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Sex-based differences in transfusion need after severe injury: Findings of the PROPPR study

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ABSTRACT

Background: Women are underrepresented in trauma research, and aggregated results of clinical trials may mask effects that differ by sex. It is unclear whether women respond differently to severe hemorrhage compared with men. We sought to evaluate sex-based differences in outcomes after severe trauma with hemorrhage.

Methods: We performed a secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratios trial. Trauma patients predicted to require massive transfusion were randomized to a 1:1:1 vs 1:1:2 plasma to platelet to red blood cell transfusion ratio. Analysis was performed according to sex, controlling for clinical characteristics and transfusion arm.

Results: A total of 134 women and 546 men were analyzed. In multivariable analysis, there was no difference in mortality at 24 hours (hazard ratio for women 0.64, 95% confidence interval 0.34–1.23, $P = .18$) or in time to hemostasis (hazard ratio 1.10, 95% confidence interval 0.84–1.42, $P = .49$) by sex. We observed no difference between sexes in volume of blood products transfused during active hemorrhage. However, after anatomic hemostasis, women received lower volumes of all products, with a 38% reduction in fresh frozen plasma (mean ratio 0.62 (95% confidence interval 0.43–0.89, $P = .01$), 49% reduction in platelets (mean ratio 0.51, 95% confidence interval 0.33–0.79, $P < .01$) and 49% reduction in volume of red blood cells (mean ratio 0.51, 95% confidence interval 0.33–0.79, $P < .01$).

Conclusion: Mortality and time to hemostasis of trauma patients with hemorrhage did not differ by sex. Although there was no difference in transfusion requirement during active hemorrhage, once hemostasis was achieved, women received fewer units of all blood products than men. Further research is required to determine whether women exhibit differences in coagulation during and after severe traumatic hemorrhage.

Introduction

Traumatic injury is the leading cause of death among persons younger than 45 years of age in the United States, accounting for an estimated 200,000 deaths per year and $214 billion in associated costs.[1] Because uncontrolled hemorrhage is the primary cause of early death after injury, efforts to improve resuscitation and techniques for hemorrhage control remain at the forefront of research. The past decade has seen a transition from traditional transfusion practices toward damage control resuscitation (DCR), which prioritizes early administration of blood products over initial delivery of crystalloid and is designed to address acute coagulopathy while limiting ongoing blood loss.[2–4] Most recently, research has focused on optimal ratios of initial blood products, with high transfusion ratios of plasma to platelets to red blood cells (RBCs) associated with decreased early mortality and deaths from exsanguination.[5–8]

Women have been shown to be underrepresented in surgical clinical research, with lower enrollment in clinical trials, and infrequent analysis and reporting of results by sex.[9–13] Such disproportionate inclusion is particularly pronounced in trauma, with its predominantly young, male population.[14–16] Consequently, even robust, multi-institutional trials only contain a small minority of female patients.[5,17,18] For example, women accounted for only

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16% of the landmark CRASH-2 trial, which remains the largest trial of patients after traumatic injury.[19] This has important implications for the development of therapies and management strategies after severe injury, which may be specific to only one sex.

Numerous studies have investigated sex-based differences in clinical outcomes after trauma, with most claiming a protective effect of female sex.[20–27] The reasons underlying this sex dimorphism have not been fully elucidated; however, one suggestion is that relative hypercoagulability of women in the first 24 hours after injury may result in improved hemostasis after traumatic hemorrhage.[28,29] Such studies have been limited by their predominantly observational design and considerable variation in resuscitation practices, with little information on sex-based differences in the current era of damage-control resuscitation. Specifically, it remains unclear whether women continue to exhibit favorable outcomes compared with men when managed with "one-size fits all" ratio-based blood product resuscitation.

Further research is needed to better understand the clinical response of injured women to current resuscitation practices and determine whether this population should be managed differently than men. We therefore sought to evaluate sex-based differences in clinical outcomes after severe trauma with hemorrhage in patients who received ratio-based damage-control resuscitation. We hypothesized that female sex would confer a protective effect attributable to early hypercoagulability, resulting in decreased mortality and time to hemostasis, and a lower overall transfusion requirement.

Methods

Study design and population

We performed a secondary analysis of the Pragmatic Randomized Optimal Platelet and Plasma Ratio (PROPPR) trial, which was performed from August 3, 2012, to December 2, 2013, under Exception from Informed Consent (EFIC) guidelines and approved by all institutional review boards at participating hospitals.[6] Detailed methods of the trial have been published elsewhere.[30] Severely injured patients with ongoing hemorrhage who were predicted to receive a massive transfusion and admitted to 1 of 12 level I North American trauma centers were prospectively randomized to either a 1:1:1 or 1:1:2 ratio of plasma to platelets to RBCs. Eligibility criteria included transfusion of at least 1 unit of blood component during prehospital transport or the first hour of arrival, but not more than 2 units before randomization. All transfusions during active hemorrhage were per ratio-based protocol. After hemostasis was achieved, further transfusions were guided per normal institutional practices, including laboratory values and clinical judgment.

