

# Blood Loss and Related Laboratory Changes after Single-Event Multilevel Surgery and Hip Reconstructive Surgery in Patients with Cerebral Palsy

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**Background:** Single-event multilevel surgery (SEMLS) and hip reconstructive surgery (HRS) often cause intraoperative bleeding, consequently increasing the probability of transfusion and postoperative laboratory changes. Therefore, it is important to assess risk factors to predict the amount of blood loss. This study aimed to evaluate blood loss, its influencing factors, and the related laboratory changes during SEMLS and HRS in patients with cerebral palsy (CP).

**Methods:** We retrospectively examined consecutive CP patients who underwent SEMLS and HRS. Surrogate markers of blood loss, including preoperative and postoperative hemoglobin (Hb), hematocrit, and changes in Hb concentration, were assessed. Albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine levels were also analyzed for related laboratory changes. Risk factors were analyzed using multiple regression and logistic regression models.

**Results:** The overall cohort comprised 1,188 patients. Of them, 1,007 and 181 underwent SEMLS and HRS, respectively. Furthermore, 72 of 181 patients underwent a concomitant Dega osteotomy. The regression model showed that low preoperative Hb concentration (p < 0.001), high albumin level (p = 0.007), low body mass index (BMI) (p = 0.002), and bilateral HRS (p < 0.001) were significant risk factors of postoperative anemia. Valproate medication was associated with Hb drop, and the risk factors for Hb level < 8 g/dL on postoperative day 2 were bilateral HRS and Dega osteotomy in the HRS subgroup. In total, 21.6% had elevated AST levels on postoperative day 2, and bilateral HRS (p < 0.001), Gross Motor Function Classification System (GMFCS) level V (p = 0.041), Dega osteotomy (p < 0.001), and high preoperative AST level (p < 0.001) increased the risk of AST elevation.

**Conclusions:** We have summarized the estimated blood loss and related laboratory changes after SEMLS and HRS in patients with CP and identified the risk factors. Clinical guidelines should be accordingly developed to include assessment of these risk factors and their impact in the outcomes of CP patients undergoing SEMLS and HRS.

Keywords: Cerebral palsy, Hip reconstructive surgery, Single event multilevel surgery, Blood loss

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Cerebral palsy (CP) is a permanent disorder affecting movement and posture, causing activity limitations due to non-progressive disturbances that occurred in the fetal or immature infant brain.<sup>1)</sup> The incidence of CP ranges from 2.7 to 3.2 per 1,000 live births.<sup>2,3)</sup> Two major orthopedic procedures in the lower extremity are single-event multilevel surgery (SEMLS) to improve gait for ambulatory patients (Gross Motor Function Classification System [GM-FCS] levels I–III) and hip reconstructive surgery (HRS) to reduce pain and facilitate caregiving (mainly for GMFCS levels IV–V). However, lower limb procedures for CP often cause intraoperative bleeding, which in turn increases the probability of transfusion and postoperative laboratory changes. Therefore, it is important to assess risk factors and predict the probability of perioperative bleeding.

CP is a major risk factor for malnutrition and iron deficiency anemia.<sup>4,5)</sup> Further, blood loss and transfusion rate have been shown to be higher in combined femoral and acetabular osteotomy in patients with neuromuscular disease.<sup>6)</sup> In addition, CP patients often have seizure disorders that are usually treated with the anticonvulsant valproate, which has been reported to increase the risk of perioperative bleeding during orthopedic surgery by interfering with coagulation factors and liver function.<sup>7-11)</sup> However, few studies have investigated the perioperative hematologic changes in CP patients undergoing SEMLS or HRS. Consequently, the purpose of this study was to evaluate blood loss and its influencing factors and to investigate related laboratory changes during SEMLS and HRS in patients with CP.

# METHODS

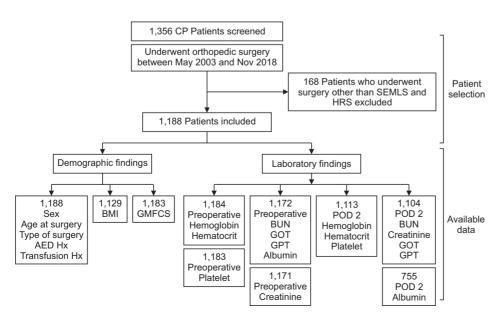
#### Patients and Study Design

This retrospective study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-1901-514-110), which is a tertiary referral center for CP. Informed consent was waived due to retrospective nature of this study.

