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Original Research

Effectiveness and Clinical Patterns of Iron Supplementation as a Method of Bloodless Treatment in Patients Experiencing Bleeding after Obstetrical Surgery

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Abstract

Background: Some patients refuse blood transfusions despite the risk of hematological complications, such as anemia and iron deficiency, associated with obstetrics treatments and surgery. Therefore, this study aims to investigate the effectiveness and safety of iron supplementation, a major method of bloodless treatment, and retrospectively examine the clinical characteristics and patterns of individuals who underwent bloodless treatment after obstetrical surgery. **Methods**: We collected medical records of patients who consented to and underwent bloodless treatment between September 2001 and October 2016, and retrospectively analyzed these data. **Results**: In the vaginal delivery group, 57.1% were nullipara and 42.9% were multipara. Among all patients, 34.9% were not prescribed iron supplements before and after parturition, with 50% and 20.5% of the patients in the vaginal delivery and cesarean groups delivering without being prescribed iron supplements. Of the patients in the cesarean section group, 73.5% were administered iron supplements after parturition compared with only 40.5% in the vaginal delivery group. The mean time from surgery to discharge was 4 days and was significantly longer in the cesarean section group (6 days) than in the vaginal delivery group (2 days). Sixteen patients underwent a hemoglobin test during an outpatient visit at a mean of 48 days after surgery. The cesarean section group exhibited lower hemoglobin levels than the vaginal group on postoperative day (POD) 1. In an examination of changes in hemoglobin levels on POD 1 and before operation, the cesarean section group exhibited reduced hemoglobin levels compared to the vaginal delivery group. **Conclusions**: Obstetrical procedures, including vaginal delivery and cesarean section, were successfully performed via bloodless treatment in patients for whom substantial blood loss was expected. Thus, bloodless treatment using iron supplements may be a scientific, evidence-based option for patients who refuse blood transfusions.

Keywords: anemia; gynecologic surgical procedure; hemoglobin; iron supplements

1. Introduction

"Bloodless treatment" is an internal or surgical treatment performed without blood or blood supplements. It is a cutting-edge treatment method in which hemostatic and hematopoietic agents, plasma expanders, and state-of-the-art medical equipment are used to reduce bleeding and maximize blood production [1]. Bloodless treatment reduces the risk for inappropriate blood transfusions and prevents infections that can result from blood transfusions, including hepatitis or transmission of human immunodeficiency virus, leading to acquired immune deficiency syndrome (AIDS). It reduces the risk for side effects caused by the use of stored blood, which has reduced oxygen-carrying capacity, and reduces pain and scarring due to its non-invasive invasive nature [2]. There has been increasing interest and preference for bloodless treatment worldwide. Bloodless treatment is especially important during obstetrical surgery in patients who cannot receive blood transfusions due to sudden and excessive bleeding, which commonly occurs. Pregnant women are at high risk for iron deficiency and anemia due to drastic physiological changes during pregnancy and the increased demand for blood to support fetal development [3]. Anemia is the most common hematological complication of peri-, intra-, and postpartum bleeding, and pregnant mothers with anemia are at higher risk for blood transfusions, premature birth, and cesarean section compared to those without anemia [4]. Anemia during pregnancy is a clinically significant problem because it is associated with an increased risk of puerperal infection, maternal fatigue, and maternal mortality [5]. Despite the risk for hematological complications associated with obstetrical treatments and surgery, such as anemia and iron deficiency, some patients refuse to receive blood transfusions and, instead, elect to undergo bloodless treatment. Bloodless treatment offers an alternative solution to physicians experienc-

ing a significant medical dilemma due to patients' refusal of blood transfusions. Domestic research investigating bloodless treatment for managing anemia and iron deficiency caused by postoperative bleeding is relatively lacking compared to international research. To the best of our knowledge, no study has examined the effectiveness of bloodless treatment in patients with severe anemia (hemoglobin <5 g/dL) and iron deficiency who are at risk for death. In the present study, we investigated the effectiveness and safety of iron supplementation, a major method of bloodless treatment, and retrospectively examined the clinical characteristics and patterns of individuals who underwent bloodless treatment as documented in their medical records.

