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Efficacy of intraoperative periarticular Ranawat solution in reducing hidden blood loss and transfusion requirements in hip fracture hemiarthroplasty: a randomized controlled trial

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ABSTRACT

Aims: This randomized controlled trial evaluated the efficacy of intraoperative periarticular Ranawat solution injection in reducing total and hidden blood loss (HBL), as well as allogeneic blood transfusion (ABT) rates, in elderly patients undergoing bipolar hemiarthroplasty for intra-articular hip fractures.

Methods: In this single-center trial (NCT06701695), 84 patients (aged 65-95) undergoing bipolar hemiarthroplasty between May 2020 and February 2022 were randomized to receive either the Ranawat solution injection or no injection. Primary outcomes were total blood loss (TBL), HBL, and ABT rate. Secondary outcomes included intraoperative blood loss (IBL), postoperative drainage volume, and hospital stay duration.

Results: The injection group included 41 patients (14 males, 34.1%; mean age 82.6±6.96 years), whereas the control group comprised 43 patients (18 males, 41.8%; mean age 81.5±8.47 years).The injection group showed significantly lower HBL (327.4±148.8 mL vs. 442.2±168.9 mL, p=0.013) and TBL (1100.2±423.4 mL vs. 1330.3±434.2 mL, p=0.049) compared to controls. ABT was required in 34.1% of the injection group versus 58.1% in controls (p=0.043). Ranawat solution reduced HBL by 26% and TBL by 17.2%. No significant differences were found in IBL or drainage volume, and no injection-related adverse effects were observed.

Conclusions: Intraoperative periarticular Ranawat solution injection effectively reduces perioperative blood loss and transfusion requirements in elderly patients undergoing hemiarthroplasty for hip fractures, supporting its use to enhance outcomes and safety in this population.

Introduction

Hip fractures among elderly individuals represent a significant global public health issue due to the high morbidity, mortality, and healthcare costs associated with their management. With the global increase in life expectancy, the incidence of fragility-related hip fractures continues to rise markedly. Recent epidemiological projections estimate that fragility-related hip fractures could surpass six million cases annually worldwide by the year 2050, highlighting an urgent need for effective clinical strategies to improve outcomes in this vulnerable population (1).

Surgical intervention for hip fractures, such as hemiarthroplasty, is associated with considerable perioperative blood loss. Postoperative anemia following hip fracture surgery has been linked to delayed functional recovery, increased morbidity, prolonged hospital stays, and elevated mortality rates (2). Moreover, a substantial proportion of patients who

suffer from hip fractures require allogeneic blood transfusions (ABT), with reported rates ranging from 26.2% to 39.5% (3,4). Unfortunately, ABT may elevate the risk of surgical site infections, increase healthcare expenses, and extend hospital stays for this vulnerable population. On the other hand, a significant yet often overlooked aspect of perioperative blood loss in hip fracture surgery is "hidden blood loss (HBL)," referring to the blood lost into tissue compartments and not directly measurable intraoperatively. Foss and Kehlet (5) reported HBL to be up to six times greater than visible intraoperative loss, posing substantial risks for patient recovery.

Numerous strategies have been employed to mitigate perioperative blood loss, including topical epinephrine (EP) infusion, controlled hypotensive anesthesia, periarticular cocktail injections, and the application of cold saline (6-8). Periarticular cocktail injections have garnered attention due to their localized effects, directly targeting tissues surrounding the surgical site and thus minimizing systemic exposure and side effects (9,10). Despite this growing interest, the efficacy of specific cocktail formulations such as the Ranawat solution, comprising bupivacaine, dexamethasone, EP, and cefuroxime, has not been extensively evaluated for HBL reduction in hip fracture surgeries.

Therefore, this study aimed to evaluate the effectiveness of intraoperative periarticular Ranawat solution injections, in reducing total and HBL, and, consequently, the need for ABT in elderly patients undergoing hemiarthroplasty for intra-articular hip fractures. We hypothesized that this technique would significantly reduce perioperative blood loss and thus decrease ABT needs compared to standard procedures without periarticular injection.

