Widespread of total knee arthroplasty perioperative blood management techniques based on tranexamic acid: barriers and opportunities

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Current interest of orthopaedic surgeons in tranexamic acid (TXA) is rapidly increasing in the literature, and controversial issues, appropriately highlighted by intelligent and deep comments (1-3), deserve some reflections. Perioperative total knee replacement (TKR) clinical management has significantly improved in the last 10 years due to the widespread, highly effective and safe blood loss control with different protocols that incorporate the use of TXA. It is amazing how the rediscovery by the Orthopaedic community of an old medication (TXA has been in use during more than 50 years by different manufacturers under different commercial names such as Transamin, Cyclokapron, Amcha or Amchafibrin, for various indications related to non-orthopaedic bleeding) has transformed the perioperative management of orthopaedic elective procedures that involved significant postoperative bleeding such as total knee arthroplasty after tourniquet release. But besides the arthroplasty field, major benefits in the use of this medication have also been elicited in other areas of orthopaedics and traumatology that reinforce the interest in the drug and provide valuable experience. It is worth mentioning, among other fields of interest, the survivorship increase of severely traumatized patients with early TXA administration, a key aspect that became recognized by most prestigious opinion leaders and publications, not without controversy (4,5).

Due to TXA long history that included patent extinctions, and similarly to what happened with aspirin, a very low price can be obtained in many settings that further supports the spread towards universal use. On the contrary, sponsorship has not prompted, despite robust evidence, the modification of the drug label incorporating new but well-proven indications of TXA, after solidly published academic research, which would further support its potential use. Furthermore, regulatory bodies have not yet reacted ex officio and, although the overwhelming available literature strongly supports some indications in orthopaedic procedures, off-label use is the current status in many countries.

While most of the current debate is centred in the TXA administration, it should be strongly stressed that patient blood management that may avoid transfusion after TKR and facilitate early recovery and discharge, is considerably ampler than the mere TXA administration. Perioperative blood loss control and, in general, new approaches to patient blood management have been incorporated into current clinical pathways in the best clinical practices to perform knee reconstructive procedures. These strategies certainly contribute to fulfil the clinical aim of early functional restoration of the patient, including early discharge in fast-track protocols, while decreasing bleeding-associated complications such as postoperative anemia.

Patient blood management based on preoperative, intraoperative and postoperative actions include strategies designed for hematopoiesis optimization, proactive blood loss and bleeding minimization, or even maximization of tolerance to anemia. Each and any of these pillars may help the patient and the orthopaedic units to increase the quality of delivered care, and increasing evidence supports different therapeutic gestures with proven causal effect in the desired aims of postoperative early functional recovery and decreased postoperative complications. However, variables

to combine for further refining the protocols are so numerous that both newcomers and units with experience may be uncertain about which protocol should be selected and which innovative view is worth trying to offer their patients and institutions the best possible option.

This is why the protocol in place should be multimodal (6), and the surgical technique is not a minor aspect in the protocol. Many centres have already incorporated the use of "low-dose, high volume" local infiltration anaesthetics including adrenalin in the injection. Limited release with minimally invasive surgery is also widely performed. Intramedullary femoral plug is also incorporated if the implant does not seal the guide introduction hole. Tourniquet was released after wound closure. The use of vacuum drainage is less and less popular, but specifically avoided in the blood loss control, where drainage is clamped for 1-2 h after surgery, then maintained for 24 h without vacuum and only by gravity, or even avoided at all in surgery without postoperative drains. When all these surgical gestures are included and standardized, multivariate regression analysis clearly shows that the influence of TXA is highly significant, and transfusion occurs almost 8 times more (OR =8.89) when it is not used. However, we could also confirm that transfusion was similarly refrained (OR =7.39) by an adequate preoperative hemoglobin (worst under 12 g/dL in TKR). This is one reason why a zero transfusion rate can be obtained in TKR when both strategies are combined over the surgical standardization in other substantial gestures that avoid blood loss (7).

