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Abstract

Introduction. Craniosysnostosis surgical corrections are routine procedures in the pediatric neurosurgical field. However, these procedures result in significant blood loss. Tranexamic acid (TXA) is an antifibrinolytic drug which has demonstrated a significant reduction in perioperative blood loss in many pediatric surgical procedures such as cardiac surgery and scoliosis surgery. We conducted a systematic review to evaluate protocols of TXA use in pediatric craniosynostosis procedures and its effect on intra-operative blood loss and transfusions.

Material and methods. A comprehensive literature review of the National Library of Medicine (PubMed) database was performed to identify relevant studies. We included any clinical study reporting on blood loss or blood transfusion for pediatric craniosynostosis surgery with intraoperative use of tranexamic acid, with the following limits: publication date from inception to May 2019; reports in English.

Results. Thirteen studies were eligible for our review. Of the 13 studies, 4 were prospective, randomized, double-blind controlled trials, 9 were retrospective studies, tailored as a "before-after" studies, comparing blood loss and transfusion without/with TXA. TXA significantly decreases the number and volume of packed red blood cell transfusions and the rate of transfusion in children undergoing craniosynostosis surgery. Significantly fewer fresh frozen plasma transfusions were required in the TXA groups in 2 randomized studies. Length of stay in hospital was significantly lower with the use of TXA in three studies. Advantages of TXA administration also include an excellent patient tolerance of side effects, ease of administration and low cost.

Conclusion. TXA significantly reduces blood loss and the need for transfusions in children undergoing craniosynostosis surgery. TXA administration should be a routine part of strategy to reduce blood loss and limit transfusions in these procedures.

Keywords: Craniosynostosis; blood loss; blood transfusion; tranexamic acid

1. Introduction

Craniosysnostosis surgical corrections are routine procedures in the pediatric neurosurgical field. However, these procedures result in significant blood loss, especially in patients younger than 18 months, weighing < 10 kg, in patients with craniofacial syndromes and those with multiple suture involvement [1, 2]. Intraoperative total blood volume lost can be greater than 100% of the estimated preoperative volume [3] and should be considered as the major complication of these procedures, especially in syndromic craniosynostoses. Efforts to reduce perioperative blood loss have focused on endoscopic surgery, preparation with erythropoietin, autologous predonation, use of cell salvage, acute normovolemic hemodilution, and more recently intraoperative use of antifibrinolytics [5, 6]. Unlike other alternatives, antifibrinolytics are able to prevent further bleeding by stabilizing microclots formed at a surgical wound.

Tranexamic acid (TXA) is an antifibrinolytic drug which has demonstrated a significant reduction in perioperative blood loss in many pediatric surgical procedures such as cardiac surgery and scoliosis surgery [7 ,8]. Interest in using TXA in craniosynostosis surgery has appeared since publication of randomized-controlled studies in 2011 [9-11]. Despite accumulation of evidence regarding its effectiveness, TXA was not unanimously employed in pediatric neurosurgery teams: Goobie et al [12] reported a total of 1638 cases of cranial vault reconstruction from 2010 to 2015 in 31 institutions but antifibrinolytic administration occurred in only 59.5%. Similary, the Synostosis Research Group reported that TXA was routinely used in 3 sites but never in 2 others [13].

By conducting this systematic review, we aimed to evaluate protocols of TXA use in pediatric craniosynostosis procedures and its effect on intra-operative blood loss and transfusions.

2. Materials and Methods

A comprehensive literature review of the National Library of Medicine (PubMed) database was performed to identify relevant studies. We used the following keywords: “craniosynostosis” and “tranexamic acid”. We included any clinical study reporting on blood loss or blood transfusion for pediatric craniosynostosis surgery with intraoperative use of

tranexamic acid, with the following limits: publication date from inception to May 2019; reports in English. The references from the reports included were also manually searched to find further references and reported studies not identified using our initial search strategy. We did not included studies with other anti-fibrinolytics such as aprotinin, and aminocaproic acid. Ethics committee approval was not required for our research protocol.

3. Results

3.1 Selection of reports and study design

Thirteen studies were eligible for our review. Of the 13 studies, 4 were prospective, randomized, double-blind controlled trials [9, 10, 14, 15], 9 were retrospective studies, tailored as a "before-after" studies, comparing blood loss and transfusion without/with TXA [16-24]. Study characteristics are presented in Table 1 and 2. A total of 729 patients were included: 160 in the randomized studies and 569 in the observational studies.