Methods

Study design

This study was a single-center randomized controlled trial at our tertiary trauma center. The study protocol and design were approved by the Ankara City Hospital, No. 1 Clinical Research Ethics Committee (decision no.: E1-19-3292, date: 22.02.2019). Additionally, the study was registered in the ClinicalTrials.gov Protocol Registration System (trial number NCT06701695). All researchers involved in the study have agreed to the most recent version of the Helsinki Declaration. Patients enrolled in the study provided their consent after receiving comprehensive information included in the consent forms. The reporting procedures adhered to the guidelines outlined in the Consolidated Standards of Reporting Trials (11).

Inclusion and exclusion criteria

One hundred thirteen consecutive patients with intra-articular hip fracture (femoral neck fracture) (age range sixty-five to ninety-five) who were admitted to our institution and underwent bipolar hemiarthroplasty from May 2020 to February 2022, were initially assessed for eligibility, and 84 patients eligible for inclusion were randomized to either receive intraoperative periarticular Ranawat solution injections or not receive any injection at this institution. The exclusion criteria included: 1) extra-articular hip fractures (pertrochanteric fractures), 2) patients receiving any form of anti-aggregant, anticoagulant, or anti-thrombotic therapy prior to sustaining a hip fracture, 3) pathological fractures, periprosthetic fractures, or revision procedures, 4) presence of intolerance or allergy to any of the drugs utilized in the study, and 5) refusal to participate in this study (Figure 1).

Randomization

Upon obtaining informed consent, random numbers generated by statistical software were used to allocate patients based on their order of admission. Subsequently, patients were assigned to either the intraoperative periarticular Ranawat solution injection group or the control group (which did not receive intraoperative injections) in a 1:1 ratio using these random numbers. The randomization numbers were securely enclosed in opaque, sequentially numbered envelopes. These sealed envelopes were accessed by an independent researcher solely during the patient's anesthesia. During the trial, patients were kept unaware of their group assignments, ensuring they remained blinded to the study parameters. While the surgeon possessed knowledge of the group allocations, he was not directly involved in patient data analysis.

Description of cohort

In the study, patients were divided into two distinct groups: the "injection group", comprising those who received an intraoperative periarticular Ranawat solution injection, and the "non-injection group", comprising those who did not receive such injections. The periarticular injection solution used in our study was designed by adopting the cocktail sample used by Ranawat Orthopedic Center after knee and hip surgery (12). This regimen has been variously utilized in patients undergoing arthroplasty and has demonstrated its efficacy in reducing postoperative morbidity (12-14). Patients in the injection group were administered a 100 mL periarticular solution comprising 200 mg of bupivacaine (40 mL), 8 mg of dexamethasone (2 mL), 2 mg of 1:1000 EP (2 mL), 750 mg of cefuroxime (7.5 mL), and standard saline solution (48.5 mL). This solution was prepared in two 50 mL syringes. The first syringe containing 50 mL of the cocktail was injected into the capsule and gluteal muscles prior to femoral stem insertion. Following joint capsule closure, the second syringe containing 50 mL of the periarticular Ranawat solution injection was injected into the fascia lata muscle, subcutaneous tissue, and wound layers.

