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Does Hemostasis with Controlled Arterial Hypertension Before Surgical Wound Closure in Total Knee Arthroplasty Affect the Amount of Bleeding and Transfusion Need?

Total Diz Artroplastisinde Cerrahi Yara Kapatılması Öncesinde Kontrollü Arteriyel Hipertansiyon ile Yapılan Hemostazis Kanama Miktarını ve Transfüzyon İhtiyacını Etkiler mi?

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ABSTRACT

Objective: We aimed to assess the efficacy of hemostasis while controlled augmentation of arterial blood pressure before surgical closure after total knee arthroplasty (TKA).

Materials and Methods: This retrospective cohort involved data collected from the medical files of 87 patients (62 women, 25 men) who underwent TKA using hypotensive epidural anesthesia (HEA). Patients were allocated into two groups. Group I (n=44) received HEA, while Group II (n=43) had controlled arterial hypertension before surgical closure. Perioperative hemoglobin and hematocrit levels, systolic and diastolic blood pressure, and the amount of erythrocyte suspension transfusion were compared between the two groups.

Results: The average age of our series was 66.41 ± 6.17 (range: 57-78) years. Notably, the amount of bleeding on postoperative 1st, 2nd, 4th, 12th, and 24th (p=0.031, 0.032, 0.001, 0.001, 0.001, respectively) hours was significantly less in Group II. There were no significant differences between the two groups for complications, operative duration, perioperative bleeding, duration of follow-up and hospitalisation, and compared descriptives.

Conclusion: Our data indicated that controlled elevation of mean arterial pressure before surgical closure might allow the achievement of meticulous hemostasis after TKA. Further prospective, randomised, controlled trials on more extensive series are warranted to verify our preliminary results.

Keywords: Bleeding, controlled hypertension, hypotensive epidural anesthesia, hemostasis, total knee arthroplasty

ÖZ

Amaç: Total diz artroplastisinde (TDA) cerrahi yaranın kapatılmasından önce kontrollü olarak arttırılan arteriyel kan basıncı ile yapılan hemostazisin etkinliğinin değerlendirilmesi amaçlanmıştır.

Materyal ve Metot: Veriler hipotansif epidural anestezi (HEA) ile TDA ameliyatı olmuş 87 hastanın (65 kadın, 25 erkek) tıbbi kayıtlarından retrospektif olarak toplanmıştır. Hastalar cerrahi yaranın kapatılmasından önce kontrollü arteriyel hipertansiyon uygulanmasına göre iki gruba ayrılmıştır. Grup I (n:44) HEA uygulanan hastaları, grup II (n:43) cerrahi yara kapatılmasından önce kontrollü arteriyel hipertansiyon (operasyon öncesindeki ortalama arteriyel kan basıncından daha yüksek) uygulanan hastaları içermektedir. Temel tanımlayıcılar olarak peroperatif hemoglobin ve hematokrit seviyeleri, sistolik ve diasitolik kan basıncı, transfüze edilen eritrosit süspansiyonu miktarları iki grup arasında kıyaslanmıştır.

Bulgular: Gruplardaki ortalama yaş 66,41+6,17 (57-78) dir. Operasyon sonrası 1.(p=0,031), 2.(p=0,032), 4.(p=0,001), 12.(p=0,001), 24.(p=0,001) saatlerdeki kanama miktarı grup II de anlamlı olarak daha düşüktü (Sırasıyla, p=0.031, 0.032, 0.001, 0.001, 0.001). Komplikasyon, cerrahi süre, peroperatif kanama, hastanede yatış ve takip süresi, peroperatif hemoglobin değeri, transfüze edilen eritrosit süspansiyonu miktarı ile peroperatif sistolik-diasitolik kan basıncı değerleri açısından gruplar arasında istatistiksel bir fark yoktu.

Sonuç: Bulgularımız TDA'da cerrahi yara kapatılması öncesinde ortalama arteriyel kan basıncının kontrollü olarak yükseltilmesinin daha ayrıntılı bir şekilde kanama kontrolü yapılmasına olanak verdiğini göstermektedir. Bizim bu şekildeki ilk bulgularımızı daha büyük vaka serilerinde yapılan prospektif, randomize, kontrollü çalışmalar destekleyecektir.