3.2 Analysis of protocols

Protocols of TXA administration varied from one study to another. A loading dose was commonly used, with doses ranging from 10 mg/kg [14, 15, 18, 20-22] to 100 mg/kg [16], usually infused over 15 minutes after induction of general anesthesia and before skin incision. A continuous infusion until skin closure was performed in all studies, with different protocols: 5 mg/kg/h [10, 14, 18, 20-23] or 10 mg/kg/h [9, 16, 17, 19, 24].

In their study, Goobie et al [10] reported that a 50 mg/kg bolus dose followed by an infusion of 5 mg/kg/h could maintain TXA plasma concentrations above the *in vitro* thresholds reported for inhibition of fibrinolysis (10 µg/mL) and plasminogen-induced platelet activation (16 µg/mL). But in a further study, the same author reported that a loading dose of 10 mg/kg over 15 min followed by a 5 mg/kg/h maintenance infusion was sufficient to produce a steady-state TXA plasma concentrations above the 16 µg/mL threshold [25].

No TXA was used postoperatively except in two recent studies [15, 22]. Kurnik et al. [22] compared a continous infusion during the 24 hours after the end of surgery to an infusion

stopped 4 hours postoperatively. Blood loss volume showed no difference between the 2 groups, neither did length of stay in the pediatric intensive care unit. Fenger-Eriksen et al. [15] used a protocol with a bolus dose of 10 ml/kg before incision followed by 8 hours' continuous infusion of 3 mL/kg/h.

3.3 Keys results of each study

3.3.1 Population and procedures

Studies compared efficacy of TXA for both syndromic and non syndromic craniosynostoses. Unfortunately, these 2 groups were grouped together in most of the studies [10, 14-16, 19, 20], and small numbers of complex craniosynostoses did not allow particular conclusions on syndromic craniosynostoses, supposed to be more hemorrhagic when compared to non syndromic. Furthermore, we observed the same confusion for monosutural and multisutural craniosynostoses.

Martin et al. [17] compared only sagittal craniosynostosis operated using a similar technique whatever the age of the child in order to maximize the uniformity of the patients included. In this study, as expected, the use of TXA was significantly associated with a lower total volume of packed red blood cell (PRBC) transfused. No significant correlation between duration of surgery or length of hospitalization was observed between the 2 groups with/without TXA. Martin et al. [23] collected a large cohort of patients less than 15 months of age operated on for single suture nonsyndromic craniosynostosis by the same interdisciplinary surgical team (a craniofacial surgeon and a pediatric neurosurgeon). They used the same TXA protocols as Goobie et al. [10], and TXA-use was associated with a significant reduction in estimated intraoperative blood loss, cell saver volume transfused, red cell transfusion volume and length of stay in hospital.

Engel et al. [18] studied the value of TXA during fronto-orbital advancement in isolated metopic craniosynostosis only, with the same resulting benefit in reduction of blood loss and

transfusion with TXA. Interestingly, the mean duration of the postoperative hospital stay was significantly lower in the TXA group.

Only one report studied the effect of TXA in craniosynostosis treated with minimally invasive techniques versus open procedures [16]. In this study, the sole parameter influenced by the use of TXA was the median weight-adjusted estimated blood loss in the mini-invasive procedure group. The other parameters such as weight-adjusted calculated blood loss, PRBC transfusion did not attain any statistical difference; moreover there was no difference whatever the parameters studied in the open procedure group. These results suggest an important bias in the estimation of data.

3.3.2 Blood loss and blood transfusion

Various parameters were studied in these reports including age, gender, weight, primary or redo surgery, ASA status, urine output, pre- and postoperative hematocrit/hemoglobin/platelet count/fibrinogen concentration, fluid therapy, but the most remarkable were PRBC transfusion volume and estimated/calculated blood loss. Because visual estimation of blood loss is known to be inaccurate in these procedures, blood loss volume was either estimated (EBVlost = Estimated red cell volume lost x hematocrit preop/100) and adjusted per kilogram of patient body weight, or calculated (CBL = RCM preop + RCM transfused – RCM postop) / average hematocrit; RCM indicates red cell mass = 0,7 x volume transfused) (12,21,23,26).

In 10 of the 13 studies, results were obviously the same: the use of TXA significantly reduces the volume of PRBC transfusion when compared to the placebo group [9, 10, 14, 15] or to a group without TXA [17-19, 21, 23, 24]. In 2 studies [16, 20], the volume of PRBC transfused was similar between the TXA+ / TXA- groups of patients undergoing open procedures. However, in Hansen et al's report [20], the TXA protocol used low-dose TXA infusion: standard loading dose of 10 mg/kg over 15 minutes followed by a 5 mg/kg/h infusion until skin closure. This result underlines the need for an optimal dose regimen for TXA to find the most effective

hemostatic effect. Although blood loss is considered to be more difficult to evaluate, results showed similar conclusions in favour of the benefit of TXA. When considered, the mean calculated blood loss [10, 14, 15, 18] or the estimated blood loss [19-21, 23, 24] were significantly lower in the TXA+ group, except for Dadure et al. [9].

