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Outcomes of perioperative management in Jehovah's Witness patients undergoing surgeries with a risk of bleeding: A retrospective, single-center, observational study

조선대학교 대학원

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ABSTRACT

출혈 위험성이 있는 수술을 받은 여호와의 증인 환자를 위한 주술기 관리의 효과 - 후향적, 단일 기관, 관찰 연구

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배경 및 목적: 여호와의 증인 환자들은 종교적인 신념으로 동종혈액 수혈을 받는 것을 거부한다. 일부 수술을 주술기 출혈로 인하여 수혈이 요구되는 경우가 많다. 수혈이 필요할 정도의 빈혈 또는 출혈을 예방하기 위해, 마취과 의사들은 혈액 보존 전략 (blood conservation strategy; BCS)들을 주술기 동안 여호와의 증인 뿐만 아니라 무수혈을 원하는 환자들에 적용하고 있다. 하지만, 다른 수혈 거부 환자들과 달리, 여호와의 증인 환자에게 수혈이 필요할 정도의 출혈과 빈혈에 대한 주술기 관리 있어, 마취과의사들은 수혈을 해야 하나, 하지 않아야 하는 결정의 갈림길에서 윤리적, 임상적, 의학적 고민에 직면하는 경우가 많다. 이에 주술기 BCS 적용 여부와 혈액학적 검사 결과를 전자 의료 기록 검토를 통해 분석하여, 여호와의 증인 환자에서 무수혈 수술을 안전하게 시행할 수 있는지와 주술기 수혈을 허락하는 환자들과 비교하여 무수혈의 임상적 결과를 비교 분석하고자 하였다.

대상 및 방법: 2010년 1월 1일부터 2020년 7월 30일까지 출혈 위험이 있는 수술을 받았던 수혈을 거부한 여호와의 증인 59명 (JW 그룹) 환자와 수혈을 허용한 비여호와의 증인 362명 (Non-JW 그룹) 환자의 자료를 수집하였다. 출혈의 위험이 있는 수술들을 다음과 같이 정의했다: 복부 수술, 산부인과 수술, 고관절 수술, 무릎 수술, 그리고 척추 수술. 일차 변수는 주술기 사망률이었고, 이차 변수는 주술기 BCS 적용 빈도, 수술 후 발생한 질환 및 합병증, 그리고 주술기 혈액학적 검사 (complete blood count, coagulation tests, and blood chemistry tests) 결과 변화 이였다.

결과: JW 그룹의 사망률은 통계적으로 차이가 없었지만 0%로 Non-JW 그룹 (3%) 보다 낮았다 (p = 0.19). BCS의 적용은 JW 그룹과 Non-JW 그룹 사이에 유의하게 다르지 않았다 (p = 0.071) 철분 제제 및 기타 전신 지혈제들을 JW 그룹에서 더 많은 사용되었고 (p = 0.001), 항섬유소 용해제는 Non-JW 그룹에서 더 많이 사용되었다 (P = 0.007). 수술중 출혈혈액 회수법 (intraoperative blood salvage) 의 빈도는 집단 간 유의한 차이가 없었다. 수술 후 감염은 JW 그룹의 환자 0%, Non-JW 그룹의 8.4% 환자에서 발생하였으며 (p = 0.013), 파종성 혈관내 응고(disseminated intravascular coagulation)은 JW 그룹 (3.4%) 에 비해 Non-JW 그룹 (16%) 에서 유의하게 높았다 (p = 0.008). 수술 후 평균 헤모글로빈과 혈소판의 수 (수술 종료 후 2일 이내) 는 JW 그룹 (11.0 g/dL, 254.8×10^3/mm^3) 에서 Non-JW 그룹 (9.8 g/dL, 228.3×10^3/mm^3) 보다 더 유의하게 높았다 (p = 0.001, p = 0.028). 수술 후 활성화부분트롬보플라스틴시간 (Activated Partial Thromboplastin Time), 프로트롬빈시간 (Prothrombin Time), 국제 표준화 비율 (International Normalized Ratio) 은 JW 그룹에 비해 Non-JW 그룹에서 유의하게 연장되었다 (p < 0.001). 수술 후 혈당, 혈액요소질소 (Blood Urea Nitrogen), 크레아티닌 (Creatinine) 은 그룹 간의 유의한 차이를 보이지 않았다 (p ≥ 0.216). 마취 시간과 재원 일수는 Non-JW 그룹 (216.8분, 22.5일) 에서 JW 그룹 (154.6분, 15.3일) 보다 유의하게 길었다 (p < 0.001). 수술 중 출혈은 JW 그룹 (337 mL) 에서 Non-JW 그룹 (1557.7 mL) 보다 유의하게 적었다 (P < 0.001).

결론: 적극적인 BCS를 적용한 여호와의 증인 환자들은 수혈을 허락한 환자들과 비교하여 출혈량 및 빈혈의 빈도가 유의하게 낮았다. 또한, 여호와의 증인 환자는 수술 후 감염, 혈액 응고 이상 및 파종성 혈관내 응고 등의 합병증의 빈도가 낮았지만, 신장 이상은 없었다. 이는 출혈 감소를 위한 의사들의 적극적인 주술기 관리로 수혈을 거부하는 여호와의 증인 환자들이 유의한 합병증이 없이 출혈 위험성이 있는 수술들을 안전하게 받을 수 있다는 근거를 제시하고 있으며, 수혈이 주술기 합병증을 증가시키는 위험인자로 작용함을 보여 주였다.

Ⅰ. INTRODUCTION

Allogeneic blood transfusions for controlling hypovolemia due to perioperative bleeding and intrinsic anemia are associated with increased morbidity and mortality [1]. Therefore, perioperative blood conservation strategies (BCSs) are recommended to minimize the exposure of patients to allogeneic blood [2, 3]. However, patients who refuse blood transfusion may have a risk of severe perioperative anemia despite the application of BCSs [4].

