EFFICACY OF TRANEXAMIC ACID IN COMBINATION WITH CONVENTIONAL THERAPY FOR TREATMENT OF PPH

Ayinur Nahar Hamid[1] Rokeya Begum[2]

Summary

Haemorrhage is the leading cause of maternal mortality, accounting for about 35% of all maternal deaths. About 14 million women around the world suffer from Post Partum Hemorrhage (PPH) every year. Of them, about 2% die with an average interval of 2-4 hrs from onset of bleeding. Tranexamic Acid (TXA) is the most effective of the available anti-fibrinolytics, which has been shown to be very useful in reducing blood loss and incidence of blood transfusion in different surgeries. The study was done to see the efficacy of injectable tranexamic acid in addition to conventional treatment in control of atonic PPH. In this study, women having atonic PPH following vaginal delivery were grouped into two, A & B. Group A received 2 amp inj.TXA (Tranexamic acid) i.v immediately after diagnosis of PPH and Group B received 10ml distilled water i.v. Both groups received all other necessary measures for control of PPH and outcomes were recorded in a preformed data collection sheet. All data were analyzed by computer based software Statistical Packages for Social Science (SPSS) version 15.The results showed that tranexamic acid significantly reduced the volume of blood loss in atonic PPH, 1141.23±489.91 ml in study group versus 1365.25±428.22 ml in control group.PPH control within 2 hr with medical therapies occurred more in TXA group (88.09%) than in control group (57.14%). Invasive procedures were less required in TXA group than in control group ,condom catheter in 4 pt. (9.52%) compared to 11(26.19%) in control group. Hysterectomy was done in 1 case of TXA group compared to 7 cases of control group. TXA also significantly reduced the necessity of blood transfusion in PPH, 26.19% in TXA group compared to 54.76% in control group. So one gm i.v. tranexamic acid given along with other conventional measures at the diagnosis of atonic PPH significantly reduces the amount of blood loss, requirement of blood transfusion, necessity of invasive procedures.

Key words: Tranexamic acid; Post Partum Hemorrhage; Vaginal delivery.

Introduction

Every minute of every day, a woman dies in pregnancy or child birth. The biggest killer is Post Partum Hemorrhage (PPH) the successful treatment of which is a challenge for both the developed and developing worlds. Management of PPH involves early recognition, assessment and resuscitation. Various methods are available to try to stop the bleeding from pharmacological methods to surgical methods [1].

Tranexamic acid (TXA) is the most effective of the available anti-fibrinolytics, which as a class provide worthwhile reductions in blood loss and need for allogeneic red cell transfusion [1]. Tranexamic acid (TXA) is a potent antifibrinolytic agent that blocks lysine binding sites on plasminogen molecules and inhibits conversion of plasminogen to plasmin. Plasmin is responsible for dissolution of fibrin clots. As TXA inhibits formation of plasmin, it enhances the effectiveness of the patient's own haemostatic mechanisms. Consequently clot breakdown (Fibrinolysis) is inhibited and excessive or recurrent bleeding is reduced [2]. Intravenous administration of tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery, orthotopic liver transplantation, total hip or knee arthroplasty, and urinary tract surgery [3]. Tranexamic acid has been shown to be very useful in reducing blood loss and incidence of blood transfusion in these surgeries. In this study, efficacy of intravenous tranexamic acid was investigated in treating atonic PPH following vaginal delivery.

1. Assistant Professor of Obstetrics and Gynaecology Chittagong Medical College, Chittagong
2. Professor of Obstetrics and Gynaecology Chittagong Medical College, Chittagong

Correspondence: Dr. Ayinur Nahar Hamid
Email: anh_ctg@yahoo.com
Cell : 01819 610106

