USING OF INTRAOPERATIVE CELL SALVAGE AND TRANEXAMIC ACID AS

PROTECTIVE FACTOR FOR POSTOPERATIVE ANEMIA APPEARANCE IN

PATIENTS WITH TOTAL HIP OR KNEE ARTHROPLASTY

Master Thesis for obtaining the academic degree

Master of Science

in the study programme Patient blood Management

submitted by

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Krems, Austria, 1.11.2021

STATUTORY DECLARATION

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ACKNOWLEDGEMENTS / DEDICATIONS

To my Family which have understanding for my work. To my teachers who direct me in right way. Special thanks to the Chief of the Orthopaedic Surgery Deparment, General Hospital Valjevo, Dr Aleksandar Vukićević and to Quality Assurance Director of the Regional Hospital Valjevo Dr Mira Vuković, who support me in this work.

ABSTRACT

Background: The purpose of this study was to investigate intraoperative pharmacological and nonpharmacological methods and techniques in reducing blood loss in patients following total hip(THA) or knee arthroplasty(TKA).

Methods: A retrospective cross-sectional study was conducted in patients undergoing TKA or THA surgery, electively performed at the General Hospital Valjevo, Valjevo, Serbia, in 2014 when the principles of Patient Blood Management (PBM) were not applied at all or in part, and in 2019 when PBM principles were applied as standard.

Results: This study includes 114 patients with TKA and 84 patients with THA procedures. In total 197 orthopaedic patients (46 male and 151 female). We found that there was significant statistical difference for THA Hb min (postoperative haemoglobin) between tranexamic acid (TXA) only group and TXA+ intraoperative cell salvage (ICS) (p=0.000) and group ICS only and TXA+ICS (p=0.001). 83.8% of all patients developed postoperative anaemia (PA) defined by haemoglobin < 12 g/dL in both sexes). Using multivariate logistic regression and ROC curve analysis, it was shown that the use of (TXA) with (ICS) in patients without preoperative anemia reduced the incidence of PA (p=0.000; odds ratio = 0.081 with 95% Confidence Interval from 0.025 to 0.256). Post Operative Anemia Risk Index (POARI) score was invented and cut-point value as predictor for PA is (-6).

Conclusions: Preoperative diagnosis and treatment of anemia are necessary in orthopedic patients since the use of TXA with ICS together strongly reduces PA in patients without preoperative anemia.

Keywords:

Patient Blood Management; Intraoperative cell salvage; Tranexamic acid; Postoperative anemia; Total knee arthroplasty; Total hip arthroplasty

ABSTRAKT

Hintergrund: Ziel dieser Studie war die Untersuchung intraoperativer pharmakologischer und nicht-pharmakologischer Methoden und Techniken zur Reduzierung des Blutverlustes bei Patienten nach totaler Hüft (THA)- oder Knieendoprothetik (TKA).

Methoden: Eine retrospektive Querschnittsstudie wurde bei Patienten durchgeführt, die sich einer TKA- oder THA-Operation unterzogen, die elektiv im Allgemeinen Krankenhaus Valjevo, Valjevo, Serbien, im Jahr 2014 durchgeführt wurde, als die Prinzipien des Patient Blood Management (PBM) ganz oder teilweise nicht angewendet wurden , und im Jahr 2019, als PBM-Prinzipien als Standard angewendet wurden.

Ergebnisse: Diese Studie umfasst 114 Patienten mit TKA und 84 Patienten mit THA. Insgesamt 197 orthopädische Patienten (46 Männer und 151 Frauen). Wir fanden heraus, dass es einen signifikanten statistischen Unterschied für THA Hb min (postoperatives Hämoglobin) zwischen der Gruppe nur mit Tranexamsäure (TXA) und TXA+ Intraoperative Cell Salvage (ICS) (p=0,000) und der Gruppe nur ICS und TXA+ICS (p=0,001) gab. 83,8% eine postoperative Anämie entwickelten (PA definiert durch Hämoglobin < 12 g/dl bei beiden Geschlechtern). Mittels multivariater logistischer Regression und ROC-Kurvenanalyse wurde gezeigt, dass die Anwendung von TXA mit ICS bei Patienten ohne präoperative Anämie die Inzidenz von PA reduzierte (p=0.000; odds ratio = 0.081 mit 95% Confidence Interval von 0.025 bis 0.256). Der Post-Operative Anemia Risk Index (POARI)-Score wurde erfunden und der Cut-Point-Wert als Prädiktor für PA ist (-6).

Schlussfolgerungen: Eine präoperative Diagnostik und Therapie der Anämie ist bei orthopädischen Patienten notwendig, da die Anwendung von TXA mit ICS zusammen die PA bei Patienten ohne präoperative Anämie stark reduziert.

