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Rapid Literature Review

Pre-operative administration of tranexamic acid in hip fracture surgery

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Background

The use of Tranexamic acid (TXA) as an antifibrinolytic agent is established in reducing peri- and postoperative blood loss in surgery [1]. As the fibrinolytic system is activated after the injury and continues to increase during surgery, blood loss in interchochanteric fractures is substantially greater than that in elective total hip arthroplasties. Therefore, it is important to evaluate the safety and effectiveness of TXA in hip fractures [1].

The CCE was requested to undertake a review of the evidence around the safety and efficacy of pre-operative administration of tranexamic acid in patients who will be undergoing hip surgery.

Objectives

To determine the safety and efficacy of pre-operative administration of tranexamic acid (TXA) in hip fracture surgery in the reduction of blood loss (i.e., total or post-operative) and reduction of adverse (thromboembolic) events.

Results

A targeted search (Appendix Table 2 & 3) resulted in four systematic reviews/meta-analyses being selected for this review (Appendix Table 2):

1. A meta-analysis comparing the local administration of TXA in the area of the peri-operative blood loss and the control groups (placebo or nothing) to reduce blood loss in intertrochantic fractures [1].

2. A systematic review and meta-analysis on the effect of intravenous (IV) TXA compared to placebo or nothing, on blood loss and thromboembolic risk in hip fracture surgery [2].

3. A meta-analysis of studies comparing IV TXA with placebo or normal saline [3], and

4. A systematic review on the efficacy and safety of TXA administration in hip fracture surgery [4].

The list of the individual studies included in the selected literature and a description of their quality is found in Appendix, Table 5.

Summary of findings

Moderate to high quality systematic reviews and meta-analyses included in this review suggest that local or intravenous administration of TXA compared to placebo, no treatment or normal saline, resulted in a significant reduction in total blood loss; and no increased risk of thromboembolic events between the TXA and control groups. (Table 1).

As the timing (pre, post or during surgery) and doses of TXA administered varied considerably across included studies in reviews, it is impossible to draw conclusions regarding an optimal dose and/or timing of TXA across studies [2-4]. See Appendix, Table 5.

Table 1. Summary of results from reviews reporting the efficacy (blood loss) and safety (thromboembolic events) of TXA administration in hip fracture patients

Source	No of studies	Mode of admin	Comparator	Blood Loss	Safety (i.e., Thromboembolic events)
Wang (2017) [1]	4 RCT	Local IV or IM	None or saline	**Significant reduction** of total blood loss (WMD = -131.49, 95% CI: -163.63 to -99.35, P=0.00) in the TXA group	**No significant difference in the incidence of DVT** was found between the groups (RD=0.004, 95% CI, -0.02 to 0.03, P=0.7) No significant difference was found in the incidence of PE between the groups (RD=0.00, 95% CI, -0.03 to -0.03, P=0.976)
Baskaran (2017) [2]	6 RCT 2 Cohort	IV	Normal saline	Patients receiving TXA had a **reduced mean total blood loss** of 442.9 mL (95% CI, 426.5-459.3; p<0.00001), and reduced operative blood loss of 88.5 mL (95% CI, 59.9-117.2; p<0.00001)	**No significant increase in VTE risk** (odds ratio, OR 1.59; 95% CI 0.67-3.75; p>0.29) or significant difference on duration of surgery seen with IV TXA usage (p>0.06)
Zhang (2017) [3]	8 RCT	IV	Placebo or saline	TXA group had a **significant decrease in the total blood loss** (WMD =-277; 95% CI: -335 to -220; P = 0.00) and less hidden blood loss (WMD =-246, 95% CI: -252 to -241, P=0.00)	**Pooled results show no significant difference in the rate of thrombotic events between the TXA and control groups** (RD = 0.02, 95% CI:-0.01 to 0.05; P=0.262)
Farrow (2016) [4]	7 RCT	Topical and IV	Placebo or saline	**Post-operative total blood loss was less in those who received intravenous TXA** compared to the placebo/ control group (MD: -341; 95% CI: -672 to -9.87; I^2: 100%; inconsistency (χ^2) P < 0.00001; n =197)	**No increased risk of thromboembolic events** (RD: 0.01; 95% CI: -0.03, 0.05; I^2: 68%; Inconsistency (χ^2) P = 0.007; n = 683)

Key: WMD –weighted mean differences; RD – risk difference; CI – confidence interval; admin – administration; IV- intravenous; IM – intramuscular; VTE – venous thromboembolism; DVT – deep vein thrombosis; MD – mean difference

Discussion

Wang (2017) and colleagues are the first to demonstrate the efficacy and safety of the local administration of TXA in the area of the peri-operative blood loss. They conclude that high-quality RCTs with long-term follow-ups are still required to assess the long-term safety of TXA due to the small sample sizes and short follow-up periods of the included studies [1]. However, results from this meta-analysis should be interpreted cautiously as in two out of the four included RCT, TXA was administered post-operatively [1].

In the other three reviews, TXA was mainly administration pre-operatively (i.e., prior to incision or at induction), however administration protocols varied. This included TXA being administered pre-operatively using a bolus at induction (10-20 $mg.kg^{-1}$ to 1g), IV infusion during surgery, and a dose post-surgery (3-24 hours) [2-4]. As the timing and doses of TXA administered varied considerably, it is impossible for subgroup analysis regarding an optimal dose and/or timing of TXA across studies [2-4].

