（別添様式）

未承認薬・適応外薬の要望に対する企業見解

1．要望内容に関連する事項

会社名	ホスピーラ・ジャパン株式会社	
要望された医薬品	要望番号	Ⅲ－④－7
	成分名（一般名）	Aminocaproic acid（アミノカプロン酸）
	販売名	Aminocaproic acid・Amicar Injection
	未承認薬・適応外薬の分類（該当するものにチェックする。）	☑ 未承認薬 ☐ 2009年4月以降に、FDA又はEMAで承認されたが、国内で承認されていない医薬品 ☑ 上記以外のもの　1964 年 FDA 承認 ☐ 適応外薬 ☐ 医師主導治験や先進医療B（ただし、ICH-GCPを準拠できたものに限る。）にて実施され、結果がまとめられたもの ☐ 上記以外のもの
要望内容	効能・効果（要望された効能・効果について記載する。）	線維素溶解（fibrinolysis）に伴う著しい出血に対する止血促進作用 線維素溶解に伴う著しい出血とは、人工心肺を伴う心臓手術、血液腫瘍疾患、胎盤早期剥離、前立腺がん、肺がん、胃がんなどの悪性新生物に対する手術後、および外傷後にしばしば認められる。
	用法・用量（要望された用法・用量について記載する。）	4～5 g を最初の 1 時間で静注、続いて 1 時間当たり 1g を静注、止血が得られるまで約 8 時間継続する。

	備　　考 （該当する場合はチェックする。）	□小児に関する要望 （特記事項等）
希少疾病用医薬品の該当性（推定対象患者数、推定方法についても記載する。）		約　　人 ＜推定方法＞
現在の国内の開発状況	□現在開発中 〔 □治験実施中　　□承認審査中 〕 ■現在開発していない 〔 □承認済み　　□国内開発中止　　■国内開発なし 〕 （特記事項等）	
企業としての開発の意思	□あり　　■なし （開発が困難とする場合、その特段の理由） 本邦では類似効能を有する薬剤として、以下の薬剤が承認され使用されている。 ⅰ．凝固系促進薬：フィトナジオン、メナテトレノン、 ⅱ．線溶系抑制薬：トラネキサム酸、カルバゾクロム、トロンビン 特に、トラネキサム酸は、アミノカプロン酸と同様の機序により繊維素溶解を阻害し止血促進作用を示すため、 アミノカプロン酸の代替薬になり得ると考えられることから、本剤の医療上の必要性は必ずしも高くないと考えられる。さらに、米国で承認されている弊社製品は後発品であり、米国先発品の承認時の申請データに対してもアクセスすることはできず、その承認も 1964 年（昭和 39 年）であることを考慮すると、本邦で新有効成分として開発することは困難である。	
「医療上の必要	１．適応疾病の重篤性 □ア　生命に重大な影響がある疾患（致死的な疾患） □イ　病気の進行が不可逆的で、日常生活に著しい影響を及ぼす疾患 □ウ　その他日常生活に著しい影響を及ぼす疾患 ■エ　上記の基準に該当しない （上記に分類した根拠） 血管腫瘍疾患、心臓疾患等に対する手術等に伴う著しい出血に対する治療薬	

性に係る基準」への該当性（該当するものにチェックし、類した拠つて載分し根にい記する。）	であるが、原疾患に対するものではないため。 ２．医療上の有用性 □ア　既存の療法が国内にない □イ　欧米の臨床試験において有効性・安全性等が既存の療法と比べて明らかに優れている □ウ　欧米において標準的療法に位置づけられており、国内外の医療環境の違い等を踏まえても国内における有用性が期待できると考えられる ■エ　上記の基準に該当しない （上記に分類した根拠） 本邦では類似効能を有する薬剤として、トラネキサム酸等があり、アミノカプロン酸と同様の機序により繊維素溶解を阻害し止血促進作用を示すため、アミノカプロン酸の代替薬になり得ると考えられることから、本剤の有用性は高くないと考える。
備考	

以下、タイトルが網かけされた項目は、学会等より提出された要望書又は見解に補足等がある場合にのみ記載。

2．要望内容に係る欧米での承認等の状況

欧米等 6 か国での承認状況（該当国にチェックし、該当国の承認内容を記載する。）	■米国　□英国　□独国　□仏国　□加国　□豪州 〔欧米等 6 か国での承認内容〕

	欧米各国での承認内容（要望内容に関連する箇所に下線）	
米国	販売名（企業名）	先発品： AMICAR Injection (Xanodyne Pharmaceutical) 後発品： AMINOCAPROIC ACID INJ, USP (Hospira Inc., LUITPOLD)
	効能・効果	線維素溶解（fibrinolysis）が出血の一因にな

