The Journal of Maternal-Fetal & Neonatal Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ijmf20

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To cite this article: Jessian L. Munoz, Alison M. Kimura, Elly Xenakis, Donald H. Jenkins, Maxwell A. Braverman, Patrick S. Ramsey & Kayla E. Ireland (2022) Whole blood transfusion reduces overall component transfusion in cases of placenta accreta spectrum: a pilot program, The Journal of Maternal-Fetal & Neonatal Medicine, 35:25, 6455-6460, DOI: 10.1080/14767058.2021.1915275

To link to this article: https://doi.org/10.1080/14767058.2021.1915275

Published online: 26 Apr 2021.

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE
2022, VOL. 35, NO. 25, 6455–6460
https://doi.org/10.1080/14767058.2021.1915275

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ORIGINAL ARTICLE

Whole blood transfusion reduces overall component transfusion in cases of placenta accreta spectrum: a pilot program

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ABSTRACT

Objective: Placenta accreta spectrum (PAS) is a group of placental invasion pathologies associated with significant morbidity to both mother and fetus. The majority of patients with PAS will require a blood transfusion at time of delivery and subsequent cesarean hysterectomy. The optimal approach to maternal acute blood loss resuscitation is currently unknown.

Methods: Here, we present a cohort analysis of 34 patients with pathology-confirmed PAS treated with either whole blood ($n = 16$) or component therapy ($n = 18$) for initial intraoperative resuscitation.

Results: We observed comparable results in post-operative outcomes with fewer overall transfusions and subsequently, lower volumes of resuscitation (p=.03) with whole blood initial resuscitation.

Conclusions: Whole blood transfusion may represent a viable option for initial resuscitation with lower resuscitation volumes and transfusion-associated complications without directly effecting post-operative outcomes in cases of PAS.

ARTICLE HISTORY
Received 12 February 2021
Revised 2 April 2021
Accepted 7 April 2021

KEYWORDS
Placenta accreta; whole blood; blood transfusion; cesarean hysterectomy; abnormal placentation

Introduction

Placenta accreta spectrum (PAS) represents a continuum of placental invasive disorders characterized by severe maternal morbidity and mortality [1]. PAS is associated with increased risk of intensive care unit (ICU) admission, genitourinary tract injury, hysterectomy, prolonged hospital admission, and massive blood transfusion. Transfusion of blood products occurs in up to 70–80% of cases, in response to the often-life-threatening hemorrhage associated with PAS [2]. It is recommended that tertiary centers for the care of PAS cases have established capabilities for massive transfusion and associated protocols [3]. The most common protocols for blood transfusion involve infusion of multiple blood products or components in varying ratios. Recommendations for ideal blood product replacement in obstetric patients have been limited to consensus opinion, protocols adapted from trauma literature and case series [4]. Alternatively, the utility of whole blood transfusion for obstetric hemorrhage has been previously described [5].

Whole blood transfusion was initially employed by the military during World War II with a notable increase in battlefield survival when compared to blood product component transfusion [6]. Since then, whole blood has become key in trauma resuscitation in the setting of civilian hemorrhage [7–9]. When compared to whole blood, component therapy provides a diluted form of blood secondary to multiple preservatives with greater transfusion volumes for patients. In obstetrics, universal transfusion with whole blood has not been recommended or adopted due to a lack of research supporting its utility. With respect to PAS, case reports and small series of whole blood transfusion for PAS cases have been published [10,11].

In 2018, the University Hospital System/University of Texas Center for Placenta Accreta Spectrum initiated a protocol for the utilization of whole blood for suspected cases of PAS at our institution. Within our protocol, patients with antenatally suspected PAS are initially transfused with whole blood and further resuscitative needs default to traditional component transfusion. Our objective for this study was to report the

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post-operative outcomes of patients who underwent this tiered transfusion protocol for maternal hemorrhage during PAS surgical management.