Schlüsselwörter:

Patient Blood Management; Intraoperative Zellrettung; Tranexamsäure; Postoperative Anämie; Totalendoprothetik des Knies; Totalendoprothetik der Hüfte

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1. Introduction

Anaemia was defined by the World Health Organization (WHO) criteria as a haemoglobin (Hb) concentration of less than 13 g/dL in men and less than 12 g/dL in women [1]. However, among the population older than 60 years, anaemia, recently defined by levels of Hb < 12 g/dL in both sexes, is mostly of mild degree, from 10–12 g/dL [2]. Preoperative anaemia is a common condition in surgical patients and is independently associated with increased perioperative and 30-day morbidity and mortality rate [3,4]. On the other hand, postoperative anaemia (PA) is associated with poor postoperative outcomes, such as prolonged hospital stay, a higher incidence of postoperative renal failure and other organ dysfunction, and more frequent postoperative delirium due to reduced oxygen carrying capacity [5,6]. Osteoarthrosis is a progressive, degenerative disease of joints, mostly affecting the hip and knee joints. The damage of cartilage can be caused by injury, aging or loading by heavy weight [7]. Major orthopaedic operations such as total hip arthroplasty (THA) and total knee arthroplasty (TKA) can be associated with multiple complications [8]. In surgery for THA and TKA, major bleeding can occur and blood transfusion rates can be 45% ± 25% and 44% ± 15% respectively [9]. Beside benefits like better oxygenation and the correction of haematological status, transfusion of red blood cells (RBC) has many known complications. Errors in transfusion medicine, which most frequently involve misidentification of the patient, and may have life-threatening consequences [10]. There can also be issues with blood storage [11]. Patient blood management (PBM) is a strategy which applies several methods to reduce blood loss and transfusion, avoiding harm for the patients. The PBM system comprises a number of evidence-based interventions that can be applied before, during or after major surgery [12]. One way to save or recover red blood cells is the use of intraoperative cell salvage (ICS) devices. This is an important tool mostly used in cardiac, vascular and orthopaedic surgery, where demands for blood products are high [13]. Moreover, by using this type of device, patients receive their own blood and risks from allogenic blood are reduced.

An additional method for decreasing blood loss and lowering the risk of transfusion during surgical procedures is the use of antifibrinolytic drugs [14]. Another method for minimizing risk of bleeding during knee surgery is the use of a tourniquet. The tourniquet is a compressing device, used to control venous and arterial circulation to an extremity (lower extremity in TKA) for a period of time [15]. The introduction of PBM guidelines and their multidisciplinary strategies can improve patient outcomes [16]. According to guidelines, the use of cell saver devices, tranexamic acid (TXA), and techniques that minimize blood loss are highly recommended [17]. In accordance with the above, we considered it important in this study to assess the effects of demographic, anthropometric, hematological, and transfusion indicators, together with applied methods and techniques to prevent intraoperative and postoperative bleeding and postoperative anemia in patients undergoing knee or hip arthroplasty surgery.

2. Methods

This study was a retrospective, cross-sectional study in a cohort consisting of patients with elective, unilateral TKA or THA, hospitalized in Orthopaedic Department of General Hospital Valjevo, Valjevo, Serbia. This study was approved by Ethics Committee of General Hospital Valjevo, Valjevo, Serbia, 01.06.2021. (OBV 01-4417/2021). Inclusion criteria were scheduled surgeries of elective, unilateral TKA or THA, performed by one of two chief surgeons with using: (1) operative approaches which minimize bleeding (tourniquet and TXA at TKA or TXA only at THA), or (2) ICS techniques only, or (3) ICS techniques in combination with TXA. Exclusion criteria were urgent surgeries, thromboembolic events in near past, chronic cardiac disease, neurological diseases, or malignant disease. The Data were collected from electronic patient database (Hospital Informatic System— "Heliant"), and operative protocols for Department of Orthopaedics and Blood bank. Patients were operated during 2014, at THA (with TXA only and ICS only), TKA (with tourniquet and TXA and ICS only compared to 2019. (with tourniquet and with the use of ICS techniques in combination with TXA in both interventions). Cross-sectional analysis was performed between two groups of patients, divided on the basis of the presence/absence of PA. PA was defined as the occurrence of Hb < 120 g/L (in both sexes) in the postoperative period during hospitalization until the patient's discharge. The blood count samples were collected preoperatively, marked as maximum Hb or haematocrit value. The minimal Hb or haematocrit value was the minimal level during hospital stay until the patient's discharge. Samples were analysed by Abbott CELL-DYN Ruby analyser [18]. ICS was performed with the "Xtra" device (Sorin, Italy). Blood aspirated from the operative field was mixed with unfractionated heparin 25,000 i.u. dissolved in 500 mL of saline solution (0.9% NaCl), then filtered through a 40-micron filter, and centrifuged up to 5600 rpm according to manufacturer recommendations. Washing was performed with saline solution in a bowl with a volume of 125 mL, with standard protocol of washing ('Pstd' 800 mL of saline solution for washing 300 mL of collected blood from operating field) according to device manufacturer [19]. Washed and salvaged RBC were reinfused through 170-micron filter for blood transfusion. All salvaged, washed RBC were reinfused in operating room at the end of surgical procedure in the operating theatre. TXA was given in two doses. The first dose was applied as a bolus infusion 10 min before induction of general anaesthesia in dose of 15 mg/kg. The second dose was given on the first day after surgery in dose of 10 mg/kg. All patients in the study underwent general endotracheal anaesthesia (GEA). Induction in GEA was performed with propofol, and muscle relaxation was achieved using rocuronium bromide. The analgesia was with fentanyl citrate. The prescribed doses of drugs were adjusted according to the patient's body weight and according to the valid instructions for their use. Intraoperatively, continuous three-channel ECG monitoring was performed, with continuous monitoring of capillary blood saturation with oxygen as a non-invasive measurement of blood pressure at intervals not exceeding 5 min. Hourly diuresis was also monitored. The duration of all surgical procedures was from 45 to 65 min.