Materials and methods

It was a prospective randomized clinical study done in Obstetrics and Gynaecology department of Chittagong Medical College Hospital in one year from July 2012 to June 2013. Total 84 women were included in the study who were clinically diagnosed with atonic PPH following vaginal delivery. Women for whom there was a clear contra-indication for TXA e.g. myocardial infarction, stroke, deep vein thrombosis, renal failure and women having PPH due to traumatic cause, retained placenta , blood coagulation disorder were excluded from the study. Diagnosis of PPH was made when lower long skirt (Petticoat) of the parturient was completely soaked with blood, amount of clotted blood following delivery measures about two handful (Ajla) or a sanitary pad completely soaked with blood has to be changed frequently in less than two hour [4]. Diagnosis of atonic PPH was made when uterus was found flabby on abdominal palpation following delivery of placenta. Randomization was done by the rule of odds and even i.e. all odd cases were given TXA 1 gm (2 ampoule each containing 500mg/5 ml) iv single dose and even cases received 10 ml of distilled water at the beginning of diagnosis of atonic PPH [3]. All cases also received conventional measures for management of PPH including, uterine massage, inj. Oxytocin 20 unit in 1 liter of fluid i.v. @ 30d/min. Inj. Ergometrine 0.2 mg was given i.m. if woman did not have Pre-eclampsia, Hypertension or cardiac disease. Tab. Misoprostol (200µg) 5 tablet was given per rectally as 3rd line treatment if woman had no bronchial asthma or high fever. Baseline information was collected from both study & control group in a preformed data collection sheet. Women were followed up till control of PPH and outcome was obtained in the same data collection sheet.

Primary outcome was measured by the proportion of women whose PPH was controlled within 2 hr with medical therapies only. When PPH continued beyond 2 hr, it was regarded as uncontrolled. Secondary outcome was measured by proportion of women who need mechanical intervention like condom catheter; surgical intervention like hysterectomy. Total volume of blood loss in each patient was assessed by clinical estimation (Considering saturated sanitary pad 100 ml, blood full kidney dish or two handful of clotted blood as 500ml, PPH limited to bed only 1000ml, PPH spilling onto floor 2000ml). Number of units of blood transfusion given was also recorded in data collection sheet. All data were compiled, checked and edited after collection, then data was analyzed by computer based soft ware Statistical Packages for Social Science (SPSS-15 Chicago, IL,USA). The results were expressed as frequency, percentage and mean ± SD for continuous variable like age, parity, gestational age. Quantitative data (Age, parity, gestational age, pulse, systolic BP, diastolic BP, estimated volume of blood loss) was analyzed by Student's t test. Categorical variables (Use of uterotonic drugs, PPH controlled in 2 hr, need of intervention and blood transfusion in both groups) was analyzed by Chi square (χ^2) test. Statistical significance was set at p value less than <0.05 and confidence interval set at 95% level.

Observation and Results

The subject characteristics in two groups were similar with no statistically significant difference between age, parity, gestational age at delivery (Table I).

Active Management of Third Stage of Labour (AMTSL) was done in all participants except 2 women in TXA group and 3 women in control group (Table II).

Uterotonic drugs: Table III shows the use of different uterotonic drugs in both groups, the difference between two groups was not statistically significant.

Estimated volume of blood loss was significantly lower in tranexamic acid group than in control group (1141.23±489.91 vs 1365.25±428.22 ml) (Table IV).

Thirty seven 37(88.09%) women in tranexamic acid group had PPH control in 2 hr, while 5 (11.91%) need further non-medical intervention. In control group, PPH stopped in 24(57.14%) women in 2 hr, while PPH continued in 18 (42.86%) women after 2 hr in spite of uterotonic drugs. 4 women in TXA group and 11 women in control group needed condom catheter which is statistically significant. TXA significantly reduced

the need of surgical intervention (1 pt, in TXA group versus 7 pt. in control group, p value <0.05). Blood transfusion rate was significantly lower in TXA group than placebo group (p value 0.001). Number of units of blood required was also significantly lower in TXA group than placebo group (Table V).

Table I : Distribution based on subject characteristics in two groups (n=84)

Groups	Age (year) (mean ±SD)	Parity (mean ±SD)	Gestational age (week) (mean ±SD)
Study (n=42)	24.47±3.92	2.11±1.02	38.8±1.73
Control (n=42)	23.92±4.16	2.23±0.84	38.57±1.32
p- value	0.53	0.47	0.49

Table II : Comparison of AMTSL done in two study group (n=84)

AMTSL done	Group A (Case) (n=42) No. (%)	Group B (Control) (n=42) No. (%)	p value
Yes	40(95.24%)	39(92.86%)	0.64^{ns}
No	2(4.76%)	3(7.14%)	
Total	42 (100.0%)	42 (100.0%)	

Table III : Comparison of uterotonic drugs in two study group (n=84)

