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The effect of preoperative intravenous iron administration on patient outcomes in the spectrum of placenta accreta: a retrospective case-control study

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Abstract

Background We aimed to investigate the effect of preoperative intravenous (IV) iron administration on maternal outcomes in patients with placenta accreta spectrum (PAS).

Methods The study group comprised 72 patients diagnosed with PAS who underwent surgery and received IV iron preoperatively. The control group consisted of 71 patients who underwent the same diagnosis but did not receive IV iron. We recorded and compared the groups' demographic and obstetric findings, laboratory results, preoperative and postoperative blood product requirements, operation duration, characteristics, hospital stay, and neonatal outcomes.

Results We compared the IV iron group's data to that of the control group and found that the study group needed significantly less erythrocyte suspension (ES) transfusions during surgery (32 (44.4%)) and after surgery (56 (77.8%)) than the control group ($p < 0.05$). Total ES transfusion requirement (1.38 ± 0.896) and total fresh frozen plasma (FFP) transfusion requirement (0.55 ± 0.785) in the study group were significantly less than the control group ($p < 0.05$). Postoperative hospital stay (hours) was also significantly shorter in the study group (56.34 ± 15.06) than in the control group (83.18 ± 21.64) ($p < 0.05$). The use of Bakri balloon tamponade was significantly higher in the control group (38 (52.8%)) than in the study group (12 (16.9%)) ($p = 0.00$), and the number of bilateral hypogastric artery ligations and total abdominal hysterectomy was significantly lower in the study group (13 (18.1)/2.8) than in the control group (53 (74.6)/19 (26.8)) ($p < 0.05$). There was no statistically significant difference between the groups in terms of the use of compression sutures, lower uterine segment resection, or adjacent organ damage ($p > 0.05$).

Conclusions Preoperative IV iron administration positively affects intraoperative bleeding, operative time, blood product requirement, peripartum hysterectomy requirement, and hospital stay.

Keywords Intravenous iron, Placenta accreta, Postpartum hemorrhage

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Introduction

Placenta accreta spectrum (PAS) is an obstetric condition caused by abnormal adhesion of the placenta to the uterine wall, posing a significant risk to maternal health. If the damaged endometrium doesn't get reepithelialized, trophoblasts can move deep into the myometrium and even into organs nearby. Irving and Hertig first described the placenta as a partial or complete abnormal attachment to the uterine wall [1].

PAS remains a cause of serious maternal mortality and morbidity, including massive hemorrhage during labor, disseminated intravascular coagulopathy (DIC), sepsis, hysterectomy, blood transfusion complications, adjacent organ injury, and prolonged hospital stay, depending on the extent of invasion [2, 3]. It is extremely important to develop new strategies for the treatment and patient management of PAS, which has become more common in parallel with the increasing cesarean delivery rates worldwide. For example, a multidisciplinary approach to PAS patients may result in a decrease in maternal morbidity [4].

In patients with PAS, there is a high probability that there will be more bleeding than normal during labor. Accordingly, it is recommended to optimize hemoglobin levels in PAS patients before delivery [5, 6]. We designed this study to investigate the effect of preoperative intravenous (IV) iron supplementation on maternal outcomes.

Materials and methods

This retrospective case control study was performed at a territory hospital. The cesarean section rate in Turkey is among the highest in the world. Because of this, the administration of PAS cases, which are becoming more prevalent annually, is becoming increasingly critical. Patient management is reviewed in the gynecology and obstetrics unit of our hospital at the commencement of each academic year (September) in light of recent literature. The decision was made to implement preoperative intravenous iron as a preoperative optimization for PAS patients as a consequence of the 2020 evaluations. Since January 2020, our hospital, a tertiary care center, has routinely administered 1000 mg IV iron carboxymaltose to patients with a diagnosis of PAS as part of preoperative preparation at the 34th gestational week. This application was made regardless of the patients' anemia and blood ferritin levels. The 34th week was taken as the basis because there may be an emergency operation at any time. We administer the application regardless of the patient's hemoglobin level. We determined the study group as 72 patients who received follow-up and treatment for PAS in our hospital between January 2020 and June 2023. We selected 71 patients who received follow-up and treatment for PAS in our hospital before January

2020, but did not receive preoperative IV iron administration, as the control group.