Jehovah's Witnesses (JWs) are members of a Christian denomination that refuses blood transfusion. They believe that the Bible strictly prohibits the transfer of blood or blood products into a person's body. Therefore, they do not accept transfusions of whole blood (allogeneic and autologous) or its main components (plasma, red blood cells, white blood cells, and platelets) [5-8]. They also do not allow their own blood to be transfused if it has left their body at any time [5-8]. Some of them may allow the use of blood cell fractions, erythropoietin, acute normovolemic hemodilution, and intraoperative cell salvage based on a personal decision [5-8].

Unlike in other patients who refuse transfusion, anesthesiologists often face an ethical, clinical, and medicolegal dilemma (whether or not to perform transfusion) in the management of hypovolemia (due to bleeding and intrinsic anemia) requiring transfusion in JW patients [9, 10]. Therefore, many surgeons and hospitals often avoid accepting JW patients who need surgeries associated with a high risk of bleeding or complicated surgeries that inevitably require blood transfusion.

Many studies have focused on JW patients and various other patients who desire bloodless surgeries [11-17]. They have demonstrated that most surgeries could be performed safely without transfusion, with similar incidences of infection

and mortality to surgeries involving blood transfusions [11-17]. However, because these previous studies had a small sample size or were case reports, there is still insufficient evidence on the safety of bloodless surgeries for all patients, especially JWs.

In this study, we hypothesized that JW patients could safely undergo various surgeries without allogeneic blood transfusion. We aimed to test this hypothesis to support the results of previous studies. Through a review of electronic medical records, we analyzed the applied BCSs, perioperative hematologic changes, and morbidity and mortality in JW patients who underwent various surgeries with a risk of bleeding and compared their outcomes with those of patients who received blood transfusion.

Ⅱ. MATERIALS and METHODS

1. Study Design and Ethical Statement

The Institutional Review Board (IRB) of Chosun University Hospital approved this retrospective study based on an electronic medical record review (CHOSUN 2020-08-018) on September 10, 2020. The IRB waived requirement for the written informed consent from patients because the data were anonymized before analysis, and this study had no more than minimal risk to the subject. This study was conducted in accordance with the Declaration of Helsinki of 1964 and all its subsequent revisions.

2. Study Population Selection (Fig. 1)

We collected data from 179 JW patients (JW group) aged 18–100 years who underwent surgery with a risk of bleeding from January 1, 2010, to July 30, 2020. We defined surgeries with a risk of bleeding as open abdominal surgery, open gynecologic surgery, open hip surgery, open knee surgery, and spinal surgery. As a control group (non-JW group), we randomly enrolled 430 non-JW patients aged 18–100 years who underwent surgeries with a risk of bleeding during a same period. We excluded patients with preoperative coagulopathy and American Society of Anesthesiologists physical status (ASA-PS) classification of IV and V.

3. Outcomes

3.1. Demographic Data

We assessed age, sex, weight, height, body mass index (BMI), ASA-PS, emergency status, classification of surgery, anesthesia method, anesthesia duration, hospital stay duration, perioperative input (crystalloid and colloid), and blood loss.

3.2. Perioperative BCSs

We assessed the use of perioperative antifibrinolytics, iron preparations, other systemic hemostatics, and cell salvage. Moreover, we assessed the anesthesia method, perioperative incidence of hypothermia, and intraoperative methods applied to prevent hypothermia. We defined hypothermia as a body temperature of ≤ 36.0°C.

3.3. Perioperative Transfusions

We assessed the use of packed red blood cells, platelets, fresh frozen plasma, albumin, cryoprecipitate, and blood cell salvage.

3.4. Mortality, Morbidity, and Other Complications

We assessed the incidences of death, infection, and disseminated intravascular coagulation (DIC). Postoperative infection was defined as surgical wound infection or systemic infection, septicemia, peritonitis, and other infectious complications described in the medical records. Patients with DIC were defined as those with abnormal prothrombin time (PT; ≥ 3s higher than the reference value) or thrombocytopenia (platelet count < 100,000//mm^3) during the perioperative period, or clinically evident impaired coagulation in the medical records.

3.5. Changes in Complete Blood Count, Blood Coagulation Variables, and Blood Chemistry Variables

We assessed the perioperative complete blood count (CBC; hemoglobin and platelet counts), coagulation variables (activated partial thromboplastin time [APTT], PT, and international normalized ratio [INR]), and blood chemistry variables (glucose, blood urea nitrogen [BUN], and serum creatinine [Cr]) preoperatively and postoperatively (within 2 days after the end of surgery) and before discharge evaluation. We also measured the degrees of changes in perioperative CBC, coagulation variables, and blood chemistry variables compared

with the preoperative values.

4. Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows (version 26.0; IBM Corp., Armonk, NY, USA). All data are presented as mean (95% confidence interval) or number (percentage) of patients.

The primary endpoint was the rate of mortality, and the secondary endpoints were the frequency of BCS application, perioperative morbidity, and changes in hematologic variables.

Continuous variables were analyzed using the t-test, and nominal variables were analyzed with the $\chi 2$ test or Fisher's exact test, as appropriate. For the analysis of time interval data that passed Mauchly's sphericity test, we used repeated-measures analysis of variance (ANOVA). For data that did not pass Mauchly's sphericity test, we used Wilk's lambda multivariate ANOVA. To compare two groups in a given time interval, the $\chi 2$ test was used. Statistical significance was set at $p < 0.05$.

Ⅲ. RESULTS

We enrolled a total of 421 patients (59 JW patients and 362 non-JW patients) after the review of the electronic medical records (Fig. 1). We excluded 120 patients from the JW group who underwent surgery without a risk of bleeding (n = 117) and had ASA-PS IV and V (n = 3). We excluded 68 patients from the non-JW group who underwent surgery without a risk of bleeding (n = 49) and had ASA-PS IV and V (n = 19).

