

Systemic effect of tranexamic acid on Prothrombin and clotting times in rabbits after IV injection of heparin (Experimental study)

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ABSTRACT

Aim: To evaluate the effect of a single dose of tranexamic acid (cyclokapron) in reducing the postoperative bleeding following minor oral surgery on ten rabbits on anticoagulant therapy (heparin). **Materials and Methods:** Samples of blood were collected pre and post heparin and tranexamic acid injection for measuring the Prothrombin and clotting time. **Results:** There was no significant difference between the Prothrombin time and clotting time normal and Prothrombin time and clotting time after tranexamic acid injection. **Conclusion:** A single dose of tranexamic acid given postoperatively was effective in reducing the postoperative bleeding following minor oral surgery in experimental rabbit on heparin anticoagulant therapy without changing the regular heparin regimen doses. The same regimen may be applied on hospitalized patient on heparin anticoagulant therapy
Key Words: Tranexamic acid, Heparin, rabbit, Prothrombin time, clotting time.

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INTRODUCTION

Tranexamic acid is an antifibrinolytic agent and its predecessor epsilon amino caproic acid have been used to treat postoperative bleeding for over 30 years.

The use of tranexamic acid has superseded the use of epsilon amino caproic acid which not only has a shorter plasma half life but also is less potent and more toxic.⁽¹⁾ Tranexamic acid has been used in the prophylaxis and treatment in patients at high risk of intra- and postoperative haemorrhage such as haemophiliacs and patients on thrombolytic therapy and has been found to be highly effective without significant side effect.⁽¹⁻⁶⁾

Tranexamic acid used in dentoalveolar surgery as a day case to control of bleeding following third molar surgery.⁽⁷⁾ It is also used as mouthwash in those patients with prosthetic heart valve under anticoagulant.⁽⁵⁾ In other combination preparation used of tranexamic acid as mouthwash and systemically to control of bleeding in hereditary bleeding disorder (hemophilia).⁽⁶⁾

Heparin is widely used for prevention and treatment of thromboembolic diseases, the anticoagulant response to heparin vari-

es widely among the patients possibly because of variation in the plasma concentration of binding protein. Increasing the dose of heparin the risk of bleeding will be increased.⁽⁸⁾

Tranexamic acid may be given alone or together with standard doses of coagulation factor concentrate. However, it should not be given to patients with inhibitory antibodies receiving activated Prothrombin factor concentrates (such as FEIBA or Autoplex) as this may provoke thromboembolism. If treatment with both agents is deemed to be necessary, it is recommended that at least six hours should elapse between the last dose of APCC (Activated Prothrombin Coagulation Factor Concentrated) and the administration of tranexamic acid. By contrast, tranexamic acid may be usefully used in combination with recombinant factor VIIa to enhance haemostasis.⁽¹⁾

Tranexamic acid is usually given in tablet form at a typical dose of 3 or 4 grams (in divided doses) daily for an adult. Gastrointestinal upset (nausea, vomiting and diarrhoea) may rarely occur as a side effect, but these symptoms usually resolve if the dosage is reduced. It may also be gi-

ven by intravenous injection, but it must be infused slowly as rapid injection may result in dizziness and hypotension. A syrup formulation is also available for paediatric use: The syrup contains 500 mg tranexamic acid in each 5ml, and the usual dose for children is 25 mg/Kg up to three times daily. The drug may be of particular use in controlling oral bleeding associated with eruption of teeth. The drug is excreted by the kidneys, and the dose must be reduced if there is renal impairment in order to avoid toxic accumulation.⁽¹⁾

The aim of the present study was to evaluate the effect of pre-operative administration of tranexamic acid (Cyclokapron) in preventing prolonged postoperative bleeding in rabbits on anticoagulant (heparin).

MATERIALS AND METHODS

Twelve New Zealand rabbits of both sexes, 4–6 months old with average weight of 2000 gm were used for this study and they numbered from one to twelve on their backs using special paint.

Drugs and Materials Used in the Study:

The following drugs and materials were used in this study (Figure 1):

1. Exacyl (tranexamic acid) 0.5g/5ml ampoules from Sanofi Winthrop Industry, France.
2. Heparin 5.000 IU/UI/ml (5ml= 25.000 IU/UI vial from Leo Pharmaceutical Products, Denmark.
3. Anesthesia: General anesthesia was used, it includes:
Ketamine HCl dose (15mg/ 1 Kg body weight)
Xylzine HCl dose (5mg/ 1 Kg body weight)
Given at same time intramuscular.
4. Haematocrit–capillaries, made in Germany.
5. Medijet disposable syringes of 1ml for drugs administration and blood sample collection.

