Review article

Role of Tranexamic Acid in Oral Surgery

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Abstract

Background: Tranexamic acid is a synthetic lysine derivative that exerts its antifibrinolytic effect by reversibly blocking lysine binding sites on plasminogen and thus preventing fibrin degradation. In case of dental surgery, post operative bleeding is a common problem which if uncontrolled can result in increased loss of blood and delayed wound healing. Patients with bleeding and clotting disorders and patients on anti coagulant therapy have tendency for excessive bleeding. In such cases the use of tranexamic acid becomes more significant in dental surgeries. By understanding the pharmacokinetics and pharmacodynamic aspects of the tranexamic acid we can gain a through knowledge about its properties which will aid its use in oral surgery.

Key Words: *Tranexamic acid, surgery, bleeding.*

Introduction

Tranexamic acid is an anticoagulant is used to reduce the blood coagulability to an optimal level to help in providing protection against thromboembolic effects in patient undergoing oral surgeries. This is attained in case of minor risk of spontaneous bleeding. Patients reporting for invasive dental procedures are expected to cause more bleeding.

Consideration regarding whether the anticoagulant treatment as to be continued, modified or discontinued at some point of the the treatment has to be considered. In such situations the dentist has to take into consideration regarding the patient's ability to attain haemostasis in cases of continuation of anticoagulants and in cases of withdrawal of anticoagulants. To avoid these consequences per procedural care.

Tranexamic acid is a synthetic derivative of the amino acid lysin which exhibit its antifibrinolytic effect, through the reversible blocking of lysin binding sites on the plasminogen molecules. Intravenous administration of tranexamic acid has been routinely used for many years to reduce hemorrhage during and after surgical procedures like coronary artery bypass, scoliosis surgery, oral surgery, orthotopic liver transplantation, total hip or knee arthroplasty, and urinary tract surgery[1,2]. A complete drug history is important in patients taking anti coagulants. There is also influence of certain medications which may interfere with haemostasis and prolonged bleeding. Drugs such as alcohol, heroin can result in bleeding[3]

Tranexamic acid is an active trans stereoisomers of amino-methyl cyclohexane carboxylic acid and has been shown to have powerful antifibrinolytic properties. It was first described by Okamoto in 1962[4].

Tranexamic acid is available in both systemic and topical forms. Systemic form of treatment is not advised in patients with oral anticoagulants as it may result in thromboembolism. Concentration of trance amid acid is hardly detectable in plasm after the use in the form of mouth wash and it ha insignificant effect in inhibition of the fibrinolysis [5,6]. Tranexamic acid shows accelerated wound healing [7]. Thus it is significant to know the role of Blood loss and subsequent transfusions are associated with major morbidity and mortality [8,9]. Thus the use of antifibrinolytics can result in reduction of blood loss in cardiac surgery, trauma, liver surgery and solid organ transplantation and non-surgical diseases. The evidence of their efficacy has been mounting for years [10,11]. Synthetic lysine-analogue tranexamic acid (TXA, trans-4-aminomethylcyclohexane-1-carboxylic acid), along with ε-aminocaproic acid (ε-ACA), were first patented by S. Okamotoin 1957 [12]. Okamoto and Okamoto (1962) drew attention to tranexamic acid (AMCA) as a more potent inhibitor of the fibrinolytic enzyme system than aminocaproic acid, first introduced by Okamoto (1959). Further research by Melander et al. (1964) and Okamoto

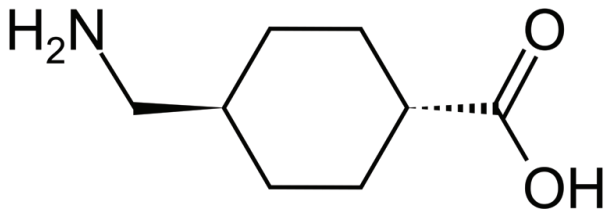
et al. (1964) showed that the cyclohexane derivative consisted of two isomers, the more active being the synthetic amino-acid tranexamic acid.This was found to be at least ten times more potent than amino caproic acid and the effect to last longer, and Anderson et al. (1965) found it to be seven times more potent. The use of amino caproic acid in the control of haemorrhage after the extraction of teeth in haemophilia has been investigated by Melander (1964) (1968).[13]

Several factors , may operate together to cause haemorrhage. For instance, in the presence of defective small vessel constriction or low-grade disseminated intravascular coagulation the action of the normal fibrinolytic response may be sufficient to initiate haemorrhage.[14]

Mechanism of Action:

The main action of the amino caproicacid compounds is to compete with lysine binding sites on plasminogen and plasmin. They inhibit the activation of plasminogen by streptokinase, urokinase and tissue activator. The binding of the heavy chain of plasmin to fibrin in monomerism is achieved by lysin binding sites, the blocking of these sites by amino caproic acid causes yo ichiometric inhibition of plasmin, with the formation of the inactive complex between plasmin and amino caproic acid. It will be no ted from the excellent view by D Colleen that the rate of that the rate of binding of alpha 2 plasmin is dependant on the availability of free ridual plasmin. In the presence of free residual plasmin is rapidly inactivated by alpha 2 to. Antiplasim Conversely, when the lysine residues are blocked, either by fibrin monomer or by amino-caproic acid, inactivation by alpha2-antiplasmin is reduced. This potent action of amino caproic acid as an inhibitor of plasmin in physiological fibrinolysis on a substrate of fibrinogen or fibrin has been recognised only fairly recently much of earlier studies was carried out . Similarly amino caproic acid is relatively inactive against the hydrolytic action of plasmin synthesis . Thus striking action of amino caproic acid Isco block the action of plasmin on fibrin . The interaction between plasminogen, plasmin, activator and fibrin complex. Tissue activators adsorbent to fibrin and in the presence of plasminogen mediate proteolytic cleavage of the terminal part of plasminogen, changing native Glu- plasminogen into Lys- plasminogen. The latter has higher affinity for the fibrin than the native. Plasminogen promote the resolution of fibrin with thrombus rather than causing the digestion of circulating fibrinogen during the fibrinolytic process. Plasmin is change form plasminogen by further cleavage of an internal Arg- Lys peptide bond in plasminogen . Plasmin also has affinity for fibrin. Thus consideration of fibrinolytic inhibitors must include their effective enzymes site but also their ability to interfere with the binding of the various components. The problem is further complicated by the type of activator studied. Tissue has greater affinity for urokinase[15]

Pharmacology of Tranexamic Acid:



Tranexamic acid is a synthetic derivative of the amino acid lysine and it inhibits fibrinolysis by blocking lysine binding site on the plasminogen. It is a competitive inhibitor of activation of plasminogen to plasmin and at higher a concen- trations and a non-competitive inhibitor of plasmin. Topical application of tranexamic acid has the potential to inhibit local fibrinolysis at the site of bleeding but with minimal systemic absorption. In this way, it could reduce bleeding and the need for blood transfusion without systemic side effects such as throm- boembolic events.

TXA is a synthetic lysine-analogue antifibrinolytic [16] that competitively inhibits the activation of plasminogen to plasmin; at high concentrations it non-competitively blocks plasmin, thus TXA inhibits the dissolution and degradation of fibrin clots by plasmin. The binding of TXA to plasminogen is 6 to 10 times more potent that of ε-ACA [17]. TXA has been shown to increase thrombus formation in a dose-dependent fashion in animal models, in contrast to aprotinin, which inhibits thrombus formation [18].

Suppression of fibrinolysis by tranexamic acid is manifested in surgical patients by reductions in blood levels of D-dimer, but the drug has no effect on blood coagulation parameters. Concurrent administration of heparin does not influence the activity of tranexamic acid. A series of cyclic compounds were founding have more potent fibrinolytic activity than EACA. One of the most suitable was AMCHA(4-aminomethyl-cyclohexane carboxylic acid). The potency of this compound, which is a mixture of stereoisomers, is due

to the residues in the trans-isomer, known as tranexamic acid which forms about 20-25% of the parent mixture. Tranexamic acid is some 10times more potent than EACA. It is such that that the potency of the compound depend on critical distance between the essential amino carboxylic acid groups[19].

Pharmacokinetics:

Maximum plasma concentrations of tranexamic acid are attained within 3 hours of an oral dose; the presence of food in the gastrointestinal tract has no effect on the pharmacokinetic parameters of the drug. Elimination after intravenous administration is triexponential, and over 95% of each dose is eliminated as unchanged drug in the urine. The total cumulative excretion after an intravenous dose is approximately 90% after 24 hours.

Of the total amount of circulating tranexamic acid, 3% is bound to plasminogen. The drug crosses the blood-brain barrier and the placenta, but excretion into breast milk is minimal. Tranexamic acid is not detectable in saliva after systemic (oral) administration, and mouth washing with 5% w/v aqueous solutions of the drug results in plasma drug concentrations below 2 mg/L[20]

Indications:

Tranexamic acid can be used in patients with haemophilia for two to eight days ie. Short term use to prevent haemorrhage during replacement therapy following tooth extraction. T XA is the only drug that can be used safely for reducing blood loss. Infusion of IV TXA to trauma patients within three hours of trauma has successfully saved many lives per year 1,000 trauma patients in Tanzania, India and the UK [21]

It can be used in other cases like excessive bleeding, mensuration, trauma and other surgery.