Outcomes

Our primary outcome was 24-hour mortality. Secondary outcomes included 30-day mortality, time to hemostasis, and number and type of transfused blood products in the time from randomization until hemostasis was achieved (prehemostasis period) and the number and type of blood products used after hemostasis was achieved up to 24-hours postadmission (posthemostasis period). Anatomic hemostasis was defined as control of surgical bleeding in the operating room or resolution of contrast blush in the interventional radiology suite per the attending surgeon and confirmed by no further transfusions during the next 2 hours. Massive transfusion was defined as requiring 10 or more units of blood within 24 hours, and the Critical Administration Threshold (CAT) required the receipt of at least three units of blood within the first hour of admission.[31] Descriptive statistics were used to analyze additional outcomes including death owing to exsanguination at 24 hours and 30 days and adverse events.

Statistical analysis

Baseline demographic, physiologic, and biochemical information; Injury Severity Score (ISS); Abbreviated Injury Score (AIS); time of death; time to hemostasis; and units of plasma, platelets, and RBCs given in the prerandomization, prehemostasis, and posthemostasis periods were obtained. Descriptive statistics were expressed as frequencies and percentages for categorical variables and as medians and interquartile ranges (IQRs) for quantitative variables.

We used Cox regression to evaluate the sex-based differences in mortality and time to hemostasis and presented results as hazard ratios with 95% confidence intervals. Poisson regression with robust standard errors was used to evaluate differences in blood products transfused with results presented as mean ratios and 95% confidence intervals. For all multivariable models, covariates were selected a priori based on clinical relevance. All analyses included age; sex; race; weight; height; mechanism of injury; base deficit; international normalized ratio (INR); AIS head, chest, abdomen, extremities, external, face, and neck; transfusion arm (1:1:1 vs 1:1:2); and study center. For model covariates with missing data (height, weight, INR, and base deficit) multiple imputation (MI) was performed using the multivariable imputation by chained equations (MICE) with 20 imputed data sets from predictive mean matching, using the same covariates as in the fitted models.[32]

Several sensitivity analyses were performed to assess robustness of the results to model assumptions. These included comparisons of multiple imputation analyses to available-case analyses that ignored missing data, comparisons of models with random effects versus fixed effects for sites, and comparison of analyses with versus without adjustment for covariates. Results of all sensitivity analyses were similar to those presented. To assess for effect modification by sex, we performed additional analyses separately to assess interaction terms for sex with treatment arm and interactions between sex with age >50 years (a surrogate for postmenopausal status) for all primary outcomes and all blood product variables. Results were presented with estimates and 95% confidence intervals (CIs) from adjusted analyses, and statistical significance was assessed using 2-sided tests at a significance level $P \leq .05$ for all analyses. Statistical analyses were performed using R v3.3.2 (R, Vienna, Austria) including the packages "metaphor," "survival," "mice," "sandwich," and "lmtest."[33]

Results

A total of 680 patients were analyzed, of which there were 546 men (80%) and 134 women (20%). Demographics, baseline physiologic, and coagulation (thromboelastography [TEG]) data are presented in Table I. Compared with men, women were older, with an overall higher Injury Severity Score (F: 29 [21–41] vs M: 26 [16–38]), higher proportion of severe head injury with AIS $\geq$ 3 (F: 44 [33%] vs M: 109 [20%]), and lower initial hemoglobin (F: 10.4 [8.4–12.1] vs M: 12.1 [10.6–13.5]). Expected differences included greater height and weight for men compared with women. Of the subset of patients with TEG measures, there were no significant differences in initial TEG r-time, k-time, alpha angle or maximum amplitude between men and women.

We observed no difference in mortality at 24 hours or 30 days or in time to hemostasis by sex (Table II). The proportion of deaths attributable to exsanguination at 24 hours was the same in the overall male and female cohorts (M: 12% vs F: 12%). Similar proportions of men and women required massive transfusion or met the Critical Administration Threshold. Similarly, total

Table I
Baseline characteristics of patients enrolled in the PROPPR trial by sex and randomized treatment arm ($N = 680$)

