A comparative study of restrictive and liberal transfusion strategy on postoperative cognitive dysfunction following lower limb orthopedic surgery

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Abstract

Postoperative cognitive dysfunction (POCD) is one of the major complications after operation in elderly patients. In various studies it was shown that perioperative blood transfusion was an independent risk factor for development of POCD in aged patients. So, the current study was a comparative study to assess and analyze the effect of liberal transfusion and restrictive transfusion in orthopedic surgery patients.

Material & Methods: In a prospective randomized study 80 patients with the age more than 65 years undergoing lower limb orthopedic surgery from November 2013 to October 2015 were included. After all investigations the patients were given combined spinal and epidural anaesthesia. They were divided into two groups – Restrictive group and Liberal group and were given blood transfusion accordingly. The incident of POCD, MMSE score were noted and compared.

Observation: We observed that no statistical difference was observed in the groups with respect to age, sex, body weight, ASA grade, level of education, preoperative MMSE scores, length of surgery, preoperative haemoglobin levels, intraoperative blood loss. There was no significant difference for MMSE score at preoperative examination. 17.5% patients in restrictive transfusion group and 20% patients in liberal transfusion group developed POCD.

Conclusion: Lliberal transfusion strategy was not superior to restrictive transfusion strategy in terms of a better postoperative cognitive functioning.

Key words: Cognitive, Restrictive, Liberal

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Introduction

Brain function is frequently affected postoperatively, suggested by depressed level of consciousness and impairment of attention, memory and reaction time. Patients may experience complete amnesia for several hours after general anesthesia in spite of being apparently awake, and as a consequence it is not uncommon for patients to ask the same questions over and over again. Cognition refers to the set of interwoven processes, such as memory, language and problem solving, that we develop to generate structures and strategies to apply to our perceptions. All of these different forms of cognitive disturbances that can occur after surgery are to be distinguished from gross neurological disturbances like dementia and delirium which include memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgment.

Postoperative cognitive dysfunction (POCD) means one or more cognitive functions are affected after surgery and anaesthesia. Nearly all patients have one or more cognitive function disturbance in immediate postoperative period. Often it is short lasting, transient, not causing any major complication. However in patients with high risk there can be significant morbidity in terms of cognitive disturbance. The incidence of delirium has been estimated to approximate 10% in elderly patients after major elective surgery, but to be higher after cardiac surgery and hip surgery. Preoperative cognitive deficit has a direct bearing on postoperative emergence and perioperative morbidity. Early cognitive decline after surgery is largely reversible by 3 months.

Risk factors for POCD other than age are duration of anesthesia, respiratory complications, infectious complications, second operation, and level of education. These changes are sometimes severe enough to alter the personality of the affected person, or to interfere with their ability to perform normal activities.

All these changes in mental function occurring after an operation actually affect the process of cognition, which is why they are bundled under the term POCD [Post-Operative Cognitive Dysfunction]. The available literature does not allow drawing definitive conclusions on the possible differences in effects on cognition postoperatively in patients receiving liberal transfusion and restrictive transfusion. The current study will be comparative study targeted to assess and analyze the effect of liberal transfusion and restrictive transfusion in orthopedic surgery patients. This information will be crucial to improve anaesthesia safety and outcome.

Material& Methods

After obtaining the approval from the Ethical Committee of S.C.B Medical College and Hospital and the written informed consents from all patients, 80 consecutively admitted patients with the age more than 65 years undergoing lower limb orthopedic surgery from November 2014 to October 2015 were enrolled in the present study. The limitation of our study was that our sample size was small because we had to exclude many patients. Larger sample size will be required to validate our study. Also there were very limited study available in literature. The exclusion criteria were as follows: ASA physical status >II, preoperative cognitive dysfunction, unwilling to comply with the procedures, inability to understand the language (Odiya), hearing loss or a failure in combined spinal epidural anesthesia. During preoperative assessment all patients enrolled were informed about the study objectives and protocol.

Routine electrocardiogram, pulse oximetry and noninvasive blood pressure were continuously monitored after the patients admitted to the operating room. Combined spinal epidural anesthesia was given to patients. A 16G Touhy needle was introduced into the epidural space at the L2-L3 vertebral level via a midline approach using loss of resistance technique. A single-orifice epidural catheter was inserted cranially, 3-5 cm into the epidural space and secured.

