

Impact of Crystalloid to PRBC Ratio in Patients with Exsanguinating Penetrating Abdominal Injuries: The Conundrum of Resuscitation

Chrissy Guidry, Marie Unruh, Marquinn Duke, Peter Meade, Norman E McSwain Jr, Juan C Duchesne

ABSTRACT

Background: When intraoperative hemostatic resuscitation (IHR) implements high transfusion ratios of FFP:PRBC (>1:2), there is an associated increased survival in patients with exsanguinating penetrating abdominal injuries (EPAI). The impact of crystalloids: PRBC during IHR has not been analyzed. We hypothesize that minimizing the amount of intraoperative crystalloids:PRBC in combination with high ratio FFP: PRBC will correlate with a survival benefit in patients with EPAI.

Methods: This was a 9-year retrospective analysis of patients with EPAI at a Level 1 Trauma Center. EPAI was defined as any patient who received >20 units of PRBC during IHR. Intraoperative ratio for FFP:PRBC was recorded, and patients were placed in three separate categories accordingly: high (>1:2), mid (1:4 - 1:2), and low ratio (<1:4) groups. Quantity of crystalloids used during each category was recorded and a ratio of crystalloids:PRBC calculated. Logistic regression model was applied to analyze impact of crystalloid:PRBC on mortality, comparing the high FFP:PRBC ratio group to the low FFP: PRBC ratio group.

Results: Intraoperative high ratio FFP:PRBC conveyed a 32% overall survival benefit when compared with low ratio groups. Patients that received a high ratio FFP:PRBC when compared to low ratio group, received less intraoperative crystalloids (calculated crystalloids:PRBC ratios 1:3.4 vs 1:1.1; $p = 0.001$). Our logistic regression demonstrated a survival benefit with a high FFP:PRBC [OR 95% 0.19 , CI (0.05-0.33), $p = 0.003$] and the calculated low crystalloid:PRBC [OR 95%; 0.11 CI (0.01-0.59), $p = 0.001$].

Conclusion: We were able to demonstrate a survival advantage in patients with EPAI that received IHR of a high ratio of FFP:PRBC and a low ratio of crystalloids:PRBC. These findings suggest that in patients with EPAI requiring massive volumes of PRBC, the ratio of intraoperative FFP:PRBC should be high and crystalloids:PRBC should be low.

Keywords: Resuscitation, Crystalloid, Hemorrhage, Trauma.

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RESUMEN

Antecedentes: Cuando hemostasis de reanimación intraoperatorias (IHR) implementa la alta proporción de FFP:PRBC (>1:2), hay aumento de la sobrevivencia en pacientes con lesiones penetrantes abdominales exsanguinantes (EPAI). El impacto de cristaloides, PRBC durante IHR no han sido

analizadas. Hipotetizamos que minimizar cantidad de volume de cristaloides: PRBC junto con una alta relación FFP:PRBC se correlacionan con un beneficio de supervivencia en pacientes con EPAI.

Métodos: Este es un 9-año análisis retrospectivo de EPAI pacientes en un Centro de Trauma Nivel I. EPAI: los pacientes que recibieron >20 unidades de PRBC durante IHR. Intraoperatoria relación de FFP:PRBC fue grabada y los pacientes fueron divididos en grupos en consecuencia: 1. Alto (>1:2), 2. Media (1:4 - 1:2), y 3. Relación Baja (<1:4). Cantidad de cristaloides:PRBC fue calculado. Modelo de regresión logística se aplicó para analizar impacto de cristaloides:PRBC sobre la mortalidad, comparar la alta FFP:PRBC relación a Baja FFP:PRBC relación entre grupos.

Resultados: Intra-operatoria alto ratio FFP:PRBC transmitió un 32% de supervivencia global beneficio cuando en comparación con baja relación entre grupos. Los pacientes que recibieron un alto vs baja proporción FFP:PRBC recibido menos cristaloides (calculado cristaloides:PRBC ratios 1:3 vs 1:1; $p = 0,001$). La regresión logística ha demostrado un beneficio en la supervivencia con un alto FFP:PRBC [OR = 0.19 , IC (0.05-0.33), $p = 0,003$], y el calculo de bajo cristaloides: PRBC [OR = 0.11 IC (0.01 - 0.59), $p = 0.001$] .

Palabras claves: Resucitacion, Crystaloides, Fluidos, Resultados, Transfusion de plasma, Transfusion de sangre.

