

THE EXPERIMENTAL EVALUATION OF THE EFFECTIVENESS OF HAEMOSTATIC DRUGS FOR ENDOSCOPIC HAEMOSTASIS OF GASTROINTESTINAL BLEEDING

ABSTRACT

BACKGROUND

This article highlights the problems of bleeding from the upper gastrointestinal tract, which appear with a frequency of 100 - 120 cases per 100,000 population. Overall mortality is 10-14%, postoperative - from 12 to 35% and has no tendency to decrease. The article discusses the results of haemostatic effectiveness of drugs used for the injection method of endoscopic haemostasis, which were conducted on laboratory rats, based on the Clinical Experimental Laboratory (CEL) and the B. Atchabarov's Institute at S.D. Asfendiyarov KazNMU.

METHODS

In the experiment were used methods such as simulation of bleeding from the gastric mucosa; a comparative analysis of the haemostasis effectiveness of 3 drugs (aminocaproic acid, Dicynonum, Tramin) used for local administration in the endoscopic haemostasis. Laboratory blood tests to study the effect of these drugs on thrombogenic and fibrinogenic activity of blood. The study was conducted on 37 white laboratory rats and were conducted two series of experiments in each series animals were divided into 3 groups, depending on the used type of haemostatic medication.

RESULTS

Comparative analysis of haemostatic effect in the experiment demonstrated high effectiveness of Tramin as by time of haemostasis, 3-4 minutes, as well as by quality of formed thrombus. Laboratory studies demonstrated that the introduction of Tramin saves platelet levels within the normal range as well as reduces bleeding time in 1.3 times compared to aminocaproic acid and 1.4 compared to Dicynonum.

CONCLUSION

The obtained results allow to recommend the Tramin for injection endoscopic haemostasis of gastrointestinal bleeding.

KEYWORDS

Gastrointestinal Hemorrhage, Tranexamic Acid, Endoscopic Hemostasis

INTRODUCTION

One of the current problems of modern clinical medicine is bleeding from the upper gastrointestinal tract, which appear with a frequency of 100 - 120 cases per 100,000 population [1, 2]. Overall mortality

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is 10-14%, postoperative - from 12 to 35% and has a tendency to decrease [3].

Introduction into clinical practice of the widely-channel endoscopes and modern video information systems opened a new stage in the diagnosis and treatment of acute gastrointestinal bleeding. New technologies in endoscopic surgery, provide primarily, a good review, allow productively reveal a source of bleeding and conduct adequate primary haemostasis [3, 4].

The most widely used methods of injection endoscopic haemostasis in which to submucosal space next to the source of bleeding in defect of the gastric mucosa or duodenal ulcer by means of an injector, conducted through the channel of an endoscope, are introduced various haemostatic solutions; Hydrogen peroxide [5], Epinephrine [6], Aethoxysklerol [7].

The disadvantages of these methods include the duration of haemostasis, the necessity to introduce a large number of haemostatic solutions, necrosis development at the injection site of an organ's paries, with the formation of an acute erosions and ulcers. In this regard, increases risk of occurrence of serious complications of bleedings and perforation, frequently occurring even with conventional therapeutic doses of [8 -11, 18, 20].

The imperfection of the known methods of endoscopic haemostasis, due to technical limitations of separate ones dictate the necessity to improve the known methods of haemostasis, the search for new effective

ways and means, differentiation of indications for their use.

The work represents experimental studies on 37 laboratory rats, performed on the basis of clinical experimental laboratory (CEL) and scientific clinical diagnostic laboratory (SCDL) of B. Atchabarov's Institute at S.D. Asfendiyarov KazNMU.

The main objective of the research – to undertake a comparative evaluation of haemostatic effectiveness of drugs used for the injection method of endoscopic haemostasis.

To solve the above object, the authors set three tasks:

- 1) Simulation of bleeding from the gastric mucosa,
- 2) Conduction of comparative analysis of the haemostasis effectiveness of 3 drugs (aminocaproic acid, Dicynonum, Tramin) used for local administration in the endoscopic haemostasis and
- 3) Laboratory blood tests to study the effect of these drugs on thrombogenic and fibrinogenic activity of blood;

Of listed drugs, scientific and practical interest represents Tramin (the drug of tranexamic acid) is a synthetic derivative of the amino acid lysine. The effect of the drug is associated with its ability to reversibly block the lysine-binding sites in molecule of plasminogen, thereby preventing interaction of plasmin, plasminogen with lysine sites in the fibrin polymer [12-14, 17, 19].

