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RESEARCH

EARLY BLOOD TRANSFUSION MAY PREVENT POSTOPERATIVE COGNITIVE DYSFUNCTION AFTER HIP ARTHROPLASTY IN ELDERLY PATIENTS

Abstract

Introduction: The number of joint arthroplasties in the elderly continues to increase with the increase in elderly population. Postoperative cognitive dysfunction is an important complication after surgery in elderly patients. However, the exact cause of postoperative cognitive dysfunction and factors contributing to its development remain unknown. We aimed to determine whether blood loss during or after surgery and the approach for the replacement of this loss affected postoperative cognitive dysfunction frequency and duration.

Materials and Method: A prospective study of elderly (>75 years) patients who underwent total/partial hip arthroplasty due to femoral neck or intertrochanteric fractures was conducted. Patients were randomised into two groups. The first group underwent transfusion when haemoglobin values reduced below 9.0 mg/dL, whereas the second group underwent earlier blood transfusion according to the volume of blood loss during and after surgery. All groups were similar in terms of factors considered to be associated with postoperative cognitive dysfunction. An experienced neurologist assessed patients' cognitive functions using the Standardized Mini-Mental Status Examination test and clinical examinations pre- and postoperatively.

Results: In total, 48 patients in the first group and 13 in the second group (early intervention group) were diagnosed with postoperative cognitive dysfunction. The duration of cognitive dysfunction was significantly lower in the second group (10.8±1.2 vs. 8.9±1.5 days; p<0.001).

Conclusion: Although the causal relationship between blood loss and postoperative cognitive dysfunction has not been elucidated in this study, our results demonstrate that postoperative cognitive dysfunction frequency and duration may be reduced by early replacement of blood loss in elderly patients who undergo total/partial hip arthroplasty.

Keywords: Arthroplasty, Replacement, Hip; Cognitive Dysfunction; Blood Loss, Surgical; Blood Transfusions

ARAŞTIRMA

KALÇA ARTROPLASTİSİ GEÇİREN YAŞLI HASTALARDA ERKEN KAN REPLASMANI AMELİYAT SONRASI BİLİŞSEL DİSFONKSİYONU ÖNLEYEBİLİR

Öz

Giriş: Yaşlanan insanlardaki eklem artroplastilerinin sayısı yaşlı nüfus artışı ile birlikte artmaya devam etmektedir. Postoperatif bilişsel disfonksiyon, yaşlı hastalarda cerrahiden sonra önemli bir komplikasyondur. Bununla birlikte, postoperatif bilişsel disfonksiyonun kesin nedeni ve gelişimine katkıda bulunan faktörler bilinmemektedir. Ameliyat sırasında veya sonrasında kan kaybının ve bu kaybın yerine konulma yaklaşımının postoperatif bilişsel disfonksiyon sıklığını ve süresini etkileyip etkilemediğini saptamak amaçlandı.

Gereç ve Yöntem: Femur boynu veya intertrokanterik kırıklara bağlı total/parsiyel kalça artroplastisi yapılan yaşlı (>75 yaş) hastalar prospektif olarak incelendi. Hastalar randomize olarak iki gruba ayrıldı. Birinci gruba hemoglobin değerleri 9.0 mg / dL'nin altına düştüğünde transfüzyon yapıldı, ikinci gruba cerrahi sırasında ve sonrasında kan kaybı hacmine göre kan transfüzyonu yapıldı. Tüm gruplar, postoperatif bilişsel disfonksiyon ile ilişkili olduğu düşünülen faktörler açısından benzerdi. Deneyimli bir nörolog, hastaların bilişsel işlevlerini, Standardize Mini-Mental Test, klinik muayene kullanarak operasyon öncesi ve sonrası değerlendirildi.

Bulgular: Birinci grupta 48 ve ikinci grupta (erken müdahale grubu) 13 hasta postoperatif bilişsel disfonksiyon tanısı aldı. Bilişsel disfonksiyon süresi ikinci grupta (10.8±1.2 vs. 8.9±1.5 gün; p<0.001) anlamlı derecede düşüktü.

