Relationship of epidural patient-controlled analgesia with postoperative bleeding after unilateral total knee arthroplasty: a propensity score-matching analysis

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Although epidural patient-controlled analgesia (PCA) to control postoperative pain after total knee arthroplasty (TKA), the relationship of epidural PCA with postoperative bleeding remains controversial. Therefore, we aimed to evaluate the effect of epidural and intravenous PCA on postoperative bleeding in patients undergoing unilateral TKA. Total of 2467 patients who underwent TKA were divided to intravenous PCA (n = 2339) or epidural PCA (n = 128) group. After 1:1 propensity score-matching, 212 patients were analyzed to assess the associations between the perioperative blood loss and epidural PCA between the groups. Mean postoperative blood loss was significantly greater in epidural PCA than in intravenous PCA (900.9 ± 369.1 mL vs. 737.8 ± 410.1 mL; \( P = 0.007 \)). The incidence of red blood cell (RBC) administration (> 3 units) was significantly higher in epidural PCA than in intravenous PCA (30.2% vs. 16.0%; OR 2.5; 95% CI 1.201–5.205; \( P = 0.014 \)). Epidural PCA may be strongly related to postoperative bleeding and the incidence of RBC transfusion of more than 3 units after unilateral TKA, as compared to intravenous PCA. Therefore, the use of epidural PCA may be carefully considered for postoperative pain management in TKA.

Total knee arthroplasty (TKA) is usually associated with serve postoperative pain due to the occurrence of the extensive surgical trauma of the muscle and bone tissue, as well as tourniquet compression and decompression of the operated leg. The inadequate control of postoperative pain may result in chronic postoperative pain and poor outcomes1–3. Epidural pain management yields superior pain relief as compared with parenteral regimens during the postoperative period4. In patients who have undergone TKA, epidural patient-controlled analgesia (PCA) or continuous nerve blocks leads to the quicker application of intense physical therapy—the most fundamental factor of good postoperative knee rehabilitation—as compared with intravenous PCA5, 6. The prevention of blood loss during and after knee surgery is important, as the incidences of respiratory tract infection and wound infection are reported to be significantly greater in patients receiving allogeneic blood transfusions, compared with those receiving no blood transfusion7. Moreover, transfused patients are more likely to have greater in-hospital mortality, hospital stay, and total costs per admission8.

Previous studies have described the relationship between regional anesthesia and decreased blood loss during orthopedic surgery9–12. However, the effects of epidural PCA on postoperative bleeding remain controversial. Furthermore, most studies have limitations such as unbalanced demographics and intraoperative variables between groups, or an inadequate power to evaluate the differences between groups. In particular, significant predictors for transfusion, such as preoperative hemoglobin, age, female gender, body mass index, creatinine, intraoperative blood loss, and intraoperative fluids, should be controlled before comparison13. In the present

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study, we aimed to compare postoperative blood loss and transfusion requirement between epidural PCA and intravenous PCA via propensity score-matching analysis in a large cohort of patients undergoing unilateral TKA.

**Results**

**Patient characteristics and preoperative laboratory values.** A total of 2600 patients who underwent unilateral TKA between January 2000 and September 2016 were included in this study. We excluded those with peripheral nerve block (n = 31), those without continuous PCA use (n = 22), and incomplete data (n = 80). Accordingly, this study included 2467 patients who were divided into an intravenous PCA (n = 2339) or epidural PCA (n = 128) group (Fig. 1). The primary diagnosis and incidence of re-do TKA in both the PCA groups were not significantly different (Table 1). Table 1 demonstrates the preoperative laboratory values between the 2 groups.

