 16 years old or older and had been admitted to a hospital with an acute hip fracture. Studies comparing preoperative interventions other than geriatric multicomponent assessment to either placebo or usual care were eligible. Furthermore, inclusion required reporting an incidence of delirium as primary or secondary outcome using a diagnostic tool designed specifically to detect delirium. Our secondary outcomes were a need for pharmacological treatment of delirium defined as the use of antipsychotics, duration of delirium and mortality.

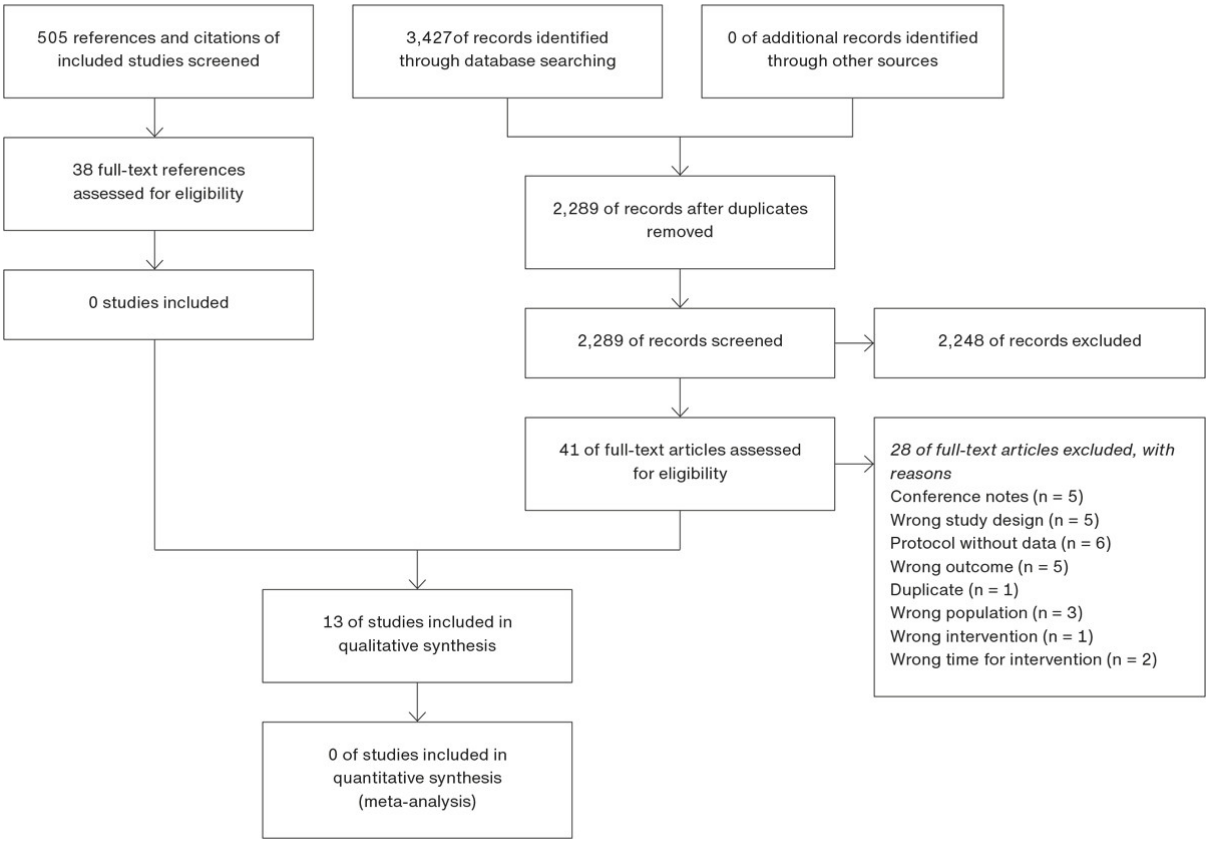
A generic search string was prepared in collaboration with an information specialist and subsequently adapted for the electronic databases MEDLINE, EMBASE, Central, Cinahl and Web of Science from their inception to 10 December 2021. There were no restrictions regarding language or publication date.