Tranexamic acid in oral surgery and its use in the form of mouth wash:

The treatment is to prevent bleeding after oral/ dental surgery in patients who are taking anticoagulants. It is an effective alternative to reducing patients' anticoagulants before surgery, then increasing them afterwards.

This treatment allows you to keep taking your normal dose of anticoagulant. Any bleeding in the mouth is controlled by tranexamic acid working directly on the bleeding area[22].

It is very important to follow the following methods,

Use the mouth rinses four times a day starting on the day of dental or any oral surgery. Use the first dose of 5-10 minutes prior to the extraction.

Rinse your mouth with 5ml for a period of two minutes each time. Be aware not to swallow any of the mouthwash after dental or other oral surgeries.

By using tranexamic acid in form of mouth rinses showed reduction in plasma levels.[23]

Determination of bleeding disorders prior to dental procedures includes:

Tests associated with the evaluation of bleeding complications for dental patients undergoing surgery include (1) complete blood count (CBC), (2) blood smear (3) bleeding time (BT), (4) prothrombin time (PT) (5) international normalization ratio (INR) (6) partial prothrombin time (PTT) (7) serum fibrinogen which measures the level of fibrinogen in the serum; (8) fibrin degradation products, (9) protamine paracoagulation test, (10) euglobulin clot lysis test [24]

Topical usage of TXA:

The topical use of TXA has been examined by Cochrane[25] Although the authors found reliable evidence that topical TXA reduces bleeding and blood trans-fusion in surgical patients, the risk of thromboembolism is unclear, as many studies do not report this complication or are underpowered. Topical administration results in a ten fold less plasma concentration of TXA when compared to intravenous administration. The surgical extraction of third molars under day case surgery is one of the most frequently performed oral surgical procedures. Bryant *et al*.[26] reported an almost 6-fold increase in the total number of dentoalveolar procedures carried out as day cases under general anaesthesia over the past 20 years with third molar surgery showing a 7-fold increase. Day case surgery patients have unique needs, distinct from those of traditional overnight or long-stay in-patients. The disadvantages of day case surgery are that patients may present for surgery improperly prepared or may be discharged from direct supervision before they have adequately recovered. Their post-operative needs are

central to achieving complete recovery and ensuring there are no unplanned readmissions to hospital. Chye *et al* [27]. reported a readmission rate to hospital of 0.25%,compared with 2.5% and 1.9% was reported.

Side effects of tranexamic acid:

Oral:

Tranexamic acid can cause serious side effects, including:

· Blood clots. The risk of serious blood clots may be increased when tranexamic acid is taken with:

o hormonal contraceptives, especially if you are taking higher than your normal dose of birth control, are overweight, or if you smoke cigarettes

o medicines used to help your blood clot

o some medicines used to treat leukaemia

· problems with your vision (including colour vision);

· sudden numbness or weakness, especially on one side of the body;

· sudden headache, confusion, problems with vision, speech, or balance;

· sudden chest pain or trouble breathing;

· pain or swelling in one or both legs;

· migraine headache;

· pale skin, feeling light-headed or short of breath, rapid heart rate, trouble concentrating; or

· feeling like you might pass out.

Cutaneous Adverse Effects:

Drug eruption, epidermal necrolysis, and bulbous eruption. [28,29]

Conclusion

In the past, the management of patients therapeutically anticoagulated with various anticoagulants requiring dental extractions has posed a dilemma to the attending dental surgeon. The following factors have probably contributed to the favourable evolution of the management of these patients: increased training and experience of dentists; improved dental status of patients, minimizing necessity for multiple extractions and increasing awareness of local fibrinolysis in the oral cavity and the use of local measures. Thus the review about Tranexamic acid would aid to know in use in dentistry and it's method of usage , available forms, indications contra indications and other factors would help in gaining a brief knowledge about TXA.

Ethical Clearance-Nil

Source of Funding- Nil

Conflict of Interest -Nil

References

1. Kambo I, Bedi N, Dhillon BS, Saxena NC. A critical appraisal of cesarean section rates at teaching hospitals in India. International Journal of Gynecology & Obstetrics. 2002 Nov 1;79(2):151-8.
2. Thorsen S, Clemmensen I, Sottrup-Jensen L, Magnusson S. Adsorption to fibrin of native fragments of known primary structure from human plasminogen. Biochimica et Biophysical Acta (BBA)-Protein Structure. 1981 May 29;668(3):377-87.
3. Brown RS, Thwaites BK, Mongan PD. Tranexamic acid is effective in decreasing postoperative bleeding and transfusions in primary coronary artery bypass operations: a double-blind, randomized, placebo-controlled trial. Anesthesia & Analgesia. 1997 Nov 1;85(5):963-70.
4. Watts G. Utako Okamoto. The Lancet. 2016 Jun 4;387(10035):2286. OkamotoS.Ref.to British Patent Specification1957;770,693.
5. Gai MY, Wu LF, Su QF, Tatsumoto K. Clinical observation of blood loss reduced by tranexamic acid during and after caesarian section: a multi-enter, randomized trial. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2004 Feb 10;112(2):154-7.
6. Yang H, Zheng S, Shi C. Clinical study on the efficacy of tranexamic acid in reducing postpartum blood lose: a randomized, comparative, multicenter trial. Zhonghua Fu Chan Ke Za Zhi. 2001 Oct;36(10):590-2.
7. Lindoff C, Rybo G, Astedt B. Treatment with tranexamic acid during pregnancy, and the risk of

