Application of Perioperative Transfusion Trigger Score in Patients Undergoing Surgical Treatment of Malignant Tumor

Fan Zhang^{1,4} · Ze-Bing Zheng² · Zhao-Qiong Zhu¹ · De-Xing Liu¹ · Jin Liu³

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Abstract The present study aimed to investigate the clinical effects of the brand new perioperative transfusion trigger score (POTTS) system in patients undergoing malignant tumor surgeries. 442 cases of patients diagnosed with malignant tumor were randomly selected (from January 2012 to December 2016) from Zunyi Medical University and were divided into 3 experimental groups. Patients in the POTTS group were transfused by the POTTS guideline perioperatively, while patients in the 7–10 g group were treated by the traditional transfusion guidelines existed (restrictive transfusion strategy), patients in the 10 g group should be transfused to keep the Hb level no less than 10 g/dL (liberal transfusion strategy). Baseline information, operation time, bleeding volume, transfusion amount, incision healing time, postoperative complications, metastasis and recurrence were observed and recorded. Postoperative short-term mortality was comparable of the 3 groups, 3 cases of death all occurred in 10 g group, there was no significant difference in the incidence of postoperative complications, including infectious

complications and coagulation related complications. Follow-up to date, there were 25 cases, 29 cases and 29 cases of tumor recurrence and metastasis in the three groups, but no statistical difference observed. The present findings show that the POTTS transfusion system is more advantageous with regard to save blood and relieve economic burdens of patients, and does not affect the long-term recurrence and metastasis rate of malignant tumor.

Keywords POTTS · Transfusion · Malignant tumor · Prognosis

Introduction

Transfusion decisions are always made according to existing transfusion guidelines. However these guidelines have big differences on a worldwide scale [1–7]. Comparing transfusion guidelines in different countries around the world, we can draw a conclusion that red blood cell transfusion should be considered when Hb < 6 g/dL or 7 g/dL. 6 g/dL is recognized as the lowest threshold for patients to be transfused in existing transfusion guidelines. It is also generally accepted by these guidelines that if the Hb level of patients is more than 10 g/dL, transfusion procedure should not be started. Many patients have Hb between 6 and 10 g/dL during perioperative period, but there is no detailed RBC transfusion guideline for patients whose Hb between 6 and 10 g/dL. Blood usage in operating room accounts for 50% of the whole blood usage amount of China, but there exists no objective transfusion guidelines for those patients whose Hb between 6 and 10 g/dL yet [8–12]. In other words, doctors are making transfusion decisions for these patients without scientific evidence everyday. Directed towards the above blind zones, a

✉ Fan Zhang
zzbhaofan@sina.com

¹ Department of Anesthesiology, The Affiliated Hospital of Zunyi Medical University, Zunyi 563000, Guizhou, People's Republic of China

² Department of Pediatric Surgery, The Affiliated Hospital of Zunyi Medical University, Zunyi 563000, Guizhou, People's Republic of China

³ Department of Anesthesiology and Translational Neuroscience Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, People's Republic of China

⁴ Department of Anesthesiology, Zunyi Medical University, Zunyi 563003, Guizhou, People's Republic of China

brand new ‘Perioperative Transfusion Trigger Score (POTTS)’ system has been designed out by the research team of West China Hospital leaded by professor Jin Liu to tackle this hard clinical problem. Large sample, multicenter, randomized and double blind clinical study according to this guideline system has also been carried out around the whole country. The POTTS system will be used as evidence for transfusing red blood cells to patients with Hb between 6 and 10 g/dL during the perioperative period. Clinicians can perform dynamic scoring according to the patient’s condition. In order to truly achieve individual blood transfusion.

The present study evaluated the safety and feasibility of POTTS with regard to malignant tumor patients and received a satisfactory curative effect. The details are reported as follows.

Materials and Methods

Patients

This study had registered at clinicalTrials.gov (no.NCT01597232) before the start. A total of 442 patients consecutively hospitalized at 28 medical centers from January 2012 to December 2016 were formally included into this clinical study. During the course of this study, 19 patients were excluded out of this research: 12 patients were excluded for violation of research program or inconformity with the inclusion criteria; 1 patients was excluded for violation of research program; 6 patients were excluded in the 10 g group; the entry number of three groups were 121 cases, 162 cases and 140 cases finally.