We evaluated CP patients who underwent SEMLS and HRS in our hospital between May 2003 and November 2018. Those who underwent procedures other than SEMLS and HRS were excluded. We reviewed the medical records via the clinical data warehouse (CDW) in our hospital (Healthcare Information and Management Systems Society, stage 7). For statistical independence, only data from each patient's first surgery were included in the study.<sup>12)</sup> Research assistants collected the data from CDW, and two of the authors (JJM and MSP) validated patients' demographic characteristics and risk factors.

#### **Consensus Building**

Related articles on PubMed were retrieved using the following search terms and reviewed: "cerebral palsy," "bleeding tendency," "risk," and "transfusion." Five authors (JJM, KHS, KML, MSP [orthopedic surgeons with 2, 16, 17, and 19 years of experience, respectively], and SSK [a statistician]) met for consensus, and the candidate risk factors of postoperative anemia, albumin drop, and liver enzyme and creatinine elevation were chosen as follows: patient age at the index surgery, GMFCS level, body mass index (BMI), preoperative anemia, valproate medication, and type of surgery.



**Fig. 1.** Flow diagram of patient selection and patients with available data. CP: cerebral palsy, SEMLS: single-event multilevel surgery, HRS: hip reconstructive surgery, AED: anti-epileptic drug, Hx: history, BMI: body mass index, GMFCS: Gross Motor Function Classification System, BUN: blood urea nitrogen, GOT: glutamicoxaloacetic transaminase, GPT: glutamicpyruvic transaminase, POD: postoperative day.

GMFCS is a known major risk factor for postoperative complication,<sup>6,13,14)</sup> and thus we assessed the medical record of each patient's GMFCS level. Further, given that patients diagnosed with tetraplegia had a 3.5 times higher risk of malnutrition than those with diplegia or hemiplegia,<sup>4,5)</sup> we also collected data on the patients' weight, height, and BMI.

Meanwhile, we searched records of preoperative consult to the pediatric neurology department regarding the patients' history of seizure and anti-epileptic drugs. The patients were grouped into those who took valproate perioperatively and those who did not.

#### Type of Surgery

In general, SEMLS was mainly performed to improve gait in GMFCS level I–III. Preoperative three-dimensional gait analysis was used to plan procedures, and the indications for individual procedures were consistent with medical understanding at the time of treatment. Surgical procedures including tendon lengthening/transfer and osteotomy were performed based on considerations of both clinical and gait analysis findings.<sup>15-17)</sup>

HRS was performed in CP patients with hip displacement (migration percentage > 33%). The goals of the intervention were a painless, stable hip and prevention of recurrence of hip displacement. All patients underwent a femoral varus derotational osteotomy.<sup>18)</sup> The medial soft-tissue release consists of the release of the adductor longus tendon; if the abduction angle obtained was  $< 30^{\circ}$ , an additional soft-tissue release involving the adductor brevis, gracilis, and semitendinosus or semimembranosus was performed. After the femoral varus derotational osteotomy, open reduction was additionally performed if a concentric reduction was not seen in intraoperative fluoroscopic examination. A modified Dega osteotomy was performed based on either a preoperative radiographic finding of acetabular defects or an intraoperative finding of insufficient coverage (migration percentage) of the femoral head after the femoral varus derotational osteotomy and open reduction.<sup>19)</sup>

SEMLS and HRS were further categorized into four groups: SEMLS (soft), SEMLS (bone), unilateral HRS, and bilateral HRS. SEMLS (soft) was defined as an SEMLS comprising tendon lengthening and tendon transfer, excluding bony procedure. Soft-tissue procedures in GMFCS level IV–V patients for facilitating therapeutic standing and wheelchair sitting or for preventing hip displacement were also included in the SEMLS (soft) group. Meanwhile, SEMLS (bone) was defined as an SEMLS that includes bony procedures such as the femoral derotational osteotomy, tibial derotational osteotomy, and foot osteotomy. Unilateral HRS was defined as HRS performed in only one limb. In our institute, HRS is performed bilaterally.<sup>20)</sup> However, staged operations during single hospitalization were performed according to the attending clinician's discretion. Therefore, unilateral HRS in this study was defined as the first surgery in staged operation. We only included

