Low risk of thromboembolic complications with tranexamic acid after primary total hip and knee arthroplasty

Gillette BP, DeSimone LJ, Trousdale RT, Pagnano MW, Sierra RJ.: Clin Orthop Relat Res. 2013 Jan; 471(1):150-4. Source: Department of Orthopedic Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

BACKGROUND: The use of antifibrinolytic medications in hip and knee arthroplasty reduces intraoperative blood loss and decreases transfusion rates postoperatively. Tranexamic acid (TXA) specifically has not been associated with increased thromboembolic (TE) complications, but concerns remain about the risk of symptomatic TE events, particularly when less aggressive chemical prophylaxis methods such as aspirin alone are chosen.
QUESTIONS/PURPOSES: We determined whether the rate of symptomatic TE events differed among patients given intraoperative TXA when three different postoperative prophylactic regimens were used after primary THA and TKA.
METHODS: We retrospectively reviewed 2046 patients who underwent primary THA or TKA and received TXA from 2007 to 2009. The three chemical regimens included aspirin alone, warfarin (target international normalized ratio, 1.8-2.2), and dalteparin. Primary outcome measures were venous TE events, including symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterioocclusive events, including myocardial infarction and cerebrovascular accident. Patients judged to be at high risk for TE due to recent cardiac stent placement or strong personal/family history of TE disease were excluded.
RESULTS: For aspirin, warfarin, and dalteparin, the rates of symptomatic DVT (0.35%, 0.15%, and 0.52%, respectively) and nonfatal PE were similar (0.17%, 0.43%, and 0.26%, respectively). There were no fatal PE. Among the three groups, we found no difference in the rates of symptomatic DVT or PE with or without stratification by ASA score.
CONCLUSIONS: A low complication rate was seen when using TXA as a blood conservation modality during primary THA and TKA with less aggressive thromboprophylactic regimens such as aspirin alone and dose-adjusted warfarin.

Uso del acido tranexámico endovenoso reduce las tranfusiones alogénicas en el reemplazo total de cadera y rodilla. Metaanálisis

Ho Km, Ismail H. Anaesth Intensive Care, 2003 Oct; 31 (5): 529-37.

Conclusión: El Ácido Tranexámico ha sido utilizado para reducir la hemorragia y requerimiento transfusional en el reemplazo total de cadera y rodilla. En este meta-análisis se analizan 15 trabajos científicos prospectivos, controlados que demuestran que el Ácido Tranexámico reduce la proporción de pacientes que requieren transfusión de sangre, teniendo en cuenta la cantidad de sangre perdida y las unidades utilizadas. El tratamiento con Ácido Tranexámico no incrementa el riesgo de complicaciones tromboembólicas (trombosis venosa, embolia pulmonar, accidentes cerebrales o infarto agudo de miocardio). La administración endovenosa del Ácido Tranexámico (AROTRAN) es segura y activa en la reducción de la pérdida de sangre y la reducción del número de transfusiones de sangre utilizadas en dichas intervenciones vs. control.

El Hospital Clinic de Barcelona reduce en un 70% las transfusiones durante la cirugía de prótesis de rodilla.

Hospital Clinicas Barcelona. ABC Periódico Electrónico Madrid, 2009

Conclusiones: El uso del Ácido Tranexámico disminuye drásticamente la pérdida sanguínea durante la cirugía. Este nuevo programa de ahorro de sangre podría ser útil también en otras cirugías ortopédicas y traumatológicas. En conjunto significa que para colocar una prótesis de rodilla a 200 pacientes antes de implantar la administración del Ácido Tranexámico se requerían 320 unidades de concentrados de hematíes. Para intervenir el mismo número de pacientes tras administrar Ácido Tranexámico el número de bolsas han pasado a ser de 66. Además debido a la disminución de las perdidas sanguíneas inducida por el Ácido Tranexámico los pacientes que habían recibido el fármaco tenían en el momento del alta mayores niveles de glóbulos rojos en la circulación que los pacientes intervenidos cuando no se administraba el tratamiento activo.
La administración del tratamiento no se asoció con efectos adversos especialmente complicaciones tromboembólicas que son las que más se temen cuando se usa Ácido Tranexámico.

Efecto de un bolo intravenoso de Ácido Tranexámico en la pérdida de sangre durante el reemplazo total de Cadera.

Rajaesparan K y Col J. Bone Joint Surg Br. 2009 Jun; 91 (6) : 776-83

Conclusion: Estudiaron el efecto sobre la pérdida de sangre con la administración de un bolo intravenoso de Ácido Tranexámico (AROTRAN) durante la inducción de la anestesia controlando además el potencial efecto protombotico de la droga, realizando venografias de control posterior al tratamiento. Se estudiaron 37 pacientes con tratamiento activo y

37 con placebo, detectándose una menor hemorragia en el post operatorio, y menor número de unidades transfundidas con el Ácido Tranexámico no evidenciándose episodios de trombosis venosa en las venografías. Se concluye que la administración de un bolo de 1 gr. endovenoso de Ácido Tranexámico en forma estandarizada preoperatorio, es costo efectivo en la reducción de la pérdida de sangre y en la disminución del requerimiento transfusional durante la cirugía de reemplazo de cadera.

El ácido tranexámico reduce la pérdida de sangre en artroplastias de cadera segmentada: Un estudio randomizado doble ciego de 39 pacientes con osteoartritis.

Niskanen Ro, Korkala OL. Acta Orthop. 2005 Dec; 76 (6): 829-32.

Conclusión: El Ácido Tranexámico reduce la pérdida de sangre y la necesidad de transfusiones de sangre en artroplastias de rodilla. La pérdida total de sangre fue menor en el grupo con Ácido Tranexámico respecto al grupo control, no observándose complicaciones tromboembólicas. El Ácido Tranexámico parece ser una droga económica y efectiva para la reducción de la pérdida de sangre en la artroplastias de cadera segmentada por osteoartritis.

Tranexamic acid reduces early post-operative blood loss after total knee arthroplasty: a prospective randomised controlled trial of 29 patients.

Orpen NM, Little C, Walker G, Crawfurd EJ: Knee. 2006 Mar;13(2):106-10. Epub 2006 Feb 17. Department of Orthopaedics, Northampton General Hospital, Northampton NN1 5BD, UK.