INTRODUCTION

Damage control laparotomy (DCL) increases survival rates in patients with exsanguinating penetrating abdominal injuries (EPAI).¹⁻⁴ In this group of patients, the combination of trauma induced coagulopathy (TIC), metabolic acidosis, and hypothermia compose the lethal death triad associated with severe tissue injury and tissue hypoperfusion. Civilian and military studies have demonstrated a survival benefit when a close ratio resuscitation of fresh frozen plasma (FFP) to packed red blood cells (PRBC) is used in EPAI.⁵⁻⁹

Resuscitation strategies in patients with EPAI have evolved throughout the years. Military resuscitation during 1960s used aggressive crystalloid resuscitation with no predefined transfusion ratio of blood component therapy. Fluid administration focused on crystalloid use in an effort to balance inputs and outputs.^{10,11} This approach failed to address the coagulopathy associated with severely injured patients in hemorrhagic shock.

Currently, the goal during intraoperative hemostatic resuscitation (IHR) consists of component therapy resuscitation that targets replacement of depleted blood volume, restoration of tissue perfusion and effective

correction of coagulopathy. This resuscitation strategy has been accepted by many civilian trauma centers with overall improvement in outcomes.^{5-9,12-14} The etiology leading to this improvement could be multifactorial. During close ratio resuscitation, the goal should consist of FFP matched to PRBC in a 1:1 fashion while minimizing crystalloid utilization. No Level 1 data exist to support the amount of crystalloids that should be incorporated during IHR in exsanguinating patients, and the impact of crystalloid:PRBC ratio on mortality during IHR has not been analyzed. We hypothesize that minimizing the intraoperative crystalloid:PRBC ratio in combination with a high ratio for FFP:PRBC will correlate with a survival benefit in patients with EAPI.

METHODS

This is a 9-year retrospective review of adult patients with EAPI at a Level 1 urban trauma center. EAPI was defined as a penetrating abdominal injury requiring at least 20 units of PRBC in the operating room. Clearly defining hemorrhage is a difficult task, and our study population differs from patients commonly used in definitions of massive transfusion (where 10 units of blood is given over 24 hours). This patient population was selected in particular to study the most severe cases hemorrhagic shock. Patients were identified through the institutional trauma registry under an IRB-approved protocol.

A massive transfusion protocol (MTP) was activated for all patients included in this study. The MTP was changed in 2007 at our institution to have a goal of a matched 1:1 ratio of FFP:PRBC. However, this goal was not perfectly obtained during IHR for all patients. Therefore, patients were then separated into three groups according to the intraoperative ratio transfused for FFP:PRBC: High (>1:2), mid (1:4 - 1:2), and low ratio (<1:4). Intraoperative ratios were analyzed on patients' initial visit to the OR only. Crystalloid infusion guidelines are not part of the MTP at our institution. Each liter of crystalloids given was defined as 1 unit (1 liter = 1 unit). Fractional units of crystalloids were used in the comparison. In each group, the correlating crystalloid:PRBC ratio was then calculated.

Demographic and clinical data were retrieved from the trauma registry which included patients' age (years), emergency department initial systolic blood pressure (mmHg), initial hemoglobin (gm/dl), initial base deficit (mEq/l), and injury severity score (ISS). A focus of this study was to evaluate, specifically, intraoperative resuscitation on outcomes. Therefore, intraoperative units of PRBC, units of FFP and units of crystalloids (1 unit = 1 liter) were also recorded. Operating room (OR) mortality was obtained as well as overall 30-day mortality.

Statistical Methods

Univariate analysis of continuous data was done with the Student's t-test on variables of age, initial systolic blood pressure, initial hemoglobin, initial base deficit and ISS. The mean amount of PRBC, FFP and crystalloids was studied by using analysis of variance (ANOVA). Using a chi-squared model, mortality differences were analyzed for each group. Logistic regression model, eliminating for confounders, was used in order to identify variables associated with improved survival by comparing high ratio to low ratio groups.

RESULTS

During the 9-year study at a level 1 trauma center, a total of 64 patients with penetrating abdominal injuries required greater than 20 units PRBCs during intraoperative resuscitation in the patients' initial surgery. Of the 64 patients transfused, 27 had a high IHR ratio of FFP:PRB (>1:2), 21 had a mid IHR ratio of FFP:PRBC (1:4 - 1:2), and 17 had a low IHR ratio of FFP:PRBC (<1:4). The correlating crystalloid:PRBC mean ratio was calculated in each IHR ratio group: High 1:3.4, mid 1:1.3, low 1:1.1 (Table 1).