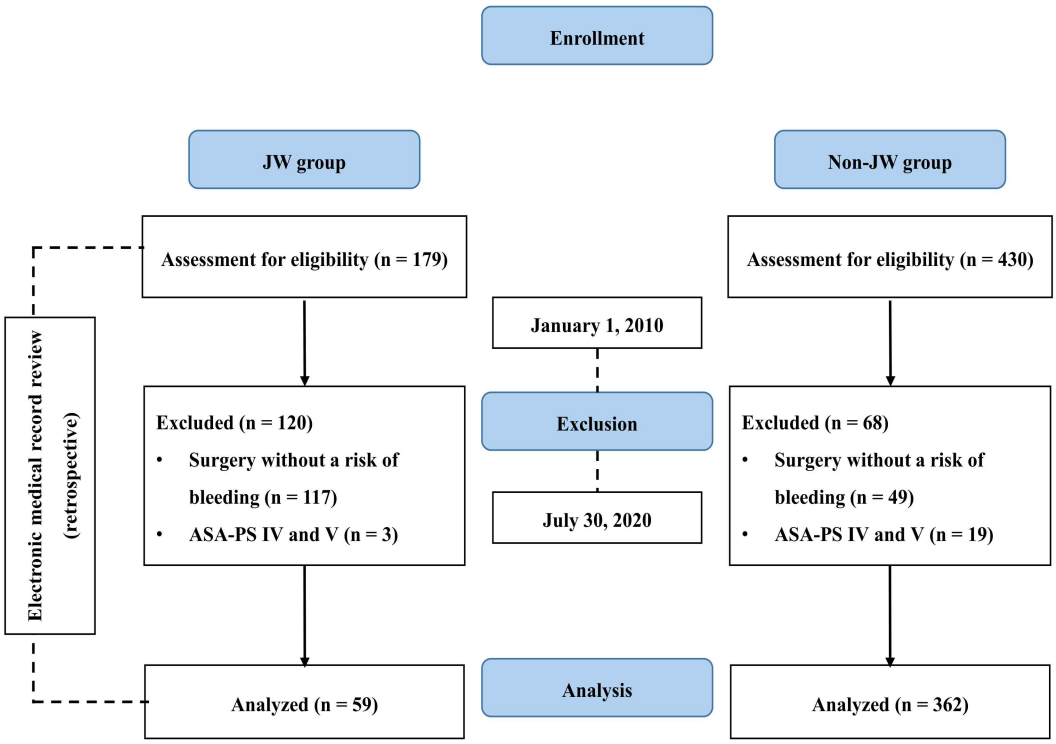

Fig. 1. Flowchart of patient inclusion. ASA-PS, American Society of Anesthesiologists physical status; JW, Jehovah's Witness.

1. Demographic Data (Tables 1-4)

Significant differences in age, height, weight, and BMI were observed. The numbers of female patients and emergency surgeries were higher in the JW group than in the non-JW group ($p \leq 0.001$). The ASA-PS classification significantly differed between groups ($p < 0.001$, Table 1). The proportions of patients with ASA-PS I and II were higher in the JW group than in the non-JW group, whereas there were more ASA-PS III patients in the non-JW group than in the JW group. The durations of anesthesia and hospital stay were longer in the non-JW group than in the JW group ($p < 0.001$) (Table 1).

Table 1. Demographic data (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Age (y)	62.8 (58.0, 67.6)	65 (63.4, 66.5)	0.317
Female sex	50 (84.7)	226 (62.4)	0.001*
Weight (kg)	60.5 (57.8, 63.1)	63.4 (61.5, 65.3)	0.230
Height (cm)	156.7 (154.3, 159.1)	157.6 (155.9, 159.4)	0.688
BMI (kg/m^2)	24.6 (23.68, 25.52)	33.82 (26.32, 41.33)	0.331
ASA-PS (Ⅰ/Ⅱ/Ⅲ)	21/33/5 (35.6/55.9/8.5)	54/206/102 (14.9/56.9/28.2)	< 0.001*
Emergency (no/yes)	38/21 (64.4/35.6)	324/38 (89.5/10.5)	< 0.001*
Anesthesia duration (h)	154.6 (133.8, 175.4)	216.8 (201.9, 231.8)	< 0.001*
Hospital stay (d)	15.3 (12.7, 18)	22.5 (20.3, 24.7)	< 0.001*

Values are expressed as mean (95% confidence interval) or number (percentage) of patients. ASA-PS, American Society of Anesthesiologists physical status; BMI, body mass index; JW, Jehovah's Witness. *$p < 0.05$ was considered to indicate statistical significance.

Surgeries with a risk of bleeding showed significant differences between groups ($p < 0.001$, Table 2). In the JW group, spinal surgery was the most common surgery performed, followed by open gynecologic surgery, open knee surgery, open hip surgery, and open abdominal surgery. In the non-JW group, open hip surgery was the most common surgery performed, followed by spinal surgery, open gynecologic surgery, open knee surgery, and open abdominal surgery.

Table 2. Classification of surgeries (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Open abdominal surgery	5 (8.5)	50 (13.8)	< 0.001*
Open gynecologic surgery	15 (25.4)	55 (15.2)	
Open hip surgery	5 (8.5)	118 (32.6)	
Open knee surgery	14 (23.7)	50 (13.8)	
Spinal surgery, 1 level	10 (16.9)	22 (6.1)	
Spinal surgery, 2 levels	6 (10.2)	16 (4.4)	
Spinal surgery, > 3 levels	4 (6.8)	51 (14.1)	

Values are expressed as number (percentage) of patients. JW, Jehovah's Witness. *$p < 0.05$ was considered to indicate statistical significance.

The perioperative (intraoperative and postoperative) blood loss was smaller in the JW group than in the non-JW group ($p < 0.001$, Table 3). The intraoperative infused volume of crystalloid was lower in the JW group than in the non-JW group ($p < 0.001$, Table 4). Perioperative colloid was less frequently infused in the JW group (16.9%) than in the non-JW group (35.1%) ($p = 0.006$, Table 4).