Materials and methods

Study design and population

We conducted a prospective observational cohort of women who presented to the University Hospital System/University of Texas Center for Placenta Accreta Spectrum program between November 2018 and October 2020. Institutional review board (IRB) approval was obtained from the University of Texas Health San Antonio and University Hospital System prior to obtaining cohort information. Inclusion criteria included maternal age between 18 and 55 years with a viable pregnancy and antenatal suspicion for PAS by sonographic findings, MRI or increased *a priori* risk based on maternal comorbidities such as presence of previa and multiple prior cesarean sections. Exclusion criteria were the following: fetal death and associated fatal congenital anomalies. In addition, since store whole blood is group O with low titers of anti-A and anti-B antibodies (per transfusion medicine protocol) patients were ineligible for whole blood transfusion if they were known Rh negative or had a positive antibody screen.

Low titer cold-stored O RhD positive whole blood (LTO + WB) is utilized for eligible females that are RhD positive with a negative antibody screen. The LTO + WB donor population is tested for anti-A/anti-B IgM agglutinin and must have a titer of <1:256 to reduce the risk of hemolysis in non-O blood group recipients. IgG agglutinin titers are not tested. To reduce the frequency and risk of transfusion-related acute lung injury (TRALI), we exclude high risk multiparous female donors and collect units from male donors. All the LTO + WB units are collected in citrate phosphate dextrose adenine (CPDA-1) anticoagulant with a 35-day expiration. To preserve platelet function within the units, the units are not leukoreduced and platelet function is adequate for 14–21 days of expiration.

In 2015, we established the University Hospital System/University of Texas Center for Placenta Accreta Spectrum to provide a protocol-driven multidisciplinary approach to the management of PAS cases in south central Texas. According to our protocols, patients were managed by a multidisciplinary team including maternal-fetal medicine, urology, gynecologic oncology, blood bank, interventional radiology, and trauma surgery. Final diagnosis of PAS is determined by a board-certified pathologist with expertise in gynecology.

With respect to blood product management, patients either underwent routine component transfusion or whole blood transfusion. Up to 4 units of whole blood were allotted for each scheduled delivery, following the usage of these, any additional blood product transfusion followed the component protocol. Four units of whole blood was chosen during this pilot study in collaboration with transfusion medicine specialists to preserve limited resources during research phase of study. Component transfusion at our institution follows the 1:1:1 red blood cells, platelets, and plasma replacement. Decision for intraoperative blood transfusion was determined by the surgical and anesthesia teams in the event of estimated blood loss (EBL) >1500 ml or changes from baseline vital signs. EBL was determined by the primary surgeon with consideration for collection canisters and operative equipment.

Data were collected and stored using a REDCap electronic data capture tool hosted at the University of Texas Health San Antonio. REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN) is a secure, web-based application designed to support data capture for research studies (https://redcap.vanderbilt.edu).

Study outcomes

Maternal demographic, prenatal, and sonographic information was obtained retrospectively from electronic medical records. Our primary outcome was a maternal surgical morbidity composite including blood product transfusion >4 units, ICU admission, intraoperative acidosis (as determined by intraoperative blood gas analysis), and post-operative length of stay >4 days. In addition, significant morbidity associated with post-operative infection and reoperation was assessed.

Statistical analysis

Sample size analysis was performed to determine the number of subjects required for this study. To detect a 50% reduction with 80% power and a $p=.05$ in maternal composite morbidity with a whole blood transfusion protocol, a total of 32 subjects were required given the reported 89% baseline morbidity experience by PAS subjects [12]. Normal distribution was determined by the Shapiro–Wilk test greater than 0.05. Pearson's chi-square (χ^2), Fisher's exact test, and

Table 1. Demographics of study group.