After study selection, the references and citations of the included studies and relevant reviews were screened to retrieve any additional relevant studies. The detailed search strategy is presented in **Appendix** (https://ugeskriftet.dk/files/a09210679_supplementary.pdf).

Two reviewers (CF and CS) independently screened titles and abstracts for inclusion criteria using the web-based screening tool Rayyan [14]. The same two reviewers screened potential studies in full text for final inclusion. Any discrepancies were solved by a third author (KW).

The search results are summarised in a PRISMA flow diagram (**Figure 1**).

FIGURE 1 PRISMA 2009 flow diagram of search strategy.



Two reviewers (CF and CS) independently retrieved data from the included studies using a predefined data extraction form. The form was designed and completed in a piloted form and subsequently adjusted prior to the final data collection. Disagreements were resolved by two additional authors (KW and AM).

The data retrieved included study design, country, number of participants, mean age, gender, American Society of Anesthesiology (ASA) score, Mini- Mental State Examination (MMSE) score at admission, type of preventive intervention, whether the intervention was compared with placebo or not, usual care or nothing, incidence of delirium, reported odds ratio or relative risk of delirium, method used to measure delirium, measurement time interval, time of first measurement, need for pharmacological treatment (antipsychotics), duration of delirium and mortality.

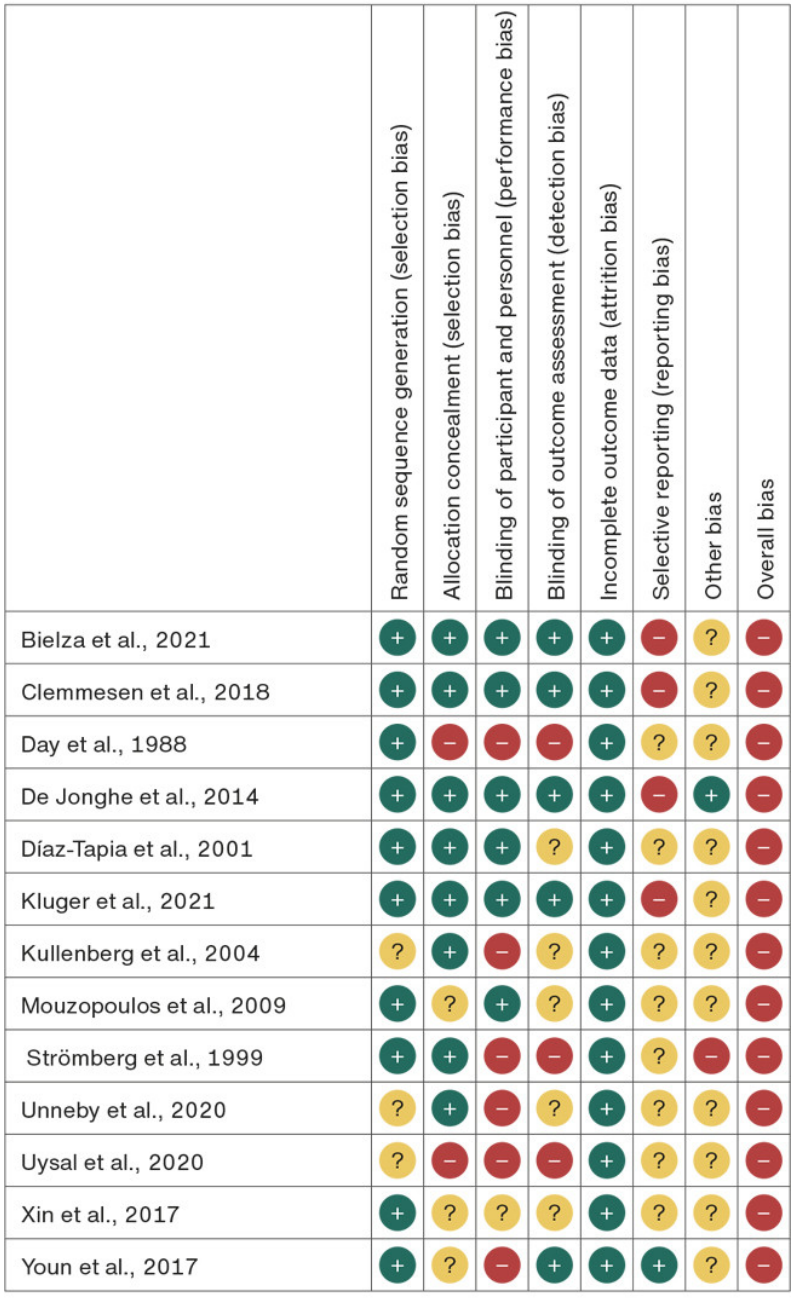
The primary outcome was defined as incidence of delirium based on criteria from a well-defined tool. The secondary outcomes were need for antipsychotics, duration of delirium and mortality.

