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Impact of length of red blood cells transfusion on postoperative delirium in elderly patients undergoing hip fracture surgery: A cohort study

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ABSTRACT

Purpose: The purpose of the present study was to test whether older red blood cells (RBCs) transfusion results in an increased risk of postoperative delirium (POD) and various in-hospital postoperative complications in elderly patients undergoing hip fracture surgery.
Materials and methods: Patients (≥65 years) who underwent hip fracture surgery were enrolled, 179 patients were divided into two groups according to the storage time of the RBCs. The shorter storage time of RBCs transfusion group comprised patients who received RBCs ≤14 days old and the longer storage time of RBCs transfusion group comprised patients who received RBCs >14 days old. The blood samples were collected before anaesthesia induction, 4 and 24 h after RBCs transfusion for the determination of proinflammatory mediators, malondialdehyde, and superoxide dismutase activity.
Results: There was no difference in the baseline characteristics, the incidence of POD, and the in-hospital postoperative complications between the shorter storage time of RBCs transfusion group and the longer storage time of RBCs transfusion groups ($P > 0.05$). Compared with the shorter storage time of RBCs transfusion group, the longer storage time of RBCs transfusion caused significantly longer duration of POD ($P < 0.05$). There were significantly increased plasma levels of IL-8 and malondialdehyde at 24 h and IL-1β at 4 h after RBCs transfusion in the POD group compared with the non-POD group ($P < 0.05$).
Conclusion: Transfusion of the longer storage RBCs is not associated with a higher incidence of POD or in-hospital postoperative complications, but with longer duration of POD in elderly patients undergoing hip fracture surgery.

Introduction

Postoperative delirium (POD) is a common complication after major surgery in the geriatric population with a reported incidence ranging from 10% to 62%, depending on the study and type of surgery [1–3]. Although POD can be resolved during hospitalisation, it may have long-term consequences, including prolonged length of stay, reduced functional capacity, high rate of institutionalisation, and increased morbidity and mortality [1–3]. Accumulating evidence has suggested that enhanced inflammatory response and oxidative damage are closely linked to the cognitive impairments in patients who developed POD [4–6]. Many known risk factors, including advanced age, lower levels of education, and pre-existing cognitive impairments have been related to the occurrence of POD [1–3], but these factors are largely limited to demographic characteristics and are not modified. Therefore, identification of other modifiable risk factors is an important issue.

Red blood cells (RBCs) transfusion is lifesaving and an important part of supportive care for surgical patients [7]. It has been demonstrated that RBCs are transfused perioperatively in more than 50% of the elderly patients undergoing hip fracture surgery [8]. However, accumulating evidence has indicated that transfusion of blood especially in prolonged storage may adversely

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affect clinical outcomes [8–10]. A number of clinical studies have suggested that transfusion of longer storage time of RBCs results in worse outcomes, including infection, deep vein thrombosis, hypoxia, multisystem organ dysfunction, and mortality [8–14]. One explanation for these unfavourable results could be that prolonged storage of RBCs can cause significant functional and structural changes and subsequently lead to enhanced inflammatory responses and oxidative damage [14]. Nevertheless, the effects of length of RBCs storage on brain dysfunction such as POD have not been described in elderly patients undergoing hip fracture surgery.

Hip fracture is a common surgery in the elderly and is often associated with substantial blood loss that requires RBCs transfusion [7]. The aim of the present study was to test the hypothesis that longer storage time of RBCs increases the incidence of POD in elderly patients undergoing hip fracture surgery. To test this hypothesis, patients were divided into two groups according to the storage time of the RBCs. The shorter storage transfusion group comprised patients who received RBCs ≤14 days old and the longer storage transfusion group comprised patients who received RBCs >14 days old.

Materials and methods

Study design and patients

This is a prospective, observational, and cohort pilot study conducted from 2012 to March 2015. The experimental protocol was approved by the local Clinical Research Ethics Committees. The written informed consents were obtained from all the patients or their relatives. Three hundred and thirty-six consecutive patients aged 65 years or more who underwent elective hip fracture surgery were enrolled. In the present study, we purposely included patients whose haemoglobin level was <10 g/dl before surgery, or who were likely to receive RBCs intra-operatively. Furthermore, only patients received RBCs were included in this study. The exclusion criteria were as follows: ASA physical status ≥IV; preoperative delirium; unwilling to comply with the experimental procedures; inability to understand the language (Mandarin Chinese); hearing loss, or a failure in spinal anaesthesia, receiving more than 4 units of RBCs. Among the eligible 336 patients, 179 patients were included in the final data analyses (Fig. 1).

