Tranexamic Acid and Its Application in Oral Surgery. Systematic Review *

Ácido tranexámico y su aplicación en cirugía oral. Revisión sistemática

Ácido tranexâmico e sua aplicação em cirurgia oral. Revisão sistemática

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ABSTRACT

Background: Tranexamic acid (TXA) is a synthetic analogue of lysine, which inhibits fibrinolysis by reducing the conversion of plasminogen into plasmin, thereby promoting the preservation of the clot formed in the operated area and reducing the risk of bleeding. It is eventually used as a complement in oral surgery. **Purpose**: To analyze the evidence on the effectiveness in hemostasis, appropriate dose, safety margin, benefits, and postoperative evolution of TXA used in oral surgery. **Methods:** The systematic review was structured from a search tree (PubMed, Google Scholar, ProQuest, and Scopus), with the keywords and Boolean connector: Tranexamic Acid AND Oral Surgery. The search was limited to the English, Portuguese, and Spanish languages; open-access articles; systematic reviews, meta-analyses, randomized clinical trials, and case reports. We established a secondary selection based on the title and abstract of the articles according to the purpose of the study. **Findings:** The literature reports an efficacy of 80 % of TXA in reducing bleeding risk during and after surgical procedures, which optimizes the procedures. **Conclusions:** Topical or intravenous TXA in doses not exceeding 20 mg has proven to be effective to reduce the risk of bleeding in oral surgery.

Keywords: antifibrinolytic; blood dyscrasias; complications; dentistry; drug therapy; hemorrhage; oral surgery; oral surgical procedures; therapeutics; tranexamic acid

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RESUMEN

Antecedentes: El ácido tranexámico (ATX) es un análogo sintético de la lisina que inhibe la fibrinólisis al reducir la conversión de plasminógeno en plasmina, lo que favorece la preservación del coágulo formado en el área operada y reduce el riesgo de sangrado. Eventualmente se utiliza como complemento en cirugía oral. **Objetivo**: Analizar la evidencia sobre la efectividad en hemostasia, dosis adecuada, margen de seguridad, beneficios y evolución postoperatoria de los ATX utilizados en cirugía bucal. **Métodos**: La revisión sistemática se estructuró a partir de un árbol de búsqueda (PubMed, Google Académico, ProQuest y Scopus), con las palabras clave y conector booleano: Ácido Tranexámico Y Cirugía Oral. La búsqueda se limitó a los idiomas inglés, portugués y español; artículos de acceso abierto; revisiones sistemáticas, metanálisis, ensayos clínicos aleatorizados e informes de casos. Se estableció una selección secundaria a partir del título y resumen de los artículos según el propósito del estudio. **Hallazgos**: La literatura reporta una eficacia del 80 % del ATX para reducir el riesgo de sangrado durante y después de los procedimientos quirúrgicos, lo que optimiza los procedimientos. **Conclusiones**: El ATX tópico o intravenoso en dosis no superiores a 20 mg ha mostrado ser eficaz para reducir el riesgo de sangrado en cirugía oral.
Palabras clave: ácido tranexámico; antifibrinolítico; cirugía oral; complicaciones; discrasias sanguíneas; hemorragia; odontología; procedimientos quirúrgicos orales; terapéutica; terapia de drogas

RESUMO

Antecedentes: O ácido tranexâmico (ATX) é um sintético da lisina que inibe a fibrinólise ao reduzir a conversão de plasminogênio em fibrinolisina, o que favorece a preservação do coágulo formado na área operada e reduz o risco de sangramento. Eventualmente se utiliza como complemento em cirurgia oral. **Objetivo**: Analisar a evidência sobre a eficácia da hemostasia, dosagem adequada, margem de segurança, benefícios e evolução pós-operatória do ATX usado na cirurgia bucal. Métodos: A revisão sistemática se estruturou a partir de uma árvore de busca (PubMed, Google Scholar, ProQuest e Scopus), com as palavras-chave e o conector booleano: Ácido Tranexâmico Y Cirurgia Oral. A busca é limitada aos idiomas inglês, português e espanhol; artigos de acesso aberto; revisões sistemáticas, metanálisis, ensaios clínicos aleatórios e informes de casos. Estabeleceu uma seleção secundária a partir do título e resumiu os artigos de acordo com o objetivo do estudo. **Resultados**: A literatura relata uma eficácia de 80% de ATX para reduzir o risco de sangramento durante e após os procedimentos cirúrgicos, o que otimiza os procedimentos. **Conclusões**: O ATX tópico ou intravenoso em dose não superior a 20 mg demonstrou ser eficaz para reduzir o risco de sangramento em cirurgia oral.
Palavras clave: ácido tranexâmico; antifibrinolítico; cirurgia oral; complicações; discrasias sanguíneas; hemorragia; odontologia; procedimentos cirúrgicos bucais; terapêutica; terapia de drogas

INTRODUCTION

Tranexamic acid (ATX) was introduced by Japanese scientists Utako and Shosuke Okamoto in 1960. Since then, its use in the medical, surgical, and dental fields has expanded. This drug improves hemostatic control in the patient, reducing bleeding complications in treatments that involve handling tissues with risk of blood loss (1). TXA (4-aminomethylcyclohexane carbolic acid) is an antifibrinolytic drug, a synthetic analogue of lysine. This drug inhibits fibrinolysis by reversibly competing with fibrin for lysine-binding sites on plasminogen (1).