Tourniquet was induced 30 min before the end of surgical procedure with pressure of 300 mm Hg and removed in moment of leaving operating room. All patients received routine thromboprophylaxis according to the recommendations from [20,21]. Dosage of thromboprophylactic drug Fraxiparine® (nadroparin calcium) was adjusted according to the patient's weight and the recommendations of Canadian manufacturer whose products are registered in Serbia. Fraxiparine® was given subcutaneously, 12 h before and 12 h after surgery, and then once daily to the third postoperative day: (1) for body weight < 50 kg—0.2 mL (Anti-Xa IU = 1900 IU); (2) for body weight from 50 kg to 69 kg—0.3 mL (Anti-Xa IU = 2850 IU) and (3) for body weight from ≥ 70 kg—0.4 mL (Anti-Xa IU = 3800 IU). From the fourth post-operative day onwards, for the next seven days, Fraxiparine was given once daily (0.3 mL, 0.4 mL or 0.6 mL), depending on the above body weight intervals (<50 kg, from 50 kg to 69 kg, >70 kg). Demographic data of patients, height, weight, body mass index (BMI), hypertension, Hb maximum (preoperative), hematocrit maximum (preoperative), Hb minimum (lowest level in the postoperative period), hematocrit minimum (lowest level in the postoperative period), RBC salvaged volume, allogeneic RBC units, and Fresh Frozen Plasma (FFP) units (postoperative), and any complications, including postoperative thrombosis, re-bleeding, and wound infection or sepsis, until hospital discharge were documented. Estimated values for total blood volume and total RBC volume loss were also calculated for each patient [22] according to the following formulas:

PBV = k1 height (m3) + k2 weight (kg) + k3 (1) where k1 = 0.3669, k2 = 0.03219, k3 = 0.6041 for men; and k1 = 0.3561, k2 = 0.03308, k3 = 0.1833 for women.

Total RBC volume loss = PBV (Hematocrit maximum (preoperative) - Hematocrit minimum (postoperative) (2)

All patients were transfused according to recommendations of European Society of Anesthesiology [23].

2.1 Statistical Methods

Continuous numerical data sets were described by the mean and standard deviation. The attributive or ordinal variables were described by the frequency of outcomes and percentages. Univariable analysis was performed using Pearson chi-square test or Fisher's exact test for categorical variables and Student t test for continuous variables.

Comparing between non – parameter data between different groups were performed by Kruskal-Wallis and Mann-Whitney tests. Parameter data were analyzed using ANOVA with Bonferoni correction. Binary logistic regression method with stepwise variable selection was used for multivariate analysis of postoperative anemia risk factors. The evaluation of the validity of the logistic regression model implied an assessment of its goodness-of-fit measure and its accuracy. A goodness-of-fit model was made by estimating the Nagelkerke R Square. The accuracy of the logistic regression model was assessed using discrimination and adequacy. Discrimination measures were conducted to prove how adequately a model can distinguish patients with postoperative anemia from patients without postoperative anemia. The analysis of the adequacy of logistic models and the estimate of the retention of variables or their interactions was made using the Hosmer–Lemeshow method. Discrimination validity of scores of the newly constructed Post-Operative Anemia Risk Index (POARI) obtained by logistic regression model and other continuous variables in distinguish PA positive from PA negative patients was estimated by Receiver Operating Characteristic (ROC) procedure. "Cut point" value, sensitivity, specificity, positive predictive value, and negative predictive value were obtained by applying the maximum Youden index. The accepted level of significance was $p = 0.05$. Statistical programs IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY and MedCalc Software version 12.5.0.0 (MedCalc Software Ltd., Ostend, Belgium) were used for data processing.

2.2 Development and interpretation of POARI Score

The number of appropriate points assigned to each variable equal to its regression coefficient (B coefficient in the resulting multivariate logistics model) divided by 0.5, followed by rounding to the nearest whole number. The points for each risk factor were then summed to obtain the total number of points (score) for a patient. The caracter „no“ in Table 5. means absence of caracteristic, in our Thesis, absence of PA. The caracter „yes“ means presence of this caracteristic. Negative points like (- 4) or (- 5) are assigned in case that predictors have protective effect. (They are negative to probability of PA, and they have negative B coefficient in multivariate model). Positive points are assigned if predictors have significant risk factors (if they increase risk of PA). For instance , if patient was into group without preoperative anemia and procedures such as ICS and TXA were performed, his/her score for developing anemia is (– 5). In group without pre OP anemia (Hb > 120g/l) even Total RBC volume loss >463.2 ml will not cause postop anemia and these patients will get score (- 4) (The absence of anemia is protective factor towards post OP anemia). In group of patients with anemia, Total blood volume < 4.544 ml will be defined as risk factor (First, Anemic group, second Total blood volume < 4.544 ml) and these patients get score +3, calculated in table 6. The most points will be assigned to patients in anemic group, RBC salvaged volume >125 ml, by patients with TKA and with weight ≤73 kg. These patients will get score +5 which mean that their risk from PA anemia is high.