thrombo-embolic complications. Thrombosis and haemostasis. 1993 Aug;70(2):238-40.

8. Akopov SE, Suzuki S, Fredieu A, Kidwell CS, Saver JL, Cohen SN. Withdrawal of warfarin prior to a surgical procedure: time to follow the guidelines?. Cerebrovascular Diseases. 2005;19(5):337-42.

9. Alexander R, Ferretti AC, Sorensen JR. Stop the nonsense not the anticoagulants: a matter of life and death. The New York state dental journal. 2002 Nov;68(9):24-6.

10. Beirne OR. Evidence to continue oral anticoagulant therapy for ambulatory oral surgery. Journal of oral and maxillofacial surgery. 2005 Apr 1;63(4):540-5.

11. Carter G, Goss AN, Lloyd J, Tocchetti R. Current concepts of the management of dental extractions for patients taking warfarin. Australian dental journal. 2003 Jun 1;48(2):89-96.

12. Okamoto S, Hijikata-Okunomiya A, Wanaka K, Okada Y, Okamoto U. Enzyme-controlling medicines: introduction. InSeminars in thrombosis and hemostasis 1997 Dec (Vol. 23, No. 06, pp. 493-501). Copyright© 1997 by Thieme Medical Publishers, Inc.

13. Okamoto K, Iba T, Uchiyama T, Kawasugi K, Koga S, Mayumi T, Koike K, Gando S, Kushimoto S. Expert consensus for the treatment of disseminated intravascular coagulation in Japan. Thrombosis research. 2010 Jan 1;125(1):6-11. 14.MelanderB, GlinieckiG, GranstrandB, HanshoffG.Theantifibrinolyticallyactiveisomer of AMCH Abstracts of the Xth International CongressofHae- matology, Stockholm,Aug30-Sept41964:G68.

15. Little JW, Miller CS, Henry RG, McIntosh BA. Antithrombotic agents: implications in dentistry. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. 2002 May 1;93(5):544-51.

16. Lockhart PB, Gibson J, Pond SH, Leitch J. Dental management considerations for the patient with an acquired coagulopathy. Part 2: Coagulopathies from drugs. British dental journal. 2003 Nov 8;195(9):405.

17. Patton LL, Ship JA. Treatment of patients with bleeding disorders. Dental clinics of North America. 1994 Jul;38(3):465-82.

18. Rice PJ, Perry RJ, Afzal Z, Stockley IH. Antibacterial prescribing and warfarin: a review. British dental journal. 2003 Apr 26;194(8):411.

19. Scully C, Wolff A. Oral surgery in patients on anticoagulant therapy. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics. 2002 Jul 1;94(1):57-64.

20. Jover Cerveró A, Poveda Roda R, Bagán JV, Jiménez Soriano Y. Dental treatment of patients with coagulation factor alterations: An update. Medicina Oral, Patología Oral y Cirugía Bucal (Internet). 2007 Sep;12(5):380-7.

21. Wahl MJ. Dental surgery in anticoagulated patients. Archives of internal medicine. 1998 Aug 10;158(15):1610-

22. Hirsh J, Dalen JE, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D. Oral anticoagulants: mechanism of action, clinical effectiveness, and optimal therapeutic range. Chest. 2001 Jan 1;119(1):8S-21S

23. Cochrane E. Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. International journal of qualitative methods. 2006 Mar;5(1):80-92.

24. Bryant RE. Graph-based algorithms for boolean function manipulation. Computers, IEEE Transactions on. 1986 Aug;100(8):677-91.

25. Chye PW, Skeath PR, Su CY, Lindau I. New and unified model for Schottky barrier and III–V insulator interface states formation. Journal of Vacuum Science and Technology. 1979 Sep;16(5):1422-33.

28. Sindet-Pedersen S, Ramström G, Bernvil S, Blombäck M. Hemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. New England Journal of Medicine. 1989 Mar 30;320(13):840-3.

29. Pemberton MN, Oliver RJ, Theaker ED. Miconazole oral gel and drug interactions. British dental journal. 2004 May 8;196(9):529.