Plasminogen comes from the liver and is transformed into plasmin by the tissue plasminogen activator (TPA). This activator together with plasminogen binds to C-terminal lysine residues on fibrin, leading to localized plasmin formation and cleavage of fibrin. As a result, the conversion of plasminogen to plasmin is reduced. This enzyme breaks down fibrin clots, fibrinogen, and other plasma proteins (procoagulant factors V and VIII). Thanks to the reduction of plasmin, the blood clot is preserved, generating an efficient hemostatic process, and reducing the risk of bleeding events (1).

TXA is soluble in water and has a pH between 6.5 and 8. It is used as a supplement in oral surgery for anticoagulated patients, and its most frequent presentations are an oral solution and a

topical agent (2). Since its discovery, TXA has been widely used in the medical field during major surgeries. The research question in this literature-based study was, what is the TXA effectiveness in reducing the risk of bleeding complications in distinct types of dental surgery, such as simple or surgical extractions, dentoalveolar surgery, placement of dental implants, bone regeneration, and periodontal surgery?

The purpose of the study is to analyze the evidence on the effectiveness of TXA in reducing bleeding, dosage, safety margin, benefits, and precautions in oral surgery, based on current evidence. Findings will provide up-to-date evidence for the use of TXA in dental procedures, specifically oral surgery.

MATERIALS AND METHODS

For this systematic review of literature, the term "Tranexamic Acid" and "Oral Surgery" were combined with the Boolean connector "AND." The search for titles focused on articles categorized by the University of Oxford in levels of evidence up to B/2b. The time range was five years (2018-2022), and the search was conducted in October 2022. The search for bibliographic content was structured based on a search tree (secondary information), through the PubMed, Google Scholar, ProQuest, and Scopus databases.

The inclusion criteria/search limits were English, Portuguese, and Spanish languages; open-access articles; and systematic reviews, meta-analyses, randomized clinical trials, and case reports. The exclusion criteria were articles of non-competent studies to our analysis. One filter included duplicated titles across the databases. A second selection was conducted by the team through an analysis of titles and abstracts. Team members completed individually a detailed reading of each article and then conducted a new selection of relevant content as a group (Figure 1).

RESULTS

The search for articles resulted in 69 titles of which 34 were discarded. The final sample consisted of 35 articles of which 10 were meta-analyses (28.5 %), 6 were systematic reviews (17.1 %), 8 literature reviews (22.9 %), 1 randomized parallel trial (2.9 %), and 10 case reports (28.5 %) (Table 1).

Of the 35 titles chosen to conduct the literature analysis, 3 studies presented arguments associated with the safety and cytotoxicity of TXA, 9 articles were about the different ways of administration and presentation of TXA, 12 focused on the use of TXA in patients with blood dyscrasias receiving hematological treatment, 7 were about complications and adverse effects of TXA, 3 compared the use of different antifibrinolytics with TXA, 5 evaluated the bleeding reduction when using TXA, 4 related to the application if TXA in different areas, and 1 highlights the TXA pro-inflammatory and anti-inflammatory effect. Eight studies provide information on two issues with different impact (Table 1).