The operation of PAS patients has been performed by our experienced PAS team in our centre for 8 years. Both groups of patients were retrospectively analysed on the basis of the information recorded in the electronic registration system in the hospital and the information in the physical files of the patients. PAS was detected according to sonographic findings and in the presence of at least one of the findings that increase the risk of invasion (loss of hypoechoic area between the placenta and uterus, placental lacunes, increased vascularity at the uterovesical junction, entry of myometrial and placental tissues into neighbouring organs), the patient was followed up with the diagnosis of PAS [7]. Additionally, a histopathological examination determined the definitive diagnosis of PAS in all patients included in the study. Patients with multiple pregnancy, additional pregnancy complications such as preeclampsia, diabetes, HELLP syndrome, intrauterine exitus fetus, iron allergy and hematological diseases such as hemophilia, platelet dysfunction were excluded. The primary outcomes are the reduction in hemoglobin and the transfusion of blood products. The secondary outcomes include the length of hospital stay, the operation time, and the additional surgical interventions that are undertaken.

In our hospital, PAS surgery starts with a median abdominal incision. Then, the fetus is delivered with a vertical incision made in the uterine fundus. The main purpose is uterus-preserving surgery, the bladder is dissected from the lower uterine segment. Then, the placenta is removed from the bed and the bleeding status is controlled. First, bleeding is tried to be controlled with compression sutures or lower segment resection. If bleeding continues, therapeutic bilateral hypogastric artery ligation and, if necessary, Bakri balloon tamponade is used. Despite all these, a decision for hysterectomy is made in cases such as continuing bleeding, instability of the patient, invasion of adjacent organs and tissues. Intraoperative blood product transfusion decision is made according to the amount of bleeding and the vital signs of the patient. However, it may not be possible to talk about a standard procedure order in PAS surgery and this order is individualized according to the patient's condition.

We recorded the patients' demographic and obstetric characteristics, such as age, height, weight, body mass index (BMI), gravida, parity, number of caesarean section operations, number of uterine curettages, history of uterine surgery, history of placenta previa, and smoking habit. We also recorded preoperative hemoglobin (Hb), hemocrit (htc), platelet (Plt), reticulocyte distribution width (RDW), activated partial thromboplastin time (Aptt), prothrombin time (Pt), ferritin levels, and postoperative Hb, htc, and Plt values. We noted the patients'

status for both emergency and elective operations. We recorded the blood products transfused during or after the operation, the duration of the operation, and the procedures used to control bleeding, including compression sutures, Bakri balloons, lower uterine segment resections, bilateral hypogastric artery ligations, hysterectomy requirements, and any damage to neighboring organs. We also recorded the fetal gestational week, birth weight, first and fifth minute Apgar scores, umbilical cord pH, gender, and the status of the neonatal intensive care unit (NICU) admission.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). We used the Shapiro-Wilk test to find out whether continuous data were normally distributed. While mean \pm standard deviation was used for normally distributed continuous variables, median (interquartile range (IQR)) was used for others. In the comparison of two independent groups, the Mann-Whitney U test was used if there was no normal distribution, and the Independent Samples t-test was used if there was. Differences between categorical data were evaluated using the chi-square test. Categorical variables were expressed as numbers (%). A Pearson Chi-square test was used for the comparison of intraoperative and postoperative ES transfusion requirements between the groups and expressed as odds ratio (%). A logistic regression analysis was used to investigate the associations between study group and surgery duration. The odds ratio (OR) and its 95% confidence interval were calculated. $p < 0.05$ was considered significant.

Results

The study included a total of 143 pregnant women diagnosed with PAS. Upon evaluating the demographic and obstetric data of the study and control groups (Table 1), we found no significant difference between the groups in terms of age, gravida, parity, or number of abortions

(p values of 0.369, 0.700, 0.167, and 0.808, respectively). There was no difference according to previous cesarean section between the groups ($p = 0.260$), and the rate of previous curratage in the study group was significantly higher than in the control group (0 [0–1]) versus (0 [0–0]) ($p = 0.002$). The number of previous uterine surgeries was significantly higher in the control group 62 (87.3%) vs. 51 (70.8%) ($p = 0.015$), and the number of previous placenta previa was significantly higher in the study group (8 (11.1%) vs. (2 (2.8%), $p = 0.045$). Both groups were similar in terms of BMI values ($p = 0.695$).