In practical healthcare Tramin is widely known as an effective haemostatic drug and is assigned to the intravenous and intramuscular injections [10, 13, 14]. For endoscopic injection haemostasis, the drug is not previously used. In this connection, the given work is foreground and claims to the invention [14-17].

METHODS

Tasks:

- 1) Simulation of bleeding from the gastric mucosa on animals;
- 2) Undertake a comparative analysis of haemostatic effects of the drugs (aminocaproic acid, Dicynonum, Tramin) after their local administration around the source of bleeding (gastric mucosa);

3) Conduct laboratory studies of blood - to study the influence of drugs (aminocaproic acid, Dicynonum, Tramin) on thrombogenic and fibrinogenic activity;

Experimental studies were carried out on laboratory rats, based on the Clinical Experimental Laboratory (CEL) and the B. Atchabarov's Institute at S.D. Asfendiyarov KazNMU.

While conducting experiments we followed to the "Guidelines for Ethical Conduct in the Care and Use of Non-human Animals in Research" (or also called "Animal testing regulations") [9, 15]. The operations were performed under ether mask anaesthesia with premedication of Calypsol, entered intrapleural, at the rate of 10 mg / kg. Laparotomy access along the median line. The experiments were performed in the operating of CEL compliance with the rules of aseptic and antiseptics.

Conducted 2 series of experiments, in each series animals were divided into 3 groups, depending on the used type of haemostatic medication (Table. 1).

RESULTS

In the first series of experiments, included 18 animals in which were simulated a bleeding from gastric mucosa: Upper midline laparotomy (Fig.1). In the wound was outputted and autopsied a stomach.

After the evacuation of the gastric contents, were producing scarification of the mucous membrane, thereby causing bleeding (Fig.2). Haemostatic drug was administered to the animal after the beginning of bleeding, and was estimated duration, the massiveness and time of haemostasis of bleeding.

In applying of aminocaproic acid average duration of bleeding was 5-6 min.

When using Dicynonum the average duration of bleeding was 7-9 minutes, the average length of bleeding in using Tramin 3-4 minutes.

Thus, according to the results of study the highest haemostatic efficiency demonstrated Tramin as by time of haemostasis, 3-4 minutes, as well as by quality of formed thrombus (formed, tightly fixed) (Fig. 3)

Groups	Haemostatic preparations	Series I	Series II
I	Aminocaproic acid	6	3
II	Dicynonum	6	3
III	Tramin	6	3
Total:		18	9

Table 1. The distribution of animals per group



Fig.1. Upper midline laparotomy



Fig.2. Intramural administration of the haemostatic drug into the bleeding region