Drugs	Group A (Case) (n=42) No. (%)	Group B (Control) (n=42) No. (%)	p value
Oxytocin+ Ergometrine+ Misoprostol	33 (78.57%)	32 (76.19%)	0.79^{ns}
Oxytocin+ Misoprostol	09 (21.43%)	10 (23.81%)	
Total	42 (100.0%)	42 (100.0%)	

Table IV : Comparison of estimated volume of blood loss between two groups (n=84)

Blood loss (ml)	Group A (Case) (n=42)	Group B (Control) (n=42)	p value
Mean±SD	1141.23±489.91	1365.25±428.22	0.02s

Table V : Comparison of outcome variables between two groups (n=84)

Variables	Group A (Case) (n=42) No. (%)	Group B (Control) (n=42) No. (%)	p value
PPH control in 2 hr with medical therapy	37 (88.09%)	24 (57.14%)	0.01
Mechanical intervention (Condom catheter)	4 (9.52%)	11 (26.19%)	0.01
Surgical intervention (Hysterectomy)	01(2.38%)	07(16.67%)	0.02
Blood transfusion needed	11 (26.19%)	23(54.76%)	0.001
Units of blood transfusion needed (Mean±SD)	0.286±0.554	1.286±0.289	0.001

Discussion

Post Partum Haemorrhage (PPH) is a clinical problem of indisputable importance to patients, clinicians and to those interested in achieving equity in reproductive health. PPH can transform a normal woman in labour to a critically ill patient within minutes. The management of such a patient is a real test for the thought processes, resources, organizational effort and the education of a labour ward and its staff [5].

Introduction of an effective drug for treatment of atonic PPH is a key to achieve safe motherhood. Tranexamic acid is a potent inhibitor of fibrinolysis was first reported by Okamoto in 1962 [6]. Since then TXA has been widely used for treatment of various types of bleeding, e.g. menorrhagia, traumatic bleeding, during and after surgical procedures like coronary artery bypass, liver transplantation, total hip or knee arthroplasty. TXA was shown to be very useful in reducing blood loss and incidence of blood transfusion in these surgeries [3]. Several studies also demonstrated the efficacy of TXA in decreasing blood loss following vaginal delivery, during and after Caesarean delivery [6-13].

In previous studies & trials, dose regimens of TXA vary widely. Movafegh A et al used tranexamic acid as 10 mg/kg body weight in 200 ml normal saline [10]. Yang et al used tranexamic acid as 1gm and 0.5 gm dose in 3rd stage of labour [12].

Ducloy-Bouthors A. et al used high dose of tranexamic acid (4 gm loading dose over 1 hr followed by 1 gm/hr over 6 hr [13]. In emergency situation, the administration of a fixed dose is more practicable since weighing women with PPH would be difficult. Therefore a fixed dose of one gm TXA was used in this study regardless of weight of the women. Same dose was also administered in studies done by Gohel M et al, Shahid A et al, Gungordok K et al [3, 6,7]. It is within the dose range which has been shown to inhibit fibrinolysis and provide haemostatic benefit. On the basis of experience in surgery, the dose selected is efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg) [14].

The subject characteristics in both TXA and control group in present study were similar with no statistically significant difference between two groups regarding age, parity, gestational week, application of active management of 3rd stage of labour, use of uterotonic drugs etc. It is consistent with other studies previously done [6-13] .

In majority of studies previously done, blood loss was measured two hours postpartum. demonstrating significant reduction of blood loss after administering inj.TXA [6-12]. Present study also demonstrated that estimated volume of blood loss was significantly lower in TXA group (1141.23 ± 489.91 ml) than control group (1365.25±428.22 ml, p=0.02). The reason of larger volume of blood loss in present study was due to use of TXA after diagnosis of PPH when already 500ml blood was lost.

In present study, PPH controlled with medical therapies within 2 hr in 88.09% women of TXA group whereas in 57.14% women in control group, it is also highly significant (p=0.01).This finding corresponds with preliminary study in Tunisia by Halouani A. et al which showed 80% control of PPH with TXA loading dose and iv infusion along with uterotonics [1]. But in study by Ducloy-Bouthers et al, PPH stopped only after uterotonics and packed RBC transfusion in 93% of women in TXA group versus 79% of controls (P=0.016) [13].