Characteristic	Men			Women		
	Overall ($N = 546$)	1:1:1 Arm ($N = 263$)	1:1:2 Arm ($N = 283$)	Overall ($N = 134$)	1:1:1 Arm ($N = 75$)	1:1:2 Arm ($N = 59$)
Age, years, median (IQR)	33 (24–47)	33 (24–47)	34 (34–47)	41 (26–60)	46 (28–62)	34 (23–57)
Race, *n* (%)						
White	334 (61%)	155 (59%)	179 (63%)	100 (75%)	55 (73%)	45 (76%)
Black	167 (31%)	84 (32%)	83 (29%)	20 (15%)	10 (13%)	10 (17%)
Other	46 (8%)	25 (10%)	21 (7%)	14 (10%)	10 (13%)	4 (7%)
Hispanic Ethnicity, *n* (%)	91 (17%)	43 (16%)	48 (17%)	29 (22%)	18 (24%)	11 (19%)
Weight, kg, median (IQR) [$N = 605$]	81.7 (72.7–95.3)	80 (72.6–95)	84 (73.9–98.5)	69.6 (60–81.7)	70 (59–82.2)	68.8 (61.1–81.7)
Height, m, median (IQR) [$N = 586$]	1.78 (1.73–1.83)	1.78 (1.73–1.83)	1.78 (1.73–1.83)	1.65 (1.62–1.68)	1.63 (1.61–1.67)	1.65 (1.62–1.70)
Blunt mechanism, *n* (%)	256 (47%)	124 (47%)	132 (47%)	102 (76%)	61 (81%)	41 (69%)
ISS, median (IQR)	26 (16–38)	25 (16–38)	26 (17–38)	29 (21–41)	34 (22–45)	27 (20–34)
AIS head $\geq$ 3, *n* (%)	109 (20%)	46 (17%)	63 (22%)	44 (33%)	25 (33%)	19 (32%)
AIS chest $\geq$ 3, *n* (%)	329 (60%)	143 (54%)	186 (66%)	84 (63%)	46 (61%)	38 (64%)
AIS abdomen $\geq$ 3, *n* (%)	274 (50%)	138 (52%)	136 (48%)	66 (49%)	43 (57%)	23 (39%)
AIS extremities $\geq$ 3, *n* (%)	274 (50%)	138 (52%)	136 (48%)	66 (49%)	43 (57%)	23 (39%)
Systolic blood pressure $\leq$ 90, *n* (%) [N = 658]	205 (39%)	98 (38%)	107 (39%)	50 (39%)	29 (40%)	21 (38%)
Pulse $\geq$ 120, *n* (%) [$N = 677$]	242 (44%)	120 (46%)	122 (43%)	58 (44%)	28 (38%)	30 (51%)
Respiratory rate/minutes, median (IQR) [$N = 621$]	21 (18–26)	20 (17–27)	21 (18–26)	20 (16–24)	20 (18–25)	20 (16–24)
Hemoglobin, g/dL, median (IQR) [$N = 652$]	12.1 (10.6–13.5)	12.1 (10.7–13.5)	12.1 (10.5–13.6)	10.4 (8.4–12.1)	10.3 (8.2–12)	10.4 (8.6–12.2)
INR, ratio, median (IQR) [$N = 436$]	1.3 (1.18–1.52)	1.22 (1.15–1.51)	1.3 (1.2–1.52)	1.3 (1.17–1.62)	1.3 (1.17–1.6)	1.29 (1.17–1.72)
Platelets, median (IQR) [$N = 634$]	211 (165–256)	212 (168–255)	209 (165–259)	222 (154–295)	215 (154–287)	235 (159–298)
Base excess, mmol/L, median (IQR) [$N = 619$]	−8 (−12.3 to −4)	−7.9 (−12.2 to −3.7)	−8.4 (−12.8 to −4.4)	−8.9 (−14 to −5.2)	−8.9 (−14.7 to −4.9)	−8.8 (−12.8 to −5.9)
Base excess $\leq$ −4, *n* (%) [$N = 619$]	380 (76%)	183 (74%)	197 (79%)	97 (80%)	55 (79%)	42 (82%)
TEG R-time, minutes, median (IQR) [$N = 555$]	3.8 (2.9–4.7)	3.8 (2.9–4.7)	3.7 (2.8–4.7)	3.9 (2.8–4.7)	3.8 (2.8–4.4)	4.1 (2.8–4.9)
TEG K-Time, minutes, median (IQR) [$N = 529$]	1.5 (1.2–2)	1.4 (1.2–1.9)	1.6 (1.2–2.1)	1.3 (1–1.8)	1.2 (1–1.8)	1.6 (1.2–2)
TEG alpha angle, %, median (IQR) [$N = 548$]	70.1 (63.6–74.3)	71.2 (65.6–74.6)	69.3 (62.9–73.5)	70.3 (65.7–74.8)	71.7 (67.4–75.5)	68.5 (64.4–72.4)
TEG maximum amplitude, mm, median (IQR) [$N = 549$]	60.4 (54.3–64.8)	61.5 (55.8–65.1)	59.5 (52.1–64.3)	61.1 (51.7–67.6)	61.9 (53.5–68.8)	59.2 (47.7–66.8)
TEG LY-30, %, median (IQR) [$N = 547$]	0.3 (0–2.1)	0.3 (0–1.9)	0.5 (0–2.3)	0.3 (0–3.0)	0.2 (0–4.1)	0.5 (0–1.9)

ISS, injury severity score.
Note: Sample sizes for each variable are equal to 680 unless noted in square brackets [*N*].

volumes of blood products in the prerandomization, prehemostasis, and posthemostasis periods did not differ by sex. We also examined prespecified thrombosis-related complications, including deep vein thrombosis, symptomatic and asymptomatic pulmonary embolism, and stroke and found no differences between sexes.