Anahtar Kelimeler: Kanama, hemostazis, hipotansif epidural anestezi, kontrollü hipertansiyon, total diz artroplastisi

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INTRODUCTION

Many orthopedic surgeries are associated with remarkable and unpredictable blood loss. This condition is attributed to the texture of bony and soft tissues that impedes effective hemostasis.[1] Total knee arthroplasty (TKA) is an efficient therapeutic procedure for severe knee osteoarthritis (OA) with good long-term outcomes. Despite improvement in techniques, blood loss after TKA constitutes a concern of surgeons. Up to 70% of patients who underwent total joint arthroplasty may receive a blood transfusion.[2]

Blood transfusion has substantial risks, such as prolonged hospitalisation, transmission of infectious diseases, immunologic, hemolytic and anaphylactic reactions, and increased mortality. Thus, preoperative red blood cell mass expansion, autologous blood transfusion, and reduction of perioperative blood loss using careful hemostasis, drugs, and controlled hypotension have been described to avoid unnecessary blood transfusions. Each of these methods possesses advantages and disadvantages. There is a seek for an effective, practical, and safe method to omit unnecessary allogeneic blood transfusion.[1,3] Patients with a low baseline hemoglobin level are more likely to receive a blood transfusion.[4]

Hypotensive epidural anesthesia (HEA) is a technique to diminish blood loss. It involves the concomitant use of an extensive epidural block and an intravenous infusion of low-dose epinephrine. This approach provides hemodynamic stability, reduces intraoperative blood loss, and allows a dry surgical field.[5] Epidural anesthesia has been shown to decrease blood loss during TKA without applying a tourniquet.[6]

Parameters influencing blood loss associated with TKA are hypertensive patients, prolonged duration of surgery, and lower preoperative hemoglobin levels. To reduce the use of allogeneic blood transfusion, arterial blood pressure must be adjusted preoperatively in hypertensive patients, and lower preoperative hemoglobin levels must be restored.[7]

Prediction of blood loss also involves intraoperative and postoperative aspects as well. Applying novel and effective management strategies may aid surgeons in diminishing blood loss and transfusion risk.[3] Controlled hypotension is frequently utilised during total joint arthroplasties, and the quantity of hemorrhage monitored the blood pressure from the surgical field. Controlled intraoperative hypotension can provide a diminution of intraoperative and postoperative blood loss. Post-operative hypertension is supposed to be linked with an increased risk of transfusions.[8]

Identifying factors is a critical step for establishing an adequate blood management strategy. We aimed to assess the efficacy of hemostasis performed by controlled augmentation of arterial blood pressure before surgical closure after TKA in patients receiving hypotensive anesthesia.

MATERIALS AND METHODS

Ethics Committee Approval: The study was approved by the Memorial Sisli Hospital Ethics Committee (Date: 03.06.2023, decision no: 003). The study was planned under the Helsinki Principles. Written informed consent was obtained from all patients.

Design: This retrospective cohort was performed in our tertiary care centre's orthopedics and traumatology department.

Participants: Our target population was the patients who underwent elective unilateral TKA and received HEA without a tourniquet between February 2016 and January 2019.

Procedure: Data were derived from the medical files of 87 patients (62 women, 25 men) with an average age of 66.41 ± 6.17 (range: 57-78). Patients were allocated into two groups to administer controlled arterial hypertension before surgical closure. Group I (n=44) received HEA, while Group II (n=43) had controlled arterial hypertension (up to preoperative mean arterial blood pressure) before surgical closure.

Inclusion criteria were a history of unilateral TKA without tourniquet and administration of HEA. Exclusion criteria were history of bleeding disorders, refractory hypertension, previous history of myocardial infarction, valvular heart disease, unstable angina, stroke, thrombocytopenia, hematological disease, malignant disease, abnormal liver function, acute infection, use of anticoagulants, a refusal for blood transfusion, or need for revision arthroplasty.

All patients were routinely hospitalised a day before surgery. Preoperative American Society of Anaesthesiologists (ASA) scores[9] and baseline descriptive data, including sex, age, side of knee osteoarthritis, comorbidity, and complications were recorded. Blood pressure was monitored, and the mean arterial pressure was recorded every 6 hours. Routine antihypertensive treatment was maintained for hypertensive patients.

