Clinical Study

Reducing Blood Loss in Revision Total Hip and Knee Arthroplasty: Tranexamic Acid Is Effective in Aseptic Revisions and in Second-Stage Reimplantations for Periprosthetic Infection

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1. Introduction

Revision arthroplasty procedures are mostly associated with higher blood loss than primary implantations [1]. Subsequently, there is a greater demand for allogeneic blood transfusion during and after these operations [2]. Even though blood transfusions today are safer than in the past, they are still accommodated by adverse events like allergic reactions or other negative side effects [3]. The transfusion of allogeneic blood products may be associated with adverse patient outcome as well as increased morbidity and mortality [4, 5]. In arthroplasty procedures, blood transfusions have been reported to be a risk factor for periprosthetic infection [6].

For patient safety and economic reasons a variety of methods to minimize the use of blood products have been developed and summarized under the concept of patient blood management [7–9]. Particularly, one of the antifibrinolytic agents, tranexamic acid (TXA), has been studied broadly in recent years. A significant impact on perioperative blood conservation in primary hip and knee arthroplasty without increasing the risk of thromboembolic events has
been reported [10–25]. However, there is only minimal literature on the effect and complication rates of TXA in revision procedures, including septic revisions.

Therefore, the purpose of this study was to evaluate if the usage of TXA in revision hip and knee arthroplasty (i) reduces the perioperative blood loss, (ii) lowers the intra- and postoperative transfusion rates, and (iii) does not increase the rate of deep vein thrombosis (DVT) or pulmonal embolism (PE).

2. Material and Methods

We performed a prospective cohort study after establishing a standard operating procedure (SOP) for the use of tranexamic acid in our department. Starting in July 2015, every patient undergoing revision total hip arthroplasty (rTHA) or revision total knee arthroplasty (rTKA) received a bolus of 10 mg/kg bodyweight (BW) TXA as well as a continuous dose of 1 mg/kgBW/h intraoperatively. The patients received the bolus prior to skin incision. Up to December 2016, 96 rTHA patients and 51 rTKA patients could be included in this study. The inclusion criteria were patients undergoing any type of aseptic revision of one or more prosthetic components (except isolated liner exchange) or reimplantation in a two-stage procedure for periprosthetic infection. The explanation procedures for periprosthetic infection were not included. Patients with allergy to TXA, a history of thromboembolic events, or DVT/PE were excluded from the study. The inclusion criteria were patients undergoing revision of hip and knee procedures for periprosthetic infection. The exclusion criteria were identical in the TXA- and no-TXA-group.

Revision procedures from January 2014 to June 2015, before starting the SOP, were used as retrospective control group. Each prospective cohort of revision patients receiving TXA was compared to a retrospective cohort without TXA. In this manner, 96 prospectively collected rTHA patients with TXA were compared to 103 retrospectively collected rTHA patients without TXA application. Likewise, the prospectively assessed 51 rTKA patients receiving TXA were compared to 52 retrospectively assessed rTKA patients who did not receive TXA.

Subgroup analyses were carried out to examine the effect in aseptic revisions and in reimplantation procedures separately.

From the patients’ records, the following parameters were investigated: the operative procedures, the preoperative blood levels of hemoglobin as well as on postoperative days one, three, and five, hematocrit, and creatinine, including hemostasis indicators (international normalized ratio, partial thromboplastin time, antithrombin, and fibrinogen) as well as the operative risk factors like preoperative anemia, history of thromboembolic events, infection, fracture, tumor, and cardiac, renal, or pulmonary dysfunction. The risk factors were represented by the ASA score [26]. Furthermore, given blood products and the postoperative occurrence of complications were registered. The main outcome variables were the calculated blood loss as well as the thromboembolic complications like DVT and PE.

The perioperative blood loss was calculated according to the Brecher formula [27]. Variables required for the computation are the patient’s blood volume, the preoperative hematocrit (Ht), the Ht at the postoperative day 5 (POD 5), and all given blood products including intraoperative cell salvage. Patient’s blood volume was calculated using height, weight, and gender of the patient [28, 29]. Compared to other methods used for the assessment of perioperative blood loss, the Brecher formula is one of the few methods that take the so-called hidden blood loss into account [27].