Sonuç: Çalışmamızda kan kaybı ile postoperatif bilişsel disfonksiyon arasındaki nedensel ilişki aydınlatılamamış olmasına karşın, sonuçlarımız total / parsiyel kalça artroplastisi geçiren yaşlı hastalarda kan kaybının erken replasmanı ile postoperatif bilişsel disfonksiyon sıklığının ve süresinin azaltılabileceğini ortaya kondu.

Anahtar sözcükler: Artroplasti, Replasman, Kalça; Kognitif Disfonksiyon; Kan Kaybı, Cerrahi; Kan Transfüzyonu

INTRODUCTION

The number of joint arthroplasties (TJAs) among the elderly has dramatically increased over the last 20 years. This uptrend in the number of TJAs has been predicted to synchronically continue with the growth in elderly population. Although successful results, such as improved physical activity and decreased pain, are obtained from TJAs, some individuals experience cognitive dysfunction postoperatively. Postoperative cognitive dysfunction (POCD), which may last for up to 3 months, is known to be associated with mortality. Reportedly, the incidence of POCD after TJA is 15%–30% (1, 2).

The pathophysiology of POCD remains unclear. Currently, the most valid theory is the microemboli theory, which suggests that microemboli develop during the surgery and occlude vascular structures within the brain. Another theory suggests that POCD develops due to general anaesthesia; however, researchers have failed to find a significant association between general anaesthesia and POCD (3-5). Other predisposing factors are considered to be older age, medications used for analgesia and prior cognitive impairments (6, 7). However, evidence regarding the association between these factors and POCD remains limited.

One of the seldom addressed issues in studies investigating the causes of POCD is blood loss during and after the surgery. We hypothesised that an association between POCD and blood loss during and after surgery may exist. In this study, we aimed to clarify whether cognitive dysfunction can be prevented and/or whether the cognitive dysfunction period can be shortened through early blood replacement in patients by performing early transfusion according to the volume of blood loss from drain and aspirator tube.

MATERIALS AND METHOD

Elderly patients older than 75 years who had undergone open surgery for femoral neck or intertrochanteric fractures were included in this prospective study. Exclusion criteria were as follows: (1) the presence of a haematological disorder, (2) the history of another operation at the same surgical site, (3) the presence of respiratory or heart failure, (4) the presence of a disease that may adversely affect clotting, (5) the presence of a malignant neoplasm, (6) the presence of any type of cognitive dysfunction or a history of cognitive dysfunction, and (7) a preoperative haemoglobin value less than 9.5 mg/dl. From January 2013 to July 2017, 263 patients who met our inclusion/exclusion criteria were identified at our centre (Karabuk University Education and Training Hospital). Warfarin use was detected in 18 patients due to cardiological diseases and cardiology was consulted; these patients were switched to enoxaparin sodium instead of warfarin.

Ethical approval was obtained from the Karabuk University Clinical Research Ethical Committee. All patients provided informed consent. The study was conducted according to the Helsinki Declaration and Good Clinical Practice guidelines.

Preoperatively, all patients underwent cognitive function evaluation by an experienced neurologist using the Standardized Mini-Mental Test (SMMT). The validity and reliability analyses of SMMT were conducted by Güngen and colleagues (8). The cut off score of SMMT 23/24 was found to have the highest sensitivity (0.91), specificity (0.95), positive and negative predictive values (0.90 and 0.95) and kappa score (0.86). Interrater reliability analysis showed high correlation (r:0.99) and kappa value (0.92). SMMT evaluates following sub-dimensions: orientation, registration, attention and calculation, recall, language and praxis. For illiterate patients the modified version of SMMT was used (9). In addition to SMMT, clinical examinations were used to assess cognitive function. If necessary, cranial computed tomography (CT) was also performed.