INTRODUCTION: Extensive blood loss related to knee arthroplasty is quite normal and many patients require blood transfusions. Surgery and the use of pneumatic tourniquets lead to an increase in the activity of the fibrinolytic system, which in turn may accentuate the blood loss. Drugs that inhibit the fibrinolytic system may thus be used to reduce blood loss. Tranexamic acid (TA) acts by binding to one of the enzymes at the start of the coagulation cascade, so inhibiting the fibrinolytic system. A concern is that this inhibition may have the side effect of increasing thromboembolic disease, a common complication of joint replacement surgery. We aimed to confirm the reductions in blood loss and to assess the impact of TA usage on clinical and sub-clinical DVT.
METHOD: We performed a prospective, randomised, double blind, controlled trial, using patients due to undergo primary unilateral total knee arthroplasty. Patients were

randomised to receive either 15 mg/kg of tranexamic acid or a similar volume of normal saline at the time of cementing of the prosthesis. Perioperative blood loss was recorded and patients were screened for DVT with duplex ultrasound assessment of both legs on the fifth post-operative day.
RESULTS: A statistically significant (p=0.006) decrease in blood loss in the early post-operative period was noted in the group receiving tranexamic acid. This was not associated with a significant difference in total blood loss (p=0.55) or in transfusion requirements. There was no of evidence in DVT in either group on duplex ultrasound screening of the lower limbs.
INTERPRETATION: One injection of 15 mg/kg of tranexamic given at the time of cementing the prosthesis in total knee arthroplasty, before deflation of the tourniquet, significantly decreases the amount of blood loss in the early post-operative period. The treatment was not associated with an increase in thromboembolic complications.

Effectiveness of tranexamic acid in routine performance of total knee replacement surgery.

Camarasa Godoy MA, Serra-Prat M, Palomera Fanegas E: Rev Esp Anestesiol Reanim. 2008 Feb;55(2):75-80. Servicio de Anestesiología, Reanimación y Clínica del Dolor, Hospital de Matar, Barcelona.

OBJETIVES: To evaluate the effectiveness of treatment with tranexamic acid, compared to absence of antifibrinolytic treatment, in reducing transfusion rates and the number of units of packed red blood cells required in patients undergoing total knee replacement surgery.
MATERIAL AND METHODS: We reviewed the medical records of all patients who underwent total knee replacement surgery in a general hospital in 2006. Information was recorded on treatment with tranexamic acid, use of other antifibrinolytic drugs, hemoglobin and hematocrit levels before surgery and 3 days after surgery, patients requiring transfusions, units of packed red blood cells administered, and whether or not drains were clamped within 4 hours. Complications attributable to tranexamic acid (thromboembolic or systemic complications) and preoperative treatment with erythropoietin were also recorded.
RESULTS: Data for 166 patients were analyzed. Of these, 120 (72.3%) received tranexamic acid, 15 (9%) received epsilon-aminocaproic acid, and 31 (18.7%) received no antifibrinolytic treatment. Transfusions were given to 17 patients, of whom 6 (5.0%) had received tranexamic acid, 2 (133%) had received epsilon-aminocaproic acid, and 9 (29.0%) had received no antifibrinolytic treatment. The mean numbers of packed red blood cell

units transfused in each group were as follows: 0.075 in the tranexamic acid group, 0.200 in the epsilon-aminocaproic acid group, and 0.645 in the group with no antifibrinolytic treatment (P < .001). The mean decrease in hemoglobin levels 5 days after surgery was 3.04 g/dL in the tranexamic acid group, 3.55 g/dL in the epsilon-aminocaproic acid group and 3.76 g/dL in the group with no antifibrinolytic treatment (P < .001).
CONCLUSIONS: Tranexamic acid is effective in reducing the percentage of patients requiring transfusions and in the number of units of packed red blood cells required in total knee replacement surgery. No complications attributable to this treatment were found.

Efectos del ácido tranexámico en la muerte, eventos vasculares oclusivos y transfusión de sangre en pacientes traumatizados con hemorragia significativa. (CRASH-2): Un ensayo randomizado, controlado con placebo.

Ian Roberts & colab. The Lancet. Col 377, N 9771, 26 March 2011

Antecedentes: El ácido tranexámico puede disminuir el sangrado en pacientes que habían aceptado ser sometidos a cirugía. Hemos averiguado los efectos de la administración temprana de una escasa cantidad de ácido tranexámico, efectos éstos relativos a: causa de muerte, accidentes vasculares oclusivos y la recepción de transfusión de sangre, en pacientes traumatizados.

Métodos: Se emprendió este ensayo clínico (randomizado y con grupo placebo-control) en 274 hospitales de 40 países. A 20.211 pacientes adultos, que habían sufrido un traumatismo, y se encontraban aquejados de, o con riesgo de sufrir hemorragia grave, se los asignó de manera randomizada (dentro de las 8 horas de ocurrido el problema) a serles administrando ácido tranexámico o placebo. La dosis de ácido tranexámico era de 1 g a lo largo de 10 minutos y, luego una infusión de 1 g a lo largo de 8 horas (se administraba el placebo de la misma manera). La randomización se había "equilibrado" según el hospital, con una secuencia de reparto basada sobre un "bloque" de ocho, creado por un generador, aleatorio y computarizado, de números. Tanto los participantes como el personal del estudio (investigadores pertenecientes al estudio así como el personal del centro coordinador del ensayo) desconocían a quienes se administraría el tratamiento. El desenlace primario lo integraba la muerte en el hospital, dentro de las 4 semanas de causado el traumatismo, y las causas fueron incluídas en las siguientes categorías: hemorragia, oclusión vascular (infarto del miocardio, ataque y embolia pulmonar); falla multiorgánica, heridas en la cabeza, y otros. Todos los análisis se condujeron como

"Intention to treat" (la expresión “intention to treat” literalmente “intento de tratar” designa un análisis sobre resultados de eficacia medicamentosa).

Este estudio ha sido registrado bajo ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Hallazgos: A 10.096 pacientes, se los había asignados al ácido tranexámico y 10.115 al placebo, de los cuales, respectivamente, 10.060 y 10.067 fueron sometidos a análisis. La mortalidad por cualquier causa se vió disminuída de manera importante mediante el ácido tranexámico (1463 [14·5%] en el grupo del ácido tranexámico "contra" 1613 [16·0%] el grupo del placebo; riesgo relativo 0·91, 95% CI (CI, en estadística, es el intervalo de confianza.) 0·85–0·97; p=0·0035). Quedó disminuido de modo muy significativo el riesgo de muerte por hemorragia (489 [4·9%] "contra" 574 [5·7%]; riesgo relativo 0·85, 95% CI 0·76–0·96; p=0·0077).