When transfused blood volumes were analyzed by sex and transfusion arm in unadjusted analysis, there were no significant differences between men and women in the prehemostasis period. However, in the posthemostasis period—after anatomic hemostasis was achieved and patients were not transfused per study protocol—men in the 1:1:2 transfusion arm received significantly higher volumes of platelets and packed RBCs compared with women in the 1:1:2 arm (Fig 1). Men in the 1:1:2 group also received significantly more platelets in the posthemostasis period than men in the 1:1:1 group (mean 3.95 units, standard deviation [SD] 7.7 vs 2.01 units, SD 4.9, $P < .001$), whereas there was no difference posthemostasis platelet volume across treatment groups for women (1:1:2 mean 2.38 units, SD 4.0 vs 1:1:1 2.12, units, SD 3.4, $P = .71$). This suggests that, although men in the low-transfusion ratio group required more platelets after anatomic hemostasis had been achieved compared with men in the high-transfusion ratio group, women did not demonstrate this difference in need across transfusion arms. However, this result must be interpreted with caution because the interactions between sex and treatment arm were not statistically significant.

In multivariable analysis, sex was not significantly associated with 24-hour mortality (HR 0.64, 95% CI 0.34–1.19, $P = .16$) or 30-day mortality (HR 0.75, 95% CI 0.47–1.20, $P = .23$) or time to hemostasis (HR 1.10, 95% CI 0.84–1.42, $P = .49$) after adjusting for treatment arm and relevant patient and injury characteristics (Fig 2, *A*). Sex was similarly not associated with volume of blood products transfused in the prerandomization or prehemostasis periods in adjusted analysis. However, in the posthemostasis period, female sex was independently associated with a 38% reduction in fresh frozen plasma (mean ratio [MR] 0.62 (95% CI 0.43–0.89, $P = .01$), 49% reduction in platelets (MR 0.51, 95% CI 0.34–0.76, $P < .01$), and 49% reduction in volume of RBCs (MR 0.51, 95% CI 0.33–0.79, $P < .01$) transfused (Fig 2, *B*). We observed no significant interaction effect between sex and treatment arm or sex and age >50 years for any outcome investigated. Full model results available as Supplementary Tables (S1–S6).

Finally, we examined coagulation profiles for separate TEG measures (r-time, k-time, alpha angle, maximum amplitude, and LY-30) throughout the study period and found similar values for women and men across multiple time points.

Discussion

In this analysis of severely injured patients with hemorrhage who received ratio-based DCR, we found no difference between women and men in mortality or time to hemostasis after

Table II
Outcomes by sex and randomized treatment arm for patients enrolled in the PROPPR trial ($N = 680$)

Characteristic	Men			Women		
	Overall ($N = 546$)	1:1:1 Arm ($N = 263$)	1:1:2 Arm ($N = 283$)	Overall ($N = 134$)	1:1:1 Arm ($N = 75$)	1:1:2 Arm ($N = 59$)
24-hour mortality, *n* (%)	77 (14%)	30 (11%)	47 (17%)	23 (17%)	12 (16%)	11 (19%)
30-day mortality, *n* (%)	124 (23%)	51 (20%)	73 (26%)	40 (30%)	24 (32%)	16 (27%)
24-hour exsanguination, *n* (%)	65 (12%)	22 (8.4%)	43 (15%)	16 (12%)	9 (12%)	7 (12%)
30-day exsanguination, *n* (%)	68 (13%)	25 (9.6%)	43 (15%)	18 (13%)	11 (15%)	7 (12%)
Achieved hemostasis, *n* (%)	447 (82%)	227 (86%)	220 (78%)	110 (82%)	64 (85%)	46 (78%)
Time to hemostasis, minutes, median (IQR)	136 (93–208.5)	143 (95–206.5)	128.5 (90–209.2)	146.5 (94–244.8)	153 (102–247.5)	137.5 (89–227.8)
Massive transfusion, *n* (%)	216 (40%)	98 (37%)	118 (42%)	53 (40%)	35 (47%)	18 (31%)
Critical administration threshold, *n* (%) [$N = 678$]	481 (88%)	219 (84%)	262 (93%)	114 (85%)	62 (83%)	52 (88%)
Prerandomization plasma, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Prerandomization platelets, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Prerandomization RBC, median (IQR)	2 (1–2)	2 (1–2)	2 (1–2)	2 (1–3)	2 (2–3)	2 (1–2)
Pre-hemostasis plasma, median (IQR)	3 (2–8)	5 (2–9)	3 (1–6.5)	3.5 (2–7)	5 (2–14)	3 (1–5)
Pre-hemostasis platelets, median (IQR)	6 (0–12)	6 (6–12)	6 (0–6)	6 (6–12)	6 (6–18)	6 (0–6)
Pre-hemostasis RBC, median (IQR)	6 (3–12)	5 (2–10)	6 (4–13.5)	6 (3–11)	6 (3–13.5)	6 (3–9.5)
Posthemostasis plasma, median (IQR)	0 (0–2)	0 (0–2)	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–4)
Posthemostasis platelets, median (IQR)	0 (0–6)	0 (0–0)	0 (0–6)	0 (0–6)	0 (0–6)	0 (0–6)
Posthemostasis RBC, median (IQR)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)

Note: Samples sizes are equal to 680 for 24-hour mortality and hemostasis, 676 for 30-day mortality and 30-day exsanguination, 621 for posthemostasis blood product variables, and 557 for time to hemostasis.

