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Short communication

Cholinergic enhancers for preventing postoperative delirium among elderly patients after hip fracture surgery: A meta-analysis

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1. Introduction

Delirium is commonly experienced by patients after hip fracture surgery (HFS) and is associated with poor functional recovery and increased morbidity [1]. Although many approaches to preventing delirium have been explored, including multidisciplinary geriatric care, the incidence of delirium remains high in this setting (30–50%) [2,3]. As acetylcholine concentrations are associated with cognition, disruption of the cholinergic system has been proposed as a key pathogenesis of postoperative delirium among elderly patients [4].

Cholinergic enhancers (CE) are drugs that enhance the cholinergic system by stimulating acetylcholine production or inhibiting acetylcholinesterase [5]. These drugs may be useful for preventing or treating delirium, although this effect requires confirmation [6–8], as inconsistent results have been reported regarding the ability of CEs to prevent postoperative delirium. Furthermore, no meta-analyses have focused on patients who underwent HFS [9,10].

Therefore, the present meta-analysis evaluated whether the use of CE reduced the incidence and severity of postoperative delirium, compared to a placebo, among elderly patients after HFS.

2. Materials and methods

2.1. Literature search

This meta-analysis was performed in accordance with the updated Preferred Reporting Items for Systematic Review and Meta-analysis Protocols guidelines (Supplementary Appendix S1). The PubMed-Medline, Embase, Google Scholar, Korea-Med, and Cochrane Library databases were searched in June 2017 using the following key terms: (hip fracture OR femur neck fracture OR femur intertrochanteric fracture) AND (delirium OR postoperative delirium OR acetylcholine OR cholinesterase inhibitors OR donepezil OR rivastigmine OR galantamine OR citicoline OR carnitine OR acetyl-carnitine). An overview of the search strategy is presented in Supplementary Appendix S2. No limitations were imposed regarding the surgical procedure or type of hip fracture. The inclusion and exclusion criteria were established before initiating the search. To be included, the trials had to be randomized, double-blinded, and controlled to ensure a high level of quality. We did not restrict the reports based on the language of

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publication. This study was exempted from our institutional review board's review, as it did not involve human subjects.

2.2. Study selection

Two independent reviewers (BHY and JIY) screened the titles and abstracts to identify relevant trials. The inclusion criteria were:

- patients who were > 65 years old and underwent HFS;
- CE treatment (citicoline, acetylcholine, carnitine, acetyl-carnitine, rivastigmine, donepezil, or galantamine);
- a placebo comparator treatment;
- the outcomes included the incidence of delirium and cognitive function score.

The exclusion criteria were:

- a non-randomized study (e.g., research articles, reviews, basic science articles, comments, letters, and protocols);
- average patient age of < 65 years.

If an updated report involved the same cohort of patients, we only included the updated report and did not include the original report.

2.3. Outcome measures and data extraction

The primary outcome of interest was defined as the incidence of postoperative delirium during the hospitalization, which was diagnosed using the Confusion Assessment Method (CAM) because only CAM criteria was the available from all included studies [11]. The corresponding authors of reports with insufficient information regarding delirium data were contacted to determine if the trial was eligible for inclusion in this meta-analysis [10]. One study [12] evaluated patients at 2 weeks, 4 weeks, and 6 weeks after surgery. We only included data from the 2-week evaluation, as the incidence of delirium peaks during the first three postoperative days, and delirium at 4–6 weeks is thought to be related to other factors [13]. As one study [9] evaluated patients at postoperative days 1, 2, 3, and 4, we included the data from the day on which the greatest number of patients was evaluated. The secondary outcome of interest was defined as delirium severity, which was assessed using the delirium rating scale [14] and the mini-mental state examination [15].

The two reviewers extracted the following data for each eligible trial and entered it into a spreadsheet: last name of the first author, publication year, study design, number of patients, enrolment period, type of drug and duration of use, mean age at the operation, and the duration of follow-up.

2.4. Quality assessment and publication bias

The two reviewers also independently evaluated the quality of each eligible trial using the criteria from the Cochrane Handbook for Systematic Reviews of Interventions. These criteria include seven items:

- random sequence generation;
- allocation concealment;
- blinding of the participants and researchers;
- blinding of the outcome data;
- incomplete outcome data;
- selective reporting;
- other biases.

We also assessed the possibility of publication bias using Begg's funnel plot and Egger's test.

2.5. Statistical analysis

The relative risks and 95% confidence intervals (CIs) were calculated for dichotomous outcomes using crude 2×2 tables whenever possible, although the Mantel–Haenzel method was used to calculate the risks if any cell(s) had a value of zero [16]. For dichotomous outcomes, odds ratio and 95% CI were calculated. Continuous outcomes were compared using the standardized mean difference (SMD; pooled mean change between pretreatment and posttreatment outcome values) along with their 95% confidence intervals (CI). Heterogeneity between comparable studies was tested using the Chi^2 and I^2 tests, based on *P*-values of > 0.1 and I^2 values of $< 50\%$. As there was no significant heterogeneity among the three included studies ($P = 0.87$), we used a fixed-effects model to analyse the data. All analyses were performed using Comprehensive Meta-analysis software (version 3.3; Biostat, Englewood, NJ).

3. Results

3.1. Included studies

The literature search returned 1902 reports. After a primary review, 40 potentially eligible reports were subjected to a detailed review, and three trials were ultimately included in the final analysis [9,10,12]. The study flow chart is shown on Fig. 1, and the characteristics of the included studies are summarized in Table 1. The three trials included 159 patients, with 73 patients in the CE group and 86 patients in the placebo group. The overall incidence of postoperative delirium was 23.3% (37/159), with incidences of 16.4% (12/73) in the CE group and 29% (25/86) in the placebo group.

3.2. Results of the analysis

The fixed-effects model revealed that the use of CE was associated with a decreased risk of postoperative delirium (odds ratio: 0.327, 95% CI: 0.146–0.735, $P = 0.007$). However, there was no significant difference in the severity of delirium between the CE and placebo groups (Fig. 2).

3.3. Quality assessment and publication bias

In all of the included trials, the patients were randomized using an established allocation sequence and the researchers were blinded to the allocation. However, it is unclear whether the included trials fulfilled all relevant quality assessment criteria (Fig. 3). The Begg's funnel plot was symmetrical, and Egger's test for bias revealed a *P*-value of 0.117 (Supplementary Appendix S3). But, it was not possible to perform detailed analyses of the small study effect because there were insufficient observations.

4. Discussion

Hip fractures among elderly individuals are a major public health problem that may become worse as a result of population aging [17]. Postoperative delirium is the most common complication that is associated with HFS [18], and is related to many adverse outcomes, including prolonged hospitalization, poor functional recovery, persistent cognitive impairment, need for institutional care, and mortality [19]. To the best of our knowledge, no meta-analysis has focused on postoperative delirium that was related to HFS among elderly patients. Our meta-analysis revealed that CE use was associated with a decreased risk of postoperative delirium, but not with a decreased severity of the delirium.

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