

## The Effect of Tranexamic Acid (Cyclokapron) on Post-Surgical Bleeding Following the Removal of Impacted Lower Wisdom Teeth in Healthy Individuals

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### ABSTRACT

**Aims:** To evaluate the effect of local irrigation with tranexamic acid in minimizing post-operative bleeding following the removal of impacted lower wisdom teeth. **Materials and Methods:** This clinical trial was conducted at the Department of Oral and Maxillofacial Surgery / College of Dentistry / University of Mosul. The sample recruited comprised twenty healthy subjects who required surgical removal of clinically as well as radiographically evident impacted lower wisdom teeth. The sample was subdivided into two groups of ten subjects each. The first group which is the control group included ten subjects where after removal of the tooth, local irrigation of socket was carried out with normal saline. The second group which is the trial group comprised ten subjects also, but in which tranexamic acid (injectable solution) in diluted form was used for local irrigation of socket. Both solutions were of equal amount. Estimation of amount of blood loss immediately following surgery was the criterion for comparison and was based on weight of gauze used before and after application over extraction socket. **Results:** The results showed a statistically significant decrease in the amount of blood loss in the trial group when compared with the control group. **Conclusions:** Tranexamic acid as commercially available or freshly prepared oral rinse may be used as an aid for the reduction or prevention of postoperative bleeding following the removal of third molars in healthy subjects as well as in patients with bleeding problems.

**Key words:** Tranexamic acid, antifibrinolytic agents, oral surgery.

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### INTRODUCTION

Tranexamic acid (Cyclokapron – TEA) is an antifibrinolytic agent and its predecessor epsilon aminocaproic acid has been used to reduce or prevent postoperative bleeding in patients with bleeding problems for many years<sup>(1)</sup>. Tranexamic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules<sup>(2)</sup>.

The indication for using this drug is for reduction or prevention of excessive bleeding in patients having a high risk of intra and post operative hemorrhage (during

general and oral surgery) due to a bleeding disorder such as hemophilia, or patients receiving anticoagulant therapy and it has been found to be highly effective without significant side effects. Tranexamic acid may be given alone or in combination with standard doses of coagulation factor concentrates. In some studies the use of tranexamic acid has been compared with other local haemostatic agents<sup>(3-10)</sup>. In dentoalveolar surgery, tranexamic acid can be used to control bleeding following lower third molar surgery<sup>(11)</sup>. Tranexamic acid is usually available in tablet form (500 mg) and the typical dose is 3 or 4 grams (in

divided doses) daily for an adult. Gastrointestinal upset (nausea, vomiting and diarrhea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. It may also be given as an intravenous injection (10–25mg / kg) but it must be infused slowly as rapid injection may result in dizziness and hypotension. For oral surgical procedures, a mouth wash is available at a concentration of 4.8%, it is used as 10 ml rinse for 2 minutes / 4 times daily for 5–7 days. A syrup formulation is also available for pediatric use<sup>(2)</sup>. The drug is excreted by the kidneys, and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation<sup>(12)</sup>.

Due to the scarcity of the commercially available mouthwash, the current clinical trial intended to use a diluted injectable form of tranexamic acid as an alternative for irrigation of third molar extraction wound in healthy subjects.

#### MATERIALS AND METHODS

This clinical trial was conducted at the Department of Oral and Maxillofacial Surgery / College of Dentistry / University of Mosul. The sample recruited comprised twenty apparently healthy subjects according to the following criteria:

1. No history of allergy to any medication.
2. No history of having a hemorrhagic diathesis or anticoagulants intake.
3. Female patients who are pregnant, lactating or having oral contraceptives were excluded.
4. All patients should have not taken any non-steroidal anti-inflammatory analgesics within 1 week of surgery.
5. Only cases of soft tissue impaction, as confirmed both clinically and radiographically, were included. The rationale was to exclude bone removal as one of the factors which affect post operative bleeding. This meant that only vertical soft tissue impactions were included.
6. Non-smoker.

The age of patients ranged between 21 to 32 years of both genders who required surgical removal of clinically as well as radiographically evident impacted lower wisdom teeth. Before the trial was com-

menced, any acute stage of dental infection (pericoronitis) was rendered chronic by antibiotics with or without incision and drainage. In addition, each patient was requested to use chlorhexidine mouthwash 0.2% , 15 ml for 30 seconds / twice daily for one week before surgery.