**Intraoperative and postoperative variables.** The patients in the intravenous PCA group were more likely to receive inhalation anesthesia (P < 0.001). In contrast, epidural PCA use was more frequent in patients who received regional anesthesia (P < 0.001) (Table 2). In total patients, 1992 (77.9%) patients underwent blood transfusion during intra- or postoperative period. Although the estimated blood loss during operation in the intravenous PCA group was greater than that in the epidural PCA group, the amount of red cell transfusion and fresh frozen plasma were not significantly different between the groups (Table 2). Other fluid administration data and urine output are presented in Table 2. The postoperative variables are provided in Table 3. Numerical rating scale (NRS) in maximal pain intensity at the postoperative anesthetic care unit and the ward on postoperative day 0 was significantly lower in epidural PCA group compared with intravenous PCA group (P < 0.001). The operation site drainage, total blood loss, and significant blood loss were greater in the epidural PCA group than in the intravenous PCA group (P < 0.001) (Table 3). In addition, blood loss after transfer to ward was greater than both during operation and in recovery room.

**Results of propensity matching.** All the variables of propensity score-matched patients (n = 212) are listed in Tables 4, 5 and 6. The American Society of Anesthesiologists (ASA) class, preoperative protein values, inhalation anesthesia use, regional anesthesia use, and intraoperative variables (crystalloid and colloid amounts, estimated blood loss, and urine output) significantly differed between the intravenous PCA (n = 2339) and epidural PCA (n = 128) groups before matching (Tables 2, 3). After propensity score-matching, the patient char-
Table 1. Unmatched preoperative characteristics and preoperative laboratory values between the intravenous PCA and epidural PCA groups. Data are presented as mean ± standard deviation or number (%), as appropriate. PCA patient-controlled analgesia, ASA American Society of Anesthesiologists, INR international normalized ratio, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase, BUN blood urea nitrogen. Others include avascular necrosis, desmoplastic fibroma, fibrous dysplasia, pigmented villonodular synovitis, spontaneous osteonecrosis, valgus knee, spastic diplegia of cerebral palsy, and fused knee.

| Variables                  | Intravenous PCA (n = 2339) | Epidural PCA (n = 128) | P value |
|----------------------------|-----------------------------|------------------------|---------|
| Gender, female (%)         | 2053 (87.8%)                | 112 (87.5%)            | 0.927   |
| ASA class                  |                             |                        |         |
| I/II                       | 233 (10.0%)/2019 (86.3%)    | 10 (7.8%)/110 (85.9%)  | <0.001  |
| III/IV                     | 87 (3.7%)/0                 | 7 (5.5%)/1 (0.8%)      |         |
| Age (years)                | 68.0 ± 7.6                  | 68.4 ± 7.6             | 0.567   |
| Weight (kg)                | 62.5 ± 9.6                  | 61.7 ± 9.4             | 0.370   |
| Height (cm)                | 153.6 ± 7.2                 | 153.0 ± 7.0            | 0.359   |
| Body mass index (kg/m²)    | 26.4 ± 3.4                  | 26.3 ± 3.2             | 0.590   |
| Primary diagnosis          |                             |                        |         |
| Osteoarthritis             | 2139 (91.4%)                | 122 (95.3%)            | 0.124   |
| Rheumatoid arthritis       | 37 (1.6%)                   | 0                      | 0.152   |
| Infectious arthritis       | 82 (3.5%)                   | 2 (1.6%)               | 0.238   |
| Traumatic knee injury      | 21 (0.9%)                   | 2 (1.6%)               | 0.446   |
| Ankylosing knee            | 4 (0.2%)                    | 0                      | 0.640   |
| Others                     | 65 (2.8%)                   | 2 (1.6%)               | 0.410   |
| Re-operation               | 207 (8.8%)                  | 11 (8.6%)              | 0.921   |
| Preoperative laboratory values |                         |                        |         |
| Hemoglobin level (g/dL)    | 12.6 ± 1.3                  | 12.7 ± 1.4             | 0.402   |
| Platelet count (x 10³/μL)  | 248.3 ± 64.8                | 251.7 ± 60.7           | 0.566   |
| Prothrombin time (INR)     | 1.0 ± 2.1                   | 1.0 ± 0.1              | 0.814   |
| AST level (U/L)            | 23.6 ± 9.6                  | 24.6 ± 11.4            | 0.213   |
| ALT level (U/L)            | 19.9 ± 11.5                 | 20.3 ± 14.0            | 0.701   |
| ALP level (U/L)            | 75.9 ± 26.8                 | 74.5 ± 25.1            | 0.560   |
| Total bilirubin level (mg/dL) | 0.7 ± 0.3                  | 0.7 ± 0.2              | 0.160   |
| Protein level (g/dL)       | 6.8 ± 0.5                   | 6.9 ± 0.5              | 0.047   |
| Albumin level (g/dL)       | 3.9 ± 0.3                   | 3.8 ± 0.3              | 0.051   |
| Creatinine level (mg/dL)   | 0.8 ± 0.5                   | 0.9 ± 0.5              | 0.166   |
| BUN level (mg/dL)          | 17.2 ± 5.8                  | 17.5 ± 6.7             | 0.603   |
| Uric acid level (mg/dL)    | 4.8 ± 1.3                   | 5.0 ± 1.5              | 0.077   |
| Glucose level (mg/dL)      | 128.7 ± 46.5                | 124.4 ± 38.2           | 0.299   |
| Sodium level (mEq/L)       | 141.0 ± 2.5                 | 141.5 ± 2.0            | 0.061   |
| Potassium level (mEq/L)    | 4.1 ± 0.4                   | 4.1 ± 0.4              | 0.781   |

