Safety and Effectiveness of the Topical Application of Tranexamic Acid to Reduce Drainage of Elderly Femoral Neck Fractures After Total Hip Arthroplasty: An observational pilot study

Guoshun Huang[1], Feng Han[1], Haifeng Wu[1], Tao Fan[1], Weidong Guo[1*]

[1]Department of Orthopedics, The Sixth Hospital of Shanxi Medical College, Taiyuan 030003, China

[*]**Address correspondences to** Weidong Guo. Department of Orthopedics, The sixth hospital of Shanxi Medical College, No. 213 North Street, Taiyuan City, Shanxi Province, 030003, China. Tel: +86-0351-2132388. Email: m13935102726@163.com.

Acknowledgments: None.

Declaration of conflict of interest: None.

Abstract

Background: There is a common disease of femoral neck fractures in elderly patients. And the incidence of postoperative wound bleeding and hyperfibrinolysis is very high. Tranexamic acid (TXA) has a certain effect in decreasing blood loss in orthopaedic surgery. A randomized controlled trial will assess the safety and effectiveness of TXA in decreasing drainage of elderly femoral neck fractures after total hip arthroplasty.

Methods: 144 elderly femoral neck fractures are randomly and evenly divided into experimental group and control group, the experimental group receives 3g of infused retrogradely into the drainage tube tranexamic acid mixed in 100ml of saline after the operation and the control group receives an equivalent volume bolus of saline-infused retrogradely into the drainage after the operation. Observation indicators include drainage volume, total drainage volume, and the postoperative hemoglobin loss on the 1st, 2nd, and 3rd day after operation, postoperative wound healing, cardiovascular and cerebrovascular events, and pulmonary embolism, etc. Data analysis was performed using SPSS 25.0 software and GraphPad InStat.

Results: The estimated drainage volume was significantly lower in the experimental group than control group on the first day after operation and the second day after operation ($p < 0.05$). And the hemoglobin and hematocrit levels on the first day after operation, the second day after operation, and the third day after operation in the experimental group were higher than those in the control group ($P < 0.05$). Moreover, there was no significant difference in coagulation function between the two groups, and a lack of significant intergroup differences in the postoperative complications, such as the incidences of deep vein thrombosis, pulmonary embolism, myocardial infarction, reoperation, and readmission or in terms of mortality rates.

Conclusion: This clinical study demonstrated that topical application of TXA administration safely reduced drainage and blood loss without affecting the coagulation function for elderly femoral neck fractures after total hip arthroplasty.

Abbreviations: TXA=Tranexamic acid; PE=Pulmonary embolism; DVT=Deep vein thrombosis; BMI=Body mass index; MI=Miocardial infarction.

keywords: Tranexamic acid; Total hip arthroplasty; Elderly femoral neck fractures; Reduce drainage; Randomized.

Tob Regul Sci.™ 2021;7(5): 1878-1888

DOI: doi.org/10.18001/TRS.7.5.109

Introduction

Femoral neck fracture is a common hip fracture in the elderly worldwide[1]. Primary total hip arthroplasty in the treatment of elderly femoral neck fractures has a significant effect[2], which has become an important method for the treatment of such fractures. Although skilled surgical techniques and minimally invasive surgical concepts can reduce the cost of surgery to a certain extent. However, bleeding and hyperfibrinolysis often lead to massive hemorrhage in the early postoperative period and postoperative drainage [3]. Because the elderly patients are complicated with basic diseases and have poor tolerance to blood loss, anemia does great harm to the elderly patients. It not only affects the functional recovery of hip joint [4-5], but also affects the cardiopulmonary function, and even induces serious cardiovascular and cerebrovascular accidents[6]. Anemia has also been associated with several complications such as infection, immunologic reaction, and morbidity, and placed a high burden on the affected patients[7]. Recently, reducing postoperative blood loss is a hot and difficult point in the perioperative period of total hip arthroplasty.

