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Preventive and therapeutic effects of tranexamic acid on postpartum bleeding

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ABSTRACT

Postpartum hemorrhage is among the leading causes of maternal mortality throughout the world. Severe blood loss contributes to the increased blood transfusion risk with its concerned inherent adverse events and therefore increased rate of emergency re-operative interventions such as arterial ligation or hysterectomy. It also can lead to protracted anemia, particularly in low or median income countries. Extended application of antifibrinolytic agents such as tranexamic acid has been customary for long years to stop or reduce blood loss in postpartum period. However, there are not enough reliable evidence to approve the real efficacy of these drugs. In this brief and summary review, we pointed to a few conducted studies. The PubMed was searched for keyword including postpartum hemorrhage, tranexamic acid, cesarean section, vaginal delivery, and blood loss prevention. The articles with language other than English were excluded from our review. We concluded that more convincing information is needed to determine the precise effects of tranexamic acid, and its benefits against adverse effects.

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Introduction

Pregnancy and childbirth impose 536000 deaths annually to women population throughout the world. 99% of this mortality rate belong to undeveloped and developing countries(1). Postpartum hemorrhage (PPH) is the leading or at least among the five top causes of death(2). 14 million women suffer from PPH each year, of whom 1-2% die within 2-4 hours after the onset of bleeding 2 to 11% of them show anemia later in their life (3) . In developed countries, PPH leads to 13% mortality rate of parturients(4). Blood transfusion may be needed for 1% of women with PPH after vaginal delivery, which can be elevated to 5% after cesarean section (CS). Blood transfusion has its own inherent adverse effects such as the danger of contamination with blood borne viruses (5). Risk of blood borne infection is displaced with adverse event ABO or other blood reactions in more developed countries in where complete blood screening is performed. (6,7). According to World Health Organization (WHO) definition, PPH occurs when the clinical amount of blood loss is about 500 ml after vaginal delivery or 1000 ml after CS. Even lesser volume (under 200 ml) of blood loss is considered as health threatening factor for parturient specially in low and median income countries with high prevalence of anemia (8). PPH usually occurs due to

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uterine atony, genital tract trauma, and remained placenta after baby delivery (9). Any experience which can increase uterine tension accounts as a risk factor for PPH, including primiparity, protracted and boosted labor, multiparity, placental abruption, anesthesia, obesity and macrosomia. That is interesting that a vast mainstream of women going through postpartum bleeding show few risk factors for their pregnancies, meaning poor prognosis of PPH occurrence (2). Aside from main causes of PPH, abnormal homeostatic alterations can facilitate bleeding during pregnancy. Homeostatic and coagulation systems undergo many changes during pregnancy. These changes moves the coagulation system to hypercoagulability state and reduced bleeding tendency (10). This is a physiologic protection against PPH happening. Up to now, it was thought that low level of fibrinogen was a consequence of severe bleeding, and a strong relation between low fibrinogen level and severity of PPH have demonstrated the critical role of fibrinogen in PPH (11). Extended tissue damage during delivery can cause fibrinolysis and coagulopathy leading to hemorrhage. Regarding to this concept, the role of antifibrinolytic medications, mainly tranexamic acid (TA) and aprotinin in PPH management is essentially emphasized (12). Some of randomized clinical trials (RCTs) showed the efficacy of prophylactic oxytocin in diminishing blood loss in PPH (8). Therapeutic steps of postpartum bleeding include uterotonic medications, blood replacement, and different surgical and invasive interventions such as intrauterine tamponed packing, arterial occlusion by artificial embolization, uterine compression by multiple sutures, arterial ligation, and eventually hysterectomy (8,13,14). Emergency hysterectomy following PPH perform is reported in 0.04 to 1.25% of deliveries (15). TA and other antifibrinolytic agents are proposed to stop or reduce bleeding during surgery in a systematic review (12), with 211 RCTs containing a total of 20781 participants. Relative risk of blood transfusion reduced by TA and aprotinin about 34 and 39%, respectively and they decreased the required blood volume transfusion by 1.1 units. In this study, the necessity for reoperation such as arterial ligation or hysterectomy decreased the bleeding significantly in the antifibrinolytic group. No substantial variation demonstrated for mortality rate and risk of thrombotic events between patients receiving and not receiving anti-fibrinolytic agents. According to fifth Millennium Developmental Goal expression, maternal mortality should be reduced 75% by the year 2015 (16). To attain this target, PPH occurrence should be critically reduced and PPH management should be overhauled because bleeding is responsible for about 25% of maternal mortality. Several conducting studies have shown the capacity of antifibrinolytic drugs in reducing of PPH and its consequences.

