Effect of intraoperative HES 6% 130/0.4 on the need for blood transfusion after major oncologic surgery: a propensity-matched analysis

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OBJECTIVES: To evaluate the effect of the intraoperative use of hydroxyethyl starch on the need for blood products in the perioperative period of oncologic surgery. The secondary end-points included the need for other blood products, the clotting profile, the intensive care unit mortality and length of stay.

METHODS: Retrospective observational analysis in a tertiary oncologic ICU in Brazil including 894 patients submitted to oncologic surgery for a two-year period from September 2007. Patients were grouped according to whether hydroxyethyl starch was used during surgery (hydroxyethyl starch and No-hydroxyethyl starch groups) and compared using a propensity score analysis. A total of 385 propensity-matched patients remained in the analysis (97 in the No-hydroxyethyl starch group and 288 in the hydroxyethyl starch group).

RESULTS: A higher percentage of patients in the hydroxyethyl starch group required red blood cell transfusion during surgery (26% *vs.* 14%; $p = 0.016$) and in the first 24 hours after surgery (5% *vs.* 0%; $p = 0.015$) but not in the 24- to 48-hour period after the procedure. There was no difference regarding the transfusion of other blood products, intensive care unit mortality or length of stay.

CONCLUSION: Hydroxyethyl starch use in the intraoperative period of major oncologic surgery is associated with an increase in red blood cell transfusions. There are no differences in the need for other blood products, intensive care unit length of stay or mortality.

KEYWORDS: Tetrastarch; Adverse Events; Blood Transfusion; Surgical Blood Loss; Surgery; Cancer.

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INTRODUCTION

Fluid expansion is critical during surgery and in post-operative care. The ideal fluid type (crystalloids or colloids) and the optimum dosage of fluids are much debated issues (1-4). Hydroxyethyl starches (4) are widely used as fluid expanders in the perioperative period and are the preferred colloids in many intensive care units (ICU) (5,6).

Hydroxyethyl starch (HES) may impair blood coagulation by reducing the levels of von Willebrand factor and factor VIII and by decreasing the platelet count and function (7-10). It has been suggested that the new generation HES (third generation, low molecular weight, low degree of substitution) is less prone to cause blood coagulation disorders than the old compounds (11), but this issue remains controversial (7,12,13) primarily because few studies evaluated the issue (4). In the perioperative period, even the new generation starches inspire concerns about their safety, especially in terms of coagulation disorders (1,7,13-15).

Patients submitted to oncologic surgery are subjected to long surgery procedures, with a great need of fluid resuscitation and blood products transfusion. It has been suggested that surgical cancer patients are more prone to being transfused with blood products than non-cancer patients (16). No study has evaluated the effects of the intraoperative use of a new generation HES on the intraoperative and postoperative red blood cells and other blood products transfusion in patients submitted to elective major oncologic surgery.

We hypothesized that patients submitted to oncologic surgery that received a new generation HES during surgery

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would require more red blood cells transfusions during and after the surgery than patients that did not receive HES. To test our hypothesis, we evaluated whether a new generation HES led to more red blood cell transfusions during the first 48 hours after major elective oncologic surgery than patients that received only crystalloids using a propensity-matched approach. Secondary objectives included clotting profile, use of blood products other than red cells, ICU length of stay and mortality between the two groups.

PATIENTS AND METHODS

Study design: Retrospective analysis of medical records.

Patients: The Ethics Committee of the Hospital AC Camargo approved this study and waived patient consent due to its retrospective observational nature. From September 2007 to September 2009, all patients admitted to the hospital ICU (three units with a total of 33 beds) of our teaching hospital after an elective major oncologic surgery (head and neck, neurological, thoracic, abdominal and other sites) were included in the study.

Data collection: In the hospital, all data are recorded in a computerized physician order entry and an electronic medical record system. We collected the data recorded during the surgery and the following 48 hours. During the intraoperative period, we collected the number of packs of blood products transfused (red blood cells, fresh frozen plasma, platelets and cryoprecipitate), the surgery length and the volume of crystalloids and colloids infused. During ICU admission, we collected the simplified acute physiology score 3 (SAPS 3) and performed laboratory exams that included creatinine levels and clotting profile (composed of the platelets count and prothrombin time (PT)). During the 48-hour period after the surgery, we collected the number of packages of blood products transfused and performed laboratory exams, including serum creatinine. We divided the 48-hour period after the surgery into two periods of 24 hours because the hypothetical HES side effect could be evanescent. The data were analyzed for three consecutive periods: the intraoperative period, the period from the end of the surgery to the first 24 hours after post-surgery (24-hour period) and the period between from 24 to 48 hours after the surgery (24- to 48-hour period). The patients were categorized in two groups according to the use of HES during the intraoperative period (HES and No-HES group). The patients in the HES group received at least 500 mL of new generation HES (Voluven® - 6% 130/0.4, Fresenius, Germany).