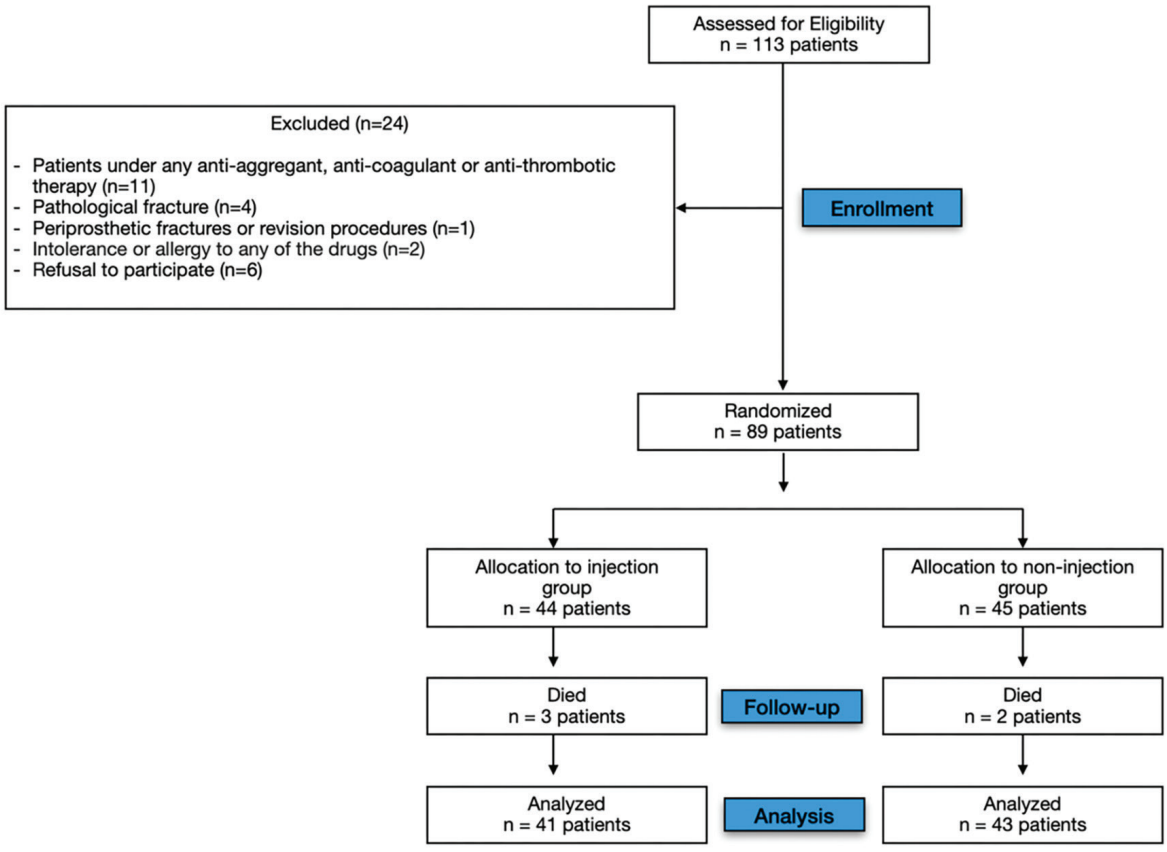

Figure 1. Flowchart of the study

Surgical procedures and postoperative rehabilitation

All surgical procedures were performed by the same surgeon using an anterolateral (Watson-Jones) approach and a cementless bipolar hemiarthroplasty prosthesis (Echo® Femoral Hip System-Zimmer-Biomet, Warsaw, IN). All patients underwent the same perioperative procedure. Elastic above-the-knee stockings are initiated at the diagnosis of hip fracture and continue to be worn for at least three more weeks postoperatively. Upon admission to our emergency services, the appropriate dosage of enoxaparin sodium, adjusted for patient weight, was promptly administered to all individuals presenting with hip fractures. This regimen was systematically maintained until the patients were discharged. All patients have been prescribed oral aspirin or enoxaparin sodium. The medical staff followed the patients' postoperative suction drains. Postoperative daily hemoglobin (Hb) values of the patients were examined. According to our clinical approach, 300 cc erythrocyte suspension was transfused to patients with Hb values <7-8 g/dL or with anemia symptoms such as dizziness, headache, weakness, and palpitations. On the 1st postoperative day, the patients were mobilized to full weight bearing, and the standard rehabilitation process was applied.

Data collection

Age, sex, body mass index (BMI) (kg/m^2), preoperative and postoperative first three days' hematocrit (Hct) and Hb (g/dL) values, intraoperative blood loss (IBL), postoperative drainage volume, number of ABT, length of stay were collected prospectively by an investigator and entered into a database with all clinical information.

Calculation of blood loss

IBL was determined through anesthesia recordings during the operation, which included the measurement of blood suction bottles and the weight of surgical swabs.

The calculation of total blood volume (TBV) was conducted using the Nadler method (8,15) in the following manner:

$TBV=k_1xH_3 + k_2xW + k_3$

For males, $k_1=0.3669$, $k_2=0.03219$, and $k_3=0.1833$; for females, $k_1=0.3561$, k2=0.03308, and $k_3=0.1833$.

H=height (m) and W=weight (kg).

The calculation of total blood loss (TBL) was conducted using the Gross formula (16) method as follows:

TBL=TBV × (preoperative Hct-postoperative 3-day Hct) / Mean Hct

Each erythrocyte suspension volume containing 300 mL administered to the patient, was introduced to TBL separately. The total HBL was determined by deducting the visible blood loss from the TBL volume (15).