Factor	Whole blood ($n = 16$)	Component ($n = 18$)	p Value
Age	32.4 ± 5.9	31.3 ± 5.28	.57[a]
BMI	32.1 ± 7.0	34.5 ± 3.8	.23[a]
Gravity	4 (3.5, 5.8)	5 (3.8, 7)	.54[b]
Parity	3 (2, 3)	3.5 (2, 4.3)	.27[b]
History of CD	16 (100)	16 (89)	.49[c]
Number of prior CD	2 (2, 3)	3 (1.8, 4)	.62[b]
Tertiary referral	14 (88)	13 (72)	.41[c]
Gestational age at delivery	34 (31, 34)	34 (25, 34.8)	.70[b]
PAS by ultrasound			
Previa	2 (13)	5 (28)	.41[c]
Accreta	4 (25)	12 (67)	**.02[c]**
Increta	1 (6)	0	.47[c]
Percreta	9 (56)	1 (6)	**.002[c]**
Diabetes	1 (6)	1 (6)	1.0[c]
Hypertension	2 (13)	2 (11)	1.0[c]
Anemia	5 (31)	8 (45)	.18[d]
Emergent delivery	7 (44)	5 (28)	.33[c]
Public insurance	9 (56)	16 (89)	**.05[c]**

BMI: body mass index; CD: cesarean delivery; PAS: placenta accreta spectrum.
Values presented as mean ± SD, median [P25, P75] or *N* (column %).
p Values: [a]*t*-test, [b]Mann–Whitney's test, [c]Fisher's exact test, and [d]chi-squared.
Bold values suggest $p < .05$.

Mann–Whitney's *U* tests were used when appropriate. Categorical factors were summarized using frequencies and percentages, while continuous measures summaries used means ± SD or median and range as appropriate. *p* Values <.05 were considered significant for two-tailed analysis. Statistical analysis was performed using SPSS software (version 26) (SPSS Inc., Chicago, IL).

Results

During the 2-year study period, we evaluated 64 cases of antenatally suspected PAS. Thirty-six of these cases had pathology-confirmed PAS, among these, two did not receive any form of blood transfusion. Thus, 34 PAS cases were assessed and delivered at the University Hospital System/University of Texas Center for Placenta Accreta Spectrum program between November 2018 and October 2020. During this time period, 16 patients (47%) received whole blood for initial hemorrhage resuscitation while 18 patients (53%) received standard blood component resuscitation. While the whole blood transfusion protocol aimed at initial whole blood resuscitation, coordination required prior antepartum admission which was not achievable in all cases, resulting in 18 cases without whole blood initial resuscitation. Table 1 presents the baseline demographics of this population with no significant differences with the incidental exception of public source of insurance (p=.04). The overall distribution of suspected PAS pathologies (as determined by ultrasonography) was significantly different reflecting worsening suspected pathology in the whole blood cohort (p=.002).

Operative characteristics of both study groups are presented in Table 2. No significant differences were noted with respect to operative time, supplemental procedures (uterine artery embolization or urinary stent placement), genitourinary tract injury, development of disseminated coagulopathy, post-operative hemoglobin, or overall length of stay. Overall, the transfusion of blood products such as fresh frozen plasma and total RBC units was significantly reduced (p=.001, p=.003, respectively). Overall transfusion volumes were significantly different between the two groups (2607 ml vs. 4683 ml, p=.03). Thus, whole blood initial resuscitation resulted in a lower volume of transfusion for PAS patients.

No significant difference was noted between the whole blood and component therapy groups with respect to the primary study outcome, nor the individual composite components (Table 3). The number of criteria met within the composite was also not statistically different. Length of stay both in the ICU and overall post-operative were unchanged with use of whole blood. One case of an intra-abdominal abscess was encountered in the component therapy group. No cases of transfusion-associated circulatory overload (TACO) or TRALI were noted.

Discussion

Blood transfusions comprise 2–6% of maternal morbidity nationally [13]. In the setting of PAS, blood transfusion is performed in the overwhelming majority of patients (>70%) secondary to life-threating hemorrhage. The current incidence of PAS ranges from 1:270 to 1:1500 with a time-dependent increase in

Table 2. Operative characteristics.