| Table 1. Summary of Patient Data    |                             |  |  |
|-------------------------------------|-----------------------------|--|--|
| Variable                            | Value (n = 1,188)           |  |  |
| Patient information                 |                             |  |  |
| Sex (male : female)                 | 735 : 453                   |  |  |
| BMI (kg/m <sup>2</sup> )            | 18.2 ± 4.8                  |  |  |
| GMFCS level (I : II : III : IV : V) | 436 : 315 : 180 : 148 : 104 |  |  |
| Age at surgery (yr)                 | 12.4 ± 7.9                  |  |  |
| Type of surgery                     |                             |  |  |
| SEMLS (soft : bone)                 | 1,007 (696 : 311)           |  |  |
| HRS (unilateral : bilateral)        | 181 (68 : 113)              |  |  |
| Dega pelvic osteotomy               | 72                          |  |  |
| AED medication                      | 139 (12)                    |  |  |
| Valproate                           | 44 (4)                      |  |  |
| Laboratory finding                  |                             |  |  |
| Hemoglobin                          |                             |  |  |
| Preoperative                        | 13.7 ± 1.3                  |  |  |
| POD 2                               | 12.2 ± 2.1                  |  |  |
| Hemoglobin drop                     | 1.9 ± 1.7 (14)              |  |  |
| Hematocrit                          |                             |  |  |
| Preoperative                        | 40.6 ± 3.5                  |  |  |
| POD 2                               | 34.9 ± 5.7                  |  |  |
| Hematocrit drop                     | 5.7 ± 5.3 (14)              |  |  |
| Albumin                             |                             |  |  |
| Preoperative                        | 4.5 ± 0.3                   |  |  |
| POD 2                               | 3.7 ± 0.4                   |  |  |
| Albumin drop                        | 0.8 ± 0.4 (18)              |  |  |
| Transfusion after surgery           | 70 (6)                      |  |  |

Values are presented as mean  $\pm$  standard deviation, number (%), or mean  $\pm$  standard deviation (%).

BMI: body mass index, GMFCS: Gross Motor Function Classification System, SEMLS: single-event multilevel surgery, HRS: hip reconstructive surgery, AED: anti-epileptic drug, POD: postoperative day. the first surgery to warrant statistical independence.<sup>12)</sup> Bilateral HRS in this study was defined as simultaneous bilateral hip reconstruction.

#### **Data Collection**

Data on patient's age, sex, BMI derived from weight and height during the time of surgery, type of surgery, GMFCS level, perioperative hemoglobin (Hb), hematocrit, albumin, and other coagulation factors (aspartate aminotransferase [AST], alanine aminotransferase [ALT], blood urea nitrogen, and creatinine), past medical history of valproate administration, and postoperative transfusion were collected from medical records.

Laboratory values of Hb, hematocrit, albumin, AST/ ALT, and creatinine on postoperative day 2 were also collected. Hb levels on postoperative day 2 were further assessed according to raw Hb level, Hb level < 8 mg/dL, and difference in Hb from preoperative Hb level. AST and ALT levels were further dichotomized at a cutoff of 40 IU/L, with elevated AST defined as levels above 40 IU/L. The creatinine level was also dichotomized at a cutoff of 0.8 g/dL, with elevated creatinine defined as levels above 0.8 g/dL.

#### **Statistical Analysis**

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables. Descriptive statistics used include mean, standard deviation, and frequency. The effects of age at surgery, type of surgery, GMFCS, BMI, valproate medication use, and preoperative laboratory findings were investigated using multiple regression analysis, where the dependent variables were postoperative Hb level, Hb drop, and albumin drop.<sup>21)</sup> A logistic regression analysis was conducted to investigate the trend between binary categories of each dependent variable and each risk factor.<sup>22)</sup> The multiple linear models were accepted as valid for an estimation of the responses using the adjusted  $R^2$ . A larger adjusted  $R^2$  was preferred in terms of model selection. The significance of the logistic regression models could be tested using likelihood test or Wald's test, and validity of models for estimating the responses was assessed using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC). A smaller AIC or BIC value is preferred in terms of model selection. All statistical analyses were performed using the SAS ver. 9.4 (SAS Institute, Cary, NC, USA). All p-values were two-tailed, and p < 0.05 was considered statistically significant.