2. Materials and Methods

The Soonchunhayng University Bucheon Hospital (Bucheon, South Korea), the research facility at which the present study was performed, has been operating a bloodless treatment center since September 2001. Patients who wish to undergo bloodless treatment due to religious beliefs or personal reasons can consult a bloodless treatment coordinator at the time of hospital admission. However, they must sign a consent form relinquishing the medical staff of liability for any complications that may result from the decision not to receive blood transfusions and their desire to undergo bloodless treatment. The authors collected medical records of patients who consented to and underwent bloodless treatment between September 2001 and October 2016, and retrospectively analyzed these data. The primary purpose of this study was to provide basic data regarding obstetrical bloodless treatment by analyzing medical records documenting iron supplementation and anemia indicators of patients who consented to bloodless treatment and underwent obstetrical surgery or treatment. Patients fulfilling the following criteria were included: parturition (vaginal delivery or cesarean section) after 20 weeks of pregnancy; hysterectomy due to aggravated postpartum bleeding during hospitalization after parturition; and vaginal delivery or cesarean section after intrauterine fetal death was confirmed after 20 weeks of pregnancy. Patients who died during hospitalization, experienced a miscarriage before 20 weeks of pregnancy or did not undergo obstetrical surgery or treatment after hospitalization were excluded. History of iron supplementation, type(s) of iron supplements used, administration route(s), date of initial supplementation, hospitalization, surgery, and discharge, hemoglobin levels (before iron supplementation, before parturition, within one and three days after parturition, at the time of discharge, and at the time of outpatient follow-up following discharge), age, height, weight, body mass index (BMI), blood type, and obstetrical history (Term birth-Preterm birth-Abortion-Living children (T-P-A-L)) were investigated. Patients who delivered vaginally were categorized as either primipara or multipara, and those who underwent cesarean section were categorized as either first Cesarean section or multiple cesarean sections (≥ 2). Statistical analyses were performed using SPSS Statistics Standard version 25 (IBM Corp., Armonk, NY, USA). Differences with a two-tailed p value less than 0.05 were considered to be statistically significant. All data underwent the Shapiro-Wilk normality test, and results per time point are expressed as mean $\pm$ standard deviation or median (interquartile range). Depending on the type of a variable or the number of patients for each variable, the Student's t-test or Pearson's chi-squared test, Fisher's exact test or Mann-Whitney test, and ANOVA, the Kruskal-Wallis test, or ANCOVA were performed to examine any significant differences. To calculate the retrospective power of an observed effect, we performed the post power analysis in consultation with a biostatistician. The post power analysis was performed using PASS version 12 (NCSS, LLC, Kaysville, UT, USA).

3. Results

The mean age of obstetrical patients, who underwent bloodless treatment at the institution between 2001 and 2016, was 32.5 years. The mean age of the vaginal delivery and cesarean section groups was 31.9 and 33 years, respectively, with no statistical difference. Among the patients, 65.1% were in their 30s, 26.4% were in their 20s, and 8.5% were in their 40s. There was no significant difference in obstetrical history between the vaginal delivery and cesarean section groups. The mean gestational age of all patients at the time of parturition was 38.1 weeks. Infants delivered by vaginal delivery group had a mean gestational age of 39 weeks, which was significantly older than that of cesarean section group (37.2 weeks). One patient from each group delivered after intrauterine fetal death was diagnosed. Among the patients in the cesarean section group, most (56.1%) underwent the procedure for the first time; two patients from this group underwent their fourth cesarean section. In the vaginal delivery group, 57.1% were nullipara, and 42.9% were multipara (Table 1).