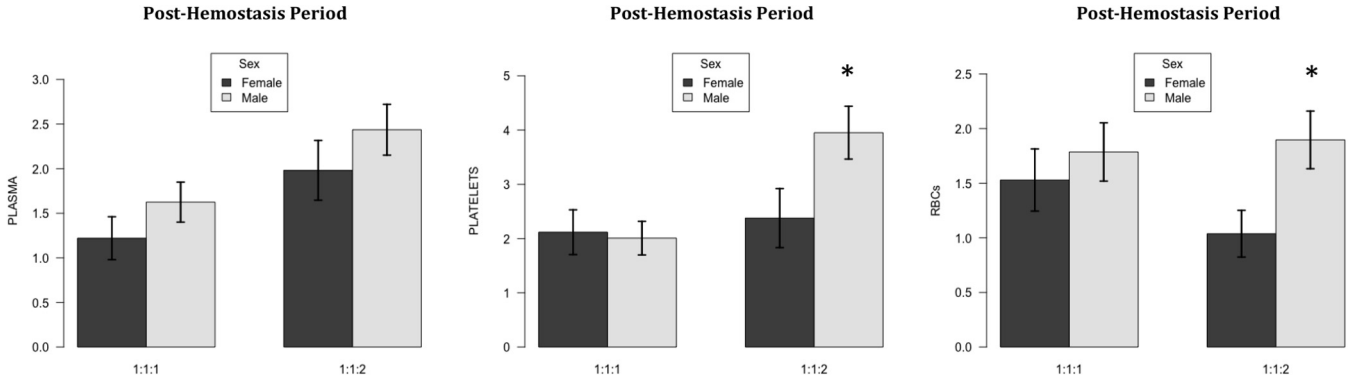

Fig 1. Mean units of blood products by sex and treatment arm for the posthemostasis period. $^{*}P < .05$ between men and women within transfusion arm.

accounting for patient characteristics and transfusion ratio. Blood product requirement also did not differ between sexes during the period of on-protocol resuscitation. However, once anatomic hemostasis had been achieved, women received significantly fewer units of all blood products than men. These results suggest that although women and men did not react differently during the time of acute hemorrhage, there may still be physiologic differences between sexes that become clinically relevant after initial hemostasis is achieved.

Numerous efforts have been made to assess the effect of sex on clinical outcomes after traumatic injury, with most suggesting favorable outcomes for women. In one of the largest studies of patients with severe trauma with hypotension, Haider et al[21] found lower mortality in hormonally active women 13 to 64 years of age compared with men and postmenopausal women. Similarly, Trentzsch et al[27] in their analysis of 3,887 matched pairs of severely injured trauma patients found women to have both lower mortality and lower rate of multiple organ failure and sepsis. Other retrospective studies found no difference in mortality, but lower rates or less severe morbidity in women compared with men.[23,26,34] Although few studies considered transfusion requirement, Deitch et al[25] in their analysis of 4,106 major trauma patients found premenopausal women to receive less blood than male patients. Although these studies benefit from large sample sizes, they represent heterogeneous patient populations with respect to injury severity and have limited information on transfusion and resuscitation strategy—notably, nearly all analyzed data from before the advent of DCR.

In recent years, attention has turned to evaluating sex-based differences in coagulopathy after trauma. Early studies using TEG to evaluate baseline differences in coagulopathy found female sex to be associated with increased measures of whole blood coagulability.[35,36] Female trauma patients have since been shown to be more hypercoagulable than men within the first 24 hours after trauma, but without an apparent difference in transfusion requirements.[28,29] Brown et al[37] specifically examined coagulopathic trauma patients with an admission INR of $\geq$1.5 and found women to have a twofold higher risk of mortality with similar risk of multiple-organ failure as male patients, suggesting that any protective effect of female sex is negated when acute traumatic coagulopathy is present. Finally, Rowell et al[38] examined sex-based differences in response to high (1:1) and low (1:2) transfusion ratios in massively transfused trauma patients and found no mortality benefit in women receiving high transfusion ratios, which is in contrast to men who exhibited improved survival in the high-ratio group. These authors questioned whether women may not experience the same benefit from high-ratio resuscitation as men because of underlying differences in coagulation profile.

