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Intra-articular only Compared with Combined Intra-venous and Intra-articular Tranexamic Acid in Total Perioperative Blood Loss in Primary Unilateral Total Knee Arthroplasty: A Retrospective Study

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Abstract

Background: Intravenous (IV), Intra-Articular (IA) Administration of Tranexamic Acid (TXA) and combined administration of IV and IA TXA for patients who received primary Total Knee Arthroplasty (TKA) have been reported in several literatures. However, IV TXA may cause unwanted side effects as increasing dose. Our study wants to compare the effect in total blood loss of IA TXA only and combined therapy with IA and IV TXA in patients undergoing primary total knee arthroplasty.

Methods: The retrospective study included all patients received primary unilateral TKA from May 2014 to June 2016 at Kaohsiung Veterans General Hospital. There were 782 knees included. These knees were divided into three groups: IA TXA only, combined IA and IV TXA, and without TXA using. All patients were operated under spinal or general anesthesia using tourniquet and cemented posterior stabilized type implant. Estimated postoperative blood loss was calculated as OSTHEO Formula.

Results: In these 782 knees on the study, there were 566 women (72.38%) and 216 men (27.62%). Mean age was 69.93±8.25 years of age. There was no significant difference over gender and age between these three groups. The group of IA-only showed significant reduced total blood loss compared with the group of combined IA IV TXA (P=0.016) and the group of none of TXA using(P=0.000).

Conclusions: Intraoperative intra-articular TXA is an effective and convenient method to reduce total blood loss in the patient undergoing primary TKA and even with better efficacy than perioperative combined therapy of IV and IA TXA in our study.

Keywords: Total Blood Loss; Total Knee Arthroplasty; Tranexamic Acid

Abbreviations

IA	:	Intra-Articular
IV	:	Intravenous
TKA	:	Total Knee Arthroplasty
TXA	:	Tranexamic Acid

Introduction

Total Knee Arthroplasty (TKA) is worldwide effective treatment for end stage of osteoarthritic knee. Despite of accuracy and precise operative technique within the operative procedure, perioperative blood loss is still a popular issue in perioperative complication of TKA which was proved to increase morbidity [1]. According to many studies, the estimated blood loss of TKA is 800 ml to 1800 ml [2-5]. Due to perioperative massive hemorrhage, allogenic blood transfusion becomes a necessary management for resuscitation. However, this also takes some substantial risks of viral or bacterial infection, transfusion related disease, such as Transfusion-Related Acute Lung Injury (TRALI). Besides, the risk of surgical wound site infection, urinary tract infection, and respiratory tract infection after allogenic blood transfusion are revealed as well [6-9]. The above-mentioned problems will increase hospital cost. Therefore, to prevent the perioperative total blood loss is an important issue and needs to be resolved.

Nevertheless, Intravenous (IV) Tranexamic Acid (TXA) may cause unwanted side effects with increasing dose that require

medical attention, such as gastrointestinal disturbances, allergic dermatitis, giddiness, hypotension, venous and arterial thrombosis or thromboembolism and neurologic symptoms including visual impairment, convulsions, headache, mental status changes, myoclonus [10,11]. The concentration of TXA in joint fluid already prove to be the same to the serum concentration [12]. Several studies revealed that Intra-Articular (IA) TXA can reduce systemic absorption of TXA to only 30 percentages which compared to the equivalent IV dose of TXA [13-15]. If we could use the less equivalent IV dose of TXA to reach the effectiveness of hemostatic reaction, the side effect of systemic TXA can be reduced or avoided. Therefore, we reviewed the histories of patients receiving unilateral primary TKA in our hospital from May 2013 to June 2016. Our study hypothesis is IA TXA only has the same effect comparing to the combined therapy with IA and IV TXA in total blood loss in patients undergoing unilateral primary TKA. This is a retrospective study and approved by IRB committee of Kaohsiung Veterans General Hospital (VGHKS17-CT4-13).

Materials and Methods

We reviewed the histories of patients who were accepted unilateral primary cemented Total Knee Arthroplasty (722 cases and 782 knees) from May 2014 to June 2016 at Kaohsiung Veterans General Hospital. We divided these 782 knees into three groups: IA TXA only (305 knees), combination therapy of IA and IV TXA (125 knees), and without TXA (352 knees) using. The dose of IA TXA is 2gm and the dose of combined therapy is IA TXA (2gm) and IV TXA with different regimen depends on operator. All patients were operated by experienced joint surgeons under spinal or general anesthesia using pneumatic tourniquet and similar cemented posterior stabilized type implant. Patient was put in the supine position with thigh tourniquet using and inflating before incision to 230-300 mmHg. The tourniquet was deflated before or after wound closure base on the surgeon preference. Drainage tube was not used in every case and was according to the surgeon preference.

We used Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) formula to calculate perioperative total blood loss. This formula is often used in orthopedic surgery as a standardized method for calculating blood loss to prevent the intra-operative blood loss artificial calculation bias and invisible blood loss [16-18]. Our exclusion criteria included known TXA allergic history, coagulation disorder, and missing data for calculation of OSTHEO formula and TXA dose administration.

