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Original Study

The Effects of Blood Transfusion on Delirium Incidence

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A B S T R A C T

Background: Both anemia and blood transfusion could be precipitating factors for delirium; hence in postoperative patients with anemia at high risk for delirium, it is controversial whether transfusion is the best option. The aim of this study is to investigate the association of anemia and delirium and the role of blood transfusion within the multicomponent prevention strategy of delirium.
Methods: We conducted a substudy of a multicenter randomized controlled trial. Four hundred fifteen patients aged 65 to 102 years old admitted for hip fracture surgery were enrolled. Delirium was assessed daily using criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition. Data on hemoglobin values and transfusion were collected from the electronic medical records.
Results: One hundred fifteen (32.5%) patients experienced delirium during hospitalization, 238 (57.5%) had a hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) at any time during hospitalization, and 140 (33.7%) received a blood transfusion. Anemia (a hemoglobin level $\leq$ 6.0 mmol/L [9.7 g/dL]) was associated with delirium (odds ratio, 1.81; 95% confidence interval, 1.15-2.86). Blood transfusion was a protective factor for delirium in patients with the lowest measured hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) (odds ratio, 0.26; 95% confidence interval, 0.10-0.70).
Conclusion: Low hemoglobin level is associated with delirium, and receiving a blood transfusion is associated with a lower delirium incidence. It would be interesting to investigate the effect of blood transfusion as part of the multicomponent treatment of delirium in patients with anemia.

Delirium has an incidence of 37% to 46% in a general surgery population and is associated with a higher risk of hospital-acquired complications.[1,2] By reducing the incidence of delirium, negative sequels for the patient can be prevented, and health care-related costs can be reduced.[2]

Delirium is by definition caused by the direct physiological consequences of a general medical condition, mostly a combination of different factors.[3] Taking away these underlying factors in a multicomponent approach is the cornerstone of the prevention and treatment strategy of delirium.[2] Because anemia is potentially one of the precipitating factors for postoperative delirium, prevention or treatment of perioperative anemia should be part of this multicomponent approach.[4–6] The quickest way to treat anemia is through a blood transfusion, but transfusion in itself is identified as a risk factor for delirium as well.[7] Blood transfusion can lead to a systemic inflammatory response, which can result in neuroinflammation in patients with a reduced functional reserve of the brain.[8–12]

There have been a number of randomized controlled trials (RCTs)[13–16] that demonstrate a lower transfusion threshold is as safe as a conservative transfusion strategy. They all showed either no benefit or increased harm from lower transfusion thresholds, but they did not specifically include delirium as an outcome. Consequently, in postoperative patients with anemia at high risk for delirium or with prevalent delirium, it is still controversial whether transfusion is the

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best option for delirium management. Therefore, the aims of this study were: (1) to investigate the association of anemia with delirium incidence and (2) to explore the effects of blood transfusion on delirium incidence.

Methods

Study Design and Setting

Data from a multicenter RCT of which the protocol[17] and the results[18] have been published previously were used. This trial investigated whether prophylactic in-hospital use of melatonin could prevent delirium after hip fracture, which could not be demonstrated. The study was conducted between November 2008 and May 2012 in the surgical, orthopedic, and trauma surgery wards of the Academic Medical Center and Tergooi Hospitals in The Netherlands. The study was undertaken in compliance with the Helsinki Declaration and Good Clinical Practice Guidelines and approved by the Medical Ethics Committee of the Academic Medical Centre. From all patients, or a legal representative in case of cognitive impairment, written informed consent was obtained. The trial was registered with the Dutch Clinical Trial Registry (NTR1576).

Participants

Patients aged 65 years or older who were admitted for any kind of surgical treatment of hip fracture were enrolled in the original trial.[18] Patients were excluded in the trial if they had been transferred from another hospital, if postoperative admission to the ICU or coronary care unit was anticipated, if they were already taking melatonin, or if they were unable to speak or understand Dutch. For the present study, we also excluded patients without available hemoglobin and transfusion data.