Perioperative mean arterial blood pressure was measured immediately after surgery and on 1, 2, 4, 8, 12, 16, 20, and 24 hours postoperatively. The operative duration and the average mean arterial pressure at 12 and 24 hours were noted.

The amount of intraoperative blood loss was measured using the blood collected in suction. The quantity of irrigation fluid and the weight of gauze sponges were considered when calculating the amount of blood loss. The drain was removed after

24 hours, and the collection amount was measured on 1, 2, 4, 12, and 24 hours. For this purpose, we have noted the additional amount of blood accumulating over the preceding quantity.

Patients in this study were monitored intraoperatively by the anesthetist and were evaluated in the postoperative period clinically and with a complete blood count. Hemoglobin levels were evaluated preoperatively and 1, 24, and 48 hours after surgery. Blood was transfused based on the clinical assessment. Criteria for blood transfusion were either Hb level <9 g/dL, hematocrit <28, or Hb level <10 g/d L or hematocrit <30 presenting with symptoms of acute anemia such as tachycardia, fatigue, pallor of lips, dizziness, shortness of breath, or lightheadedness. The amount of erythrocyte suspension transfusion was recorded.

All patients received 1 g of 10% tranexamic acid injectable solution (*Transamine®, Teva Pharmaceuticals, Istanbul, Türkiye*) through the intravenous route. The injections were performed 30 minutes before and after surgery and 3 hours after. All patients underwent HEA, and body temperature was kept above 36.0 ºC.

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is commonly used to evaluate treatment effects in OA.[10] The Knee Society Score (KSS) is a measure of which higher scores indicate less severity. The KSS is comprised of the Knee Society Knee Score (KSKS) and the Knee Society Function score (KSFS).[11]

Standard surgical methods were employed in all patients, and the operations were performed in a supine position by the same surgical team. Midline anterior incision and medial parapatellar approach were routinely adopted. Cephalosporins were routinely applied for 24 hours after operation for infection prophylaxis.

In all cases, a total knee prosthesis (*Genesis II®, Smith Nephew, Memphis, USA*) that allows posterior cruciate ligament retention was used and fixed with cement. The femoral milling orifice was occluded with a bone plug. The patellar replacement was not performed in any of our TKA procedures. All patients received periarticular injections. The preoperative blood pressure was controlled for hypertensive patients to below 140/90 mmHg.

In Group I, surgical closure was performed after meticulous hemostasis and placement of a drain. In Group II, systolic blood pressure was restored to the preoperative levels and hemostasis was achieved under these conditions. Surgical closure and drainage tube placement were performed after hemostasis was completed. All perioperative transfusions were recorded. Hypotensive epidural anesthesia was maintained two days postoperatively, and 0.2% ropivacaine (2 mg/ml) was administered. Analgesia after discontinuation of HEA was provided by acetaminophen 1 g and tramadol 75 mg. Low-molecular-weight heparin, enoxaparin (*Clexane®, Sanofi, Istanbul, Turkey*) was initiated on the 12th hour postoperatively. After removing the drainage tube on the first postoperative day, patients were mobilised with Canadian walking sticks.

Outcome Measures: Baseline descriptive data, including age, sex, and body-mass index, were recorded. The side of involvement, ASA scores, preoperative and postoperative hemoglobin and hematocrit levels, amount of erythrocyte suspension transfusion, WOMAC, KSKS, and KSFS values were compared between the two groups under investigation.

Statistical Analysis: Our data were analysed with Statistical Package for Social Sciences version 21.0 for Windows software (*SPSS Inc., Chicago, Illinois, USA*). Descriptive data were presented as counts and percentages. The p-value was accepted as <0.05. Normality was tested using the Shapiro-Wilks test. A Chi-square test was utilised for categorical variables. Quantitative variables with normal distribution were tested with a parametric and independent variables t-test. Quantitative variables without normal distribution were analysed using a non-parametric Mann-Whitney U test.