The perioperative thrombosis prophylaxis included a daily dose of 40 mg enoxaparin given subcutaneously to all patients for a minimum of 28 days beginning on postoperative day 1. Patients presenting clinical signs for DVT were examined using Doppler ultrasound. Suspected PE were diagnosed or ruled out via CT pulmonary angiography. Any complication was recorded during a follow-up period of three months postoperatively.

All surgical procedures were performed by 10 senior surgeons. Reimplantations in two-stage exchange procedures were performed 6-12 weeks after explantation and antibiotic spacer implantation. If a tourniquet was used in rTKA procedures, it was placed at the level of the upper thigh and inflated to 350 mm Hg prior to cementing the prosthetic components. The tourniquet was deflated after wound closure and application of compression dressing.

Data was collected using the hospital information system. The statistical analyses were performed using SPSS 22 (IBM Corporation, Armonk, NY). Descriptive analysis was carried out and distribution diagrams were used to control for Gaussian distribution. Levene’s test assessed the equality of variances of the given variables.

Student’s t-test was used to compare means between the TXA and no-TXA groups if normal distribution and equal variances were present. Welch’s test was used if no equal variances were found. Mann-Whitney U test was applied if no normal distribution was encountered. Cross tabulation was used for nominal scaled variables like the complication frequency. For all tests, two-sided significance was assumed for p values below .05. Post hoc computed power analyses for the t-tests of the mean blood loss were carried out for rTHA and rTKA groups (.999 and .912).

The study was approved by the Ethics Committee of the University under the number S-413/2014 and registered at the Federal Institute for Drugs and Medical Devices filed under the number NIS 3377. Therefore, it is in accordance with the ethical standards on human experimentation.

3. Results

Between January 2014 and December 2016, a total of 517 rTHA or rTKA were performed at our institution. 215 patients had to be excluded because either patients did not receive TXA according to the protocol or patients received TXA for individual reasons prior to the start of the SOP. The remaining 199 patients undergoing rTHA and 103 patients undergoing rTKA could be included in the study. The preoperatively recorded demographic data and blood variables showed no statistically significant differences between the TXA group and the no-TXA group (Table 1).
Table 1: Demographic data and preoperative blood variables. Given are mean values (SD), except the absolute amounts for female gender.

| Demographic data             | TXA                  | No TXA                | p-value |
|------------------------------|----------------------|-----------------------|---------|
|                              | Revision THA n=96    | Revision THA n=103    |         |
|                              | Revision TKA n=51    | Revision TKA n=52     |         |
| **Age [years]**              |                      |                       |         |
| Revision THA                 | 66.1 (13.5)          | 68.6 (11.3)           | 0.16†   |
| Revision TKA                 | 65.3 (15.2)          | 66.1 (12.4)           | 0.78    |
| **Female gender, N (%)**     |                      |                       |         |
| Revision THA                 | 57 (59%)             | 56 (54%)              | 0.48    |
| Revision TKA                 | 26 (51%)             | 28 (54%)              | 0.77    |
| **Height [m]**               |                      |                       |         |
| Revision THA                 | 1.69 (0.11)          | 1.69 (0.10)           | 0.68    |
| Revision TKA                 | 1.70 (0.10)          | 1.69 (0.11)           | 0.57    |
| **Weight [kg]**              |                      |                       |         |
| Revision THA                 | 76.6 (16.1)          | 77.6 (18.6)           | 0.69    |
| Revision TKA                 | 85.2 (21.2)          | 88.0 (22.3)           | 0.51    |
| **Calculated blood volume [ml]** |                |                       |         |
| Revision THA                 | 4943 (870)           | 4865 (877)            | 0.86    |
| Revision TKA                 | 5205 (948)           | 5265 (1070)           | 0.77    |
| **ASA score**                |                      |                       |         |
| Revision THA                 | 2.52 (0.78)          | 2.48 (0.58)           | 0.65†   |
| Revision TKA                 | 2.47 (0.64)          | 2.44 (0.57)           | 0.81    |
| **Preoperative Ht**          |                      |                       |         |
| Revision THA                 | 0.386 (0.051)        | 0.388 (0.047)         | 0.71    |
| Revision TKA                 | 0.391 (0.053)        | 0.391 (0.041)         | 0.97    |
| **INR preop.**               |                      |                       |         |
| Revision THA                 | 1.01 (0.07)          | 1.01 (0.07)           | 0.51    |
| Revision TKA                 | 1.01 (0.06)          | 1.01 (0.06)           | 0.71    |