			る場合、AMICAR は止血促進に有用である。 致命的な状況では、適切な血液製剤による輸血及び他の緊急措置が要求される場合がある。 線維素溶解出血は心臓手術（心臓バイパス手術の有無にかかわらず）、門脈大静脈吻合術、無巨核球性血小板減少症（再生不良性貧血を伴う）等の血液疾患、急性及び致命的な胎盤早期剥離、肝硬変、前立腺癌、肺癌、胃癌、頸癌等の腫瘍性疾患に対する外科療法合併症としばしば関連する。 尿線溶は、通常は正常な生理現象であるが、外科的血尿（前立腺切除術後及び腎摘出術後）又は非外科的血尿（多嚢胞あるいは腫瘍性の泌尿生殖器系疾患を伴う）に関連する過度の尿路線維素溶解出血の一因となる。
		用法・用量	AMICAR（aminocaproic acid）Injection は、通常の互換性のある静脈注射用の溶剤（滅菌注射用水、注射用塩化ナトリウム液、5%ブドウ糖液、リンゲル液等）を用い点滴投与される。 滅菌注射用水は静脈注射に対して互換性があるが、溶解液は低浸透圧である。**非希釈の AMICAR INJECTION の静脈内への急速注射は推奨されない。** 線維素溶解活性上昇による出血症候群に対しては、250mL に希釈した AMICAR Injection 16mL から 20mL（4g から 5g）を、最初の 1 時間で点滴投与し、続いて、1 時間あたり 50mL に希釈した本剤 4mL（1g）を継続点滴投与することが示唆される。本治療法は通常 8 時間又は出血が抑制されるまで継続される。 溶液および容器が観察可能な場合は必ず, 投与前に微粒子および変色の目視検査を行うこと。
		備考	先発品である、Xanodyne Pharmaceutical 社の Amicar Injection（供給中止）の効能・効果、用法・用量を記載した。

	英国	販売名（企業名）	
		効能・効果	
		用法・用量	
		備考	
	独国	販売名（企業名）	
		効能・効果	
		用法・用量	
		備考	
	仏国	販売名（企業名）	
		効能・効果	
		用法・用量	
		備考	
	加国	販売名（企業名）	
		効能・効果	
		用法・用量	
		備考	
	豪国	販売名（企業名）	
		効能・効果	
		用法・用量	
		備考	

欧米等 6 か国での標準的使用状況（欧米等 6 か国で要望内容に関する承認がない適応外薬についてのみ、該当国にチェックし、該当国の標準的使用内容を記載する。）

□米国　□英国　□独国　□仏国　□加国　□豪州

〔欧米等 6 か国での標準的使用内容〕

	欧米各国での標準的使用内容（要望内容に関連する箇所に下線）	
米国	ガイドライン名	
	効能・効果（または効能・効果に関連のある記載箇所）	
	用法・用量（または用法・用量に関連のある記載箇所）	
	ガイドラインの根拠論文	
	備考	
英国	ガイドライン名	
	効能・効果（または効能・	

		効果に関連のある記載箇所）	
		用法・用量（または用法・用量に関連のある記載箇所）	
		ガイドラインの根拠論文	
		備考	
	独国	ガイドライン名	
		効能・効果（または効能・効果に関連のある記載箇所）	
		用法・用量（または用法・用量に関連のある記載箇所）	
		ガイドラインの根拠論文	
		備考	
	仏国	ガイドライン名	
		効能・効果（または効能・効果に関連のある記載箇所）	
		用法・用量（または用法・用量に関連のある記載箇所）	
		ガイドラインの根拠論文	
		備考	
	加国	ガイドライン名	
		効能・効果（または効能・効果に関連のある記載箇所）	
		用法・用量（または用法・用量に関連	

		のある記載箇所）	
		ガイドラインの根拠論文	
		備考	
	豪州	ガイドライン名	
		効能・効果（または効能・効果に関連のある記載箇所）	
		用法・用量（または用法・用量に関連のある記載箇所）	
		ガイドラインの根拠論文	
		備考	

3. 要望内容に係る国内外の公表文献・成書等について

（1）無作為化比較試験、薬物動態試験等に係る公表文献としての報告状況

＜文献の検索方法（検索式や検索時期等）、検索結果、文献・成書等の選定理由の概略等＞

Aminocaproic acid の止血促進作用についての無作為化比較試験を調査するため、Embase を用い、タイトルに“aminocaproic”を含み、文献中に”blood loss”を含む文献の検索を行った上で、ヒトを対象とした無作為化比較試験を抽出した。

Database: Embase <1989 to 2016 January 05>, Embase <1988 to 2016 Week 01>

Search Strategy:

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1 aminocaproic.ti. and blood loss.af. (130)

2 remove duplicates from 1 (63)

3 limit 2 to (human and english language and randomized controlled trial) (27)

Aminocaproic acid の止血促進作用は Tranexamic acid、Aprotinin あるいはプラセボを対照として検討されていた。
本剤は、FESS、心肺バイパス術を伴う胸部大動脈手術、心臓手術、脊椎矯正手術、冠動脈バイパス術等の多様な手術において、Tranexamic acid、Aprotinin と同等あるいはプラセボに優る術後出血抑制効果を有すると報告されていた。

Effect of intravenous tranexamic acid and epsilon aminocaproic acid on bleeding and surgical field quality during functional endoscopic sinus surgery (FESS).