The corresponding authors of the included articles were contacted for clarification of study results as needed.

Two reviewers (CF and CS) assessed the risk of bias in all included studies using the following domains of the Cochrane Risk of Bias Assessment Tool: adequate sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other biases [15]. Studies were rated as having a high overall risk of bias if they were rated high risk or unclear within one or more domains, in accordance with Cochrane's recommendations [15].

Certainty of evidence was determined using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (**Figure 2**) [16].

FIGURE 2 "Risk of bias" summary: review authors' assessments of each risk-of-bias item for each included study.



RESULTS

A PRISMA flow diagram is presented in Figure 1. The initial search yielded 3,427 titles, and a total of 2,289 abstracts were screened after removal of duplicates. In all, 13 randomised controlled trials were eligible for inclusion [17-29] with a total of 2,222 participants [17-29]. The studies originated from different parts of the world, including Europe, Oceania, Asia and South America [17-29].

All participants had a hip fracture and were admitted to a hospital for acute surgery [17, 18, 22-28]. The participants were all treated in an orthopaedic ward or a specialised hip fracture unit [17, 19-25, 28, 29]. Eight

studies excluded patients with existing preoperative delirium, and six studies excluded patients with dementia [18, 23-28]. One study required cognitive impairment testing at admission to the hospital prior to inclusion [27].

A total of 11 unique interventions were reported [17-29]. All studies reported the primary outcome, incidence of delirium (intervention: 11%-76%. Comparison 13%-71%) [17, 18, 22-28].

The primary outcomes from included studies are summarised in **Table 1**.

TABLE 1 Summary of findings: incidence of delirium.

		Incidence of delirium, n/N (%)			
Reference	Intervention	I	C	OR (95% CI)	p-value
Bielza et al., 2021 [19]	Venofer	17/125 (14)	17/125 (14)	1.00 (0.49-2.06)	0,999
Clemmesen et al., 2018 [17]	Methylprednisolone	10/59 (17)	19/58 (33)	0.42 (0.17-1.00)	0.048
Day et al., 1988 [22]	Thiamin hydrochloride	11/28 (39)	12/32 (38)	1.07 (0.38-3.06)	1.00
De Jonghe et al., 2014 [24]	Melatonin	55/186 (30)	49/192 (26)	1.23 (0.78-1.93)	0.40
Díaz-Tapia et al., 2001 [18]	Citicoline	4/35 (11)	8/46 (17)	0.61 (0.17-2.22)	0.60
Kluger et al., 2021 [29]	Dexamethasone	6/40(15)	9/39 (23)	0.65 (0.22-1.65)	0.36
Kullenberg et al., 2004 [23]	Femoral nerve block	6/40 (15)	12/40 (30)	0.41 (0.14-1.24)	0.17
Mouzopoulos et al., 2009 [25]	Fascia iliaca block	11/102 (11)	25/105 (24)	0.39 (0.18-0.84)	0.02
Strömberg et al., 1999 [28]	Reorientation[a]	15/116 (13)	14/107 (13)	0.99 (0.45-2.16)	1.00
Unneby et al., 2020 [21]	Femoral nerve block	88/116 (76)	85/120 (71)	1.29 (0.72-2.31)	0.383
Uysal et al., 2020 [20]	Femoral nerve block	5/46 (11)	9/45 (20)	0.49 (0.15-1.59)	0.227
Xin et al., 2017 [26]	Hypertonic saline	7/60 (12)	23/60 (38)	0.21 (0.08-0.55)	0.001
Youn et al., 2017 [27]	Rivastigmine patch	5/31 (16)	14/31 (45)	0.23 (0.07-0.77)	0.013