All possible patients were screened firstly, Inclusive criteria: perioperative hemoglobin level less than 10 g/dL, patients diagnosed with malignant tumor. Exclusive criteria: emergent operation, high risk patients with ASA score V and above, unambiguously diagnosed with hematological system diseases including defects of oxygen carrying capacity of hemoglobin, hypervolemic blood dilution, malignant tumor with distant metastasis, unresectable tumor, or involving two types or above malignant tumors.

Study Procedure

Based on the aim of blood transfusion that maintaining the balance of oxygen supply and oxygen consumption, the investigators hypothesized that index of transfusion trigger for patients with hemoglobin level between 6 and 10 g/dL could be calculated by parameters including infusion rate of adrenalin for maintaining normal cardiac output, fraction of inspired oxygen, core temperature, and angina. To verify this hypothesis, the investigators presented Perioperative Transfusion Score (POTTS) for the trigger of transfusion according to the patient’s history and monitoring parameters, and the investigators designed a randomized controlled clinical trial to test this score. Formally included subjects were randomized into 3 experimental groups according to inclusion sequence: POTTS guided group (individualized dynamic scoring group), transfusion management were made according to the POTTS score system. 7–10 g group, the Hb levels were maintained to 7–10 g/dL according to existing guidelines or doctors experiences (restrictive transfusion group). 10 g group, patients were transfused that their perioperative Hb levels were no less than 10 g/dL (liberal transfusion group) (Table 1).

Perioperative period in this study refers to the period from surgery to discharge. For patients in POTTS guided group, the whole perioperative period, whether intraoperative or post-operative consideration of blood transfusion needs to be scored before transfusion immediately. The subjects were scored according to POTTS, and blood transfusion was guided according to POTTS score. Erythrocytes were only transfused when hemoglobin levels fell below POTTS score. Examples of POTTS scoring application: (1) POTTS was 6 points: if Hb > 6 g/dL, no allogeneic erythrocyte suspension needed; if Hb < 6 g/dL, allogeneic erythrocyte suspension should be infused to maintain Hb (> 6 g/dL). (2) POTTS > 10 points: If Hb > 10 g/dL no allogeneic erythrocyte suspension required; if Hb < 10 g/dL, allogeneic erythrocyte suspension should be infused to maintain Hb (>10 g/dL). The required amount of blood transfusion was estimated by calculating the minimum number of transfusion units to reach the POTTS score at this time. Even if patients need blood transfusion in the ward after operation, POTTS

Table 1 Perioperative transfusion trigger score

Score	Epinephrine required for cardiac output	Oxygen concentration SpO ₂ ≥ 95%	Central temperature	Angina
0	No	≤ 35%	< 38 °C	None
1	≤ 0.05 µg/kg min	36–50%	38–40 °C	Exercise or labor induced
2	≥ 0.06 µg/kg min	≥ 51%	> 40 °C	Daily activity or rest induced

The above points plus 6 points as the total POTTS score, the highest score is 10. If the total score is greater than 10 points, according to 10 points. SpO₂, Pulse Oxygen Saturation

dynamic score must be performed first to determine whether or not to transfuse blood according to the score.

The main purpose of this study is to prove that POTTs-guided transfusion protocol can be safely applied to patients with malignant tumors whose Hb level is between 6 and 10 g/dL during perioperative period. POTTs can effectively save perioperative red blood cell transfusion, reduce the cost of red blood cell transfusion, and do not increase mortality or incidence of serious complications. Primary outcome indicators: (1) mortality and short term complications within 30 days after operation, overall survival rate after discharge. (2) Secondary outcome indicators: the proportion and amount of erythrocyte input, the occupancy rate and duration of ICU, the duration of hospitalization, the cost of blood transfusion and the healing of surgical incision.

Results

Bilateral test was used for statistical analysis, and the test level was 0.05. PASW Statistics 18 software was used for statistical analysis.