## RESULTS

A total of 1,188 patients were evaluated in this study (Fig. 1). Of these, 1,007 (85%) and 181 (15%) underwent SEMLS and HRS, respectively. Further, 72 of 181 (40%) patients in the HRS group underwent a concomitant Dega

| Table 2. Hemoglobin Drop and Transfusion in Major Category of Patients |                  |                 |            |            |                      |                |                           |
|--|------------------|-----------------|------------|------------|----------------------|----------------|---------------------------|
| GMFCS  | Type of surgery  | No. of patients | Preop Hb   | POD 2 Hb   | POD 2 Hb<br>< 8 g/dL | Hb drop        | Transfusion after surgery |
| I  | SEMLS (soft)     | 335             | 13.7 ± 1.3 | 12.8 ± 1.3 | 0                    | 0.9 ± 0.9 (6)  | 0                         |
|  | SEMLS (bone)     | 100             | 13.5 ± 1.2 | 11.2 ± 1.8 | 4 (4)                | 2.3 ± 1.7 (17) | 1 (1)                     |
|  | SEMLS (soft)     | 188             | 13.8 ± 1.3 | 12.7 ± 1.3 | 0                    | 1.1 ± 1.0 (8)  | 1 (1)                     |
|  | SEMLS (bone)     | 122             | 13.6 ± 1.3 | 11.1 ± 1.6 | 2 (2)                | 2.5 ± 1.5 (18) | 2 (2)                     |
|  | SEMLS (soft)     | 98              | 13.9 ± 1.2 | 12.6 ± 1.2 | 0                    | 1.3 ± 0.9 (9)  | 0                         |
|  | SEMLS (bone)     | 68              | 13.7 ± 1.4 | 10.6 ± 1.9 | 5 (7)                | 3.2 ± 1.7 (23) | 0                         |
|  | HRS (unilateral) | 2               | 12.8 ± 0.9 | 10.6 ± 1.7 | 0                    | 2.2 ± 0.8 (17) | 0                         |
|  | HRS (bilateral)  | 13              | 13.7 ± 1.0 | 9.2 ± 1.4  | 2 (15)               | 4.5 ± 1.7 (33) | 4 (31)                    |
| IV   | HRS (unilateral) | 29              | 13.7 ± 1.5 | 10.2 ± 1.3 | 0                    | 3.5 ± 1.9 (26) | 4 (14)                    |
|  | HRS (bilateral)  | 50              | 13.4 ± 1.3 | 9.0 ± 1.7  | 14 (28)              | 4.4 ± 1.8 (33) | 15 (30)                   |
| V  | HRS (unilateral) | 33              | 13.5 ± 1.1 | 10.2 ± 1.6 | 2 (6)                | 3.2 ± 1.9 (24) | 9 (27)                    |
|  | HRS (bilateral)  | 46              | 13.5 ± 1.3 | 9.3 ±1.4   | 8 (17)               | 4.1 ± 1.9 (31) | 19 (41)                   |

Values are presented as mean ± standard deviation, number (%), or mean ± standard deviation (%). GMFCS: Gross Motor Function Classification System, Hb: hemoglobin, Preop: preoperative, POD: postoperative day, SEMLS: single-event multilevel surgery, HRS: hip reconstructive surgery.