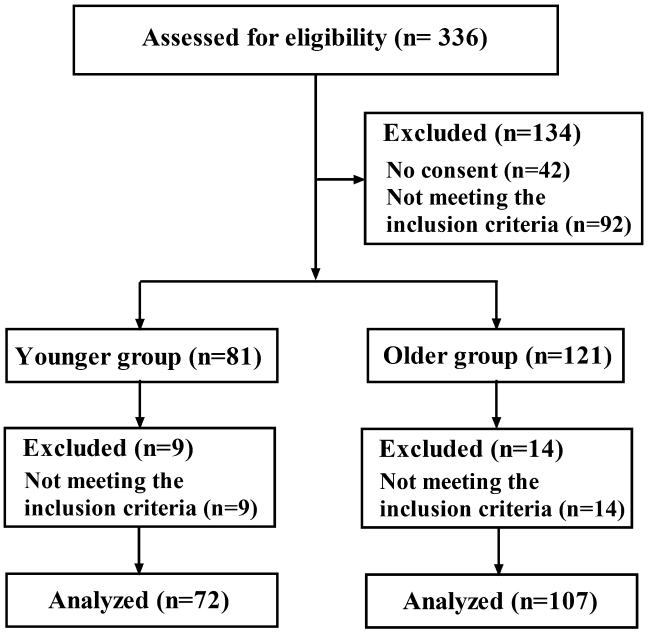

Fig. 1. The diagram showing patients' flow through the study.

Anaesthesia and monitoring

All the patients received no premedication. Spinal anaesthesia was performed as described previously [6]. All participants routinely received postoperative analgesia with tramadol 12 mg/kg plus ondansetron 16 mg for 2 days. Electrocardiogram, pulse oximetry, and invasive blood pressure were continuously monitored during anaesthesia. Ringer's lactate was administrated before anaesthesia induction and during surgery. Blood loss was estimated by quantitative measurement of blood loss (e.g., suction and sponge). When estimated intra-operative blood loss was greater than 500 ml, the same volume of hydroxyethyl starch (130/0.4, Fresennius, Beijing, China) was infused. When mean arterial pressure ≤60 mmHg or systolic blood pressure ≤90 mmHg, an intravenous injection of 6 mg ephedrine was applied.

Transfusion protocol

The decision to transfuse is based on haemoglobin level by immediate intra-operative arterial blood gas analysis. Blood transfusion strategy was performed according to the criteria in our institution. The patients with a haemoglobin level < 8 g/dl were transfused. Patients with a haemoglobin level from 8 to 10 g/dl were transfused only if they had relevant symptoms, and those with a haemoglobin level > 10 g/dl were not transfused.

The RBCs are leukocyte-reduced ($90\% < 1 \times 10^6$) before storage and are reconstituted with 90–110 ml saline adenine glucose mannitol to a hematocrit value of 60%, which enables a maximum storage time of 35 days. Because it has been demonstrated that storage lesions become apparent after about 2 weeks [14], thus the enrolled patients were consecutively received either shorter storage time of leukodepleted RBCs (≤14 days old) or longer storage time of leukodepleted RBCs (>14 days old). In our study, the cutoff value of 14 days to divide two groups of stored blood may be arbitrary. However, we chose this specific cutoff value based on the largest randomised controlled study assessing blood storage time related complications [11].

POD diagnosis

Before the study, the anaesthesiologist performing assessment was trained to follow standard procedures and was also trained by a psychiatrist to use the Confusion Assessment Method for the intensive care unit (CAM-ICU) criteria (Chinese version). During the study period, patients were assessed for delirium once daily before surgery and multiple time points within 5 days after randomisation or up to hospital discharge (if hospital stay was shorter). The Confusion Assessment Method for CAM-ICU was used by evaluating the following four clinical features: 1, acute onset of cognitive changes with a fluctuating course; 2, inattention; 3, disorganised thinking; and 4, altered level of consciousness. The diagnosis of POD was based on the presence of the first two (acute onset or fluctuation course and inattention) plus either the third (disorganised thinking) or the fourth (altered level of consciousness) of the above items as previously described [1,7]. In our institution, we infused propofol to treat POD patients only with a sedation-agitation scale score of ≥5, as assessed by the Ricker sedation-agitation scale as described previously [15]. During treatment, safety and tolerability were assessed by monitoring vital signs, electrocardiogram, and adverse events.