Table 2. Unmatched intraoperative variables between the intravenous PCA and epidural PCA groups. Data are presented as mean ± standard deviation or number (%), as appropriate. PCA patient-controlled analgesia.

| Variables                  | Intravenous PCA (n = 2339) | Epidural PCA (n = 128) | P value |
|----------------------------|-----------------------------|------------------------|---------|
| Type of anesthesia         |                             |                        |         |
| Inhalation                 | 2031 (86.8%)                | 23 (18.0%)             | <0.001  |
| Total intravenous          | 48 (2.1%)                   | 0                      | 0.102   |
| Regional                   | 260 (11.1%)                 | 105 (82.0%)            | <0.001  |
| Intraoperative variable    |                             |                        |         |
| Crystalloid use (mL)       | 974.9 ± 590.8               | 1165.7 ± 590.1         | <0.001  |
| Colloid use (mL)           | 402.5 ± 291.0               | 219.9 ± 259.9          | <0.001  |
| Packed red blood cell use (U) | 0.3 ± 0.7                   | 0.2 ± 0.5              | 0.621   |
| Fresh frozen plasma use (U) | 0.01 ± 0.20                 | 0                      | 0.602   |
| Estimated blood loss (mL)  | 77.6 ± 198.7                | 29.7 ± 113.2           | 0.007   |
| Operation site drainage (mL) | 3.3 ± 60.8                   | 0                      | 0.538   |
| Urine output (mL)          | 195.3 ± 226.8               | 316.1 ± 324.0          | <0.001  |
Packed red blood cell transfusion of > 3 units were also significantly more in the epidural PCA group compared with the intravenous PCA group (32 (30.2%) vs. 17 (16.0%), \( P = 0.014 \)). The percentage of significant blood loss in transfusion of > 3 units was associated with epidural PCA (odds ratio, 2.5; 95% confidence interval, 1.201–5.205; the epidural PCA group was about twice over the intravenous PCA group (25(23.6%) vs. 13(12.3%), \( P = 0.052 \)).

Sparing effects of regional anesthesia are believed to result from the diminished sympathetic tone of vessels in reduction of blood loss in patients undergoing knee surgery are crucial. After the propensity score-matching greater in-hospital mortality, and longer hospital stay in total hip or knee surgery, therefore, the prevention and reduction of postoperative bleeding are more important than that of intraoperative bleeding. The allogenic blood transfusion can lead to a higher incidence of the respiratory tract and wound infection, prevention and reduction of postoperative bleeding are more important than that of intraoperative bleeding.