Of the patients who delivered and underwent bloodless treatment at this research facility, 16.7% were self-administering iron supplements that were not prescribed. There was no association between iron supplementation and the method of delivery. The patients were categorized as unused, pre-only, post-only, and pre + post based on when iron supplements were used. The pre-only group included patients who have not prescribed iron supplements after parturition. Similarly, the post-only group only included patients who have not prescribed iron supplements before parturition. Among all patients, 34.9% were not prescribed iron supplements before and after parturition, with 50% and 20.5% of the patients in the vaginal delivery and cesarean groups delivering without being pre-scribed iron supplements, respectively (Table 2).

Because a significant difference was found in the percentage of patients categorized as unused, pre-only, post-only, and pre + post according to the method of delivery,

Table 1. Clinical characteristics of obstetrical patients who underwent bloodless treatment.

	Total	Cesarean delivery	Vaginal delivery	*p*-value[1]
	n = 258 (%)	*n* = 132 (%)	*n* = 126 (%)	
Age (years)	32.5 ± 4.7	33 ± 4.4	31.9 ± 5.0	0.122
				0.077
Twenties	68 (26.4)	27 (20.5)	41 (32.5)	
Thirties	168 (65.1)	94 (71.2)	74 (58.7)	
Forties	22 (8.5)	11 (8.3)	11 (8.7)	
Height (cm)	160 ± 5.3	159 ± 5.5	160.9 ± 4.8	0.116
Weight (kg)	69.9 ± 8.9	71.2 ± 9.5	68.5 ± 8.0	**<0.05**
Body mass index (kg/m^2)	27.3 ± 3.2	28.1 ± 3.3	26.5 ± 2.9	**<0.001**
Obstetrics history (T-P-A-L)				
Term birth	0.7 ± 0.8	0.7 ± 0.8	0.6 ± 0.9	0.071
Preterm birth	0.1 ± 0.5	0.2 ± 0.5	0.1 ± 0.5	0.183
Spontaneous abortion	0.2 ± 0.6	0.2 ± 0.6	0.2 ± 0.5	0.632
Artificial abortion	0.2 ± 0.5	0.1 ± 0.4	0.2 ± 0.7	0.695
Abortion (total)	0.4 ± 0.8	0.3 ± 0.7	0.4 ± 0.8	0.980
Living child	0.7 ± 0.9	0.7 ± 0.8	0.7 ± 1.0	0.302
Weeks of delivery	38.1 ± 2.5	37.2 ± 2.9	39 ± 1.6	**<0.001**
Intrauterine fetal death				1.000
No	256 (99.2)	131 (99.2)	125 (99.2)	
Yes	2 (0.8)	1 (0.8)	1 (0.8)	
Number of delivery				**<0.001**
Primary cesarean section	74 (28.7)	74 (56.1)	0 (0.0)	
Repeat (second) cesarean section	43 (16.7)	43 (32.6)	0 (0.0)	
Repeat (third) cesarean section	13 (5.0)	13 (9.8)	0 (0.0)	
Repeat (fourth) cesarean section	2 (0.8)	2 (1.5)	0 (0.0)	
Vaginal delivery (nulliparas)	72 (27.9)	0 (0.0)	72 (57.1)	
Vaginal delivery (multiparas)	54 (20.9)	0 (0.0)	54 (42.9)	

Values are expressed as mean ± standard deviation or median (interquartile range). T-P-A-L, term birth-preterm birth-abortion-living children. [1]*p*-values calculated using the Student's *t*-test and Mann-Whitney U test, or Pearson's chi-squared test and Fisher's exact test. Bold indicates that the *p*-value is significant.

the as-sociation between the timing of iron supplement prescription and the method of delivery was examined. The unused group exhibited significant differences compared to the post-only and pre + post groups. The cesarean section group was prescribed more iron supplements after parturition than the vaginal delivery group. No association was found between pre-only iron supplementation and the method of delivery; in contrast, however, post-only iron supplementation was associated with the method of delivery. Of the patients in the cesarean section group, 73.5% were administered iron supplements after parturition compared with only 40.5% in the vaginal delivery group (Table 3).