There was no statistical difference demonstrated when comparing patient demographics and clinical data between a high vs mid vs low ratio: age 25 ± 13 years vs 23 ± 14 years vs 24 ± 11 ($p = 0.54$), mean initial systolic pressure 88 ± 26 mm Hg vs 92 ± 31 mm Hg vs 90 ± 28 mm Hg ($p = 0.21$), mean initial hemoglobin 9.3 ± 1.2 vs 10.1 ± 1.4 vs 9.9 ± 1.5 ($p = 0.53$), mean initial base deficit -9.9 ± 4.2 vs -9.6 ± 5.7 vs -9.1 ± 4.8 ($p = 0.45$), and the mean ISS 27 ± 11 vs 25 ± 8 ($p = 0.71$) (Table 2).

The mean PRBC units used in intraoperative resuscitation in each group was not statistically significant in high vs mid vs low (32 vs 31 vs 33, $p = 0.79$). However, units of FFP and crystalloids used was found to be statistically significant between high vs mid vs low: mean units of FFP 26 vs 12 vs 7 ($p = 0.001$) and mean units (liters) crystalloids 9.2 vs 17 vs 29 ($p = 0.002$). (Table 3 and Fig. 1). We suspect the profound difference between the high vs mid vs low groups is due to differences in the MTP before 2007 and after 2007, when the protocol was changed from 1:4 to 1:1 of FFP:PRBC. After the initiation of 1:1, we suspect that the protocol was not perfectly achieved initially but rather slowly adapted to reflect current compliance to the protocol.

When comparing outcome mortality, high vs mid vs low groups demonstrated 30-day mortality of 56 vs 76 vs 88% ($p = 0.009$) and intraoperative mortality 19 vs 19 vs 29% ($p = 0.13$) (Table 4 and Fig. 2).

In a logistic regression model after adjusting for age, ISS and systolic pressure, multivariate analysis showed that patients with EAPI demonstrated a survival benefit with a

high FFP:PRBC IHR ratio [OR 0.19, (95% CI 0.05-0.39), $p = 0.19$] when compared to the low ratio FFP:PRBC ratio IHR. Additionally, a survival benefit was demonstrated in a low calculated ratio of crystalloid:PRBC [OR 0.11, (95% CI 0.01-0.59), $p = 0.001$] when compared against the high calculated ratio of crystalloid:PRBC (Table 5).

Intraoperative ratios of component therapy were calculated for FFP:PRBC and separated into three different groups: high (>1:2), mid (1:4 - 1:2) and low ratio (<1:4). The correlating crystalloid:PRBC ratio was then calculated in each group. The means for each group are represented here.

Component therapy in all ratio groups show a consist amount of PRBC. The utilization of FFP decreased from high to low ratio while crystalloid use increased. Patients in the low ratio group received the least amount of FFP with concomitant greatest amount of crystalloids. This group had the highest intraoperative mortality, 29% and overall 30-day mortality, 88% (see Figs 1 and 2).

Trends showing increase in mortality from high ratio to low ratio. Patients in the low ratio group, who received the greatest volume of crystalloids, had the highest overall mortality.

Table 1: Intraoperative ratio groups

	High ratio (n = 27)	Mid ratio (n = 21)	Low ratio (n = 17)
Mean FFP:PRBC ratio	1:1.2	1:2.5	1:4.7
Mean crystalloid:PRBC	1:3.4	1:1.3	1:1.1

FFP: Fresh frozen plasma; PRBC: Packed red blood cells

Table 2: Univariate analysis comparing FFP:PRBC groups high mid and low

	High ratio (n = 27)	Mid ratio (n = 21)	Low ratio (n = 17)	p-value
Age (SD)	25 (13)	23 (12)	24 (11)	0.54
ED SBP (SD)	88 (26)	92 (31)	90 (28)	0.21
Initial hemoglobin (SD)	9.3 (1.2)	10.1 (1.4)	9.9 (1.5)	0.53
Initial base deficit (SD)	-9.9 (4.2)	-9.6 (5.7)	-9.1 (4.8)	0.45
ISS (SD)	27 (11)	25 (8)	27 (10)	0.71

SD: Standard deviation; SBP: Systolic blood pressure; ISS: Injury severity score

Table 3: Components in intraoperative resuscitation

	High ratio (n = 27)	Mid ratio (n = 21)	Low ratio (n = 17)	p-value
Mean PRBC (units)	32	31	33	0.79
Mean FFP (units)	26	12	7	0.001*
Mean crystalloids (liters)	9.2	17	29	0.003*

PRBC: Packed red blood cells; FFP: Fresh frozen plasma; *Statistical significance