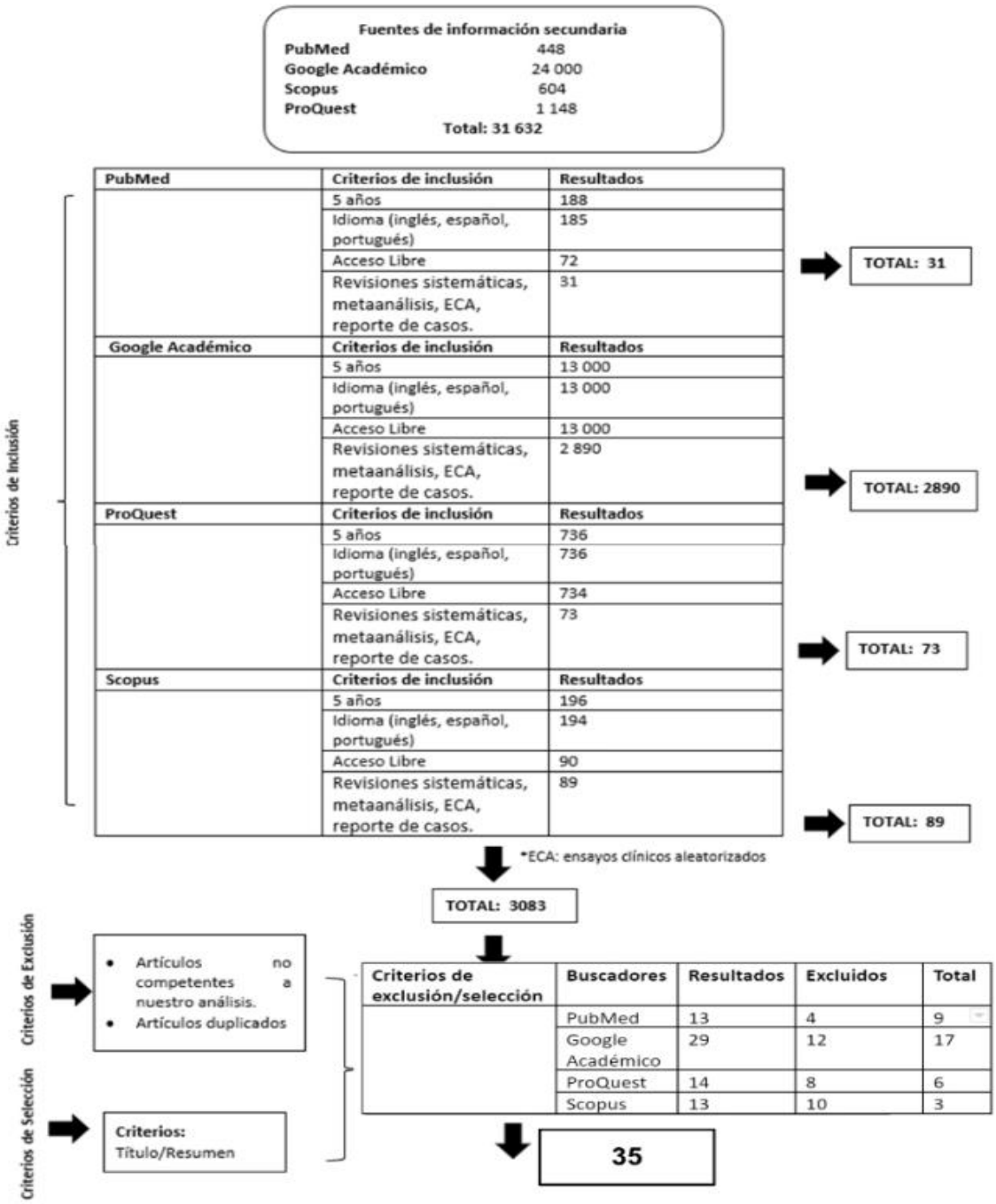

FIGURE 1
Flowchart of Article Search and Selection (in Spanish)
Source: the authors.

TABLE 1
Studies Included in the Systematic Review, by Database

Author, year, country	Title	Type of study	Journal	Content
		PubMed		
Wang, et al., 2018. China (3)	The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty	Metanalysis	Medicine (Baltimore)	Ways of administration and presentation
Franco, et al., 2018. Italy (4)	Glanzmann's thrombasthenia: the role of tranexamic acid in oral surgery	Case study	Case Reports Dent	Complications and adverse effects
Engelen, et al., 2018. The Netherlands (5)	Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions	Systematic review	Cochrane	Safety and cytotoxicity. Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Johansson, et al., 2022. Sweden (6)	Impact of direct oral anticoagulants on bleeding tendency and postoperative complications in oral surgery: a systematic review of controlled studies	Systematic review of controlled trials	Oral Surg Oral Med Oral Pathol Oral Radiol	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Van Galen, et al., 2019. The Netherlands (7)	Antifibrinolytic therapy for preventing oral bleeding in patients with hemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions	Systematic review	Cochrane	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Sharma, et al., 2019. India (8)	Management of haemostasis during dental extraction in a Bernard-Soulier syndrome child	Case study	BMJ Case Reports	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Ullah, et al., 2022. Pakistan (9)	Is antifibrinolytic therapy effective for preventing hemorrhage in patients with hemophilia undergoing dental extractions? A systematic review and meta-analysis	Metanalysis	Clin Appl Thrombosis / Hemostasis	Complications and adverse effects. Bleeding reduction.
Kurasawa, et al., 2022. Japan (10)	Delayed epistaxis which was developed after orthognathic surgery with Le Fort I osteotomy and managed by endoscopic cauterization	Case study	Case Reports Dent	Use of TXA in different areas.