Table 3. Perioperative blood loss (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Total blood loss (mL)	337 (229.3, 444.7)	1557.7 (1343.6, 771.8)	< 0.001*
Intraoperative	134 (73.7, 194.3)	667 (572.9, 761.1)	< 0.001*
Postoperative	203 (111.6, 294.5)	893.4 (716.2, 1070.6)	< 0.001*

Values are expressed as mean (95% confidence interval). JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

Table 4. Perioperative crystalloid and colloid (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Perioperative crystalloid (mL)			
Intraoperative	897.5 (769.3, 1025.6)	1841.1 (1702.2, 1980.1)	< 0.001*
Postoperative	1764.1 (852.4, 2675.8)	9622.9 (7533.2, 11712.6)	0.647
Perioperative colloid infusion (yes)	10 (16.9)	127 (35.1)	0.006*

Values are expressed as mean (95% confidence interval) or number (percentage) of patients. JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

2. Perioperative BCSs (Tables 5-7)

The use of BCSs, such as perioperative antifibrinolytics, iron preparations, and other systemic hemostatics, was not significantly different between the JW and

non-JW groups (p = 0.071, Table 5). Iron preparations and other systemic hemostatics were more frequently used in the JW group than in the non-JW group (p < 0.001); however, antifibrinolytics were less frequently used in the JW group (p = 0.007). The use of cell salvage was not significantly different between groups. None of the patients received other BCSs, such as erythropoietin and prothrombin complex concentrate.

Table 5. Perioperative antifibrinolytics, iron preparations, and systemic hemostatics (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Blood conservation strategies (yes)	36 (61)	175 (48.3)	0.071
Antifibrinolytics (yes)	6 (10.2)	95 (26.2)	0.007*
Iron preparations (yes)	9 (15.3)	12 (3.3)	< 0.001*
Other systemic hemostatics (yes)	22 (37.3)	47 (13)	< 0.001*
Cell salvage (yes)	6 (10.2)	31 (8.6)	0.686

Values are expressed as number (percentage) of patients. JW, Jehovah's Witness.
*p < 0.05 was considered to indicate statistical significance.

The anesthesia methods did not show significant differences between groups (p = 0.709, Table 6). In the JW group, balanced anesthesia was the most preferred method, followed by total intravenous anesthesia, inhaled anesthesia, and neuroaxial anesthesia. In the non-JW group, balanced anesthesia was also the most preferred method, followed by inhaled anesthesia, total intravenous anesthesia, and neuroaxial anesthesia.

Table 6. Anesthesia methods (n = 421)

	JW group	Non-JW group	p Value

	(n = 59)	(n = 362)	
Inhaled anesthesia	10 (16.9)	71 (19.7)	0.709
Balanced anesthesia	31 (52.5)	179 (49.6)	
Total intravenous anesthesia	11 (18.6)	53 (14.7)	
Neuroaxial anesthesia	7 (11.9)	58 (16.1)	

Values are expressed as number (percentage) of patients. JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

The incidences of intraoperative and postoperative hypothermia were significantly different between groups (p = 0.013 and p = 0.003, respectively; Table 7). All JW patients experienced mild hypothermia (35.5℃ < temperature≤ 36.0℃), whereas normal body temperature and mild hypothermia were observed in 10% and 90% of patients receiving blood transfusion, respectively.

Protocols for preventing hypothermia were more frequently applied in the non-JW group than in the JW group (p < 0.001), which included forced-air warming (p < 0.001) and intravenous fluid warming (p = 0.006, Table 7).

Table 7. Incidence of hypothermia and its prevention methods (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Incidence (≥ 36.0 ℃/< 36.0 ℃)			
Intraoperative	0/59 (0/100)	31/331 (8.6/91.4)	0.013*
Postoperative	0/59 (0/100)	40/322 (11/89)	0.003*
Prevention methods (yes/no)			
Overall	23/36 (39/61)	243/119 (67.1/32.9)	< 0.001*

Forced-air warming	23/36 (39/61)	236/93 (71.7/28.3)	< 0.001*
IV fluid warming	3/56 (5.1/94.9)	61/246 (19.9/80.1)	0.006*
Passive warming	2/57 (3.4/96.6)	23/281 (7.6/92.4)	0.398

Values are expressed as numbers (percentages) of patients. JW, Jehovah's Witness; IV, intravenous; Passive warming, warming of patients with a warm blanket. *p < 0.05 was considered to indicate statistical significance.

3. Perioperative Transfusions (Table 8)

The overall rate of perioperative transfusion was significantly different between the JW (15.3%) and non-JW (74.3%) groups (p < 0.001, Table 7). The JW group did not receive any packed red blood cells, platelets, fresh frozen plasma, or cryoprecipitate. Albumin was administered to 4 (6.8%) patients in the JW group and 83 (22.9%) patients in the non-JW group (p = 0.003). Autologous blood transfusion after cell salvage was administered in 6 (10.2%) patients in the JW group and 31 (8.6%) patients in the non-JW group (p = 0.686).

Table 8. Perioperative transfusion (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Overall (yes)	9 (15.3)	269 (74.3)	< 0.001*
Packed red blood cells (yes)	0 (0)	256 (70.7)	< 0.001*
Platelets (yes)	0 (0)	52 (14.4)	< 0.001*
Fresh frozen plasma (yes)	0 (0)	95 (26.2)	< 0.001*
Albumin (yes)	4 (6.8)	83 (22.9)	0.003*
Cryoprecipitate (yes)	0 (0)	104 (10.2)	0.005*

Cell salvage (yes)	6 (10.2)	31 (8.6)	0.686

Values are expressed as number (percentage) of patients. JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

4. Mortality, Morbidity, and Other Complications (Table 9)

The mortality rate in the JW group was 0%, which was lower than that in the non-JW group (3%) without a statistically significant difference (p = 0.370). Massive bleeding occurred in 3.4% of patients in the JW group and 11.8% of those in the non-JW group, but the difference was not statistically significant (p = 0.064). Postoperative infection occurred in 0% of patients in the JW group and 8.4% of patients in the non-JW group (p = 0.013, Table 9). Early discontinuation of surgery occurred in 0% of patients in the JW group and 0.9% of patients in the non-JW group (p = 1.000). The incidence of DIC was higher in the non-JW group (16%) than in the JW group (3.4%, p = 0.008).