Factor	Whole blood ($n = 16$)	Component ($n = 18$)	p Value
Admission hemoglobin (g/dl)	10.5 ± 1.5	10.7 ± 1.3	.626[a]
Operative time (min)	319.6 ± 161.1	230.7 ± 128.5	.08[a]
Urinary stent placement	13 (81)	11 (61)	.27[c]
Uterine artery embolization	8 (50)	3 (17)	.076[c]
EBL (ml)	2600 (2000, 4750)	3000 (1875, 5250)	.90[b]
Component transfusion			
Whole blood	3.5 (1.3, 4)	–	–
Red blood cells	0 (0, 2)	4.5 (2, 6.8)	**.003[b]**
Platelets	0 (0, 0.8)	0 (0, 1)	.89[b]
Fresh frozen plasma	0 (0, 3.3)	3 (0, 5)	**.001[b]**
Cryoprecipitate*	0 (0, 0)	0 (0, 0)	.18[b]
Volume transfused (ml)**	2607	4683	**.03[a]**
GU injury	3 (19)	3 (17)	1.0[c]
Intentional cystotomy	3 (19)	3 (17)	1.0[c]
Incidental cystotomy	0	2 (11)	.49[c]
Ureteral injury	1 (6)	0	.47[c]
PAS by Pathology			
Accreta	1 (6)	4 (22)	.34[c]
Increta	3 (19)	3 (17)	1.00[c]
Percreta	12 (75)	11 (61)	.47[c]
Post-operative Hemoglobin (g/dl)	10.3 ± 2.0	10.3 ± 2.4	.98[a]
Post-operative LOS	4 (3, 5.8)	4 (2.8, 5)	.44[b]

EBL: estimated blood loss; GU: genitourinary; PAS: placenta accreta spectrum.
Values presented as mean ± SD, median [P25, P75] or *N* (column %).
p Values: [a]*t*-test, [b]Mann–Whitney's test, and [c]Fisher's exact.
Bold values suggest $p < .05$.
*One patient in each group received cryoprecipitate.
**Utilizing standard transfusion volumes as follows: whole blood (500 ml), red blood cells (350 ml), fresh frozen plasma (300 ml), six pack of platelets (250 ml), and cryoprecipitate (150 m).

Table 3. Post-operative outcomes.

Factor	Whole blood ($n = 16$)	Component ($n = 18$)	p Value
Maternal surgical morbidity outcome composite	7 (44)	12 (67)	.30[b]
Transfusion >4 units	4 (25)	10 (56)	.09[c]
ICU admission	7 (44)	11 (61)	.31[b]
Intraoperative acidosis	2 (13)	3 (17)	1.0[c]
LOS >4 days	7 (44)	6 (33)	.73[b]
Number of criteria met	1.3 ± 1.1	1.7 ± 1.3	.40[a]
ICU LOS	0 (0,1)	1 (0,1)	.60[d]
Infection	0	1 (6)	1.0[c]
Reoperation	1 (6)	0	.47[c]

ICU: intensive care unit; LOS: length of stay.
Values presented as mean ± SD, median [P25, P75] or *N* (column %).
p Values: [a]*t*-test, [b]chi-squared, [c]Fisher's exact test, and [d]Mann–Whitney's *U*-test.

detection [14]. Data suggest patients with antenatally suspected PAS should be managed in a tertiary care center with support from a multidisciplinary team with adequate blood bank capacity [15].

The primary outcome was a maternal surgical morbidity composite which included common measures of morbidity associated with PAS (ICU admission, transfusion greater than 4 units, intraoperative acidosis, and prolonged post-operative length of stay). Our data show comparable post-surgical outcomes between both transfusion modalities both in composite measure. This study was unfortunately not powered to determine individual variables of operative cases such as emergent delivery or utilization of uterine artery embolization.