The animals were collected about one week before the procedure, they examined veterinary of any clinical signs and symptoms of medical problems, and a good environment was established include food and

water.



Figure (1): Materials and drugs used in the study

Samples Collection:

1. About 1–1.5 ml of blood was collected from each animal included in the study. The blood samples were aspirated from the ear or thigh vein according to the clarity of the vein. This sample was sent to laboratory screening for the Prothrombin time and clotting time using Ducks Method. The data recorded were considered as control (Figures 2 and 3).



Figure(2): Blood sample collected from ear vein



Figure (3): Capillary tube filled with blood for clotting time measurement (Ducks method)

2. The same animals injected a heparin solution subcutaneously at a dose of 0.025 ml (0.01 ml/Kg) according to the

instruction leaflet, and then waiting for 1 hour and then a blood sample of 1–1.5 ml was aspirated and sent to the laboratory for measuring the Prothrombin time. At the same time the clotting time was measured using Ducks Method (Figure 4).



Figure (4): Intravenous injection of heparin

3. The same animals injected a 0.2 ml of tranexamic acid (Exacyl) intravenously waiting for 30 minutes. Then a blood sample of 1–1.5 ml was aspirated and sent to the laboratory for measuring the Prothrombin time. At the same time the clotting time was measured using Ducks method. After that a minor oral surgery was done by reflection of mucoperiosteal flap in the mandibular posterior region and then replaced to its position

and sutured. This was done for monitoring the bleeding and/or ecchymosis that may occur following the drug administration

The rabbits were become under clinical observation daily for 7 days for any signs of bleeding and/or infection.

Analysis of data was done using 2-tailed type 1 Student's t-test to analyze the data and statistical significance was defined as a *p* value of less than, or equal to, 0.05.

RESULTS

Of the 12 rabbits that included into the study, two rabbits were eliminated from the statistical analysis because they died before completing the data. The cause of death may be due to hypovolemia as about 3–4 ml of blood was aspirated and other amount lost due to operation at about 1 hour interval so that the data of the remaining 10 rabbits were analyzed statistically for the level of significant.

Table (1) showed that there was a significant difference ($p \leq 0.05$) between the postoperative Prothrombin time following heparin injection and the Prothrombin time normal.

Table (1): The relation between the Prothrombin time following heparin injection and Prothrombin time normal

Groups	No.	Mean (Seconds)	±SD	SE	t-value	p-value
Pt Hep	10	14.900	1.197	0.379		
Pt Normal	10	12.000	0.000	0.000	7.66	0.000
Difference	10	2.900	1.197	0.379		

No.: Number; SD: Standard deviation; SE: Standard error; Pt Hep: Prothrombin time following heparin injection; Pt Normal: Prothrombin time measured preoperatively.

Table (2) showed that there was no significant difference in the Prothrombin time following the administration of Cyclokapron and Prothrombin time normal ($p > 0.05$).

Regarding the clotting time the same results have been obtained in that Table (3) estimated a high significant difference

in the clotting time between the preoperative and post heparin injection in that the last one showed a highly increase in the clotting time. In the other hand, no significant difference found in the mean clotting time between the preoperative and post Cyclokapron injection as shown in Table (4).

Table (2): The relation between the Prothrombin time following Cyclokapron injection and Prothrombin time normal

Groups	No.	Mean (Seconds)	±SD	SE	t-value	p-value
Pt Cyclo	10	12.200	0.789	0.249		
Pt Normal	10	12.000	0.000	0.000	0.80	0.443
Difference	10	0.200	0.789	0.249		

No.: Number; SD: Standard deviation; SE: Standard error; Pt Cyclo: Prothrombin time following Cyclokapron injection; Pt Normal: Prothrombin time measured preoperatively.

Table (3): The relation between the clotting time following heparin injection and preoperative clotting time

Groups	No.	Mean (Seconds)	±SD	SE	t-value	p-value
Ct Pre	10	128.0	23.5	7.4	5.29	0.000
Ct Hep	10	190.0	28.7	9.1		

No.: Number; SD: Standard deviation; SE: Standard error; Ct Pre: Clotting time measured preoperatively; Ct Hep: Clotting time following heparin injection.