Regarding the frequency of iron supplementation before parturition, Albumax solution (soln; Hanlim pharma, Seoul, Korea) and Feroba-You SR (Bukwang Pharmacy, Seoul, Korea) were the most commonly prescribed oral supplements in descending order, and Venoferrum injection (inj; Vifor Pharma, St. Gallen, Switzerland) and Ferinject inj (2 mL; Vifor Pharma, St. Gallen, Switzerland) were the most commonly prescribed intravenous supplements in descending order. The mean frequencies of Albumax soln and Feroba-You SR—the most commonly prescribed oral supplements before parturition—were 50.65 and 67.58, respectively. The mean frequencies of Venoferrum inj and Ferinject inj (2 mL) were 5.87 and 1.58, respectively. Regarding the frequency of iron supplementation after parturition, Albumax soln and Hemo-Q soln (Daewoong Pharmaceuticals Co., Ltd., Seoul, Korea) were the most commonly prescribed oral supplements in descending order, and Venoferrum inj and Ferinject inj (2 mL) were the most commonly prescribed intravenous supplements in descending order. The mean frequencies of Albumax soln and Hemo-Q soln, the most commonly used oral supplements after parturition, were 41.51 and 40.58, respectively. The mean frequencies of Venoferrum inj and Ferinject inj (2 mL), the most commonly used intravenous supplements, were 5.27 and 1.70, respectively. The volume of bleeding during parturition was recorded in milliliters. In the vaginal delivery group, the research facility does not routinely record the volume of bleeding, except in special cases. For this reason, the volume of bleeding was examined only for the 132 patients in

Table 2. Characteristics of iron supplement prescriptions in obstetrical patients who underwent bloodless treatment.

	Total	Cesarean delivery	Vaginal delivery	*p*-value[1]
	n = 258 (%)	*n* = 132 (%)	*n* = 126 (%)	
Self-administration before delivery				1.000
No	215 (83.3)	110 (83.3)	105 (83.3)	
Yes	43 (16.7)	22 (16.7)	21 (16.7)	
Prescription time				**<0.001**
Unused	90 (34.9)	27 (20.5)	63 (50.0)	
Pre only	20 (7.8)	8 (6.1)	12 (9.5)	
Post only	81 (31.4)	53 (40.2)	28 (22.2)	
Pre + Post	67 (26.0)	44 (33.3)	23 (18.3)	
Prescription time + Self-administration before delivery				**<0.001**
Unused	70 (27.1)	23 (17.4)	47 (37.3)	
(Self-administration) + Pre only	55 (21.3)	23 (17.4)	32 (25.4)	
Post only	65 (25.2)	41 (31.1)	24 (19.0)	
(Self-administration) + Pre + Post	68 (26.4)	45 (34.1)	23 (18.3)	
Prescription before delivery				0.206
No	135 (52.3)	64 (48.5)	71 (56.3)	
Yes	123 (47.7)	68 (51.5)	55 (43.7)	
Prescription after delivery				**<0.001**
No	110 (42.6)	35 (26.5)	75 (59.5)	
Yes	148 (57.4)	97 (73.5)	51 (40.5)	
Combined prescription before delivery				0.096
Single	59 (67.8)	32 (61.5)	27 (77.1)	
Two-combined	25 (28.7)	19 (36.5)	6 (17.1)	
Three-combined	3 (3.4)	1 (1.9)	2 (5.7)	
Combined prescription after delivery				0.079
Single	59 (39.9)	33 (34.0)	26 (51.0)	
Two-combined	74 (50.0)	54 (55.7)	20 (39.2)	
Three-combined	14 (9.5)	10 (10.3)	4 (7.8)	
Four-combined	1 (0.7)	0 (0.0)	1 (2.0)	