Perioperative transfusion policy: The hospital transfusion policy recommends that patients should be admitted to the operating room with a hemoglobin level greater than 10 mg/dL and platelet count above 50×10^3 units/mL. Coagulation disorders, as assessed by aPTT and PT, were treated with preoperative fresh frozen plasma transfusion until both values were within the normal range (international normalized ratio and aPTT ratio less or equal to 1.5). Other causes of coagulopathy, such as vitamin K deficiency, were assessed as appropriate. Blood transfusion during surgery is left to the discretion of the anesthesiologist and surgeon. All anesthesiologists in the hospital are part of a small team that follows protocols for surgery resuscitation and blood transfusion. There are five major surgical teams in the hospital (thoracic, abdominal, pelvic, neurological and soft tissue) and each has a closed staff, i.e., surgery at each specific site is usually performed by a very restricted number of surgeons. The ICU policy for transfusion suggests that red blood cell packs should be transfused if the hemoglobin level is below 7 g/dL or below 8 g/dL with signs of active bleeding and/or impaired tissue perfusion (delayed capillary refill time, elevated lactate levels and nonchloremic metabolic acidosis) (17). Transfusion with hemoglobin levels above 9 g/dL was not encouraged and was performed only at the discretion of the intensivist if massive blood lost was detected (high output in the drain with hemodynamic instability). Platelets were transfused if the total count was less than 50×10^3 units/mL with active bleeding or after neurosurgery. Cryoprecipitate transfusion was indicated in patients with fibrinogen levels less than 100 mg/dL. Fresh frozen plasma was administered if the coagulation times were two-fold higher the normal value range in patients with active bleeding or after neurosurgery.

Colloid use policy: At the time of the study, the only synthetic colloid available at our institution was a new generation 6% HES 130/0.4 (Voluven®). HES was administered at the discretion of the anesthesiologist during surgery. HES use on the ICU postoperative period is not part of our postoperative resuscitation protocol and is discouraged. Albumin was not used during the postoperative period of elective oncologic surgery.

Statistical analysis: Categorical and continuous data are presented as percentages and the mean $\pm$ SD (or median and 25%-75% interquartile range [IQR]), respectively. Categorical variables were compared using the Chi-square or Fisher exact test, as appropriate. Quantitative continuous variables were compared using an unpaired t test or Mann-Whitney test for parametric or nonparametric variables, respectively.

Patients were clustered according to the administration of HES during surgery. Because the use of colloids was not randomized, there were two unbalanced groups (Table 1). Because this was a retrospective analysis (patients were not randomized), the creation of a propensity score is an effective method to reduce bias. Propensity-matched analyses are increasingly being used in research due to its ability to improve the power of retrospective and prospective non-randomized analysis (18,19). Propensity score has been defined as the ''condition probability of being treated given the covariates'' (20). Propensity-matched analyses are able to take into account as many variables related to the outcome evaluated as needed, which reduces bias (20).

To construct the propensity score, a logistic regression was fitted, and variables were chosen for inclusion according to the methods of Brookhart et al. (18). We included variables that could be related to the study outcomes based on the propensity score. To identify the variables potentially associated with the outcome, a univariate analysis was performed to evaluate potential variables related to blood transfusion during the entire perioperative period (from the surgical procedure to up to 48 hours after surgery). The variables included on the propensity score were as follows: age, gender, body-mass index, metastatic disease, surgery length, volume of crystalloid infused and surgical sites. Although age and body mass index were not associated with the outcome, we believed that they were important variables that could alter the fluid dynamics during the surgical procedures and included them in the model (21). The best caliper was 0.05, which was obtained by the Austin method (22). After the propensity score was created, the

Table 1 - Baseline characteristics of the patients that received hydroxyethyl starch (HES group) and crystalloid during major oncologic surgery.