Tranexamic acid(TXA), an antifibrinolytic hemostatic drug.It could inhibit the conversion of plasminogens to plasmin to stabilize clotting[8]. Several studies have demonstrated that it could effectively reduce blood loss[9-11]. As a result of the CRASH-2 trial, which demonstrated reduced mortality in trauma patients who received TXA, the WHO added TXA to the essential drugs list[12,13]. Lee et al., 11 similarly reported a transfusion rate three times lower in patients who received TXA before hemiarthroplasty[14]. However, there are relatively few reports on the application of tranexamic acid in primary total hip arthroplasty in elderly patients with a simple femoral neck fracture, and the observation of postoperative drainage and blood loss is also less.

In this study, we sought to determine the effects and safety of infused retrogradely into the drainage tube TXA on elderly patients undergoing total hip arthroplasty. Furthermore, we aim to determine whether infused retrogradely into the drainage tube, TXA reduces drainage volume and blood loss, and secondly, TXA reduces the incidence of postoperative complications.

2.Materials and methods

2.1 Study design

144 elderly femoral neck fractures in our hospital from January 2018 to January 2021 were randomized divided into two groups: the experimental group(n=67 cases) and or the control group(n=67 cases). The researchers systematically explained the role, purpose, and process of the study to their families. Their families voluntarily signed the informed consent form to participate in this study. This study was approved and recognized by the ethics committee of our hospital. The flowchart is shown in Figure 1.

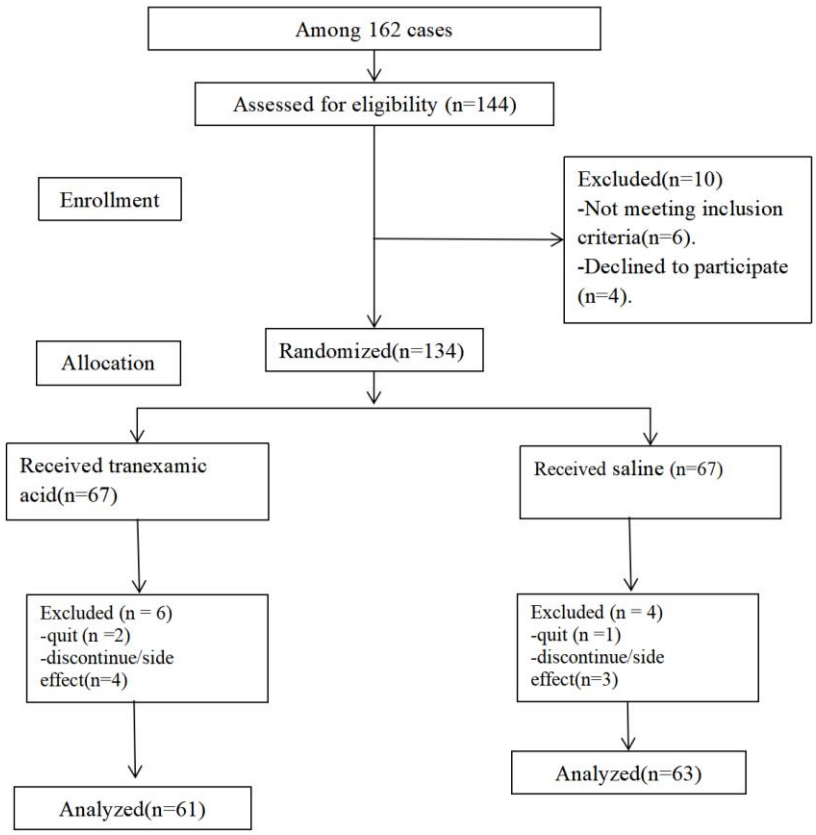


Figure 1. Flow chart showing recruitment.

2.2 Inclusion and exclusion standard

Inclusive criteria: ① The patient was diagnosed as old femoral neck fracture with osteoporosis before operation and planned to undergo unilateral total hip arthroplasty; ② There were no signs of pulmonary infection or infection in other parts of the body; ③ age:≥65 years; ④ The subjects were willing to cooperate and implement the experiment.