After strict screening test, 442 cases of malignant tumor patients were included. According to statistical analysis, preoperative baseline data of three groups were comparable. Among the main research indicators, postoperative short-term mortality was comparable of the three groups, 3 cases of death all occurred in 10 g group. There was no significant difference in the incidence of complications and the incidence of infectious complications, coagulation related complications (18.2% vs 19.1% vs 24.3%)(Table 2). There were 25 cases, 29 cases and 29 cases of tumor recurrence

Table 2 Postoperative short-term complications compared between groups

Complications n/N (%)	POTTs (N = 121)	7–10 g (N = 162)	10 g (N = 140)	P value
	22/121 (18.2%)	28/162 (17.3%)	31/140 (22.1%)	0.54
Cardiovascular system	1/121	0	2/140 (1.4%)	0.21
Heart failure	1	0	0	
Atrial fibrillation	0	0	1	
Myocardial infarction	0	0	1	
Nervous system	0	0	1/140 (0.7%)	0.33
Hydrocephalus	0	0	1	
Respiratory system	6/121 (4.9%)	13/162 (8.0%)	8/140 (5.7%)	0.44
Atelectasis	1	1	0	
Pleural effusion	2	1	0	
Respiratory failure	1	0	0	
Pulmonary infection	2	8	8	
Pulmonary edema	0	2	0	
Empyema	0	1	0	
Digestive system	4/121 (3.3%)	5/162 (3.1%)	4/140 (2.9%)	0.98
Gastroparesis	1	0	0	
Abdominal abscess	1	1	1	
Necrotizing pancreatitis	1	0	0	
Bile leakage or bile leakage	1	2	1	
Anastomotic leakage	0	0	1	
diarrhea	0	0	1	
Digestive tract bleeding	0	1	0	
Gastrointestinal infection	0	1	0	
Urogenital system	0	4/162 (2.5%)	1/140 (0.7%)	0.09
Reproductive system infection	0	0	1	
Urinary tract infection	0	3	0	
Acute renal insufficiency	0	1	0	
Other complications	11/121 (9.1%)	6/162 (3.7%)	15/140 (10.7%)	0.05
Incision infection	2	1	4	
SIRS/sepsis	1	0	1	
CVP catheter infection	2	0	0	
Venous thrombosis				

Data are presented as the frequency or percentage

CVP central venous pressure

Table 3 Postoperative survival situations compared between groups

	POTTS (N = 121)	7–10 g (N = 162)	10 g (N = 140)	P value
Death n/N (%)	22/121 (18.2%)	31/162 (19.1%)	34/140 (24.3%)	0.41
Cause of death				
Recurrence and metastasis	20	25	26	
Hepatic failure	0	2	1	
Digestive tract bleeding	0	0	1	
Systemic infection	0	0	0	
Sudden death	1	0	0	
Cerebral infarction	0	0	1	
MOF	0	0	1	
Fever	0	1	0	
Renal failure	0	1	0	
Myocardial infarction	0	0	1	
Unknown	1	2	3	

Data are presented as the frequency or percentage

MOF multiple organ dysfunction

Figure 1 Life curves of the POTTS transfusion guideline compared with groups

and metastasis in the three groups, but no statistical difference (Table 3, Fig. 1).

Among Secondary research indicators, the transfusion rate of red blood cells in the whole perioperative period was significantly different among the three groups (33.9% vs 63.0% vs 96.4%, $P < 0.001$). The transfusion amount in POTTS group was significantly lower than that in the other two groups. Perioperative plasma transfusion rate was 28.9% in POTTS group, which was the lowest among the three groups, 50% in 7–10 g group and 49.3% in 10 g group. The median perioperative plasma transfusion volume in POTTS group was 311 mL, which was significantly lower than that in the other two experimental groups

($P = 0.01$). Compared with the other two groups, the 10 g group received more platelet products during the perioperative period. There was no significant difference in other blood products transfusion, albumin and cryoprecipitation transfusion among the three groups (Table 4). Other outcome indicators including hemoglobin recovery, incision healing time, and whether ICU treatment and the total time, discharge time and the total hospitalization; social economic issues related to the subjects, including the hospitalization costs, blood products infusion costs, the quality of life and satisfaction, no obvious differences were statistically significant.