The amount of bleeding after unilateral TKA, as a result of tourniquet use during the operation. Therefore, the prevention and reduction of postoperative bleeding are more important than that of intraoperative bleeding. The allogenic blood transfusion can lead to a higher incidence of the respiratory tract and wound infection, greater in-hospital mortality, and longer hospital stay in total hip or knee surgery, therefore, the prevention and reduction of blood loss in patients undergoing knee surgery are crucial. After the propensity score-matching of preoperative and intraoperative variables, we found that the amount of postoperative bleeding was greater in the epidural PCA group than in the intravenous PCA group. Using a univariate conditional logistic regression model, we found that the incidence of packed red blood cell transfusion of > 3 units was associated with epidural PCA (odds ratio, 2.5; 95% confidence interval, 1.201–5.205; \( P = 0.014 \)).

Discussion
Our current analysis indicates that the amount of intraoperative bleeding was relatively small, compared to the amount of bleeding after unilateral TKA, as a result of tourniquet use during the operation. Therefore, the prevention and reduction of postoperative bleeding are more important than that of intraoperative bleeding. The allogenic blood transfusion can lead to a higher incidence of the respiratory tract and wound infection, greater in-hospital mortality, and longer hospital stay in total hip or knee surgery, therefore, the prevention and reduction of blood loss in patients undergoing knee surgery are crucial. After the propensity score-matching of preoperative and intraoperative variables, we found that the amount of postoperative bleeding was greater in the epidural PCA group than in the intravenous PCA group. In addition, significant blood loss was more in the epidural PCA group compared with the intravenous PCA group [32 (30.2%) vs.17 (16.0%), \( P = 0.014 \)]. The percentage of significant blood loss in the epidural PCA group was about twice over the intravenous PCA group [25(23.6%) vs. 13(12.3%), \( P = 0.052 \)].

Using a univariate conditional logistic regression model, we found that the incidence of packed red blood cell transfusion of > 3 units was associated with epidural PCA (odds ratio, 2.5; 95% confidence interval, 1.201–5.205; \( P = 0.014 \)).

| Variables | Intravenous PCA (n = 2339) | Epidural PCA (n = 128) | \( P \) value |
|-----------|---------------------------|------------------------|--------------|
| Postoperative hypotension | 268 (11.5%) | 8 (6.3%) | 0.069 |
| Postoperative ICU admission | 17 (0.7%) | 3 (2.3%) | 0.047 |
| Re-admission | 44 (1.9%) | 1 (0.8%) | 0.365 |
| Hospital stay (day) | 17.1 ± 9.2 | 15.4 ± 7.9 | 0.043 |

Table 3. Unmatched postoperative variables between the intravenous PCA and epidural PCA groups. Data are presented as mean ± standard deviation or number (%), as appropriate. PCA, patient-controlled analgesia, ICU, intensive care unit. Postoperative hypotension = systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg within postoperative day 3, NRS = numerical rating scale.
is not currently recommended\textsuperscript{16}. Bruce and colleagues reported that the appropriate evaluation of bleeding risk preoperatively, tourniquet use during surgery, maintenance of normothermia perioperatively, and use of antifibrinolytic agents were important measures for the prophylaxis of perioperative bleeding\textsuperscript{16}. However, most of the studies to date that have evaluated the risk factors of postoperative bleeding in patients undergoing TKA have certain limitations, including unbalanced demographic data and intraoperative variables between groups, or a relatively small sample size in each group\textsuperscript{13}. In particular, the significant predictors of transfusion, such as preoperative hemoglobin level, age, female gender, body mass index, creatinine level, intraoperative blood loss, and intraoperative fluid use, should be controlled before comparison. Some reports have demonstrated that there is a significant relationship between epidural PCA and bleeding tendency after surgery. Nielsen and colleagues reported that the reduction in stress response with epidural PCA might indirectly affect platelet dysfunction\textsuperscript{17}. Similarly, Modig and colleagues reported that elevated fibrinolytic activity developed after epidural PCA administration, as compared to parenteral analgesia administration, as compared to postoperative pain\textsuperscript{18}. Although postoperative infection after TKA is an infrequent complication, it is strongly related to patient morbidity and increased hospital costs. Several studies have described postoperative infection as a risk factor for TKA failure\textsuperscript{19, 20}. Fehring and colleagues demonstrated that infection was one of the most frequent reasons for early failure, which requires revision of TKA\textsuperscript{19}. The allogenic transfusion of blood products is known as a significant risk factor for postoperative infection. Chang and colleagues demonstrated that there is a significant dose-dependent relationship between transfusion and the infection rate\textsuperscript{21}. Houbiers and colleagues demonstrated that the corrected relative risk for postoperative bacterial infection was 3.6 for a transfusion of more than 3