Exclusion criteria: ① The liver function and renal function were abnormal before operation; ② Severe coagulation dysfunction or thrombocytopenia; ③ Patients had a history of pathological fracture; ④ The patients had a history of severe varicose veins of lower extremity; ⑤ The patient had a history of anemia; ⑥ The patient had taken aspirin, statins or other anticoagulants before operation; ⑦Unwilling to participate our research.

2.3 Interventions

The experimental group: Patients receive 3g of infused retrogradely into the drainage tube tranexamic acid mixed in 100ml of saline after the operation, and the drainage tube is clamped for 2 hours after the operation.

Control group: The patients receive an equivalent volume of bolus of saline-infused retrogradely into the drainage tube after the operation.

All patients were routinely given antibiotics to prevent infection, and low molecular weight heparin calcium was used to prevent venous thrombosis. Indications for removal of drainage tube: 1) The drainage volume in 24 hours was

less than 50 ml; 2) The drainage fluid was removed when the color became clear; 3) The drainage tube should not be placed for more than three days.

2.4 Primary outcome

The primary outcome of the safety index is everyday change in postoperative wound healing, cardiovascular and cerebrovascular events, pulmonary embolism, lower extremity deep venous thrombosis, activated partial thromboplastin time, prothrombin time, thrombin time, fibrinogen. The drainage volume, total drainage volume, and postoperative hemoglobin loss on the 1st, 2nd, and 3rd days after operation were recorded as effective indexes.

2.5 Secondary outcomes

Secondary outcome measures assessed include changes in the incidence of postoperative complications such as incision infection, subcutaneous hematocele, deep vein thrombosis, urinary tract infection, pulmonary infection, etc.

2.6 Statistical analysis

All data were analyzed by SPSS 25.0, and GraphPad InStat. The statistical results are expressed by mean ± standard deviation (± s), the data comparison is conducted by t-test and the correlation analysis is conducted by person linear phase. For non-parametric measures like VAS and WOMAC, differences between baseline and post-treatment scores for each group are computed by the Wilcoxon signed rank test. $P < 0.05$ was the difference with statistical significance.

3. Results

3.1 Clinical data

Between January 2018 and January 2021, 144 patients were assessed for eligibility in this study. Of these, 10 elderly were excluded for the following reasons:6 patients did not meet inclusion criteria; 4patients refused participation. Finally, 124 participants were inclusion the analysis (Figure 1). In addition, the groups were similar regarding age, sex, body mass index(BMI), the rate of smoking, preoperative hemoglobin, preoperative hematocrit, preoperative albumin, preoperative cholesterol, and preoperative coagulation function (Table 1). There was no statistical significance between the two groups among those clinical data before intervention ($P>0.05$).

Table 1 Comparison of clinical data between the two groups

	Experimental group(n=61)	Control group(n=63)	t/χ2	*P*
Age(years)	74.05±6.91	71.35±7.09	3.25	0.24
Sex			3.28	0.42
Male(n%)	38(62.3%)	36(57.1%)		
Female(n%)	23(37.7%)	27(42.9%)		
BMI	22.7±2.28	21.4±2.76	1.209	0 .33
Smoking	37(60.7%)	39(61.9%)	1.96	0.59
Preoperative levels				
Hemoglobin(g/dl)	11.8±1.4	12.4±1.2	1.216	0 .074
Hematocrit(%)	35.7±3.3	36.4±4.3	1.874	0 .243
Albumin(g/dl)	3.77±0.34	3.67±0.34	2.219	0 .821
Cholesterol(mg/dl)	156.7±46.2	161.4±36.4	2.224	0 .423
Activated partial prothrombin time(s)	33.2±3.22	32.1±2.18	1.986	0 .372
Prothrombin time(s)	12.7±1.3	12.7±1.8	2.187	0 .076
Thrombin time(s)	13.5±0.37	12.8±0.45	1.768	0 .123
Fibrinogen(g/L)	2.18±1.17	3.12±1.28	0.987	0 .438

Note: Compared with the control group, significant difference as P<0.05.