3. Results

This study includes 114 patients with TKA and 84 patients with THA procedures. In total 197 orthopaedic patients (46 male and 151 female), average age of 63.54 years ± 8.58 years. Description of continuous variables is shown by (Table 1 for THA and table 2 for TKA). Comparing groups by Mann Whitney test, we found that there was significant statistical difference for THA Hb min (postoperative haemoglobin) between TXA only group and TXA+ICS (p=0.000) and group ICS only and TXA+CS (p=0.001). Also, for TKA we found statistically significant difference between groups for Hb min between groups ICS + TXA + tourniquet and other two groups (p=0.000) respectively. According to RBC transfusions and amount of Crystalloid sollution in Operating Room (OR) and ward of semi-intensive care we found statistically significant difference for TKA (p=0.000 for RBC, p=0.001 for solution in the OR and p=0.000 for semi-intensive care). Concerning THA we found statistically significance results for RBC blood transfusions and amount of crystalloid solutions from group TXA + ICS towards other two groups respectively (p=0.000).

From whole population of patients, 165 (83.8%) developed PA. Compared to patents without PA, patients with PA have lower values of weight, BMI, Hb maximum, Hb minimum, hematocrit maximum, hematocrit minimum, total blood volume, and RBC salvaged volume (Table 3). In addition, patients with PA have greater total RBC volume loss, more allogeneic RBC units, and more FFP unit transfusions compared to non-PA patients. With regard to other continuous variables, there was no difference between PA versus (vs.) non-PA patients. With receiver operating characteristic (ROC) procedure we found three highly significant indicators that powerfully determine patients with PA versus non-PA. The criteria values of these indicators (variables) for the detection of patients with PA were: for weight ≤ 73 kg, for total blood volume ≤ 4.544 L, and for total RBC volume loss > 463.2 mL (Table 4). With univariate analyses, in comparison to non-PA patients, we have shown that patients with PA have less frequent ICS procedures plus TXA therapy (87.5% vs. 44.2%), frequently preoperative anemia (100% vs. 66.7%), lower incidence of the absence of preoperative anemia in the subgroup with ICS + TXA (87.5% vs 33.3%), less frequent increased body weight

(90.6% vs. 69.7%), less frequent RBC salvaged volume > 125 mL (71.9% vs. 46.7%), less frequent patients with THA and RBC salvage > 125 mL (37.5% vs. 15.8%) and less frequent presence of total blood volume ≤ 4.544 L (84.4% vs. 55.2%) (Table 5). On the other hand, in patients with PA compared to non-PA patients, the following characteristics are more common: total RBC volume loss > 463.2 mL, weight ≤ 73 kg, and more patients with TKA and with weight ≤ 73 kg (Table 5). By applying multivariate regression analysis, we identified two independent risk factors and two protective interactions between predictors for PA and after which we made the allocation of appropriate points to form the POARI score (Table 6): (1) the interaction between group (ICS plus TXA) and preoperative anemia (no); - 5 points; (2) total RBC volume loss > 463.2 mL (no); - 4 points; (3) total blood volume ≤ 4.544 mL (yes); + 3 points and (4) the interaction between RBC salvaged volume > 125 mL (yes) and with TKA and weight ≤ 73 kg (yes); + 5 points. The model above showed a moderate level of goodness of- fit (Nagelkerke R Square = 0.455) and very good adequacy (Hosmer–Lemeshow test Chi square = 3.098; p = 0.876) and discriminating characteristics (AUROC = 0.863 with 95% confidence interval from 0.808 to 0.908, p = 0.000, SN = 83.03% with 95% confidence interval from 91.1% to 88.4%, SP = 81.25% with confidence interval from 63.6% to 92.8%, PPV = 95.8% with confidence interval from 91.1% to 98.4% and NPV = 48.1 with 95% confidence interval from 34.3% to 62.2%). POARI score > - 6 with 95% confidence interval was the criteria for detection of PA risk (Table 6 and Figure 1).

Average POARI score in the non-PA group of patients was - 7.50 ± 2.54, (which means that their risk for PA was low) while in the group of patients with PA it was - 2.00 ± 3.91. (Their risk for PA was relatively high)