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| Table 3. Factors Affecting Her | noglobin Level on Postope | erative Day 2 |                  |                 |
|--------------------------------|---------------------------|---------------|------------------|-----------------|
| Variable                       | Coding                    | Estimate      | 95% CI           | <i>p</i> -value |
| Intercept                      |                           | 5.25          | 4.020 to 6.487   | < 0.001         |
| Preoperative hemoglobin        |                           | 0.62          | 0.553 to 0.689   | < 0.001         |
| Preoperative albumin           |                           | -0.39         | -0.664 to -0.106 | 0.007           |
| Preoperative platelet          |                           | 0.00          | -0.001 to 0.001  | 0.590           |
| Age at surgery (yr)            |                           | 0.01          | 0.000 to 0.021   | 0.059           |
| Body mass index                |                           | 0.03          | 0.011 to 0.047   | 0.002           |
| Type of surgery                |                           |               |                  |                 |
| SEMLS (soft)                   | Base                      |               |                  |                 |
| SEMLS (bone)                   | (1/0)                     | -1.53         | -1.700 to -1.356 | < 0.001         |
| HRS (unilateral)               | (1/0)                     | -2.05         | -2.461 to -1.649 | < 0.001         |
| HRS (bilateral)                | (1/0)                     | -3.11         | -3.465 to -2.758 | < 0.001         |
| Addition of Dega               | (1/0)                     | -0.21         | -0.623 to 0.208  | 0.327           |
| GMFCS                          |                           |               |                  |                 |
| Level I                        | Base                      |               |                  |                 |
| Level II                       | (1/0)                     | -0.24         | -0.426 to -0.051 | 0.013           |
| Level III                      | (1/0)                     | -0.38         | -0.611 to -0.154 | 0.001           |
| Level IV                       | (1/0)                     | -0.28         | -0.564 to -0.004 | 0.047           |
| Level V                        | (1/0)                     | -0.23         | -0.585 to 0.121  | 0.197           |
| Valproate medication           | (1/0)                     | -0.02         | -0.444 to 0.408  | 0.934           |

Multiple regression was used to estimate factors affecting hemoglobin level. A study of the residuals indicated that the assumption of normality and homogeneity of variance was satisfied. Adjusted  $R^2$  was 0.582.

CI: confidence interval, SEMLS: single-event multilevel surgery, HRS: hip reconstructive surgery, GMFCS: Gross Motor Function Classification System.

pelvic osteotomy. Forty-four patients were using valproate at the time of the surgery, and 70 received blood transfusion after surgery (Table 1).

Among patients with GMFCS level V who underwent bilateral HRS, 41% of those who received transfusion had an average Hb drop of 4.1  $\pm$  1.9 (Table 2). In our regression model, the major risk factors that affected Hb levels on postoperative day 2 were preoperative anemia (p <0.001), preoperative albumin (p = 0.007), BMI (p = 0.002), and type of surgery (p < 0.001). Further, GMFCS level was also associated with Hb level on postoperative day 2 (Table 3). The risk factors of Hb drop on postoperative day 2 were the type of surgery (p = 0.024) and preoperative Hb (p =0.030). In subgroup analysis in the HRS group, the risk factors were age at the time of operation (p = 0.002) and valproate medication (p = 0.036) (Table 4). Meanwhile, only bilateral HRS (p = 0.008) was a risk factor for Hb level < 8 mg/dL on postoperative day 2. In subgroup analysis in the HRS group, risk factors included bilateral HRS (p = 0.012) and Dega osteotomy (p = 0.004) (Table 5). The risk factors of albumin drop on postoperative day 2 were bilateral HRS (p < 0.001), Dega osteotomy (p < 0.001), and preoperative albumin (p < 0.001). GMFCS level was also associated with a decreased albumin level.

Of the 1,104 patients with available postoperative AST and ALT data, 239 (21.6%) had elevated AST. The risk factors for AST elevation on postoperative day 2 were bilateral HRS (p < 0.001), GMFCS level V (p = 0.041), Dega osteotomy (p < 0.001), and preoperative AST level (p < 0.001). Further, 46 of 1,104 (4.2%) patients had elevated ALT. The risk factors for ALT elevation on postoperative day 2 were BMI (p = 0.037) and preoperative ALT (p < 0.001). There were 44 of 1,104 (4.0%) patients with an elevated creatinine level. The risk factors for creatinine elevation on postoperative day 2 were age at the time of operation (p < 0.001) and preoperative Hb (p < 0.001).