	Overall data			Propensity-matched		
	No-HES (n = 280)	HES (n = 614)	*p*-value	No-HES (n = 97)	HES (n = 288)	*p*-value
Age, years	61 ± 16	57 ± 16	<0.001	59 ± 17	58 ± 16	0.54
Male, n (%)	136 (49)	316 (52)	0.42	48 (50)	143 (50)	0.98
SAPS 3	46 ± 13	47 ± 11	0.43	46 ± 14	46 ± 12	0.97
BMI, kg/m^2	26 ± 6	26 ± 5	0.94	27 ± 5	26 ± 5	0.66
Metastatic disease, n (%)	85 (31)	187 (31)	0.98	31 (32)	85 (30)	0.65
Any chronic comorbidity, n (%)	242 (86)	475 (77)	0.002	79 (81)	227 (79)	0.58
Total operative time, hours	3 (2-5)	6.2 [5-8.5]	<0.001	5 (3-6)	5 [4-6.2]	0.14
Crystalloid volume received, L	2.0 [1.0-2.5]	4.5 [3.0-6.5]	<0.001	3 [2.0-4.5]	3.5 [2.0-4.5]	0.18
HES volume received, L	0	1 [0.5-1.1]		0	1 [0.5-1.0]	
Site of surgery			<0.001			0.23
Abdominal	128 (46)	458 (74)	<0.001	57 (59)	195 (68)	0.11
Head and neck	50 (18)	73 (12)	0.016	8 (8)	29 (10)	0.60
Central nervous system	49 (17)	45 (7)	<0.001	14 (14)	37 (13)	0.69
Thoracic	27 (10)	30 (5)	0.007	12 (12)	20 (7)	0.09
Soft tissue	21 (7)	6 (1)	<0.001	4 (4)	5 (2)	0.24
Other	5 (2)	2 (1)	0.034	2 (2)	2 (1)	0.26

BMI = body mass index; HES = hydroxyethyl starch; SAPS 3 = simplified acute physiology score 3.

patients were matched according to their respective propensity scores. As reported in the current literature, matching on the propensity score has now been clearly demonstrated to be the best method to attempt to provide an unbiased estimation of the treatment effect (19). First, based on the crude analysis, we pre-defined a match considering one patient without HES use to a maximum of three patients with HES use. The match procedure was performed with an optimal matching method, and to avoid overinflation, we did not permit replacement of matched patients. The number of patients analyzed using the propensity score was smaller than the total number of patients studied because matching was not possible for all patients. Our analysis was performed with fewer patients than the original study population. Even with fewer patients, an analysis using the propensity score is more reliable than traditional statistical methods because imbalance between groups is reduced (18,23). The correct construction of the propensity score was performed with the box-plot method. After the propensity score matches were performed, we performed a diagnostic to ensure good balance in the matched population through the bias reduction method and the stabilized standardized difference (because we were using 1:N matching instead of 1:1 matching) (19,22). After matching, the groups were compared using conventional statistical tests.

We performed an additional analysis using ''corrected total volume'' (CTV) instead of crystalloid volume as a variable in the propensity score (see Appendix). CTV was defined as total crystalloid volume × 0.3 plus 1.4 × infused colloid volume (21,24,25). This alternative analysis was conducted to balance the effective volume used for expansion in both groups (see Appendix for details). All the statistical analysis were performed in SPSS 19.0, and a *p*-value of 0.05 for was considered significant for all comparisons.

RESULTS

We included 894 patients; 614 received HES, and 280 received only crystalloids during surgery. Before the use of the propensity score, the patients in the HES group had longer surgical times, had received more crystalloids, were younger and were less likely to have any comorbidity compared with the No-HES group (Table 1). There were also differences regarding the surgery site between groups. After the creation of the matched groups, 385 propensity-matched patients (97 in the crystalloids group and 288 in the HES group) were analyzed. Patients in the paired groups had similar baseline characteristics (Table 1). The median volume of infused HES was 1 L [0.5-1.0]. No patient received less than 0.5 L. Creatinine values were similar for both groups in all the observation periods. The incidence of acute kidney injury (AKI) (defined according to the RIFLE criteria of risk, i.e., an increase of serum creatinine of 50% or more over the baseline) (26,27) was similar between the groups (7% versus 7%, p>0.99). More detailed results regarding the other propensity matched analysis (using CTV), standard logistic regression and non-propensity matched results analysis can be found in the Appendix.

Red blood cells and other blood products transfusions: The variables related to transfusion of red blood cell pack transfusion for all the perioperative transfusions are shown in Table 2. Most patients in both groups did not require blood products transfusion. In the HES group, a higher percentage of patients received red blood cell transfusion in the intraoperative and 24-hour postoperative period, but the percentage was similar for the 24- to 48-hour postoperative period (Figure 1). For the patients in both groups that received red blood cell transfusions, the number of packs per patient was higher in the HES group during the intraoperative period (0.55 *versus* 0.39; $p = 0.028$). No patient in the No-HES group received a blood transfusion after surgery. There was no difference regarding the use of fresh frozen plasma, cryoprecipitate and platelets concentrate in any period.

The patients that received HES had a small but statistically significant lower hemoglobin level at ICU admission (11.2 ± 1.9 *versus* 12.0 ± 1.7; $p<0.001$) but not at the 24-hour (11.1 ± 1.8 *versus* 11.3 ± 1.6; $p = 0.11$) and 48-hour (10.2 ± 1.7 *versus* 10.2 ± 1.5; $p = 0.20$) postoperative periods.

