TITLE: Prophylactic Tranexamic Acid Administration for Patients Undergoing Hip and Knee Replacement: Clinical Effectiveness, Cost-Effectiveness, and Guidelines

DATE: 16 June 2015

RESEARCH QUESTIONS

1. What is the clinical effectiveness of the administration of tranexamic acid for blood conservation in patients who are undergoing hip or knee replacement surgery?

2. What is the cost-effectiveness of the administration of tranexamic acid for blood conservation in patients who are undergoing hip or knee replacement surgery?

3. What are the evidence-based guidelines regarding the administration of tranexamic acid for blood conservation in patients who are undergoing hip or knee replacement surgery?

KEY FINDINGS

Nine systematic reviews and meta-analyses, 21 randomized controlled trials, four economic analyses, and one evidence-based guideline were identified regarding the use of tranexamic acid for blood conservation in patients who are undergoing hip or knee replacement surgery.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and May 31, 2015. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.
SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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<th>Table 1: Selection Criteria</th>
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<td><strong>Population</strong></td>
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g = gram; IV = intravenous; OR = operating room.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

Nine systematic reviews and meta-analyses, 21 randomized controlled trials, four economic analyses, and one evidence-based guideline were identified regarding the use of tranexamic acid for blood conservation in patients who are undergoing hip or knee replacement surgery. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Due to the large volume of relevant literature identified, inclusion was limited to articles published from 2013 to 2015.

OVERALL SUMMARY OF FINDINGS

Systematic Reviews and Meta-Analyses

Nine relevant systematic reviews and meta-analyses\(^1\)\(^-\)\(^9\) were identified. Six examined the use of tranexamic acid (TXA) for knee arthroplasty,\(^2\)\(^-\)\(^6\)\(^,\)\(^8\) two for hip arthroplasty,\(^1\)\(^,\)\(^9\) and one review examined both knee and hip arthroplasty.\(^7\) Bolus intravenous (IV) doses of TXA were studied against a range of comparators, including: placebo,\(^1\) placebo or no treatment,\(^7\) topical TXA,\(^5\) intra-articular or topical TXA\(^2\) and unspecified control:\(^2\)\(^-\)\(^4\)\(^,\)\(^6\)\(^,\)\(^8\)

- Versus placebo or no treatment, in the TXA group:
  - total blood loss was significantly reduced\(^1\)\(^,\)\(^7\)
fewer patients required blood transfusion\(^1,7\)
- there was no increased incidence of deep vein thrombosis (DVT)\(^7\)

- **Versus unspecified control**, in the TXA group:
  - total blood loss was significantly reduced\(^3,6,8\)
  - postoperative blood loss was significantly reduced\(^3,6,8\)
  - postoperative blood loss was reduced, but the reduction was not statistically significant\(^4\)
  - hemoglobin loss was significantly reduced\(^3\)
  - transfusion rate was significantly reduced\(^2,3,6,8\)
  - the impact on transfusion requirements varied between studies in one systematic review\(^4\)
  - the number of blood units transfused per patient was significantly reduced\(^3,6,8\)
  - the volume of blood transfusion was significantly reduced\(^8\)
  - intraoperative blood loss was not significantly reduced\(^3\)
  - the rate of thromboembolic events was reduced, but the reduction was not statistically significant\(^2\)
  - no significant difference in venous thromboembolism\(^8\) or DVT\(^3,6\)
  - no increased incidence of DVT\(^4\)
  - no significant difference in pulmonary embolism\(^3,6\)
  - no increased incidence of pulmonary embolism\(^4\)
  - no significant difference in other adverse events\(^3,8\)

- **IV versus intra-articular administration**:
  - no significant differences in effectiveness were reported between treatment groups\(^2\)
  - intra-articular TXA was determined to be safer than IV TXA due to a “reduced rate of transfusion and thromboembolic events”\(^2\)

- **IV versus topical administration**:
  - no significant differences in blood loss, transfusion requirement, or thromboembolic complications were reported\(^5\)

Overall, the conclusions of the reviews supported the use of TXA:
- TXA can be used routinely to decrease intra- and post-operative blood loss with hip arthroplasty\(^1\)
- TXA can be incorporated into blood saving protocols without worrying about adverse events\(^4\)
- “TXA should be considered for routine use in primary knee and hip arthroplasty to decrease blood loss.”\(^7\)

**Randomized Controlled Trials**

Twenty one randomized controlled trials (RCTs)\(^10-30\) were identified. Fifteen studies examined knee arthroplasty,\(^10-18,20-22,24,25,28\) four studies examined hip arthroplasty,\(^19,27,29,30\) and one study evaluated knee and hip arthroplasty.\(^23\) The following RCTs may have been included in the systematic reviews and meta-analyses summarized above; therefore, the following results may represent some duplication.