Table 9. Incidences of death, infection and disseminated intravascular coagulation (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Death	0 (0)	10 (3)	0.370
Infection	0 (0)	29 (8.4)	0.013*
DIC	2 (3.4)	58 (16)	0.008

Values are expressed as number (percentage) of patients. DIC, disseminated intravascular coagulation; JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

5. Changes in CBC, Blood Coagulation Variables, and Blood Chemistry Variables

5.1. Changes in CBC

The perioperative hemoglobin level was not significantly different between groups ($p = 0.075$, Table 10). However, the hemoglobin level at each time point was higher in the JW group than in the non-JW group ($p \leq 0.006$, Table 10). The incidence of hemoglobin < 10 g/dL was lower in the JW group than in the non-JW group throughout the perioperative period ($p \leq 0.005$, Table 10). The difference between the postoperative and preoperative hemoglobin levels was lower in the JW group (-1.1 g/dL) than in the non-JW group (-1.7 g/dL), with a mean difference of 0.55 g/dL ($p = 0.002$, Table 11). The difference between the discharge and preoperative hemoglobin levels did not show a significant divergence between groups, with a mean difference of 0.08 g/dL ($p = 0.822$, Table 11).

The perioperative platelet count was significantly different between groups ($p = 0.018$, Table 10). At each time point, the postoperative platelet count was higher in the JW group than in the non-JW group ($p = 0.028$, Table 10), whereas the preoperative and discharge platelet counts were not significantly different between groups. The incidence of postoperative platelet count < 150,000 was lower in the JW group (5.1%) than in the non-JW group (20.4%, $p = 0.005$); however, the incidence of low platelet count before surgery and at discharge did not show significant differences (Table 10). Both groups showed decreased postoperative platelet counts and increased discharge platelet counts (Table 11). However, the degrees of change between the postoperative and preoperative platelet counts and between the discharge and preoperative platelet counts were not significantly different (Table 11).

Table 10. Perioperative complete blood count (hemoglobin and platelet counts) (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Hb (g/dL)			0.075
Preoperative	12.1 (11.7, 12.4)	11.5 (11.2, 11.7)	0.003*
Postoperative	11 (10.6, 11.3)	9.8 (9.6, 10.0)	< 0.001*
Discharge	10.5 (10.1, 10.9)	9.8 (9.6, 10.0)	0.006*
Hb (< 10 g/dL)			
Preoperative	3 (5.1)	89 (24.6)	0.001*
Postoperative	15 (25.4)	205 (56.6)	< 0.001*
Discharge	25 (42.4)	224 (61.9)	0.005*
Platelets ($\times 10^3/mm^3$)			0.018*
Preoperative	266.2 (246.3, 286)	267.3 (255.9, 278.8)	0.918
Postoperative	254.8 (233.6, 276.1)	228.3 (218.1, 238.5)	0.028*
Discharge	343.7 (299.1, 388.3)	320.7 (307.2, 334.2)	0.233
Platelets ($< 15\times 10^3/mm^3$)			
Preoperative	3 (5.1)	43 (11.9)	0.121
Postoperative	3 (5.1)	74 (20.4)	0.005*
Discharge	1 (1.7)	30 (8.3)	0.102

Values are expressed as mean (95% confidence interval) or number (percentage) of patients. Hb, hemoglobin; JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

Table 11. Degree of changes in perioperative complete blood count (hemoglobin and platelet counts) (n = 421)

Difference from baseline value	JW group (n = 59)	Non-JW group (n = 362)	p Value
Hb (g/dL)			
Hb (post-pre)	-1.1 (-1.4, -0.8)	-1.7 (-1.9, -1.5)	0.002*
Mean difference	0.55 (0.20, 0.89)		
Hb (dis-pre)	-1.6 (-2, -1.2)	-1.7 (-1.9, -1.4)	0.822
Mean difference	0.08 (-0.58, 0.73)		
Platelets ($\times 10^3/mm^3$)			
PLT (post-pre)	-2.2 (-3.2, -1.1)	-0.7 (-1.3, -0.1)	0.057
Mean difference	27.70 (8.51, 46.88)		
PLT (dis-pre)	77.5 (35.1, 119.9)	53.3 (39.7, 67)	0.210
Mean difference	24.17 (-13.64, 61.97)		

Values are expressed as mean (95% confidence interval). Hb, hemoglobin; Baseline value, value measured at the preoperative period; Hb (post–pre), difference between postoperative and preoperative Hb levels; Hb (dis–pre), difference between discharge and preoperative Hb levels; PLT (post–pre), difference between postoperative and preoperative platelet counts; PLT (dis–pre), difference between discharge and preoperative platelet counts; JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

5.2. Changes in Blood Coagulation Variables

The perioperative APTT, PT, and INR were higher in the non-JW group than in the JW group (p < 0.001, Table 12), whereas they did not show a significant difference between groups in the preoperative period. However, the incidence of prolonged APTT (≥ 45 s) was not significantly different between groups throughout the perioperative period. The incidences of prolonged PT (≥ 12.6 s)

and elevated INR (≥ 1.28) were higher in the non-JW group than in the JW group at the end of surgery ($p < 0.001$) and before discharge ($p < 0.001$, Table 12).

The difference between discharge and preoperative APTT was lower in the JW group (-0.5 s) than in the non-JW group (2.8 s), with a mean difference of -3.36 s ($p < 0.001$, Table 13), whereas the difference between postoperative and preoperative APTT was not significantly divergent between groups. The differences between postoperative and preoperative PT and between discharge and preoperative PT were lower in the JW group than in the non-JW group ($p \leq 0.005$, Table 13). The differences between postoperative and preoperative INR and between discharge and preoperative INR did not show significant divergence between groups ($p \geq 0.372$, Table 13).