C = control group; CI = confidence interval; I = intervention group; OR = odds ratio.
a) Large clock, calendar, radio, TV set, telephone, own clothing and home visits.

Two studies reported the secondary outcome, need for antipsychotics [17, 24]. The threshold need for antipsychotic pharmaceuticals was not defined in any study. Both studies found no difference between the groups of intervention and comparison [17, 24]. Three studies reported duration of delirium [21, 24 ,25]. One study found a significantly shorter duration of delirium using fascia iliaca block (FIB) in the intervention group [25].

Five studies reported mortality [17, 24, 28], although only two studies reported 90-day mortality. None of the three studies reporting on 90-day mortality found any difference between treatment and control groups [17, 24, 28].

Our secondary outcomes are summarised in **Table 2**.

TABLE 2 Summary of additional findings: secondary outcomes.

	Need for pharmacological treatment					Duration of delirium, days							
	I		C			I		C			90-day mortality, n/N (%)		
Reference	n/N (%)	mg, median (IQR)	n/N (%)	mg, median (IQR)	p-value	median (IQR)	mean (± SD)	median (IQR)	mean (± SD)	p-value	I	C	p-value
Clemmesen et al., 2018 [17]	7/59 (12)	-	9/58 (15)	-	0.60	-	-	-	-	-	7/59 (12)	7/58 (12)	1.00
De Jonghe et al., 2014 [24]	-	4.0 (1.5-7.5)	-	5.0 (3.8-8.3)	0.20	2 (1.0-3.0)	-	2 (1.0-3.0)	-	1.00	39/186 (21)	41/192 (21)	1.00
Mouzopoulos et al., 2009 [25]	-	-	-	-	-	-	5.22 (± 4.28)	-	10.97 (± 7.16)	0.001	-	-	-
Unneby et al., 2020 [21]	-	-	-	-	-	-	3.8 (± 2.8)	-	4.1 (± 3.0)	0.499	-	-	-

C = control group; I = intervention group; IQR = interquartile range; SD = standard deviation.

Five studies used the Confusion Assessment Method as a measure with which to screen for perioperative delirium [17-19, 25, 27]. Two studies used the Short Portable Mental Status Questionnaire [23, 28], one study used the Abbreviated Mental Test [22], one study used the criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [24], one study used the Organic Brain Syndrome Scale [21], one study used

the Memorial Delirium Assessment Scale [29], one study used the Delirium Rating Scale-R-98 [20] and one study used the Nursing Delirium Screening Scale [26]. Seven studies screened the participants for perioperative delirium once daily [17, 18, 20, 21, 24, 25, 28]. The remaining four studies either did not report the screening interval or screened less than once daily throughout the hospitalisation period [19, 22, 23, 26, 27, 29].

All interventions had a low or very low certainty of evidence determined by the GRADE approach, Figure 2.

All studies were rated as having an overall high risk of bias due to a high or unclear risk in at least one domain (Figure 2).

Adequate randomisation was reported in ten studies [17-19,22-24-29], whereas allocation concealment was adequate in eight of the 13 studies [17-19, 21, 23, 24, 28, 29]. Seven of the studies failed to provide a satisfying description of their blinding [17, 18, 20, 21, 23, 25-28]. None of the studies had missing data [17, 18, 22-28]. Only one study had a low risk of selective reporting [27] and in eight studies the risk was unclear due to missing trial protocols [18, 20, 23, 25, 26, 28]. Only one study had a satisfying description of other potential bias [24].