Upon examining the parameters in the maternal blood samples taken during the peripartum period of the groups (Table 2), we found no significant difference between the preoperative Hb, Htc, Plt, RDWCV, RDWSD, aPTT, and PT levels between the groups (p values were 0.140, 0.532, 0.057, 0.305, 0.625, 0.358, and 0.727, respectively). This was true even though the study group had higher postoperative Hb (10.48 ± 1.71), Htc (30.51 ± 4.84), and Plt (202.236 ± 68.44) values than the control group (9.07 ± 1.19 , 26.52 ± 3.39 , and 176.35 ± 59.82) (p values of 0.001, 0.001, and 0.017, respectively). The difference between preoperative and postoperative Hb values was (-1.8 [1.5]) g/dl in the control group and (-1.1 [2.28]) g/dl in the study group, which was significantly less in favor of the study group ($p = 0.001$). Peripartum random ferritin levels were lower in the study group (20 ± 20.33) than in the control group (29.57 ± 24.62) ($p = 0.030$).

When the neonatal outcomes of the groups were examined (Table 3), there was no significant difference in terms of gestational age, birth weight, fetal gender, umbilical cord artery blood gas pH value, and NICU admission rates between the study and control groups (p values: 0.562, 0.550, 0.562, 0.095, and 0.142, respectively). The 1st minute Apgar score (8 [6–9]) and 5th minute Apgar score (9 [8–10]) were significantly higher in the study group than in the control group (p values: 0.025 and 0.010, respectively).

Table 1 Comparison of demographic and obstetric characteristics of the groups

	Study group (n:72)	Control group (n:71)	<i>p</i> value
Age (years)Mean \pm SD	32.1 \pm 6.04	33.04 \pm 5.59	0.369*
GravidaMedian [IQR]	4 [2]	3 [2]	0.700**
ParityMedian [IQR]	2 [2]	2 [2]	0.167**
AbortusMedian [IQR]	0 [1]	0 [1]	0.808**
History of previous cesarean section Median [IQR]	2 [1.75]	2 [2]	0.260**
History of previous curettageMedian [IQR]	0 [1]	0 [0]	0.002**
History of previous uterine surgery n (%)	51 (70.8%)	62 (87.3%)	0.015***
Previous history of placenta previa n (%)	8 (11.1%)	2 (2.8%)	0.045***
BMI (kg/m ²)Mean \pm SD	28.48 \pm 3.81	27.98 \pm 2.95	0.695*

*Independent Sample t test, **Mann Whitney U test, ***Chi-Squared test. A value of $p < 0.05$ is significant. Bold p values indicate statistically significant

Table 2 Comparison of maternal laboratory parameters of the groups

	Study group (n:72)	Control group (n:71)	p value
Preoperative Hb (g/dl) <i>Mean ± SD</i>	11.40 ± 1.36	11.10 ± 0.99	0.140*
Preoperative Htc (%) <i>Mean ± SD</i>	33.40 ± 3.98	33.02 ± 3.10	0.532*
Preoperative PLT ($\times 10^3/\mu\text{l}$) <i>Mean ± SD</i>	221.53 ± 79.12	228.36 ± 72.56	0.057*
Preoperative RDWCV (%) <i>Mean ± SD</i>	14.61 ± 2.14	14.89 ± 2.5	0.305*
Preoperative RDWSD (fL) <i>Mean ± SD</i>	45.06 ± 5.94	44.37 ± 5.32	0.625*
Preoperative aPTT (saniye) <i>Mean ± SD</i>	29.16 ± 6.55	28.11 ± 4.28	0.358*
Preoperative PT (saniye) <i>Mean ± SD</i>	12.72 ± 1.18	12.88 ± 1.5	0.727*
Preoperative Ferritin (ml/ng) <i>Mean ± SD</i>	20 ± 20.33	29.57 ± 24.62	0.030*
Postoperative Hb (g/dl) <i>Mean ± SD</i>	10.48 ± 1.71	9.07 ± 1.19	0.001*
Postoperative Htc (%) <i>Mean ± SD</i>	30.51 ± 4.84	26.52 ± 3.39	0.001*
Postoperative PLT ($\times 10^3/\mu\text{l}$) <i>Mean ± SD</i>	202.236 ± 68.44	176.35 ± 59.82	0.017*
Preoperative - Postoperative Hb difference (g/dl) <i>Median [IQR]</i>	-1.1 [2.28]	-1.8 [1.5]	0.001**