A 25G Quincke's needle was placed into the subarachnoid space one space lower until it returned clear CSF. All groups then received 0.5% hyperbaric bupivacaine intrathecally.

Surgery was performed by the same surgical team. No pre-operative medication was administered and patients received no sedatives during surgery. Patients were randomly assigned to the restrictive or liberal transfusion strategy group using a random number table and a sealed envelope technique. Patients in the restrictive transfusion group received blood transfusion only if haemoglobin concentration was <8 g/dl or when symptoms of anemia developed, while patients in liberal transfusion group received blood transfusion to keep their haemoglobin concentration more than 10.0 g/dl. Haemoglobin levels were measured 1 day before surgery, and on the 1st, 2nd and 7th days after surgery. To maintain haemodynamic stability, Ringer's lactate and hydroxyethyl starch (HES) were administered during surgery.

Patients who experienced hypotension (SBP <90 mmHg or mean blood presseure <60 mmHg) were treated by incremental doses of ephedrine. All enrolled patients received postoperative analgesia using 2ml 0.5% bupivacaine diluted with 8ml of distilled water and 0.5ml butorphanol through the epidural catheter as whenever required by the patient

Cognition assessment: Mini mental state examination (MMSE) was used to exam the preoperative cognitive function on a scale of 0(poor) to 30(good) in a quiet room. Cognitive function was assessed by the same attending anesthesiologist between 8 a.m. and 9 a.m. preoperatively and 1st, 2nd and 7th day after surgery.

Statistics: Statistical analysis was performed using SPSS 19.0 software for Windows. Descriptive results of continuous variables were presented as mean±SD. Categorical data were expressed as counts. Intergroup comparisons were compared by the independent sample t-tests. For comparison of qualitative parameters, Chi-square or Fischer exact test was used. For the haemoglobin levels after randomization, data were expressed as medians and interquartile ranges; $p<0.05$ was considered to be statistically significant.

Observation

We divided patients into 2 groups on the basis of type of transfusion they received –

1. Group 1 – 40 patients who received Restrictive Transfusion
2. Group 2 - 40 patients who received Liberal Transfusion

Table 1: Age in years (Mean±2 SD)

	Mean ± SD	t-value	p-value
Group 1 [Restrictive Transfusion]	71.8±7	1.194	0.769
Group 2 [Liberal Transfusion]	72.7±7.2		

In the study mean age of patients was 71.8±7 yrs for restrictive transfusion and 72.7±7.2 yrs for liberal transfusion, with t-value 1.194 and p-value 0.769.

Table 2: Sex

Sex	Group 1[Restrictive Transfusion]		Group 2[Liberal Transfusion]	
	No.	%	No.	%
Male	27	67.5	29	72.5
Female	13	32.5	11	27.5
Total	40	100	40	100

χ^2 =0.238, p-value = 0.626

In restrictive transfusion group there were 67.5% males and 32.5% females. In liberal transfusion group there were 72.5% males and 27.5% females, with χ^2 =0.238 and p-value = 0.626.

Table 3: Various characteristics of the study groups

Variables	Restrictive Transfusion	Liberal Transfusion	p-value
Preoperative MMSE Scores	29.8±1	29.7±1	0.409
Preoperative Haemoglobin levels(g/dl)	11.1±1	10.8±1	0.677
Blood loss (ml)	518.25±204.6	500.3±267	0.076
Length of Surgery (min)	79.6±6.64	79.0±6.66	>0.05
Ringer's lactate(ml)	801.8±167	676.1±120.4	<0.05
Hydroxyethyl starch(ml)	730±108	490.5±108.2	<0.05

In the study mean preoperative MMSE score of patients was 29.8±1 for restrictive transfusion and 29.7±1 for liberal transfusion (p-value 0.409). Preoperative haemoglobin level(g/dl) of patients was 11.1±0.5 for restrictive transfusion and 10.8±0.5 for liberal transfusion,(p-value 0.677) and mean blood loss(ml) of patients was 518.25±204.6 for restrictive transfusion and 500.3±267 for liberal transfusion (p-value 0.076).