Procedures

Within 24 hours of admission, all patients aged 65 years or older with emergent hip fracture were screened for eligibility and asked to participate by a member of the research team, which consisted of geriatricians and trained research nurses with experience in geriatrics. Surgery usually took place on the first or second day of hospitalization, in accordance with national guidelines.

In case of postoperative delirium, all patients were treated according to standard procedures and assessed for delirium severity and duration. The multicomponent treatment consisted of non-pharmacological interventions and treatment of any underlying disease according to the hospital guidelines, combined with antipsychotics (most frequently, haloperidol) in case of a clinical diagnosis of hyperactive or mixed delirium. Daily medication adjustment took place depending on the clinical judgment of the consulting geriatric team and/or the attending physician. Antipsychotic medication was standardized as much as possible, with escape medication in case of acute aggravation. No antipsychotics were given for preventive purposes. Patients on psychiatric medication, apart from their delirium medication, could continue their prescriptions throughout the study period.[17]

Data Assessment

At baseline, demographic data, medical history, medication use, and surgery-related characteristics were recorded. Functional status was assessed with the 15-item modified Katz Index of Activities of Daily Living,[19] based on the 2 weeks prior to admission. This instrument was completed by the patient or, in case of cognitive impairment, by his or her closest relative. Functional impairment was calculated as the sum of activities of daily living with impairment.[19] Primary caregivers were asked to complete the Informant Questionnaire on Cognitive Decline short form (IQCODE-sf) by recalling the 2 weeks before the hip fracture and comparing this period with 10 years earlier.[20,21] Cognitive impairment was defined as a score of 3.4 or higher on this questionnaire or a record of dementia in the patient's medical history.[22] The number and severity of comorbidities was scored with the Charlson Comorbidity Index.[23] Patients were asked whether they had ever experienced an episode of delirium.

Fracture characteristics, type of anesthesia, type of surgery, length of stay, in-hospital deaths, hemoglobin levels, and the number and date of transfusions were obtained from the electronic medical records. Data on 30-day mortality were obtained at a follow-up contact with the patient or caregiver. We used two different variables to assess anemic state: the lowest hemoglobin level measured during hospitalization and hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) during hospitalization (yes/no). The latter cutoff point was chosen because transfusion is considered below this level in The Netherlands.[24]

Delirium was assessed by a member of the research team using criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.[25] Each patient was assessed daily during the first 8 study days or until discharge. For patients who had delirium on day 8, daily clinical assessments were continued to determine the duration of delirium, until discharge. This assessment incorporated all patient information from medical and nursing records for the previous 24 hours. In addition, the Delirium Observation Screening Scale[26] was completed for each patient during each nursing shift.

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22.0. Baseline differences between patients with and patients without delirium and with and without blood transfusion for the different study groups (prevention/treatment) were compared using a chi-square test or Mann-Whitney U test, as appropriate.

To determine if anemia is associated with delirium, all eligible patients were included. Given the close temporal relationship between the first occurrence of hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) and the onset of delirium, that is, mostly occurring on the day of surgery or the day after, we decided to assess the association between hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) and delirium *at any time* during hospitalization, instead of focusing only on patients in whom delirium first occurred the day *after* a hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) was measured. We performed a logistic regression with hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) during hospitalization (yes/no) as an outcome measure. Age and Charlson Comorbidity Index >1 (because the median score was 1) were added as covariates. In a backward selection, variables with a P value > .05 were discarded from the model.

To study an effect of transfusion on delirium incidence, we included only patients with a lowest measured hemoglobin level $\leq$ 6.0 mmol/L (9.7 g/dL) at any time during their hospital stay. Patients in the group that received a transfusion were only included when the transfusion took place before delirium onset. Because transfusion and delirium timing were both only known per day, patients that received their transfusion on the same day as delirium onset were excluded. Also, patients that received transfusions in more than one separated period (for example, on day 1 and 4) were excluded. For the control group, there were no other exclusion criteria. A logistic regression was performed with delirium incidence as the outcome variable and lowest measured hemoglobin level, age, Charlson Comorbidity Index >1 and Katz-ADL as covariates. In a backward selection, variables with $P > .05$ were discarded from the model.