Table 4: 30-day mortality and OR mortality

	High ratio (n = 27)	Mid ratio (n = 21)	Low ratio (n = 17)	p-value
30-day mortality (%)	15/27 (56%)	16/21 (76%)	15/17 (88%)	0.009*
OR mortality (%)	5/27 (19%)	4/21 (19%)	5/17 (29%)	0.13

OR: Operating room; TICU: Trauma intensive care unit; *Statistical significance

Table 5: Logistic regression model for mortality

	p-value	Odds ratio (95% CI)
High FFP:PRBC ratio	0.003*	0.19 (0.05 - 0.33)
Low crystalloid:PRBC ratio	0.001*	0.11 (0.01 - 0.59)
ISS	0.13	1.02 (0.98 - 1.101)
SBP	0.43	1.34 (0.43 - 4.17)

PRBC: Packed red blood cells; ISS: Injury severity score; SBP: Systolic blood pressure; *Statistical significance

The logistic regression model for mortality compared high ratio FFP:PRBC to low ratio FFP:PRBC, while low ratio crystalloid:PRBC was compared to high ratio crystalloid:PRBC

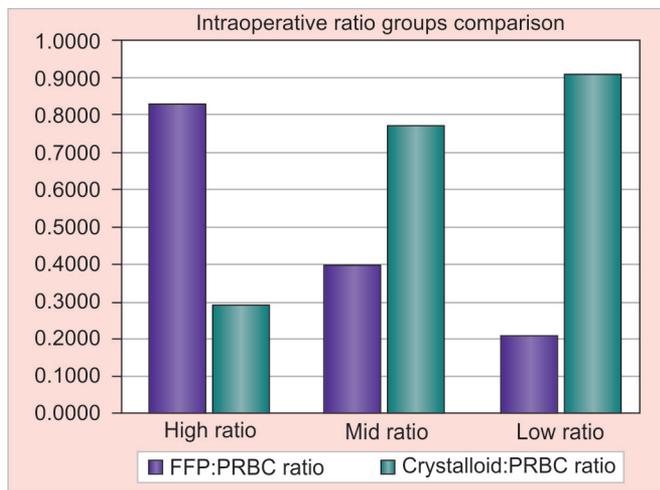


Fig. 1: Components in intraoperative resuscitation

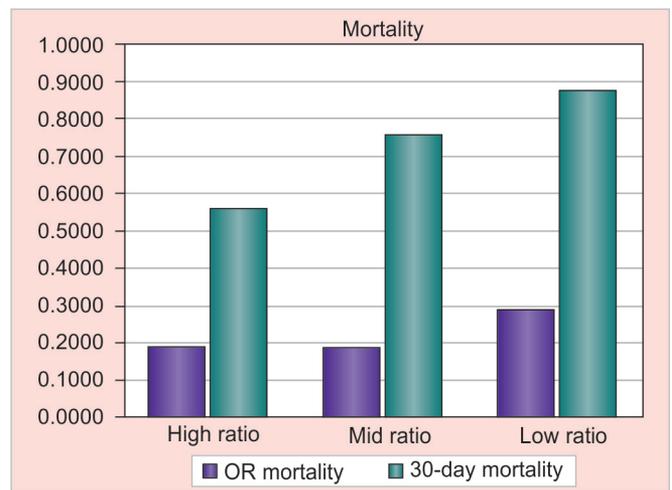


Fig. 2: Logistic regression model for mortality

DISCUSSION

Exsanguinating injuries are the cause of death in up to 40% of trauma victims.¹⁵ Survival has improved in the range of 6 to 50% by implementing hemostatic resuscitation as part of massive transfusion protocols.¹⁶ This volume replacement therapy aims to correct hemodynamic stability, TIC and tissue hypoperfusion. During the history of trauma resuscitation, crystalloids have been the standard of fluid resuscitation^{10,11,17,18} with ongoing recommendations of moderation and adaptations.^{12,19-21} Current advanced trauma life support (ATLS) guidelines call for initial infusion of 1 to 2 l of crystalloid followed by transfusion of PRBC if transient or no response, when hemorrhagic shock is suspected.^{22,23} Using a newer strategy, damage control resuscitation (DCR) conveys a survival benefit⁵⁻⁸ while integrating early IHR with a goal of a fixed transfusion of 1:1 of FFP:PRBC, restriction of crystalloid infusion and permissive hypotension in conjunction with principles of damage control surgery.¹²

In this study, the principles of DCR were observed in the high ratio group. Components involved during IHR (FFP, PRBC and crystalloids) were analyzed. The quantity of PRBC given in each group was not statistically different among high, mid and low groups, $p = 0.79$. While the quantity of FFP given was statistically less from the high to low groups, 26 to 7 ($p = 0.001$), the mean liters of crystalloids given intraoperatively was statistically greater from high to low groups 9.2 to 29 ($p = 0.003$). This increase in intraoperative infusion of large volumes of crystalloid has many potential adverse consequences in the exsanguinating trauma patient. As it was demonstrated in our study, patients that received large volumes of crystalloids with low quantities of FFP carried the highest overall mortality, 88%.