RESULTS

Retrospective analysis of data derived from the medical files of 87 patients (62 women, 25 men). Patients were allocated into two groups to administer controlled arterial hypertension before surgical closure. Group I (n=44) received HEA, while Group II (n=43) had controlled arterial hypertension (up to preoperative mean arterial blood pressure) before surgical closure. Group I consisted of 31 women and 13 men with an average age of 66.82 ± 5.96 (58-76). Group II (n=43) was comprised of 31 women and 12 men with an average age of 66.00 ± 6.42 (57 to 78). In Group II, perioperative surgical closure systolic pressure was 122.35 ± 10.44 mmHg (range: 108-142), and perioperative surgical closure diastolic pressure was 80.21 ± 12.16 (range: 65-106). Two groups exhibited similar features for age (p=0.894), sex distribution (p=0.927), side of involvement (p=0.326), comorbidities (p=0.911), ASA scores (p=0.826), and complications (p=0.987) (Table 1).

The survey of 2 groups in terms of operative duration, perioperative bleeding and bleeding in the postoperative 2nd hour were compared. Groups I and II exhibited similar outcomes for operative duration (p=0.167) and perioperative bleeding (p=0.888); however, the amount of bleeding in the postoperative 2nd hour was significantly less in Group II (p=0.032) (Table 2).

Table 1.

Variable		Groups		p-value
		I (n=44)	II (n=43)	
Age (years)		66.82 ± 5.96	66.01 ± 6.42	0.894
Sex	Female	31	31	0.927
	Male	13	12	
Side of involvement	Right	22	26	0.326
	Left	22	17	
Comorbidity	Diabetes mellitus	3	2	0.911
	Hypertension	8	8	
	DM & HT	1	2	
	No	32	31	
ASA Score	I	31	30	0.826
	II	12	11	
	III	1	2	
Complication	Wound infection	1	1	0.987
	No	43	42	

DM: Diabetes mellitus; HT: Hypertension; ASA: American Society of Anaesthesiologists.

Table 2. A survey of quantitative variables in 2 groups (Independent Samples T-test).

Variable	Groups		p-value
	I (n=44)	II (n=43)	
Operative duration (minutes)	64.09 ± 6.27	70.16 ± 5.26	0.167
Perioperative bleeding (mL)	256.25 ± 31.12	270.35 ± 29.12	0.888
Postoperative 2nd hour bleeding (mL)	110.57 ± 16.47	95.58 ± 21.61	**0.032***

*: Statistically significant.

Two groups were similar for the duration of follow-up (p=0.821), body-mass index (p=0.786), duration of hospitalisation (p=0.770), hemoglobin levels pre-operatively (p=0.200), postoperatively 1st hour (p=0.865), postoperatively 1st day (p=0.528), and postoperatively 2nd day (p=0.296). The amount of erythrocyte suspension transfusion (p=0.203), pre-operative systolic (p=0.848) and diastolic pressures (p=0.878), peroperative systolic (p=0.956) and diastolic pressures (p=0.878), postoperative 1st hour systolic (p=0.808) and diastolic pressures (p=0.983), postoperative 2nd hour systolic (p=0.838) and diastolic pressures (p=0.892), postoperative 4th hour systolic (p=0.852) and diastolic pressures (p=0.848), postoperative 12th hour systolic (p=0.983) and diastolic pressures (p=0.882), postoperative 24th hour systolic (p=0.683) and diastolic pressures (p=0.969). In Group II, postoperative bleeding was significantly less than in Group I on 1st (p=0.031), 4th (p=0.001), 12th (p=0.001), and 24th hours (p=0.001) (Table 3).

Table 3. The survey of quantitative variables in 2 groups.

Variable	Group	Mean rank	Total rank	Mann-Whitney U test	Z	p-value
Duration of follow-up (months)	I	43.40	1909.50	919.500	-0.226	0.821
	II	44.62	1918.50			
Body-mass index (kg/m^2)	I	43.28	1904.50	914.500	-0.272	0.786
	II	44.73	1923.50			
Duration of hospitalisation	I	43.33	1906.50	916.500	-0.293	0.770
	II	44.69	1921.50			
Preoperative Hb level (g/dL)	I	47.27	2080.00	802.000	-1.282	0.200
	II	40.65	1748.00			
Postoperative 1st hour Hb level (g/dL)	I	43.57	1917.00	927.000	-0.170	0.865
	II	44.44	1911.00			
Postoperative 1st day Hb level (g/dL)	I	41.86	1800.00	854.000	-0.631	0.528
	II	45.14	1941.00			
Erythrocyte suspension transfusion (units)	I	47.07	2071.00	811.000	-1.274	0.203
	II	40.86	1757.00			

Table 3. Continue.