Statistical Analysis

We used Chi-square test and Kruskal-Wallis equality-of-populations rank test to confirm the demographic data of gender and age between these three groups were without significant difference. The total blood loss in the three groups was analyzed by Kruskal-Wallis equality-of-populations rank test. The effects of age, gender, groups and drain placement on blood loss were analyzed by Generalized Linear Model regression. The value of P was lesser than 0.05 being considered to have significant result.

Results

Of the total 782 knees in the study, there were 566 women (72.38%) and 216 men (27.62%). The IA only TXA group included 305 knees with 220 women and 85 men with a mean age of 70.34 ± 8.10 years. The combined IA and IV group has 125 knees including 95 women and 30 men with a mean age of 70.03 ± 9.25 years. Without any TXA group has 352 knees (251 women and 101 men) with a mean age of 69.55±8.03 years. The demographic data revealed no significant difference over gender and age between these three group by Chi-square test and Kruskal-Wallis equality-of-populations rank test respectively (Table 1).

	Group			P value
	None	IA	IA & IV	
No.	352	305	125	
Gender				0.597*
female	251	220	95	
male	101	85	30	
Age	69.55 (8.03)	70.34 (8.10)	70.03 (9.25)	0.402**
* Chi-square test ** Kruskal-Wallis equality-of-populations rank test				

Table 1: Demographic data.

Mean total blood loss in the group of IA-only TXA was 446.22±266.45ml, and 522.99 ± 304.52ml in the IA and IV TXA using group. Besides, mean blood loss in without TXA using group was 678.17±319.04 ml. The Result of Kruskal-Wallis equality-of-populations rank test of total blood loss disclosed the IA group had significant decrease of total blood loss in the group comparing to the group of none or combined IA and IV TXA group. (P=0.001). Combined IA and IV TXA group had significant less blood loss than the group not using any TXA. (P=0.0001) (Table 2).

Group	Mean	Sta. Dev.	P value
None	678.17	319.04	0.0001
IA	446.22	266.45	
IA & IV	522.99	304.52	

Table 2: Result of Kruskal-Wallis equality-of-populations rank test of total blood loss between different groups.

In generalized linear model, the result of total blood loss of male revealed significantly more than female. (P=0.008). Total blood loss in the group of IA-only showed significant less blood loss compared with the group of IA combined IV TXA (P=0.016) and the group of none of TXA using (P=0.000). The total blood loss with drainage tube did not relate to more total blood loss than without drainage tube. (P=0.019) (Table 3).

	Coef.	Std. Err.	z	P>z	[95% Conf.]	[Interval]
Age	-0.87	1.29	-0.67	0.500	-3.41	1.66
Gender (male vs. female)	63.61	23.92	2.66	0.008	16.73	110.50
None vs. IA & IV	137.70	31.41	4.38	0.000	76.15	199.26
IA vs. IA & IV	-76.05	31.48	-2.42	0.016	-137.75	-14.36
Drain (yes vs. no)	-87.01	37.19	-2.34	0.019	-159.91	-14.12
_cons	652.34	101.73	6.41	0.000	452.95	851.73

Table 3: Generalized linear model regression of age, gender, groups and drain on total blood loss.

Discussion

Many interventions including intraoperative hypotension, autologous blood transfusion, intraoperative blood salvage, navigation, Minimally Invasive Surgery (MIS), use of Tourniquet, IV or IA TXA, antifibrinolytic agent are tried to control the perioperative total blood loss [19-22]. In all of the interventions for reducing total blood loss, tranexamic acid medication seems to be a convenient, effective and not expensive method. TXA is a competitive inhibitor of plasminogen activation. If the serum concentration of TXA up to 10-15 mg/mL, it can decrease fibrinolytic activity of plasmin by approximately 80 percentages. This reaction can stabilize formed clots, reduce active bleeding and improve the reperfusion related hyperfibrinolysis after off use of tourniquet. More than 95 percentages of TXA can rapidly excrete to urine in 24 hours in people whose renal function have not impaired. The half time of TXA showed about 3 hours [12]. Thereby, several randomized control trials for patient undergoing primary TKA found that no matter use of intravenous IV TXA only, intra-articular IA TXA only or combination therapy with IV and IA TXA, all of them show significant results on reducing total blood loss [23-25]. A Systematic Review and Meta-analysis analyzed published reports which were collected from several electronic databases, they proved the significantly fair efficacy of IV TXA in simultaneous bilateral TKA patients and also provides the evidence of the safety owing to no significant differences in length of stay, operation time or the incidence of adverse effects such as infection (P = 0.42), deep venous thrombosis (P = 0.88) and pulmonary embolism after TXA medication [26]. IA TXA can lead only 30 percentages systemic absorption of the same dose of IV TXA and the pharmacokinetics study also proved the concentration of TXA in joint fluid already prove to be the same to the serum concentration [12-15]. Therefore, the safety and efficacy of IA TXA can be thought to have the equal results as IV TXA. May JH's study randomized 131 patients to comparing the IV with IA TXA of total blood loss prevention in TKA by Nadler formula. They concluded IA TXA is not inferior to IV TXA in decreasing blood loss and blood transfusion rate in TKA without increasing complications [27].