Interpretación: En el presente estudio, el ácido tranexámico ha disminuído, con seguridad, el riesgo de muerte en pacientes aquejados de traumatismo hemorrágico. Sobre la base de estos resultados, debería tenerse en cuenta la administración de ácido tranexámico a pacientes aquejados de traumatismo hemorrágico.

Estudio financiado por: El Programa británico de Evaluación Tecnológica de la salud (UK NIHR Health Technology Assessment programm), Laboratorios Pfizer, la Fundación BUPA (BUPA Foundation) y la Fundación Caritativa J.P. Moulton (J P Moulton Charitable Foundation).

Tranexamic acid and thrombosis.

[No authors listed] Prescrire Int. 2013 Jul;22(140):182-3.

Tranexamic acid is an antifibrinolytic drug. It therefore reduces bleeding but, in certain situations, it may expose patients to a risk of thrombosis. It is used for the treatment of various types of bleeding, including menorrhagia, haematuria, certain surgical procedures and trauma. Its harm-benefit balance is favourable in certain situations associated with serious bleeding.The harm-benefit balance is different in minor bleeding: the expected benefits are smaller because the condition is not serious, and the risk of thromboembolism may be higher without the haemodilution associated with severe bleeding. Various drug regulatory agencies have received reports of thrombotic events attributed to tranexamic acid. In a case-control study using data from the British General Practice Research Database, women taking tranexamic acid had a 3-fold higher risk of developing deep vein thrombosis. There was a wide 95% confidence interval, ranging from

0.7 to 15.8; thus, a major increase in the risk of thrombosis cannot be ruled out. Only one comparative randomised trial assessed thrombotic events in 53 women receiving tranexamic acid for menorrhagia; too few patients were studied to determine the risk. Clinical trials conducted in serious haemorrhage or in patients undergoing surgery with a high risk of bleeding have not shown an increased risk of thrombosis with tranexamic acid. In practice, as of early 2013, the harm-benefit balance of tranexamic acid is favourable in severe traumatic bleeding. But when bleeding is not life-threatening, the thrombotic risk is too poorly documented to justify exposing patients to a plausible and inadequately evaluated risk.

The frequency of thrombotic events among adults given antifibrinolytic drugs for spontaneous bleeding: systematic review and meta-analysis of observational studies and randomized trials.

Ross J, Al-Shahi Salman R: Curr Drug Saf. 2012 Feb;7(1):44-54. Source: Division of Clinical Neurosciences, Centre for Clinical Brain Sciences, University of Edinburgh, UK.

AIMS: The antifibrinolytic drug tranexamic acid (TXA) improves survival after trauma. Antifibrinolytic drugs may also improve outcome after spontaneous bleeding, so we conducted a systematic review of the frequency of thrombotic events associated with their use after spontaneous bleeding, to help design future randomized controlled trials.

METHODS: We sought trials or observational studies of ≥20 adults involving any antifibrinolytic drug (TXA, epsilonaminocaproic acid (EACA) or aprotinin) for spontaneous (non-traumatic, non-surgical/iatrogenic), non-heamophiliac bleeding. We searched the Cochrane Central Register of Controlled Trials, OVID Medline from 1966, EMBASE from 1980, and the bibliographies of relevant articles in October 2009. We meta-analysed proportions of patients with thrombotic events, using a random effects model.

RESULTS: We found 57 studies involving 5,049 patients, 3,616 (72%) of whom had spontaneous subarachnoid haemorrhage. 3,414 (68%) patients received TXA-based treatment and 1,635 (32%) received EACA. The frequencies of limb ischaemia and myocardial infarction were <1% for TXA and EACA. The frequency of deep vein thrombosis or pulmonary embolism was 1.9% (95% confidence interval (CI) 1.1 to 2.9) for TXA and 3.0% (95% CI 1.8 to 4.6) for EACA. The occurrence of cerebral infarction was restricted to studies of subarachnoid haemorrhage when compared to other indications, both for TXA (9.7% [95% CI 5.5 to 14.8] versus 0% [95% CI 0 to 0.5]) and for EACA (7.7% [95% CI 1.8 to 17.4] versus 0% [95% CI 0 to 2.1]).

CONCLUSIONS: Thrombotic events have occurred infrequently with antifibrinolytic drugs after spontaneous bleeding apart from subarachnoid haemorrhage, so further exploration of their safety and efficacy after spontaneous bleeding is justified in randomized trials.

Tranexamic acid in decreasing blood loss during and after caesarean section.

Shahid A, Khan A: J Coll Physicians Surg Pak. 2013 Jul;23(7):459-62. Source: Department of Obstetrics and Gynecology, Dow University of Health Sciences, Karachi.

OBJECTIVE: To determine the effectiveness of tranexamic acid (TXA) in reducing blood loss during and after caesarean section (CS), as well as its safety.
STUDY DESIGN: A randomized double-blind placebo controlled study.
PLACE AND DURATION OF STUDY: The Lyari General Hospital, Karachi, from March 2009 till April 2011.
METHODOLOGY: Women undergoing lower segment caesarean section (LSCS) were enrolled. The patients were randomized to receive either injection TXA or distilled water just before the surgery. Blood loss was collected and measured. First from the time of placental delivery to the end of LSCS and later from the end of LSCS to two hours postpartum. Haemoglobin, urine analysis, liver and renal functions were tested in both the groups. Mean values blood loss were compared using t-test with significance at $p < 0.05$.
RESULTS: Tranexamic acid significantly reduced the quantity of blood loss from placental delivery to the end of LSCS which was 356.44 ± 143.2 ml in the TXA group versus 710.22 ± 216.72 ml in the placebo group ($p < 0.001$). It also reduced the quantity of blood loss from the end of LSCS to 2 hours postpartum which was 35.68 ± 23.29 ml in the TXA group versus 43.63 ± 28.04 ml in the placebo group ($p = 0.188$), was not significant. No complications or side effects were reported in either group.
CONCLUSION: Tranexamic acid significantly reduced the amount of blood loss during the LSCS, but it did not reduce the blood loss significantly after the caesarean section. Its use was not associated with any side effects or complication like thrombosis. TXA can be used safely and effectively in women undergoing LSCS to reduce intraoperative blood loss.