Postoperative 2nd day Hb level (g/dL)	I	46.49	2045.50	836.500	-1.046	0.296
	II	41.45	1782.50			
Postoperative 1st hour amount of bleeding (mL)	I	49.75	2189.00	693.000	-2.153	**0.031***
	II	38.12	1639.00			
Postoperative 4th hour amount of bleeding (mL)	I	52.63	2315.50	566.500	-3.235	**0.001***
	II	35.17	1512.50			
Postoperative 12th hour amount of bleeding (mL)	I	53.09	2336.00	546.000	-3.425	**0.001***
	II	34.70	1492.00			
Postoperative 24th hour amount of bleeding (mL)	I	54.14	2382.00	500.000	-3.788	**0.001***
	II	33.63	1446.00			
Preoperative systolic blood pressure	I	43.49	1913.50	923.500	-0.191	0.848
	II	44.52	1914.50			
Preoperative diastolic blood pressure	I	43.59	1918.00	928.000	-0.153	0.878
	II	44.42	1910.00			
Peroperative systolic blood pressure	I	44.15	1942.50	939.500	-0.055	0.956
	II	43.85	1885.50			
Peroperative diastolic blood pressure	I	43.59	1918.00	928.000	-0.153	0.878
	II	44.42	1910.00			
Postoperative 1st hour systolic blood pressure	I	43.35	1907.50	917.500	-0.242	0.808
	II	44.66	1920.50			
Postoperative 1st hour diastolic blood pressure	I	43.94	1933.50	943.500	-0.021	0.983
	II	44.06	1894.50			
Postoperative 2nd hour systolic blood pressure	I	44.55	1960.00	922.000	-0.204	0.838
	II	43.44	1868.00			
Postoperative 2nd hour diastolic blood pressure	I	44.36	1952.00	930.000	-0.136	0.892
	II	43.63	1876.00			
Postoperative 4th hour systolic blood pressure	I	44.50	1958.00	924.000	-0.187	0.852
	II	43.49	1870.00			
Postoperative 4th hour diastolic blood pressure	I	44.51	1958.50	923.500	-0.191	0.848
	II	43.48	1869.50			
Postoperative 12th hour systolic blood pressure	I	44.06	1938.50	928.500	-0.021	0.983
	II	43.94	1889.50			
Postoperative 12th hour diastolic blood pressure	I	44.40	1953.50	928.500	-0.149	0.882
	II	43.59	1874.50			
Postoperative 24th hour systolic blood pressure	I	42.91	1888.00	898.000	-0.408	0.683
	II	45.12	1940.00			
Postoperative 24th hour diastolic blood pressure	I	44.10	1940.50	941.500	-0.038	0.969
	II	43.90	1887.50			

Hb: Hemoglobin; *: Statistically significant.

Two groups did not display any significant differences for preoperative (p=0.714) and postoperative (p=0.330) WOMAC, preoperative (p=0.748) and postoperative (p=0.282) KSKS, as well as preoperative (p=0.653) and postoperative KSFS (p=0.890) (Table 4).

Table 4. The survey of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee

Variable	Group	Mean	Total rank	Mann-Whitney U test	Z	p-value
Preoperative WOMAC	I	44.98	1979.00	903.000	-0.366	0.714
	II	43.00	1849.00			
Postoperative WOMAC	I	41.45	1824.00	834.000	-0.974	0.330
	II	46.60	2004.00			
Preoperative KSKS	I	43.15	1898.50	908.500	-0.321	0.748
	II	44.87	1929.50			
Postoperative KSKS	I	41.17	1811.50	821.500	-1.076	0.282
	II	46.90	2016.50			
Preoperative KSFS	I	42.82	1884.00	894.000	-0.440	0.653
	II	45.21	1944.00			
Postoperative KSFS	I	43.65	1920.50	930.500	-0.139	0.890
	II	44.36	1907.50			

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KSKS: Knee Society Knee Score; KSFS: Knee Society Function Score.