Values are expressed as number (%). [1]*p*-values calculated using Pearson's chi-squared test or Fisher's exact test. Bold indicates that the *p*-value is significant.

the cesarean section group, which was 528.4 ± 313.8 mL. Only six patients in the cesarean section group and none in the vaginal delivery group underwent autotransfusion. Six patients in the cesarean section group and three in the vaginal delivery group underwent uterine artery embolization after parturition. Four patients in the cesarean section and none in the vaginal delivery group underwent a hysterectomy. The mean time from the first iron supplementation to parturition was 29 days for all patients, 29.5 days for the cesarean section group, and 29 days for the vaginal delivery group. No significant statistical difference in the mean interval from the first iron supplementation to parturition was found between the two groups. The vaginal delivery group started iron supplementation on the day of parturition (day 0, 24 h), and the cesarean section group started one day after surgery. The mean duration of hospitalization after parturition was 6 days, and was greater in the cesarean section group (8 days) than in the vaginal delivery group (3 days). The mean time from surgery to discharge was 4 days and was significantly longer in the cesarean section group (6 days) than in the vaginal delivery group (2 days). Sixteen patients underwent a hemoglobin test during an outpatient visit at a mean of 48 days after surgery (Table 4).

Although the dates of preoperative iron supplementation and postoperative hemoglobin testing varied between the obstetrical patients at this research facility, most patients generally underwent the test within one month before parturition and one day after. Most patients in the cesarean section group generally underwent the test, even until 3 days after surgery, and did not undergo an additional hemoglobin test on the day of discharge, although there were special exceptions. Most patients did not undergo a hemoglobin test during the outpatient follow-up period after parturition. In an examination of hemoglobin levels at different time points before and after surgery regardless of iron supplementation, the hemoglobin level measured on a postoperative day (POD) 1 (10.43 g/dL) was lower than that measured before the operation (11.76 g/dL). The cesarean section group exhibited lower hemoglobin levels than the vaginal group on POD 1. In an examination of changes in

Table 3. Multiple testing corrections for varying timings of iron supplement prescription.

Compare	Difference of proportion	*p*-value by Chi-Squared Test[1]	*p*-value by Bonferroni Correction[2]
Unused *vs.* Pre only	67.1 – 58.2 = 8.9	0.385	0.385 × 4 = 1.540
Unused *vs.* Post only	67.1 – 36.9 = 30.2	<0.001	<0.001 × 4 = <**0.001**
Unused *vs.* Pre + Post	67.1 – 33.8 = 33.3	<0.001	<0.001 × 4 = <**0.001**
Pre only *vs.* Post only	58.2 – 36.9 = 21.3	0.037	0.037 × 4 = 0.148
Pre only *vs.* Pre + Post	58.2 – 33.8 = 24.4	0.040	0.040 × 4 = 0.160
Post only *vs.* Pre + Post	36.9 – 33.8 = 3.1	0.976	0.976 × 4 = 3.904

[1]*p*-values calculated using Pearson's chi-squared test. [2]*p*-values calculated using Bonferrorni correction. Bold indicates that the *p*-value is significant.

Table 4. Iron supplement administration, hospitalization, and testing period in obstetrical patients who underwent bloodless treatment.

	Total	Cesarean delivery	Vaginal delivery	*p*-value[1]
	(*n* = 258)	(*n* = 132)	(*n* = 126)	
Dosing period before delivery (day)	*n* = 87 29 (10.0–69.0)	*n* = 52 29.5 (10.5–70.5)	*n* = 35 29 (10.0–68.0)	0.852
Period of initiation of administration after delivery (day)	*n* = 81 1 (0.0–1.0)	*n* = 53 1.0 (0.0–2.0)	*n* = 28 0.0 (0.0–1.0)	<**0.05**
Total hospital stay (day)	*n* = 258 6.0 (3.0–8.0)	*n* = 132 8.0 (7.0–8.0)	*n* = 126 3.0 (3.0–4.0)	<**0.001**
Delivery date and discharge date period (day)	*n* = 258 4.0 (2.0–6.0)	*n* = 132 6.0 (5.0–6.0)	*n* = 126 2.0 (2.0–2.0)	<**0.001**
Delivery date and outpatient examination period (day)	*n* = 16 48 (22.0–76.0)	*n* = 10 48 (35.0–76.0)	*n* = 6 37.5 (11.0–76.0)	0.550

