EDITORIAL

Does Intravenous or Intraarticular Tranexamic Acid (TXA) Reduce Joint Bleeding Following Arthroscopic Anterior Cruciate Ligament (ACL) Reconstruction and Arthroscopic Meniscectomy? Can Intraarticular Use be Harmful to Chondrocytes?

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Knee arthroscopy to carry out partial removal of the meniscus and reconstruction of the anterior cruciate ligament (ACL) is common and efficacious, albeit a potential adverse event is intraarticular bleed after surgery. When this adverse event takes place, besides the concomitant pain, the patient commonly needs a joint aspiration (arthrocentesis) to avert loss of range of motion (ROM). Occasionally this problem leads to a poor result of surgery as a result of loss of ROM. That is why the utilization of tranexamic acid (TXA) has been taken into account with the aim of diminishing postoperative hemarthrosis and its potential associated adverse events (1–3).

Some reports have advised the utilization of intravenous TXA (IV-TXA) or intraarticular TXA (IA-TXA) in arthroscopic reconstruction of the ACL, considering it appears to diminish the level of bleeding after surgery and its adverse events: pain, swelling and loss of ROM (1–3). But, some authors have published that IA-TXA could damage the chondrocytes (4). Besides, good outcomes have been obtained after using IV-TXA in arthroscopic partial removal of the meniscus (5). The objective of this editorial is to try to elucidate whether TXA must be employed in arthroscopic reconstruction of the ACL and arthroscopic partial removal of the meniscus and by what technique (IA-TXA or IV-TXA).

Tranexamic acid (TXA) in arthroscopic reconstruction of the ACL

Intravenous tranexamic acid (IV-TXA)

In 2015, Karaaslan et al assessed the efficacy of IV-TXA to reduce knee intraarticular bleed and related aching in a prospective, randomized double-blind trial (level of evidence 1) (1). In this study 105 patients who underwent arthroscopic reconstruction of the ACL were randomly allocated to the IV-TXA group (n = 53) or to the control group (n = 52), which did not have TXA. Before inflating the tourniquet, IV-TXA was administered in bolus form at 15 mg/kg 10 minutes. Then, 10 mg/kg/h were sustained for 3 hours following conclusion of the surgical procedure. In the control group, an equal volume of placebo was administered at the same rate and by the same route. Drained amount of blood was determined 24 hours following the surgical procedure. Pain was evaluated utilizing a visual analogue scale (VAS) in the third day after surgery and at the second and third weeks after the surgical procedure. The Lysholm knee score scale was utilized to evaluate patient contentment and articular function in the second and fourth weeks after surgery. Substantial differences were found between the amount of liquid drained (60 ml [IV-TXA group] versus 150 ml [control group], as well as the grade of intraarticular bleed in weeks 1 and 2 postoperatively.

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Furthermore, pain results ameliorated in the IV-TXA group after the third postoperative day (VAS score 1.4) compared to the control group (VAS score, 2.9). At the end of the second and third weeks after surgery, the VAS scores were considerably lower in the IV-TXA group than in the control group. Regarding Lysholm's score at the end of the second postoperative week, on average it was 70 in the control group and 75 in the IV-TXA group; at the end of the fourth week, on average the score was 75 in the control group and 80 in the IV-TXA group. A substantial difference in the Lysholm score was found between the two groups. Albeit the ROM was analogous between the groups at the end of the fourth postoperative week, on average it was 107° in the IV-TXA group and 103° in the control group on the second postoperative day. Mean intraarticular bleed figures at the end of the first and second postoperative weeks were substantially lower in the IV-TXA group than in the control group, and the necessity for joint aspiration in the IV-TXA group throughout the initial period after surgery was considerably less than in the control group. No infections were found in either group. Besides, no patients suffered from deep vein thrombosis on the third day after surgery. The outcomes of this report indicated that IV-TXA diminished the volume of intraarticular bleed after surgery, reduced the necessity for joint aspiration following arthroscopic reconstruction of the ACL, diminished pain, and ameliorated ROM of the joint in the early period after operation. Moreover, no adverse events were encountered.

In a randomized controlled trial (level of evidence 1), Felli et al assessed the influence of IV-TXA in patients experiencing arthroscopic reconstruction of the ACL to lessen joint bleed (2). Eighty successive patients experiencing arthroscopic reconstruction of the ACL were prospectively assessed. Patients were randomly allocated to 1 of 2 groups: In the study group (IV-TXA), 15 mg/kg TXA were used. In the control group TXA was not used. The circumference of the patella, ROM, the Coupens and Yates score, the VAS score for pain evaluation, and the strength of quadriceps muscle were measured on the first, seventh and fifteenth postoperative days and at the first and third months after surgery. The amount of blood in the intraarticular drainage was measured in the first postoperative day. Any adverse events, such as fever (>37.5°C), intraarticular bleed, or infection, were also documented. A statistically significant decrease in drainage blood amount and Coupens and Yates score was encountered on the first postoperative day in the IV-TXA group compared to the control group. On the seventh day after surgery, a substantial amelioration was encountered in the mean values of Coupens and Yates, ROM, and strength of quadriceps muscle. On the fifteenth day after syrgery, substantial ameliorations in Coupens and Yates value, circumference of the patella, strength of quadriceps muscle, and VAS values were found in the IV-TXA group. Fever was encountered 13 times in the control group and 2 times in the IV-TXA group. No dissimilarities in results or adverse events were observed at 3 months. IV-TXA diminished intraarticular bleed and the quantity of blood drained by suction, ameliorated ROM and the strength of quadriceps muscle, and decreased the number of fever events throughout the first two weeks after operation. The utilization of IV-TXA following arthroscopic reconstruction of the ACL ameliorated results in the initial period after surgery.