Statistical Analysis

To demonstrate the robustness of this study, we performed a post-hoc power analysis using G*Power version 3.1.9.4. This analysis is intended to assess the sufficiency of our sample size. Remarkably, the results indicated that our study achieved a power of 99%, with an alpha level (α) set at 0.05. The substantial level of statistical power reinforces the reliability and validity of our findings, indicating that the sample size was adequately large to identify significant effects. The statistical analysis was conducted SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). To evaluate the normality of distribution, the Kolmogorov-Smirnov test was utilized. Categorical variables were presented as counts and percentages and compared using either the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were described as means and standard deviations. Normally distributed continuous variables were compared using independent samples Student's t-test, while non-normally distributed continuous variables were compared using the Wilcoxon-Mann-Whitney U test. A two-sided p-value less than 0.05 was considered statistically significant.

Results

Of the 84 (52 female and 32 male) eligible for this study, 41 patients were randomized to the injection group and 43 patients were randomized to the non-injection group. The average age of the cohort was 81.5±7.69, ranging from 65 to 95 years. There was no statistically significant difference between groups regarding age, sex, BMI, and length of stay (p=0.548, p=0.222, p=0.801, p=0.071, respectively) (Table 1).

Blood loss

A detailed statistical analysis is illustrated in Figure 2. The mean TBL for the non-injection group was recorded at 1330.3±430.4 mL; while the injection group had a mean TBL of 1100.2±420.3 mL. The measured HBL was 442.2±168.9 in the non-injection group and 327.4±148.8 in the injection group. A total of 14 patients (34.1%) in the injection group and 25 patients (58.1%) in the non-injection group received at least one allogenic blood transfusion. These findings indicate that HBL and TBL values were significantly higher in the non-injection group (p=0.013, p=0.049, respectively). Hence, indirectly, ABT rates were lower in our injection group (p=0.043). Furthermore, our findings showed that patients who received intraoperative periarticular Ranawat solution injections had a 26% decrease in HBL and a 17.2% decrease in TBL compared to the non-injection group. However, there was no statistically significant difference between groups regarding IBL and postoperative drainage volume (p=0.745 and p=0.705, respectively). Detailed analysis is provided in Table 2. This study recorded no adverse effects or postoperative complications associated with periarticular injections of Ranawat solution.

Discussion

The principal finding of our study was that intraoperative periarticular Ranawat solution injections significantly reduced HBL by approximately 26%, and TBL by 17.2%, thereby reducing postoperative ABT requirements in elderly patients undergoing hemiarthroplasty for hip fractures.

HBL has several causes, including procedural factors such as hemolysis (17), infiltration into tissues during surgery (18), incision length (19), operation duration, and trauma-to-surgery interval (20), as well as patient-related factors like BMI and age. Our findings, aligning with previous studies, confirm that HBL constitutes a significant portion of TBL, highlighting the clinical importance of controlling hidden perioperative bleeding. Foss and Kehlet (5) reported that HBL could represent up to 75% of total perioperative blood loss in hip fractures, while Lei et al. (21) emphasized substantial HBL following hip surgery. Our study demonstrated a 26% reduction in HBL with intraoperative periarticular Ranawat solution injections, strongly supporting its effectiveness.

Table 1. Demographic data of the patients in the study age, BMI, length of stay, and sex

		Mean	SD	Min.	Max.	p-value*
Age	Group I (n=41)	82.6	6.96	65	93	0.548
	Group II (n=43)	81.5	8.47	65	95	
BMI (kg/m^2)	Group I (n=41)	28.2	4.12	18.4	35	0.801
	Group II (n=43)	28.1	4.99	19.4	45.2	
Length of stay (day)	Group I (n=41)	6.7	3.12	2	15	0.071
	Group II (n=43)	11.2	10.13	3	56	

Table 1. Continued

		Mean	SD	Min.	Max.	p-value*
				Number	Percent (%)	p-value*
Sex	Group I (n=41)		Male	14	34.1	0.222
			Female	27	65.9	
			Total	41	100	
	Group II (n=43)		Male	18	41.8	
			Female	25	58.2	
			Total	43	100	

*: p<0.05 was considered statistically significant
SD: Standard deviation, Min.: Minimum, Max.: Maximum, BMI: Body mass index