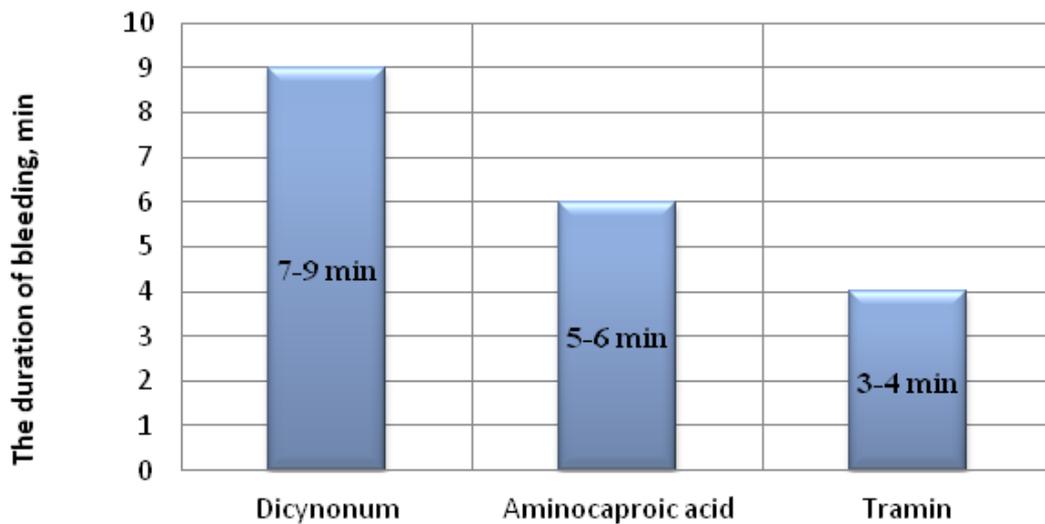


Fig. 3. The duration of the bleeding, depending on the administered haemostatic drug



Fig. 4. Femoral vein catheterisation



Fig. 5 Blood collection from the femoral vein

№	Indicators	Aminocaproic acid			Dicynonum			Tramin		
		5 min	10 min	15 min	5 min	10 min	15 min	5 min	10 min	15 min
1	Leucocytes	15.96	11.4	6.62	7.05	6.8	6.2	6.19	6.20	6.50
2	Erythrocytes	8.66	9.2	9.70	7.95	8.2	8.6	7.94	8.6	9.86
3	Haemoglobin	13.7	14.8	16.4	11.8	12.3	13.2	14.1	14.8	15.3
4	Haematocrit	39.6	44.6	49.9	34.9	36.8	39.8	42.4	43.2	45.1
5	Platelets	408	389	363	594	706	841	1055	1056	1086
6	Coagulation time	4.8	5.2	4.6	5.1	4.8	5.4	3.8	4.1	3.8
7	Bleeding time	9.4	9.2	9.6	9.7	8.6	8.3	6.8	6.4	5.8

Fig. 6. Results of laboratory studies in animals of Series II

In a second series of experiments, in animals were performed laboratory tests of blood with the purpose of comparative analysis on blood parameters, including haemoglobin, erythrocytes, platelets, coagulation time by Sukharev.

For intravenous administration of the drug and the subsequent blood sampling, all animals was performed venesection with the catheterisation of femoral vein (Fig. 4).

For blood sampling was used Vacutainers that collect blood in a predetermined amount and to ensure its tightness (Fig. 5). The fence was conducted every 5, 10, 15 min.

Laboratory studies were carried out in the scientific clinical diagnostic laboratory of B. Atchabarov's Institute at S.D. Asfendiyarov KazNMU. To determine the blood test was used hematologic analyser sysmexxs -1000i, which gives the results

of the analysis of blood samples by 24 parameters, including haemostatic parameters.

DISCUSSION AND CONCLUSION

The results of the conducted laboratory researches lead to the following conclusions; (Fig. 6).

- 1) Application of compared haemostatic preparations are not adversely affect the basic indicators of the blood (Erythrocytes, haemoglobin, Haematocrit etc.).
- 2) Intravenous injection of Tramin saves platelet levels within the normal range.
- 3) Coagulation time and bleeding are reduced in 1.3 times when administered Tramin compared to aminocaproic acid and 1.4 compared to Dicynonum.

Conclusions:

- 1) The comparative analysis of the haemostatic effect

in the experiment has shown high efficiency Tramin as by time of haemostasis, 3-4 minutes, as well as by quality of formed thrombus;

2) Laboratory studies demonstrated that the introduction of Tramin saves platelet levels within the normal range as well as reduces bleeding time in 1.3 times compared to aminocaproic acid and 1.4 compared to Dicynonum.

3) The obtained results allow to recommend the Tramin for injection endoscopic haemostasis of gastrointestinal bleeding.