4. Discussion

In our study, the combined effects of demographic, anthropometric, and haematological predictors of postoperative anemia were assessed, together with the use of various pharmacological and/or non-pharmacological procedures for the control of intra- and postoperative bleeding in patients with THA or TKA. With multivariate logistic regression analysis, we have shown that in orthopedic patients undergoing THA or TKA surgery, without preoperative anemia, the use of TXA in combination with the ICS procedure achieves a protective effect on PA development (odds ratio = 0.081) (Table 6). Hence, in order to eliminate preoperative anemia, the early preoperative differential diagnosis of anemia and its appropriate therapy can significantly reduce the incidence of PA in patients undergoing THA or TKA surgery, in whom ICS and TXA would be administered intraoperatively. The

recommends, 4–8 weeks before the procedure, oral or intravenous iron supplementation and/or erythropoietin therapy to surgery patients with preoperative anemia in whom nutritional deficiencies are absent or have been corrected along with a restrictive transfusion policy [23]. Note that

recommends erythropoietin therapy only in cases of absence of the target therapeutic effect (achieving Hb ≥ 13 g/dL) with iron supplementation. Independent of the protective factors for PA discussed above, in patients with THA or TKA, only in the absence of total RBC volume loss > 463.2 mL, the risk for PA is significantly lower (odds ratio = 0.115). As total RBC volume loss is (Formula 2) dependent on the difference between maximum and minimum values of hematocrit in blood count, patients without total RBC volume loss > 463.2 mL have smaller amount of blood loss intra- and postoperatively comparing to preoperative values of hematocrit. Brecher et al. [24] have shown that use of mathematical modelling can rapidly estimate a patient's blood loss and allows more judicial and informed decision on what (if any) blood conservation techniques are to be employed in a specific patient. POARI > - 6 score is criteria for the risk of developing PA. In the absence of risk factors as specified in the multivariate logistic model (Table 6), orthopaedic patients with presence of both protective factors (absence of preoperative anemia and using of ICS with TXA and absence of total volume loss > 463.2 mL), will not have PA with a probability of 81.2% Muñoz et al. [25], in their review and recommendations, show that orthopaedic patients at risk of developing severe postoperative anemia should be identified on the basis of RBC mass (reflected by Hb concentration on the day of preoperative assessment), the lowest Hb concentration that the patient can tolerate (transfusion trigger), and the expected blood loss. However, even in cases where both protective factors are present (Table 6), patients with THA or TKA will develop PA with probability of 83% in case of the total blood volume < 4.544 mL (POARI score = (- 6). These patients are candidates for early PA with intravenous iron as early as possible, prior hospitalization, during hospitalization and home recovery. Patients with short height and low body weight (Formula (1)), with a reduced level of circulating volume, and their potential intraoperative blood loss, in proportion to their circulating volume, can be potentially higher and can result in PA. Kotzé et al. [26] described that the early use of intravenous iron can improve outcomes of orthopaedic patients developing PA, allogeneic blood transfusion, increased hospital stay, or re-admission. Desai et al. [27] emphasize that, before a surgical procedure, "females should be optimized to the same level of Hb as males to 13 g/dL since both sexes lose comparable amounts of blood in similar surgical procedures, but females have a relatively lower circulating volume which means they lose proportionally more".

Patients with TKA will have four times higher risk for PA (Table 6) if their weight is ≤ 73 kg and blood salvaged > 125 mL. Vieira et al. [28] have shown that ICS device has a high recovery rate of RBC and high percentage of eliminating residual heparin, plasma proteins, albumins, and platelets. To avoid more postoperative bleeding at patients with TKA and weight ≤ 73 kg combined with a volume of salvaged RBC volume greater than 125 mL, we recommend LMWH therapy in preventing doses for thromboembolic events in accordance with their weight and according to Australian Product information for nadroparin-calcium [29]. The Australian Medicines Administration has reduced the doses of LMWH (nadroparin-calcium) according to the patient's body weight compared to European doses, due to reports of high intraoperative and prolonged postoperative bleeding in orthopedically operated patients. So, according to them, orthopedic patients of 80 kg, 12 h before and 12 h after surgery, and then once daily to the third postoperative day, doses of 0.3 mL nadroparin-calcium (Anti-Xa IU = 2850 IU) are recommended, while the same doses in Europe are given to patients up to 69 kg. In Australian Product information for nadroparin-calcium, is stated: "Other mechanisms that contribute to the antithrombotic activity of nadroparin include stimulation of tissue factor pathway inhibitor (TFPI), activation of fibrinolysis via direct release of tissue plasminogen activator from endothelial cells, and the modification of haemorrheological parameters (decreased blood viscosity and increased platelet and granulocyte membrane fluidity)“.

In their meta-analysis, Smith et al. [30] described greater intra-operative blood loss in non-tourniquet compared to tourniquet assisted surgery, although they found no difference in total blood loss or transfusion rate. However, in our study, we showed that intraoperative blood loss and total RBC volume loss (both intra and post operatively bleeding) were independent predictors of PA (Table 6). In our study, because the risk factor for postoperative anemia was significant only in patients with TKA, in order to more adequately control and reduce intraoperative blood loss to 125 mL, we consider the use of tourniquet during limited time, (last 20-30 minutes of operation, usually after implementation of knee prosthesis and applying orthopaedic cement) and/or additional intraoperative topical application of TXA as potentially useful preventive procedures.

Many studies have shown that patients with PA have prolonged hospital stay [6]. With univariate analysis we found no difference in days of hospital stay between patients with PA vs. non-PA patients (Table 3).