Table 2 - Univariate analysis of factors related to red blood cell transfusion.

	Perioperative RBC transfusion		
	No (n = 624)	Yes (n = 270)	*p*-value
Age, years[$]	58 ± 16	58 ± 15	0.73
Male, n (%)[$]	329 (53)	123 (46)	0.049
SAPS 3	45 ± 12	49 ± 11	<0.001
BMI, kg/m^2 [$]	27 ± 6	26 ± 5	0.069
Metastatic disease, n (%)[$]	168 (27)	106 (39)	<0.001
Any chronic comorbidity, n (%)	505 (81)	212 (79)	0.41
Total operative time, hours[$]	5 (3-7)	7 (5-9)	<0.001
Crystalloid volume received, L[$]	3.0 [1.6-4.5]	5.5 [4.0-7.1]	<0.001
HES volume received, L	0.5 [0.0-1.0]	1.0 [0.5-1.5]	<0.001
Site of surgery[$]			<0.001
Abdominal	379 (60)	207 (77)	
Head and neck	96 (15)	27 (10)	
Central nervous system	75 (12)	19 (7)	
Thoracic	50 (8)	7 (3)	
Soft tissue	20 (3)	7 (3)	
Other	4 (1)	3 (1)	

BMI = body mass index; HES = hydroxyethyl starch; SAPS 3 = simplified acute physiology score 3; $ = variables included in the propensity-score.

The transfusion rate was similar between the groups when we employed the propensity analysis that included CTV (Additional Table 2). The results of the non-propensity analysis (see Appendix, Additional Table 3 and 4) showed that red blood cell transfusion was more frequent in the HES patients. The multivariate analysis showed that the factors associated with red blood cell transfusion in the perioperative period included age, metastatic disease, total operative time, crystalloid volume used and colloid use (any dose). Thoracic and head and neck surgery were protective factors against transfusion (see Additional Table 5).

Secondary objectives: Patients in the HES group showed lower levels of platelets at ICU admission compared to the No-HES group (Table 3). The international normalized ratio (INR) was also higher in the HES patients at ICU admission and in the first 24 hours after surgery (Table 3). Table 4 shows the coagulation values for transfused and non-transfused patients in both groups (No-HES and HES).

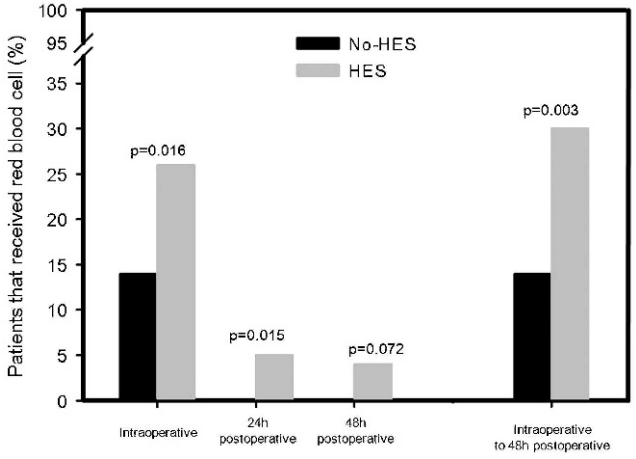

Figure 1 - Percentage of patients that received red blood cell transfusion on each studied period.

The INR was higher in transfused No-HES patients than in non-transfused No-HES patients. The INR was also higher in the transfused HES patients than the non-transfused HES patients at ICU admission. There were no differences between transfused patients in the HES and No-HES groups regarding platelet count or INR at any period studied. Non-transfused HES patients also had a higher INR than non-transfused No-HES patients.

ICU mortality and length of stay were similar between HES and No-HES groups (Table 3).

DISCUSSION

In this retrospective analysis using a propensity-matched cohort of surgical patients, HES use was associated with more frequent red blood cells transfusions during major oncologic surgery and in the first 24 hours after the procedure. ICU length of stay and mortality were the same for both groups.

There is an intense debate involving HES use in critically ill patients. HES are considered more efficient volume expanders than crystalloids; i.e., less volume is needed to obtain the same hemodynamic effect (28,29). A recent randomized controlled trial suggested that patients with penetrating trauma required less total volume when resuscitated by HES compared with saline; there was no difference, however, in patients with blunt trauma (30). A recently published trial in septic patients suggested that less fluid was needed to reach hemodynamic stability in patients resuscitated with HES (31). A larger multicenter randomized trial has shown no difference regarding the total fluid need in septic patients (24). The need for less fluid to obtain the same hemodynamic effect would be particularly interesting during the intraoperative period, when hemodynamic optimization associated with less total fluid volume may be beneficial (32).