Administration route, dosage, and timing of TXA in TKR may produce never-ending debates. But the importance of the multimodal approach needs to be underlined, where surgical technique and other variables are adequately standardized to bear any comparison among blood management strategies. In our view, only appropriately designed comparative studies, and specially RCTs, will provide adequate proof of evidence to solve some of the variable TXA administration issues. In this sense, we focus on the discussion about intravenous administration versus intraarticular (so-called topical) administration in an earlier study (8). Basically, a phase III RCT (as requested by the national regulator) was performed to validate non-inferiority of topical intraarticular administration of TXA in primary TKR. Our incentive was the intrinsic variability of a large Anaesthesiology Department in our institution, with significantly different approaches among the anaesthesiologists, a sequential patient management with one anaesthesiologist in charge at the operating room and a second one in charge at the recovery room. To facilitate the implementation of our blood management strategy, we felt a single dose at the operating room administered intraarticularly would be the most predictable approach for standard practice. Therefore, the trial was performed with same surgeons in a special unit where a small team of anaesthesiologists participating in the study were in charge of both the operating room and the recovery room, and could systematically perform the postoperative management as per protocol in any of the two arms of the trial. With the robust results that we obtained (no transfusion in any of the groups), we felt confident to spread this topical, intraarticular administration to the standard practice, empowering the surgeon to intraoperatively perform the TXA treatment. We should recommend that similar approaches are used to solve other issues about TXA administration.

Experimental studies under experimental conditions, such as RCTs, cannot avoid a major limitation to spread the obtained results when only adequately selected patients are studied. This is a good reason to develop parallel cohort and controlled effectiveness studies during standard clinical practice after appropriate protocol definition. In our initial setting, we dropped the transfusion rate from 27% in 2010 to 7% in 2014, just by incorporating topic TXA to our standardized surgical technique but without patient selection (including complex cases) or preoperative management of anemia (including patients with preoperative haemoglobin between 11-13 g/dL and not just above 13 g/dL). Preoperative management of anemia has been recently spread to all our patients and a future audit may confirm if the experimental results are reproduced in standard clinical practice. Of note, more complex patients are being controlled and challenging indications are spreading with intraarticular TXA, although caution needs to be recommended as exclusion criteria in the trial, with limitations to use TXA, may not be disregarded. However, previous reports (9) have shown that intraarticular TXA administration in dose up to 3 g may not be absorbed to the systemic circulation, and large series are needed to eventually confirm its safety in complex cases with previous thromboembolic events. Other research lines, such as topic and intravenous combined treatment are under way and may provide more efficient patient blood management, but much research is needed to further clarify and obtain the maximum benefit from these innovative approaches.

In summary, multimodal approaches to patient blood management in TKR have proven some progress to

enhance early patient recovery including the control of the transfusion rate and the postoperative blood loss. Topical intraarticular TXA has been a major progress to empower the surgeon to easily control treatment variables and transform TXA administration in a supplementary surgical gesture with proven efficacy and safety. This way may be followed to clarify the role of different alternative options in TXA administration, including patient complexity (preoperative anemia, important surgical releases, knee revision surgery), with surgical scenarios that should be standardized to avoid divergent outcomes that may be related to surgical variables and not to the protocol.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Sabatini L, Atzori F. Topical intra-articular and intravenous tranexamic acid to reduce blood loss in total knee arthroplasty. Ann Transl Med 2015;3:S18.
2. Chen JY, Chia SL, Lo NN, et al. Intra-articular versus intravenous tranexamic acid in primary total knee replacement. Ann Transl Med 2015;3:33.
3. Danninger T, Memtsoudis SG. Tranexamic acid and orthopedic surgery-the search for the holy grail of blood conservation. Ann Transl Med 2015;3:77.
4. Levy JH. Antifibrinolytic therapy: new data and new concepts. Lancet 2010;376:3-4.
5. Gruen RL, Mitra B. Tranexamic acid for trauma. Lancet 2011;377:1052-4.
6. Moráis S, Ortega-Andreu M, Rodríguez-Merchán EC, et al. Blood transfusion after primary total knee arthroplasty can be significantly minimised through a multimodal blood-loss prevention approach. Int Orthop 2014;38:347-54.
7. Rodriguez-Merchán EC, Ortega-Andreu M, Padilla-Eguiluz NG, et al. Effectiveness of a low volume intraarticular tranexamic acid administration in a multimodal protocol. Blood Coagulation & Fibrinolysis. (In press).
8. Gómez-Barrena E, Ortega-Andreu M, Padilla-Eguiluz NG, et al. Topical Intra-Articular Compared with Intravenous Tranexamic Acid to Reduce Blood Loss in Primary Total Knee Replacement: A Double-Blind, Randomized, Controlled, Noninferiority Clinical Trial. J Bone Joint Surg Am 2014;96:1937-44.
9. Wong J, Abrishami A, El Beheiry H, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. J Bone Joint Surg Am 2010;92:2503-13.

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