Tranexamic acid for preventing postpartum haemorrhage.

Novikova N, Hofmeyr GJ: Cochrane Database Syst Rev. 2010 Jul 7;(7):CD007872. Source: Women's Health and Neonatology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, Sydney, NSW, Australia, 2050.

BACKGROUND: Postpartum haemorrhage (PPH) is a common and occasionally life-threatening complication of labour. Several options for preventing PPH are available, but further advances in this field are important, especially the identification of safe, easy to use, and cost-effective regimes. Tranexamic acid, which is an antifibrinolytic that is used widely to prevent and treat haemorrhage, merits evaluation to assess whether it meets these criteria.
OBJECTIVES: To determine, from the best available evidence, whether tranexamic acid is effective for preventing PPH.
SEARCH STRATEGY: We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (12 September 2009).
SELECTION CRITERIA: All published, unpublished and ongoing randomised controlled trials (RCTs) evaluating the use of tranexamic acid alone or in addition to uterotonics in the third stage of labour or during caesarean section to prevent PPH.
DATA COLLECTION AND ANALYSIS: Two review authors independently assessed for inclusion all the potential studies identified as a result of the search strategy. We entered the data into Review Manager software and checked for accuracy.
MAIN RESULTS: We included two RCTs. One RCT of unclear quality of 273 women compared tranexamic acid in two doses (0.5 g intravenously and 1 g intravenously) with aminomethylbenzoic acid (0.5 g intravenously) and with no treatment in women who had vaginal birth. We excluded the aminomethylbenzoic acid arm of this trial (92 patients).Another RCT of 180 women who underwent caesarean section compared tranexamic acid (1 g intravenously given 10 minutes before incision) with placebo.Blood loss greater than 400 ml was less common in women who received tranexamic acid after vaginal birth or caesarean section in the dosage of 1 g or 0.5 g intravenously (two studies, 453 women, risk ratio (RR) 0.51, 95% confidence interval (CI) 0.36 to 0.72). Mean blood loss was lower in the group of women who received intravenous tranexamic acid postpartum (two studies, 361 women, mean difference (MD) -75.17 ml, 95% CI -108.23 ml to -42.12 ml).No serious side effects were reported in women who received tranexamic acid in these trials.
AUTHORS' CONCLUSIONS: Tranexamic acid decreases postpartum blood loss after vaginal birth and after caesarean section based on two RCTs of unclear quality which reported on only a few outcomes. Further investigations are needed on efficacy and safety of this regimen for preventing PPH.

Treatment of heavy menstrual bleeding of endometrial origin: randomized controlled trial of medroxyprogesterone acetate and tranexamic acid.

Goshtasebi A, Moukhah S, Gandevani SB: Arch Gynecol Obstet. 2013 Nov;288(5):1055-60.

PURPOSE: This study aimed at comparing the efficacy of medroxyprogesterone acetate (MPA) and tranexamic acid (TA) for treating heavy menstrual bleeding of endometrial origin (HMB).
METHODS: A randomized controlled trial was carried out in three gynecology clinics in Tehran, Iran. Ninety women with the HMB of endometrial origin were randomized into the study: 44 patients took MPA for 21 days from day 5 and 46 patients took tranexamic acid for 5 days from day 1 of menses for three consecutive menstrual cycles. Blood loss was measured using the pictorial blood loss assessment chart (PBAC); hematological assessments were made before intervention and after treatment. SF-36 and HMB Questionnaire (MQ) were given to assess quality of life. Statistical analysis was performed using t test, Paired t test, χ(2), Mann-Whitney, Wilcoxon signed-rank test, and repeated measure analysis.
RESULTS: PBLC mean score, duration of bleeding and Hb values as well as quality of life were significantly improved in both groups ($P < 0.05$). But there was no significant deference between groups. More drug complication and less satisfaction were reported by MPA group ($P = 0.003$ and $P = 0.002$, respectively).
CONCLUSIONS: Long-term use of MPA is as effective as Tranexamic acid in treating HMB and increasing quality of life. However, bleeding irregularity side effects of MPA might limit its use.

Tranexamic acid for the treatment of heavy menstrual bleeding: efficacy and safety.

Leminen H, Hurskainen R: Int J Womens Health. 2012;4:413-21. Source: Department of Obstetrics and Gynecology, Hyvinkää Hospital, Hyvinkää, Finland.

Tranexamic acid has proven to be an effective treatment for heavy menstrual bleeding (HMB). It reduces menstrual blood loss (MBL) by 26%-60% and is significantly more effective than placebo, nonsteroidal anti-inflammatory drugs, oral cyclical luteal phase progestins, or oral etamsylate, while the levonorgestrel-releasing intrauterine system reduces MBL more than tranexamic acid. Other treatments used for HMB are oral contraceptives, danazol, and surgical interventions (endometrial ablation and hysterectomy). Medical therapy is usually considered a first-line treatment for idiopathic HMB. Tranexamic acid significantly improves the quality of life of women treated for HMB. The recommended oral dosage is 3.9-4 g/day for 4-5 days starting from the first day of the menstrual cycle. Adverse effects are few and mainly mild. No evidence exists of an

increase in the incidence of thrombotic events associated with its use. An active thromboembolic disease is a contraindication. In the US, a history of thrombosis or thromboembolism, or an intrinsic risk for thrombosis or thromboembolism are considered contraindications as well. This review focuses on the efficacy and safety of tranexamic acid in the treatment of idiopathic HMB. We searched for medical literature published in English on tranexamic acid from Ovid Medline, PubMed, and Cinahl. Additional references were identified from the reference lists of articles. Ovid Medline, PubMed, and Cinahl search terms were "tranexamic acid" and "menorrhagia" or "heavy menstrual bleeding." Searches were last updated on March 25, 2012. Studies with women receiving tranexamic acid for HMB were included; randomized controlled studies with a description of appropriate statistical methodology were preferred. Relevant data on the physiology of menstruation and the pharmacodynamics and pharmacokinetics of tranexamic acid are also included.