HES and other colloids are not related to any robust positive clinical outcome, such as mortality or reduced ICU length of stay (33). In the recently published 6S Trial, septic patients that were randomized to fluid resuscitation with HES had higher mortality, suggesting that at least in this specific population, HES use should be strongly discouraged (24). The doubtful greater efficiency of HES may be counteracted by significant side effects, including coagulation abnormalities and AKI (13). The impact of these side effects on outcome, especially for HES 6% 130/0.4, is largely unknown (4).

Oncologic patients may have coagulation abnormalities related to their illness and chemotherapy side effects (34). We aimed to evaluate the effects of HES on the perioperative need for blood transfusion in this specific population. This outcome is important because blood transfusion may be associated with worse outcome after oncologic surgery, including long-term survival (35-38). Blood transfusion is not harmless and has been associated with several clinical side effects, including transfusion related acute lung injury and fluid overload (39). In critically ill patients, blood transfusion is associated with poorer outcomes (39).

Our propensity-matched data showed that HES use is independently related to a greater need for red blood cell transfusion in the perioperative period. As previously reported, even low doses of HES could result in coagulation abnormalities (14). In addition to requiring more red blood cell transfusions, HES patients also had lower hemoglobin levels at ICU admission, suggesting that the difference was not only due to over transfusion of the HES group.

Table 3 - Secondary objectives.

	No-HES n = 97	HES n = 288	*p*-value
ICU mortality and LOS			
ICU mortality, n (%)	1 (1)	6 (2)	0.69
ICU LOS, days [IQ]	1 (1-2)	1 (1-2)	0.48
Clotting profile			
Platelet count at ICU admission	219 [165-293] $\times 10^3$	191 [141-239] $\times 10^3$	0.003
Platelet count at the 24-hour postoperative period	200 [153–262] $\times 10^3$	193 [142–250] $\times 10^3$	0.22
Platelet count during the 24- to 48-hour postoperative period	190 [143–302] $\times 10^3$	188 [135–235] $\times 10^3$	0.24
PT (INR) at ICU admission	1.12 [1.06-1.21]	1.19 [1.10-1.29]	<0.001
PT (INR) at the 24-hour postoperative period	1.16 [1.07-1.25]	1.19 [1.10-1.31]	0.027
PT (INR) during the 24- to 48-hour postoperative period	1.29 [1.17-1.37]	1.27 [1.14-1.41]	0.94

PT = prothrombin time; INR = international normalized ratio; ICU = intensive care unit; LOS = length of stay.

Corroborating with our results, other studies have shown a higher need for blood products in critically ill patients who received HES (24,40). Patients with blunt trauma resuscitated with HES required more blood transfusions than patients who received saline, although this conclusion is likely confounded by a higher injury severity in the HES-resuscitated patients (30). Our standard multivariate analysis showed that colloid use was a risk factor for the perioperative need for red blood cell transfusion. When we performed the CTV analysis, both groups had similar transfusion rates. Nevertheless, because this analysis included fewer patients (with only 41 patients in the No-HES group – see Appendix), it is possible that the smaller sample reduced the power of the study to detect any difference.

It can be argued that because the use of HES is associated with a greater degree of plasma volume expansion, and considering that the two groups were paired to the crystalloid volume infused, our findings may be related only to the increased hemodilution caused by HES use (41). The increase in the frequency of red blood cell pack transfusions in the HES group in the main propensity analysis might to some degree be related to the expansion effect of HES and not to its impact on blood coagulation. The lack of difference in the CTV analysis corroborates this hypothesis. It should be stated that the effectiveness of HES as a dilutional agent appears to be reduced after major injury (42) and that our patients also used a small volume of starch that was below the suggested maximum daily dose of 50 mL/kg.

There were small differences in the coagulation profile between the HES and No-HES groups. Those differences are likely without clinical significance because the values were very similar between the groups (Table 3). There were no differences in the coagulation profile (including the INR and platelet count) between the transfused patients in both groups (Table 4). The higher need for transfusions cannot be explained by the differences in coagulation features after surgery.

In our multivariate analysis, thoracic surgery was a protector factor against transfusion. It may be speculated that because restrictive fluid therapy is frequently used in thoracic surgery (43), patients received less fluid, with less hemodilution and bleeding related to dilutional coagulopathy, and therefore required less red blood cell transfusion.

The ICU length of stay and mortality were similar between groups, but our analysis was likely underpowered to detect a significant difference in a population with low mortality (below 2%) and short ICU length of stay (one day of median ICU stay). In the univariate analysis, ICU length of stay was higher in the HES group than in the No-HES group (Additional Table 6).

There are several limitations in our analysis. First, this study has a single-center retrospective analysis design.

