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Review

Pharmacological interventions for preventing delirium in the elderly

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ABSTRACT

Delirium is a common occurrence in older hospitalised patients, particularly in the setting of surgical intervention and acute illness. Delirium is associated with a number of adverse clinical and social outcomes with higher financial cost and risk of developing dementia, as well as increased likelihood of need for residential care. Current interventions for the prevention of delirium typically involve recognition and amelioration of modifiable risk factors and treatment of underlying conditions that predispose the individual to delirium. A number of pharmacological strategies for delirium prevention have been tested. Antipsychotic medications are used for treatment of agitation in the setting of delirium when other measures have failed, but their efficacy in prevention is limited by study heterogeneity and concerns about tolerability. Acetylcholinesterase inhibitors are effective in the symptomatic treatment of Alzheimer's disease but do not appear to be effective in preventing delirium. Melatonin and melatonin agonists have a rather benign side effect profile and show promise for prevention of delirium in medically unwell individuals. The alpha-2 agonist, dexmedetomidine may be helpful in the intensive care unit setting but intravenous route of administration and need for close clinical supervision limits its use in the wider hospital environment. Other agents such as benzodiazepines, corticosteroids, statins and gabapentin have been suggested but lack evidence to support their role in delirium prevention. To date, there is inconsistent and conflicting data regarding the efficacy of any particular pharmacological agent although some interventions do show promise. Larger, well-designed, placebo-controlled clinical trials are needed.

Contents

Abbreviations: CI, confidence interval; CAM, confusion assessment method; ICU, intensive care unit; IQR, interquartile range; NNT, numbers needed to treat; OR, odds ratio; RR, relative risk; SD, standard deviation; vs, versus.

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1. Introduction

Delirium is a syndrome of disturbed consciousness characterised by cognitive impairment and attentional deficits that usually develop over a short period of time and fluctuate in intensity [1]. About 20% of hospitalised older adults have delirium [2], although the diagnosis is not established in at least one of every 3 cases [3]. Delirium is particularly common following major surgery (50%) and affects most intensive care unit (ICU) patients [4].

Delirium is associated with poor clinical outcomes, including higher risk of dementia and admission to residential care, as well as greater mortality [5]. Delirious patients experience more postoperative complications and readmissions [6], poorer functional outcomes [7], and increased length of hospital stay [8]. The annual cost of delirium to the health care system in the United States is estimated to fall between 38 billion and 152 billion dollars [9]. Delirium may persist for several weeks in up to a third of patients, and this has been associated with further increases in morbidity and mortality [10].

Risk factors associated with delirium, include older age, pre-existing cognitive impairment, disruption of the circadian rhythm, dehydration, malnutrition, sensory deprivation and use of certain medications [11]. Major surgery increases the risk of delirium, with critical contributing factors including the type of surgery, medications administered, length of surgery, transfusion requirements, patient's age and whether the surgery was elective [12]. Some of these risk factors are amenable to change.

Current approaches to the prevention of delirium in hospitalised patients rely mostly on the use of non-pharmacological strategies [13]. These typically involve addressing multiple risk factors in a systematic manner together with education, environmental manipulation and assertive geriatric medicine involvement. The Hospital Elder Life Programme, developed by Inouye and colleagues [14], targets six common risk factors for delirium (cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment and dehydration) in a systematic manner using a multidisciplinary team of experienced nurses, therapists, trained volunteers and geriatricians. The intervention was initially tested in 852 individuals aged 70 years and older admitted to a general medicine service of a teaching hospital and compared to usual care [15]. The intervention was safe, well tolerated and resulted in a reduction in the incidence of delirium (10% vs 15% in the intervention and usual care groups respectively, odds ratio [OR]: 0.60, 95% confidence interval [95%CI]: 0.39–0.92). The severity and recurrence rates of the delirium were not affected by the intervention.

Several pharmacological interventions to prevent delirium in older people have been tested, although their effectiveness remains uncertain. The purpose of this review is to provide a concise overview of these interventions and some recommendations for clinical practice.