Use of tranexamic acid to reduce bleeding in burns surgery

Tang YM, Chapman TW, Brooks P: J Plast Reconstr Aesthet Surg. 2012 May;65(5):684-6.

We describe, for the first time, the use of topical tranexamic acid as an adjunct to traditional methods in the control of bleeding in burns surgery. We illustrate our use with a case example and continue to discuss the reasons we believe it is a useful, effective and safe means of achieving haemostasis.

Reducing Postburn Injury Anemia in a Jehovah's Witness Patient

Barsun A, Sen S, Palmieri TL, Greenhalgh DG: J Burn Care Res. 2013 Oct 11

Anemia is a complication of severe burn injury. Burn patients who refuse blood transfusions, such as Jehovah's Witnesses, present difficult challenges, and treatment paradigms need to be altered to reduce blood loss and increase red cell restoration. In this report the authors present a case of a 36-year-old Jehovah's Witness who suffered a 35% TBSA burn injury. In addition to standard burn injury treatment, the authors attempted to reduce blood loss with a combination of intraoperative (tranexamic acid) and perioperative (erythropoietin, intravenous iron) strategies.

Tranexamic acid decreases blood loss during transurethral resection of the prostate.

Kumsar S, Dirim A, Toksöz S, Sağlam HS, Adsan O. Cent European J Urol. 2011;64(3):156-8.

INTRODUCTION: Postoperative blood loss after prostate surgery is thought to be associated with an increase in urinary fibrinolytic activity. Tranexamic acid (TXA) is both a potent inhibitor of plasminogen and urokinase activators and a low molecular weight substance that is excreted unchanged in the urinary tract and can be administered both orally and intravenously. We investigated the effect of TXA on the amount of blood loss during transurethral resection of the prostate (TURP).
MATERIALS AND METHODS: Forty patients with registry numbers ending in even numbers were allocated to the treatment group; those ending in odd numbers were used as controls and received no treatment. The treatment group received 10 mg/kg TXA by intravenous infusion during the first half hour of the operation, while the control group of patients received no medication. Serum hemoglobin was measured before and after surgery. The volume and hemoglobin concentration of the irrigation fluid, resected prostate weight, and duration of resection were recorded.
RESULTS: The mean loss of hemoglobin per gram of resected prostate tissue was 1.25 g in the TXA group and 2.84 g in the control group. Total hemoglobin loss in the irrigating fluid and hemoglobin loss per 1 gram of prostate tissue was lower in the group of patients given TXA than in the control group ($p = 0.018$ and $p < 0.001$).
CONCLUSION: Reduced bleeding during TURP as a result of TXA treatment may lead to better surgical conditions and, as a consequence, shorter operative times and lower irrigating fluid volumes.

Intraoperative use of tranexamic acid to reduce transfusion rate in patients undergoing radical retropubic prostatectomy: double blind, randomised, placebo controlled trial.

Antonella Crescenti, anaesthetist, Giovanni Borghi, medical doctor, Elena Bignami, anaesthetist, junior research executive, Gaia Bertarelli, statistician, Giovanni Landoni, anaesthetist, senior research executive, Giuseppina Maria Casiraghi, anaesthetist, Alberto Briganti, urologist, senior research executive, Francesco Montorsi, professor of urology, Patrizio Rigatti, professor of urology, and Alberto Zangrillo, professor of anaesthesiology and intensive care. BMJ. 2011; 343: d5701.

Objectives: To determine the efficacy of intraoperative treatment with low dose tranexamic acid in reducing the rate of perioperative transfusions in patients undergoing radical retropubic prostatectomy.
Design: Double blind, parallel group, randomised, placebo controlled trial.
Setting: One university hospital in Milan, Italy.

Participants: 200 patients older than 18 years and undergoing radical retropubic prostatectomy agreed to participate in the trial. Exclusion criteria were atrial fibrillation, coronary artery disease treated with drug eluting stent, severe chronic renal failure, congenital or acquired thrombophilia, and known or suspected allergy to tranexamic acid.
Interventions: Intravenous infusion of tranexamic acid or equivalent volume of placebo (saline) according to the following protocol: loading dose of 500 mg tranexamic acid 20 minutes before surgery followed by continuous infusion of tranexamic acid at 250 mg/h during surgery.
Main outcome measures: Primary outcome: number of patients receiving blood transfusions perioperatively. Secondary outcome: intraoperative blood loss. Six month follow-up to assess long term safety in terms of mortality and thromboembolic events.
Results: All patients completed treatment and none was lost to follow-up. Patients transfused were 34 (34%) in the tranexamic acid group and 55 (55%) in the control group (absolute reduction in transfusion rate 21% (95% CI 7% to 34%); relative risk of receiving transfusions for patients treated with tranexamic acid 0.62 (0.45 to 0.85); number needed to treat 5 (3 to 14); P=0.004). At follow-up, no patients died and the occurrence of thromboembolic events did not differ between the two groups.
Conclusions: Intraoperative treatment with low dose tranexamic acid is safe and effective in reducing the rate of perioperative blood transfusions in patients undergoing radical retropubic prostatectomy.

Tranexamic Acid Treatment of Life-Threatening Hematuria in Polycystic Kidney Disease.

Turki AlAmeel, and Michael West. Published online 2011 Jun 1. Int J Nephrol. 2011; 2011: 203579.

A 41-year-old woman with autosomal dominant polycystic kidney disease had chronic kidney disease class IV. She presented 10 days postpartum with a 4-day history of severe hematuria, left flank pain, and anemia, hemoglobin 62 g/L. CT scan showed massively enlarged kidneys with multiple cysts; several cysts bilaterally had high attenuation consistent with hemorrhage. Hematuria persisted over several days despite intensive conservative measures that included vitamin K1, 4 units of plasma, transfusion of 10 units of packed RBCs, Darbopoeitin, and DDAVP. Antifibrinolytic therapy was given with tranexamic acid 1000 mg p.o. t.i.d for one day then OD. The hematuria stopped within 24 hours and did not recur after tranexamic acid therapy ended. Over the next 4 years there were 3 hospitalizations each with severe gross hematuria requiring blood transfusion for acute anemia. The hematuria responded well to further treatment with tranexamic acid.

