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Ahmed F. Khan

Beaumont Hospital- Wayne, ahmed.khan2@beaumont.org

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Cover Page Footnote

The author thanks Dr. J. Meza and Dr. N. Yee for their participation in consensus decisions while evaluating the quality of the studies reviewed.

INFORMED CONSENT:

Intra-articular tranexamic acid during total knee arthroplasty

AHMED F. KHAN, Beaumont Hospital, Wayne, MI, ahmed.khan2@beaumont.org

ABSTRACT An informed consent conversation regarding bleeding risk prior to total knee arthroplasty in an elderly patient with chronic kidney disease.

Keywords: *tranexamic acid, total knee arthroplasty, informed consent*

Clinical Context

AA is a 92-year-old woman with a past medical history of advanced osteoarthritis of the knee and chronic kidney disease with anemia. She presents with her family to our clinic as a new patient because her previous doctor refused to refer her for total knee arthroplasty (TKA), citing her chronic anemia. He told her the bleeding risk was too great and she would not survive surgery.

Her family says she sits at home and screams in pain all day long. She is almost deaf, so the family has a hard time consoling her and the high volume screaming is wearing on their nerves. She is able to walk short distances with great difficulty, limiting her quality of life. The patient, who makes her own medical decisions, has said that she doesn't care if she bleeds to death; she wants relief from her pain. She begged for a referral for knee replacement surgery.

The patient's vehement request stimulated a brief discussion with an orthopedic surgeon. Strategies for reducing this patient's bleeding risk were discussed, including tranexamic acid use. Micromedix® was consulted and Stage III chronic kidney disease is not a contraindication for tranexamic acid (TXA). The orthopedic surgeon was familiar with its use in hip surgery, but deferred to anesthesiology for dosing and administration protocols. He had not used it for total knee arthroplasty (TKA) but said that he didn't see any particular problem with trying it in this clinical setting.

Pre-operative evaluation showed no cardiopulmonary disease and, other than the problems already mentioned, the patient was in reasonable health. Her age was a consideration, but the patient's preference guided recommendations. Due to the concern for blood loss with surgery and the concurrent baseline anemia, we explored methods of tranexamic acid use for TKA in our surgical planning process.

Clinical Question

Is intra-articular (IA) tranexamic acid superior to intravenous (IV) tranexamic acid in preventing blood loss when used in total knee arthroplasty?

AHMED F. KHAN is a Family Medicine resident at Beaumont Hospital, Wayne, MI.



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Related Literature

A PubMed search was done using the search terms “tranexamic[tiab] AND knee[tiab] AND (intra-art*[tiab] OR intraart*[tiab] OR topical[tiab]).” This returned 153 results. All of these abstracts were reviewed, searching for randomized trials that compared intra-articular (or topical) tranexamic acid against systemic tranexamic acid. Trials were excluded if they did not investigate transfusion rate as an outcome. Additionally, systematic reviews and meta-analyses were reviewed to find additional trials that were not identified by the PubMed search. Ultimately, 22 trials were discovered for review.¹⁻²²

The papers were all read and assessed for potential sources of biases. The following study properties were considered in assessing the quality of the evidence:

- Successful randomization
- Blinding of surgeons, patients and outcome assessors
- Well-described transfusion indications
- Description of methods used to randomize patients to each group
- Description of methods used to conceal allocation before it occurs
- Low rates of attrition
- Intention-to-treat data analysis
- Lack of reliance on funding from pharmaceutical companies
- No conflicts of interest amongst investigators

The transfusion rate and venous thromboembolism (VTE) rate were recorded for IV and IA groups in all trials. Transfusion rates were determined by the number of patients who required transfusion based on pre-determined criteria. Patients receiving multiple units were considered the same as those who only received one unit. VTE rates were determined by calculating rates of deep vein thrombosis or pulmonary embolism. Only trials that reported measuring these outcomes were considered to have results; if no mention of measured VTE outcomes, trials were considered to have missing data.

The findings of these 22 trials can be found in the [Appendix](#). Results were mixed: most trials did not have a clinically significant difference in transfusion rates. Ten trials slightly favored IV tranexamic acid and six favored IA. Most trials demonstrated a difference in absolute event rates less than 5%, which would have a NNT of 20. Only one trial⁴⁹ demonstrated a significant difference. This trial favored IV therapy (0/50 transfusions) over IA therapy (9/50 transfusions, NNT 6). However, it suffered from a small sample size and poor description of methods, making it a low quality trial due to high risk of bias.

With regards to venous thromboembolism, similar results were found. Most trials did not favor either IV or IA therapy. Three trials did favor IV therapy, while one trial favored IA therapy. The effect size was about 2-6%, resulting in a NNT of 17-50.

Many of the trials were of low quality, due to small sample sizes or methods that result in excessive potential bias. Given the low quality of trials that are available, it was determined this evidence was a SORT level B, indicating limited quality patient-oriented evidence.²³

Informed Consent

Flesch-Kincaid Grade Level for the following passage is 5.9.

“Most people have knee surgery because of bad arthritis. After healing, their knee pain and walking get better. You had your other knee replaced in the past. That took all the pain away in your other knee. Your experience helps you understand what it is like to have knee surgery. You wish you had this knee done sooner. Now, your other doctor said it was too risky to do the surgery, but you want it anyway.