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; Ht, hematocrit; INR, international normalized ratio; SD, standard deviation; †Welch’s test

For the rTHA group, the most common indication for revision was aseptic loosening of one or more components. Half of the patients presented with this diagnosis. The second most common reason for rTHA was infection or septic loosening with 22% in the TXA-group. 10% of patients were revised because of periprosthetic fracture in the TXA-group and 8% because of hip dislocation. In contrast, the most common indication in the rTKA group was infection beforehand with 41% in the TXA-group, followed by aseptic loosening with 35%. Between the TXA group and the no-TXA group, there were no significant differences concerning the indications for revision surgery (p=.43 for rTHA and p=.25 for rTKA).

Almost one-third of all cases were reimplantations in two-stage revisions for periprosthetic infection. In rTHA and rTKA, the numbers of exchanged components showed no statistically significant differences between the TXA group and the no-TXA group (p=.69 and p=.06, Table 2).

Regarding the use of a tourniquet in the rTKA groups, we found a statistically significant reduced application in the TXA-group with 55% vs 86% in the no-TXA-group (p=.01).

We found a statistically significant decrease in mean calculated blood loss with the usage of TXA in rTHA and rTKA (Table 3, Figures 1 and 2). In rTHA patients, calculated blood loss was 2916 ml ± 1226 ml with TXA compared to 3611 ml ± 1474 ml without TXA (p<.001). In rTKA patients, a blood loss of 2756 ml ± 975 ml with TXA was calculated compared to 3441 ml ± 1100 ml without TXA (p=.0012).

Revision THA patients receiving TXA showed a significant higher Ht on POD 5 (p=.03) as well as a statistically significant lower amount of transfused packed red blood cells (RBC, p=.04) than rTHA patients without TXA.

No thromboembolic events were registered in the no-TXA rTKA group and both TXA groups. One patient undergoing a rTHA without TXA was diagnosed with pulmonary embolism. Therefore, no statistically significant difference regarding the thromboembolic events was found between the TXA and the no-TXA groups.

3.1. Subgroup Analysis. Four separate subgroup analyses were carried out to determine if the blood sparing effect of TXA could be registered for aseptic revisions in THA and TKA.
| Components being revised                      | TXA Revision THA n=96 | No TXA Revision THA n=103 | p-value |
|-----------------------------------------------|------------------------|---------------------------|---------|
| **Revision THA**                              |                        |                           |         |
| Acetabular component                          | 43                     | 43                        | 0.63    |
| Femoral component                             | 22                     | 26                        |         |
| Both components                               | 10                     | 16                        |         |
| Reimplantation of both components in two-stage revisions | 21                     | 18                        | 0.44    |
| **Revision TKA**                              |                        |                           | 0.06    |
| Femoral component                             | 9                      | 2                         |         |
| Tibial component                              | 1                      | 3                         |         |
| Both components                               | 20                     | 20                        |         |
| Reimplantation of both components in two-stage revisions | 21                     | 27                        | 0.28    |

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; *: significant; †: Welch’s test.

