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DIGEST AND REVIEWS

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The use of tranexamic acid in arthoplasty of large joints (literature review)

V. A. Filipenko, O. O. Pidgaiska, K. S. Poplavska, S. S. Hubskyi

Sytenko Institute of Spine and Joint Pathology National Academy of Medical Sciences of Ukraine, Kharkiv

Endoprosthesis of large joints is an efficient method to restore the functional capacity of a limb, to increase the patient's motor activity, to eliminate the pain syndrome and to recover self-service. However, there is a risk of certain complications, one of which is massive blood loss. There have been recent publications on the feasibility of the use of tranexamic acid in the arthroplasty of large joints to prevent and reduce blood loss. The objective is to identify the trends in the use of tranexamic acid in orthopedics and traumatology to prevent blood loss in the arthroplasty of large joints without increasing the risk of other complications. Methods. The search for the scientific information was conducted in Google Scholar, PubMed, World Digital Library, ScienceDirect. Results. The literature review is devoted to the topical issue of the present day's orthopedics, which is the use of tranexamic acid to prevent blood loss in arthroplasty of large joints. According to the studies, the use of tranexamic acid significantly reduces the overall blood loss without increasing the risk of complications such as thromboembolism. The risk of complications of infectious genesis and of those due to the blood transfusion is also reduced using tranexamic acid. It is determined that the combined intra-articular and intravenous injection of tranexamic acid is more efficient than the application of either method separately. However, the comparative results of the ways of administration and the dosage regimen are quite ambiguous. The question of the optimum dose of the medication, which would provide maximum efficiency, without increasing the risk of complications is still to establish. It is advisable to conduct further research on the use of tranexamic acid to determine the efficiency of the ways of injection, dosing regimen taking into account the patients' demographic features, their age, concomitant pathology, time of surgery and other factors. Key words. Tranexamic acid, intravenous and intra-atricular injection, dose-response effect, large orthopedic surgical treatment, blood loss.

Ендопротезування великих суглобів є ефективним методом щодо відновлення функціональної спроможності кінцівки, підвищення рухомої активності хворих, усунення больового синдрому та відновлення самообслуговування. Проте залишається ризик певних ускладнень, одним з яких є масивна крововтрата. Останнім часом трапляються публікації щодо доцільності застосування транексамової кислоти (ТК) в разі ендопротезування великих суглобів із метою профілактики та зменшення обсягу крововтрати. Мета. Визначити тенденції використання в ортопедії та травматології транексамової кислоти для запобігання крововтраті під час ендопротезування великих суглобів і зменшення ризику виникнення інших ускладнень. Методи. Пошук наукової інформації проведено в системах Google Scholar, PubMed, World Digital Library, ScienceDirect. Результати. Огляд літератури присвячено актуальному питанню сучасної ортопедії — застосуванню ТК для запобігання крововтраті під час ендопротезування великих суглобів. Згідно з дослідженнями застосування ТК значно знижує загальну крововтрату без збільшення ризику ускладнень у вигляді тромбоемболії. Загроза виникнення ускладнень інфекційного генезу та внаслідок проведення гемотрансфузії також зменшується за умов використання ТК. Визначено, що поєднання внутрішньосуглобового та внутрішньовенного введення ТК є ефективнішим порівняно зі застосуванням кожного способу окремо. Проте результати щодо порівняння шляхів введення та режиму дозування досить неоднозначні. Залишається відкритим питання щодо виявлення оптимальної дози препарату, яка б забезпечила максимальну ефективність дії без підвищення ризику виникнення ускладнень. Доцільним є проведення подальших досліджень використання ТК із визначенням ефективності шляху введення препарату, режиму дозування з урахуванням демографічних особливостей пацієнтів, їхнього віку, наявності супутньої патології, часу хірургічного втручання та інших показників.