Our analyses have shown that using ICS procedures in combination with therapy with TXA in patients without preoperative anemia, reduce PA risk comparing to referal category - patients without TXA and CS (odds ratio = 0.081; p = 0.000) – Table 6. Besides, ICS procedures only at patients without preoperative anemia has no significant effects in reducing risk for reference category patients with TXA only (p = 0.999). Thus, patient without preoperative anemia get (- 5) points [2×(-2.517)] = -5.034, rounded to (- 5). The patient, without preoperative anemia, with ICS only get 0 points, (ICS only have no protective factor according to our calculations)- Table 6. According from above, we conclude that only combination of ICS and TXA therapy have protective effects towards PA.

The significance of construction of POARI score is in quantification of independent risks for PA calculated by multivariate analyses. This means that between independent predictors for PA there is no significant multicollinearity. In further investigations, POARI score should be expanded, to identify other potential independent predictors for PA, which have not represented in this study.

Limitations of this study are a single center and retrospective design, specifically a relatively small sample size that is particularly relevant to the group of patients without PA. In connection with the above, we defined anemia, in both sexes, as Hb < 12 g/dL, since we predominantly considered old patients (72.6%), which is inconsistent with the WHO definition of anemia [1]. Moreover, in the study population, we did not record the chronic use of non-steroidal anti-inflammatory drugs, for which The

has made special recommendations due to the connection of their application with major or prolonged intraoperative and/or postoperative bleeding in orthopedic surgery [26]. In accordance with the mentioned recommendations, in the population of patients with preoperative anemia, we did not record the type of anemia according to its cause

5. Conclusions

Using Patient blood management principles and guidelines, intraoperative cell salvage and the use of tranexamic acid together represent a powerful protective factor to prevent postoperative anemia, exclusively in the patient population without preoperative anemia.

Routine monitoring of red blood cell total volume loss is mandatory during hospitalization, since the absence of total red blood cell volume loss > 463.2 mL reduces the chance of developing postoperative anemia. The total blood volume < 4544 mL represents a serious risk for the development of postoperative anemia, and therefore orthopedic patients with the mentioned finding should optimize the level of hemoglobin, in both sexes, in order to be ≥ 13 g/dl. Further research is needed to investigate more aspects of risk factors and the prevention of postoperative anemia in orthopaedic patients.

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TABLES

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Table 1. Descriptive statistics for continuous variables for patients with THA

Variables	N	Mean	SD
Age (years)	83	57.98	10.07
Height (m)	83	1.70	0.07
Weight (kg)	83	79.47	10.71
Body mass index (kg/m2)	83	26.52	3.32
Hemoglobin maximum (g/L)	83	129.63	20.61
Hemoglobin minimum (g/L)	83	99.55	19.18
Hematocrit maximum (%)	83	38.41	0.07
Hematocrit minimum (%)	83	29.48	0.06
Total blood volume (L)	83	4.61	0.77
Total RBC volume loss (ml)	83	418.07	0.77
RBC salvaged volume (ml)	83	144.41	31.73
RBC (units)	83	0.52	1.06
Fresh frozen plasma (units)	83	0.07	0.34
Hospital days in the intensive care unit	83	0	0
Hospital days in the semi-intensive care unit	83	8.28	3.51
Hospital days in the ward	83	5.51	4.26
Total hospital days	83	14.02	5.03
Crystalloid solutions in the operating room (bottles a 500 ml)	83	5.61	2.76
Crystalloid solution in the semi-intensive care unit (bottles a 500 ml)	83	7.80	4.34
Crystalloid solution in the ward (bottles a 500 ml)	83	0.25	1.10
Crystalloid solution throughout hospitalization (bottles a 500 ml)	83	13.57	6.93

SD – standard deviation, n – number of patients, RBC – red blood cells, FFP – fresh frozen plasma, n=83.

Table 2. Descriptive statistics for continuous variables for patients with TKA

Variables	N	Mean	SD
Age (years)	114	67.67	6.35
Height (m)	114	1.71	7.07
Weight (kg)	114	76.60	15.32
Body mass index (kg/m2)	114	25.27	2.80
Hemoglobin maximum (g/L)	114	127.85	13.87
Hemoglobin minimum (g/L)	114	103.42	19.18
Hematocrit maximum (%)	114	37.58	4.36
Hematocrit minimum (%)	114	31.68	4.78
Total blood volume (L)	114	4.85	0.59
Total RBC volume loss (ml)	114	355.81	241.63
RBC salvaged volume (ml)	114	148.5	63.19
RBC (units)	114	0.23	0.75
FFP (units)	114	0.07	0.35
Hospital days in the intensive care unit	114	0.04	0.28
Hospital days in the semi-intensive care unit	114	8.97	4.21
Hospital days in the ward	114	6.27	4.21
Total hospital days	114	14.02	5.03
Crystalloid solutions in the operating room (bottles a 500 ml)	114	4.46	2.91
Crystalloid solution in the semi-intensive care unit (bottles a 500 ml)	114	8.15	5.39
Crystalloid solution in the ward (bottles a 500 ml)	114	0.97	3.01
Crystalloid solution throughout hospitalization (bottles a 500 ml)	114	13.57	6.93

SD – standard deviation, n – number of patients, RBC – red blood cells, FFP – fresh frozen plasma, n=114.