Tranexamic acid produces antifibrinolytic effects via complex interactions with plasminogen, displacing plasminogen from the fibrin surface. Chronic renal impairment is considered a relative contraindication to use of tranexamic acid due to reports of ureteric clots and acute renal failure from cortical necrosis. We conclude that tranexamic acid can be used safely in some patients with CKD and polycystic kidney disease to treat severe hematuria.

Tranexamic acid reduces blood loss during percutaneous nephrolithotomy: a prospective randomized controlled study.

Kumar S, Randhawa MS, Ganesamoni R, Singh SK. J Urol. 2013 May;189(5):1757-61.

PURPOSE: Bleeding is a significant morbidity associated with percutaneous nephrolithotomy. This study was conducted to evaluate the safety and efficacy of the antifibrinolytic agent tranexamic acid in reducing blood loss in patients undergoing percutaneous nephrolithotomy.
MATERIALS AND METHODS: A total of 200 patients undergoing percutaneous nephrolithotomy were randomized into 2 equal groups. Patients in the tranexamic acid group received 1 gm tranexamic acid at induction followed by 3 oral doses of 500 mg during 24 hours, while those in the control group did not receive tranexamic acid. The patient demographics and clinical data of the 2 groups were compared.
RESULTS: Baseline patient demographics were similar in both groups. Mean hemoglobin decrease in the tranexamic acid group was significantly lower than that of the control group (1.39 vs 2.31 gm/dl, $p < 0.0001$). Mean operative time in the tranexamic acid group was significantly lower than that in the control group (48.3 vs 70.8 minutes, $p < 0.0001$). The stone clearance rate was similar in both groups (91% vs 82%, $p = 0.06$). The blood transfusion rate was lower in the tranexamic acid group (2% vs 11%, $p = 0.018$), as was the complication rate (33% vs 59%, $p < 0.0001$). Two patients with a solitary functioning kidney in the tranexamic acid group required ureteral stenting to relieve anuria due to clot obstruction.
CONCLUSIONS: The use of tranexamic acid in percutaneous nephrolithotomy is safe, and is associated with reduced blood loss and a lower complication rate.

ACIDO TRANEXÁMICO EN HEMORRAGIAS DIGESTIVAS

Systematic review: tranexamic acid for upper gastrointestinal bleeding.

Gluud LL, Klingenberg SL, Langholz SE. Aliment Pharmacol Ther. 2008 May;27(9):752-8. Epub 2008 Feb 4. Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark. liselottegluud@yahoo.dk

BACKGROUND: Tranexamic acid may reduce upper gastrointestinal bleeding and stabilize patients before endoscopic treatments. AIM: To review randomized trials on tranexamic acid for upper gastrointestinal bleeding.
METHODS: Manual and electronic searches of The Cochrane Library, MEDLINE, EMBASE and Science Citation Index were combined. Intention-to-treat random effect meta-analyses were performed and results presented as RRs with 95% confidence intervals.
RESULTS: Seven double-blind randomized trials on tranexamic acid vs. placebo were included. Of 1754 patients randomized, 21% were excluded. Only one trial included endoscopic treatments or proton pump inhibitors. Five per cent of patients on tranexamic acid and 8% of controls died (RR: 0.61, 95% CI: 0.42-0.89). No significant differences were found on bleeding, bleeding-related mortality, surgery or transfusion requirements. Adverse events were unclearly reported. Data from three of the included trials suggested that tranexamic acid did not significantly increase the risk of thromboembolic disease.
CONCLUSIONS: The present review suggests that tranexamic acid may reduce all-cause mortality. However, because of limitations in the internal and external validity of included trials, additional evidence is needed before treatment recommendations can be made.

Clinical practice and evidence in endoscopic treatment of bleeding peptic gastroduodenal ulcer.

Adamsen S, Bendix J, Kallehave F, Moesgaard F, Nilsson T, Wille-JÃ¸rgensen P. Department of Gastrointestinal Surgery D-113, Copenhagen University Hospital Herlev, Herlev, Denmark. sven. Scand J Gastroenterol. 2007 Mar;42(3):318-23.

OBJECTIVE: To investigate treatment practice in non-variceal upper gastrointestinal bleeding (NVUGIB) caused by gastroduodenal ulcer and how it adheres to the best evidence as documented in randomized studies and meta-analyses.

MATERIAL AND METHODS: The literature was surveyed to identify appropriate practices, and a structured multiple choice questionnaire developed and mailed to all departments in Denmark treating UGIB.
RESULTS: All 42 departments responded. All had therapeutic gastroscopes and equipment necessary for endoscopic haemostasis; 90% of departments had written guidelines. Adjuvant pharmacologic treatment included tranexamic acid in 38%. Proton-pump inhibitors (PPIs) were used by all departments, with 29% starting prior to endoscopic treatment. Eight departments (19%) used continuous PPI infusion, three of them starting with a bolus dose. In 50% of departments an anaesthesiologist was always present regardless of whether endotracheal intubation (routinely used by 10%) was used or not. Ten percent did not treat Forrest IIa and IIb ulcers, while IIc ulcers were treated by 36%. In 10% of departments clots were never removed, while in 2/3 attempts were made to remove resistant clots by mechanic means. Seven departments (17%) used monotherapy with epinephrine, while 59% always used dual therapy; 19% injected less than 10 ml. In rebleeding, 92% attempted endoscopic treatment before surgery, and used epinephrine in 79% of cases, while the remainder used epinephrine or polidocanol at the discretion of the endoscopist. Two out of three departments used high-dependency or intensive-care units for surveillance. Seventeen percent applied scheduled second-look gastroscopy.
CONCLUSIONS: Practice is variable, even in areas with established evidence based on randomized controlled studies, such as dosage and way of administration and duration of PPI treatment, injection treatment used as monotherapy and the volumen used, including ulcers with clots for treatment, and the use of scheduled second-look endoscopy. Since the rebleeding rate has remained unchanged for decades, and rebleeding implies increased surgery and mortality rates, appropriate practices must be promoted in order to improve results. Development and implementation of national guidelines may facilitate the process.

Tranexamic acid is beneficial as adjunctive therapy in treating major upper gastrointestinal bleeding in dialysis patients.

Sabovic M, Lavre J, Vujkovac B. Nephrol Dial Transplant. 2003 Jul;18(7):1388-91.