Table 4 Comparison of secondary indicators in each groups

Blood products	POTTS (N = 121)	7–10 g (N = 162)	10 g (N = 140)	P value
Intraoperative RBC rate n/N (%)	29/121 (23.9%) # †	80/162 (49.4%) #	125/140 (89.3%) †	< 0.001
Intraoperative RBC amount* (U)	1.5 (0–20) # †	3 (0–25) #	4 (0–18.5) †	< 0.001
Postoperative RBC rate n/N (%)	30/121 (– 24.8%)	43/162 (– 26.5%)	34/140 (– 24.3%)	0.89
Postoperative RBC amount * (U)	3 (1.5–6)	3 (0–7)	3 (1.5–6.5)	0.44
Perioperative RBC rate n/N (%)	41/121 (33.9%) # †	102/162 (63%) #	135/140 (96.4%) †	< 0.001
Perioperative RBC amount * (U)	3 (0–23) # †	4 (0–32) #	5 (0–30) †	< 0.001
Intraoperative FFP rate n/N (%)	24/121 ^{#†} (– 19.8%)	55/162 (– 33.9%)	52/140–37.1%	0.01
Intraoperative FFP amount * (ml)	156 (0–2800) # †	198 (0–2300)	212 (0–1780)	0.03
Postoperative FFP rate n/N (%)	17/121 (–14%)	30/162 (–18.5%)	17/140 (–12.1%)	0.86
Postoperative FFP amount* (ml)	222 (0–1150)	257 (0–2200)	303 (0–7500)	0.42
Perioperative FFP rate n/N (%)	35/121 (28.9%) # †	81/162 (–50%)	69/140 (–49.3%)	0.001
Perioperative FFP amount * (ml)	311 (0–5350)) # †	435 (0–4400)	342 (0–4400)	0.01
Perioperative transfusion of other blood products				
Platelet*U	1 (0–2) #	0 (0–1) #	1 (0–86)	0.03
Cold precipitation *U	1 (0–20)	1 (0–18)	1 (0–21)	0.86
Albumin * (g)	25 (0–265)	36 (0–420)	27 (0–503)	0.26
Hb recovery				
Pre-Hb (g/dL)	11.4 ± 1.9	11.4 ± 2.1	11.9 ± 2.0	0.06
Post-24 h Hb (g/dL)	9.22 ± 1.75 ^{# †}	9.78 ± 1.73 [#]	10.88 ± 1.43 [†]	< 0.001
Discharge Hb (g/dL)	9.83 ± 1.43 [#]	9.92 ± 1.51 [#]	10.68 ± 1.33	< 0.001

Data are presented as percentage

RBC red blood cell, Hb hemoglobin

*Non normal distribution data are presented as median (minimum, maximal). [#]*P* < 0.05 compared with 10 g group; [†]*P* < 0.05 compared with 7–10 g group

Discussion

Transfusion management, one of the mostly ‘can not be missing’ emergency treatment methods of contemporary medicine, however induces wide ranges of concerns with regard to sharply increased blood demand, blood supply and demand imbalance [13–15]. Simultaneously, transfusion related acute and chronic complications have been continuously reported. Recent researches point out that transfusion may overshadow the patients’ long-term outcome as well as life quality [1, 16–19]. Especially for those who are diagnosed with malignant tumor, the impact of transfusion administration on the recurrence and metastasis of tumor remains the center of world medicine debates. The above reasons force clinicians to think twice when transfusion may be conducted.