Several researches rendered better effectiveness for reducing perioperative blood loss by combined therapy (IV and IA TXA) use than IV use alone and placebo. Besides, no thromboembolic complications were observed in both two groups. Our doses of combined therapy and IV or IA alone are lower or similar to these studies, our TXA dose can be considered to have similar safety [25]. The result of our study also revealed combined IA and IV TXA group had significant less blood loss than the group not using any TXA. (P=0.0001) (Table 2). One 2014 study, which also compared combined therapy with IA TXA group, total of 126 patients were randomly allocated to topical group, combined group, or control group. The result of statistics found the mean total blood loss, which was calculated by Nadler formula, was 126 mL in the combined group lower to the topical group. However, there was no significant difference between the 2 groups (P=0.063). Small number of cases may cause limited result and bias of this study. Our study reviewed 782 knees, who were accepted unilateral primary cemented total knee arthroplasty, the mean estimated total blood loss is calculated by OSTHEO formula, which can be avoid to ignore the hidden blood loss. This formula uses perioperative hemoglobin values and correlates them with the blood management techniques. Besides, it also compares the calculated total blood loss with the estimated total blood loss. The combined group didn't have the better effectiveness of reducing blood loss then the IA TXA along group which was clearly found in our study. Although the combined TXA has the significant efficacy of blood preservation and no obvious complication is noticed which is proved in several published studies [25,28,29].

Eun-Kyoo Song, presented one randomized control trial to assess the combined therapy with IV and IA TXA in the patient who accepted primary navigational TKA. They collected 200 patients and randomly divided in one of the 4 groups as below: control, IV, IA, and combined IV and IA groups. This study used evident loss from drain, total blood loss based on Gross method as well as hemoglobin balance method to evaluate the perioperative total blood loss. The conclusion showed the blood loss in combined group (535.55 mL) is not significantly less than IV (585 mL) or IA group (514 mL). The postoperative swelling or transfusion rate of combined group is also not superior to IV or IA TXA only group. They suggested not using additional amount of TXA because the combined regimen may not be clinically useful [30]. Our result also found that it's unnecessary to administrate additional IV TXA in the same effectiveness of blood reducing. Despite the incidence of complication which is related to systemic absorption of TXA needs further research to get detail data. The limitation of our study included we didn't collect underlying diseases to realize the bleeding tendency, anticoagulant or antiplatelet medication of patient. The post-operative complication, functional result data such like postoperative range of motion, the condition of knee

swelling of the patients are not recorded. Our IA TXA dose is 2gm, but the regimen of IV TXA, which the maximum dose of IV TXA is lesser than 1.5gm, is variable depending on operator.

The association of total blood loss in TKA with gender is controversial. One retrospective study evaluated the perioperative blood loss and the hidden blood loss following TKA by Gross formula calculation. The result found that no significant differences between gender in hidden blood loss [31]. However, one prospective randomized study also tried to find out the factors affecting blood loss in total knee arthroplasty. The study rendered the mean volume of blood loss and of transfused blood was larger in male than female patients. But, this factor didn't reach statistical significance. But higher pre-operative hemoglobin value and the blood transfusion rate are impressed in male patients. Despite having no statistically significant result, the author thought gender may be a factor affecting blood loss in TKA [32]. The result of our study found that men have more perioperative total blood loss than women who accept TKR (P=0.008). Gender in our study is considered to be an independent risk factor in the total blood loss. The statistical analysis in our study showed no more total blood loss in the patient who had drainage tube compared with the patient who didn't have drainage tube. One meta-analysis study analyzed eighteen studies involving 3495 patients who undergoing elective hip and knee arthroplasty and reported closed suction drainage would increase blood transfusion without major benefits. However, increasing frequently reinforcement of wound dressings in the group managed without drains is noticed. This study may ignore the invisible loss over the dressing [33]. Reviewed published studies, which compared closed-suction drain in total joint arthroplasty with no drain placement, they rendered the group without drain placement has persistent wound oozing and this problem has significantly more than the group with drain [31-35]. Besides, some studies evaluated the total blood loss of total joint arthroplasty by calculating the change of hemoglobin and reported no significant difference between two groups with drain and without drain placement [34, 36-38]. The patients managed without drain may have invisible blood loss when we don't calculate them. And this accounts for the result of our study why the patients with drain don't have more total blood loss than the patient without drain.

Conclusion

Intraoperative intra-articular tranexamic acid is an effective and convenient method to reduce total blood loss in the patient undergoing primary Total Knee Arthroplasty and it disclosed better efficacy than perioperative combined therapy of IV and IA tranexamic acid in this study. Male patients have more total blood loss compared with female patients, gender may be considered to be an independent factor in TKA.

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