Dunphy & Williams, 2018. Ukraine (11)	Immune thrombocytopenic purpura presenting with spontaneous gingival hemorrhage in pregnancy	Case study	BMJ Case Reports	Use of TXA in different areas.
		Google Scholar		
Zhao, et al., 2019. China (12)	Comprehensive assessment of tranexamic acid during orthognathic surgery: A systematic review and meta-analysis of randomized, controlled trials	Metanalysis	J Cranio-Maxillo-Facial Surg	Ways of administration and presentation. Bleeding reduction.
Mei & Qiu. 2019. China (13)	The efficacy of tranexamic acid for orthognathic surgery: a meta-analysis of randomized controlled trials	Metanalysis	Int J Oral Maxillofac Surg	Ways of administration and presentation. Bleeding reduction.
de Vasconcellos, et al., 2017. Brazil (14)	Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials	Metanalysis	J Craniomaxillofac Surg	Ways of administration and presentation. Use of TXA in patients with blood dyscrasias receiving hematological treatment. Complications and adverse effects.
Montroy, et al., 2017. Canada (15)	The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis	Metanalysis.	Transfus Med Rev	Complications and adverse effects. Bleeding reduction.
Owattanapanich, et al., .2019. Thailand (16)	Efficacy of local tranexamic acid treatment for prevention of bleeding after dental procedures: A systematic review and meta-analysis	Metanalysis.	ScienceDirect	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Bensi, et al., 2018. Italy (17)	Postoperative bleeding risk of direct oral anticoagulants after oral surgery procedures: a systematic review and meta-analysis	Metanalysis.	Int J Oral Maxillofac Surg	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Yates, et al., 2018. Canada (18)	Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis	Metanalysis.	Transfusion	Complications and adverse effects. Comparison of the use of different antifibrinolytics with TXA.

Bajkin, et al., 2020. United States (19)	Dental implant surgery and risk of bleeding in patients on antithrombotic medications: a review of the literature	Systematic review	Oral Surg Oral Med Oral Pathol Oral Radiol	Use of TXA in different areas.
Murdaca, et al., 2020. Italy (20)	Tranexamic acid adverse reactions: a brief summary for internists and emergency doctors	Literature review	Clin Mol Allergy	Safety and cytotoxicity. Comparison of the use of different antifibrinolytics with TXA.
Stelea, et al., 2018. Romania (21)	Assessing the bleeding risk in patients using direct oral anticoagulants submitted to dental surgery procedures: a systematic review	Systematic review	Rom J Oral Rehab	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Franchini & Mannuccio, 2020. Italy (22)	The never-ending success story of tranexamic acid in acquired bleeding	Literature review	Haematologica	Complications and adverse effects.
Cerviño, et al., 2019. Italy (23)	Advances in antiplatelet therapy for dentofacial surgery patients: focus on past and present strategies	Literature review	MDPI Journal	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Karasneh, et al., 2021. United States (24)	Bleeding control interventions for invasive dental procedures in patients with inherited functional platelet disorders: a systematic review	Systematic review	Oral Surg Oral Med Oral Pathol Oral Radiol	Ways of administration and presentation.
Picetti, et al., 2019. England (25)	What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies	Systematic review	Blood Coagul Fibrinolysis	Ways of administration and presentation.
Barrett, et al., 2020. United Kingdom (26)	Influence of tranexamic acid on inflammatory signaling in trauma	Literature review	Semin Thromb Hemost	Proinflammatory and anti-inflammatory effect.
Chen, et al., 2021. Taiwan (27)	Does tranexamic acid reduce risk of mortality on patients with hemoptysis?	Metanalysis	Medicine (Baltimore)	Ways of administration and presentation.
Pirlog, et al., 2018. Romania (28)	A systematic review of the hemorrhage risk for patients on antithrombotic medication after dental procedures	Systematic review	World J Dent	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
ProQuest				

Monteilh, et al., 2020 (29)	Nebulized tranexamic acid for pediatric post-tonsillectomy hemorrhage: a report of two cases	Case study	Clin Pract Cases Emerg Med	Use of TXA in diverse areas.
Dermendjieva, et al., 2021. United States (30)	Nebulized tranexamic acid in secondary post-tonsillectomy hemorrhage: case series and review of the literature	Systematic review	Clin Pract Cases Emerg Med	Ways of administration and presentation.
Boccio, et al., 2020. United States (31)	Topical tranexamic acid for hemostasis of an oral bleed in a patient on a direct oral anticoagulant	Case study	Clin Pract Cases Emerg Med	Ways of administration and presentation.
Poppe & Grimaldo, 2020. United States (32)	A case report of nebulized tranexamic acid for post-tonsillectomy hemorrhage in an adult	Case study	Clin Pract Cases Emerg Med	Complications and adverse effects.
Shadamarshan, et al., 2021. India (33)	Post-dental extraction bleeding: Emphasis on the diagnosis of rare coagulation disorders	Case study	Clinical Case Reports	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
Ehrhard, et al., 2019. Switzerland (34)	Severe enoral bleeding with a direct oral anticoagulant after tooth extraction and heparin bridging treatment	Case study	Case Reports in Emergency Medicine	Use of TXA in patients with blood dyscrasias receiving hematological treatment.
		Scopus		
O'Connor, et al., 2022. United States (35)	Le Fort I maxillary osteotomy in a Jehovah's Witness patient: strategies for minimizing blood loss and maximizing safety	Case study	Maxillofac Plast Reconstr Surg	Bleeding reduction.
Gkiatas, et al., 2022. Greece (36)	Topical use of tranexamic acid: Are there concerns for cytotoxicity?	Systematic review	World J Orthop	Safety and cytotoxicity.
Modir, et al., 2022 (37).	A randomized parallel design trial of the efficacy and safety of tranexamic acid, dexmedetomidine and nitroglycerin in controlling intraoperative bleeding and improving surgical field quality during septorhinoplasty under general anesthesia	Randomized parallel trial	Med Gas Res	Comparison of the use of different antifibrinolytics with TXA.