Table 4 - Characteristics of the transfused and non-transfused patients in the HES and No-HES groups.

	No-HES			HES			Comparison between No-HES and HES	
	No-Tx (n = 85)	Tx (n = 12)	p	No-Tx (n = 207)	Tx (n = 81)	p	No-Tx	Tx
Age, years	59 ± 17	65 ± 12	0.22	58 ± 16	58 ± 16	0.94	0.87	0.17
Male, n (%)	43 (51)	5 (42)	0.27	108 (52)	35 (43)	0.11	0.44	0.65
SAPS 3	45 ± 14	54 ± 11	0.040	45 ± 11	48 ± 11	0.040	0.81	0.13
Metastatic disease, n (%)	22 (26)	9 (75)	0.011	55 (26)	30 (37)	0.12	0.96	0.047
Platelets count at ICU admission	215 [170-285] $\times 10^3$	207 [129-289] $\times 10^3$	0.56	200 [149-251] $\times 10^3$	173 [124-245] $\times 10^3$	0.12	0.034	0.42
Platelet count at the 24-hour postoperative period	201 [155–265] $\times 10^3$	188 [122–250] $\times 10^3$	0.38	200 [155–258] $\times 10^3$	180 [112–266] $\times 10^3$	0.17	0.60	0.91
Platelet count during the 24- to 48-hour postoperative period	182 [143–314] $\times 10^3$	191 [100–232] $\times 10^3$	0.39	190 [155–258] $\times 10^3$	158 [109–239] $\times 10^3$	0.021	0.68	0.81
PT (INR) at ICU admission	1.11 [1.06-1.18]	1.18 [1.15-1.25]	0.007	1.15 [1.08-1.25]	1.24 [1.14-1.40]	<0.001	0.003	0.31
PT (INR) at the 24-hour postoperative period	1.15 [1.06-1.23]	1.18 [1.13-1.45]	0.15	1.18 [1.09-1.27]	1.20 [1.11-1.33]	0.18	0.11	0.95
PT (INR) during the 24- to 48-hour postoperative period	1.24 [1.06-1.36]	1.30 [1.27-1.32]	0.69	1.28 [1.14-1.42]	1.27 [1.15-1.39]	0.60	0.44	0.76

TX = red blood cell pack transfusion; BMI = body mass index; HES = hydroxyethyl starch; SAPS 3 = simplified acute physiology score 3.

Second, the propensity score analysis was unable to match for unmeasured variables. Third, due to its retrospective nature, we were unable to control for personal preferences variables regarding red blood cell transfusion and specific tumor staging (which could be related to technical difficulties during the surgical procedure), although we included metastatic disease in the propensity score. Fourth, although our hospital has strict policies for transfusion and perioperative fluid therapy, we cannot guarantee that these protocols were followed in all of the patients analyzed. Triggers for transfusion were also unavailable for analysis. Fifth, our study was underpowered to evaluate the ICU length of stay and mortality.

Our finding that HES use is associated with a greater need for blood transfusion is biologically plausible and has been reported in other clinical scenarios (24,40). If these findings are confirmed in large, prospective studies, HES use should be questioned in the subjects undergoing elective oncologic surgery due to its unproven clinically efficacy over crystalloids (4,13). The surgical procedures on oncologic patients have specific aspects that need further study.

The intraoperative use of HES 6% 130/0.4 during major elective oncologic surgery is associated with an increase in red blood cell transfusions in the perioperative period of major oncologic surgery. There were no differences in ICU length of stay and mortality. Further randomized clinical trials in this specific population are urgently needed.

AUTHOR CONTRIBUTIONS

Zampieri FG designed the study, collected the data and wrote the manuscript. Ranzani OT performed the statistical analysis and reviewed the manuscript. Morato PF, Campos PP helped in the data collection and reviewed the manuscript. Caruzo P helped in the data collection, performed the statistical analysis, and reviewed the manuscript.

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APPENDIX

Results of propensity score using corrected total volume and the results of standard multivariate analysis

Impact of intraoperative HES 6% 130/0.4 on the need for blood transfusion after major oncologic surgery: A propensity-matched analysis

Corrected total volume (CTV) analysis: Our propensity score analysis using CTV instead of infused crystalloid volume resulted in 97 patients in the No-HES group and 162 patients in the HES group. The major difference between this analysis and the previous analysis was the use of the corrected total volume (CTV) as a variable instead of the volume of infused crystalloid. We sought to minimize the role of hemodilution as a trigger to transfusion; i.e., the propensity-matched patients in this analysis would have received the same amount of plasma expansion. Because the expansion effects of colloids are different from crystalloids, we created a variable that would account for the corrected amount of fluid expansion received (CTV). We defined the CTV in patients in the No-HES group as equivalent to the crystalloid volume infused multiplied by 0.3 (1). The CTV in the HES group was defined as the sum of the crystalloid volume multiplied by 0.3 plus the volume of HES multiplied by 1.4 (CTV = [crystalloid volume $\times$ 0.3] + [1.4 $\times$ colloid volume]). The use of the 1.4 ratio aimed at accounting for the theoretical greater expansion effects of the colloids (2,3).