Values are expressed as median (interquartile range). [1]*p*-values calculated using the Student's *t*-test and Mann-Whitney U test. Bold indicates that the *p*-value is significant.

hemoglobin levels on POD 1 and before operation, the cesarean section group (–1.57) exhibited reduced hemoglobin levels compared to the vaginal delivery group (–1.11) (Table 5). The results of the post power analysis achieved 80.453% power (**Supplementary Data 1**) and 75.817% power (**Supplementary Data 2**) to reject the null hypothesis of equal.

4. Discussion

Pregnant women experience an increased demand for blood due to drastic psychological changes during pregnancy and fetal development. As the amount of hemoglobin supplying oxygen throughout the body decreases (i.e., as iron levels decrease), morbidity and mortality increase for both mother and infant, who are at risk for iron-deficiency anemia caused by complications. Anemia in pregnancy increases the risk for blood transfusions, preterm birth, and cesarean section [6–8], and has a negative impact on the infant, leading to 5 min Apgar scores <7, intensive care unit admission, and low birth weight relative to gestational age. For this reason, anemia correction(s) during pregnancy is essential [4].

Routes of iron supplementation to correct anemia are largely divided into oral and intravenous. Various factors including the severity of anemia, supplement cost, possibility of switching to an alternative iron supplement in the future, and tolerance to oral supplements should be considered when choosing an iron supplement. Most patients prefer easy-to-use, inexpensive, and safe oral supplements (e.g., ferrous fumarate, ferrous gluconate, ferrous sulfate, polysaccharide-iron complex). However, most patients who use oral agents (especially ferrous sulfate) experience adverse gastrointestinal reactions [9], drug absorption problems, and other adverse reactions and exhibit low compliance and early treatment termination [10–13].

Intravenous supplements are used for patients who cannot tolerate adverse reactions, wish to restore their iron stores more quickly, or cannot restore their iron stores with oral supplements due to heavy uterine bleeding. Most of these patients are elderly pregnant, or have gastrointestinal disease(s). Available intravenous iron supplements include ferric carboxymaltose, ferric gluconate, ferumoxytol, iron sucrose, iron isomaltoside, and iron dextran. Intravenous supplements are recommended for patients with severe iron deficiency anemia or those who require rapid correction during late pregnancy. Intravenous iron supplements supply iron more quickly than oral supplements without causing the side effects associated with oral supplementation. Intravenous supplements are generally used after the second trimester of pregnancy, and several studies have reported an

Table 5. Changes in hemoglobin levels over time in obstetrical patients who underwent bloodless treatment.