Source: the authors.

DISCUSSION

Bleeding is one of the most frequent complications during oral surgery procedures. To manage it, various techniques are used. One of them is the application of TXA, due to its antifibrinolytic properties that promote the preservation of the clot in the surgical site, therefore reducing bleeding. Ullah, *et al*., (9) confirm this in a study that shows a reduction in the risk of intraoperative and postoperative bleeding of up to 84 % during oral surgical procedures. Zhao, *et al*., (12) and Mei & Qiu (13) reported a blood loss reduction by 153.97 ml and 159.73 ml respectively, which confirms the effectiveness of TXA as a hemostatic agent. Zhao, *et al*., (12) informs of a side effect of TXA, that is, a hematocrit reduction of 3.17 g/dl. However, Mei & Qiu (13) clarify that this value did not show a notable influence on value ranges or clinical results.

Based on the evidence analyzed, the oral surgeon has at their disposal a wide range of antifibrinolytic drugs that help achieve intraoperative and postoperative hemostasis. TXA has better hemostatic properties than other antifibrinolytics, as mentioned by Yates, *et al*. (18), when comparing TXA and aminocaproic acid. They concluded that ATX did not present any significant risk of complications from its administration and noted that the perioperative systemic use of ATX significantly reduced the risk of bleeding adverse events by 7 % when compared to aprotinin. However, Modir, *et al*. (37), when comparing the effects of dexmedetomidine, nitroglycerin, and TXA, showed a shorter postoperative recovery time in patients in the TXA group. Times were 26.8 min, 22.2 min, and 21.8 min, respectively.

As a pharmacological alternative in patients sensitive to TXA, Murdaca, *et al*., (20) mention ethamsylate, a synthetic molecule different from lysine that is being considered a good substitute in sensitive patients, even though TXA continues to be the first-line therapy for use. All medications have the potential to generate unwanted side effects, and TXA is no exception. As Franco, *et al*., (4) state, the most common adverse effects are nausea and diarrhea, which do not compromise the patient's general health. There is controversy regarding the use of TXA in patients with significant comorbidities such as a history of thromboembolism and liver, kidney, and heart dysfunction, thus avoiding its use in such cases is advisable. In this regard, Yates, *et al*. (18) evaluated the adverse effects of ATX in healthy patients and those with systemic disorders, showing that the risk of presenting an TXA-related adverse event is similar in both groups.

One of the complications that may concern the surgeon about using antifibrinolytic drugs is venous thromboembolism. Facing this challenge, de Vasconcellos, *et al*., (14) and Montroy, *et al*. (15) showed that topical or intravenous application of TXA does not promote thromboembolic events. This is an advantage of this drug; thus, its administration can be considered safe when necessary.

Prompt action by the surgeon, in the event of a severe hemorrhage, improves the patient's prognosis. Franchini and Mannucci (22) argue that administering ATX within the first hour of presenting the event is more beneficial, since an administration after 3 h is associated with an increased risk of death from hemorrhage.

The TXA administration routes are diverse: topical (rinse, aerosols) and oral (syrup, tablets), each of them being useful depending on the type of procedure to be performed. However, its availability varies between countries, which restricts its use. In oral surgery, the main form of TXA administration is either oral or topical, which is performed with a TXA-soaked gauze in the operating field. Boccio, *et al*. (31) question the effect of the oral route due to its little or no systemic absorption. In contrast, Wang, *et al*. (3) found that the topical effect is comparable to intravenous administration, thus achieving clot preservation and avoiding a hemorrhagic event. However, in

major and invasive procedures, such as bone reconstruction due to trauma or orthognathic surgery, intravenous administration is necessary.

With respect to the dosage, the suggested dose ranges between 10 mg/Kg and 20 mg/Kg fulfills its antifibrinolytic function by reducing blood loss as shown by Zhao, *et al*. (12), Mei & Qiu (13), and Picetti, *et al.* (25). Regarding the postoperative management, TXA rinses for 2 to 7 days prevent hemorrhagic events, as mentioned by de Vasconcellos, *et al.* (14), when used in concentrations of 4.8 % to help the patient's early recovery (24). Dermendjieva, *et al*., (30) allude to another form of administration of TXA, nebulization, which is used predominantly in tonsillectomy surgeries or when there is minimal cooperation from the patient.