This alternative propensity analysis included 41 patients in the No-HES group and 118 patients in the HES group (Additional Table 1). There was no difference in the need for red blood cell transfusion between the groups when this analysis was performed (Additional Table 2). The international normalized ration (INR) was higher at ICU admission in the HES group, but the other coagulation variables were similar (Additional Table 3).

Study results of standard analysis: The second approach was a standard multivariate logistic regression. The stepwise backward method was used to determine the factors associated with red blood cell transfusion in the perioperative time. The initial model consisted of all of the independent variables that had a p value of less than 0.25 in the bivariate analysis associated with red cell blood transfusion or between the HES and non-HES groups in the 894 patients (the Hosmer-Lemeshow logistic regression). The variables were removed one at a time if they did not contribute to the model assessed according to a likelihood ratio test ($p < 0.050$). The continuous variables were checked for the assumption of linearity in the logit. Single colinearity was evaluated with Pearson's correlation between the independent variables, and multi-colinearity was evaluated with the variance inflation factor. The odds-ratios and

Additional Table 1 - CTV propensity score analysis.

	No-HES (n = 41)	HES (n = 118)	*p*-value
Age, years	61 ± 14	57 ± 17	0.19
Male, n (%)	18 (44)	66 (56)	0.18
SAPS 3	49 ± 19	47 ± 13	0.52
BMI, kg/m^2	27 ± 4	26 ± 5	0.22
Metastatic disease, n (%)	13 (32)	39 (33)	0.87
Any chronic comorbidity, n (%)	33 (81)	91 (77)	0.65
Total operative time, hours	5.0 [3.8-6]	6.0 [4.0-7.0]	0.10
CTV, L	1.4 [1.1-1.8]	1.9 [1.3-3.2]	0.51
Site of surgery			0.69
Abdominal	26 (63)	82 (70)	
Head and neck	3 (7)	13 (11)	
Central nervous system	4 (10)	10 (9)	
Thoracic	6 (15)	9 (8)	
Soft tissue	2 (5)	3 (3)	
Other	0	1 (1)	

Legend: BMI = body mass index; HES = hydroxyethyl starch; SAPS 3 = simplified acute physiology score 3; CTV = corrected total volume.

Additional Table 2 - Main study outcomes of the CTV propensity analysis.

	No-HES (n = 41)	HES (n = 118)	*p*-value
Intraoperative period			
Patients that received red blood cells, (%)	10 (24)	32 (27)	0.73
Patients that received fresh frozen plasma, (%)	4 (10)	1 (1)	0.016
Patients that received platelets, (%)	0	0	-
Patients that received cryoprecipitate, (%)	0	2 (2)	>0.99
24 h postoperative period			
Patients that received red blood cells, (%)	0	5 (4)	0.33
Patients that received fresh frozen plasma, (%)	0	0	-
Patients that received platelets, (%)	0	1 (1)	>0.99
Patients that received cryoprecipitate, (%)	0	3 (2)	0.55
24-48 h postoperative period			
Patients that received red blood cells, (%)	0	1 (1)	>0.99
Patients that received fresh frozen plasma, (%)	0	0	-
Patients that received platelets, (%)	0	0	-
Patients that received cryoprecipitate, (%)	0	0	-
Combined intraoperative and postoperative periods			
Patients that received red blood cells in the intraoperative and first 24 hours, (%)	10 (24)	35 (30)	0.52
Patients that received red blood cells in the intraoperative and first 48 hours, (%)	10 (24)	36 (31)	0.46

HES = hydroxyethyl starch.

corresponding 95% confidence intervals for each variable were computed. The discriminative ability of the model to predict the outcome of patients was assessed by the area under the receiver operating characteristic (AUC) curve. The calibration ability for the model was evaluated with Hosmer-Lemeshow goodness-of-fit statistics.

The major outcomes regarding the need for blood transfusion on crude analysis are displayed in Additional Table 4. The major difference between propensity-matched *versus* standard analysis was that before matching, the need for blood products other than red blood cell packs was more common in the HES patients. The HES patients in the unmatched analysis received fresh frozen plasma during surgery more frequently than the No-HES patients. The need for cryoprecipitate was also more frequent in the HES patients in the first 24 hours after the procedure.

