blood advances

POINT Antifibrinolytic therapy for preventing VWD-related postpartum hemorrhage: indications and limitations

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This article has a companion Counterpoint by Ragni.

Introduction

In women of reproductive age, the risk of postpartum hemorrhage (PPH) is obviously well established, but optimal management and prevention is still an unsettled area.[1] This is particularly the case in women with underlying von Willebrand disease (VWD) who have an increased risk of PPH ranging from an approximate fivefold risk in single institution case series[2,3] to a smaller but still significant risk in larger case control studies.[4,5] Not surprisingly, this risk increases the more severe the VWD[6] and varies by genotype.[7] Despite this increased risk, the clinician should not immediately attribute the PPH to the VWD as in general the leading causes of PPH are uterine atony, trauma, and placental abnormalities.[1] Besides addressing these causes in the VWD patient with PPH, certainly raising the VWF level if it has not yet normalized is in order, although how intensive and frequent dosing should be is still in question.[8-10] Typically, additional treatment includes antifibrinolytic therapy given the increased fibrinolysis in general associated with hemorrhage from the mucosal uterine surface.[11] Also, data are accruing in favor of antifibrinolytic therapy,[12] as a blood-conserving agent particularly in surgery[13,14] and in menorrhagia.[15] Figure 1 depicts the various options in preventing and managing PPH. This commentary will focus on antifibrinolytic therapy in the prevention of PPH, whereas the accompanying counterpoint will focus on blood volume–based VWF dosing to prevent PPH in women with VWD.

Studies of antifibrinolytic therapy in treating and preventing PPH

Since the initial case report of its use in primary PPH 21 years ago,[16] there is now a growing body of literature in studying its use in general (ie, not just specific to VWD) in the obstetrical setting in the prevention and reduction of PPH.[17] Given the other causes noted often in "play" during PPH, it is unclear if the increase in fibrinolysis is a primary or secondary change. The potential benefits and risks of tranexamic acid (TA) are outlined in Table 1.

The largest randomized study of TA in PPH >800 mL to date in women undergoing vaginal delivery (VD), albeit open label, was a French study.[18] This study showed a significantly lower blood loss in the TA group than in the control group ($P = .041$). Importantly, the duration of bleeding and progression to severe PPH and blood transfusion were both less frequent than in controls.[18] Since then, a larger, albeit case control, study showed no difference in estimated blood loss,[19] although there were significantly fewer women in the TA arm who needed parenteral iron.[19] Although the World Health Organization guidelines do include consideration of TA for the treatment of PPH in women in general with PPH, the recommendation is lukewarm: "the use of tranexamic acid is recommended for the treatment of PPH if oxytocin and other uterotonics fail to stop the bleeding or if it is thought that the bleeding may be partly due to trauma. (Weak recommendation, moderate-quality evidence)."[20(p255)] An ongoing international study, a double-blind placebo controlled randomized control trial, the World Maternal Antifibrinolytic (WOMAN) study, with a target accrual of 20 000, should be adequately powered for efficacy and also for severe maternal morbidity (hysterectomy, venous thromboembolism) and maternal death.[21]

As for the use of TA preemptively (ie, to prevent PPH in women in general undergoing childbirth), the data have been generally favorable. Most of these studies of TA prophylactically are in women undergoing a cesarean section (CS) rather than a VD. A recent systematic review and meta-analyses of TA for PPH prevention in women undergoing VD or CS has been reported.[22] This review was composed of 25 randomized studies (22 CS, 3 VD) and involved 4747 participants. Typical dosing of TA was 1 g IV 10 minutes before the CS. There was marked statistical reduction overall in the incidence rate of PPH and severe PPH and specifically in the reduction of the following parameters in the CS studies: intraoperative, postoperative, and total blood loss by a mean volume of 141.25 mL (95% confidence interval [CI], −186.72 to −95.79; $P < .00001$), 36.42 mL (95% CI, −46.50 to −26.34; $P < 0.00001$), and 154.25 mL (95% CI, −182.04 to −126.47, $P < .00001$). A similar statistically significant decrease

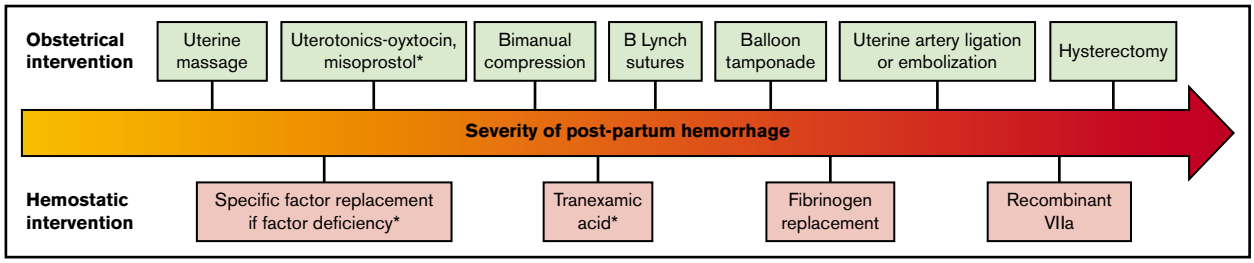

Figure 1. Interventions in PPH. Direction of arrow depicts escalation of therapy if worsening PPH, with obstetrical interventions in green and hemostatic interventions in red. *Denotes consideration in prevention of PPH if underlying bleeding disorder and/or placental previa, twin gestation, or antepartum hemorrhage. Professional illustration by Patrick Lane, ScEYEnce Studios.