It is worth noting that Zhang (2017) includes one study (out of 8 included RCTs) where TXA is administered post-operatively [3]. Although Baskaran (2017) and Farrow (2016) report data based on the pre-operative administration of TXA, there was one particular study that is included in both meta-analyses where TXA is administered topically as well

as intravenously [2, 4] (Appendix, Table 2). Therefore, conclusions made by the authors must be interpreted with caution [2-4].

Of the three systematic reviews and meta-analyses, only Farrow specifically excludes patients of hip arthroscopy or any form of non-trauma hip surgery [4]. Nevertheless, authors of the three reviews conclude that patients receiving TXA had a significant reduction in total blood loss compared to those receiving the control or placebo [2-4], particularly in patients aged < 76 years old [4]. These conclusions are based on low quality of evidence [4].

Synthesised literature consistently report a reduction in total blood loss and no significant increase in safety risks (i.e., risk of thromboembolic events or VTE) with the administration of TXA [2-4] in hip fracture patients. Importantly, Baskaran (2017) reports a high risk of bias for post-operative VTE incidence analysis and there was high heterogeneity in VTE detection methods across the included studies [2]. Consequently, authors of another systematic review conclude that the presence of the associated thromboembolic risk with TXA use remains unclear [4].

Conclusions

In the area of total blood loss, the intravenous administration of TXA [2-4] based on low to high quality of evidence, and the local administration of TXA [1] based on high quality evidence, could reduce post-operative or total blood loss in hip fracture surgery. In the area of safety, low quality evidence suggests an unclear risk [4] or no increased risk of thromboembolic events associated with the intravenous administration of TXA [2, 3]. Although TXA is administered pre-operatively in majority of the included studies, this was not controlled for in the selected literature [1-4]. No conclusions can be made on the optimal regimen, dosage and timing of TXA administration in hip fracture surgery [2-4]. These findings are consistent with TXA use in other orthopaedic procedures [4].

References

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Appendix

Inclusion/Exclusion Criteria

Table 2. Inclusion/Exclusion criteria

Population	*Include:* Hip fracture, hemiarthroplasty patients, proximal femoral fracture *Exclude:* Hip arthroplasty, total hip replacement
Intervention	Tranexamic acid administered pre-operatively
Comparator	Placebo or control
Outcomes	Blood loss, safety
Publications	Synthesised literature

Search strategy

The class of antifibrinolytics (i.e., tranexamic acid) was not mentioned within the scope of the ARHQ systematic review (2017) that was identified in the previous CCE literature review on hip fractures [7]; and the only relevant studies were isolated to the use of Tranexamic acid POST hip and knee arthroplasty.

The search was limited to synthesised literature from the two major medical databases, and performed on 19th February 2018.

Table 3. The following databases and search strategies were followed

Database	Search terms	Filters	Results
Pubmed Clinical Queries	Tranexamic acid AND hip fracture	Filter English; Humans	24
Cochrane Database of Systematic Reviews	#1: Tranexamic acid		1514
	#2: Hip fracture or hemiarthroplasty or intertrochanteric or proximal femoral fracture		4314
	#3: 1 AND #2	None	29

Table 4. Ratings of the quality of the selected systematic reviews and meta-analyses using AMSTAR [6]

	Wang (2017)	Baskaran (2017)	Zhang (2016)	Farrow (2016)
Components to be assessed				
Was an 'a priori' design provided?	?	?	?	?
Was there duplicate study selection and data extraction?	Y	Y	Y	Y
Was a comprehensive literature search performed?	Y	Y	Y	Y
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	Y	?	?	?
Was a list of studies (included and excluded) provided?	N	N	N	N
Were the characteristics of the included studies provided?	Y	Y	Y	Y
Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	Y
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	N	Y	Y
Were the methods used to combine the findings of studies appropriate?	Y	Y	Y	Y
Was the likelihood of publication bias assessed?	Y	Y	Y	N
Was the conflict of interest stated?	Y	Y	Y	Y
Overall AMSTAR rating	**9/11**	**7/11**	**8/11**	**7/11**

Table 5. List of individual studies included in the selected literature and a description of their quality

Studies	TXA Administration	Study Type	Wang (2017)	Baskaran (2017)	Farrow (2016)	Zhang (2016)
Virani	Post-op	RCT	+			
Athanasios	Post-op	RCT	+			
Lei	Pre-op	RCT	+			
Mohib	Pre-op	RCT	+	+	+	+
Emara	Pre-op	RCT		+	+	+
Tengberg	Pre-op	RCT		+	+	+
Vijay	Pre-op	RCT		+	+	
Zuffery	Pre-op	RCT		+	+	+
Wang	Post-op	RCT				+
Ji	Pre-op	RCT				+
Zhu	Pre-op	RCT				+
Sadeghi	Pre-op	RCT		+	+	+
Lee	Pre-op	Cohort		+	+	
Shiva	Pre-op	Cohort		+		
Overall quality of included studies as described by the literature			High quality with low risk of bias	Low risk of bias was seen across studies for total and peri-operative blood loss. High risk of bias for post-operative VTE incidence analysis	3 RCTs were mainly low risk; 3 RCTs were either unclear risk or low-high risk. The non-randomised cohort was at serious risk of bias.	Moderate to high quality RCTs