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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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Author Reply to "The Dangers and Concerns of Intra-articular Tranexamic Acid" and "Regarding 'Intra-articular Injection of Tranexamic Acid Reduced Postoperative Hemarthrosis in Arthroscopic Anterior Cruciate Ligament Reconstruction: A Prospective Randomized Study'"

It has been our privilege to receive feedback on our study from researchers from around the world. Thus, we have the opportunity to discuss the topic in more depth.

In Dr. Siegel's letter, he raised concerns about the effect of tranexamic acid (TXA) on articular cartilage in terms of safety. Indeed, a number of studies have shown that a higher concentration of TXA might have a detrimental effect on animal[1] or human[2] chondrocytes. However, as we know, there is always a gap between in vitro studies and the real clinical scenario. First, the cell culture conditions in these studies might not truly reflect the surrounding cartilage tissue in a postoperative knee joint, such as the complete absence of any drug clearance and tissue distribution in these in vitro or ex vivo experimental models. Second, a post-arthroscopic knee may be filled with some irrigation fluid and hemarthrosis, which might further lower the true concentration of TXA. Parker et al.[2] showed that TXA had no effect on the glycosaminoglycan content of human articular chondrocyte—laden hydrogels after 6 hours of exposure (with concentrations up to 40 mg/mL). Siegel also mentioned the study by McLean et al.,[3] who found that after exposure to 10% TXA for 16 hours, there was a 96% rate of cellular death of tendon and 66% rate of cellular death of synovium. However, these negative clinical effects have never been reported in patients receiving arthroplasty or spine surgery. Therefore, the conditions in these experiments might far exceed any protocols realistically encountered in clinical applications. We believed that the optimal dosage of topical TXA still needed to be clarified. In addition, the long-term effect of TXA on human articular cartilage remained unknown.

Another issue is the cost of TXA. The cost of 10 mL of TXA (100 mg/mL) is approximately $30 to $40 in Taiwan. Therefore, we believed that the cost/performance of TXA was acceptable in this clinical application.

In their letter, Gobbi et al. raised concerns about using drain output as the method chosen to evaluate blood loss. They pointed out that a 24-mL output reduction, although statistically significant, might not appear to be clinically significant. In previous literature, TXA was shown to exert its beneficial effects not only by reducing blood loss but also through its anti-inflammatory effects, which might improve analgesia, promoting early rehabilitation in total knee arthroplasty patients.[4] This might explain the significantly lowered visual analog scale score in our patients. In our study, patients without the use of TXA might have had an average 80 mL of drain output on the first day.[5] In the study by Karaaslan et al.,[6] patients might have had 150 mL of hemarthrosis after anterior cruciate ligament reconstruction if TXA was not used. We believed that this amount of hemarthrosis might cause, in some patients, discomfort and functional disability. Therefore, we still routinely use intra-articular drainage on the first postoperative day.