Intraarticular TXA (IA-TXA)

In 2019, in a prospective comparative study (evidence level 2), Chiang et al assessed the influence of IA-TXA in 304 patients experiencing arthroscopic reconstruction of the ACL. Single-bundle reconstructions utilizing autologous hamstring tendon grafts were always used (3). Patients were randomly allocated into 2 groups: Patients in the study group 1 (IA-TXA group) underwent the ACL reconstruction with 10 ml of IA-TXA (100 mg/mL). Patients in the control group underwent the ACL reconstruction without IA-TXA. Intraarticular suction drainage was located in the articulation and closed for 2 hours following the end of the operation. Drainage volume was measured 24 hours after the surgical procedure. In the third postoperative day and in the fourth postoperative week, clinical assessments were carried out utilizing the functional score of the International Knee Documentation Committee (IKDC), the ROM, and a VAS. In the first 24 hours after operation, a substantial reduction in the volume of drainage was found in the IA-TXA (IA-TXA group, 56.1 mL; control group, 80.1 mL). At the third postoperative day and fourth postoperative week, substantially inferior pain scores were found in the IA-TXA group. But, at the fourth postoperative week, clinical function scores were similar in both groups. In patients experiencing arthroscopic reconstruction of the ACL, IA-TXA substantially diminished intraarticular bleed in the first 24 hours after surgery. IA-TXA also diminished pain and the grade of intraarticular bleed in the initial period after surgery. Systemic adverse events or necessity for joint aspiration were not encountered throughout the follow-up period. Consequently, Chiang et al determined that IA-TXA seems to be an efficacious and reasonably innocuous method to diminish bleed and pain after surgery in patients experiencing arthroscopic reconstruction of the ACL (3).

Intravenous TXA (IV-TXA) in arthroscopic meniscectomy

To define whether TXA is useful in ameliorating short-run results of swelling, pain, and function following arthroscopic partial removal of the meniscus, Nugent et al planned in 2019 a prospective double-blind randomized controlled trial (level of evidence 2) of 41 patients experiencing arthroscopic partial removal of the meniscus and compared patients managed with IV-TXA (study group) with patients managed with placebo (normal saline – control group) (REGISTER: ACTRN12618001600235 (Australian New Zealand Clinical Trials Registry) (5). One gram of IV-TXA was administered in 100 ml of normal saline (study group) or 100 ml of normal saline (control group) at induction prior to the anesthetist inflated the tourniquet. The anesthetist injecting the IV-TXA or placebo was not

blinded, but all the other physicians implicated were. Patients were assessed by a blind observer on the third, fourteenth and thirtieth postoperative days, with ROM, swelling, pain intensity (VAS), and Lysholm and Tegner´s knee scores. Patient demographics were alike in the two groups. In the IV-TXA group, there was a nonsignificant amelioration in ROM and swelling at 2 weeks; but, there was a substantial amelioration in Tegner's score at the third postoperative day. Side events were alike in the two groups. Nugent et al determined that 1 g of IV-TXA in arthroscopic partial removal of the meniscus could ameliorate initial functional result without augmenting risk. Nevertheless, they noted the necessity for a bigger study to ratify their outcomes and to further assess any possible benefits (5).

The influence of intraarticular TXA (IA-TXA) on chondrocytes *in vitro*

As stated by Parker et al in 2018, IA-TXA had been beforehand demonstrated to be efficacious in diminishing blood loss in unicompartmental knee arthroplasty (UKA) and arthroscopic reconstruction of the ACL. But, prior to their report, the consequences on human joint cartilage were not known. In their report, they studied any detrimental consequences of IA-TXA on chondrocytes to determine whether there was an innocuous amount for the utilization of IA-TXA in arthroscopic surgery (4). They hypothesized that TXA would produce dose-dependent harm to human joint cartilage. In a 2D model they studied a number of parameters in human chondrocytes (cell morphology, adhesion, metabolic activity, viability) by augmenting concentration (0 mg/ml to 40 mg/ml) and duration of exposure to IA-TXA (0 to 12 hours). This investigation was done again, eliminating cell adhesion, in a 3D model and established in viable samples of joint cartilage. Concentrations of more of 20 mg/ml caused atypical chondrocyte morphology as well as a decrease in cell adhesion and metabolic activity linked with augmented chondrocyte apoptosis. But, the cellular matrix was not influenced by TXA concentration or duration of exposure to IA-TXA. Concentrations under 20 mg/ml seemed to protect the chondrocytes. The outcomes of this *in vitro* study revealed cytotoxicity in chondrocytes when exposed to high concentrations of IA-TXA, such as those estimated after advised dose of IA-TXA. This consequence was dose-dependent; therefore, a concentration between 10 mg/ml and 20 mg/ml may be innocuous (4).

In conclusion, some reports appear to encourage the utilization of IV-TXA in patients experiencing reconstruction of the ACL and arthroscopic partial removal of the meniscus to reduce articular postoperative bleeding and its adverse events (pain, inflammation, loss of ROM, necessity for joint aspiration) (1, 2, 5). Concerning the utilization of IA-TXA, one *in vitro* report has shown that IA-TXA is cytotoxic to chondrocytes when exposed to high concentrations, such as those estimated after advised use of IA-TXA. Moreover, such cytotoxicity is dose-dependent. The aforementioned report demonstrated that that a concentration of 10 mg/ml to 20 mg/ml may be innocuous. But, when IA-TXA concentrations augment above 20 mg/ml, they can damage chondrocytes (4). My opinion is that until well-designed analyses can ratify that IA-TXA is not cytotoxic to chondrocytes, its utilization must not be recommended. Currently, in patients experiencing arthroscopic reconstruction of the ACL and arthroscopic partial removal of the meniscus, it appears safer to utilize IV-TXA.

References

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