DISCUSSION AND CONCLUSION

Total knee arthroplasty is usually performed with a bloodless field, and blood loss after TKA can occur in obvious or hidden forms.[12] Hypotensive epidural anesthesia can be preferred for TKA, and diminished intraoperative blood loss during HEA allows clear vision without a tourniquet.[13]

We noted that postoperative bleeding was significantly less in Group II at all postoperative intervals. We did not encounter any rebound bleeding in the recovery room; these findings were consistent with relevant publications.[14,15] This may be due to the prolonged hypotensive state stabilising the intravascular clotting in the operated knee before the mean arterial pressure was increased. Our data support that controlled elevation of the systolic blood pressure and performance of hemostasis in this setting before surgical closure can be helpful for adequate hemostasis.

Total knee arthroplasty without a tourniquet allows the surgeon to achieve more effective intraoperative hemostasis and abate the postoperative bleeding. The remarkably diminished blood loss leads to a lesser need for transfusion. Tourniquet use is associated with the augmentation of postoperative blood loss. Avoiding tourniquet use offers benefits like decreased postoperative pain and early mobilisation if surgeons abstain from using a tourniquet.[16,17] Using a tourniquet is linked with altering thrombotic and fibrinolytic activities.[18] The incidence of embolic events is increased[19], and releasing the inflated tourniquet may have adverse metabolic consequences.[20] Further trials are encouraged to unveil the impacts of HEA and various methods conducted to diminish intraoperative blood loss during TKA.[21]

The risk for bleeding and blood transfusions is complex and multifactorial, and adequate preoperative preparation is essential.[3] During TKA, there is considerable blood loss, which increases morbidity and mortality rates. Specific methods, such as using pneumatic cuffs, minimally invasive surgery, and anti-fibrinolytic agents, aid in the reduction of hemorrhage.[22] Hu et al. suggested that possible influential factors of total blood loss included gender, type of prosthesis, and drainage.[2] We sought a method that would minimise blood loss in patients who underwent TKA. Our novel method yielded that it can be easily applicable with minimal risk. Since postoperative blood loss in the drains is unpredictable and varies over a wide range, surgeons should take additional measures to keep hemoglobin and hematocrit levels within the safe range. Our data imply that controlled elevation of arterial blood pressure and performance of hemostasis under these conditions before surgical closure may yield a practical, safe, reliable, and effective way to reduce blood loss and the need for blood transfusion after TKA, an elective major surgery. This approach must be performed in close collaboration with the anesthesiology team, and hemodynamic stability must be preserved during the controlled elevation of mean arterial pressure before hemostasis. We encountered no significant complications in both groups, including hemodynamic instability and thromboembolic events.

In conjunction with Kourtzis et al.,[1] it is desirable for every surgeon to avoid risk when applying a novel method and to keep in the safe zone with sufficient options. Since postoperative blood loss cannot be predicted, every technique must be administered safely. Preserving the mean arterial blood pressure within normal limits is essential in reducing blood loss via the drains.[1]

Marked blood loss during TKA may cause higher rates of transfusion, which may negatively influence surgical outcomes and lead to more excellent rates of complication. It is, therefore, essential to develop novel methods to decrease postoperative blood loss. Every patient must be evaluated concerning demographic and clinical features, and the hemostatic approach must be tailored individually to diminish risks implicated with TKA, like thromboembolic events and hemodynamic instability. In other words, recognition of patient-specific risk factors linked with blood loss may allow clinicians to prepare for perioperative hazardous outcomes and take proper measures.[3]

In conclusion, our data indicate that controlled elevation of mean arterial pressure before surgical closure may allow the achievement of meticulous hemostasis after TKA. Therefore, our results are promising to protect candidates of TKA against unpredictable or substantial blood loss. However, further prospective, randomised, controlled trials on more extensive series are warranted to verify our preliminary results. Some limitations must be considered during the interpretation of our results. This study reflects the experience of a single center and a surgical team. Retrospective design, relatively small sample size, and possible confounding factors such as ethnicity and socio-economical aspect may restrict the extrapolation of our results to larger populations.

Ethics Committee Approval: This study was approved by the Memorial Sisli Hospital Ethics Committee (Date: 03.06.2023, decision no: 003). The study was conducted in accordance with the principles of the Helsinki Declaration.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – YA; Supervision – MHC; Materials – MHC; Data Collection and/or Processing – MHC; Analysis and/or Interpretation – MHC; Writing –MHC.

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