The sample was randomly subdivided into two groups of ten subjects each according to the solution that was intended to be used for irrigation of surgical wound before and after its closure. The allocation was in a randomized manner. The first group (control group) included ten subjects where local irrigation was carried out using 10 ml of normal saline (0.9% NaCl –Made in Iraq). In the second group (trial group), which also included ten subjects, 10 ml of tranexamic acid (injectable solution) in diluted form was to be used for local irrigation following the removal of the lower third molar. The design of trial was to be in a double blind manner; i.e., neither the operator nor the patient had knowledge of the solution to be used. An independent member prepared on each extraction occasion either 10ml of normal saline, each 5ml in a 5ml graduated disposable syringe or 10ml of freshly prepared diluted solution of injectable tranexamic acid (Exacyl, 500mg in 5 ml ampoule, Sanofi – Winthrop, France) with each 5ml in a 5ml graduated disposable syringe . Dilution of the latter solution was based on the assumption that tranexamic acid used as mouth wash was at a concentration of 4.8% and to achieve such a concentration from the available injectable type, 1.25 ml of tranexamic acid from ampoule was to be diluted to 5ml with distilled water. For each group, the syringe was labeled with a specific number indicating the specific solution and upon completion of trial, access to the identity of solution was possible for the operator. In the control group, after extraction, local irrigation of socket wound was carried out with 5ml of normal saline in a 5ml graded disposable syringe before closure of flap followed by soaking a piece of dry gauze with another 5ml of the same solution which was to be bitten on gently for thirty minutes. That piece of gauze was then weighed in an electronic scale (Mettle , Electronic Scale, Switzerland) before it was disposed and replaced with a dry one.

It should be noted that each piece of gauze used was weighed dry for both groups before surgery. The weight of gauze following surgery represented both the amount of saliva and blood lost at the same time. Surgery carried out was standardized for all subjects: Mandibular block injection of a single cartridge of 1.8 ml 2% xylocaine solution with 1:80.000 adrenaline (Septodont-France), a standard Ward flap design was raised commencing from the mesio-buccal aspect of the lower second molar, the flap was reflected with a Howarths periosteal elevator and retraction with a Bowdler Henry flap retractor. Tooth extraction was performed by simple luxation with an elevator followed by forceps removal. Any situation in which tooth sectioning and / bone removal was mandatory, the case would be excluded from the trial. Upon completion, a single interrupted stitch was placed immediately distal to the lower second molar tooth. Duration of surgery was recorded from incision to suturing. Each patient was requested to sit on a side chair for thirty minutes, after that the piece of gauze was removed, weighed then discarded and replaced with a new one. Verbal and written postoperative instructions were handed out to each patient. In

addition, antibiotics and analgesics were prescribed.

Estimation of amount of blood loss following surgery for each group was the criterion for comparison and was based on difference of weight of gauze after application over extraction socket for the two groups<sup>(13)</sup>.

In regard to statistical analysis, the Student's t- test was used to compare both groups. Means were significant if  $p < 0.05$ .

## RESULTS

The allocation of sample according to age and sex is shown in Table (1). The duration of surgical procedures ranged from 4 to 7 minutes with an average duration of 5.2 minutes. In the control group, the mean weight of gauze before application was 1.185 mg while after application over the extraction wound, the mean weight was 4.83mg as shown in Table (2). In the trial group, the mean weight of gauze before application was 1.254 mg while after 30 minutes following application over the extraction wound, the mean weight was 3.345 mg as shown in Table (2).

Table (1): Age and sex distribution of sample.

Age (years)	Sex	
	Male	Female
21-32 (Mean 26.3)	13	7

Table (2): Mean weight of gauze before and after application in control and trial groups.

Group	No.	Weight of gauze	Mean(mg) ± SD	t- test	P -value
Control	10	Dry	1.185± 0.416	-7.82	0.0000*
		After 30 min.	4.83 ± 1.41		
Trial	10	Dry	1.254 ± 0.329	- 9.15	0.000*
		After 30 min	3.345 ± 0.643		

SD: Standard deviation, df=18. \*significant difference at  $p < 0.05$ .