Patients were re-evaluated postoperatively. A neurological consultation was requested for patients with cognitive dysfunction. The cognitive functions and mentioned tests were assessed by experienced Neurology Specialists. Patients were

followed-up according to the recommendations of the Neurology Department. Also, the verifications of diagnosis of cognitive dysfunction were made by Neurology Department

Patients were randomly divided into two groups according to the order of surgery. In the first group, blood replacement was performed if follow-up haemoglobin value dropped below 9 mg/dl. In the second group, blood replacement was performed according to the expected volume of blood loss, which was calculated on the basis of the volume of blood loss during the surgery and loss from the drainage/aspiration tube postoperatively. Consultations from the Neurology, Chest Diseases and Cardiology Departments were requested for patients with cognitive dysfunction. Patients were monitored for 21 days. If cognitive dysfunction lasted more than 21 days, patients were transferred to the Neurology Department.

Patient age, sex, height, weight, operation type, pre- and postoperative haemoglobin values, blood volume from drain and aspirator and fluid replacement values were recorded. Additionally, patients were examined in terms of postoperative complications, and complications were carefully monitored. For monitoring, chest x-ray; cranial CT; extremity Doppler ultrasonography and assessment of biochemical parameters, such as sodium, potassium, chlorine and D-dimer levels, were performed. Venous blood was drawn from the upper extremity in which fluid replacement was not performed. Patients whose cognitive functions were impaired in both groups were followed for the re-establishment of preoperative cognitive function. Blood replacement was administered in the form of erythrocyte suspension. After 4 units of erythrocyte suspension, fresh frozen plasma was added.

Standardized anaesthesia and analgesia protocols were applied to each patient to avoid the possible effect of type of anaesthesia and analgesia on the results. The anaesthesia protocol was as follows: Induction was performed with 2–3 mg/kg propofol, 0.6–1 mg/kg rocuronium, 1 mcg/kg fentanyl and 0.05 mg/kg midazolam. Remifentanyl and sevoflurane were used for the maintenance of anaesthesia. Rather than opioids, diclofenac sodium and contramal retard were selected for analgesia.

The SPSS statistical software package (SPSS, version 22.0 for Windows; SPSS, Inc., Chicago, Illinois, USA) was used to perform all statistical evaluations. Descriptive statistics were expressed as mean±sd deviation for intermittent and continuous numerical variables, whereas categorical variables were expressed as the number of observations and percentage (%). Shapiro–Wilk test was used to investigate whether the distribution of variables was normal. Mann–Whitney *U*-test, which is a nonparametric method, was used to compare nonnormally distributed data. For normally distributed data, independent variable *t*-test was used. Using the parametric paired t-test and the nonparametric Wilcoxon test, we compared the patients' pre-test and post-test SMMT score. Categorical variables were compared using Pearson's Chi-squared test, and Fisher's exact Chi-squared test was used in diagonal tables with small expected frequencies. A *p*-value of <0.05 was considered significant in all statistical analyses.

RESULTS

The first group included 129 patients (mean age, 83.4±5.9 years), and the second group included 134 patients (mean age, 82.9±5.2). There was no statistically significant difference between the groups in terms of age (p=0.466), sex (p=0.745), educational status (p=0.206), operation type (p=0.064), the presence of a chronic disease (p=0.238), the diagnosis of diabetes mellitus (p=0.751) or hypertension (p=0.742), preoperative haemoglobin value (p=0.259), the volume of blood loss from drain (p=0.184) or aspirator (p=0.158) tube and body mass index (BMI) value (p=0.172) as well as biochemical biomarkers. Demographic and clinical characteristics of patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of patients.