| Variables | Intravenous PCA (n = 106) | Epidural PCA (n = 106) | P value |
|-----------|---------------------------|------------------------|---------|
| Gender, female (%) | 89 (84.0%) | 92 (86.8%) | 0.710 |
| ASA class | | | |
| I/II | 8 (7.5%)/93 (87.7%) | 9 (8.5%)/91 (85.8%) | 0.918 |
| III/IV | /5 (4.7%)/0 | /6 (5.7%)/0 | |
| Age (years) | 69.3 ± 7.4 | 68.7 ± 7.4 | 0.627 |
| Weight (kg) | 61.9 ± 9.3 | 61.6 ± 8.8 | 0.820 |
| Height (cm) | 154.3 ± 7.2 | 153.1 ± 7.2 | 0.235 |
| Body mass index (kg/m\(^2\)) | 26.0 ± 3.2 | 26.2 ± 3.0 | 0.547 |
| Primary diagnosis | | | |
| Osteoarthritis | 103 (97.2%) | 101 (95.3%) | 0.727 |
| Rheumatoid arthritis | 0 | 0 | – |
| Infectious arthritis | 0 | 2 (1.9%) | 0.500 |
| Traumatic knee injury | 1 (0.9%) | 1 (0.9%) | 1.000 |
| Ankylosing knee | 0 | 0 | – |
| Others | 4 (3.8%) | 2 (1.9%) | 0.687 |
| Re-operation | 9 (8.5%) | 10 (9.4%) | 1.000 |
| Preoperative laboratory values | | | |
| Hemoglobin level (g/dL) | 12.7 ± 1.4 | 12.7 ± 1.4 | 0.906 |
| Platelet count (x 10\(^3\)/µL) | 241.0 ± 62.5 | 252.5 ± 61.9 | 0.168 |
| Prothrombin time (INR) | 1.0 ± 0.1 | 1.0 ± 0.1 | 0.637 |
| AST level (U/L) | 23.2 ± 7.9 | 24.1 ± 11.9 | 0.520 |
| ALT level (U/L) | 18.6 ± 10.0 | 19.9 ± 14.7 | 0.486 |
| ALP level (U/L) | 76.6 ± 23.3 | 74.4 ± 25.9 | 0.552 |
| Total bilirubin level (mg/dL) | 0.6 ± 0.4 | 0.7 ± 0.2 | 0.182 |
| Protein level (g/dL) | 6.8 ± 0.4 | 6.9 ± 0.5 | 0.314 |
| Albumin level (g/dL) | 3.8 ± 0.3 | 3.8 ± 0.3 | 0.688 |
| Creatinine level (mg/dL) | 0.9 ± 0.8 | 0.8 ± 0.3 | 0.602 |
| BUN level (mg/dL) | 18.4 ± 6.7 | 17.6 ± 6.7 | 0.335 |
| Uric acid level (mg/dL) | 4.8 ± 1.3 | 1.9 ± 1.3 | 0.677 |
| Glucose level (mg/dL) | 125.1 ± 39.2 | 125.7 ± 38.6 | 0.912 |
| Sodium level (mEq/L) | 141.1 ± 2.7 | 141.4 ± 2.0 | 0.258 |
| Potassium level (mEq/L) | 4.2 ± 0.4 | 4.1 ± 0.4 | 0.421 |