Key words. Tranexamic acid, intravenous and intra-atricular injection, dose-response effect, large orthopedic surgical treatment, blood loss

The main goal of community health is to maximize human performance. Carrying out of such surgical intervention as endoprosthesis of large joints is directed first of all on restoration of functional ability of an extremity, increase of motor activity of patients, elimination of a pain syndrome and restoration of possibility of self-care. However, there is a risk of complications, one of which is massive blood loss. Recently, there have been publications on the feasibility of using tranexamic acid (TA) in arthroplasty of large joints to prevent and reduce blood loss. Tranexamic acid is an antifibrinolytic agent. The main effect of this agent is its ability to reversibly block lysine binding sites in the plasminogen molecule, thereby preventing the interaction of plasmin with lysine sites in the fibrin polymer. In these processes, fibrin is not destroyed. In addition, TA enhances collagen synthesis, which helps preserve the fibrin matrix and increases the strength of the blood clot. Together, both of these effects of TA contribute to the stabilization of the blood clot.

The purpose of the study: to identify trends in the use of tranexamic acid in orthopedics and traumatology to prevent blood loss during arthroplasty of large joints, thereby reducing the risk of other complications.

Material and methods

The search for scientific information for assessment was conducted in search engines Google Scholar, PubMed, World Digital Library, ScienceDirect.

Results and their discussion

The average amount of blood loss during and after arthroplasty is from 500 to 1,500 ml. In 50 % of patients after joint replacement, postoperative anemia is observed in the absence of TA administration [1, 2]. Therefore, there is a need for blood transfusion, which is performed in approximately 20 % of cases [3, 4]. According to the authors, the frequency of blood transfusions is approximately 11 % in the case of total knee arthroplasty, 18% in hip arthroplasty [5–8]. Other sources indicate that up to 38 % of patients require a blood transfusion [6, 7, 9], which can lead to a number of complications, such as: infectious joint damage, immunosuppression, cardiovascular dysfunction, accidental antigen mismatch, even death.

There is a lot of information in the literature about the effect of intravenous TA in comparison with its topical application [8–11]. Intravenous administration of the drug allows to significantly reduce blood loss and reduce the frequency of blood transfusions, and for the most part to completely avoid transfusions of blood components.

However, there is a risk of thromboembolic disorders, namely after hip arthroplasty: asymptomatic deep vein thrombosis of the lower extremities occurs in 40–60 % of patients, pulmonary embolism (PE) in 0.9–2.8 %, which, in its turn, leads to complications ranging from the early postoperative period to fatalities at different times after surgery [7, 9]. The question of intra-articular administration of TA agents remains unresolved. The introduction of the agent into the joint allows to achieve the maximum concentration of the drug in the area of blood loss, increases hemostasis in this area with minimal systemic effects [12, 13]. Inhibition of local fibrinolytic activity helps to prevent resorption of the formed clot, which increases its volume and strength, thus enhancing microvascular hemostasis [12, 14]. The reduction in blood loss after topical administration of TA is an average of 400 ml [15–17]. In studies on topical administration, the authors used TA in different doses and methods of its administration: 15 mg/kg TA, dissolved in 100 ml of saline, injected into the joint for 10 min, followed by suturing the wound; 1 g per 10 ml of saline; 1.5 g in saline to wash the joint after cementation for 5 minutes; 2 g after suturing the wound; 3 g per 100 ml of saline, when half of the fluid is washed the joint before suturing, and half remains in it after closing the wound, etc.

In the case of intravenous administration, the agent is distributed in both cellular and extracellular spaces. TA rapidly penetrates the joint fluid and synovial membranes, reaching the same concentration as in blood plasma. The half-life of the agent in the joint fluid is about 3 hours. Elimination of TA after administration at a concentration of 10 mg/kg occurs by renal filtration, in one hour approximately 30 % of the agent is excreted, 55 % in 3 hours, 90 % in 24 hours [18]. The advantage of topical TA administration is minimal systemic absorption. The concentration of the agent in plasma was approximately 70 % lower than under conditions of equivalent intravenous administration [3].