Table 3. Assessment of differences between orthopaedic patients without vs. with postoperative anemia according to continuous variables

Variables	Postoperative anemia (hemoglobin <120 g/L)		p (t statistic)
	no (n1 = 32) Mean ± SD	yes (n2 = 165) Mean ± SD	
Age (years)	63.91 ± 8.46	63.47 ± 8.62	0.794 (0.261)
Height (m)	1.72 ± 0.08	1.70 ± 0.07	0.148 (1.454)
Weight (kg)	84.00 ± 12.81	75.94 ± 11.55	**0.000** (3.548)
Body mass index (kg/m2)	28.30 ± 3.31	26.17 ± 3.22	**0.001** (3.396)
Hemoglobin maximum (g/L)	145.72 ± 13.15	125.21 ± 15.65	0.000 (7.813)
Hemoglobin minimum (g/L)	127.56 ± 7.25	96.62 ± 15.25	**0.000** (17.705
Hematocrit maximum (%)	43.69 ± 3.92	37.56 ± 4.73	0.000 (6.883)
Hematocrit minimum (%)	38.27 ± 2.17	28.96 ± 4.61	**0.000** (17.708)
Total blood volume (L)	5.03 ± 0.60	4.72 ± 0.62	**0.012** (2.540)
Total RBC volume loss (ml)	272.40 ± 161.23	408.52 ± 248.12	**0.003** (-3.953)
RBC salvaged volume (ml)	124.16 ± 53.90	90.47 ± 84.16	**0.005** (2.913)
RBC (units)	0.03 ± 0.18	0.42 ± 0.99	**0.000** (-4.711)
FFP (units)	0.00 ± 0.00	0.09 ± 0.38	**0.002** (-3.076)
Total hospital days	13.78 ± 4.817	14.83 ± 6.11	0.361 (-0.916)
Crystalloid solution during hospitalization (bottles a 500 ml)	14.87 ± 4.80	13.31 ± 7.26	0.245 (1.166)

SD – standard deviation, n – number of patients, RBC – red blood cells, FFP – fresh frozen plasma.

Table 4. Receiver operating characteristic (ROC) parameters for weight, total blood volume and total RBC volume loss in detection of patients with postoperative anemia after hip or knee arthroplasty

Variables	AUROC (95% CI)	p	Criterion	SN (95% CI)	SP (95% CI)	PPV (95% CI)	NPV (95% CI)
Weight (kg)	0.677 (0.607 – 0.742)	0.0003	≤ 73 (64 – 82)	43.64 (35.9 – 51.6)	84.37 (67.2 – 94.7)	93.5 (85.5 – 97.9)	22.5 (15.4 – 31.0)
Total blood volume (L)	0.649 (0.578 – 0.715)	0.0016	≤ 4.544 (4.245 – 4.965)	45.45 (37.7 – 53.4)	84.37 (67.2 – 94.7)	93.7 (86.0 – 97.9)	23.1 (15.8 – 31.8)
Total RBC volume loss (mL)	0.653 (0.582 – 0.719)	0.0021	> 463.2 (069.5 – 484.5)	37.58 (30.2 – 45.4)	93.75 (79.2 – 99.2)	96.9 (89.1 – 99.6)	22.6 (15.8 – 30.6)

AUROC – area under ROC curve, SN – sensitivity, SP – specificity, PPV – positive predictive value; NPV – negative predictive value, CI – confidence interval, RBC – red blood cells.

Table 5. Univariate analysis of frequency distribution differences between orthopaedic patients without vs. patients with postoperative anemia, according to nominal variables

Variables	Categories	Postoperative anemia (hemoglobin <120 g/L)		p (χ2)
		no f1 (%)	yes f2 (%)	
Group	TXA only	4 (12.5%)	64 (38.8%)	**0.000** (20.578)
	only ICS	0 (0.0%)	28 (17.0%)	
	ICS and TXA	28 (87.5%)	73 (44.2%)	
Gender	male	11 (34.4%)	35 (21.2%)	0.107 (2.595)
	female	21 (65.6%)	130 (78.8%)	
Orthopedic surgery	THA	12 (37.5%)	72 (43.6%)	0.521 (0.413)
	TKA	20 (62.5%)	93 (56.4%)	
Preoperative anemia (hemoglobin <120 g/L)	No	32 (100.0%)	110 (66.7%)	**0.000**
	Yes	0 (0.0%)	55 (33.3%)	
Absence of preoperative anemia (hemoglobin <120 g/L) TXA only	No	28 (87.5%)	125 (75.8%)	0.170
	Yes	4 (12.5%)	55 (33.3%)	
Absence of preoperative anemia (hemoglobin <120 g/L) and only ICS	No	32 (100.0%)	150 (90.9%)	0.137
	Yes	0 (0.0%)	15 (9.1%)	
Absence of preoperative anemia (hemoglobin <120 g/L) and ICS with TXA	No	4 (12.5%)	110 (66.7%)	**0.000**
	Yes	28 (87.5%)	55 (33.3%)	
Older (greater or equal 60 years)	No	7 (21.9%)	47 (28.5%)	0.521
	Yes	25 (78.1%)	118 (71.5%)	
Increased body weight (body mass index ≥25 kg/m2)	No	3 (9.4%)	50 (30.3%)	**0.016**
	Yes	29 (90.6%)	115 (69.7%)	
Hypertension	No	20 (62.5%)	100 (60.6%)	0.841 (0.040)
	Yes	12 (37.5%)	65 (39.4)	
RBC salvaged volume >125 ml	No	9 (28.1%)	88 (53.3%)	**0.012**
	Yes	23 (71.9%)	77 (46.7%)	
Patients with TKA and RBC salvaged volume >125 ml	No	21 (65.6%)	114 (69.1%)	0.149 (0.699)
	Yes	11 (34.4%)	51 (30.9%)	
Patients with THA and RBC salvaged volume >125 ml	No	20 (62.5%)	139 (84.2%)	**0.007**
	Yes	12 (37.5%)	26 (15.8%)	
Total RBC volume loss >463.2 ml	No	30 (93.8%)	103 (62.4%)	**0.000**
	Yes	2 (6.2%)	62 (37.6%)	
Weight ≤73 kg	No	27 (84.4%)	93 (56.4%)	**0.003**
	Yes	5 (15.6%)	72 (43.6%)	
Patients with TKA and with weight ≤73 kg	No	28 (87.5%)	114 (69.1%)	**0.033**
	Yes	4 (12.5%)	51 (30.9%)	
Patients with THA and with weight ≤73 kg	No	31 (96.9%)	144 (87.3%)	0.136
	Yes	1 (3.1%)	21 (12.7%)	
Total blood volume <4.544 L	No	27 (84.4%)	91 (55.2%)	**0.003**
	Yes	5 (15.6%)	74 (44.8%)	