Table 4. Preoperative characteristics and preoperative laboratory values between the intravenous PCA and epidural PCA groups: PS-matched data. Data are presented as mean ± standard deviation or number (%), as appropriate. PCA patient-controlled analgesia, PS propensity score, ASA American Society of Anesthesiologists, INR international normalized ratio, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase, BUN blood urea nitrogen. Others include avascular necrosis, desmoplastic fibroma, fibrous dysplasia, pigmented villonodular synovitis, spontaneous osteonecrosis, valgus knee, spastic diplegia of cerebral palsy, and fused knee.
units. In the present study, we found that patients who received epidural PCA were 2.5 times more likely to receive red cell transfusion of more than 3 units, as compared to patients who received intravenous PCA. We considered that it might be associated with significant blood loss. Hence, epidural PCA for postoperative pain management following TKA may increase postoperative bleeding and transfusion, which can consequently increase the occurrence of postoperative complications. Recently, peripheral nerve block technique such as...
continuous femoral-sciatic nerve blocks is an alternative option to epidural analgesia after TKA. Moreover, it shows fewer complications over the epidural PCA. Therefore, given these considerations, epidural PCA should be carefully used for postoperative pain management in TKA.

Although we compared both groups with propensity score-matching analysis using variables obtained from retrospective studies, a randomized controlled study is warranted to identify the effect of epidural PCA on postoperative bleeding, in comparison with that of parenteral regimens. Appropriate pain management was initiated by a specialized acute pain management team at our institution, although we did not evaluate the between-serial measurements of the pain scores and the duration of PCA use during the postoperative period in the present study.

In summary, our current propensity matching analysis has indicated that epidural PCA is strongly related to postoperative bleeding and the incidence of transfusion of more than 3 units after unilateral TKA, as compared to that with intravenous PCA. Therefore, the use of epidural PCA may be carefully considered for postoperative pain management in TKA.

**Materials and methods**

**Patient characteristics.** Patients who underwent primary or revisional unilateral TKA between January 2000 and September 2016 in our institution were included. Patients who underwent bilateral TKA, patients with incomplete laboratory data or nerve block, and those without continuous PCA use were excluded. Two operators with > 10 years of experience in performing TKA performed all surgery. None of the study patients received an autologous blood transfusion or tranexamic acid during operation. All patients used tourniquets during surgery. The hemoglobin level was maintained > 8.0 g/dL. When the level of hemoglobin decreased to < 8 g/dL, packed red blood cell transfusion was started according to the anesthetic protocol of our hospital. Passive exercise and ambulation after TKA were performed according to the rehabilitation program of the orthopedic department.

**Clinical data collection.** Demographic data, preoperative laboratory values, primary diagnosis, re-do TKA, anesthetic technique, type of PCA, intraoperative variables, recovery room variables, and postoperative variables were obtained from the electronic medical records system. The Demographic data included sex, age, weight, height, body mass index, the ASA physical status classification, and preoperative laboratory values. The anesthetic techniques were classified as inhalation, total intravenous, or regional anesthesia. The intraoperative variables included the total amount of each type of fluid (crystalloid and colloid), urine output, estimated blood loss, packed red blood cell use, fresh frozen plasma use, and operation site drainage amount. The recovery room variables included the total amount of each type of fluid (crystalloid and colloid), urine output, packed red blood cell use, fresh frozen plasma use, and operation site drainage amount. The postoperative variables included packed red blood cell use, fresh frozen plasma use, operation site drainage amount, total blood loss, and significant blood loss. The operation site drainage amount is the amount of pure blood in hemovac. Total blood loss is a sum of operation site drainages during the intraoperative and postoperative period, and estimated blood loss in the operation room. Significant blood loss is defined as a loss of above 30% of circulating the total blood volume. We calculated estimated total blood volume (ETBV) according to Allen's calculation: ETBV is 70 mL/kg for males or 65 mL/kg for females. A total blood loss greater than 30% of the ETBV is considered significant blood loss. The pain intensity was assessed using the 11-point numerical rating scale (NRS; 0 = no pain, 10 = unbearable pain) by nurses. The highest NRS score in pain intensity was collected at the postoperative ambulatory care unit and the ward on postoperative day 0 were collected. The number of episodes of postoperative hypotension within postoperative day 3, the incidence of admission to the intensive care unit, total hospital stays, and incidence of re-admission for surgical complications were also recorded.