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| Variable                | Coding | Estimate | 95% CI          | <i>p</i> -value |
|-------------------------|--------|----------|-----------------|-----------------|
| Intercept               |        | 0.10     | -0.203 to 0.402 | 0.518           |
| Preoperative hemoglobin |        | -0.01    | -0.027 to 0.011 | 0.420           |
| Preoperative albumin    |        | -0.01    | -0.078 to 0.055 | 0.725           |
| Preoperative platelet   |        | 0.00     | 0.000 to 0.000  | 0.695           |
| Age at surgery (yr)     |        | 0.01     | 0.003 to 0.012  | 0.002           |
| Body mass index         |        | 0.00     | -0.006 to 0.004 | 0.633           |
| Type of surgery         |        |          |                 |                 |
| HRS (unilateral)        | Base   |          |                 |                 |
| HRS (bilateral)         | (1/0)  | 0.00     | -0.036 to 0.044 | 0.828           |
| Addition of Dega        | (1/0)  | -0.02    | -0.059 to 0.022 | 0.368           |
| GMFCS                   |        |          |                 |                 |
| Level I                 | Base   |          |                 |                 |
| Level II                | (1/0)  | -0.02    | -0.149 to 0.110 | 0.770           |
| Level III               | (1/0)  | -0.01    | -0.118 to 0.107 | 0.918           |
| Level IV                | (1/0)  | 0.02     | -0.082 to 0.119 | 0.713           |
| Level V                 | (1/0)  | -0.02    | -0.118 to 0.081 | 0.714           |
| /alproate medication    | (1/0)  | 0.07     | 0.005 to 0.141  | 0.036           |

Multiple regression was used to estimate factors affecting hemoglobin drop. A study of the residuals indicated that the assumption of normality and homogeneity of variance was satisfied. Adjusted  $R^2$  was 0.137.

HRS: hip reconstructive surgery, CI: confidence interval, GMFCS: Gross Motor Function Classification System.

#### DISCUSSION

In this study, we have identified several risk factors affecting blood loss after SEMLS and HRS in CP patients. In our regression model, preoperative low Hb concentration, high albumin level, low BMI, and bilateral HRS were found to be significant risk factors, and the GMFCS level was also associated with postoperative anemia. In bilateral HRS, the rate of Hb drop after surgery was over 30%, and valproate medication was associated with Hb drop. The risk factors for Hb level < 8 g/dL on postoperative day 2 were bilateral HRS and Dega pelvic osteotomy.

Before discussing the clinical implications of the present study, it is crucial to address its limitations. First, the study is retrospective by design. Our institute does not have a standard protocol or threshold for transfusion, and transfusion has been performed according to the surgeon's or anesthesiologist's discretion. However, we have not used tranexamic acid, cell saver, or other additive agents, and thus we believe that the population is suitable for the observational study. Second, valproate medication was dichotomized and considered as a binary variable. The blood level of valproate is believed to affect coagulation function. However, the blood level of valproate was not available in our study. Also, the effect of drugs other than valproic acid has not been discussed.

It is reasonable to consider that preoperative anemia is associated with postoperative anemia.<sup>4)</sup> However, high preoperative albumin was also associated with postoperative anemia in our study. Albumin is generally accepted as a surrogate marker of preoperative nutritional status, and it is believed that nutritional status is associated with coagulation function. However, several studies have reported that albumin affects coagulation competence and perioperative bleeding, although these studies focused on albumin replacement and cardiac surgery.<sup>23,24)</sup> Some studies have also reported that albumin may reduce platelet activation and the release of inflammatory mediators.<sup>25,26)</sup> Further studies are needed to clarify whether albumin does influence coagulation function.

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| Table 5. Risk Factors for Hemoglobin < 8 g/dL | on Postoperative Day 2 in the HRS Group |                               |
|---|---|-------------------------------|
| Variable                                      | Coding                                  | Odds ratio (95% CI)           |
| Preoperative hemoglobin                       |   | 1.35 (0.74 to 2.44)           |
| Preoperative albumin                          |   | 0.54 (0.06 to 4.98)           |
| Preoperative platelet                         |   | 1.00 (0.99 to 1.01)           |
| Age at surgery (yr)                           |   | 0.92 (0.78 to 1.09)           |
| Body mass index                               |   | 1.01 (0.84 to 1.20)           |
| Type of surgery                               |   |                               |
| HRS (bilateral)                               | (1/0)                                   | 8.78 (1.62 to 47.45)          |
| Addition of Dega                              | (1/0)                                   | 5.82 (1.76 to 19.21)          |
| GMFCS   |   |                               |
| Level II                                      | (1/0)                                   | > 999.99 (< 0.01 to > 999.99) |
| Level III                                     | (1/0)                                   | > 999.99 (< 0.01 to > 999.99) |
| Level IV                                      | (1/0)                                   | > 999.99 (< 0.01 to > 999.99) |
| Level V                                       | (1/0)                                   | > 999.99 (< 0.01 to > 999.99) |
| Valproate medication                          | (1/0)                                   | 3.70 (0.62 to 21.93)          |

Logistic regression was used to investigate the risk factors for hemoglobin < 8 g/dL on postoperative day 2 in the HRS group. The AIC was 122.3. HRS: hip reconstructive surgery, CI: confidence interval, GMFCS: Gross Motor Function Classification System, AIC: Akaike information criterion.