Table (4): The relation between the clotting time following Cyclokapron injection and preoperative clotting time

Groups	No.	Mean (Seconds)	±SD	SE	t-value	p-value
Ct Pre	10	128.0	23.5	7.4	2.01	0.062
Ct Cyclo	10	102.0	33.6	11		

No.: Number; SD: Standard deviation; SE: Standard error; Ct.Pre.: Clotting time measured preoperatively; Ct.Cyclo.: Clotting time following Cyclokapron injection.

DISCUSSION

This study has shown that systemic administration of tranexamic acid has a significant difference ($p \leq 0.05$) in reduces postoperative bleeding and had a controlling effect on intra-operative bleeding which did not achieve significance in a group of 10 rabbits.

Tranexamic acid as a mouthwash has been found to reduce the incidence of postoperative bleeding in patients with prosthetic heart valves, cardiac valvular stenosis or vascular prosthesis on continuous unchanged oral anticoagulants undergoing oral surgery.^(1, 3, 5) These patients were treated under local anaesthesia. Sindet-Pedersen and Sternbjerg⁽⁶⁾ also showed that postoperative bleeding and the need for transfusion after oral surgery under local and general anaesthesia, in haemophiliacs, was significantly reduced when tranexamic acid as a mouthwash was combined with systemic tranexamic acid. The use of the tranexamic acid mouthwash while recovering from a day case general anaesthetic is less practicable and with some patients compliance is unreliable. Although Gaspar *et al.*,⁽⁵⁾ have suggested that intravenous antifibrinolytic therapy may have a thrombotic effect on patients receiving anticoagulant therapy, there is no published evidence for this claim. Furthermore, such patients are unlikely to be considered eligible for day case surgery.

Increasing the number of patients that receiving anticoagulant therapy either for the treatment of such condition as deep venous thrombosis or an attempt to prevent recurrence of coronary thrombosis, when dental extraction or minor oral surgery procedure to be performed for such patients, the level of Prothrombin time to graduate to reduce until it maintained at 1.5–2 times the regular control level (15–30 seconds). In other cases will be not necessitate any alteration of dosage.⁽⁹⁾

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To maintain the Prothrombin time within the therapeutic level, the reduce of anticoagulant dose for 2–3 days period, hence acute clinical signs and symptoms required emergency dental interference without delay.⁽¹⁰⁾

Prothrombin time is essential laboratory screening for monitoring of patients on anticoagulant since prolongation of such a time (extrinsic and common pathway) more than the therapeutic range reflect a bleeding tendency.

Heparin is a direct acting anticoagulant drug that is mean it is initiate its therapeutic effect with ½ hour following injection subcutaneous or intramuscular.⁽¹¹⁾

In the present study, systemic administration of tranexamic acid (Exacyl) on rabbits injected with heparin showed that significant differences in reducing the Prothrombin time and clotting time level to nearly to the control level. These results agreed with those who used tranexamic acid mouthwash to control of bleeding without change of anticoagulant regimen undergoing surgical procedure.^(1, 3, 5) Similar result had been obtained by Senghore and Harris.⁽¹²⁾ They found that one intravenous preoperative dose of tranexamic acid is effective in preventing excessive postoperative bleeding in patients undergoing third molar extraction under a day case general anaesthetic and therefore facilitates safe discharge from hospital. In addition to that, in cases of hereditary coagulation defect as hemophiliac patients (Factor VIII deficiency) used Cyclokapron control of bleeding in minor oral surgical procedure, preventing post extraction bleeding and also reduce morbidity and complications such as infection and delayed healing.⁽¹³⁾

Bleeding elimination allows the early discharge of patients and reduces the possibility of their returning for rehospitalization, hence making the treatment more efficient and less costly. The use of tranexamic acid administered either as a mouthwash or systemically for hemorrhage reduction in patients with coagulation disorders.⁽¹²⁾

CONCLUSION

A single intravenous dose of 0.25 ml/Kg tranexamic acid given preoperatively was effective in reducing postoperative

bleeding following minor oral surgery in rabbits on heparin anticoagulant therapy. The application of this simple strategy can also be applied to day case patients need all dentoalveolar and periodontal surgical procedures under local or general anaesthetics who receiving anticoagulant therapy.

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