Abstract:

Introduction:

Blood loss that necessitates blood transfusion is one of the most frequent complications of major spinal surgeries. This adds to the time and cost of such surgeries, and also it is related with some potential risks including hypersensitivity reactions and blood transmitted infections, and increases the general anesthesia's risks. In recent years various prophylactic antifibrinolytics have been discussed among researchers as a solution for decreasing perioperative blood loss in orthopedic and spinal surgeries. One of such fibrinolysis inhibitors is Tranexamix acid which is considered both safe and effective and is the subject of this research. This study has been designed to evaluate the efficacy and safety of prophylactic Tranexamic acid in decreasing perioperative blood loss.

Methods:

40 patients undergoing major spinal surgeries were selected and divided into 2 groups; the experimental group receiving Tranexami acid and the control group treated with Normal Saline. In the first group,10 mg/kg of Tranexami acid was given 20 minutes after inducing the anesthesia as loading dose followed by 0.5 mg/kg/hour of the same medicine until skin closure. The control group received equal amounts of normal saline as placebo. The study was a double blind trial. Intraoperative blood loss was recorded by suctioned fluids and sponges weights. The blood loss during first and second days post operation was recorded of drains. Patients had been monitored for any potential complications related to Tranexamic acid during the first month after operation; thromboembolic events including such as ischemic heart attacks, cerebrovascular accidents, deep vein thrombosis, pulmonary emboli and renal failure.

Results:

In the case group, the mean of intraoperative, first day, and total blood loss was 574 cc, 80.5 cc, and 669.5 cc respectively which shows around 40% improvement over the control group. In Control group, the mean of interoperative, first day, and total blood loss was reported as 797 cc, 124 cc, and 921.5 cc respectively. The second day blood losses in both groups were limited to one patient. None of possible confounding factors including age, gender, instrumentation, operation length and number of spine levels undergoing surgery was meaningfully impressing the results and , and the mean of blood loss was always less in the experimental group. Finally it should be noted that none of the patients, neither in case and nor in control group, experienced complications related to Tranexamic acid during the one month follow up period.

Conclusion:

Statistical analysis does not show significant differences between the two groups, considering the all factors of age, sex, number of operated levels, instrumentation and duration of surgery. Although the results are not against the previous studies but based on these results we can't claim that Tranexamic acid is effective in preventing of blood loss, but in comparison with other studies, Tranexamic acid seems to be safe to be considered in spinal surgeries with significant excepted blood loss. We suggest further studies on Tranexamic acid's efficacy and safety in larger scales.

Keywords:

Spinal surgery, Blood loss, Tranexamic acid

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Background

Excess bleeding is a common complication in spinal surgeries which may lead to blood transfusion. Blood transfusion is related to potential risks as Alloimmunisation and blood transmitted infection such as HIV, CMV and bacterial sepsis, although modern screening methods are available. Also blood transfusion seems to be related with surgical site infection. It may increase the duration of surgery and cause pulmonary and cerebral edema due to fluid shift and hypovolumic shock.[1] In addition, allogenic blood transfusion costs about 250 USD per blood unit.[2]

Different techniques have been experienced to reduce the blood loss, including autologus blood donation before operation, appropriate positioning of patient, inducing abdominal muscle paralysis for minimizing the intra-abdominal pressure, epinephrine injection in paraspinal tissues, induced controlled hypotension, and antifibrinolytic agents. Antifibrinolytic agents have been effectively used in cardiac, orthopedic and hepatic surgeries previously.[3]

Aprotinin was the first antifibrinolytic agent which got used, but in 2006 its administration became controversial and in 2007 stopped due to its reported complications such as renal failure, myocardial infarction, cerebrovascular accidents and deaths. Efficacy and safety of some of the other antifibrinolytic agents, including tranexamic acid, have been studied during recent years.[4]

Tranexamic acid

Tranexamic acid (trans-4-aminomethyl-cyclohexane-1-carboxylic acid) is a synthetic lysine analog and competitive inhibitor of plasminogen and plasmin. Its half-life by normal renal function is about 80 minutes. It acts by saturating lysine binding sites on plasminogen and detaching plasminogene of fibrin which lead to inhibition of fibrinolysis. TA like other antifibrinolytics inhibits proteolytic effect of plasmin.[4]

TA is used in non-surgical situations such as bleedings due to leukemia, ophthalmic bleedings, recurrent hemoptysis and hereditary angioneurotic edema, and surgical purposes such as cardiac surgeries.[4]

Adverse effects of TA include head ache, weakness, confusion, blurred color vision and allergic reactions, and its main contraindications are active intravascular clotting process, hematuria, subarachnoid hemorrhage, severe renal failure and hypersensitivity.