*Independent Sample t test, ** Mann Whitney U test. A value of $p < 0.05$ is significant. Bold p values indicate statistical significant

Table 3 Comparison of neonatal outcomes of the groups

	Study group (n:72)	Control group (n:71)	p value
Birth week <i>Median [IQR]</i>	37.35 [1.8]	37.4 [2]	0.562*
Birth weight (gram) <i>Median [IQR]</i>	3095 [555]	3050 [660]	0.550*
Fetal gender n(%)			0.562**
Female	41(56.9)	37(52.1)	
Male	31(43.1)	34(47.9)	
Apgar score at 1 min <i>Median [IQR]</i>	8 [3]	7 [2]	0.025*
Apgar score at 5 min <i>Median [IQR]</i>	9 [2]	9 [1]	0.010*
Umbilical cord pH <i>Mean ± SD</i>	7.33 ± 0.057	7.30 ± 0.072	0.095***
NICU admission n(%)	33(45.8)	24(33.8)	0.142**

* Mann Whitney U test, ** Chi-Squared test, *** Independent Sample t test. A value of $p < 0.05$ is significant. Bold p values indicate statistically significant

Table 4 Comparison of surgical outcomes of groups

	Study group (n:72)	Control group (n:71)	P value
Timing of surgery n(%)			0.204*
Emergency	36(50)	43(60.6)	
Elective	36(50)	28(39.4)	
Duration of surgery(<i>minutes</i>) <i>Mean ± SD</i>	54 ± 12.77	67.6 ± 17.4	0.001**
Preoperative ES transfusion n(%)	1(1.4)	2(2.8)	0.548*
Intraoperative ES transfusion n(%)	32(44.4)	55(77.5)	0.001*
Postoperative ES transfusion n(%)	56(77.8)	65(91.5)	0.022*
Tota ES transfusion (Unit) <i>Mean ± SD</i>	1.38 ± 0.896	2.56 ± 1.528	0.001**
Total FFP transfusion (Unit) <i>Mean ± SD</i>	0.55 ± 0.785	1.28 ± 1.416	0.001**
Postoperative hospital stay (hours) <i>Mean ± SD</i>	56.34 ± 15.06	83.18 ± 21.64	0.001**
Compression suture n(%)	66(91.7)	65(91.5)	0.980*
Uterine lower segment resection n(%)	41(56.9)	38(53.5)	0.681*
Bakri balloon tamponade n(%)	12(16.9)	38(52.8)	0.001*
Bilateral hypogastric artery ligation n(%)	13(18.1)	53(74.6)	0.001*
Total abdominal hysterectomy n(%)	2(2.8)	19(26.8)	0.001*
Adjacent organ injury n(%)	2(2.8)	6(8.5)	0.132*

* Chi-Squared test, ** Independent Sample t test. A value of $p < 0.05$ is significant. Bold p values indicate statistical significant

In the evaluation of the surgical results of the groups (Table 4), there was no significant difference in terms of emergency or elective status ($p = 0.204$). Surgery duration (min) was significantly shorter in the study group (54 ± 12.77) than in the control group (67.6 ± 17.4)

($p = 0.001$). In this analysis, the logistic regression revealed that significantly lower surgery duration (OR 0.944, 95% CI: 0.922–0.967; $p < 0.001$). There was no significant difference between the two groups in terms of preoperative ES transfusion ($p = 0.548$). Intraoperative