Although TA is widely used in endoprosthesis surgery, it is not a standard procedure. The American Association of Hip and Knee Surgeons (AAHKS), the American Association of Orthopedic Surgeons (AAOS), the Hip Society, the Knee Society, and the American Society of Anesthesia and Anesthesia (ASRA) have jointly developed evidence-based guidance for the use of TA in primary arthroplasty. Scientists consider the feasibility of the time of agent

administration, route and doses of its use, the risk of thromboembolic complications [19–21].

Analyzing the results of studies on the effectiveness of this drug, which are contained mainly in systemic electronic databases, we should, first of all, pay attention to more evidence-based achievements. This is the first level of evidence study or meta-analysis, which is more reliable and combines homogeneous, selected by inclusion and exclusion criteria, only randomized comparative studies with a large number of patients. That is why we provide information from meta-analyzes on the use of different methods of drug administration, because it helps to identify more effective and safer methods.

A meta-analysis of 15 randomized clinical trials (RCTs) evaluated the efficacy and safety of intravenous TA compared with placebo in 837 patients. The analysis showed that the amount of blood loss and the number of blood transfusions per patient were significantly lower in cases where the drug was prescribed TA without a significant difference in the number of cases of thromboembolic complications [5, 22].

A systematic review and meta-analysis of topical TA in the case of knee arthroplasty involving 14 randomized trials showed a significant reduction in the number of blood transfusions ($p < 0.001$). An indirect comparison of placebo-controlled studies of topical and intravenous TA showed the advantage of the former. The number of thromboembolic complications was similar compared to placebo [10, 22].

A systematic review and meta-analysis included 211 RCTs, 20,639 patients, to compare blood transfusions and the incidence of deep vein thrombosis with or without TA (compared with placebo). If we talk about the effectiveness of blood transfusions, the use of TA both intravenously and intra-articularly showed a statistical advantage over placebo. Evaluating safety measures, it was proved that topical administration of TA had a lower risk of thrombosis [20].

In another updated meta-analysis for 2017, 18 RCTs involving 2,260 patients did not reveal a statistically significant difference in total blood loss, blood drainage or hemoglobin levels in the first day after surgery, depending on the route of administration of TA [21].

Meta-analysis of 6 RCTs with the inclusion of 701 patients to study the effectiveness of combined administration of TA compared with intravenous showed that the combined route of administration is more effective in reducing total blood loss, blood loss in drainage and hemoglobin levels. The analysis by subgroups established the best indicators in those patients who were operated without the use of a tourniquet and with topical TC of more than 1.5 g and an intravenous dose of more than 2 g, without increasing the frequency of thrombosis or thromboembolism [18].

Another meta-analysis of 6 RCTs (687 patients) also showed that the combination of both routes of TA administration was more effective than intravenous administration alone [8].

A meta-analysis of studies on the effectiveness of different doses, regimens and routes of administration of TA during and after knee or hip arthroplasty was performed. The study included 28 RCTs, 3 prospective and 5 retrospective with 5,499 patients. The greater efficiency of intra-articular TA administration compared to intravenous, and the combination of both methods of drug administration is more productive than both, which may be more favorable for reducing blood loss during and after surgery by drainage [3, 12, 23].

Another meta-analysis, which included 15 RCTs (1,495 patients), found the effectiveness of TA using both intra-articular and intravenous administration compared to individual methods or placebos. The combination of topical and intravenous TA has been shown to significantly (by an average of 458.66 ml) reduce blood loss compared with placebo. Comparison of intravenous administration with a combination of both routes is also a more effective method for total blood loss after surgery. The advantage of combination therapy over only topical administration of the drug has been proved. Regarding the risk of thromboembolic complications, the difference between the modes of administration of TA is not defined [4, 24].

A multicenter randomized clinical trial with the first level of evidence demonstrated that intravenous and intra-articular administration of TA during primary knee arthroplasty reduced blood loss to less than 350 ml. Under the conditions of combined administration there is no need to perform a blood transfusion and the frequency of symptomatic thrombotic complications is reduced (less than 2 %). In the group of patients who received the drug intravenously, the amount of blood loss was lower by an average of 50 ml compared to intra-articular injections. In the case of the latter, the amount of blood loss by drainage was 104 ml more ($p < 0.0001$) than under intravenous administration [23].