Variable	Group 1 (n=129)	Group 2 (n=134)	p
Age (mean±sd)	81.2±6.5	79.8±5.8	0.066
Sex			
Female	39	43	0.745
Male	90	91	
Operation type			
Total hip prosthesis	32	28	0.064
Partial hip prosthesis	97	106	
Chronic disease			
Absent	36	29	0.238
Present	93	105	
Educational Status			
Illiterate	81	94	0.206
Primary and High School	48	40	
Diagnosed with diabetes mellitus (n)	24	27	0.751
Diagnosed with hypertension (n)	59	64	0.742
Pre-op haemoglobin (mg/dL)	10.3±2.6	9.9±3.1	0.259
Blood volume from drain tube (cc)	868.3±86.4	852.7±102.3	0.184
Blood volume from aspirator (cc)	688.2±95.6	703.6±81.2	0.158
First day fluid replacement (cc)	2655.4±344.2	2721.6±381.5	0.141
Second day fluid replacement (cc)	2353.7±242.5	2221.7±314.6	<0.001
Third day fluid replacement (cc)	1987.1±321.6	1896.2±293.4	0.173
Fourth, fifth and sixth day fluid replacement (cc)	773.2±145.8	783.6±112.3	0.516
BMI	20.7±2.1	21.2±3.6	0.172

In total, 48 patients in the first group, and 13 patients in the second group were diagnosed with POCD ($p<0.001$). Furthermore, the duration of cognitive dysfunction was longer in patients in the first group compared to those in the second group ($p<0.001$). Clinical characteristics of complications are summarized in Table 2.

Table 2. Clinical characteristics of complications.

Variable	Group 1 (n=129)	Group 2 (n=134)	p
Time with cognitive dysfunction (days)	10.8±1.2	8.9±1.5	<0.001
Number of cognitive dysfunction [n (%)]	48	13	<0.001
Confusion	22	7	
Somnolence	11	3	
Stupor	7	3	
Coma	2	0	
Delirium	5	0	
Other complications			
Decubitus ulcer	9	2	
Aspiration pneumonia	2	1	
Anaphylactic reaction during blood replacement	6	5	

According to comparisons of pre- and post-operative SMMT total and sub-dimensions' scores, in Group 1, total and all scores were decreased significantly; In Group 2 total and sub-dimensions' scores (except registration) were decreased. However, greater decreases were observed in Group 1. Comparisons of pre- and post-operative SMMT total and sub-dimensions' scores are summarized in Table 3.

Table 3. Comparisons of pre- and post-operative SMMT total and sub-dimensions' scores.

	Group 1 (n=129)					Group 2 (n=134)				
	Pre-op Mean±sd	Post-op Mean±sd	MD	SE	p	Pre-op Mean±sd	Post-op Mean±sd	MD	SE	p
Orientation	8.41±0.73	7.28±0.86	1.12	0.11	0.001	8.69±0.64	8.23±1.09	0.46	0.10	0.001
Registration	2.56±0.50	2.01±0.72	0.55	0.07	0.001	2.36±0.54	2.41±0.68	0.05	0.07	0.465
Attention and Calculation	4.32±0.63	2.98±0.77	1.34	0.09	0.001	3.89±0.58	3.59±0.74	0.30	0.08	0.000
Recall	2.68±0.47	1.98±0.71	0.70	0.07	0.001	2.30±0.56	2.15±0.69	0.16	0.07	0.027
Language and Praxis	7.70±0.80	6.67±1.15	1.03	0.12	0.001	8.00±0.73	7.63±0.94	0.37	0.10	0.001
Total score	25.70±1.79	20.91±2.59	4.79	0.27	0.001	25.24±1.19	24.01±1.97	1.22	0.19	0.001