TA may interact with frequently used drugs such as suppressors of central nervous system, tricyclic antidepressants, Fluoxetine, oral contraceptives pills, insulin, carbamazepine and alcohol.[3, 5]

The main concerning point about TA and other antifibrinolytic agents is potential increased risk of thrombotic events.[4]

Study design

According to increasing frequency of spinal surgeries and considering previous studies on different ways to reduce blood loss, we designed a prospective, double blinded, clinical trial, to evaluate the efficacy of tranexamic acid on reduction of blood loss and its safety, in major spinal surgeries.

Our study has included these procedures as major spinal surgeries:

1- Laminectmoies at 2 levels of spine or more
2- Corrective surgeries of spondilosythesis
3- Any spinal surgery including spinal fusion

Inclusion and exclusion criteria

We defined inclusion and exclusion criteria due to TA contraindications and study's limitations. (Table no. 1)

Inclusion criteria :	The all patients more than 20 and less than 70 years old age who are candidates for major spinal surgeries including : 1- Laminectmoies at 2 levels of spine or more 2- Corrective surgeries of spondilosythesis 3- Any spinal surgery including spinal fusion
Exclusion criteria:	Less than 20 years old age
	More than 70 years old age
	Anticoagulant therapy
	Underlying coagulopathy
	Ischemic heart disease
	Hepatic failure
	TA contraindications - Severe renal failure - Active intravascular clotting process - Recent thromboembolic events - Blurred color vision - Subarachnoid hemorrhage
	Alcoholism
	Drug history including : - CNS suppressors - TCA - Fluoxetine - OCP - Insulin - Carbamzepine

We selected 40 patients in Shahid Rajaee university hospital of Qazvin, Iran between January and august of 2011, according to inclusion and exclusion criteria and results of premier tests which included: CBC diff, Hb, Hct, BUN, Cr, ALT, AST, PT, PTT, BT and CT.[1]

Patients got divided into 2 groups of 20 patients, by nurse anesthetist team and each patient identified by a digit. The first group received TA and the second Group received normal saline in the same amounts. Nor surgeon neither patient was aware the patient is receiving TA or placebo.

Dosage:

Due to limited number of cases, it was not possible to compare between different doses of TA. In our study, the patients in TA group received 10mg/kg TA, intravenous, 20 minutes after induction of anesthesia as loading dose and then 0.5 mg/kg/hour, intravenous, during operation, until skin closure.

We estimated intraoperative blood loss by suctioned fluids and weighting the used gauzes, and post operative bleedings by drains, and recorded all cases of blood transfusion. Patients received packed cell if they had Hb less than 7 or less than 9 if they were also hypotensive.

Systolic blood pressures were kept between 90-110 mmHg during operation, and between 90-120 mmHg after in ward.

The patient's consciousness, respiratory rate, force of limbs and diameter of legs examined daily during hospitalization and they had been asked for chest discomfort or pain. After discharge, we followed the patients by regular visits at hospital's clinic, during first month after surgery, , looking for cases of MI, CVA, ATN, DVT or PE.[2]

Results:

Intraoperative, first day post operation and second day post operation bleedings and all cases of blood transfusion recorded and got compared statistically.

First of all, two groups examined for being homologous as age, gender, number of operated levels and number of operations including fusion. In TA group patients were between 28 and 67 years old with mean of 43.7 years and in control group they were between 32 and 67 years old with the mean of 49.85 which were not significantly different(P=0.093). 7 patients of the TA group and 5 patients of placebo group were male, which had not significant difference (P=0.731). 5 patients of TA group and 4 patients of control group had been operated at 3 levels or more, without significant difference (P=1.0). 10 patients of TA group and 12 patients of control group had diagnosis of disc herniation, canal stenosis and spondylolisthesis and underwent fusion surgery and 10 patients of TA group and 8 patients of control group had diagnosis disc herniation and canal stenosis, which were not significantly different(P=0.751).(Table no.2)