Four studies found a significantly lower incidence of delirium (primary outcome) in the intervention group than in the control group [17, 25-27].

DISCUSSION

Summary of evidence

This systematic review included 13 studies with 11 different interventions. Four out of the 13 preventive interventions significantly reduced the incidence of delirium, our primary outcome. The four beneficial interventions were methylprednisolone (125 mg intravenously), FIB, hypertonic saline and rivastigmine patches.

The four studies with a positive effect on the incidence of delirium all reduced the delirium incidence by more than 50% [17, 25-27]. This is a clinically relevant reduction, especially since most of the effective interventions are easy to implement.

The only treatment found to also reduce the duration of delirium (secondary outcome) was FIB [25].

As all of the 13 studies were rated high with respect to the overall risk of bias, the clinical effects of the interventions should be interpreted cautiously.

Effect of single intervention on incidence of delirium

The aetiology of delirium is still not fully understood, but neuro-inflammation seems to play a role in the multifactorial disease, and a trauma such as a hip fracture appears to cause physiological stress and therefore inflammation [30]. A recent study on preoperative dexamethasone 20 mg found no reduction in the incidence of delirium (primary endpoint), but the severity of post-operative delirium was reduced [31]. The effect of methylprednisolone or dexamethasone on the incidence of delirium is debatable. Whereas results from hip fracture show potential, the effect of methylprednisolone as delirium prophylaxis is less evident for other procedures [17, 29, 31, 32].

A recent systematic review focusing on preoperative FIB failed to find sufficient data to conclude on a reduction of the incidence or severity of delirium [33]. In contrast, a review of FIB and femoral nerve block found a beneficial effect of regional analgesia in patients with no preoperative cognitive impairment [34]. FIB may reduce the incidence of preoperative delirium by decreasing pain and opioid consumption, but this effect may only be relevant in case of a prolonged waiting period from arrival at the emergency department to surgery.

Hypertonic saline has not been thoroughly investigated. A review researching pharmacological strategies for the

prevention of post-operative delirium found only our included study on hypertonic saline [35].

Delirium may be the outcome of underlying organic causes such as hypovolaemia and hypotension; causes that are easily treatable by intravenous solutions [26].

Rivastigmine for patients with active delirium has been investigated but not specifically for hip fracture patients. A review from 2011 concluded that rivastigmine shows promising pharmacological properties [36], but also reported that more high-quality studies are needed. We are, however, aware of one rivastigmine study that was halted due to an increased mortality in the rivastigmine group compared with placebo [37]. Although the study population consisted of critically ill patients, it nevertheless raises a concern as to the beneficial effect of rivastigmine and underlines that safety needs to be addressed in future trials.

At the moment, most delirium research is done post-operatively. Consequently, preoperative interventions may currently be based exclusively on transferred evidence as our study shows only low-level evidence of preoperative interventions.

Effect on duration of delirium

Whereas few clinical studies have presented data on the incidence of delirium, few studies appear to be published on the duration of delirium [38]. In our present review, FIB was the only intervention to reveal a reduction in the duration of delirium [23]. Furthermore, the FIB study was the only included study in our review to report duration of delirium as an outcome.
A trial exploring preoperative FIB suggested that administration of the block may improve early post-operative cognitive performance [39]. Post-operative results may therefore be affected by the preoperative intervention [39]. However, a recent systematic review on geriatric patients with hip fractures provided no additional information on the duration of delirium [40].

Strengths and limitations

To our knowledge, this is the first systematic review to focus on preoperative non-geriatric preventive interventions for hip-fracture patients. We are aware that reviews on multicomponent geriatric care initiated both before and after surgery exist, but our review focused on interventions that can easily be implemented in the absence of resources and expertise from the geriatric department and massive care bundles.

The strengths of this systematic review include the pre-study protocol publication and the systematic search with two screening authors with no restrictions. In addition, we attempted to reach out to corresponding authors including protocol contact persons for additional data when needed to obtain additional data or verify the absence of any data.