| Outcome variables               | TXA Revision THA n=96 | No TXA Revision THA n=103 | p-value |
|---------------------------------|------------------------|---------------------------|---------|
| **Revision THA**                |                        |                           |         |
| Surgical time [min]             | 152.6 (51.6)           | 150.0 (63.7)              | 0.7500  |
| Min; Max; Median                | 50; 290; 150           | 60; 420; 130              |         |
| Ht POD 5                        | 0.288 (0.029)          | 0.278 (0.029)             | 0.0300* |
| INR postop.                     | 1.09 (0.07)            | 1.08 (0.07)               | 0.4700  |
| RBC postop. [unit]              | 1.00 (1.11)            | 1.41 (1.49)               | 0.0280* |
| RBC transfused total [unit]     | 1.49 (1.62)            | 2.01 (1.92)               | 0.0400* |
| Transfusion rate                | 0.57 (0.50)            | 0.65 (0.48)               | 0.2600† |
| Calc. blood loss [ml]           | 2916 (1226)            | 3611 (1474)               | 0.0004† |
| DVT/PE                          | 0/0                    | 0/1                       | -/0.3500|
| Complication rate               | 0.21 (0.41)            | 0.15 (0.36)               | 0.2700† |
| **Revision TKA**                |                        |                           |         |
| Surgical time [min]             | 175.1 (43.5)           | 174.0 (53.5)              | 0.9100  |
| Min; Max; Median                | 105; 300; 165          | 120; 360; 163             |         |
| Ht POD 5                        | 0.279 (0.037)          | 0.274 (0.025)             | 0.3800† |
| INR postop.                     | 1.09 (0.07)            | 1.11 (0.09)               | 0.2200  |
| RBC postop. [unit]              | 0.78 (1.15)            | 1.13 (1.37)               | 0.1600  |
| RBC transfused total [unit]     | 1.18 (1.57)            | 1.54 (1.66)               | 0.2600  |
| Transfusion rate                | 0.47 (0.50)            | 0.58 (0.50)               | 0.2900  |
| Calc. blood loss [ml]           | 2756 (975)             | 3441 (1100)               | 0.0012† |
| DVT/PE                          | 0/0                    | 0/0                       | -/-     |
| Complication rate               | 0.23 (0.43)            | 0.29 (0.46)               | 0.5300  |

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; POD, postoperative day; Ht, hematocrit; INR, international normalized ratio; RBC, packed red blood cells; DVT, deep vein thrombosis; PE, pulmonary embolism; *: significant; †: Welch’s test.
as well as in hip and knee reimplantations for periprosthetic infection.

The demographic data of all four subgroups showed no significant difference between the TXA and no-TXA groups.

Regarding the aseptic revisions, the blood loss in the TXA groups of aseptic rTHA and aseptic rTKA was significantly decreased (2740 ml ± 1220 ml vs. 3342 ml ± 1304, p < 0.01 and 2411 ml ± 979 vs. 3053 ml ± 957, p < 0.05). The Ht on POD5 was significantly higher in both TXA groups and the total amount of transfused RBC in the TXA group of the rTHA patients was significantly lower (Table 4).

Regarding the reimplantations in two-stage exchange procedures, the blood loss in the TXA groups of reimplantation THA and TKA was significantly decreased (3544 ml ± 1052 vs. 4882 ml ± 1604, p < 0.01 and 3249 ml ± 744 vs. 3801 ml ± 1117, p < 0.05; Table 5). No reinfection occurred in the TXA or no-TXA groups within 12 months postoperatively.

4. Discussion

The results of the present study suggest that the use of TXA reduces blood loss in rTHA and rTKA without increasing the risk for thromboembolic events. The use of TXA was effective and safe, regardless of whether aseptic revisions or reimplantations in two-stage exchange procedures for periprosthetic infection were analyzed.

Substantial blood loss is one of the main issues in orthopaedic surgery, leading to an increased complication rate and the need for transfusion [9, 30]. Thus, a variety of methods like the use of TXA have been developed for minimizing blood loss.

In contrast to the abundant literature regarding TXA use in primary THA and TKA, there are only a few studies to this date examining the impact of TXA in either rTHA or rTKA [31–38]. All studies reported a benefit of TXA in revision arthroplasty without an increase in complication rates, but had specific limitations, which the current study tried to surpass. Most of the previous authors excluded reimplantations or revisions for septic loosening. For rTHA, only Kazi et al. included second-stage revision procedures into their study plan with a limited number of six reimplantations in the TXA group and six reimplantations in the control group [31]. In rTKA, Smit et al. presented data in which revision for septic loosening was not excluded, including 57 reimplantations in the TXA group and 24 in the control group [37]. Waddell et al. used a topical administration of TXA before wound closure in 20 patients with infected TKA in the first-stage revision (explantation and antibiotic spacer placement) and in 28 patients in the second-stage revision (reimplantation) [39].

To our knowledge, the current study is the first one which includes aseptic revisions as well as reimplantations in two-stage exchange procedures of THA and TKA. Unlike most of the previous authors, we recorded a high number of cases and excluded only isolated liner exchange procedures because of the expected minor blood loss. With this heterogeneity, our patient cohort reflects the everyday spectrum of a center for revision surgery.