In this study, significant reductions were observed in the number of blood products used for resuscitation as well as overall resuscitation volumes (Table 2). All 34 patients included in this cohort were Rh positive, reflective of the predominantly Hispanic patient population of south-central Texas. Rh negative patients are potentially at risk of developing antibody alloimmunization with multiple blood transfusions. The current ACOG recommendation for PAS cases is planned hysterectomy at time of delivery [16]. Thus, the risk of hemolytic disease of the newborn from Rh alloimmunization, is not a factor in blood product transfusion for these patients. Yet, as obstetric patients are within reproductive ages, the overall lifetime risk of blood transfusion antibody matching increases in the setting of exposure to multiple blood product donors. Thus, a reduction in blood product utility and subsequent reduction in donor exposure may benefit patients lifelong.

Our whole blood transfusion protocol was developed in collaboration with the Transfusion Medicine and Trauma-Emergency Surgery department at our institution. When the protocol was established, given the experimental nature of PAS transfusion with whole blood, the decision was made to transfuse up to 4 units of whole blood and then proceed with routine component transfusion protocols. Thus, we cannot conclude the efficacy of whole blood transfusion beyond the initial 4-unit resuscitation. Stotler et al. reported >39% of PAS patients require greater than 10 units of red blood cells [17]. Thus, the significant reduction in overall blood product utility with only 4 units of whole blood noted in this study shows great promise for translatable clinical application (Table 2).

The most common approach to circulatory resuscitation is a 1:1:1 ratio of red blood cells, platelets, and plasma to mimic replacement of whole blood [18]. The major difference between whole blood and packed RBC units is the volume of plasma present in the unit, with additional FFP not needed in massively transfused patients [19]. Whole blood resuscitation is considered investigational and studies comparing the efficacy of whole blood vs. component (1:1:1) transfusion, in the setting of PAS, have not been reported previously. Our study provides important insights related to comparative outcomes of PAS cases managed with whole blood vs. component therapy. In addition, further studies are required to quantify the clinical risk associated with blood transfusion reductions as these events are uncommon and were not encountered in this cohort.

There are several strengths of this study which should also be recognized. While PAS has a reported incidence of 1:1000 to 1:1500, due to the nature of a referral center, we report outcomes on 34 patients within a 2-year period. The care of all patients was coordinated by the same multidisciplinary team allowing for uniformity of care and protocols. All patient data were obtained from the electronic medical record at our system and noted to be complete for analysis. As the field of PAS management continues to evolve, the utilization of supplemental diagnostic and surgical approaches change over time. During the 2-year study period, these supplementary approaches remained uniform at our institution.

This study has several limiting factors which should be acknowledged. First, this study was completed at a single academic institution which serves as the tertiary referral center for south and central Texas. While this setting may be reflective of many hospitals in the country, the nature of our regional referral center for PAS cases allowed for the management of 34 pathology-confirmed PAS cases within a 2-year timeframe. Also, during the data collection for these cohorts, patients were not randomized to interventions but grouping depended on the pre-operative availability of coordination for intended blood transfusion approach. In addition, studies have shown the development of PAS referral centers or centers of excellence results in optimal patient outcomes but also skewing of pathologies treated as placenta percreta are most often detected on ultrasound and referred. This selection bias is noted in Table 1, patients with suspected placenta percreta were more likely to be considered for whole blood transfusion during delivery planning. Although, the final pathology diagnosis among groups (Table 2) did not differ.

Conclusions

In the setting of suspected PAS pathology, at a quaternary referral center, whole blood may be considered for initial resuscitation with similar post-operative outcomes, fewer component transfusions and fewer donor exposures. As PAS cases continue to increase, the development of novel approaches to patient management will be required to continue to optimize outcomes for complex surgical cases.

Disclosure statement

The authors report no conflict of interest.

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