In our study mean length of surgery of patients was 79.6 ± 6.64for restrictive transfusion and 79.0±6.66for liberal transfusion (p-value >0.05). The ringer's lactate(ml) requirement of patients was 801.8±267 for restrictive transfusion and 581.15±252 for liberal transfusion (p-value <0.05) and mean hydroxyethyl starch(ml) used in patients was 730.8±108 for restrictive transfusion and 390.7±108.2 for liberal transfusion (p-value <0.05).

Table 4: Number of units of blood transfused after randomization

Units of blood transfused	Group 1 [Restrictive Transfusion]	Group 2 [Liberal Transfusion]	p Value
1	18	12	
2	10	18	
3	2	6	
4	0	4	
Total units of blood transfused	44	82	<0.05

The data analysis shows that 44 units of blood were transfused in restrictive transfusion group while 82 units of blood were transfused in liberal transfusion group (p value <0.05).

Table 5: Haemoglobin(g/dl) after randomization

Haemoglobin(g/dl)	Restrictive	Liberal	P value
Before transfusion	8.1±0.4	10.0±1.0	<0.001
1 day after surgery	8.3±0.6	10.1±0.8	0.003
2days after surgery	8.4±0.6	10.3±0.8	0.002
3days after surgery	8.8±0.4	10.7±0.6	0.016

Table 6: Postoperative complications

Postoperative complications	Restrictive Group	Liberal Group	P value
Pneumonia	1	1	>0.05
Irritability	1	0	>0.05
Acute renal failure	1	1	>0.05
Cardiac failure	1	1	>0.05
Deranged liver function	1	0	>0.05
CVA	0	1	>0.05
Myocardial infarction	0	1	>0.05
Pulmonary embolism	0	1	>0.05

Table 7: Incidence of POCD

	Restrictive Group	Liberal Group	P value
Preoperative MMSE	29.8±1	29.7±1	0.409
POD 1 MMSE	27.9±6.6	27.8 ± 7.2	0.651
POD 2 MMSE	28.3±6.0	28. 4 ± 6.4	0.981
POD 7 MMSE	28.6±5.0	28.7±5.2	0.948
Incidence of POCD at POD1	25%	22.5%	0.069
Incidence ofPOCD at POD 2	20%	20%	1
Incidence of POCD at POD 7	20%	17.5%	0.082

(POD- Postoperative Day, POCD- Post Operative Cognitive Dysfunction)

Discussion

The prevalence of delirium is more in elderly patients which is associated with prolonged hospital stay with increasing morbidity and mortality. Few recent studies have shown that patients receiving intra operative blood transfusion are at high risk of developing early cognitive dysfunction. So our aim of the study was to assess and compare influence of liberal and restrictive transfusion on postoperative cognitive dysfunction. For this purpose total 80 subjects were taken and divided them into two groups, those who received restrictive transfusion (n=40) and those who received liberal transfusion (n=40).

We observed that no statistical difference was observed in the groups with respect to age, sex, body weight, ASA grade, level of education, preoperative MMSE scores, length of surgery, preoperative haemoglobin levels, intraoperative blood loss.

In liberal transfusion group there were 72.5% males and 27.5% females while in restrictive transfusion group there were 67.5% males and 32.5% females, with p-value = 0.626. So, there was no gender bias in our study [Table 2]. Within the liberal transfusion group and restrictive transfusion group there was no significant difference in MMSE score in postoperative period. So, it could be concluded that postoperative cognitive recovery was similar in males and females and gender of patient has no influence on the incidence of POCD. Some other studies like ISPOCD -1 study also showed no difference in incidence of POCD whether patient is male or female[(1)]. ISPOCD-2 study also showed no effect of gender on incidence of POCD in middle age group patients (40-60 years) in non-cardiac surgeries[(2)].

The change in MMSE score postoperatively might be also related to duration of anesthesia and surgery. We prevented bias that would have been caused by increased duration of surgery by including those patients who underwent surgery less than 120 minutes. It was likely that increased duration of surgery leads to more postoperative cognitive deterioration which was supported by study by Canet et al[(3)] who found that the incidence of POCD at 1 week was significantly lower in elderly patients undergoing minor surgery than in those undergoing major surgery under general anaesthesia. The study data analysis showed that the preoperative haemoglobin levels in liberal group was not statistically significant.