The same positive results were observed for fresh frozen plasma transfusions in the 2 recent randomized studies: significantly fewer fresh frozen plasma transfusions were required in the TXA groups [14, 15].

3.3.3 Length of stay in hospital

Length of stay in hospital was significantly lower with the use of TXA in three studies [18, 23, 24]. It was not different between groups TXA+ / TXA- in 5 [10, 14, 17, 19, 21].

3.3.4 Adverse events

No adverse effects directly related to TXA were reported in the 13 studies of the review.

4. Discussion

Our review focused on TXA. This drug was substituted for aprotinin whose marketing in France was stopped because of serious adverse events [1, 26]. Aminocaproic acid is another antifibrinolytic, 6-10 less potent than TXA and not distributed in France. In clinical practice they may have comparable efficacy [27, 28].

Unfortunately, meta-analyses which studied efficacy of antifibrinolytics in pediatric craniofacial surgery did not compare drugs one with another [4, 28, 29]. Most of the literature analyzing strategies used to reduce perioperative blood transfusion (preoperative autologous donation, preoperative erythropoietin, intraoperative cell salvage, acute normovolemic hemodilution, fibrin sealants or fibrin glue; and postoperative drain reinfusion) was nonrandomized and noncomparative. Studies with TXA were comparatively well-conducted: TXA is clinically effective in reducing allogeneic blood transfusion. Already published meta-analyses neglected other drugs such as aprotinin and aminocaproic acid [28].

TXA is a synthetic derivative of lysine which exerts an antifibrinolytic effect. It blocks lysine binding sites in a reversible manner on plasminogen molecules, which inhibits the interaction of plasminogen and plasmin with lysine residues on the surface of fibrin. This action leads to an inability of plasmin to degrade fibrin. The half-life of TXA is approximately 1.5 to 2 hours [25]: it therefore continues to stabilize the clot and prevent bleeding in the immediate postoperative period after the infusion is stopped. TXA is considered as a well-tolerated medication with rare side effects: orthostatic reactions, diarrhea and nausea are the most commonly reported. Some authors have demonstrated no increased risk of thrombogenicity associated with TXA even in cases of complicated pregnancy [30]. Goobie et al. [27] published a report from the pediatric craniofacial collaborative group on the safety of antifibrinolytic use in cranial vault reconstructive surgery: among the 591 patients who received TXA, only 2 cases (0,34 %) of postoperative seizure were described and only one case of femoral deep vein thrombosis in a patient with an indwelling femoral venous catheter. No significant difference was detected in the incidence of postoperative seizures between patients who received TXA and those who did not. Recently, Chung E et al. [31] described a case of ulnar artery thrombosis following ulnar arterial line placement in a patient who received TXA for cranial vault reconstructive surgery.

Use of TXA may significantly reduce cost of these surgical procedures by reducing length of hospital stay [18, 23, 24]. Furthermore, Dadure et al [9] reported a reduction in the median cost of perioperative treatment for blood loss in the TXA group greater than 200 US$.

Taking into account the results of this review, we can consider that TXA should be systematically proposed in pediatric craniosynostosis surgery in order to reduce blood loss and transfusion. A protocol with a loading dose of 10 mg/kg over 15 minutes after induction of general anesthesia followed by a 5-10 mg/kg/h infusion until skin closure could be safely used when considering the Goobie et al. [25, 27] study. We have used this protocol in our institution since 2011 with significant results on reducing transfusion [unpublished data].

Finally, we would like to emphasize that the use of antifibrinolytics is part of the arsenal which permits safer craniosynostosis surgical procedures but it’s not the only element. We must also consider

other methods: iron supplementation, erythropoietin as well as miniinvasive surgical techniques such as endoscopy when feasible, and surgical/anaesthesiological expert teams.

Conclusion

Tranexamic acid significantly reduces blood loss and the need for transfusions in children undergoing craniosynostosis surgery. Advantages of TXA administration also include an excellent patient tolerance of side effects, ease of administration and low cost. TXA administration should be a routine part of strategy to reduce blood loss and limit transfusions in these procedures.

Disclosure of interest

The authors declare that they have no competing interest.

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