3.2 Coagulation function

There was no significant difference in activated partial prothrombin time, prothrombin time, thrombin time, and fibrinogen level at 1 day after operation, 2 days after operation, 3 days after operation, 1 month after operation, and 3 months after operation(P > 0.05)(Table 2). This result indicated that topical application of tranexamic acid is safe, furthermore, it had no impact on coagulation function.

Table 2 Comparison of coagulation function between the two groups

	group	Number of cases	T1	T2	T3	T4	T5	T6
Activated partial prothrombin time(s)	Experimental group	61	33.2±3.22	44.22±4.11	28.93±0.75	27.73±0.83	24.15±1.17	20.89±1.44
	Control group	63	32.1±2.18	42.14±3.25	28.62±0.89	27.54±0.94	23.11±0.83	21.61±1.21
	t	-	1.986	2.245	1.123	2.128	3.217	2.347
	P	-	0.372	0.215	0.224	0.082	0.025	0.067
Prothrombin time (s)	Experimental group	61	12.7±1.3	26.21±4.15	17.32±9.51	18.14±4.19	12.19±8.95	14.19±9.14
	Control group	63	12.7±1.8	24.20±3.03	19.36±9.43	19.16±6.29	15.18±12.25	15.36±12.09
	t	-	2.187	3.245	6.125	4.289	2.385	4.936
	P	-	0.076	0.079	0.062	0.083	0.093	0.052
Thrombin time(s)	Experimental group	61	13.5±0.37	33.21±0.15	27.33±1.51	28.33±1.19	22.49±0.95	10.19±0.14
	Control group	63	12.8±0.45	32.20±0.03	29.36±1.43	29.16±1.29	25.18±0.25	9.36±0.09
	t	-	1.768	5.214	2.115	1.259	1.335	4.336
	P	-	0.123	0.088	0.081	0.203	0.902	0.512
Fibrinogen (g/L)	Experimental group	61	2.18±1.17	8.21±1.06	7.12±1.22	6.14±1.19	5.11±0.34	3.19±1.12
	Control group	63	3.12±1.28	9.11±0.13	9.16±0.23	7.16±0.29	6.18±0.41	4.26±0.29
	t	-	0.987	2.245	3.113	2.289	2.385	2.616
	P	-	0.438	0.089	0.202	0.413	0.103	0.142

Note: Compared with the control group, significant difference as P<0.05. T1: Before operation; T2:the first day after operation; T3: the second day after operation; T4: the third day after operation; T5: one month after operation; T6: three months after operation.

3.3 Drainage volume

As shown in Figure 2, the drainage volume on the first day after operation and the second day after operation in the experimental group were less than those in the control group ($P < 0.05$). There was no significant difference in drainage volume on the third day after operation between the two groups ($P > 0.05$).