In a prospective, double-blind, placebo-controlled study, 124 patients were randomized to receive intra-articular injections of TA or placebo (saline). The authors noted that topical use of the drug reduces postoperative blood loss to 300–400 ml, and patients also recorded a 16 % higher hemoglobin index compared with the placebo group [25].

The efficacy of TA under intravenous and topical administration was studied in the RCT involving 150 patients. The authors concluded that there was no statistically significant difference in blood loss or transfusion between the groups [26].

Despite the large number of high-quality studies, questions remain about the dosage regimen of the agent, i.e. the identification of a dose that would ensure high efficiency without increasing the risk of complications. In one of the system reviews of the effect of topical TA, the authors estimated the number of blood transfusions performed depending on the dose of the drug: less than 1 g, from 1 g to 2 g, more than 2 g. % confidence interval, found that each dose is effective [10].

Along with studying the effect of different doses of TA, there are studies that compare the effect of the agent on its exposure, i.e. the time spent in the joint cavity. Several RCTs have determined that the agent works better when, after injection into the joint, the drainage is closed with a clamp for 2 hours compared to 15 minutes [25]. Although there is a lot of information today that confirms the possibility of doing without a drainage system after joint replacement, the use of drainage after knee replacement continues in many orthopedic centers around the world. Drainage reduces the volume of postoperative hematoma in the joint, thereby reducing edema, the severity of pain and the risk of infectious complications. However, its use remains a controversial issue. Recently, surgeons have begun to use the technique of blocking drainage, which allows to create the effect of tamponade in the joint and, accordingly, to achieve blood loss control [1]. Adding TA to the joint enhances the effect.

In another meta-analysis, where the effect of TA was compared depending on the applied dose of intra-articular or intravenous administration (up to 2 g or more than 2 g), no statistically significant difference in blood loss was found ($p > 0.05$) [20].

Similar data were obtained after comparing the doses of TA 1.5 g and 3.0 g. The agent in this study was diluted in 100 ml of saline and irrigated the wound for 5 min after installation of all components of the knee arthroplasty. No significant difference between doses was obtained, both doses were effective [3]. It has been shown that in the case of intravenous injections, the use of TA in doses greater than 1 g is more effective than in doses less than 1 g [27].

Conclusions

Summarizing the results of many studies, it can be argued that the use of TA can significantly reduce overall blood loss without increasing the risk of thromboembolic complications compared with placebo [4, 24, 28, 29]. This reduces the incidence of infectious complications and adverse effects of blood transfusions. The combination of intra-articular and intravenous TA was more effective than the use of these methods alone. Regarding the study of the action of TA from the route of administration, ambiguous results were obtained: there are no data that would unanimously state that the intravenous route has advantages over the intra-articular or vice versa. Therefore, it is advisable to continue research on the effectiveness of the regimen and dosage of the drug, the route of its administration, taking into account the demographic characteristics of patients, comorbidities, time of surgery, etc.

Conflict of interest. The authors declare the absence of conflict of interest.

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THE USE OF TRANEXAMIC ACID IN ARTHOPLASTY OF LARGE JOINTS
(LITERATURE REVIEW)

V. A. Filipenko, O. O. Pidgaiska, K. S. Poplavska, S. S. Hubskyi

Sytenko Institute of Spine and Joint Pathology National Academy of Medical Sciences of Ukraine, Kharkiv

✉ Volodymyr Filipenko, MD, Prof. in Orthopaedics and Traumatology: filippenko1957@gmail.com

✉ Olga Pidgaiska, MD, PhD in Traumatology and Orthopaedics: podgayo@yahoo.com

✉ Karolina Poplavska, MD: karolina.krivoru@gmail.com

✉ Stanislav Hubskyi, MD: stanislav33sergeevich@gmail.com