What is TA and what does it do?

During the hemostatic development, coagulation takes place rapidly at the location of a damaged vessel to create a strong web of fibrin. At the same time, the fibrinolytic system eliminates the fibrin residue that can cause vascular closing off (17). The coagulation and fibrinolytic systems are supposed to be in a condition of dynamic equilibrium, which sustain vascular system integrated. Tranexamic acid is a strong antifibrinolytic drug that inhibits binding of lysine on plasminogen molecules and has the ability to increase capacity of the patient's own hemostatic system. Therefore, clot interruption (fibrinolysis) is inhibited and recurrent hemorrhage is diminished. Many physiologic and hemostatic alterations occur serially, while the placenta initiates to shear off the uterine wall, to stop or reduce bleeding including forcefully contracture of myometrium, elevated platelet activity, and a large burden release of coagulant factors associated with an increase in the fibrinolytic activity (18). Regarding to this conceptual theory, early administration of antifibrinolytic medications seems reasonable in the management of PPH (19-21).

Probably unwanted effects of tranexamic acid

In theory, TA may increase the risk of thromboembolic events by prevention of previously formed clots solving.

Actually, there are no or little evidence to provide any significant association between TA and thromboembolic events, as shown by systematic review of TA administration in surgical intervention (12).

A normal pregnancy is associated with increased risk of hypercoagulable states that can increase the chance of thromboembolic events during pregnancy. Pregnant women have an increased risk of thromboembolic events, when compared with non-pregnant women. The absolute risk of clinical venous thrombosis in pregnancy ranges from 0.5 to 3.0 per 1,000 pregnant women based on documented radiological studies (21, 22). Prevalence of deep vein thrombosis (DVT) does not vary between antepartum and postpartum periods and its frequency is the same for all three trimesters (22).

A population-based cohort demonstrated thromboembolic events frequency as 200 per 100,000 pregnant women per year (23). Postpartum period interval is a dangerous time for thromboembolic events because their possibility is 5

times more frequent than entire pregnancy duration. Pulmonary embolism incidence is one third of DVT and 15 times more frequent during postpartum period compared to pregnancy duration.

About 1% of TA passes through breast milk to neonate that inserts no or very slight side effects in baby. TA is a merely longstanding medication with low and mild side effects such as nausea, diarrhea, and sometimes orthostatic hypotension (24). TA effects are presented in Table 1.

Table 1. Side effects of tranexamic acid when used as Injection

Side effects of tranexamic acid when used as Injection	Frequency
Renal insufficiency	Infrequent
Deep vein thrombosis	Infrequent
Myocardial infarction	Infrequent
Stroke	Infrequent
Unusual menstrual discomfort	Not defined
Diarrhea, nausea, vomiting	Not defined
Giddiness, blurred vision, allergic dermatitis	Not defined

Review of literature

This article have a rapid and brief review of a few studies which were conducted to assess the efficacy of TA on postpartum bleeding including vaginal delivery and CS operation and all of them have performed in recent years.

In a RCT study conducted by Buthors et al. and published in 2011, 144 women with PPH diagnoses were randomly assigned in 2 groups. One group received 10 gram TA totally when blood loss volume reached to 800 ml with clinical estimation (TA group) and the other group which not given TA (control group). Conventional management except for TA was performed for both groups before blood loss volume extend to 800 ml and when it reached above the recommended limits. The primary investigated outcome was blood loss reduction, and secondary objectives were assessment of TA efficacy on PPH duration, severity of resulted anemia, transfusion, and necessity of reoperation and surgical procedures. The results showed a vivid discrepancy between two groups. Following 6 hours after admission in both groups, blood loss volume was significantly lower in TA group compared to control group. Other secondary objectives were in favors of TA group except for mild side effects which occurred in TA group. According to authors' declaration, this was the first study showed the significant priority of TA use in PPH and its high efficacy to reduce the blood loss and diminish maternal morbidity due to PPH (25).

A systematic review published in 2009, which searched all articles about antifibrinolytic agents in PPH from November 1998 up to December of 2007, performed by Ferrer et al. and included 8925 recognized records in concerned literature, among them three RCTs consisted of 461 participants met the inclusive criteria. The participants were divided randomly to two groups with 235 patients who received 1g TA and 226 subjects as control group. The primary objective was maternal mortality assessment between two groups. In this systematic review with meta-analysis, authors failed to present any information about mortality discrepancy between two groups due to poor quality of included trials, but they demonstrated a significant blood loss reduction during first 2 hours of delivery by single dose of 1g TA in intravenous (IV) route (26).