	Total	Cesarean delivery	Vaginal delivery	*p*-value[1]
	(*n* = 258)	(*n* = 132)	(*n* = 126)	
Before used	*n* = 44 10.89 ± 1.26	*n* = 22 11.03 ± 1.33	*n* = 22 10.75 ± 1.20	0.391
Before OP	*n* = 250 11.76 ± 1.34	*n* = 128 11.70 ± 1.36	*n* = 122 11.83 ± 1.32	0.305
POD 1	*n* = 257 10.43 ± 1.64	*n* = 131 10.15 ± 1.77	*n* = 126 10.72 ± 1.45	**0.01**
POD 3	*n* = 140 9.29 ± 1.90	*n* = 129 9.37 ± 1.83	*n* = 11 8.37 ± 2.51	0.230
D/C	*n* = 25 8.69 ± 2.06	*n* = 22 8.48 ± 1.71	*n* = 3 10.23 ± 4.02	0.477
OPD	*n* = 17 12.15 ± 1.29	*n* = 11 12.15 ± 0.94	*n* = 6 12.17 ± 1.89	0.614
△ Before OP- Before used	*n* = 43 0.38 ± 1.06	*n* = 22 0.13 ± 0.91	*n* = 21 0.63 ± 1.17	0.189
△ POD 1 - Before OP	*n* = 249 –1.34 ± 1.39	*n* = 127 –1.57 ± 1.53	*n* = 122 –1.11 ± 1.17	**<0.05**
△ POD 3 - POD 1	*n* = 140 –0.82 ± 0.80	*n* = 129 –0.81 ± 0.81	*n* = 11 –0.95 ± 0.75	0.409
△ D/C - POD 3	*n* = 25 0.30 ± 1.61	*n* = 22 0.10 ± 1.59	*n* = 3 1.80 ± 0.92	**0.044**
△ OPD - POD 3	*n* = 17 3.75 ± 2.18	*n* = 11 3.80 ± 1.53	*n* = 6 3.67 ± 3.25	0.265

Values are expressed as mean ± standard deviation or median (interquartile range). OP, operation; POD, postoperative day; D/C, discontinue; OPD, outpatient department. [1]*p*-values calculated using the Student's *t*-test and Mann-Whitney U test. Bold indicates that the *p*-value is significant.

increase in mean hemoglobin level without severe adverse reactions following the use of intravenous supplements in pregnant women with iron deficiency anemia in the second or third trimester [13–16].

In a study that compared oral and intravenous iron supplements for treating anemia in pregnancy, a significant difference in hemoglobin level was found between the intravenous iron sucrose and oral iron polymaltose groups [17]. Hemoglobin levels increased significantly over time in the intravenous iron sucrose group without severe side effects. Intravenous supplementation corrected anemia more quickly and effectively than oral supplementation without causing side effects [17]. In a study that divided 200 pregnant women with iron deficiency anemia into intravenous and oral administration groups and compared hemoglobin and ferritin levels after 2, 4, and 6 weeks, the intravenous administration group exhibited significantly higher hemoglobin and ferritin levels compared with the oral administration group without unusual side effects, demonstrating that intravenous iron supplementation can quickly elevate hemoglobin levels without causing side effects [18].

Patients may refuse blood transfusions due to religious beliefs or personal preferences, which poses a challenge to physicians during surgery or treatments requiring blood transfusions [18]. A blood transfusion can save the life of a patient who experiences severe or acute bleeding, and a patient's refusal to receive one can pose a dilemma to obstetricians. Approximately 1000 patients die each year as a result of refusing a blood transfusion for religious reasons, and the risk for death is significantly increasing among obstetrical patients refusing blood transfusions [19,20]. The risks for maternal death and death due to severe obstetrical hemorrhage are 6 and 3.1 times higher among obstetrical patients undergoing bloodless treatment than general patients, respectively [21]. In a study involving 134 patients who refused blood transfusions, the risk for death was 0% in those with hemoglobin levels ≥5 g/dL and 44% in those with hemoglobin levels <5 g/dL. This suggests that physicians should consider bloodless treatment when patients refuse a blood transfusion even after their hemoglobin levels drop to 5–6 g/dL [22]. Bloodless treatment is an internal or surgical treatment performed without the use of blood or blood supplements to reduce bleeding and maximize blood production within the body. Bloodless treatment reduces the risk of inappropriate blood transfusions and prevents infections that can result from blood transfusions such as hepatitis and AIDS. It also reduces the risk of side effects caused by the use of stored blood, which has reduced oxygen-carrying capacity [23].