Our study builds on this body of literature by specifically considering patients with severe hemorrhage who were managed

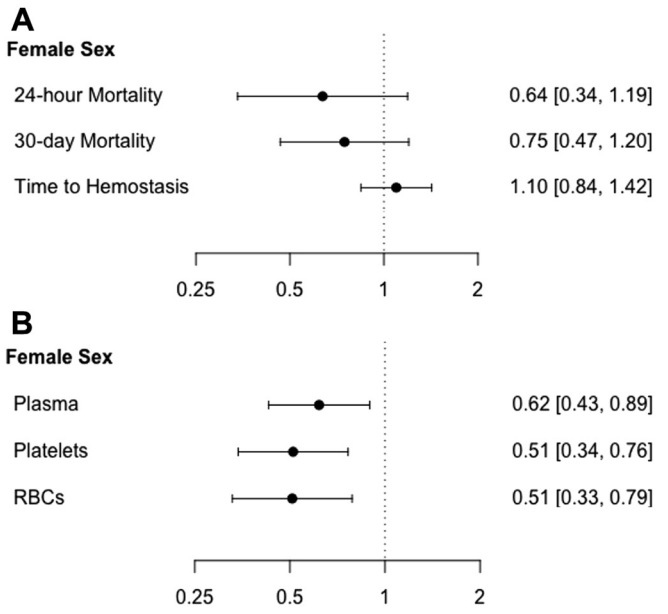

Fig 2. (*A*) Hazard ratio for clinical outcomes: female sex. Model adjusted for age; sex; race; weight; height; mechanism of injury; base deficit; INR; AIS head, chest, abdomen, extremities, external, face, and neck; and transfusion arm (1:1:1 vs 1:1:2). (*B*) Mean ratios for posthemostasis period blood transfusion volume: female sex. Model adjusted for age; sex; race; weight; height; mechanism of injury; base deficit; INR; AIS head, chest, abdomen, extremities, external, face, and neck; and transfusion arm (1:1:1 vs 1:1:2).

with modern DCR strategy and protocolized ratio-based blood product transfusion. Because of the design of the PROPPR trial, we were able to independently assess blood product use during the time of active hemorrhage and the hours after hemostasis, in addition to standard clinical outcome measures, such as mortality and major morbidity. In contrast to studies from the pre-DCR era, we found no differences between sexes regarding rate of mortality or major morbidity. Similarly, there was no difference between women and men in transfusion requirement for any blood component during the intervention phase of the study, before hemostasis. One potential explanation for these findings is that severe, active hemorrhage might negate any mild or moderate protective effect of early hypercoagulability in women. Alternatively, DCR strategy, with its early administration of plasma and platelets, might compensate for the differences in coagulopathy between men and women, resulting in comparable outcomes between the sexes during acute hemorrhage.

Given these results, we were surprised to find a significant difference in transfusion volume of all three blood components in the posthemostasis period, with women receiving nearly 50% less product than men. Approximately 75% of patients achieved hemostasis within the first 3 hours after admission. Consequently, the posthemostasis period still predominantly took place during the first 24 hours postadmission, when earlier studies have shown women to be more hypercoagulable after trauma. Our analysis suggests that the period immediately after initial hemostasis may be distinct from that of ongoing severe hemorrhage. Nevertheless, because of overall small sample size and significant missing TEG data at multiple time points throughout the study (eg, approximately 20% of patients were missing baseline TEG data), we were unable to demonstrate the differences in coagulopathy between men and women that have been consistently demonstrated elsewhere in the literature. Specifically, we were unable to directly evaluate differences in TEG values between men and women in the posthemostasis period.

Despite the differences in posthemostasis transfusion requirement, we cannot conclude based on this analysis that women should be managed with a different transfusion strategy than men in the setting of trauma-related hemorrhage. A greater proportion of the 1:1:1 group in both female and male cohorts attained hemostasis, compared with the 1:1:2 arm. Interestingly, although fewer deaths occurred from exsanguination at 24 hours with the 1:1:1 transfusion in men, there was no appreciable difference between transfusion arms in women. Because of the low number of events in the female cohort, we cannot definitively conclude that the two transfusion strategies are equivalent in women; however, this does lend support to the hypothesis of Rowell et al[38] that women may not benefit from a high transfusion ratio in the same manner as men. Similar to the main PROPPR trial, we found no increase in thrombotic complications in women managed with a high-ratio transfusion strategy, suggesting a high-ratio resuscitation protocol is also safe for women. Given the lower blood products transfused during the posthemostasis period, it may be reasonable to consider sex-specific monitoring and resuscitation protocols during this time frame.

This study must be interpreted in the context of its limitations. This is a secondary analysis of a randomized controlled trial that was not designed to address the specific questions investigated here. Women accounted for only 20% of the study population, with just 54 individuals older than 50 years of age, which limited our power to detect differences between sexes, transfusion arms, and premenopausal and postmenopausal women. Nevertheless, this population size is in line with other contemporary studies of ratio-based resuscitation.[38] We acknowledge that inherent differences between women and men—particularly body mass and blood volume—may contribute to differences in response to resuscitation with similar volume of blood product. We attempted to control for these differences by including height and weight in the model, which has been found to perform similarly to other models of body surface area.[39] Women and men tend to have different patterns of injuries and different treatment needs, which we also attempted to account for by including mechanism and all body region AIS scores in our model. Specifically, women had a higher proportion of severe head injury, and therefore head AIS was used to control for this. Nevertheless, unmeasured confounders may still remain. Because this was a pragmatic trial, transfusion during the posthemostasis period was not protocolized and driven by usual institutional practices, which introduces room for provider bias during this time frame.