Novikova et al. reviewed two RCTs, one of them with poor methodological quality, contained 273 vaginal delivery and the other with 180 women undergoing cesarean sections. They published it as a cochrane database review systematic in 2010. TA had been given in 2 doses of 0.5 and 1g IV in women with vaginal delivery and 1g just 10 minutes before surgical incision in CS women. Results showed prophylactic effectiveness of TA on reducing of bleeding during PPH. No serious side effects were associated with TA administration(27).

Goswami et al. in a prospective double blind case control study, published in 2013, investigated the efficacy of TA when given before CS. The first aim of this study was to assess the optimum dose of TA, which could reduce the maximum amount of blood loss with most safety. Ninety anemic pregnant women were designed in three groups. Group 1 (N=30) received 10 mg/kg TA, group 2 (N=30) received 15mg/kg TA (both 20 minutes before incision), and group 3 or control group received no TA. Blood loss in groups 1 and 2 were significantly lower than control group. In addition, blood loss was significantly lower in group 2 compared to group 1. Postoperative blood loss was not associated with a significant difference among all three groups. Decrease in hemoglobin (Hgb) and hematocrit (Hct) was significantly lower in groups 1 and 2 compared to control group. No considerable side effects were seen in all three groups. No subjects in study groups 1 and 2 needed blood transfusion, except two patients in control group. The authors concluded

that TA was an effective drug in decreasing blood loss during CS operation of anemic parturient women especially at higher dose of 15 mg/kg compared to10 mg/kg (28).

The volume of blood loss is higher in CS compared to vaginal delivery. Aleem et al. conducted an RCT in which 1g TA was given to 373 randomly selected pregnant women planned to have an elective CS. They put 367 subjects as control group. They concluded that TA reduced mean total blood loss in study group compared to control group (241.6 cc in study group against 510 cc in control group). They concluded that preoperative administration of TA significantly reduced blood loss during and after CS and was associated with lower reduction of Hgb and Hct, ;greatest benefits were for anemic parturient (29). A brief and rapid looking to related studies are shown in Table 2.

One of the limitations of merely all conducted studies was small population size. To minimize this problem, Shakur et al. intended to conduct a large population size RCT, named WOMAN trials (World Maternal Antifibrinolytic Trial), in which 15000 pregnant women were selected among enrolled women. The results of this study were powerful enough to determine a 25% reduction from 4% to 3% in maternal mortality or hysterectomy. They wanted to assess the effectiveness of early

Table 2. Tranexamic acid efficacy on postpartum bleeding

Author Reference	Participant quantity	Design of study	Considered outcomes	Conclusion
Buthors (25)	144	Randomized control trial	Efficacy of high dose Tranexamic acid on blood loss reduction	Significant reduction compared of blood loss
Ferrer (26)	461	Systematic review with meta-analysis	Efficacy of TA on post-partum hemorrhage mortality rate	No precise result was obtained due to poor methodic quality of RCTs
Goswami (28)	90	Case control double-blind randomized study	Efficacy of TA 10 and 15 mg dose on intra- and postoperative blood loss in anemic women undergoing low station cesarean section	Significant reduction of blood loss and need to transfusion in both 10 and 15 mg TA groups compared to control group with more reduction in 15mg group
Novikova (27)	453	Systematic review of two unclear quality concerned RCTs	Influence of TA on prevention of PPH	TA is effective in decreasing of blood loss after vaginal delivery and cesarean section
Abdel-al-eem (29)	740	RCT	Possible effect of TA on blood loss during and after elective CS	1g slowly preoperative intra-venous injection of TA reduced blood loss during and after CS, an special benefit for anemic women

TA administration on various risks concerned to blood loss in postpartum period including mortality, hysterectomy, operative intervention, need of blood transfusion, and danger of non-fatal vascular events in mothers and probable side effects on neonates (30).

Conclusion

Currently available evidence yielded from all conducted RCTs and other studies are inadequate to strongly recommend the applications of antifibrinolytic agents such as TA for the reduction of blood loss in postpartum bleeding. Many powerful RCTs such as WOMAN Trials are needed to determine the precise efficacy of TA on concerned risks of PPH.

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Conflict of Interest

The authors declare no conflict of interest.

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