sd: Standard Deviation; MD: Mean Difference; SE: Standard Error

DISCUSSION

Postoperative cognitive dysfunction leads to increased duration of postoperative hospitalization and increased economic burden. Furthermore, it is associated with increased morbidity and mortality. Aetiological factors underlying POCD can be categorised as older age, prior cognitive impairment, depression, low education level, a longer duration of anaesthesia, abnormal blood pressure, the presence of emboli and certain medications used in anaesthesia and analgesia protocols (4,6,7,10,11). However, as mentioned previously, these associations have not been proven. In a systematic review, Fong et al. (12) investigated the potential role of analgesia in the progression of POCD, and they reported that the type of analgesia or administration technique did not influence the development of POCD. In our study, we excluded patients with prior cognitive impairment, and all patients received the same anaesthetics/analgesics via the same protocols. We performed Doppler USG, thorax CT and D-dimer measurements in all patients to exclude the presence of pulmonary or micro emboli. There were no differences between the groups in terms of characteristics, such as age and the presence of hypertension. Furthermore, many factors suggested to be associated with POCD in the literature were similar between the groups. Thus, we can conclude that the most important factor affecting POCD frequency and duration in this study was the difference in the protocol used for blood replacement.

Another important issue is whether THA surgery has a causal link to cognitive dysfunction. In a meta-analysis, Scott et al. (13) have concluded that there is no association between long-term cognitive dysfunction and THA. Because of the lack of control groups, it is difficult to determine whether THA surgery leads to cognitive problems. In our study, the prevalence of POCD was 23.2%, which can be considered as a low value for individuals older than 75 years. Even though the incidence of POCD is reported to be 15%–30%, it is known that these values increase with age. Furthermore, Konekar et al. (14) have reported that POCD incidence was 40.9% in patients aged 71–80 years and 100% in patients older than 80 years. The low rate of POCD in our study may be explained by the absence of any cognitive dysfunction preoperatively in the included patients. The evaluation of patients pre- and postoperatively may help to identify factors associated with POCD. Further, it is important to consider that reduced cognitive function after THA is not surprising because these elderly patients underwent a major surgery and experienced a high level of pain. Therefore, to arrive at an accurate diagnosis, POCD should be assessed in depth pre- and postoperatively. In our study, all patients were examined by experienced neurologists.

Elderly individuals may have a predisposition to anaemia as an adverse event of surgery because of reduced haematopoiesis and blood reserves. Postler et al. (15) have stated that postoperative anaemia was detected in 53.3% of elderly patients who underwent THA. Blood transfusions are common after surgery in the elderly. After THA, blood transfusions are commonly performed according to haemoglobin levels. In recent years, indications for blood transfusion have become stricter in an attempt to reduce the frequency of transfusions due to the possibility of adverse events and complications caused by transfusion. However, in a Cochrane review published in 2012, liberal and restrictive blood transfusion protocols were compared and it was stated that restrictive transfusion strategies were not superior to liberal protocols in terms of decreasing adverse effects, including mortality, cardiac events and thromboembolism). It is also important to consider that the aged people are vulnerable to cognitive dysfunction due to natural cognitive decline with age and their intolerance to even a slight decline in brain perfusion. Thus, we preferred the liberal transfusion strategy and composed two groups on the basis of blood replacement time as follows: (1) after haemoglobin value decreased below 9.0 mg/

dL and (2) after evaluating blood loss from drain and aspirator tube. We observed that in the second group, POCD frequency was lower and the recovery time of POCD was shorter.

Patients were not followed-up in the long-term, which may be considered as a limitation of this study. The second limitation of our study may be the fact that some factors, such as the presence of depression and patient education level, which could be predisposing factors for POCD, were not evaluated. Furthermore, although oxyhaemoglobin has been reported to be a valid indicator of the requirement of postoperative blood transfusion after total hip/knee arthroplasty (16), we did not include a control group that underwent transfusion according to oxyhaemoglobin levels. To our knowledge, this is the first study to evaluate the association between blood loss and POCD after THA.

In conclusion, POCD frequency and duration can be reduced via early blood transfusion in the event of blood loss after surgery. Our results do not reflect the causal link between blood loss and cognitive dysfunctions; however, we believe that investigating such associations may be worthwhile because these have been rarely studied, and studies focusing on this topic may draw attention to the importance of physiology in patients older than 75 years. Further studies investigating the potential role of inadequate blood replacement strategies and their causal relationships with POCD are required.

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