One drawback that an oral surgeon faces is dealing with patients who have severe bleeding disorders, such as blood dyscrasias, or who are taking oral anticoagulant medications, which can cause life-threatening complications when not taken. Taking this into consideration before conducting invasive procedures is essential to gather as much information regarding the patient in order to compile a precise and correct medical record, emphasizing medication intake and a history of bleeding. There is evidence that patients taking anticoagulants through direct oral administration (DOAC) have a lower risk compared to those who take antivitamin K (VKA).

Owattanapanich, et al. (16) and Bensi, et al. (17) agree that patients who take DOAC present three times more risk of postoperative bleeding; therefore, it is necessary to consider that these patients still receive TXA therapy, which does not completely resolve the risk of blood loss. Therefore, it is critical to ponder the treatment that the anticoagulated patient is taking. Johansson, *et al*. (6) and Stelea, et al. (21) compared patients who take DOACs and VKAs, finding that patients with DOAC have a bleeding risk from 4.8 % to 22.5 %, while patients taking VKAs had a risk of 27.3 %, being safer the treatment with DOAC. Based on the evidence reviewed, we support the current trend of not changing pharmacological therapies in patients with bleeding disorders (23). Agreeing with Pirlog, *et al*. (8), who state that it is not necessary to change the therapeutic protocol if adequate hemostatic measures are in place, Stelea, *et al*. (21) recommend biting a gauze soaked in TXA for 1 h in the surgical region, repeating it three times a day for four days. Therefore, patients are no longer exposed to high thromboembolic risk after suspending their drug treatment.

Despite the advantages and benefits of TXA, there is still controversy regarding its participation in the inflammatory process of oral tissues. As a response, a comparative analysis conducted by Barrett, *et al*., (26) explain that TXA can fulfill an inhibitory function of inflammatory mediators, mainly interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α), in addition to acting at the level of the Complement pathway, inactivating protein 3 by reducing the recovery period of the affected tissue. The same authors describe a proinflammatory effect from a small sample, leading to increased levels of TNF-α and chemotactic proteins, giving it an adverse effect. Despite this, they deduced that TXA has a greater potential to create an anti-inflammatory effect.

Another aspect to address is safety and cytotoxicity. Engelen, *et al*. (5) and Murdaca, *et al*. (20) agree that TXA achieves a good safety profile and is incapable of damaging tissues. As we have analyzed, the maximum doses used in oral surgery do not exceed 20 mg when intravenously, and most interventions are used topically or as a mouthwash, with little or no systemic absorption, which gives greater control and safety for use in oral surgery. Nevertheless, Gkiatas, *et al*. (36) show that the risk of cytotoxicity is directly dependent on time and dose. Ranges greater than 20 mg to 40 mg can be harmful to the tissue because they trigger the caspase cascade, which for being proteolytic cause apoptosis of synovial fluid cells and cartilage tissue. However, it is important to consider that that study was not conducted on osteoblastic and/or osteoclastic cells, leaving this uncertainty to future research.

CONCLUSIONS

Based on the systematic literature review conducted, TXA in doses not exceeding 20 mg administered topically or intravenous, has shown to be effective in reducing the risk of bleeding during and after surgical procedures. This has been the case in both minor and major interventions, which improves operating times and reduces complications that may arise in the surgical field, thus proving its applicability in oral surgery.

RECOMMENDATIONS

One limitation of this study was the reduced number of randomized controlled trials, since most of the evidence focuses on orthopedic surgery, leaving the field open to future studies to point to the use of TXA in interventions and protocols in cases of complications in oral surgery.