Table 12. Perioperative coagulation variables (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
APTT (s)			0.002*
Preoperative	29.6 (28.5, 30.6)	30.0 (29.5, 30.5)	0.500
Postoperative	27.4 (27.0, 27.7)	29.3 (28.9, 29.8)	< 0.001*
Discharge	29.0 (28.1, 30.0)	32.8 (32.1, 33.5)	< 0.001*
APTT (≥ 45 s)			
Preoperative	0 (0)	5 (1.4)	1.000
Postoperative	0 (0)	6 (1.7)	1.000
Discharge	0 (0)	11 (3)	0.376
PT (s)			0.008*
Preoperative	11.1 (10.5, 11.7)	11.5 (11.3, 11.8)	0.181

Postoperative	11.7 (11.6, 11.8)	13.2 (12.9, 13.4)	< 0.001*
Discharge	12.5 (12.4, 12.7)	14.1 (13.7, 14.4)	< 0.001*
PT (≥ 12.6 s)			
Preoperative	4 (6.8)	49 (13.5)	0.147
Postoperative	3 (5.1)	245 (67.7)	< 0.001*
Discharge	3 (5.1)	300 (82.9)	< 0.001*
INR			0.672
Preoperative	1.0 (0.9, 1.0)	1.1 (1.0, 1.1)	0.141
Postoperative	1.0 (1.0, 1.0)	1.2 (1.2, 1.2)	< 0.001*
Discharge	1.1 (1.1, 1.1)	1.3 (1.2, 1.3)	< 0.001*
INR (≥ 1.28)			
Preoperative	2 (3.4)	25 (6.9)	0.402
Postoperative	1 (1.7)	41 (11.3)	0.018*
Discharge	1 (1.7)	232 (64.1)	< 0.001*

Values are expressed as mean (95% confidence interval) or number (percentage) of patients. APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

Table 13. Degree of changes in perioperative coagulation variables (n = 421)

Difference from baseline value	JW group (n = 59)	Non-JW group (n = 362)	p Value
APTT (s)			

APTT (post-pre)	-2.2 (-3.2, -1.1)	-0.7 (-1.3, -0.1)	0.057
Mean difference	-1.50 (-3.04, 0.04)		
APTT (dis-pre)	-0.5 (-1.9, 0.8)	2.8 (2.1, 3.5)	< 0.001*
Mean difference	-3.36 (-5.21, -1.51)		
PT (s)			
PT (post-pre)	0.6 (0, 1.2)	1.6 (1.4, 1.9)	0.005*
Mean difference	-1.03 (-1.74, -0.32)		
PT (dis-pre)	1.4 (0.9, 2)	2.5 (2.2, 2.9)	0.001*
Mean difference	-1.12 (-1.78, -0.45)		
INR			
INR (post-pre)	0.0 (0, 0.1)	0.1 (0.1, 0.2)	0.372
Mean difference	-0.07 (-0.22, 0.08)		
INR (dis-pre)	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)	0.446
Mean difference	-0.06 (-0.23, 0.1)		

Values are expressed as mean (95% confidence interval). APTT, activated partial thromboplastin time; INR, international normalized ratio; PT, prothrombin time; APTT (post–pre), difference between postoperative and preoperative APTT; APTT (dis–pre), difference between discharge and preoperative APTT; PT (post–pre), difference between postoperative and preoperative PT; PT (dis–pre), difference between discharge and preoperative PT; INR (post–pre), difference between postoperative and preoperative INR; INR (dis–pre), difference between discharge and preoperative INR; JW, Jehovah's Witness. *p < 0.05 was considered to indicate statistical significance.

5.3. Changes in Blood Chemistry Variables

The repeatedly measured perioperative blood chemistry variables were not significantly different between groups (Table 14). At each measurement point, the perioperative blood glucose, BUN, and Cr levels also did not show significant differences between groups, except for the higher preoperative glucose level in the non-JW group than in the JW group (Table 14).

The incidences of perioperative blood glucose, BUN, and Cr exceeding the normal ranges were not significantly different, although there was a higher proportion of patients with abnormal postoperative glucose levels at the end of surgery in the JW group (78%) than in the non-JW group (61.9%, p = 0.017; Table 14).

The differences between the postoperative and preoperative values of blood chemistry variables (glucose, BUN, and INR) and between the discharge and preoperative values of the same variables did not show significant divergence between groups (p ≥ 0.069, Table 15).

Table 14. Perioperative blood chemistry variables (n = 421)

	JW group (n = 59)	Non-JW group (n = 362)	p Value
Glucose (mg/dL)			0.246
Preoperative	108.6 (100.8, 116.4)	121.3 (116.1, 126.4)	0.008*
Postoperative	130.6 (121.9, 139.3)	131.9 (126.2, 137.5)	0.866
Discharge	104.2 (95.8, 112.5)	106.4 (102.5, 110.2)	0.665
Glucose (≥110 mg/dL)			
Preoperative	24 (40.7)	174 (48.1)	0.292
Postoperative	46 (78)	224 (61.9)	0.017*

Discharge	17 (28.8)	106 (29.3)	0.942
BUN (mg/dL)			0.751
Preoperative	14.6 (13.1, 16.1)	16.6 (15.5, 17.6)	0.134
Postoperative	15.0 (13.0, 17.0)	16.8 (15.7, 18.0)	0.216
Discharge	15.7 (13.8, 17.7)	16.6 (15.4, 17.9)	0.575
BUN (≥ 21 mg/dL)			
Preoperative	9 (15.3)	77 (21.3)	0.288
Postoperative	12 (20.3)	89 (24.6)	0.479
Discharge	11 (18.6)	76 (21)	0.679
Cr (mg/dL)			0.543
Preoperative	0.9 (0.7, 1.1)	0.9 (0.9, 1.0)	0.786
Postoperative	1.0 (0.8, 1.2)	0.9 (0.9, 1.0)	0.833
Discharge	0.9 (0.8, 1.1)	1.0 (0.9, 1.1)	0.739
Cr (≥ 1.4 mg/dL)			
Preoperative	7 (11.9)	33 (9.1)	0.504
Postoperative	5 (8.5)	35 (9.7)	0.772
Discharge	5 (8.5)	50 (13.8)	0.259

Values are expressed as mean (95% confidence interval) or number (percentage) of patients. BUN, blood urea nitrogen; Cr, serum creatinine; JW, Jehovah's Witness. *$p < 0.05$ was considered to indicate statistical significance.