BACKGROUND: In a pilot, non-randomized trial we tested the efficacy of tranexamic acid (TXA), a potent fibrinolytic inhibitor, as adjunctive therapy in standard treatment of major upper gastrointestinal bleeding in dialysis patients.
METHODS: Twenty consecutive patients (12 male, eight female; 63+/-8 years) with 36 episodes of major upper gastrointestinal bleeding were included in the study. In 16 episodes of bleeding TXA was used (in a dosage of 20 mg intravenously, followed for the

next 4 weeks by 10 mg/kg/48 h orally), whereas in 20 other cases of bleeding, TXA was not used. The decision to use TXA was left to the attending physician's clinical judgement, resulting in all the more severe cases of bleeding being treated with TXA.
RESULTS: Treatment including TXA was shown to be beneficial (relative to cases not treated with TXA) in terms of decreasing the rate of early re-bleeding (in the first week, 0 vs 6, P<0.05), the rate of early and late re-bleeding (in the first month, 1 vs 8, P<0.05), the rate of repeated endoscopic procedures (in the first month, 1 vs 8, P<0.05) and the number of blood transfusions needed (in the first month, 1.4+/-1.3 vs 2.6+/-1.5 units, P<0.05).
CONCLUSIONS: The results of this pilot study suggest that TXA can be beneficial in the treatment of major upper gastrointestinal bleeding in dialysis patients. This remains to be definitely confirmed in a randomized study.

Drug treatments in upper gastrointestinal bleeding: value of endoscopic findings as surrogate end points.

Hawkey GM, Cole AT, McIntyre AS, Long RG, Hawkey CJ. Gut. 2001 Sep;49(3):372-9.

INTRODUCTION: Pharmacotherapy for upper gastrointestinal bleeding has been difficult to evaluate because clinical end points are infrequent and affected by other factors.
AIMS: To evaluate whether blood in the stomach at endoscopy reflected severity of bleeding, predicted clinical outcomes, and could be altered by therapeutic agents.
METHODS: We studied 414 consecutive admissions with suspected upper gastrointestinal bleeding. Patients were randomised to receive lansoprazole 60 mg followed by 30 mg four times daily, tranexamic acid 2 g followed by 1 g four times daily, both drugs, or placebo for four days, until discharge or a clinical end point occurred. Logistic regression analysis was used to determine predictors of endoscopic changes and clinical outcomes, and to investigate the effects of drug treatments on blood in the stomach.
RESULTS: Of 414 patients with suspected upper gastrointestinal bleeding, 379 were endoscoped. Upper gastrointestinal bleeding was confirmed in 316. Sixteen required surgery within 30 days and 16 died on the index admission. Trial treatments were evaluable on a per protocol basis in 228 patients. The amount of blood in the stomach was found to reflect initial risk, with significant associations with high risk categorisation (odds ratio 3.7 (95% confidence interval 1.5-9.4) for more than a trace v none/trace), age (1.5 (1.1-1.9) per decade), and initial pulse (1.02 (1.00-1.04) per beat), and to predict rebleeding (9.2 (4.6-18.7)) and surgery (8.2 (2.9-22.9)). Other stigmata were less significant in these respects. The amount of blood in the stomach at endoscopy was

reduced significantly by both lansoprazole (0.22 (0.07-0.63)) and tranexamic acid (0.27 (0.09-0.81)), although there was no evidence of synergy.
CONCLUSIONS: Blood in the stomach reflects clinical features in patients with acute upper gastrointestinal bleeding and is reduced by treatment with lansoprazole and tranexamic acid.

Tranexamic acid for upper gastrointestinal bleeding.

Bennett C, Klingenberg SL, Langholz E, Gluud LL. Cochrane Database Syst Rev. 2014 Nov 21;11:CD006640.

Background Tranexamic acid reduces haemorrhage through its antifibrinolytic effects. In a previous version of the present review, we found that tranexamic acid may reduce mortality. This review includes updated searches and new trials. Objectives To assess the effects of tranexamic acid versus no intervention, placebo or other antiulcer drugs for upper gastrointestinal bleeding.Search methods We updated the review by performing electronic database searches (Cochrane Central Register of Controlled Trials (CENTRAL),MEDLINE, EMBASE, Science Citation Index) and manual searches in July 2014.Selection criteriaRandomised controlled trials, irrespective of language or publication status.Data collection and analysis We used the standard methodological procedures of the The Cochrane Collaboration. All-cause mortality, bleeding and adverse events were the primary outcome measures. We performed fixed-effect and random-effects model meta-analyses and presented results as risk ratios (RRs) with 95% confidence intervals (CIs) and used I^2 as a measure of between-trial heterogeneity. We analysed tranexamic acid versus placebo or no intervention and tranexamic acid versus antiulcer drugs separately. To analyse sources of heterogeneity and robustness of the overall results, we performed subgroup, sensitivity and sequential analyses.Main results We included eight randomised controlled trials on tranexamic acid for upper gastrointestinal bleeding. Additionally, we identified one large ongoing pragmatic randomised controlled trial from which data are not yet available. Control groups were randomly assigned to placebo (seven trials) or no intervention (one trial). Two trials also included a control group randomly assigned to antiulcer drugs(lansoprazole or cimetidine). The included studies were published from 1973 to 2011. The number of participants randomly assigned ranged from 47 to 216 (median 204). All trials reported mortality. In total, 42 of 851 participants randomly assigned to tranexamic acid and 71 of 850 in the control group died (RR 0.60, 95% CI 0.42 to 0.87; P value 0.007; I^2 = 0%). The analysis was not confirmed when all participants in the intervention group with missing outcome data were included as treatment failures, or when the analysis was limited to