Reference

1. Okamoto S, Okamoto U. Amino-methyl-cyclohexane-carboxylic acid: AMCHA. A new potent inhibitor of the fibrinolysis. Keio J Med. 1962; 11: 105-115. https://doi.org/10.2302/kjm.11.105
2. Ambrogio RI, Levine MH. Tranexamic acid as a hemostatic adjunct in dentistry. Compend Contin Educ Dent. 2018 Jun; 39(6): 392-401.
3. Wang F, Zhao KC, Zhao MM, Zhao DX. The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: A meta-analysis. Medicine (Baltimore). 2018 Sep; 97(36): e12270. https://doi.org/10.1097/MD.0000000000012270
4. Franco R, Miranda M, Di Renzo L, De Lorenzo A, Barlattani A, Bollero P. Glanzmann's thrombastenia: The Role of tranexamic acid in oral surgery. Case Rep Dent. 2018 Sep 5; 2018: 9370212. https://doi.org/10.1155/2018/9370212
5. Engelen ET, Schutgens RE, Mauser-Bunschoten EP, van Es RJ, van Galen KP. Antifibrinolytic therapy for preventing oral bleeding in people on anticoagulants undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev. 2018 Jul 2; 7(7): CD012293. https://doi.org/10.1002/14651858.CD012293
6. Johansson K, Götrick B, Holst J, Tranæus S, Naimi-Akbar A. Impact of direct oral anticoagulants on bleeding tendency and postoperative complications in oral surgery: a systematic review of controlled studies. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Mar; 135(3): 333-346. https://doi.org/10.1016/j.oooo.2022.07.003
7. Van Galen KP, Engelen ET, Mauser-Bunschoten EP, van Es RJ, Schutgens RE. Antifibrinolytic therapy for preventing oral bleeding in patients with haemophilia or Von Willebrand disease undergoing minor oral surgery or dental extractions. Cochrane Database Syst Rev. 2019 Apr 19; 4(4): CD011385. https://doi.org/10.1002/14651858.CD011385.pub3
8. Sharma S, Chak RK, Khanna R. Management of haemostasis during dental extraction in a Bernard-Soulier syndrome child. BMJ Case Rep. 2019 Jul 8; 12(7): e229082. https://doi.org/10.1136/bcr-2018-229082
9. Ullah K, Mukhtar H, Khalid U, Sarfraz Z, Sarfraz A. Is antifibrinolytic therapy effective for preventing hemorrhage in patients with hemophilia undergoing dental extractions? A systematic review and meta-analysis. Clin Appl Thromb Hemost. 2022 Jan-Dec; 28: 10760296221114862. https://doi.org/10.1177/10760296221114862
10. Kurasawa Y, Sato H, Katada R, Inada T, Shirota T, Shimane T. Delayed epistaxis which was developed after orthognathic surgery with Le Fort I osteotomy and managed by endoscopic cauterization. Case Rep Dent. 2022 Feb 22; 2022: 3057472. https://doi.org/10.1155/2022/3057472
11. Dunphy L, Williams R. Immune thrombocytopenic purpura presenting with spontaneous gingival haemorrhage in pregnancy. BMJ Case Rep. 2019 Jan 17; 12(1): e228309. https://doi.org/10.1136/bcr-2018-228309
12. Zhao H, Liu S, Wu Z, Zhao H, Ma C. Comprehensive assessment of tranexamic acid during orthognathic surgery: A systematic review and meta-analysis of randomized, controlled trials. J Craniomaxillofac Surg. 2019 Apr; 47(4): 592-601. https://doi.org/10.1016/j.jcms.2019.01.021