2. Methods

We completed a systematic review of Medline, PsychInfo and Embase databases, from inception to 15 March 2015, using the following strategy and search terms: (delirium OR acute confusional state) AND (prevention OR prophylaxis) AND (pharmacological OR pharmacotherapy OR antipsychotic OR haloperidol OR risperidone OR olanzapine OR quetiapine OR amisulpiride OR aripiprazole OR ziprasidone OR acetylcholinesterase inhibitors OR donepezil OR rivastigmine OR galantamine OR benzodiazepines OR sleep OR anti-inflammatories OR dexmedetomidine OR gabapentin OR clonidine OR melatonin OR ramelteon OR valproic OR statins). The electronic search was supplemented by a hand search of available references. We reviewed case-reports, case-series, case-control studies and clinical trials, but excluded studies reporting non-pharmacological interventions, as well as those that had included young people.

3. Results and discussion

The electronic search yielded 788 citations, with another 33 citations being identified as suitable through manual search. Ninety-seven full text articles were retained after a review of abstracts or of relevant summary data.

3.1. Antipsychotics

Several factors may contribute to the development of delirium – excessive dopaminergic activity is one of them [16]. Antipsychotics have been investigated extensively as a form of treatment and guidelines advocate the use of high potency non-sedating antipsychotics such as haloperidol and risperidone for the management of severe agitation when other measures have failed [17]. The evidence for their use in prevention remains questionable.

An early case series reported that intravenous haloperidol was both safe and effective in transplant recipients at high risk of delirium [18]. This was followed by a small Japanese placebo-controlled clinical trial of 78 gastrointestinal surgery patients [19]. The authors reported lower incidence of delirium in those receiving 5 mg of intravenous haloperidol for 5 days postoperatively compared with placebo saline (10.5% vs 32.5%, $p < 0.05$). In another study, Kalisvaart and colleagues [20] recruited 430 elderly participants (70 years or over) undergoing hip surgery in a large teaching hospital in the Netherlands. They received 1.5 mg of haloperidol or placebo preoperatively and also for a maximum of 3 days following surgery. The overall incidence of delirium was 15.8% (68/430) but the risk of delirium was not significantly reduced in the haloperidol group (relative risk [RR] 0.91, 95%CI 0.6–1.3). Haloperidol did, however, reduce the severity (mean difference 4, 95%CI 2–5.8, $p < 0.001$) and the duration of the episodes (mean difference 6.4 days, 95%CI 4–8, $p < 0.001$).

Vochteloo and colleagues [21] instituted a 2-year delirium surveillance protocol in elderly hip fracture patients in a busy Dutch hospital, which included the use of low-dose prophylactic haloperidol in high-risk patients (173 of 445 took part in the protocol). The authors found an overall 27% incidence of delirium in the cohort, but this rate was not lower than that of the historical comparison cohort. A similar strategy was employed in an ICU population [22]. The authors instituted a delirium prevention policy and those with a predicted risk of delirium of 50% or greater were treated with 1 mg of haloperidol 8 h. Over a 12-month period, 177 patients received haloperidol that resulted in lower incidence of delirium (65% vs 75%, $p = 0.01$) and more delirium-free days (median 20, IQR 8–27 vs median 13, IQR 3–27, $p = 0.003$) compared with a control group consisting of historical and concurrent patients who were non-compliant with the protocol and, therefore, did not receive haloperidol.

More recently, Wang et al. [23] compared intravenous haloperidol (0.5 mg bolus followed by 0.1 mg/h for 12 h, $n = 229$) versus placebo ($n = 228$) for the prevention of delirium in non-cardiac, elderly intensive care surgical patients. They reported reduced incidence of delirium within a week of surgery in the haloperidol group (15.3% vs 23.2%, $p = 0.031$). Similarly, a recent Japanese open label trial enrolled 119 participants aged 75 and older undergoing elective surgery. Participants in the intervention arm received 2.5 mg of haloperidol daily for 3 days after surgery. The incidence of delirium was similar in the intervention and usual care groups, and the use of haloperidol did not decrease the severity or duration of the episodes. The most recently completed prevention trial enrolled 119 patients 75 years and older who underwent surgery for