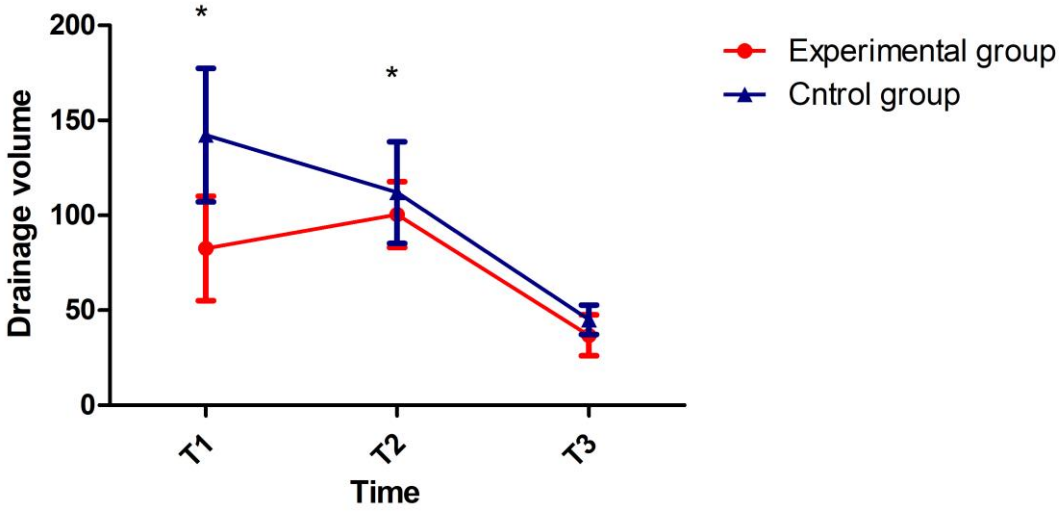
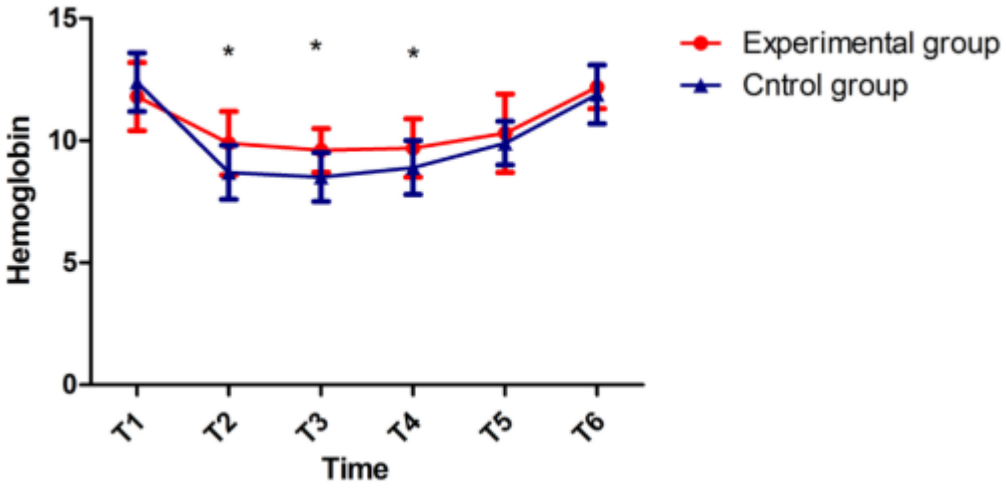


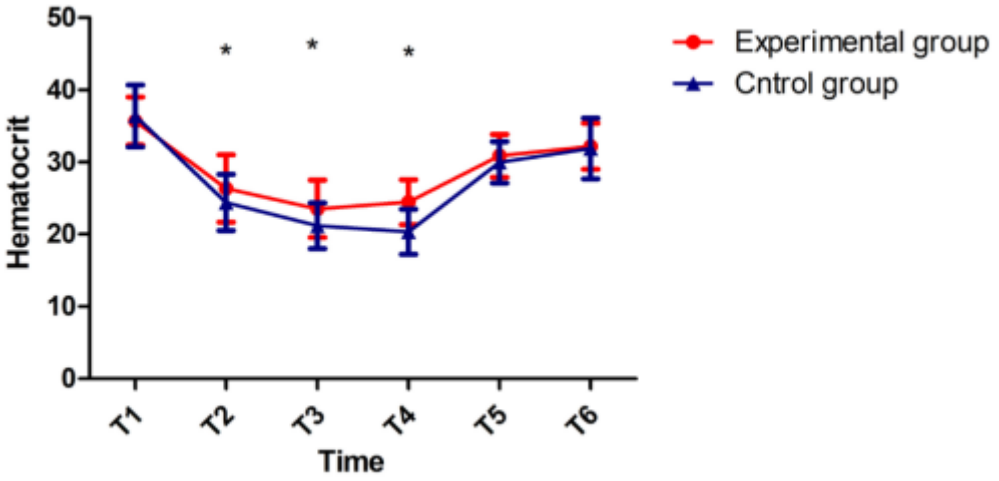
Figure 2 Comparison of drainage volume between the two groups. Note: Compared with the control group, $^{*}P<0.05$. T1: one day after operation; T2:two days after operation; T3: three days after operation.