El Shal S.M., Hasanein R.

Egyptian Journal of Anaesthesia. 31 (1) (pp 1-7), 2015.

Objective Mucosal bleeding during FESS often interferes with optimal visualization of the nasal surgical field and can impair the safety and efficiency of the procedure. This study was conducted to evaluate the efficacy of tranexamic acid and Epsilon Aminocaproic Acid to decrease bleeding and improve visualization of the surgical field during FESS.

Materials and methods A total of 90 patients ASA I-II aged from 18 to 50 years and undergoing FESS for chronic sinusitis were enrolled in this study. Surgery was performed under general anesthesia patients were randomly assigned to three equal groups (30 patients each), patients in TXA group received intravenous tranexamic acid 10 mg/kg diluted in 100 ml saline. EACA group received intravenous Epsilon Aminocaproic Acid 100 mg/kg diluted in 100 ml saline and the control group received IV 100 ml normal saline (all infusions were through 10 min). The duration of surgery, volume of blood loss, pre and postoperative hemoglobin, MAP and HR, surgical field quality surgeon satisfaction and side effects were recorded.

Results The duration of surgery was significantly less in TXA and EACA groups than the control group (121.1 +/- 7.1 min), (120.8 +/- 6.0 min), versus (146.1 +/- 7.3 min) volume of blood loss in TXA group and EACA group was comparable (195.3 +/- 32.2 ml) and (201.5 +/- 30.6 ml) but each of them has significant less blood loss than the control group (365.1 +/- 48.8 ml). The postoperative hemoglobin was significantly lower in the control group (11.9 +/- 0.4 gm/dl) compared to TXA group (12.6 +/- 0.2 gm/dl) and EACA group (12.4 +/- 0.2 gm/dl). Both TXA and EACA groups had comparable improved quality of the surgical field with most of patients classified as grade 1 and 2 according to Boezaart scale while the control group had most of patients in grade 3, accordingly the surgeon satisfaction is significantly higher in TXA and EACA groups compared to the control group. No significant difference in side effects between all groups.

Conclusion Intravenous tranexamic acid and Epsilon Aminocaproic Acid (EACA) effectively reduce bleeding during FESS and improve visualization of the surgical field and so increase the surgeon satisfaction with no significant difference between both drugs.

Comparison of epsilon aminocaproic acid and tranexamic acid in thoracic aortic surgery: Clinical efficacy and safety.

Makhija N., Sarupria A., Kumar Choudhary S., Das S., Lakshmy R., Kiran U.

Journal of Cardiothoracic and Vascular Anesthesia. 27 (6) (pp 1201-1207), 2013.

Objective To evaluate the efficacy and safety of tranexamic acid (TXA) versus epsilon aminocaproic acid (EACA) in patients undergoing thoracic aortic surgery. Design A prospective randomized study.

Setting A tertiary care center.

Participant The study was conducted on 64 consecutive adult patients undergoing thoracic aortic surgery with cardiopulmonary bypass (CPB). Interventions Group EACA received a bolus of 50 mg/kg of EACA after induction of anesthesia over 20 minutes followed by maintenance infusion of 25 mg/kg/h until chest closure.

Group TXA received a bolus of 10 mg/kg of TXA after induction of anesthesia over 20 minutes followed by maintenance infusion of 1 mg/kg/h until chest closure.

Measurements and Main Results Cumulated mean blood loss, total packed red blood cells, and blood product requirement up to 24 h postoperatively were comparable between groups. A significant renal injury (EACA 40% v TXA 16%; p = 0.04) and increased tendency for renal failure (EACA 10% v TXA 0%, p = 0.11; relative risk 2.15) were observed with EACA compared to TXA. There was increased tendency of seizure with TXA (EACA v TXA: 3.3% v 10%; p>0.05, relative risk 1.53). There was significant increase in the D-dimer from preoperative to postoperative values in Group EACA. (p< 0.01).

Conclusions Both EACA and TXA were equally effective in reducing the perioperative blood loss and transfusion requirement in patients undergoing thoracic aortic surgery. While significant renal injury was observed with EACA, there was a tendency for higher incidence of seizure with TXA. Prospective placebo-controlled trials recruiting larger sample size using sensitive biomarkers are required before any recommendations.