Within restrictive transfusion group 801.8±167ml of ringer's lactate and 730±108 ml of hydroxyethyl starch were used compared with 676.1±120.4 ml of ringer's lactate and 490.5±108.2 ml of hydroxyethyl starch in liberal transfusion group. Y.X Fan et.al[(4)] also compared on the basis of intraoperative ringer's lactate and hydroxyethyl starch used and they also concluded that patients in liberal transfusion group required lesser volume of ringer's lactate and hydroxyethyl starch compared with restrictive transfusion group.

In our study on analysis of complete MMSE score there was no significant difference at preoperative examination. At 24 hours MMSE score was 27.8±7.2 in liberal transfusion group and 27.9±6.6 in restrictive transfusion group. After 2 days MMSE score was 28.4±6.4 in liberal transfusion group and 28.3±6.0 in restrictive transfusion group. Even at 7 days MMSE score of patients within restrictive group was better than in liberal group but was not statistically significant.

The result of our study was supported by the study of Y.X Fan et.al.[(4)] who found that 21.3% patients in restrictive transfusion group and 23.9% patients in liberal transfusion group developed POD while in our study, 17.5 % patients in restrictive transfusion group and 20% patients in liberal transfusion group developed POCD. Notably, our data suggested that restrictive transfusion was not associated with a higher incidence of POCD than liberal transfusion in aged patients following major lower limb orthopedic surgeries with combined spinal epidural anesthesia.

The purpose of transfusing red blood cells is to restore oxygen transport by increasing red cell mass, thereby preventing tissue hypoxia after blood loss, or for management of anemia of diverse causes[(5)]. Blood transfusion is widely used in surgical practice, not only to increase oxygen carrying capacity, but also to replace acute severe blood loss when maintenance of normovolemia and organ perfusion is necessary[(6)].

Many factors such as hypoxia, ischaemia, cholinergic deficiency or dopamine excess, dysregulation of the hypothalamic pituitary adrenal axis, and increased neuroinflammation have been proposed in the pathogenesis of delirium[(7)]. In a study, Behrands et. al[(8)] had also identified intraoperative blood transfusion

as an independent risk factor for postoperative delirium on the first postoperative day in elderly patients undergoing major non cardiac surgery. SH Zhu et. al[9] also further identified perioperative blood transfusion of more than 3 units as a risk factor for development of POCD in aged patients following THR.

Preoperative anemia is common in aged patients scheduled for elective major orthopedic surgery including total hip arthroplasty[7]. Glance et. al[10] in a study in 2011 suggested that patients with preoperative haemoglobin <8g/dl or patients with mild to no preoperative anemia are benefited by intra-operative transfusion when there is substantial blood loss. It has been demonstrated that blood transfusion is associated with increased susceptibility to infection, immune sensitization, transfusion related lung injury, exacerbation of stress injury and postoperative SIRS[9]. A recent randomized controlled trial by Carson et.al has demonstrated that a restrictive transfusion strategy targeting haematocrit at 24% (haemoglobin= 8g/dl) significantly reduces RBC use without increasing complications or mortality after hip fracture surgery.[5]

Limitations of the study were small sample size, use of MMSE alone as neuropsychological test. Third, although current transfusion guidelines are mostly based on haemoglobin triggers, the use of physiological parameters and clinical variables in addition to haemoglobin values to guide blood transfusion may be more reasonable. Other limitations are, haemoglobin is a volume based measurement that can be affected by dehydration or hypovolemia due to different clinical scenarios that probably influence the precision of estimates.

Despite these limitations, results are believed to be significant, considering that significant number of patients are undergoing orthopedic interventions were recruited in comparison to studies reported in previous literature.

In our study no difference in short term cognitive function was seen at 24 hours and 7 days in liberal transfusion group and restrictive transfusion group.

Conclusion

From the study we concluded, liberal transfusion strategy was not superior to restrictive transfusion strategy in terms of a better postoperative cognitive functioning. Keeping in mind the adverse reactions associated with blood transfusion and the limited benefit of blood transfusion restrictive transfusion strategy may be safe and effective for aged patients following lower limb orthopedic surgeries.

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