Table 5 Comparison of the effects of intravenous iron administration on intraoperative and postoperative ES transfusion requirements between groups

	Odds Ratio	95% C.I. for Odds Ratio		p value
		Lower	Upper	
Intraoperative ES transfusion	0.232	0.113	0.481	0.000*
Postoperative ES transfusion	0.321	0.118	0.882	0.022*

ES transfusion (32 (44.4) vs. 55 (77.5); $p=0.001$) and postoperative ES transfusion (56 (77.8) vs. 65 (91.5); $p=0.022$) were significantly less common in the study group compared to the control group. Total ES transfusion requirement (1.38 ± 0.896 vs. 2.56 ± 1.528 , $p=0.001$) and total FFP transfusion requirement (0.55 ± 0.785 vs. 1.28 ± 1.416 , $p=0.001$) in the study group were significantly less than in the control group. Also, postoperative hospital stay (hours) was significantly shorter in the study group than in the control group (56.34 ± 15.06 vs. 83.18 ± 21.64 , $p=0.001$). A lot more Bakri balloon tamponades were used in the control group (38 (52.8)) than in the study group (12 (16.9)) ($p=0.001$). Also, a lot fewer bilateral hypogastric artery ligations (13 (18.1) vs. 2 (2.8), $p=0.001$, and total abdominal hysterectomy (53 (74.6) vs. 19 (26.8), $p=0.001$) were done in the study group than in the control group. There was no statistically significant difference between the groups in terms of the use of compression sutures, lower uterine segment resection, and adjacent organ damage (p values 0.980, 0.681, and 0.132, respectively).

When intraoperative and postoperative ES transfusion requirements of the groups were compared, preoperative IV iron replacement reduced the need for intraoperative ES use by 76.8% (OR: 0.232) ($p=0.000$) and postoperative ES use by 67.9% (OR: 0.321) ($p=0.022$) (Table 5).

Discussion

In our study, we found that preoperative IV iron administration to pregnant women who were followed and treated with the diagnosis of PAS provided improvement in parameters such as intraoperative bleeding, operation time, blood product requirement, peripartum hysterectomy requirement, and hospital stay time.

PAS is one of the main causes of maternal and fetal mortality and morbidity. It carries serious risks such as massive postpartum hemorrhage, surrounding organ damage, intravascular coagulopathy, massive blood transfusion and related complications, cesarean hysterectomy, renal failure, long hospital stay and even death [8, 9].

The difficulties in PAS management and treatment necessitated a multidisciplinary approach. In addition to gynecologists, a large team including urologists, anesthesiologists, gynecologic oncologists, and hematologists are required to collaborate. These patients are at risk of undergoing emergency surgery because of the possibility of bleeding before delivery. If this is not the case, it is

generally preferred to follow uncomplicated PAS patients until the 38th week of pregnancy. Due to the possibility of massive bleeding, it is appropriate to perform the surgery in centers that have the ability to provide blood products. It is also recommended that the patient's anemia be corrected before surgery [10]. There are not enough studies on the benefits of iron use in optimizing the patient before surgery [5]. However, especially in the 2nd and 3rd trimesters, IV iron use is preferred because it corrects anemia quickly and has fewer side effects [11, 12]. In our study, we aimed to investigate the effect of preoperative IV iron administration on the perioperative outcomes of patients.

We found that the duration of the operation was shorter in the study group. It was observed that pregnant women with anaemia faced more bleeding intrapartum or postpartum in the study by Kalve et al. [13]. Red blood cells are critical in all stages of hemostasis, such as platelet aggregation, thrombin and fibrin formation, and studies have shown that anemic patients have a high risk of bleeding [14]. RBCs change hemorheology by mechanically keeping platelets close to the vascular wall surface, improving their injury site contact [15]. Additionally, the phospholipids on the surface of red blood cells have the capacity to assemble coagulation factors, produce thrombin, and convert fibrinogen to fibrin [16]. Ultimately, red blood cells (RBCs) engage in active binding to both platelets and fibrin, rather than becoming ensnared in the clot [17]. Therefore, we believe that PAS patients whose red blood cell reserve has been optimised with IV iron supplementation have less intraoperative bleeding and consequently have a positive effect on operative time. In addition, we believe that postoperative Hb and Hct values were significantly higher in the study group.