3.4 Change of hemoglobin and hematocrit

The hemoglobin and hematocrit levels on the first day after operation, the second day after operation, and the third day after operation in the experimental group were higher than those in the control group (P < 0.05). There was no significant difference in hemoglobin and hematocrit levels between the one month after operation and three months after operation between the two groups (P > 0.05)(Figure 3).



（A)



(B)

Figure 3 Comparison of hemoglobin and hematocrit between the two groups. Note: Compared with the control group, $^{*}P<0.05$. *A:* Comparison of hemoglobin level between two groups; B: Comparison of hematocrit level between two groups. T1: Before operation; T2:the first day after operation; T3: the second day after operation; T4: the third day after operation; T5: one month after operation; T6: three months after operation.

3.5 Postoperative complications

The two groups did not differ in terms of the incidences of deep vein thrombosis(DVT), pulmonary embolism(PE), myocardial infarction(MI), reoperation, and readmission or terms of mortality rates. However, the two groups did not differ significantly in terms of the frequency of surgical complications, such as incision infection and dislocation (Table 3).

Table 3 Comparison of Postoperative complications between the two groups

	Experimental group(n=61)	Control group(n=63)	t/ χ^2	*P*
Incision infection	6（9.8%）	10（15.9%）	2.66	0.24
Dislocation	1(1.6%)	2(3.2%)	3.13	0.43
Miocardial infarction	2(3.3%)	5(7.9%)	0.38	0.82
Pulmonary embolism	0(0）	1（1.6%）	1.34	0.07
Deep Venous Thrombosis	3(4.9%)	6(9.5%）	1.67	0.62
Reoperation	4(6.6%)	3(4.8%)	2.19	0.24
Mortality	0(0)	2(3.2%)	2.85	0.09
Readmission	2(3.3%)	5(7.9%)	2.69	0.11

Note: Compared with the control group, significant difference as P<0.05.

Discussion

As shown in our results, the estimated drainage volume was significantly lower in the experimental group than the control group on the first day after operation and the second day after operation ($p < 0.05$). And the hemoglobin and hematocrit levels on the first day after operation, the second day after operation, and the third day after operation in the experimental group were higher than those in the control

group ($P < 0.05$). Moreover, there was no significant difference in coagulation function between the two groups, and a lack of significant intergroup differences in the postoperative complications, such as the incidences of deep vein thrombosis, pulmonary embolism, myocardial infarction, reoperation, and readmission or in terms of mortality rates.

In our study, we evaluated the safety of topical TXA in terms of surgical outcomes after total hip arthroplasty in elderly patients with femoral neck fractures. The coagulation function (such as the indexes: activated partial prothrombin time, prothrombin time, thrombin time, and fibrinogen level) had no difference after intervention between the two groups. Furthermore, the two groups did not differ significantly in terms of the incidences of postoperative complications, such as DVT, PE, MI, reoperation or incision infection, etc. The results indicated that topical application of tranexamic acid does not affect surgical healing, and it had no impact on postoperative coagulation function, it does not increase the risk of thrombosis (myocardial infarction, cerebral infarction, pulmonary embolism, lower extremity deep vein thrombosis), namely, topical application of TXA in elderly patients with femoral neck fracture in total hip arthroplasty has good feasibility and safety. This result was in accordance with previous studies[15], which demonstrated that topical application of tranexamic acid in total hip arthroplasty combined with clamping drainage tube for 2 hours is safe and effective, and it does not increase the risk of venous thrombosis.