Table 15. Degree of changes in perioperative blood chemistry variables (n = 421)

Difference from baseline value	JW group (n = 59)	Non-JW group (n = 362)	p Value
Glucose (mg/dL)			
GLU (post-pre)	22 (12.6, 31.5)	10.6 (4.7, 16.5)	0.136
Mean difference	11.43 (-3.61, 26.47)		
GLU (dis-pre)	-4.4 (-14.3, 5.4)	-14.9 (-20.5, -9.3)	0.069
Mean difference	10.44 (-0.83, 21.71)		
BUN (mg/dL)			
BUN (post-pre)	0.4 (-0.8, 1.6)	0.3 (-0.5, 1.1)	0.848
Mean difference	0.14 (-1.27, 1.54)		
BUN (dis-pre)	1.1 (-0.5, 2.7)	0.1 (-1, 1.2)	0.451
Mean difference	1.05 (-1.68, 3.77)		
Cr (mg/dL)			
Cr (post-pre)	0.0 (0.0, 0.1)	0.0 (0.0, 0.0)	0.324
Mean difference	0.05 (-0.05, 0.16)		
Cr (dis-pre)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.851
Mean difference	-0.01 (-0.17, 0.14)		

Values are expressed as mean (95% confidence interval). GLU (post–pre), BUN (post–pre), and Cr (post–pre), differences between the postoperative and preoperative levels of glucose, blood urea nitrogen, and serum creatinine, respectively; GLU (dis–pre), BUN (dis–pre), and Cr (dis–pre), difference between the discharge and preoperative levels of glucose, blood urea nitrogen, and serum creatinine, respectively; JW, Jehovah's Witness. *$p < 0.05$ was considered to indicate statistical significance.

Ⅳ. DISCUSSION

This study is meaningful in that it analyzed the outcomes of perioperative management in Korean JW patients undergoing bloodless surgeries. The results of this study showed that most JW patients safely underwent surgery without blood transfusions and without developing significant hematologic abnormalities, compared with patients who received blood transfusion under standard transfusion protocols.

1. Perioperative BCSs

Various perioperative BCSs can be used to minimize blood loss, optimize anemia tolerance, enhance hemoglobin and red blood cell production, correct coagulation defects, and promote hemostasis based on individual patient preferences. These BCSs include the administration of erythropoietin, prothrombin complex concentrate, oral or intravenous iron preparations, and antifibrinolytics; preoperative autologous donation; acute normovolemic hemodilution; autologous blood transfusion after cell salvage; and anesthetic techniques such as intraoperative induction of mild hypothermia and application of permissive hypotension [8, 10, 18-25]. Many studies have shown that patients who refuse blood transfusion, such as JWs, could safely undergo surgeries with the application of aggressive BCSs [18, 26-28].

The present study also showed that BCSs were more frequently applied in JW patients (61%), who were able to more safely undergo surgeries without allogeneic blood transfusion than patients who allowed blood transfusion (48.3%). In addition, the perioperative application of BCSs was effective in achieving hemoglobin nadirs and outcomes in JW patients similar to those in patients who received transfusion [18].

1.1. Perioperative Management with Medicines

This study showed that hemocoagulase, which is classified into the group of other systemic hemostatics, was the most common BCS applied (37.3%), followed by iron preparations (15.3%), antifibrinolytics (10.2%), and cell salvage (10.2%) in JW patients. In contrast, in non-JW patients, antifibrinolytics (26.2%) were the most common BCS applied. At our hospital, we could not use erythropoietin because of the constraints of health insurance schemes. Therefore, we preferred using antifibrinolytics, oral or intravenous iron preparations, and other systemic hemostatics. Meanwhile, although erythropoietin is an effective alternative to blood transfusion, it has another limitation of taking a long time (4 weeks) to promote sufficient erythropoiesis (3 days for erythropoiesis, 7 days for 1 unit of blood, and 28 days for 5 units of blood) [28]. Therefore, although antifibrinolytics were used in the non-JW group, erythropoietin may be ineffective in overcoming perioperative blood loss because of the time limitation.

1.2. Anesthetic techniques

Permissive or induced hypotension (systolic blood pressure of 80–90 mm Hg, mean arterial pressure of 50–65 mm Hg, or a 30% reduction in the mean arterial pressure at baseline) can be allowed to reduce perioperative blood loss in JW patients [8, 29, 30]. Effective permissive hypotension can be achieved using pharmacological agents alone or in combination with inhaled anesthetics, sodium nitroprusside, nitroglycerin, remifentanil, calcium channel blockers, β-blockers, and agents used in neuroaxial anesthesia [31]. Balanced anesthesia, total intravenous anesthesia, and neuroaxial anesthesia are preferable anesthesia methods in JW patients, considering the lower toxicity, safer recovery, and natural hypotensive effect of the anesthetic drugs [31, 32]. Nwosu et al. [32] documented that anesthesia with permissive hypotension was useful in reducing surgical blood loss and improving surgical site visibility while reducing the surgical time in selected cases, such as in patients undergoing spinal surgery [18], total hip surgery [26], or other surgeries. This study also showed that general anesthesia with opioids

and neuroaxial anesthesia was preferred, although we did not investigate whether they were used for permissive hypotension.

Induction of mild to moderate hypothermia has also been successfully used as a BCS; however, hypothermia below 35°C should be avoided to prevent coagulopathy and blood loss [10]. Mild intraoperative hypothermia (between 35.5°C and 36.0°C) was observed in all JW patients and in 91.4% of non-JW patients in this study.