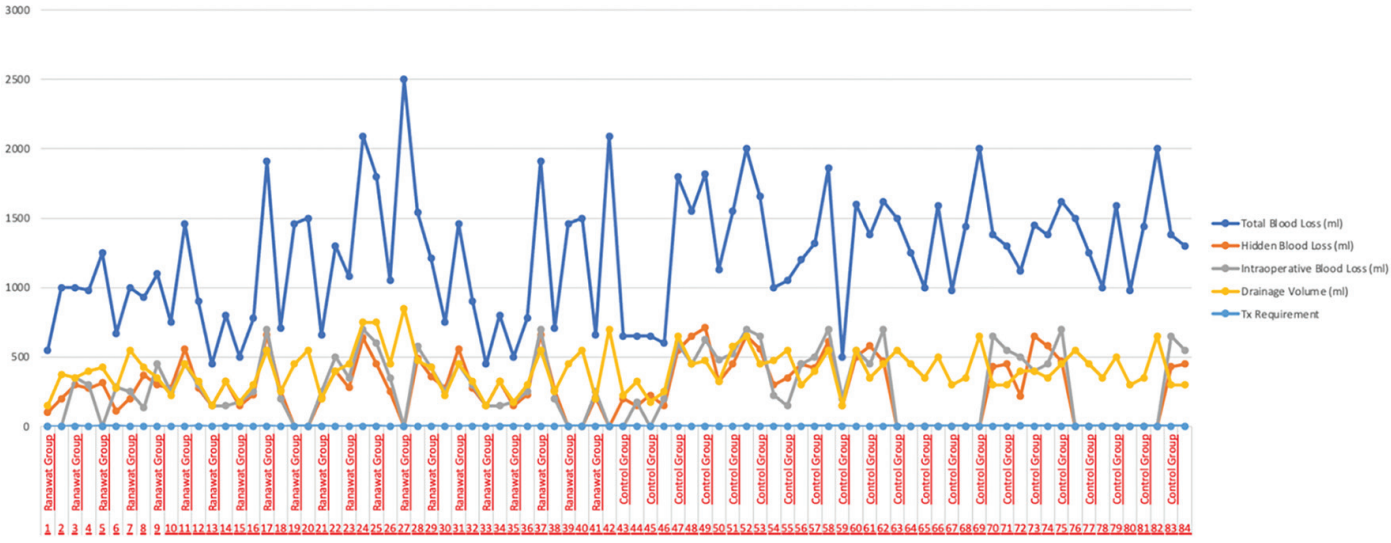

Figure 2. Statistical analysis of the variables for both the study and control groups. Total blood loss (mL), hidden blood loss (mL), intraoperative blood loss (mL), drainage volume (mL), and Transfusion (Tx) requirement

Table 2. Comparison of groups in terms of perioperative blood loss and blood transfusion requirements. HBL, TBL, and IBL

		Mean	SD	Min.	Max.	p-value*
HBL (mL)	Group I	327.4	148.8	100	660	0.013*
	Group II	442.2	168.9	150	710	
TBL (mL)	Group I	1100.2	423.4	450	2085	0.049*
	Group II	1330.3	434.2	500	2090	
IBL (mL)	Group I	447	200.7	250	750	0.745
	Group II	474.1	221.8	175	750	
Postoperative drainage volume (mL)	Group I	400	158.5	150	750	0.705
	Group II	424.2	143.2	150	700	
Transfusion requirement (Unit)	Group I	0.48	0.5	0	1	0.043*
	Group II	1	0.89	0	4	

*: p< 0.05 was considered statistically significant
SD: Standard deviation, Min.: Minimum, Max.: Maximum, HBL: Hidden blood loss, TBL: Total blood loss, IBL: Intraoperative blood loss

The observed efficacy of the Ranawat solution can primarily be explained by the pharmacologic effects of its constituents. EP is commonly used in periarticular injections. It is a sympathomimetic catecholamine that affects alpha- and beta-adrenergic receptors. Its effect on α_1 receptors produces increased vascular smooth muscle contraction (22). Moreover, EP is a platelet-stimulating agent since it causes aggregation of human platelets through α_2-adrenoceptors (23). These actions may explain the efficacy of this drug in reducing blood loss during perioperative (due to contraction of peripheral vessels) and postoperative (due to hemostatic effect) periods. On the other hand, dexamethasone, a glucocorticosteroid (GCS), also leads to decreased production of prostaglandins with their vasodilatory effects and a subsequent diminution in blood loss (24,25). Two recent randomized controlled trials assessed blood loss in patients who received GCS during periarticular infiltration, revealing a non-significant reduction in blood loss for the GCS group (25).