Finally, there was considerable variation in the timing of TEG measurements, with a substantial number of patients missing TEG values before randomization. This limited our ability to reliably assess sex-based differences in the coagulation profile, particularly during ongoing hemorrhage, and may account for our inability to detect the early hypercoagulability of women identified in other studies.

Despite these issues, our study benefits from using data from a well-designed, multicenter randomized control trial, specifically considering critically ill trauma patients with ongoing hemorrhage. There was a high degree of compliance with protocol in the original study and complete follow-up in all but 4 patients at 30 days. Because of the design of the trial, we were also able to separate transfusion requirements during ongoing hemorrhage from that after hemostasis was achieved. Commonly used large data sets, such as the National Trauma Database, typically do not contain this level of detail regarding timing of hemostasis and product transfusion, making the PROPPR trial one of the best data sets currently available to answer this question.

The physiologic mechanisms underlying the response to injury are complex, and further sex-specific research is required to more fully understand sex-based differences in outcomes after severe trauma, particularly in the setting of modern resuscitation practice.[40] Such efforts will require rigorous methodology, including consideration of the effect of sex hormones and X-linked genetic

polymorphisms on measures of coagulation. Our study suggests that, although sex-based differences may not be clinically apparent during times of massive hemorrhage, women may exhibit important differences in coagulation during the period immediately after hemostasis, and consideration should be given to identifying optimal management strategies for female trauma patients receiving massive transfusion. Prospective, multicenter studies will be required to accrue enough female patients to achieve this goal.

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Disclosure

The opinions or conclusions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of any sponsor. This manuscript has been reviewed by the PROPPR Publication Committee for scientific content and consistency of data interpretation with previous PROPPR publications.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.surg.2018.12.023.

