The Dangers and Concerns of Intra-articular Tranexamic Acid

I read with interest the article from Chiang et al.[1] entitled "Intra-articular Injection of Tranexamic Acid Reduced Postoperative Hemarthrosis in Arthroscopic Anterior Cruciate Ligament Reconstruction: A Prospective Randomized Study." The authors have done an excellent job of reporting their results and findings. After completion of the study, they concluded that "intra-articular injection of TXA [tranexamic acid] could be considered an effective and relatively safe solution to reduce postoperative bleeding." This conclusion is based on measurements of postoperative drainage and a 4-week follow-up evaluation of pain. The methodology describes the concentration of TXA as a 10% solution.

Readers of *Arthroscopy* are typically clinically active surgeons looking for advances in techniques that will improve recovery. The article of Chiang et al.[1] appears to provide an easily accepted treatment that decreases bleeding and pain. Unfortunately, this may not be the case. I was disturbed by the fact that the authors made a statement of safety that is neither proved nor referenced. The safety of TXA in terms of the articular cartilage is an area of ongoing research. There are numerous publications showing the effect of topical TXA on articular chondrocytes. Tuttle et al.[2] showed that bovine and murine chondrocytes had no viability at 48 hours when exposed to a 10% solution. They concluded that the safest concentration for chondrocyte viability was 2.5%.

Parker et al.[3] performed an in vitro study involving cellular morphology, adhesion, metabolic activity, and viability of human chondrocytes in which increases in the concentration of TXA (from 0 to 40 mg/mL) and length of exposure to TXA (from 0 to 12 hours) were analyzed in a 2-dimensional model. This analysis was then repeated, excluding cellular adhesion, in a 3-dimensional model and confirmed in viable samples of articular cartilage. Parker et al. concluded that any concentration of TXA above 2% resulted in increased chondrocyte death. At 12 hours, the viability of chondrocytes using a 4% solution was less than 3%. The authors found a 97% loss of viability at a concentration that was less than half that used by Chiang et al.[1]

Regarding topical TXA and the surrounding tissues, McLean et al.,[4] similarly to Chiang et al.,[1] used a 10% solution. They performed an in vitro study on the periarticular tissues and found that at an exposure of 10% for 16 hours, tendon showed 96% cellular death, cartilage showed 65% cellular death, and synovium showed 66% cellular death. At 1 hour, a 10% solution resulted in a 50% death rate of chondrocyte cells. With chondrocyte death or damage, the onset of symptoms may not be apparent or noted in the first 4 weeks. Evaluating the onset of symptoms in the shoulder after exposure to bupivacaine, a review by Gulihar et al.[5] found that an average of 14 months elapsed before symptomatic chondrolysis occurred.

Even if one ignores the evidence of the chondrotoxic effects of 10% TXA, one must consider the cost versus benefit of this product. Chiang et al.[1] reported a decrease in drainage of 36 mL. This is approximately 2.5 tablespoons of blood. The patient cost for this product in the American health care system is approximately $1,000.[6]

What this published study has encouraged is the use of a proven chondrotoxic drug (when used at the concentrations reported by Chiang et al.[1]), at high cost, for a decrease in blood loss of 2.5 tablespoons. If there is a need for the use of TXA, one would hope and encourage that oral or intravenous TXA would be used. This has been shown to be equally effective in reducing blood loss in hip replacement arthroplasty.[7]

Considering the potential damage to the joint, the limited benefit, and the cost of the product, it is hard to understand why this approach would be used or allowed without further ongoing research and long-term studies. One would hope that the use of 10% TXA intra-articularly in the knee joint is tempered by these concerns and delayed until long-term safety has been proved.

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Regarding "Intra-articular Injection of Tranexamic Acid Reduced Postoperative Hemarthrosis in Arthroscopic Anterior Cruciate Ligament Reconstruction: A Prospective Randomized Study"

We read with great interest the recently published article by Chiang et al.[1] on the use of tranexamic acid (TXA) in arthroscopic anterior cruciate ligament (ACL) reconstruction. Previously, the drug had been successfully used to control bleeding and reduce total blood loss in non-orthopaedic procedures[2,3]; more recently, several high-quality studies have addressed the use of TXA in joint replacement, and its efficacy in this setting is now widely recognized.[4-6] The benefits of TXA should be studied for other orthopaedic procedures that may take advantage of reduced bleeding, such as closed-joint surgery, in which hemarthrosis is a cause of pain, functional limitation, and difficulty in rehabilitation.[7]

At first reading, the study by Chiang et al.[1] draws great attention because of the number of patients included (304) and its prospective randomized design. However, we consider that more discussion is warranted regarding some of its findings and their clinical relevance.

Regarding the outcome of drainage volume, despite the statistically significant value, the 24-mL mean difference found between groups did not appear to be clinically significant. This makes it hard to explain the very clinically important difference of 3.5 points in the visual analogue scale score on the third day. Therefore, we raise the question of whether the method chosen to evaluate blood loss was the most adequate.

There are 2 main reasons we consider drain output an inadequate outcome measure in this setting. First, it is known that knee hemarthrosis after ACL reconstruction may increase in the first few days, not just in the first 24 hours, and probably for this reason, Chiang et al.[1] chose to grade the joint effusion on the third day and in the fourth week as well. Second, the use of postoperative drains after ACL reconstruction is not routine in most centers because most patients are discharged on the day of surgery and the use of drains does not appear to have clinical benefit in ACL surgery.[8] The clinical implications of TXA use could be remarkably different is a setting in which postoperative drains are not used, so care should be taken in extrapolating these findings to other settings.

Moreover, keeping the drain closed for the first 2 hours may decrease the total bleeding volume owing to tamponade and clot formation. In addition, TXA in a high intra-articular concentration could lead to the formation of clots in the drain, impairing its outflow and unpredictably affecting the outcome. In this scenario, intravenous drug use would eliminate this risk, as appears to be the case shown in the study by Karaaslan et al.,[9] in which intravenous TXA use showed 90-mL less drainage. Therefore, although the 24-hour drained volume is illustrative of the effect of TXA in a scientific study, we believe that it is not a good outcome to measure for intra-articular blood loss after ACL surgery and that these findings may have low external validity for most settings in which a drain is not used.

Chiang et al.[1] briefly discussed the administration route and the use of drains but not to the point that these limitations of the study are clear, so the aim of this letter is to enrich the discussion of these topics. At last, we would like to congratulate the authors for this excellent study, which showed a clinical difference in the visual analog scale score and in the intensity of postoperative hemarthrosis in ACL reconstruction surgery with TXA infiltration.

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