A multivariate analysis was performed to evaluate the risk factors for red blood cell transfusion from the intraoperative period up to 48 hours after the procedure (Additional Table 5). The factors associated with the red blood cell transfusions included age, metastatic disease, volume of crystalloid used, total operative time and use of any dose of HES. These factors may only highlight that patients that received blood transfusion were subject to more aggressive and/or technically difficult surgeries. Head and neck and thoracic surgery were protectors against transfusion.

The ICU length of stay was higher in the HES group (Additional Table 6).

Additional Table 3 - Secondary objectives of the CTV propensity analysis.

	No-HES n = 41	HES n = 118	*p-value*
ICU mortality and LOS			
ICU mortality, n (%)	0	2 (2)	>0.99
ICU LOS, days [IQ]	2 (1-3)	1 (1-2)	0.89
Clotting profile			
Platelet count at ICU admission	207 [154-285] $\times 10^3$	203 [141-2253] $\times 10^3$	0.22
Platelet count at the 24-hour postoperative period	202 [156–256] $\times 10^3$	212 [156–266] $\times 10^3$	0.85
Platelet count during the 24- to 48-hour postoperative period	163 [141–233] $\times 10^3$	192 [136–242] $\times 10^3$	0.76
PT (INR) at ICU admission	1.16 [1.10-1.24]	1.17 [1.09-1.31]	0.36
PT (INR) at the 24-hour postoperative period	1.15 [1.11-1.23]	1.22 [1.13-1.31]	0.04
PT (INR) during the 24- to 48-hour postoperative period	1.30 [1.24-1.38]	1.32 [1.19-1.46]	0.97

PT = prothrombin time; INR = international normalized ratio; ICU = intensive care unit; LOS = length of stay.

Additional Table 4 - Transfusion outcomes according to standard univariate analysis.

Transfusion outcomes	No-HES (n = 280)	HES (n = 614)	*p*-value
Intraoperative period, patients that received blood fraction, n (%)			
Red blood cells	24 (9)	216 (35)	<0.001
Fresh frozen plasma	7 (3)	38 (6)	0.019
Platelets	0	0	1
Cryoprecipitate	0	0	1
24-hour postoperative period, patients that received blood fraction, n (%)			
Red blood cells	7 (3)	46 (8)	0.003
Fresh frozen plasma	6 (2)	24 (4)	0.174
Platelets	2 (1)	7 (1)	0.73
Cryoprecipitate	0	16 (3)	0.004
24- to 48-hour postoperative period, patients that received blood fraction, n (%)			
Red blood cells	4 (1)	24 (4)	0.061
Fresh frozen plasma	2 (1)	2 (1)	0.59
Platelets	0	2 (1)	1.00
Cryoprecipitate	0	1 (1)	1.00
Combined intraoperative and postoperative periods			
Intraoperative period and up to 24 hours after the procedure, patients that received blood fraction, n (%)			
Red blood cells	28 (10)	231 (38)	<0.001
Fresh frozen plasma	11 (4)	53 (9)	0.011
Platelets	2 (1)	7 (1)	0.73
Cryoprecipitate	-	16 (3)	0.004
Intraoperative period and up to 48 hours after the procedure, patients that received blood fraction, n (%)			
Red blood cells	31 (11)	239 (39)	<0.001
Fresh frozen plasma	12 (4)	53 (9)	0.020
Platelets	2 (1)	9 (2)	0.52
Cryoprecipitate	-	17 (3)	0.002

Additional Table 5 - Multivariate model to predict red blood cell package transfusion on intraoperative and perioperative times (up to 48 hours).

	Betta	OR (95% CI)	*p*-value
Age[a]	0.012	1.129 (1.018-1.252)	0.021
Metastatic cancer	0.633	1.883 (1.350-2.625)	<0.001
Thoracic surgery	-1.296	0.274 (0.118-0.637)	0.003
Head and neck surgery	-0.627	0.534 (0.319-0.895)	0.017
Total operative time[c], hours	0.811	2.250 (1.459-3.470)	<0.001
Crystalloid volume received[c], l	0.652	1.919 (1.079-3.413)	0.026
Colloid	0.857	2.355 (1.471-3.772)	<0.001

[a]per 10 units increase;
[b]compared with other sites of surgery;
[c]per 01 log increase.
Model performance:
Hosmer-Lemeshow goodness of fitness test: Chi-square 11.664; $p = 0.167$.
AUC: 0.752 (95% CI: 0.717-0.786); $p < 0.001$.

Additional Table 6 - Outcomes in the standard univariate analysis.

Outcome	Non-HES (n = 280)	HES (n = 614)	*p*-value
ICU mortality, n(%)	4 (1)	13 (2)	0.60
ICU LOS, days [IQ]	1 (1-2)	2 (1-3)	<0.001