We attempted to reduce the risk of publication bias by searching for trials and contacting corresponding authors to obtain available data.

Furthermore, we performed a bias assessment and used the GRADE approach to determine certainty of evidence.

Since our main focus was preoperative interventions and preoperative delirium, our optimal design might have included a preoperative incidence of delirium. However, our pilot search uncovered that studies with preoperative reporting of delirium do not exist in patients with hip fractures.

The limitations of this systematic review include the small number of studies available. Only 13 studies met our inclusion criteria, and only nine studies included 100 patients or more. Furthermore, all 13 studies had a high risk of bias.

The inclusion and exclusion criteria were different across our included studies, and the differences in comorbidities and other risk factors may also affect our outcomes of interest. Five studies excluded patients with dementia even though known cognitive impairment is a risk factor for delirium in hip fracture patients [10, 41].

In the 13 studies included, only three interventions were identical even though four studies assessed comparable nerve blocks to placebo and two studies assessed steroids. The heterogeneity challenges conclusions about the included interventions. Some of our included interventions have been tested in post-operative settings or in other populations, but did not meet our inclusion criteria [42, 43].

Delirium is not an easy condition to detect or measure as several assessment methods were used throughout studies [44].

No funnel plot was done due to the low number of included studies, which is in accordance with the Cochrane Handbook [45]. It was not possible to perform the pre-planned meta-analysis on any of the predetermined outcomes because of the limited amount of data and the very heterogeneous nature of the interventions. Consensus on delirium criteria and assessment timing are essential for future collected data.

Possible future interventions

Several interventions would be interesting to see repeated in combination: the FIB because it is used for pain relief in hip fracture patients [33], and steroids as they have been shown to provide a modest analgesic effect and improve cognition in this patient group. Hypertonic saline may possibly be used in combination with any of our reported effective treatments for intravascular resuscitation [26].

Upon arrival in the emergency department, a preventive strategy for delirium in hip fracture patients should be initiated immediately – and if future studies show improved evidence for methylprednisolone, FIB, hypertonic saline and rivastigmine, they could be initiated either together or as single interventions. All four treatments are relatively easy, low-cost initiatives that may potentially prevent the onset of delirium.

The intervention need not substitute geriatric assessment but may constitute an initial pharmaceutical stabilization regime in the emergency department.

Including patients with dementia in trials can be difficult due to problems obtaining informed consent. Even so, it remains important to investigate patients with dementia as cognitive impairment appears to be an important risk factor for perioperative delirium [46, 47]. In addition, inclusion of patients with dementia may be a challenge since dementia patients are especially difficult to evaluate for delirium as the two mental states may present with overlapping symptoms. Furthermore, the screening tools may be unable to differentiate between the two conditions, especially if the habitual condition is unknown [48].

The 13 included studies used seven different delirium-screening tools and did not have a similar schedule for delirium screening. All included screening tools are considered accepted tools with which to detect delirium [49-52]. However, the use of different screening tools for delirium increases the heterogeneity of this review. Also, delirium is a fluctuating condition [53]; hence, not only the screening tool and delirium criteria are important, obtaining a consensus on the indication and frequency of assessment is also important for future studies.

CONCLUSIONS

Our systematic review evaluated 13 studies with 11 different interventions. Methylprednisolone, FIB, hypertonic saline and rivastigmine significantly reduced the incidence of preoperative delirium compared with placebo or standard treatments. All studies were rated as having a high risk of bias, which means that there is insufficient evidence to recommend a single preoperative non-geriatric intervention for the prevention of delirium in

patients with hip fractures.

The secondary outcomes, pharmacological treatment, duration of delirium and mortality provided no indications as to what might be the preferable treatment.

Robust conclusions are precluded by study heterogeneity and a high risk of bias in the included studies.

Future studies should use clear inclusion and exclusion criteria, employ better definitions of delirium and clearly define when and how often delirium is measured.

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