Then two groups compared by bleedings. The patients of TA group had lost (574(377.6) ml) during operation, (80.5(58) ml) during first post operation day. The patients of placebo group had lost (797 (543.7) ml) during operation, (124 (85.5) ml) during first day after surgery. None of the intraoperative bleedings (P= 0.137) and bleedings of first post operation day (P=0.067) had significant difference but both means were lower in TA group. Only one patient in each group went on bleeding during 2nd day post operation, so we did not compare

the bleedings of 2nd day separately and just considered them in total blood loss. The patients of TA group had lost (669.5(418.32) ml) and the patients of control group had lost (921.5(584.65) ml) totally, which although lower mean in TA group had no significant difference. None of the confounding factors including age (more and less than 50), gender, number of operated levels(less than 3), and length of the operation (less and more than 3 hours) and fusion, could make significant difference, although lower means in TA group. The results did not compared in the patients who had been operated in 3 levels or more, because of limited number of cases.

8 patients, 3 of TA group and 5 of control group had received allogenic blood. One of the patients of TA group received 2 units of packed cells and the two others received 3 units. One patient of the control group received 1 unit and the four others received 2 units.

The mean of blood transfusion in TA group was (0.40 (0.99) unit of packed cells) and in control group was (0.45 (0.82) unit of packed cells). Although lower mean in the TA group, the results did not lead to a significant difference (P=0.86). (Table no.3)

Considering the age(less or more than 50) and number of operated levels (less than 3) as confounding factors, the means were lower in TA group but not significantly. The means in female patients and who had undergone fusion were slightly more in TA group but without statistical meaning. Blood transfusion cases were limited to female patients and the patients who had undergone fusion.

The patients of the TA group had undergone mean of (3.07(0.466) hour) under operation. The mean of operation's duration in the placebo group had been (3.475(0.49) hour). It has been significantly less in the TA group (P=0.013). (Table no.4)

Mean of The blood loss at operation (P=0.002) and the first day after operation (P=0.003) and total blood loss (P=0.001) and their need to blood transfusion (P=0.005) were significantly higher in the patients who had undergone fusion.

None of the patients, nor in TA and neither in placebo group, experienced DVT, PE, CVA, MI, , or had raise in BUN or serum Cr more than normal levels, or died, during the first month after surgery.

Blood loss	Group	Number	Mean	SD	
At operation	Tranexamic acid	20	574.00	377.58	
	Placebo	20	797.50	543.73	P=0.139
During first post operation day	Tranexamic acid	20	80.50	57.99	
	Placebo	20	124.00	85.49	P=0.067
Total blood loss	Tranexamic acid	20	669.50	418.32	
	Placebo	20	921.50	584.65	P=0.125

	Group	Number	Mean	SD
Units of packed cells	Placebo	20	.45	.82
	Tranexamic acid	20	.40	.99
				P=0.86

	Group	Number	Mean	SD
Operation's duration	Tranexamic acid	20	3.07	.46
	Placebo	20	3.47	.499
				P=0.013

Discussion

Our study has been a prospective, double blinded clinical trial. All of the surgical procedures had been done by one surgeon and one team of surgery and anesthesia. All of the patients with renal failure excluded because of probable effect on bioavailability of TA.

In this study means of intraoperative, first post operation day, and total blood loss were lower in the TA group, considering confounding factors including age, gender, number of number operated levels, fusion and duration of operation. According to limited number of cases and the results of previous similar studies the differences, the results are considerable although not being significant statistically.

The patients receiving TA had less need to blood transfusion also, without statistical significance. Blood transfusion cases were limited to female patients and who had undergone fusion surgeries. More need to blood transfusion in female patients might be related to underlying lower levels of Hb. None of the confounding factors which mentioned above, leaded to a significant difference in need to blood transfusion. Patients of TA group had passed less under operation significantly, which is important because of imposed risks of exceeded length of anesthesia.(P=0.013)

The patients who underwent fusion surgeries had lost more blood and had more need to blood transfusion significantly, which might be related to more expanded dissection of paraspinal muscles and tissues.

We had no report of drug induced complications.

Altogether the results of our study have been compatible with the results of previous researches, both in efficacy and safety.

Suggestions

According to safety and efficacy of TA, concluded of this study and in comparison with previous ones, we strongly recommend considering prophylactic administration of

tranexamic acid in patients who are undergoing major spinal surgeries, especially in fusion surgeries and female patients.
Studies on efficacy and safety and dose adjustment of prophylactic TA in patients with renal failure would be beneficial to prevent complications of huge blood loss and worsening of renal function in these patients. Greater, multi-centric and dose dependent studies on the efficacy of TA is also suggested and may lead to a defined practical protocol.

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