**Study outcomes.** The primary outcome included the comparison of the postoperative blood loss between epidural PCA and intravenous PCA by using propensity score-matching analysis. The secondary outcome was to determine the relationship between the incidence of packed red blood cell transfusion of > 3 units and epidural PCA.

**Statistical analysis.** Data are expressed as mean ± standard deviation, or number (percent), as appropriate. The data variables included in this study were compared between the epidural PCA and intravenous PCA groups using the chi-squared test or Fisher’s exact test for categorical variables and Student’s t-test or the Mann–Whitney U test for continuous variables. We performed multiple logistic regression analysis to determine the propensity score using the following variables: sex, age, body mass index, ASA physical status class, preoperative laboratory values (platelet count, prothrombin time, and aspartate transaminase, alanine transaminase, protein, albumin, serum creatinine, blood urea nitrogen, hemoglobin, and glucose levels), anesthesi technique, re-do TKA, primary diagnosis (osteoarthritis, rheumatoid arthritis, infectious arthritis, traumatic knee injury, and ankylosing knee), and intraoperative variables (crystalloid amount, colloid amount, estimated blood loss, and operation site drainage).

After performing 1:1 propensity score-matching, continuous variables were compared using the paired samples t-test or Wilcoxon signed-rank test, as appropriate, whereas categorical variables were compared using McNemar’s test or the marginal homogeneity test, as appropriate. Model calibration was assessed using Hosmer–Lemeshow statistics ($\chi^2 = 8.996; df = 23; P = 0.996$). We conducted univariate conditional logistic regression analysis for the matched population to identify the risk of blood transfusion. In all analyses, a $P$ value of $< 0.05$ was considered statistically significant. Statistical analysis was conducted using R (version 3.1.2; R Foundation for Statistical Computing, Vienna, Austria). Conditional logistic regression analyses were performed with STATA Release 14 (StataCorp 2015; Stata Statistical Software, College Station, TX, USA).
**Ethics.** This study was performed according to the Declaration of Helsinki. The current study protocol was approved by the institutional review board of Asan Medical Center, Seoul, Korea (approval number: 2016–1233). Due to the retrospective nature of the study, informed consent was waived.

**Data availability**
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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**References**