For both groups, no significant difference was disclosed between the weights of gauze before application as shown in Table (3). On the other hand, a significant difference was noticed between the two

groups after the application of gauze over socket wound with lesser weight of gauze in trial group (3.345mg) when compared with control group (4.83mg) as demonstrated in Table (4).

Table (3): Mean weight of gauze before application in control and trial group.

Group	No.	Weight of gauze	Mean(mg) $\pm$ SD	t- test	P – value
Control	10	Dry	1.185 $\pm$ 0.416	-0.41	0.68*
Trial	10	Dry	1.254 $\pm$ 0.329		

SD: Standard deviation, df= 18. \*no significant difference at  $p < 0.05$ .

Table (4): Mean weight of gauze after application in control and trial group.

Group	No.	Weight of gauze	Mean(mg) $\pm$ SD	t- test	P – value
Control	10	After 30 min.	4.83 $\pm$ 1.41	3.02	0.0073*
Trial	10	After 30 min	3.345 $\pm$ 0.643		

SD: Standard deviation, df=18. \*significant difference at  $p < 0.05$ .

## DISCUSSION

A number of complications either alone or in conjunction with each other may accompany dentoalveolar surgery, one of these is bleeding. It has been reported that the overall incidence of postoperative bleeding following third molar extraction ranges from 0.43% to 5.8 %.<sup>(14)</sup> The majority of patients who bleed after extractions do not have any underlying hematological disorders and generally have had extractions previously without complications, suggesting a purely local factor in the occurrence of hemorrhage; for example, local infection, traumatic surgery and noncompliance to postoperative instructions<sup>(15)</sup>.

Pharmacokinetic studies in healthy individuals have shown that after intravenous administration of 10mg/kg of tranexamic acid, the highest plasma concentration was reached within one hour after injection. After oral administration of 10 to 15mg/kg of body weight, the maximum plasma concentration was reached within 3 hours<sup>(18)</sup>. Many different doses and administration regimes have been adopted for the use of

the antifibrinolytic drug tranexamic acid in oral surgery for patients with a bleeding problem. The forms described are tablet, injection solution, syrup or mouthwash. In dental practice, the latter mentioned is the most commonly used and is dispensed as 10 ml of 4.8% solution as a mouth wash for 2 minutes/ 4 times daily for 2 – 7 days post-operatively. Limited resources however, are available in which the sample included in the trial comprised healthy subjects and the effect of tranexamic acid was evaluated at a very short period (after 30 minutes). In one study, tranexamic acid (25mg/kg) versus normal saline was administered intravenously in a sample of healthy adult volunteers. The results showed a significant reduction in the postoperative blood loss in the tranexamic acid group without any untoward side effects<sup>(11)</sup>. In cases when the mouth wash is not available in the local market, it could be extemporaneously prepared using the commercial tablets or injection<sup>(12)</sup>. In one trial, a 250 mg tablet was dissolved in 10 ml of distilled water to treat patients who need oral surgery on oral anti-

coagulants<sup>(16)</sup>. In another trial, a mouth rinse of 1 ampoule (100 mg/ml in 10 ml size ampoule) of the antifibrinolytic agent was used for 2 minutes/every 6 hours for 2 days<sup>(17)</sup>. In the current trial, a significant reduction in post-operative blood loss was noticed in the tranexamic acid group when compared with the control group. It should be appreciated that pressure on the pack in addition to initial effect of tranexamic acid on the stability of blood clot may have acted both together to minimize postoperative bleeding. Since stability data for aqueous solutions is lacking, such preparations should be freshly prepared<sup>(12)</sup>. This was the case in the current trial where the preparation was immediately prepared, used for a very short period of time and over a localized area. Using a single ampoule for each patient will of course reduce any possibility of cross infection. In regard to an extended use of tranexamic acid rinse for 2–5 days postoperatively (if necessary) in healthy subjects, it is recommended that further studies are recommended.

### CONCLUSIONS

Tranexamic acid as a commercially available or freshly prepared oral rinse may be used as an aid for the reduction or prevention of postoperative bleeding following the removal of third molars in healthy subjects as well as patients with bleeding problems. This simple strategy may also be applied to all dentoalveolar and periodontal surgical procedures under local anesthesia. Further studies are encouraged in this aspect.

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