All previous revision arthroplasty studies reported a decrease in blood loss related parameters like hemoglobin drop, transfusion rate, or transfused RBC. Our study can support and strengthen this statement finding that TXA decreased the calculated total blood loss. Moreover, we registered a significant lower amount of transfused RBC as well as a significant higher Ht on POD 5 in the TXA group of rTHA patients. There was a tendency for a decreased transfusion rate and decreased transfused RBC in the TXA group of rTKA patients although not reaching statistically significant difference. The tendency for reduced transfusions and a higher postoperative Ht on POD5 results in the significant statistical difference of calculated blood loss because they are both part of the Brecher calculation formula.

For rTKA only a statistically significant difference for the calculated blood loss and not for transfused RBCs was found. The reduced application of a tourniquet in the TXA-group might have had an influence here. Although the minimum
Table 4: Main outcome variables of the subgroup analysis between aseptic revisions. Given are the mean values (SD), in addition to minimum, maximum, and median for surgical time.

| Outcome variables | TXA aseptic rTHA n=75 | No TXA aseptic rTKA n=85 | p-value |
|-------------------|-----------------------|-------------------------|---------|
| **Aseptic rTHA**  |                       |                         |         |
| Surgical time [min] | 151.1 (52.7)          | 140.0 (50.6)            | 0.1790† |
| Min; Max; Median   | 50; 290; 150          | 60; 270; 125            |         |
| Ht POD 5           | 0.290 (0.031)         | 0.280 (0.029)           | 0.0453* |
| RBC transfused total [unit] | 1.19 (1.39)    | 1.73 (1.74)            | 0.0320* |
| Transfusion rate   | 0.51 (0.50)           | 0.61 (0.49)             | 0.1833  |
| Calc. blood loss [ml] | 2740 (1220)       | 3342 (1304)            | 0.0031* |
| Complication rate  | 0.24 (0.43)           | 0.12 (0.33)             |         |
| **Aseptic rTKA**  |                       |                         |         |
| Surgical time [min] | 163.0 (38.9)          | 169.0 (46.8)            | 0.6056  |
| Min; Max; Median   | 105; 260; 150         | 120; 255; 165           |         |
| Ht POD 5           | 0.295 (0.038)         | 0.276 (0.025)           | 0.0290† |
| RBC transfused total [unit] | 1.03 (1.73)    | 1.20 (1.58)            | 0.7132  |
| Transfusion rate   | 0.37 (0.49)           | 0.48 (0.51)             | 0.4056  |
| Calc. blood loss [ml] | 2411 (979)         | 3053 (957)              | 0.0178* |
| Complication rate  | 0.25 (0.44)           | 0.25 (0.44)             | 1.0000  |

TXA, tranexamic acid; rTHA, revision total hip arthroplasty; rTKA, revision total knee arthroplasty; POD, postoperative day; Ht, hematocrit; INR, international normalized ratio; RBC, packed red blood cells; DVT, deep vein thrombosis; PE, pulmonal embolism; *: significant; †: Welch’s test.

Table 5: Main outcome variables of the subgroup analysis between reimplantations. Given are the mean values (SD), in addition to minimum, maximum, and median for surgical time.

| Outcome variables | TXA Reimplantation THA n=21 | No TXA Reimplantation TKA n=27 | p-value |
|-------------------|------------------------------|---------------------------------|---------|
| **Reimplantation THA**  |                              |                                  |         |
| Surgical time [min] | 157.9 (48.1)                 | 196.9 (94.1)                    | 0.1239  |
| Min; Max; Median   | 90; 290; 150                 | 110; 420; 175                   |         |
| Ht POD 5           | 0.280 (0.023)                | 0.268 (0.029)                   | 0.1964  |
| RBC transfused total [unit] | 2.57 (1.91)           | 3.33 (2.22)                     | 0.2571  |
| Transfusion rate   | 0.81 (0.40)                  | 0.83 (0.38)                     | 0.8517  |
| Calc. blood loss [ml] | 3544 (1052)              | 4882 (1604)                     | 0.0035* |
| Complication rate  | 0.10 (0.31)                 | 0.28 (0.46)                     | 0.1173† |
| **Reimplantation TKA**  |                              |                                  |         |
| Surgical time [min] | 192.4 (44.9)                 | 178.6 (59.5)                    | 0.3804  |
| Min; Max; Median   | 130; 300; 180                | 120; 360; 160                   |         |
| Ht POD 5           | 0.256 (0.020)                | 0.271 (0.025)                   | 0.0273  |
| RBC transfused total [unit] | 1.38 (1.32)           | 1.85 (1.70)                     | 0.3015  |
| Transfusion rate   | 0.62 (0.50)                  | 0.67 (0.48)                     | 0.7388  |
| Calc. blood loss [ml] | 3249 (744)                 | 3801 (1117)                     | 0.0464† |
| Complication rate  | 0.21 (0.41)                 | 0.33 (0.48)                     | 0.3846  |