1.3. Transfusions

Although JWs refuse allogeneic blood transfusion, some of them may allow the prevention or control of perioperative anemia with acute normovolemic hemodilution or blood cell salvage, based on a personal decision [5-8, 24]. However, we could not perform acute normovolemic hemodilution because of the policy restrictions of blood banks and technical difficulties in our hospital. Therefore, we only applied perioperative autologous blood cell salvage to minimize the need for allogeneic transfusion as an alternative technique. Although not routinely performed, the use of blood that remains in continuity with the patient's circulation can be safely accepted by JWs, on a patient-by-patient basis [33-36]. If possible, blood salvage is recommended as a backup measure in patients undergoing surgeries with a risk of moderate or low blood loss [37]. Blood salvage was applied in 10.2% of JW patients and 8.6% of non-JW patients in this study.

1.4. Surgical techniques

Surgeons should consider a staged operation or techniques that can reduce the risk of perioperative bleeding and transfusion when performing complex and lengthy surgeries in JW patients [10, 25]. The JW patients enrolled in this study underwent less complex surgeries with a short expected operative time, and none of them required a stage operation.

2. Mortality, Morbidity, and Other Complications

Preoperative correction of anemia is essential, as decreased preoperative hemoglobin is associated with increased morbidity and mortality [25]. Therefore, allogeneic blood and blood derivatives are usually transfused to compensate for significant intraoperative blood loss. However, allogeneic blood transfusion can lead to perioperative coagulopathy or even DIC, which can result in postoperative bleeding, renal failure, increased risk of infection, prolonged hospital stay, and increased postoperative morbidity and mortality, independent of patient comorbidities and preoperative hemoglobin levels [18, 38, 39].

The estimated blood loss was lower in JW patients who received perioperative BCSs, without significant morbidity outcomes, than in patients who received blood transfusion [37]. In open knee surgeries, the postoperative complication rate did not show a significant difference between the JW (3.9%) and non-JW (3.2%) groups [40]. In JW patients who underwent bloodless emergency laparotomy for a ruptured uterus, the infectious mortality rate was lower (30% vs. 40%) and the DIC incidence was lower (0.0% vs. 4.4%) than in patients who received allogeneic blood transfusion [41]. In the study by Kim et al. [42], the perioperative Cr level, as an indicator of renal injury, was not statistically significantly different between the groups. This study also showed that perioperative blood loss was lower in the JW group, resulting in a lower infused crystalloid volume and a lower incidence of colloid use during the perioperative period. Moreover, postoperative infection, coagulopathy, and DIC were more frequent in the non-JW group than in the JW group, whereas mortality, massive bleeding, and renal insufficiency were not significantly different between groups. It was assumed that the non-JW group liberally received perioperative allogeneic transfusion and fluid administration, causing abnormal coagulation profiles and increased postoperative bleeding, eventually increasing the risk of postoperative infection, DIC, and length of hospital stay.

Postoperative anemia-related mortality was relatively uncommon in JW patients [40, 43] and overall mortality was lower in patients refusing blood transfusion (3.6%) than in those who accepted transfusion (0%) [37]. In general, the postoperative hemoglobin levels in JW patients showed a significant decrease in the days after surgery, but later stabilized, without a significant difference from the non-JW group [28, 37, 42, 44]. De Bellis et al. [44] suggested that decreased hemoglobin levels were associated with perioperative bleeding and inflammatory processes, and that increased or sustained hemoglobin levels were associated with the resolution of postoperative inflammatory process, postoperative application of BCSs, and return to normal food intake. The hemoglobin levels of JW patients who received BCSs did not significantly differ from that of non-JW patients at 1 day postoperatively [40].

The perioperative hemoglobin levels decreased within the acceptable ranges in most patients in both groups [42]. Frank et al. [37] reported that the mortality rate was not significantly different between groups, although the incidence of hemoglobin nadir < 5 g/dL was higher in JW patients (4.3%) than in patients who allowed blood transfusion (0.2%). De Bellis et al. [44] reported that the lowest hemoglobin level was 7.1 g/dL with a median decrement of 2.8 g/dL (range 0–6.9 g/dL), and no patient required blood transfusion or died within 3 months after surgery among JW patients who underwent major abdominal surgeries. Chigbu et al. [41] showed that mortality was lower in the JW group (12%) than in the group that received blood transfusion (15.6%) among patients who underwent bloodless emergency laparotomies with hemorrhagic shock. Furthermore, propensity-matched studies [37, 45] showed lower morbidity and mortality rates in patients who underwent bloodless surgeries. However, it should be considered that postoperative hemoglobin < 5.0 g/dL has been shown to increase mortality in JW patients [4, 46], and specific surgeries with risks of catastrophic hemorrhage, such as postpartum hemorrhage, also increase the mortality risk in patients undergoing bloodless surgeries [47]. This study showed

the general postoperative hemoglobin change and a 5.3 g/dL perioperative hemoglobin nadir, with a 0% rate of mortality and transfusion, in JW patients.

3. Study Limitations

This study had several limitations warranting cautious interpretation of our findings. First, the retrospective analysis might have influenced the results of this study. Second, the single-center design and the small sample size of the JW group limit the generalization of our results. Third, we included many different types of surgeries, which may have resulted in unfair comparisons. Finally, we did not perform propensity matching to control for various biases. Nonetheless, the findings of this study can be useful in that they support existing findings and contribute to updating the information on the perioperative outcomes of JW patients.

Ⅴ. CONCLUSIONS

Most JW patients can safely undergo surgeries associated with a risk of bleeding without blood transfusions and with fewer hematologic abnormalities, compared with patients allowing blood transfusion. Such safe surgeries can be achieved through physicians' efforts to reduce or prevent perioperative bleeding by applying various perioperative BCSs, such as the use of medical preparations or treatments, intraoperative induction of mild hypothermia, use of hypotensive anesthesia, perioperative blood cell salvage, and application of bloodless surgical techniques (staged operation and operative time reduction). Despite the limitations of our retrospective study and the need for further studies to confirm our results and conclusions, the present findings are useful in that they support existing findings and contribute to updating the information on the perioperative outcomes of JW patients. In addition, this study also adds to the evidence that perioperative blood transfusion is associated with increased mortality and morbidity.

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Legend for Figure

Fig. 1. Flowchart of patient inclusion. ASA-PS, American Society of Anesthesiologists physical status; JW, Jehovah's Witness.