13. Mei A, Qiu L. The efficacy of tranexamic acid for orthognathic surgery: a meta-analysis of randomized controlled trials. Int J Oral Maxillofac Surg. 2019 Oct; 48(10): 1323-1328. https://doi.org/10.1016/j.ijom.2018.07.027
14. de Vasconcellos SJ, Santos T, Reinheimer DM, Faria-e-Silva AL, de Melo MF, Martins-Filho PR. Topical application of tranexamic acid in anticoagulated patients undergoing minor oral surgery: A systematic review and meta-analysis of randomized clinical trials. J Craniomaxillofac Surg. 2017 Jan; 45(1): 20-26. https://doi.org/10.1016/j.jcms.2016.10.001
15. Montroy J, Hutton B, Moodley P, Fergusson NA, Cheng W, Tinmouth A, Lavallée LT, Fergusson DA, Breau RH. The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis. Transfus Med Rev. 2018 Feb 19: S0887-7963(17): 30151-7. https://doi.org/10.1016/j.tmrv.2018.02.003
16. Owattanapanich D, Ungprasert P, Owattanapanich W. Efficacy of local tranexamic acid treatment for prevention of bleeding after dental procedures: A systematic review and meta-analysis. J Dent Sci. 2019 Mar; 14(1): 21-26. https://doi.org/10.1016/j.jds.2018.10.001
17. Bensi C, Belli S, Paradiso D, Lomurno G. Postoperative bleeding risk of direct oral anticoagulants after oral surgery procedures: a systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2018 Jul; 47(7): 923-932. https://doi.org/10.1016/j.ijom.2018.03.016
18. Yates J, Perelman I, Khair S, Taylor J, Lampron J, Tinmouth A, Saidenberg E. Exclusion criteria and adverse events in perioperative trials of tranexamic acid: a systematic review and meta-analysis. Transfusion. 2019 Feb; 59(2): 806-824. https://doi.org/10.1111/trf.15030
19. Bajkin BV, Wahl MJ, Miller CS. Dental implant surgery and risk of bleeding in patients on antithrombotic medications: A review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2020 Nov; 130(5): 522-532. https://doi.org/10.1016/j.oooo.2020.07.012
20. Murdaca G, Greco M, Vassallo C, Gangemi S. Tranexamic acid adverse reactions: a brief summary for internists and emergency doctors. Clin Mol Allergy. 2020 Sep 3; 18: 16. https://doi.org/10.1186/s12948-020-00131-8
21. Stelea CG, Dîmbu E, Sorin A, Oana E, Stelea AL, Bologa C. Assessing the bleeding risk in patients using direct oral anticoagulants submitted to dental surgery procedures. A systematic review. Rom J Oral Rehabil. 2020; 10(3).
22. Franchini M, Mannucci PM. The never-ending success story of tranexamic acid in acquired bleeding. Haematologica. 2020 May; 105(5): 1201-1205. https://doi.org/10.3324/haematol.2020.250720
23. Cervino G, Fiorillo L, Monte IP, De Stefano R, Laino L, Crimi S, Bianchi A, Herford AS, Biondi A, Cicciù M. Advances in antiplatelet therapy for dentofacial surgery patients: focus on past and present strategies. Materials (Basel). 2019 May 9; 12(9): 1524. https://doi.org/10.3390/ma1209152
24. Karasneh J, Christoforou J, Walker JS, Dios PD, Lockhart PB, Patton LL. World Workshop on Oral Medicine VII: Bleeding control interventions for invasive dental procedures in patients with inherited functional platelet disorders: A systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Apr; 133(4): 412-431. https://doi.org/10.1016/j.oooo.2021.08.003
25. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. Blood Coagul Fibrinolysis. 2019 Jan; 30(1): 1-10. https://doi.org/10.1097/MBC.0000000000000789
26. Barrett CD, Kong YW, Yaffe MB. Influence of tranexamic acid on inflammatory signaling in trauma. Semin Thromb Hemost. 2020 Mar; 46(2): 183-188. https://doi.org/10.1055/s-0040-1702169
27. Chen LF, Wang TC, Lin TY, Pao PJ, Chu KC, Yang CH, Chang JH, Hsu CW, Bai CH, Hsu YP. Does tranexamic acid reduce the risk of mortality on patients with hemoptysis? A protocol for systematic review and meta-analysis. Medicine (Baltimore). 2021 May 21; 100(20): e25898. https://doi.org/10.1097/MD.0000000000025898
28. Pirlog CD, Pirlog AM, Maghiar T. A systematic review of the hemorrhage risk for patients on antithrombotic medication after dental procedures. World J Dent 2018; 9(1): 59-67. https://doi.org/10.5005/jp-journals-10015-1508
29. Monteilh C, Rabon L, Mayer-Hirshfeld I, McGreevy J. Nebulized tranexamic acid for pediatric post-tonsillectomy hemorrhage: a report of two cases. Clin Pract Cases Emerg Med. 2021 May; 5(2): 148-151. https://doi.org/10.5811/cpcem.2021.2.50799
30. Dermendjieva M, Gopalsami A, Glennon N, Torbati S. Nebulized tranexamic acid in secondary post-tonsillectomy hemorrhage: case series and review of the literature. Clin Pract Cases Emerg Med. 2021 Aug; 5(3): 1-7. https://doi.org/10.5811/cpcem.2021.5.52549
31. Boccio E, Hultz K, Wong AH. Topical tranexamic acid for hemostasis of an oral bleed in a patient on a direct oral anticoagulant. Clin Pract Cases Emerg Med. 2020 Mar 27; 4(2): 146-149. https://doi.org/10.5811/cpcem.2020.1.45326

32. Poppe M, Grimaldo F. A case report of nebulized tranexamic acid for post-tonsillectomy hemorrhage in an adult. Clin Pract Cases Emerg Med. 2020 Aug; 4(3): 443-445. https://doi.org/10.5811/cpcem.2020.6.47676
33. Shadamarshan R A, Sharma R, Pradhan I, Kumar P. Post-dental extraction bleeding: Emphasis on the diagnosis of rare coagulation disorders. Clin Case Rep. 2021 Aug 30; 9(9): e04746. https://doi.org/10.1002/ccr3.4746
34. Ehrhard S, Burkhard JP, Exadaktylos AK, Sauter TC. Severe enoral bleeding with a direct oral anticoagulant after tooth extraction and heparin bridging treatment. Case Rep Emerg Med. 2019 Oct 29; 2019: 6208604. https://doi.org/10.1155/2019/6208604
35. O'Connor MK, Emanuelli E, Garg RK. Le Fort I maxillary osteotomy in a Jehovah's Witness patient: strategies for minimizing blood loss and maximizing safety. Maxillofac Plast Reconstr Surg. 2022 Mar 2; 44(1): 10. https://doi.org/10.1186/s40902-022-00338-6
36. Gkiatas I, Kontokostopoulos AP, Tsirigkakis SE, Kostas-Agnantis I, Gelalis I, Korompilias A, Pakos E. Topical use of tranexamic acid: Are there concerns for cytotoxicity? World J Orthop. 2022 Jun 18; 13(6): 555-563. https://doi.org/10.5312/wjo.v13.i6.555
37. Modir H, Moshiri E, Naseri N, Faraji F, Almasi-Hashiani A. A randomized parallel design trial of the efficacy and safety of tranexamic acid, dexmedetomidine and nitroglycerin in controlling intraoperative bleeding and improving surgical field quality during septorhinoplasty under general anesthesia. Med Gas Res. 2021 Oct-Dec; 11(4): 131-137. https://doi.org/10.4103/2045-9912.318857

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