“There can be problems with any surgery. I need to make sure that you understand what could go wrong with surgery. Only you can decide if you still want to go ahead with it. The three main complications of any knee surgery are bleeding, blood clots, and infection.



“Your previous doctor was worried about bleeding. You already have a low blood count. A normal blood count is higher than 12, but your level is 10.7. We expect bleeding during any surgery. That bleeding would make your blood count even lower. If your blood count drops too low, the body can’t get enough oxygen to your heart or your kidneys. That could cause damage.

“I talked to the surgeon about a special medicine. It is called tranexamic acid. This medicine increases clotting and decreases bleeding when they cut the bone. Less bleeding decreases the danger of the surgery for you. Typically they give the medicine in your vein.²⁴ Because of your kidney disease, it would be difficult to adjust the dose if we gave it to you that way. I found some research that shows we can put the same medicine directly into the joint during surgery. The quality of the research is only so-so... not really good. When we consider all of the studies together, they suggest that putting the medicine in the joint is just as good and putting it in the IV.

“Blood clots are also a possible complication after knee replacement surgery. Your history of kidney disease increases the risk of blood clots.²⁵ The medicine I talked about doesn’t seem to make this worse. In rare cases, blood clots can travel to the lungs and lead to death.²⁵ You will be put on blood thinners soon after surgery to decrease the risk of blood clots.

“We will give you antibiotics to lower the risk of infection. Even though we do our best, infection can still happen. If an infection is not able to be controlled, other surgeries may be needed.²⁶

“I think you are pretty healthy. Usually this surgery is safe. I think it will be safe for you, too. I can’t promise there won’t be a problem. What strikes me is that you are determined to have the surgery even after learning about the risks. This makes me think it is the right decision for you.

“If you have any questions regarding your knee surgery, please do not hesitate to ask.”

Epilogue

The patient had the total knee arthroplasty done outside our physician group, so I could not coordinate the care as discussed. No tranexamic acid was used—either IV or intra-articular. The patient required two units of packed red blood cells after surgery. She recovered well and was absolutely delighted with the result. She insists on kissing the doctor during every visit because he gave permission for her to have the surgery.

Based on this experience and review of the literature, we will consider making use of intra-articular tranexamic acid routine for future total knee arthroplasties.

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Appendix

Table S1. Findings in 22 trials comparing intra-articular tranexamic acid against systemic tranexamic acid.

	IV trf	IA trf	IV VTE	IA VTE	Transfusion protocol specified	Random Sequence Generation	Allocation Concealment	Attrition	Intention to Treat	Surgeon blinded	Patient blinded	Outcome Blinded	Funding	Conflict of interest	Well Randomized	
Pinsornsak 2017	7/30 (23.3%)	9/30 (30%)	0/30 (0%)	0/30 (0%)	L	?	?	?	?	H	H	H	L	L	L	
Aggarwal 2016	7/35 (20%)	0/35 (0%)	0/35 (0%)	0/35 (0%)	L	L	?	L	L	H	L	L	?	L	L	
May 2016	1/69 (1.4%)	0/69 (0%)	4/69 (5.8%)	2/69 (2.9%)	L	L	L	?	?	L	L	L	?	H	L	
Drosos 2016	4/30 (13.3%)	3/30 (10%)	0/30 (0%)	0/30 (0%)	L	L	?	L	L	?	?	?	?	L	L	
Keyhani 2016	2/40 (5%)	3/40 (7.5%)	0/40 (0%)	0/40 (0%)	L	?	?	?	?	?	?	?	L	?	L	
Chen 2016	2/50 (4%)	1/50 (2%)	0/50 (0%)	0/50 (0%)	L	L	?	L	L	H	L	L	L	L	L	
Aguilera 2015	0/50 (0%)	4/50 (8%)			L	L	L	L	L	H	H	H	L	L	L	
Gomez-Barrena 20	0/39 (0%)	0/39 (0%)			L	?	L	L	L	L	L	L	H	H	L	
Patel 2014	0/42 (0%)	1/42 (2.4%)	0/42 (0%)	0/42 (0%)	L	L	?	?	?	H	?	?	?	H	L	
Sarzaeem 2014	0/50 (0%)*	9/50 (18%)*	0/50 (0%)	0/50 (0%)	L	L	?	?	?	?	?	?	?	L	L	
Seo 2013	17/50 (34%)	10/50 (20%)	0/50 (0%)	3/50 (6%)	L	L	?	L	?	?	?	?	?	?	L	
Hedge 2013	12/??	6/??			L	?	?	?	?	?	?	?	?	L	?	
Soni 2014	3/30 (10%)	4/30 (13.3%)	0/30 (0%)	0/30 (0%)	L	?	?	L	L	?	?	?	?	L	L	
IV=intravenous administration					L	Low risk of bias										
IA=intra-articular administration					?	Uncertain / Not described										
trf=patients requiring transfusion					H	High risk of bias										

The author thanks Dr. J. Meza and Dr. N. Yee for their participation in consensus decisions while evaluating the quality of the studies reviewed.