On the other hand, topical TXA significantly reduced drainage volume on the first day after operation and the second day after operation, perioperative blood loss, and the change of hemoglobin and hematocrit levels. We observed the change of hemoglobin and hematocrit between the two groups. Accordingly, we believe that drainage volume and blood loss estimated in our study were relatively reduced and that topical TXA infused retrogradely into the drainage tube reduced postoperative bleeding. Consistent with our findings, Kwak et al. [16] reported that topical TXA reduces blood loss, transfusion requirements, and medical complications after hemiarthroplasty in elderly patients with femoral neck fractures.

Tranexamic acid is a synthetic derivative of lysine, which has a high affinity with the lysine binding site of fibrinogen. Therefore, it can block the binding of fibrinogen containing lysine residues to fibrinogens, thus inhibiting the decomposition of fibrinogens and achieving hemostasis[17-19]. TXA can inhibit the body's hyperfibrinolysis. When the hyperfibrinolysis is inhibited, it may theoretically increase the incidence of deep venous thrombosis in the body, but many relevant studies have not found that tranexamic acid can increase the incidence of deep venous thrombosis in postoperative patients [20-22]. The reason may be that the antifibrinolytic effect of tranexamic acid is mainly concentrated in the surgical and traumatic sites, but does not produce the blood-clotting effect in blood vessels. In our study, 3g of infused retrogradely into the drainage tube tranexamic acid mixed in 100ml of saline after the operation, there was no increased incidence of deep vein thrombosis and pulmonary embolism.

There were also some drawbacks in our study. Firstly, in this study, we only observed a certain dose of TXA on reducing drainage after total hip arthroplasty. Secondly, we did not carry out the long-term follow-up of the elderly patients after intervention. Thirdly, this is a small sample randomized controlled trial. Therefore, we need to expand the sample size for further clinical observation, and then optimize the treatment plan, to improve the perioperative and postoperative prognosis and prognosis of elderly patients.

In conclusion, topical application of tranexamic acid is safe and feasible to reduce postoperative drainage in elderly patients with femoral neck fracture after total hip

arthroplasty. It does not affect the coagulation function and does not increase the risk of thrombosis. It can effectively reduce postoperative drainage, especially on the first day and the second day after the operation.

Reference:

[1] You Daniel, Sepehri Aresh, Kooner Sahil et al. Outcomes of total hip arthroplasty using dual mobility components in patients with a femoral neck fracture.Bone Joint J, 2020, null: 811-821.

[2] Wang Xiao-Dong, Lan Hai, Hu Zheng-Xia et al. SuperPATH Minimally Invasive Approach to Total Hip Arthroplasty of Femoral Neck Fractures in the Elderly: Preliminary Clinical Results.Orthop Surg, 2020, 12: 74-85.

[3] Graham Jove, Bowen Thomas R, Strohecker Kent A et al. Reducing mortality in hip fracture patients using a perioperative approach and "Patient-Centered Medical Home" model: a prospective cohort study.Patient Saf Surg, 2014, 8: 7.

[4] Blanié Antonia, Bellamy Lorenn, Rhayem Yara et al. Duration of postoperative fibrinolysis after total hip or knee replacement: a laboratory follow-up study. Thromb Res, 2013, 131: e6-e11.

[5] de Jonge Tamás, Pharmacological reduction of bleeding during hip endoprosthetic replacement.Orv Hetil, 2012, 153: 1607-12.

[6] Meybohm Patrick, Kohlhof Hendrik, Wirtz Dieter Christian et al. Preoperative Anaemia in Primary Hip and Knee Arthroplasty. Z Orthop Unfall, 2020, 158: 194-200.

[7] Ponnusamy Karthikeyan E, Kim Thomas J, Khanuja Harpal S, Perioperative blood transfusions in orthopaedic surgery.J Bone Joint Surg Am, 2014, 96: 1836-44.