trials with low risk of attrition bias. Rebleeding was diagnosed for 117 of 826 participants in the tranexamic acid group and for 146 of 825 participants in the control group (RR 0.80, 95% CI 0.64 to 1.00; P value 0.07; I^2 = 49%). We were able to evaluate the risk of serious adverse events on the basis of only four trials. Our analyses showed 'no evidence of a difference between tranexamic acid and control interventions regarding the risk of thromboembolic events.' Tranexamic acid appeared to reduce the risk of surgery ina fixed-effect meta-analysis (RR 0.73, 95% CI 0.56 to 0.95), but this result was no longer statistically significant in a random-effects meta-analysis (RR 0.61, 95% CI 0.35 to 1.04; P value 0.07). No difference was apparent between tranexamic acid and placebo in the assessment of transfusion (RR 1.02, 95% CI 0.94 to 1.11; I^2 = 0%), and meta-analyses that compared tranexamic acid versus antiulcer drugs did not identify beneficial or detrimental effects of tranexamic acid for any of the outcomes assessed.Authors' conclusions This review found that tranexamic acid appears to have a beneficial effect on mortality, but a high dropout rate in some trials means that we cannot be sure of this until the findings of additional research are published. At the time of this update in 2014, one large study(8000 participants) is in progress, so this review will be much more informative in a few years. Further examination of tranexamic acid would require inclusion of high-quality randomised controlled trials. Timing of randomisation is essential to avoid attrition bias and to limit the number of withdrawals. Future trials may use a pragmatic design and should include all participants with suspected bleeding or with endoscopically verified bleeding, as well as a tranexamic placebo arm and co-administration of pump inhibitors and endoscopic therapy. Assessment of outcome measures in such studies should be clearly defined. Endoscopic examination with appropriate control of severe bleeding should be performed, as should endoscopic verification of clinically significant rebleeding. In addition, clinical measures of rebleeding should be included. Other important outcome measures include mortality (30-day or in-hospital), need for emergency surgery or blood transfusion and adverse events (major or minor).

The treatment of haematemesis and upper gastrointestinal bleeding in United Kingdom Armed Forces and other deployed units.

Arr Woodward R, Khan M. J R Nav Med Serv. 2014;100(3):308-15.

INTRODUCTION: Upper Gastro-intestinal (UGI) bleeding is a significant cause of morbidity worldwide. United Kingdom Armed Forces (UKAFs) are not immune to this condition. There is a substantial body of conflicting evidence regarding initial management and risk stratification.

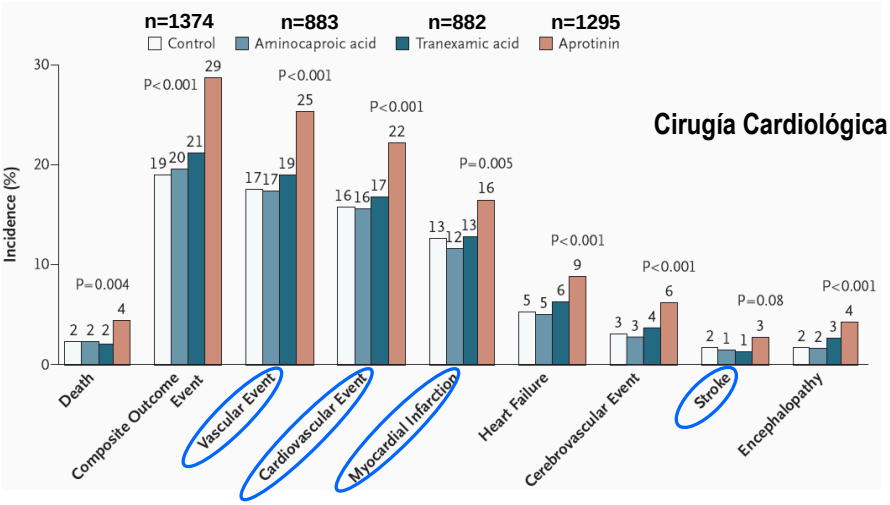
AIM: To provide the background knowledge and treatment pathways required to assess and manage a patient adequately during the first 24 hours of an episode of UGI bleeding.
ASSESSMENT: Clinical grading of hypovolaemic shock is inaccurate, but is a broad indicator of severity; the Rockall Score must not be used to assess requirement for intervention. Where laboratory assets are available, the Blatchford score is adequate to assess requirements for intervention.
MANAGEMENT: The principles of hypotensive resuscitation (target systolic blood pressure 90 mmHg for the first hour) hold true for UGI bleeds. In areas where endoscopy is available within four hours, a restrictive pattern of packed Red Blood Cell (pRBC) transfusion may be beneficial. Despite limited evidence of benefit, Proton Pump Inhibitors (PPIs) should be given routinely in UKAFs. Where available, in cases of variceal and non-variceal UGI Haemorrhage without locally available endoscopy, administration of tranexamic acid and somatostatin or octreotide should be considered.

Treatment of ulcerative colitis by the direct administration of an antifibrinolytic agent as an enema.

Kondo M, Hotta T, Takemura S, Yoshikawa T, Fukumoto K. Hepatogastroenterology. 1981 Oct;28(5):270-3.

Fibrinolytic activity in biopsied colonic mucosa was examined in patients with ulcerative colitis, and most cases were found to have increased tissue fibrinolysis -- due mainly to tissue plasminogen activator -- in the affected mucosa. Five cases, 4 with elevated tissue fibrinolysis and 1 normal, were treated with an antifibrinolytic agent, tranexamic acid (trans-AMCHA) administered as an enema, to inhibit fibrinolysis of the affected mucosa directly. In patients with elevated mucosal fibrinolysis, 2 showed complete remission after tranexamic acid enema alone, and there was one remission in response to combination treatment with oral prednisolone. One case with slightly elevated mucosal fibrinolysis showed clinical improvement, although the radiological findings were unchanged. No response was observed in one case with normal tissue fibrinolysis. It is concluded that tranexamic acid may show a therapeutic effect in ulcerative colitis with elevated mucosal fibrinolysis when administered via an enema, which allows direct contact of the drug with the affected mucosa.

Eventos Adversos: TROMBOSIS?



No eventos adversos vasculares para el TXA

Mangano DT *N Engl J Med* 2006: 354; 353-65

Eventos Adversos: TROMBOSIS?

CRASH-2

	TXA. n=10 060	placebo n=10 067	RR (IC95%)	
Mortalidad	14.5%	16%	0.91 (0.85-0.97)	p<0.01
Cualquier trombosis	1.7%	2.0%	0.84 (0.68-1.02)	p=0.08
Infarto de miocardio	0.3%	0.5%	0.64 (0.42-0.97)	p=0.04
Stroke	0.6%	0.7%	0.86 (0.61-1.23)	p=0.42
Embolia pulmón	0.7%	0.7%	1.01 (0.73-1.41)	p=0.93
Trombosis venossa profunda	0.4%	0.4%	0.98 (0.63-1.51)	p=0.91

No se obervaron aumentos eventos vasculares TXA

CRASH-2 trial collaborators, *Lancet* 2010; 376: 23-32