1. Perkins, F. M. & Kehlet, H. Chronic pain as an outcome of surgery: a review of predictive factors. *Anesthesiology* 93, 1123–1133 (2000).
2. Liu, S., Carpenter, R. L. & Neal, J. M. Epidural anesthesia and analgesia: their role in postoperative outcome. *Anesthesiology* 82, 1474–1506 (1995).
3. Kim, S. H., Yoon, K. B., Yoon, D. M., Kim, C. M. & Shin, Y. S. Patient-controlled epidural analgesia with ropivacaine and fentanyl: experience with 2276 surgical patients. *Korean J. Pain* 26, 39–45 (2013).
4. Block, B. M. *et al.* Efficacy of postoperative epidural analgesia: a meta-analysis. *JAMA* 290, 2455–2463 (2003).
5. Singelyn, F. J., Deyaert, M., Joris, D., Pendeville, E. & Gouverneur, J. M. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesth. Analg.* 87, 88–92 (1999).
6. Shojo, H., Solomonow, M., Yoshino, S., D’Ambrosia, R. & Dabezies, E. Factors affecting postoperative flexion in total knee arthroplasty. *Orthopedics* 13, 643–649 (1990).
7. Friedman, R., Homering, M., Holberg, G. & Berkowitz, S. D. Allogeneic blood transfusions and postoperative infections after total hip or knee arthroplasty. *J. Bone Joint Surg. Am.* 96, 272–278 (2014).
8. Klika, A. K. *et al.* Primary total knee arthroplasty allogenic transfusion trends, length of stay, and complications: nationwide inpatient sample 2000–2009. *J Arthroplasty* 29, 2070–2077 (2014).
9. Rosberg, B., Fredin, H. & Gustafson, C. Anesthetic techniques and surgical blood loss in total hip arthroplasty. *Acta Anaesthesiol. Scand.* 26, 189–193 (1982).
10. Twyman, R., Kirwan, T. & Fennelly, M. Blood loss reduced during hip arthroplasty by lumbar plexus block. *J. Bone Joint Surg. Br.* 72, 770–771 (1990).
11. Juelsgaard, P., Larsen, U. T., Sorensen, J. V., Madsen, F. & Soballe, K. Hypotensive epidural anesthesia in total hip arthroplasty. *Acta Anaesthesiol.* 39, 770–771 (1995).
12. Stevens, R. D., Van Gessel, E., Flory, N., Fournier, R. & Gamulin, Z. Lumbar plexus block reduces pain and blood loss associated with total hip arthroplasty. *Anesthesiology* 93, 115–121 (2000).
13. Frisch, N. B. *et al.* Predictors and complications of blood transfusion in total hip and knee arthroplasty. *J. Arthroplasty* 29(Suppl.), 189–192 (2014).
14. Popping, D. M. *et al.* Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. *Ann. Surg.* 259, 1056–1067 (2014).
15. Veering, B. T. & Cousins, M. J. Cardiovascular and pulmonary effects of epidural anaesthesia. *Anaesth. Intensive Care* 28, 620–635 (2000).
16. Bruce, W., Campbell, D., Daly, D. & Ibister, J. Practical recommendations for patient blood management and the reduction of perioperative transfusion in joint replacement surgery: *ANZ J. Surg.* 83, 222–229 (2013).
17. Nielsen, T. H. *et al.* Stress response and platelet function in minor surgery during epidural bupivacaine and general anaesthesia: effect of epidural morphine addition. *Eur. J. Anaesthesiol.* 6, 409–417 (1989).
18. Modig, J., Borg, T., Bagge, L. & Saldeen, T. Role of extradural and of general anaesthesia in fibrinolysis and coagulation after total hip replacement. *Br. J. Anaesth.* 55, 625–629 (1983).
19. Fehring, T. K., Odum, S., Griffin, W. L., Mason, J. B. & Nadaud, M. Early failures in total knee arthroplasty. *Clin. Orthop. Relat. Res.* 290, 315–318 (2001).
20. Chang, H. *et al.* Allogeneic red blood cell transfusion is an independent risk factor for the development of postoperative bacterial infection. *Vox Sang* 78, 13–18 (2000).
21. Houbiers, J. G. *et al.* Transfusion of red cells is associated with increased incidence of bacterial infection after colorectal surgery: a prospective study. *Transfusion* 37, 126–134 (1997).
22. Kopp, S. L. *et al.* Anaesthesia and analgesia practice pathway options for total knee arthroplasty: an evidence-based review by the American and European Societies of Regional Anaesthesia and Pain Medicine. *Reg. Anesth. Pain Med.* 42, 683–697 (2017).
23. Manning, J. E., Kelen, G. D. & Stacpynski, J. S. *Tintinalli’s Emergency Medicine: A Comprehensive Study Guide* 6th edn, 227 (McGraw Hill Professional, 2003).
24. Hilberath, J. N. *et al.* Blood volumes in cardiac surgery with cardiopulmonary bypass. *Perfusion* 30, 395–399 (2015).

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**Author contributions**

S.-So.C. and D.-H.K. conceived and designed the study. J.P. and H.P. helped in the acquisition of data. S.-S.J. and S.-Si.C. performed the statistical analyses. K.-D.H. and D.-H.K. drafted the manuscript with the supervision of S.-So.C. All authors read and approved the final manuscript.

**Competing interests**

The authors declare no competing interests.