References

1. Centers for Disease Control and Prevention NCfIPaC. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control: Key injury and violence data Web site. https://www.cdc.gov/injury/wisqars/overview/key_data.html. Accessed March 6, 2018.
2. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: Directly addressing the early coagulopathy of trauma. *J Trauma*. 2007;62:307–310.
3. Cotton BA, Gunter OL, Isbell J, et al. Damage control hematology: The impact of a trauma exsanguination protocol on survival and blood product utilization. *J Trauma*. 2008;64:1177–1182; discussion 1182–1183.
4. Cotton BA, Reddy N, Hatch QM, et al. Damage control resuscitation is associated with a reduction in resuscitation volumes and improvement in survival in 390 damage control laparotomy patients. *Ann Surg*. 2011;254:598–605.
5. Holcomb JB, del Junco DJ, Fox EE, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: Comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg*. 2013;148:127–136.
6. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: The PROPPR randomized clinical trial. *JAMA*. 2015;313:471–482.
7. Sperry JL, Ochoa JB, Gunn SR, et al. An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma*. 2008;65:986–993.
8. Brown LM, Aro SO, Cohen MJ, et al. A high fresh frozen plasma: Packed red blood cell transfusion ratio decreases mortality in all massively transfused trauma patients regardless of admission international normalized ratio. *J Trauma*. 2011;71(2 Suppl 3):S358–S363.
9. Mansukhani NA, Yoon DY, Teter KA, et al. Determining if sex bias exists in human surgical clinical research. *JAMA Surg*. 2016;151:1022–1030.
10. Yoon DY, Mansukhani NA, Stubbs VC, Helenowski IB, Woodruff TK, Kibbe MR. Sex bias exists in basic science and translational surgical research. *Surgery*. 2014;156:508–516.
11. Meinert CL, Gilpin AK, Unalp A, Dawson C. Gender representation in trials. *Control Clin Trials*. 2000;21:462–475.
12. Blauwet LA, Hayes SN, McManus D, Redberg RF, Walsh MN. Low rate of sex-specific result reporting in cardiovascular trials. *Mayo Clin Proc*. 2007;82:166–170.
13. Hettrich CM, Hammoud S, LaMont LE, Arendt EA, Hannafin JA. Sex-specific analysis of data in high-impact orthopaedic journals: How are we doing? *Clin Orthop Relat Res*. 2015;473:3700–3704.
14. DiMaggio C, Ayoung-Chee P, Shinseki M, et al. Traumatic injury in the United States: In-patient epidemiology 2000–2011. *Injury*. 2016;47:1393–1403.
15. Borse NN, Gilchrist J, Dellinger AM, Rudd RA, Ballesteros MF, Sleet DA. *CDC Childhood Injury Report: Patterns of Unintentional Injuries among 0-19 Year Olds in the United States, 2000-2006*. Atlanta GA: Centers for Disease Control and Prevention; 2008.
16. Sorenson SB. Gender disparities in injury mortality: Consistent, persistent, and larger than you'd think. *Am J Public Health*. 2011;101(Suppl 1):S353–S358.
17. SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med*. 2007;357:874–884.
18. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med*. 2016;375:1119–1130.
19. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): A randomised, placebo-controlled trial. *Lancet*. 2010;376:23–32.
20. Croce MA, Fabian TC, Malhotra AK, Bee TK, Miller PR. Does gender difference influence outcome? *J Trauma*. 2002;53:889–894.
21. Haider AH, Crompton JG, Chang DC, et al. Evidence of hormonal basis for improved survival among females with trauma-associated shock: An analysis of the National Trauma Data Bank. *J Trauma*. 2010;69:537–540.
22. Haider AH, Crompton JG, Oyetunji T, et al. Females have fewer complications and lower mortality following trauma than similarly injured males: A risk adjusted analysis of adults in the National Trauma Data Bank. *Surgery*. 2009;146:308–315.
23. Napolitano LM, Greco ME, Rodriguez A, Kufera JA, West RS, Scalea TM. Gender differences in adverse outcomes after blunt trauma. *J Trauma*. 2001;50:274–280.
24. Mostafa G, Huynh T, Sing RF, Miles WS, Norton HJ, Thomason MH. Gender-related outcomes in trauma. *J Trauma*. 2002;53:430–434; discussion 434–435.
25. Deitch EA, Livingston DH, Lavery RF, Monaghan SF, Bongu A, Machiedo GW. Hormonally active women tolerate shock-trauma better than do men: A prospective study of over 4000 trauma patients. *Ann Surg*. 2007;246:447–453; discussion 453–455.
26. Magnotti LJ, Fischer PE, Zarzaur BL, Fabian TC, Croce MA. Impact of gender on outcomes after blunt injury: A definitive analysis of more than 36,000 trauma patients. *J Am Coll Surg*. 2008;206:984–991; discussion 991–992.
27. Trentzsch H, Lefering R, Nienaber U, Kraft R, Faist E, Piltz S. The role of biological sex in severely traumatized patients on outcomes: A matched-pair analysis. *Ann Surg*. 2015;261:774–780.
28. Pommerening MJ, Schwartz DA, Cohen MJ, et al. Hypercoagulability after injury in premenopausal females: A prospective, multicenter study. *Surgery*. 2014;156:439–447.
29. Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ. Hypercoagulability is most prevalent early after injury and in female patients. *J Trauma*. 2005;58:475–481.
30. Baraniuk S, Tilley BC, del Junco DJ, et al. Pragmatic randomized optimal platelet and plasma ratios (PROPPR) trial: Design, rationale and implementation. *Injury*. 2014;45:1287–1295.
31. Savage SA, Sumislawski JJ, Zarzaur BL, Dutton WP, Croce MA, Fabian TC. The new metric to define large-volume hemorrhage: Results of a prospective study of the critical administration threshold. *J Trauma Acute Care Surg*. 2015;78:224–229; discussion 229–230.
32. van Buuren S, Groothuis-Oudshoorn K. MICE: Multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45:1–67.
33. Team RC. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, Web site. https://www.R-project.org/. Accessed February 9, 2018.
34. Lopez MC, Efron PA, Ozrazgat-Baslanti T, et al. Sex-based differences in the genomic response, innate immunity, organ dysfunction, and clinical outcomes after severe blunt traumatic injury and hemorrhagic shock. *J Trauma Acute Care Surg*. 2016;81:478–485.
35. Gorton HJ, Warren ER, Simpson NA, Lyons GR, Columb MO. Thromboelastography identifies sex-related differences in coagulation. *Anesth Analg*. 2000;91:1279–1281.
36. Roeloffzen WW, Kluin-Nelemans HC, Mulder AB, Veeger NJ, Bosman L, de Wolf JT. In normal controls, both age and gender affect coagulability as measured by thrombelastography. *Anesth Analg*. 2010;110:987–994.
37. Brown JB, Cohen MJ, Minei JP, et al. Characterization of acute coagulopathy and sexual dimorphism after injury: Females and coagulopathy just do not mix. *J Trauma Acute Care Surg*. 2012;73:1395–1400.
38. Rowell SE, Barbosa RR, Allison CE, et al. Gender-based differences in mortality in response to high product ratio massive transfusion. *J Trauma*. 2011;71(2 Suppl 3):S375–S379.
39. Man L, Tahhan HR. Body surface area: A predictor of response to red blood cell transfusion. *J Blood Med*. 2016;7:199–204.
40. Sethuraman KN, Marcolini EG, McCunn M, Hansoti B, Vaca FE, Napolitano LM. Gender-specific issues in traumatic injury and resuscitation: Consensus-based recommendations for future research. *Acad Emerg Med*. 2014;21:1386–1394.