Bolus IV doses of TXA were studied against a range of comparators including:
- unspecified control\(^12,14,24,30\)
- continuous TXA infusion\(^11,19\)
- weighted TXA dose\(^22\)
topical TXA\(^{18,25,26,27}\)  
- topical TXA plus bolus\(^{14,20}\)  
- topical TXA plus routine hemostasis\(^{10}\)  
- routine hemostasis\(^{21,28}\)  
- normal saline\(^{13,15,23,29}\)  
- mechanical post-operative knee flexion\(^{16}\)  
- fibrin glue\(^{28}\)  
- placebo\(^{17}\)  
- no TXA\(^{26,27}\)

The doses of TXA administered in the studies varied and included:

- **single dose**
  - 1 g IV\(^{22,23}\)
  - 1.5 g IV\(^{20,26,26}\)
  - 2 g IV\(^{10,25}\)
  - 3 g IV\(^{20}\)

- **weighted dose**
  - 10 mg/kg\(^{21,25}\)
  - 15 mg/kg\(^{12,15,17,18,29}\)
  - 20 mg/kg\(^{13,22}\)
  - 30 mg/kg\(^{11,19}\)

- **continuous dose**
  - 500 g IV followed by continuous infusion\(^{30}\)
  - 10 mg/kg bolus followed by 2 mg/kg/hour for 20 hours\(^{11,19}\)
  - 10 mg/kg/hour for 3 hours postoperatively\(^{12}\)

- **intra-articular dose**
  - 3 g\(^{12,18,26}\)
  - 1.5 g\(^{20}\)

The results of the RCTs studying bolus IV TXA for hip and knee arthroplasty were as follows:

- **Versus unspecified control**, in the TXA group:
  - mean total blood loss was significantly lower\(^{14,22,26,30}\)
  - median volume of postoperative blood loss was significantly lower\(^2\)
  - no significant difference in the number of allogenic units of red blood cells required between groups\(^{12}\)
  - mean number of patients requiring transfusions was significantly lower\(^{20}\)

- **Versus placebo**:
  - transfusion requirements were significantly lower in the TXA group\(^{17}\)
  - no thromboembolic complications were reported in either group\(^{17}\)

- **Versus routine hemostasis**:
  - total blood loss was significantly reduced in the TXA group\(^{10,21,28}\)
  - transfusion requirements were significantly higher in the control group\(^{10,21,28}\)
  - no significant difference in adverse events was reported between groups\(^{10,28}\)

- **Versus topical administration**:
  - differences in total blood loss were not statistically significant between groups\(^{10,18,27}\)
  - no significant difference in perioperative hemoglobin levels was reported between groups\(^{25}\)
  - no transfusions were required in either group\(^{18}\)
  - no significant difference in adverse events was reported between groups\(^{18,21}\)
Versus bolus plus topical TXA:
  o transfusion rate and total blood loss were similar between groups\textsuperscript{20}

Versus continuous TXA infusion:
  o mean blood loss was not significantly different between groups\textsuperscript{11,19}
  o no patients required blood transfusion in either group\textsuperscript{11}
  o no adverse events recorded in either group\textsuperscript{11}
  o no major thromboembolic events were reported in either group\textsuperscript{19}

Versus weighted dose:
  o no significant differences in intraoperative, postoperative, or total blood loss were reported between groups\textsuperscript{22}

Versus normal saline:
  o total blood loss was significantly lower in the TXA group\textsuperscript{15,23,29}
  o total fluid loss was significantly lower in the TXA group\textsuperscript{15}
  o more blood, colloid and crystalloid solutions were used to replace blood loss in the saline group\textsuperscript{13}
  o transfusion requirements were significantly lower in the TXA group\textsuperscript{13,23}
  o transfusion rates were similar between groups\textsuperscript{15,23}
  o no significant difference in DVT was reported between groups\textsuperscript{15}

Versus mechanical postoperative knee flexion:
  o total blood loss was significantly lower in the TXA group\textsuperscript{16}
  o transfusion requirements were significantly reduced in the TXA group\textsuperscript{16}
  o no significant difference in adverse events between groups\textsuperscript{16}

Conclusions
  o recommend a single dose of TXA as part of routine care\textsuperscript{11}

\textbf{Economic Evaluations}

After introducing TXA for hip arthroplasty and total knee arthroplasty, facility costs\textsuperscript{31,32,34} and man hours required per arthroplasty\textsuperscript{31,32} were reduced. One analysis determined that the addition of TXA to knee and hip arthroplasty was only cost-saving for institutions with baseline blood transfusion rates greater than 25\%.\textsuperscript{34}

\textbf{Evidence-Based Guidelines}

One evidence-based guideline\textsuperscript{35} was identified from Health Quality Ontario which recommends the use of TXA for knee and hip replacement. The recommendation also states that, because this is an off-label use of the drug in Canada, the decision should be made by the Pharmacy and Therapeutics Committee of each individual hospital.
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses


**Randomized Controlled Trials**


PubMed: PM25155138

PubMed: PM23965206

PubMed: PM23717228

PubMed: PM25534861

PubMed: PM25458093

PubMed: PM25303447

PubMed: PM23886409

Economic Evaluations

Guidelines and Recommendations

See: 5.6 Blood Management, page 75
APPENDIX – FURTHER INFORMATION:

Systematic Reviews and Meta-Analyses – General Orthopedic Surgery


Clinical Guidelines – Methodology Not Specified


Review Articles


Additional References