f – frequency, RBC – red blood cells, ICS – intraoperative cell salvage, TKA – total knee arthroplasty, THA – total hip arthroplasty, TXA – tranexamic acid.

Table 6. Parameters for PA predictors in multivariate logistic regression model with appropriate points for Post-Operative Index score construction in patients with hip or knee arthroplasty

	B	SE	Wald	p	Odds ratio	95% CI for odds ratio		Points
						Lower	Upper	
Group by preoperative anemia			18.234	**0.000**				
Group (TXA only) by preoperative anemia (no) – *Reference*								0
Group (only ICS) by preoperative anemia (no)	17.643	9543.105	0.000	0.999	45957783.656	0.000		0
Group (ICS plus TXA) by preoperative anemia (no)	–2.517	0.589	18.234	**0.000**	0.081	0.025	0.256	–5
Total RBC volume loss >463.2 ml (yes) – *Reference*								0
Total RBC volume loss >463.2 ml (no)	–2.165	0.795	7.418	**0.006**	0.115	0.024	0.545	–4
Total blood volume <4.544 ml (no) – *Reference*								0
Total blood volume <4.544 ml (yes)	1.385	0.575	5.792	**0.016**	3.993	1.293	12.333	3
RBC salvaged volume >125 ml (no) by patients TKA with weight ≤73 kg (no) – *Reference*								0
RBC salvaged volume >125 ml (yes) by patients with TKA and with weight ≤73 kg (yes)	2.289	1.087	4.437	**0.035**	9.864	1.173	82.973	5
Constant	4.352	0.886	24.131	0.000	77.665			

SE – standard error, CI – confidence interval, B – regression coefficient, TKA – total knee prosthesis, ICS – intraoperative cell salvage, TXA – tranexamic acid, RBC – red blood cells, (no) – without preoperative anemia, (yes) – with preoperative anemia

FIGURES

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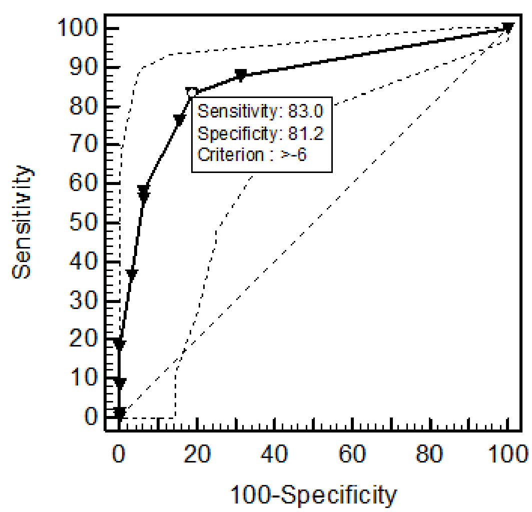
FIGURE 1. ROC CURVE FOR POST-OPERATIVE ANEMIA RISK INDEX SCORE IN ORTHOPEDIC PATIENTS WITH HIP OR KNEE ARTHROPLASTY



ABBREVIATIONS

WHO World Health Organization

Hb Hemoglobin

THA total hip arthroplasty

TKA total knee arthroplasty

PBM Patient Blood Management

ICS Intraoperative cell salvage

TXA Tranexamic acid

RBC Red blood cells

OR Operating Room

POARI Post-Operative Anemia Risk Index

ROC Receiver Operating Characteristic

PA postoperative anemia

BMI Body Mass Index

FFP Fresh Frozen Plasma

vs. versus

LMWH Low Molecular Weight Heparin