TXA, tranexamic acid; THA, total hip arthroplasty; TKA, total knee arthroplasty; ASA, American Society of Anesthesiologists; Ht, hematocrit; INR, international normalized ratio; RBC, packed red blood cells; DVT, deep vein thrombosis; PE, pulmonal embolism; *: significant; †: Welch’s test.

clinically important difference for blood loss is unclear, we believe that every reduction in blood loss is beneficial. Previous authors except Kazi et al. did not calculate the absolute perioperative blood loss and reported only indirect blood loss related parameters as main endpoints. Kazi et al. used the formula according to Gross et al. but were unable to find a difference between the TXA and the control group for the calculated blood loss in a relatively small number of 60 patients.
patients [31, 40]. We determined the overall blood loss of the procedures according to the Brecher formula which includes the hidden blood loss postoperatively and is thought to be an accurate measurement [41–43]. This may be the reason for the slightly higher calculated blood loss of the present study compared to previous publications using different calculating methods [41].

Concerning the postoperative complications, Kazi et al. were the only authors who did find a small increase in thromboembolic events for TXA patients without reaching statistical relevance. However, their small patient collection must be considered where only a few events can have a significant impact. In contrast, the current study can underline the findings of all other authors that no increased thromboembolic complications or complications overall were registered.

Regarding the systemic TXA-regime the present study is in line with most of previous studies. The range of total TXA applied was between 10 mg/kgBW given by Samujh et al. and 3 g given by Noordin et al., who did not report a strict application regime [34, 36].

There are several limitations in our study. The study was not prospectively randomized; in fact a prospective study group of revision cases receiving TXA was compared to a retrospective one without TXA. A relevant number of patients (215/517) had to be excluded from the present study either because they did not receive TXA according to the protocol due to individual reasons or because TXA was applied prior to the start of the SOP. Septic explantations as the first step of two-stage revision procedures could not be included in our study because TXA was only used in reimplantation procedures during the time of this study.

Revision arthroplasty cohorts are naturally heterogeneous. Yet, the preoperative data of our collective showed no difference between the TXA and the no-TXA groups. Even the surgical time, as one of the main indicators for blood loss, was not significantly different between the TXA and no-TXA groups. The large range of surgical times reflects the underlying heterogeneity in revision arthroplasty procedures.

Furthermore, we did not include patients with a history of DVT or PE in our study which might lessen the applicability of the general statement that TXA does not increase the risk for thromboembolic events. To this date, studies including high risk patients are still missing. Due to ethical reasons we could not perform a randomized, controlled trial in our revisions whereas the benefits of TXA in primary arthroplasty surgery as well as in other fields of surgery have been well documented. There are still concerns regarding the safety of TXA application in morbid patients. Surprisingly, data to support these concerns are nonexistent.

5. Conclusion

We conclude that TXA is a viable tool to decrease the absolute perioperative blood loss in aseptic revision procedures of THA and TKA as well as in second-stage reimplantations for periprosthetic infection. The use of TXA reduces blood transfusions and does not increase thromboembolic complications. TXA can be recommended as a standard routine for aseptic revisions and reimplantation procedures. Future investigations are warranted to clarify if TXA can also be safely administered to thromboembolic high-risk patients and if so whether or not topical use of TXA may be an alternative.

Data Availability

The original data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of the university and registered at the Federal Institute for Drugs and Medical Devices.

Consent

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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