We observed in our study that the group receiving IV iron had a lower need for blood products during or after the operation. PAS is the main cause of massive transfusion in obstetrics. Thurn et al. found PAS to be the most common cause in patients who underwent massive transfusion due to postpartum hemorrhage in their study in Sweden [18]. Although blood transfusion is life-saving in postpartum haemorrhage, it carries its own risks such as transfusion reactions, thromboembolism and blood-borne infections. In addition, intravenous iron administration is cost-effective compared to transfusion blood products [19].

In our study, the use of Bakri balloon tamponade was lower in the study group, and the rates of bilateral hypogastric artery ligation and hysterectomy were lower than in the control group. Generally used in cases such as uterine atony or widespread intracavity hemorrhage, Bakri balloon tamponade is a mechanical method to control postpartum hemorrhage, similar to the B-Lynch suture and other compression sutures. Another mechanical method, the use of a sandbag in the postoperative period to reduce bleeding, was found to be ineffective in a study [20]. Yang et al. reported in their study that they achieved 87.6% hemorrhage control in patients who used Bakri balloon tamponade [21]. Similarly, Zeng et al. observed success in bleeding control and a decrease in the need for hysterectomy in PAS patients using Bakri balloon tamponade in their study [22]. In another study conducted by Pala et al., they showed that the use of Bakri balloons in PAS cases had a positive effect on patient outcomes [23].

In our study, we observed a lower rate of peripartum hysterectomy in the group receiving IV iron. Peripartum hysterectomy is generally performed to save the mother's life in cases of life-threatening severe postpartum hemorrhage. PAS is the primary cause of peripartum hysterectomy. Pettersen et al. conducted a study in Norway that determined PAS as the most common reason among patients undergoing peripartum hysterectomy. Furthermore, the PAS group experienced the highest number of complications following hysterectomy [24].

We observed that the patients in the study group had a shorter hospital stay. In their study, Mogos et al. found that patients with placenta accreta had a longer hospitalization period and consequently a higher cost of care [25]. We believe that this finding is particularly important regarding costs in the healthcare field.

The main limitations of the study are its retrospective design and single-center nature. Another limitation of our study is that no distinction could be made according to PAS subgroups. Since the study was retrospective, the study and control groups were not completely homogeneously distributed in terms of some parameters such as ferritin, which is another limitation of the study. The strength of the study is that the study was conducted in a tertiary center where risky pregnancies are intensively followed and the surgeries were performed by an experienced team of experts. In addition, its other strengths include the application of standardized protocols for all patients, the homogeneity of the study groups, and the large number of variables investigated.

Conclusion

We observed that preoperative IV iron use positively affects the need for transfusion, hysterectomy, and hospital stay in PAS patients. PAS, which is increasingly common worldwide, is a serious cause of mortality and

morbidity for mothers and babies. There is a strong need for studies that will benefit the management of PAS, which causes life-threatening postpartum hemorrhage.

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Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work as follow: Conceptualization, A.Z.N., F.I.A., A.C.; methodology, A.Z.N., Y.D., and Ş.K.; software, F.I.A.; formal analysis, F.I.A., M.Ç.K and H.Y.; investigation, H.Y., and H.D.; resources, A.Z.N.; responsible for data collection, Y.D.; data curation, Ş.K.; writing-original draft preparation, A.Z.N., H.D. and H.Y.; writing-review and editing, A.Z.N., F.I.A.; visualization, A.Z.N.; supervision, A.C.; All authors have read and agreed to the published version of the manuscript.

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Data availability

Derived data supporting the findings of this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate

The Mersin University Clinical Research Ethics Committee, dated March 6, 2024, and numbered 2024/238, approved this study, and was conducted in accordance with the declaration of Helsinki. When patients are admitted to the hospital, a patient admission consent form is obtained. There is a statement in the patient admission consent form that patient data can be used, and this consent form is recorded with the signature of all patients and their relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

CONSORT statement

Our study adheres to CONSORT guidelines.

Clinical trials number

Not applicable.

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