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Editorial

# Early Use of Tranexamic Acid in Gastrointestinal Bleed

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Gastrointestinal (GI) bleeding is one of the causes leading to death worldwide. Approximately 47/100,000 for upper gastrointestinal bleeding (UGIB) and 33/100,000 for lower gastrointestinal bleeding (LGIB) [1]. Intravenous fluid, blood products, medications, surgical, and endoscopy procedure have been used as the treatment for GI bleeding. Tranexamic acid (TXA) has been proposed as one of the medications that reduced mortality in GI bleeding [2]. It is an anti-fibrinolytic agent that reduces bleeding in many clinical conditions especially in trauma settings [3]. However, the current guidelines do not recommend tranexamic acid for UGIB or LGIB treatment [4,5].

In Corticosteroid Randomization after Significant Head Injury (CRASH)-2 trial and CRASH-3 trial, the two TXA landmarks studies, demonstrated the time-dependent effect of TXA [6,7]. Compared to placebo, the CRASH-2 Follow Up trial showed risk ratio (RR) for mortality of 0.68 (95% CI, 0.57-0.82) in the patients receiving TXA within 1 hour after trauma and RR of 0.79 (95% CI, 0.64-0.97) in the patients receiving TXA 1-3 hours after trauma [8]. Administering TXA more than 3 hours after trauma was associated with an increased risk of death due to bleeding [6]. In the CRASH-3 trial, TXA given within 3 hours of the injury showed lower head injury-related death compare to placebo [7]. In the World Maternal Antifibrinolytic (WOMAN) trial, postpartum hemorrhage mortality was significantly lower in patients receiving TXA within 3 hours after delivery compared to the placebo group (RR=0.69, 95% CI, 0.53-0.90) but higher in TXA administration more than 3 hours after delivery (RR=1.07, 95% CI, 0.76-1.51) [9]. A meta-analysis of 40,138 patients by Gayet-Ageron et al. also showed a 10% decreased in survival for every 15 minutes of antifibrinolytic treatment delay in acute severe bleeding in traumatic and post-partum hemorrhage within 3 hours and showed no benefit after 3 hours [10].

Meta-analysis of 10 randomized controlled trials, TXA significantly reduced mortality compared to placebo in UGIB of 2,076 patients (RR=0.59, 95% CI, 0.43-0.82, p = 0.001) [11]. Unlike UGIB, a randomized clinical trial from a single center in LGIB did not show a significant difference in blood loss nor mortality benefit of TXA compared to placebo [12]. However, these studies were small and did not report the time-dependent effect of TXA result with a high risk of bias [11-17]. Investigators in the HALT-IT trial, which include 12,009 patients with 89% of patients with UGIB and 11% with LGIB studied the effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic event [18]. Patients were randomized to receive TXA 1-gram bolus followed by 3-gram infusion in 24 hours vs placebo. The primary outcome was death due to bleeding within 5 days of randomization. There was no significant difference in mortality due to bleeding between TXA vs placebo group within 24 hours (2.1% vs 2.0%), 5 days (3.7% vs 3.8%), and 28 days (4.2% vs 4.4%) of randomization. TXA was found to increase the risk of venous thromboembolic events (RR=1.85, 95%CI, 1.15-2.98) and seizure (RR=1.73, 95%CI, 1.03-2.93). Moreover, the patients who received TXA showed no significant benefit in mortality within 5 days when given within 3 hours (RR=1.10, 95% CI, 0.75-1.61) and after 3 hours (RR=0.96, 95%CI, 0.78-1.18) after the onset [18]. The latter group accounted for more than 80% of patients in the HALT-IT trial which may affect the time-dependent effect of TXA.

In conclusion, TXA has potential mortality benefits in various clinical settings such as trauma and postpartum hemorrhage especially with early use but this benefit is still lacking and does not depend on the time administration in GI bleeding based on HALT-IT trial. Rather than confirming the benefit of TXA in UGIB based on Metanalysis [11], the HALT-IT trial with negative result cast more doubts regarding the benefit of TXA in UGIB. More randomized controlled trials are needed to determine the effectiveness of timing of TXA administration on GI bleeding and mortality

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