Perioperative blood loss is a key criterion for evaluating the efficacy of periarticular injections. Recent studies support using EP-based periarticular infiltration to decrease postoperative blood loss without increasing deep-vein thrombosis risk (26,27). Lombardi et al. (28) retrospectively reported significantly lower blood loss after total knee arthroplasty with a cocktail injection of morphine, EP, and bupivacaine compared to controls ($p<0.0001$). Similarly, Gasparini et al. (22) in a prospective randomized trial observed significant reductions in TBL with nor-EP lavage (821 vs. 1,270 mL; $p<0.0001$). Our results align with these findings, demonstrating significantly reduced TBL in the injection group.

IBL and drainage volumes serve as crucial metrics for assessing the effectiveness of EP in managing postoperative bleeding. Nevertheless, the injection group did not show a significant decrease in IBL and postoperative drainage volume when compared to the control group. Our results are consistent with recent research conducted by Teng et al. (27) and Villate et al. (29). The result may be related to the time of EP administration and the methods of EP application during the procedure. Although the platelets of the spleen are immediately released after the administration of EP, the peak of the coagulation factor cannot be reached until more than 20 minutes after administration (30). Thus, the relatively short operation time of total joint arthroplasty may alter the effects of EP.

Transfusion rates indirectly indicate the efficacy of EP. Our study showed significantly lower transfusion rates in the Ranawat solution group (34.1%) compared to controls (58.1%), which aligns with prior studies on periarticular injections containing EP (9,31). However, conflicting findings exist. Gao et al. (32) found no significant transfusion differences in hip arthroplasty patients treated with tranexamic acid plus diluted EP, and Villatte et al. (29) reported similar transfusion requirements between EP infiltration and control groups ($p=0.92$). These discrepancies might reflect inconsistent transfusion criteria, often influenced by subjective patient factors alongside Hb levels.

As expected, female patients predominated in our study, though the female-to-male ratio was lower in previous reports. Recent global analyses show a decreasing female-to-male ratio for hip fractures, emphasizing the growing importance of diagnosing and treating osteoporosis in males (33,34). Enhancing physician education on osteoporosis management in men should be a priority.

We acknowledge some possible limitations in this study's scope. First, it's notable that this research is constrained by being conducted at a single-center with a relatively small sample size. Notably, the small sample size was primarily due to the COVID-19 pandemic, which made it challenging to identify eligible patients who were not on anticoagulant treatments during specific periods of our study. Second, we could not analyze how the intraoperative injection of the Ranawat solution, affects perioperative blood loss in patients who are on different anticoagulant regimens. However, in the context of ensuring standardization, recent studies investigating HBL excluded individuals receiving anticoagulant therapy before experiencing a hip fracture (7,21). This approach aligns with established reference studies and is intended to reduce potential bias in the findings. Lastly, it is important to note that an independent anesthesiologist documented the IBL, while a separate observer conducted the calculation of postoperative blood loss. This methodological distinction may introduce bias into the study.

Conclusion

Our study shows that intraoperative periarticular injection of Ranawat solution effectively reduces hidden and TBL in elderly patients undergoing bipolar hemiarthroplasty for intra-articular hip fractures. This reduction in blood loss may facilitate faster recovery, fewer transfusion-related complications, and potentially shorter hospital stays, benefiting this vulnerable patient group. However, multicenter comparative studies are necessary to validate our findings and evaluate alternative treatment strategies.

Ethics

Ethics Committee Approval: The study was approved by the Ankara City Hospital, No. 1 Clinical Research Ethics Committee (decision no.: E1-19-3292, date: 22.02.2019), which was performed in accordance with the ethical standards of the Declaration of Helsinki.

Informed Consent: Patients gave written informed consent prior to participation.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.B., E.K., G.Ö., Concept: T.K., O.B., E.K., G.Ö., Design: T.K., O.B., E.K., G.Ö., Data Collection or Processing: T.K., Ö.H.K., A.D., Analysis or Interpretation: T.K., Ö.H.K., A.D., Literature Search: T.K., Ö.H.K., A.D., Writing: T.K., O.B.

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