[8] Johansson Torsten, Pettersson Lars-Göran,Lysander Björn,Tranexamic acid in total hip arthroplasty saves blood and money: a randomized, double-blind study in 100 patients.Acta Orthop, 2005, 76: 314-9.

[9] ADVANCES IN MUSCULOSKELETAL DISEASES AND INFECTIONS - SOTIMI 2019:,Rizzo M,Russo A P et al. A comparative study of combined intravenous and topical administration of tranexamic acid with topical tranexamic acid alone for blood loss reduction after primary uncemented total hip arthroplasty.J Biol Regul Homeost Agents, 2020, 34: 105-110.

[10] Miranda I,Collado-Sánchez A,Peregrín-Nevado I et al. Use of topical tranexamic acid in primary total hip arthroplasty. Efficiency and safety. Our experience.Rev Esp Cir Ortop Traumatol, 2020, 64: 114-119.

[11] Liu Xiangcheng,Liu Jinglong,Sun Ganghe,A comparison of combined intravenous and topical administration of tranexamic acid with intravenous tranexamic acid alone for blood loss reduction after total hip arthroplasty: A meta-analysis.Int J Surg, 2017, 41: 34-43.

[12] CRASH-2 trial collaborators,Shakur Haleema,Roberts Ian et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial.Lancet, 2010, 376: 23-32.

[13] CRASH-2 collaborators,Roberts Ian,Shakur Haleema et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial.Lancet, 2011, 377: 1096-101, 1101.e1-2.

[14] Lee Conrad,Freeman Richard,Edmondson Mark et al. The efficacy of tranexamic acid in hip hemiarthroplasty surgery: an observational cohort study.Injury, 2015, 46: 1978-82.

[15] Miranda I,Collado-Sánchez A,Peregrín-Nevado I et al. Use of topical tranexamic acid in primary total hip arthroplasty. Efficiency and safety. Our experience.Rev Esp Cir Ortop Traumatol, 2020, 64: 114-119.

[16] Kwak Dae-Kyung,Jang Chul-Young,Kim Dae-Hwan et al. Topical tranexamic acid in elderly patients with femoral neck fractures treated with hemiarthroplasty: efficacy and safety? - a case-control study.BMC Musculoskelet Disord, 2019, 20: 228.

[17] Zirk Matthias,Zinser Max,Buller Johannes et al. Supportive topical tranexamic acid application for hemostasis in oral bleeding events - Retrospective cohort study of 542 patients.J Craniomaxillofac Surg, 2018, 46: 932-936.

[18] Girish Aditya,Hickman DaShawn A,Banerjee Ankush et al. Trauma-targeted delivery of tranexamic acid improves hemostasis and survival in rat liver hemorrhage model.J Thromb Haemost, 2019, 17: 1632-1644.

[19] Wang Duan,Yang Yang,He Chuan et al. Effect of Multiple Doses of Oral Tranexamic Acid on Haemostasis and Inflammatory Reaction in Total Hip Arthroplasty: A Randomized Controlled Trial.Thromb Haemost, 2019, 119: 92-103.

[20] Onodera Tomohiro,Majima Tokifumi,Sawaguchi Naohiro et al. Risk of deep venous thrombosis in drain clamping with tranexamic acid and carbazochrome sodium sulfonate hydrate in total knee arthroplasty.J Arthroplasty, 2012, 27: 105-8.

[21] Zekcer Ari,Del Priori Ricardo,Tieppo Clauber et al. Topical vs. intravenous administration of tranexamic acid in knee arthroplasty and prevalence of deep venous thrombosis: a randomized clinical trial.J Vasc Bras, 2016, 15: 120-125.

[22] Chornenki Nicholas L Jackson,Um Kevin J,Mendoza Pablo A et al. Risk of venous and arterial thrombosis in non-surgical patients receiving systemic tranexamic acid: A systematic review and meta-analysis.Thromb Res, 2019, 179: 81-86.