REFERENCES

- Hoffman JL, Aneese NJ, Schmidt KJ, Chaben AC, Smythe MA. Optimizing Anticoagulation Management Through the Use of a Hospital Engagement Network Metric for Inpatient Anticoagulant-Associated Hemorrhage. *Ann Pharmacother.* 2015 Sep 18.
- Fedorov ED, Plakhov RV, Timofeyev ME, Mikhalev AI. Endoscopic haemostasis by using argon plasma coagulation in acute gastrointestinal bleeding: the first clinical experience. *Clin Endosc.* 2003; 1: 12 - 15.
- Materials of All-Russian surgeons Conference: "Modern problems of emergency and elective surgical treatment of patients with gastric ulcer and duodenal ulcers". Saratov. 2003.
- Kim SB, Lee SH, Kim KO, Jang BI, Kim TN, Jeon SW, Kwon JG, Kim EY, Jung JT, Park KS, Cho KB, Kim ES, Kim HJ, Park CK, Park JB, Yang CH. Risk Factors Associated with Rebleeding in Patients with High Risk Peptic Ulcer Bleeding: Focusing on the Role of Second Look Endoscopy. *Dig Dis Sci.* 2015 Aug 22.
- Irwin J, Ferguson R, Weilert F, Smith A. Supratherapeutic anticoagulation at presentation is associated with reduced mortality in nonvariceal uppergastrointestinal hemorrhage. *Endosc Int Open.* 2014 Sep; 2 (3): E148-52.
- Sotnikov VN, Dubinskaya TK, Razzhivina AA. Endoscopic diagnosis and endoscopic methods of treatment of bleeding from the upper gastrointestinal tract: Textbook. M.: RMAPO. 2000: 48-52.
- Savustyanenko AV. Tranexamic acid and features of its use in heavy menstrual bleeding, 2012.
- Springer BD, Odum SM, Fehring TK. What Is the Benefit of Tranexamic Acid vs Reinfusion Drains in Total Joint Arthroplasty? *J Arthroplasty.* 2015 Aug 18.
- "European Convention for the Protection of Vertebrate Animals that are used for experimental and other scientific purposes" (Strasbourg, 1986) and the Resolution of the first Congress of Bioethics (Kiev, 2001).
- Kim C, Park SS, Davey JR. Tranexamic acid for the prevention and management of orthopedic surgical hemorrhage: current evidence. *J Blood Med.* 2015 Aug 25; 6: 239-244.
- Ralley FE. Tranexamic acid: When is enough (data) enough? *Can J Anaesth.* 2015 Aug 26.
- Dibirov MD, Mihaylin A, Doronina E. The effectiveness of endoscopic haemostasis of gastroduodenal bleeding in elderly and senile age. *Medical academic journal.* 2007; 3: 70-72.
- Schindler E, Photiadis J, Sinzobahamvya N, Döres A, Asfour B, Hraska V. Tranexamic acid: an alternative to aprotinin as antifibrinolytic therapy in pediatric congenital heart surgery. *Eur J Cardiothorac Surg.* 2011 Apr; 39 (4): 495-49.
- Karatkevich AG, Perkin EM. Comparative evaluation of endoscopic haemostasis methods in gastroduodenal ulcer bleeding. *Vestnik Heer.* 1998; 157 (2): 26-28.
- Valenzuela GA, McGroarty D, Pizzani E, Davis T Jr. Endoscopic injection therapy for acute upper GI bleeding. *Va Med.* 1989 Dec; 116 (12): 507-509.
- Chalmers RT, Darling Iii RC, Wingard JT, Chetter I, Cutler B, Kern JA, Hart JC. Randomized clinical trial of tranexamic acid-free fibrin sealant during vascular surgical procedures. *Br J Surg.* 2010 Dec; 97 (12): 1784-1789.
- Grubnik YV, Fomenko VA, Pilipenko AS. Complications of local endoscopic haemostasis in patients with bleeding from upper gastrointestinal tract. Theses and reports. 4 Mosk. Int. Congress of Endoscopic Surgery, Moscow. 26-28 April 2000: 7980- 7985.

18. Novikova N, Hofmeyr GJ. Tranexamic acid for preventing postpartum haemorrhage. *Cochrane Database Syst Rev.* 2010 Jul 7; (7): CD007872.
19. Meier A, Messmann H, Gölder SK. Endoscopic management of lower gastrointestinal bleeding [Article in German]. *Med Klin Intensivmed Notfmed.* 2015 Sep 7.
20. Laine L, Long GL, Bakos GJ, Vakharia OJ, Cunningham C. Optimizing bipolar electrocoagulation for endoscopic hemostasis: assessment of factors influencing energy delivery and coagulation. *Gastrointest Endosc.* 2008 Mar; 67 (3): 502-508.