Present study demonstrates that invasive procedures were significantly less in TXA group than control group (p value 0.02). In RCT conducted by Ducloy-Bouthers et al, invasive procedures were performed in 4 women in TXA group and in 7 women in controls (P=NS) [13]. In another study done by Ayedi M et al, no significant difference was found regarding invasive procedures in TXA and placebo group [15].

Various mechanical and surgical procedures may be adopted to stop PPH if medical treatment fails. In our institution, condom catheter is done if atonic PPH following vaginal delivery is not controlled with uterotonics. If bleeding continues till condom catheter and medical therapies, laparotomy is done. Mattress suture may be given and uterine artery ligation can be done if surgeon is skilled enough to do so. But these techniques are used here to control PPH during Caesarean section. If atonic PPH following vaginal delivery is not controlled with drugs and condom catheter, peripartum hysterectomy is done to save the life of the patient. Hysterectomy should not be delayed until the patient is in extremes or while less definitive procedures of which the surgeon has little experience are attempted. Performing hysterectomy in a timely fashion is therefore a sign of maturity of the team looking after the patient [5]. This led to high number of hysterectomy done in our study. Though hysterectomy was done in multipara women, it was a permanent disability for them with loss of menstrual and reproductive function. As TXA significantly reduced the number of hysterectomy in women with PPH, it reduced the morbidity due to hysterectomy.

Regarding blood transfusion, TXA group required significantly less blood transfusion (26.19%) than control group (54.76%) [p=0.001]. It is consistent with Tunisian preliminary study showing 20% patient requiring blood transfusion after TXA administration [1]. Even number of units of blood transfusion was significantly lower in TXA group (0.286 unit) than control group (1.286 unit) [p=0.001].Similar results were also obtained in trial by Ayedi M et al in 2011[15]. Blood is a scarce and costly resource and blood transfusion

has several rare but serious adverse effects. Worldwide, most people do not have access to safe blood. Even when it is available, it can transmit potentially fatal viral infections like HIV, hepatitis B and hepatitis C virus. As tranexamic acid safely reduced the need for blood transfusion in surgery, it has important health and economic implications in high, middle, and low income countries [16].

Administration of TXA in parturient women may raise concerns about thrombo-embolism. However previous studies have demonstrated the safety of this drug for use both in pregnant and non-pregnant patients [6-13]. In present study, none of the women showed any sign or symptom of thrombo-embolic events. Even minor side effects, like nausea, vomiting, diarrhea were not reported in any woman. No maternal death occurred in either group. Because women of both groups delivered inside the hospital and were promptly managed by an energetic and well-organized team to control PPH and to save the lives of the patients.

All the trials previously stated considered the use of tranexamic acid in the prevention of postpartum bleeding, mostly before giving incision for Caesaeian section [6-11]. Only Yang et al used TXA before expulsion of placenta in vaginal delivery [12]. Ducloy-Bouthers et al used high dose of intravenous TXA in women with PPH> 800 ml following vaginal delivery i.e., in the treatment of postpartum haemorrhage [13]. Halouani A. et al conducted a preliminary study in Tunisia since June 2012 on 30 patients of PPH following vaginal or Caesarian delivery who received TXA (Loading dose 1 g/10 minutes, then infusion of 1g/hour over 3 hours), in addition to the classic protocol including oxytocin and prostaglandins. 20% of their patients required a blood transfusion. The protocol succeeded in 80% of the cases [1]. Ayedi M et al in another study in Tunisia used TXA in atonic PPH following Caesaeian section after inefficacy of oxytocin injection and found that TXA safely reduced blood transfusions, duration of hospitalization, arterial ligation and hysterectomy [15].

Conclusion

Results of the study shows that TXA significantly reduced the volume of blood loss and controlled PPH within 2 hr along with uterotonics. It decreased the need of invasive procedures like condom catheter and hysterectomy in women with PPH. It also significantly reduced the proportion of women requiring blood transfusion for PPH and number of units of blood transfusion. So one gm iv tranexamic acid can be used as an additional measure along with conventional treatment of PPH.

Recommendation

Further studies should be carried out involving large number of participants in multiple centres to establish the efficacy and safety of tranexamic acid in treatment of PPH.

Disclosure

All the authors declared no competing interest.

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