The absolute indications of blood transfusion are to improve the ability of blood to carry oxygen molecules, to increase the body’s oxygen supply ability, and to maintain the oxygen supply and consumption balance. These physiological principles suggest that clinicians should be able to predict the patient’s oxygen supply before deciding

whether or not to take a blood transfusion. The most common clinical measure index of body oxygen balance is mixed venous oxygen saturation (SvO₂), the blood oxygen supply capability is decided by cardiac output (CO), hemoglobin (Hb), arterial oxygen saturation (SaO₂); oxygen consumption is mainly decided by metabolism and body temperature. Considering that the medical equipment needed to detect SvO₂ is too high for hospitals in developing countries, the brand new POTTS system (assessment equipment requirements lower) is designed out to evaluate the body’s oxygen supply situation, to decide whether perioperative blood transfusion therapy required. The usage of epinephrine to maintain normal cardiac output (CO), the inhalation concentration of oxygen to maintain SpO₂ no less than 95%, the central body temperature of patients were detected to score the patients and to determine the Hb level to start transfusion (for example, the POTTS score of one patient is 9, transfusion should be started when his Hb level less than 9 g/dL, only the minimal RBC transfused to keep Hb level no less than 9 g/dL). The occurrence of angina within 6 months before operation has been added to the POTTS system after several

adjustments, because heart is the most sensitive organ to systemic hypoxia, hypoxia of heart may result in most serious consequences, which increases the safety of application POTTs in patients with heart disease.

POTTs clinical research focuses mostly on assessing the safety of the POTTs system. The most important study on the clinical safety of this study is the impact of different scoring schemes on mortality and complications, and the long-term survival of cancer patients. A number of studies have compared the impact of restrictive transfusion protocols on the prognosis of patients with liberal transfusion protocols. Carson JL collected the clinical research of 19 randomized controlled studies (RCT) including 6264 subjects. Almost all of the above RCTs showed that compared with liberal transfusion strategies, restrictive transfusion strategies did not increase the incidence and mortality of postoperative adverse events. The present study also showed that only 3 cases of death happened which were all coming from the 10 g group (liberal transfusion strategy group), the remaining two groups, 7–10 g guide group (restrictive transfusion group) and POTTs (individual strategy) had no death occurred, the difference was not statistically significant ($P > 0.05$). It can be concluded that the restrictive transfusion scheme may not increase short-term mortality in cancer patients. Developed from the limited blood transfusion scheme, the individualized dynamic POTTs blood transfusion program will not increase perioperative mortality because of less blood input. But a recent meta-analysis points out that the use of restrictive transfusion strategies in high-risk (ASA III-ASA IV and above) patients with major surgery should be more cautious [20], individual transfusion strategies will just solve this problem ingeniously.

There were no significant differences in the incidence of systemic complications and overall complications between the three groups one month after operations. Compared with the 7–10 g guideline group and the 10 g group, the POTTs guideline group (individualized transfusion strategy) did not increase short-term mortality or complications ($P > 0.05$). Study from Prescott [21] including 983 subjects showed that the restrictive transfusion strategies was of great importance to reduce unnecessary blood transfusion, at the same time did not increase the mortality and incidence of complications in patients with tumor. Compared with individual strategy and restrictive transfusion strategy, although the overall strategy of liberal blood transfusion complications had no significant difference, however, 31 postoperative complications happened in 10 g group, which is the highest of 3 groups. Through statistic analysis we found that respiratory complications and other related complications in 10 g group were also the highest among 3 groups. The most worthy of attention is 4 cases of complications of venous thrombosis in patients from the

10 g group. The 10 g group was the liberal transfusion group in this study and also the largest recipient of allogeneic blood in the three study groups, and the perioperative Hb levels of which were within the highest limits currently available in the current guidelines for blood transfusion. Previous studies found that compared with liberal transfusion strategies, the incidence of postoperative pneumonia in elderly patients significantly reduced with restrictive transfusion strategies. Another study found that more than 800 mL of blood transfusion were risk factors of deep venous thrombosis (DVT) of lower extremity after artificial hip replacement. Multiple factor logistic analysis showed that there was significant correlation between DVT and hip surgery in elderly patients, which may be related to high consistency of stored blood products. POTTs clinical results also verified the risk of liberal blood transfusion strategy. If less blood transfusion is better for the prognosis of the patients. According to the above findings, we believe that patients with cancer should reduce the number of allogeneic blood transfusion [22].