Previous studies have demonstrated the deleterious effects of aggressive crystalloid administration in patients

with severe hemorrhage.²⁴⁻²⁶ Our results from this study support previous findings with evidence of decreased survival in patients with higher ratios of crystalloid:PRBC. Following major trauma, systemic inflammatory response is activated^{27,28} and capillary permeability increases causing a decrease in osmotic pressure intravascularly resulting in a loss of fluid to the interstitial space. Resuscitation with large crystalloid fluid volumes further potentiates cellular injury²⁹ from imbalances occur in extracellular and intracellular osmolarity. With massive fluid shifts, cellular regulatory mechanisms become overwhelmed and resultant dysregulation of cellular mechanisms occurs: cytosolic acidification, dilution of cellular proteins and inactivation of protein kinases.^{25,30} The problematic fluid shifts manifest systemically causing pulmonary³¹⁻³³ and cardiac complications^{25,34}, abdominal compartment syndrome³⁵⁻³⁸, gastrointestinal dysmotility²², coagulation disturbances^{39-41,42}, immunological and inflammatory mediator dysfunction.^{19,25,42-44}

Taking into consideration the multitude of detrimental effects related to crystalloid administration, an essential goal of DCR is to minimize crystalloid usage.⁴⁵ In our study, a logistic regression model demonstrated a survival advantage when FFP units was close to PRBC units, OR 0.19 (0.05 - 0.33, 95% CI), $p = 0.003$. Additionally, a low crystalloid:PRBC ratio also demonstrated a similar survival benefit, OR 0.11 (0.01 - 0.59, 95%CI), $p = 0.001$. This translates into improved outcomes with (1) less crystalloid per unit of PRBC and (2) a greater quantity of FFP per unit of PRBC. This suggesting not only a deleterious effect of crystalloids but perhaps a therapeutic effect of FFP.

The benefits of FFP are hypothesized by Pati et al to include a mechanism at the cellular level in combination of the replacement of coagulation factors. In their biological mechanism model, hemorrhagic shock induces hypoxia,

endothelial cell tight junction breakdown, inflammation, and leukocyte diapedesis. The data *in vivo* and *in vitro* suggests that FFP has beneficial effects on vascular endothelial stability and resuscitation that are independent of its effects on hemostasis. They concluded that FFP repairs and 'normalizes' the vascular endothelium by restoring tight junctions, building the glycocalyx, and inhibiting inflammation and edema while crystalloid infusion will only potentiate vascular endothelial injury further.⁴⁶

Perhaps future additions to MTPs will be standardized to include purposeful measures minimizing use of crystalloids. The advances in hemostatic resuscitation will likely further improve the survivability of trauma patients, especially in the extreme cases of hemorrhagic shock in exsanguinating abdominal penetrating injuries.

CONCLUSION

Future investigation of resuscitation will likely involve optimizing restoration of endothelial injury based on plasma and effective low volume fluid resuscitation. For patients with EPAI, there is a direct correlation with increased mortality and high infusion of crystalloid:PRBC. This suggests that minimizing the amount of intraoperative crystalloid:PRBC in patients requiring massive volumes of PRBC can improve survival.

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ABOUT THE AUTHORS

Chrissy Guidry

Department of Surgery, Tulane University School of Medicine, Section of Trauma, New Orleans, LA

Marie Unruh

Department of Surgery, Tulane University School of Medicine, Section of Trauma, New Orleans, LA

Marquinn Duke

Department of Surgery, Tulane University School of Medicine, Section of Trauma, New Orleans, LA

Peter Meade

Department of Surgery, Tulane University School of Medicine, Section of Trauma, New Orleans, LA

Norman E McSwain Jr

Department of Surgery, Tulane University School of Medicine, Section of Trauma, New Orleans, LA

Juan C Duchesne (Corresponding Author)

Director of Surgical Intensive Care Unit, Department of Surgery and Anesthesia, Section of Trauma and Critical Care Surgery, Tulane University School of Medicine, 1430 Tulane Ave., SL-22, New Orleans, LA 70112-2699, Phone: 504-988-5111, Fax: 504-988-3683 e-mail: jduchesn@tulane.edu