According to the 2006 Ministry of Health and Welfare of South Korea guidelines, a blood transfusion is required if blood loss $\geq$750 mL. Obstetrical patients are highly likely to experience blood loss $\geq$500 mL and have a high demand for blood transfusions due to uterine inertia, retained placenta, multiple pregnancies, cervical lacerations, and/or reduced blood coagulation. A patient who refuses blood transfusion and, instead, opts for bloodless treatment, should be carefully managed before, during, and after surgery [19,23]. The patient's medical history must be investigated, and thorough physical examinations must be performed before surgery to fully understand the patient's condition. Furthermore, pharmacotherapies, such as erythropoietin therapy, and iron and vitamin supplementation, must be additionally used to maintain high blood hemoglobin levels [18–24]. This requires organized multidisciplinary collaboration among different medical departments including surgery, anesthesiology, and pathology [18–24]. During surgery, it is necessary to identify potential sites of bleeding and devote extra attention to prevent bleeding. If unexpected bleeding occurs, blood loss must be mitigated by quickly stopping the bleeding using antifibrinolytics, desmopressin, and factor 7 [18–24]. After surgery, physicians must be able to quickly respond to any abnormal symptoms that the patient exhibits in the intensive care unit and consider intravenous administration of iron supplements and erythropoietin [18–24].

At this research facility, a hemoglobin test was performed before surgery, and the initial hemoglobin level was restored to normal or above normal using intravenous or oral iron supplements to minimize the need for blood transfusion. In another study from the same institution, acute normovolemic hemodilution, blood salvage (cell saver), and factor 7/8, fibrinogen, and tranexamic acid for enforcing hemostasis and reducing bleeding, were used during surgery [17]. Hemoglobin levels were maintained in the normal range by promoting blood production after surgery, as was done before surgery [17]. A domestic study reported that iron supplementation (11.2%) is the most common method of bloodless treatment followed by erythropoietin (10.7%) and aprotinin (6.5%), and iron supplements increase hemoglobin levels to facilitate oxygen supplementation within the body, even in the event of bleeding [25]. For obstetrical patients receiving iron supplementation as a bloodless treatment at this research facility, mean hemoglobin levels steadily decreased immediately after parturition until 3 days and switched direction on the day of discharge (usually 3 days after parturition), increasing thereafter. Despite blood loss that required a blood transfusion, obstetrical procedures, including normal (i.e., vaginal) delivery and cesarean section were successfully completed via bloodless treatment.

Our study had some limitations. It was a retrospective study and the number of patients involved is small. In addition, since the institution is a tertiary university hospital, there is a limitation that the study subjects cannot represent all obstetric patients. However, this is the first study to confirm that bloodless treatment may be a scientific, evidence-based option for patients who are expected to have obstetric hemorrhage.

5. Conclusions

Obstetrical procedures, including vaginal delivery and cesarean section, were successfully performed via bloodless treatment in patients for whom substantial blood loss was expected. Thus, bloodless treatment using iron supplements may be a scientific, evidence-based option for patients who refuse blood transfusions.

Availability of Data and Materials

The datasets generated and analyzed during the current study are not publicly available due to the Institutional Review Board has not approved the disclosure of patient data, but are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization, JIC and THK; Data curation, HSL; Formal analysis, JHS and SHC; Methodology, HSL and CWC; Validation, HHL; Writing—original draft, JIC and THK; Writing—review & editing, JIC, HSL, HHL, JHS, SHC, CWC, and THK. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of Soonchunhayng University Bucheon University Hospital (IRB No. 2017-01-004). Informed consent was obtained from the patients.

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Conflict of Interest

The authors do not have any conflict of interest to declare. This found is supported by JW pharmaceutical Co.

Ltd, but the company did not participate in the preparation and publication of the article. Hee-Sook Lim and Tae-Hee Kim are serving as one of the Guest editors of this journal. We declare that Hee-Sook Lim and Tae-Hee Kim had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Michael H. Dahan.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5007153.

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