87 patients died resulted from long-term postoperative complications, the most common causes of death were all tumor recurrence and metastasis. The number of deaths of POTTs group, 7–10 g group and 10 g group were 22 cases, 31 cases and 34 cases, the overall mortality rate was not statistically significant ($P > 0.05$). The survival rate of the three groups was examined by test (Log-rank). Results showed that there was no significant difference in the long-term survival between the three groups ($P = 0.43$). At present, the subjects have been followed up to 182 weeks (3.4 years), and there is no evidence that the POTTs score increases mortality because of anemia.

The biggest obstacle to the application of blood transfusion in patients with malignant tumor has been focused on whether blood transfusion will induce malignant tumor cells spreading, then lead to tumor recurrence and metastasis, reduce the survival rate and survival time finally [23–26]. So far, most scholars think that perioperative blood transfusion can lead to tumor immune escape, white blood cell components including cytokine and blood components may all play a role into this outcome. A number of studies suggest that perioperative red blood cell transfusion and postoperative tumor recurrence and metastasis are related. Kim [27] retrospectively summarized the radical resection of prostate cancer from 1993 to 2014, 2713 cases of blood transfusion and tumor recurrence were found during perioperative period, it was found that BRFS, CSS and OS factors were less in patients undergoing perioperative red blood cell transfusions. This latest study provides a more adequate basis for the hypothesis of immunological regulation of allogeneic blood transfusion. In the same year, another study [28] reviewed the oncological effects of perioperative

transfusion in patients with pancreatic duct cancer from 1992 to 2012. However the above studies are mostly retrospective observational studies, confounding factors and bias are large, which may affect the reliability of the conclusions. The POTTs study also compared the recurrence and metastasis of the three groups during the follow-up period. Metastasis occurred mainly within 1 year after the cancer surgeries. Postoperative third year almost detected no tumor recurrence in patients, no significant difference between the groups were detected ($P = 0.78$) either. The above results indicate that POTTs individual score scheme, compared to the current transfusion guidelines, will not increase the tumor recurrence and metastasis. As mentioned earlier, a large number of domestic and foreign studies have suggested that blood transfusion and tumor recurrence and metastasis are related, so the researchers assume that POTTs, as a blood saving individual research programs, blood transfusion exposure can be reduced, whether the POTTs system can reduce the tumor recurrence rate then? However, according to the existing research results, there is no evidence that this scoring scheme can reduce tumor recurrence and metastasis. The definite relationship between blood transfusion and tumor recurrence remains to be studied. Some other studies indicate that perioperative transfusion is not related to tumor recurrence, but is related to coronary atherosclerosis [29]. Francis [30] analyzed more than 20 of the retrospective study and did not get a clear conclusion on the relationship between blood transfusion and prognosis of colon cancer. Another meta-analysis concluded that blood transfusion will increase 37% cancer recurrence and metastasis related risks of patients, but after the author's depth analysis, which may be possibly related to improper control of experiment design [31]. As is reported in the foreign literature [32], 44 cases of patients from 130 cases of patients with gynecological malignant tumor received transfusion, and their relatively poor prognosis had statistical significance compared with patients without transfusion management, but the author further analyzed the data and found that the false positive results of these adverse outcomes was related to improper classification of diseases. The relationship between blood transfusion and tumor recurrence needs to be more carefully and long-termly researched.

This study also examined the impact of POTTs on perioperative blood products in subjects. The results suggest that POTTs scoring scheme can greatly reduce allogeneic blood transfusion and save blood. Over the years, blood products have been used blindly as 'supplements', resulting in a large number of 'comfort blood' phenomena [33–35]. At the beginning of the study, the surgeons often put forward questions to POTTs score for fear of wound healing and hospital stay time, 'blood transfusion can

increase the wound nutrition' wins support among people for a long time [36, 37]. The secondary research results showed that the wound healing and clearing time, ICU stay time and expenses, total hospital stay time and total hospitalization cost differences had no statistical significance among three groups of subjects. The study also verifies that the saving blood POTTs scheme do not delay any incision healing. The red blood cells and plasma infusion costs of POTTs group have been significantly reduced compared with the other two groups. Compared with the existing transfusion guidelines, POTTs reflects the advantage of reducing the economic burden of cancer patients.

In summary, According to the present research results, the POTTs scoring scheme has good clinical feasibility and may provide evidence for perioperative transfusion therapy in the future.

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