was noted in the VD studies. There was no increased risk of deep vein thrombosis or seizure. There was a relative risk of 1.74 for minor adverse events with TA for CS in terms of nausea, vomiting, headache, and dizziness.[22] Despite the relatively large number of patients and studies analyzed, the authors of this excellent systematic review and meta-analysis acknowledge the marked heterogeneity in assessing blood loss, dose and duration of TA dosing, use of concurrent uterotonics, and the degree of blinding to mention a few methodological differences in the studies analyzed. Therefore, they appropriately call for further studies as per the Cochrane methodology[22] the studies were judged to be of poor to moderate quality. In hopes of higher-quality data, there is an ongoing randomized multicenter French trial of more than 4000 patients undergoing VD and a planned one by the same group in women undergoing CS.[23]

Such studies are important as there also needs to be confirmation that TA is safe in terms of major adverse events, particularly thrombosis. The insightful hematologist who prescribes TA for bleeding always thinks of this potential risk, although it seems based on numerous studies in surgery and obstetrics and gynecology to be more theoretical than real.[12] Certainly, though, caution has be exercised in states of heightened hypercoagulability such as the peripartum state, but it is reassuring that in the above-mentioned systematic review and meta-analysis[22] there was no observed increase in thromboembolic events nor in an older study of 256 patients with a bleeding disorder treated peripartum with the antifibrinolytic agent aminocaproic acid compared with a control group of 1846 patients.[24] Renal failure was not observed in these studies, but a recent retrospective study of renal cortical necrosis was observed in 18 patients from 5 nephrology units in France over a 4-year period.[25] All patients had severe PPH and had received TA at a loading dose of 1 to 4 g, and 16/18 received a maintenance dose over 2 to 16 hours. Importantly, all 18 patients necessitated hemodialysis, and 6 months postpartum 8/18 (44%) have remained dialysis dependent. This seemed to correlate with the duration of TA exposure.[25] Unfortunately, this was a case finding study without a denominator of the total number of patients reported in that region who received TA over that 4-year period. Another French study of 68 postpartum women admitted to the intensive care unit with postpartum renal failure showed by univariate regression analysis an association with TA use ($P = .03$), but this did not hold upon multivariate regression analysis.[26] A separate French report suggested an association of acute renal injury postpartum with a high dose TA of 4 g prompting a French Periodic Safety Update Report such that doses that high are no longer typically administered.[19]

It should be emphasized that these studies of TA postpartum were done in women without a documented bleeding disorder. There have been no randomized studies of TA for PPH prevention in the bleeding disorder patient including VWD, and even case reports and case series are sparse.[27] This, however, has not precluded advisement to consider TA postpartum in the United Kingdom Haemophilia Centre Doctors Organization guideline for the diagnosis and management of VWD.[28] Recently, the Kingston Ontario group reported their experience of 62 women with an inherited bleeding disorder, mostly VWD, since the advent of their electronic medical record in 2002 till 2015. In 47 pregnancies, women were prescribed at discharge TA 1 g orally 3 times a day with a median duration of 3 weeks postpartum (5-42 days). TA use was associated with a significant reduction in delayed PPH ($P < .049$). Only 7 cases of delayed PPH in 36 pregnancies (19%) prescribed TA post-discharge were observed compared with 11/26 pregnancies (42%) not treated with TA.[29] No adverse events were reported. TA was used at discharge in those patients deemed at high risk of delayed PPH. The authors did not specify their criteria for "high risk." This report is encouraging and warrants further, more systematic study not only to reduce delayed PPH but also immediately postpartum to decrease the risk of primary PPH in VWD patients in childbirth and delivery. Only 1% of TA is excreted in breast milk (http://www.medicines.org.uk/emc/medicine/27753).

In summary, it is well established that the VWD patient undergoing childbirth has a higher rate of PPH both immediate and delayed. In light of the majority of studies showing that women at delivery in general benefit prophylactically from TA, it is not a "leap of faith" to extrapolate these results in the VWD patient; however, given particularly the emerging risk of renal failure, the use of prophylactic TA should be individualized pending more efficacy and safety data in VWD women. In considering the risk benefit, it would seem reasonable to use TA 1 g IV load at delivery in the (a) type 2 VWD patient, (b) type 3 VWD patient, and (c) "severe" type 1 patient who has not normalized her levels in the third trimester.[8,30]

Table 1. Potential benefits and risks of TA for PPH prevention

Benefits	Risks
Less postpartum blood loss	Minor side effects: nausea, vomiting, headache, and skin reactions
Fewer red cell units transfused	Arterial thromboembolism
Less use of additional uterotonics	Venous thromboembolism
Less need for postpartum parenteral iron infusions	Acute kidney injury including renal cortical necrosis and risk of end-stage renal disease
Shorter length of stay	Seizures

TA can be considered thereafter in these patients at 1 g orally 3 times a day for 7 to 21 days postpartum in tracking postpartum flow in terms of changing frequency of sanitary napkins <2 hours just as the clinician would intervene if menstrual flow was this frequent during menstruation. In the type 1 patient who has normalized her VWF levels, expectant management is reasonable postpartum unless she undergoes a CS or has a prior history of PPH or an increased bleeding score >10, extrapolating from the Italian registry data that a score >10 predicts future bleeding events.[31] Obviously, there are no data comparing TA head-to-head with VWF replacement, but as is the case in severe hemophilia or type 3 VWD, antifibrinolytic therapy in general is an adjunctive treatment as opposed to the primary role of replacement therapy in normalizing the deficient level.

Authorship

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