Low BMI is considered to indicate poor nutritional status, which affects coagulation competence. Particularly, malnutrition is common in patients with CP due to various reasons such as spasticity, aspiration, and feeding difficulty.<sup>5)</sup> However, it is challenging to measure the height and weight to calculate the BMI in patients with GMFCS level IV or V due to flexion contractures, lack of weightbearing and head control, hip displacement, and scoliosis. Furthermore, HRS is generally performed in patients with GMFCS level IV-V. Other practical methods for assessing nutritional status in patients with CP will be needed.

Predictably, the rate of Hb drop on postoperative day 2 was higher among those who underwent bilateral HRS and those with additional periacetabular pelvic osteotomies than those who underwent soft-tissue procedures alone.<sup>13,14</sup> A previous study reported that longer duration of surgery is an independent risk factor for transfusion,<sup>6</sup> which is consistent with our findings. The operation time for bilateral HRS tends to be longer, and the procedure exposes more surfaces and cancellous bone for bleeding. Also, while a pneumatic tourniquet can be used in other bony procedures of the lower extremities, it cannot be used in femoral and acetabular osteotomies, leaving patients more vulnerable to intraoperative blood loss.

There has been little consensus on the threshold for

postoperative red blood cell transfusion in patients with CP, with thresholds ranging from Hb concentrations of 6 to 10 g/dL, depending on the physician's discretion.<sup>27)</sup> In the United States, the CRIT study on 284 intensive care units in 213 U.S. hospitals showed that the Hb concentration before a transfusion in adult surgical patients was 8.8  $\pm$  1.8 g/dL.<sup>28)</sup> In our study, we assumed that Hb < 8 g/dL would be the threshold for transfusion.

CP patients with higher GMFCS levels tend to have more severe epilepsy events and thus in more need of antiepileptic medications including valproate. The effect of valproate on blood loss has been controversial. Valproate and its byproducts are known to be hepatotoxic and may cause thrombocytopenia.<sup>29)</sup> However, while some argued that it has minimal disruptive effect on coagulation homeostasis,<sup>9)</sup> one study reported that valproate administration substantially increased intraoperative bleeding.<sup>30)</sup> In the subgroup analysis in the HRS group, one of the risk factors for Hb drop was valproate medication (p = 0.034). Our cohort was quite large, and the effect size of valproate medication was small (0.073 g/dL), and thus it is uncertain whether valproate has a clinically meaningful difference. We believe that the small effect size resulted in the controversy about the effect of valproate on perioperative bleeding.

Of the 1,104 patients with available postoperative

AST and ALT data, the AST level increased in 21.6%, while only 4.2% of patients had elevated ALT. While the risk factors for AST elevation were mostly procedure-related (e.g., bilateral HRS, Dega osteotomy, GMFCS level V, and preoperative AST), the risk factors for ALT elevation were unrelated to the operation. Further, while both AST and ALT reflect liver function, AST is also related to muscular damage.<sup>31)</sup> Therefore, it can be inferred that patients undergoing more intensive surgical procedures are at higher risk of AST elevation.

We have summarized the estimated blood loss and related laboratory changes after SEMLS and HRS in patients with CP and identified the risk factors. Preoperative low Hb, high albumin level, low BMI, bilateral HRS, and concomitant Dega pelvic osteotomy were found to be significant risk factors, and within the bilateral HRS group, valproate intake was statistically significant. The findings of our study may not be new, as many of the factors are equally applied to any typically developing children undergoing orthopedic procedures. However, an equivalent study on CP patients with large series has not been done yet. Clinical guidelines should be accordingly developed to include assessment of these risk factors and their impact on the outcomes of CP patients undergoing SEMLS and HRS.

# **CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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