Impact of tranexamic acid or epsilon aminocaproic acid on blood loss in cardiac surgery: A randomized controlled trial.

Gatling J., Horricks J.E., Lauer R., Jamison R., Kim U., Applegate R.L.

Anesthesia and Analgesia. Conference: 2011 Annual Meeting of the International Anesthesia Research Society, IARS 2011 Vancouver, BC Canada. Conference Start: 20110521 Conference End: 20110524. Conference Publication: (var.pagings). 112 (5 SUPPL. 1) (no pagination), 2011.

Introduction: Antifibrinolytics are routinely used for surgery with cardiopulmonary bypass (CPB). Epsilon aminocaproic acid (E) and tranexamic acid (T) have been shown to reduce bleeding and blood transfusion in this population. While both have shown benefit compared to placebo, few studies have directly compared them.

Methods: IRB approved, double blind, randomized trial (NCT01248104) comparing impact of E or T on blood loss following CPB, in consenting adults undergoing primary cardiac surgery. Exclusions included multiple valve, ascending aorta reconstruction or repeat sternotomy procedures. After induction of anesthesia: E received 100 mg/kg given over 15 minutes, followed by infusion of 10 mg/kg/hr; T received 10 mg/kg over 15 min, followed by infusion of 1 mg/kg/hr. This dosing reflects the relative potency of T to E. Infusions were continued throughout surgery until 4 hours after separation from CPB. Drugs were delivered in a blinded fashion in identical volumes and infusion rates based on patient weight. All other care decisions such as invasive monitoring, anesthetic technique, transfusion decisions, and postoperative care were at the discretion of the attending physicians. Data collection included demographics, type of surgery, duration of CPB/surgery and outcomes including ventilator hours and length of stay. Impact on blood loss was determined by POD2 change in Hb and RBC volume (estimated blood volume*hematocrit change + PRBC*0.55; includes impact of blood loss and transfusion following CPB). Statistical

analysis with p<0.05 considered significant was performed using JMP 8.0.2. Continuous data were compared using the t-test. Ordinal and nominal data were compared using Chi-Square**.**

Results: Data from 51 patients (E=26; T=25) have been analyzed to date. There were no intergroup differences in age, gender, BMI, baseline lab values or surgery duration. Perioperative risk assessed by P-POSSUM was numerically higher in E. Outcome measures were numerically worse in T (Table 1) but did not reach statistical significance.

Discussion: These results suggest E and T may have different impacts on outcome after CPB. While only 27% of subjects were transfused, lower than reported in a recent comparison, T had a larger decrease in Hb with a larger decrease in PRBC volume by POD2 despite more frequent and larger average volume PRBC transfusion. Assessment of blood loss following CPB may be improved by calculating change in Hb or RBC volume, since these reflect the result of both blood loss and transfusion and may be less affected by differences in blood volume.

A prospective, randomized, double-blinded single-site control study comparing blood loss prevention of tranexamic acid (TXA) to epsilon aminocaproic acid (EACA) for corrective spinal surgery.

Verma K., Errico T.J., Vaz K.M., Lonner B.S.

BMC surgery. 10 (pp 13), 2010.

Introduction: Antifibrinolytics are routinely used for surgery with cardiopulmonary bypass (CPB). Epsilon aminocaproic acid (E) and tranexamic acid (T) have been shown to reduce bleeding and blood transfusion in this population. While both have shown benefit compared to placebo, few studies have directly compared them.

Methods: IRB approved, double blind, randomized trial (NCT01248104) comparing impact of E or T on blood loss following CPB, in consenting adults undergoing primary cardiac surgery. Exclusions included multiple valve, ascending aorta reconstruction or repeat sternotomy procedures. After induction of anesthesia: E received 100 mg/kg given over 15 minutes, followed by infusion of 10 mg/kg/hr; T received 10 mg/kg over 15 min, followed by infusion of 1 mg/kg/hr. This dosing reflects the relative potency of T to E. Infusions were continued throughout surgery until 4 hours after separation from CPB. Drugs were delivered in a blinded fashion in identical volumes and infusion rates based on patient weight. All other care decisions such as invasive monitoring, anesthetic technique, transfusion decisions, and postoperative care were at the discretion of the attending physicians. Data collection included demographics, type of surgery, duration of CPB/surgery and outcomes including ventilator hours and length of stay. Impact on blood loss was determined by POD2 change in Hb and RBC volume (estimated blood volume*hematocrit change + PRBC*0.55; includes impact of blood loss and transfusion following CPB). Statistical analysis with p<0.05 considered significant was performed using JMP 8.0.2. Continuous data were compared using the t-test. Ordinal and nominal data were compared using Chi-Square.

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Assessment of blood loss following CPB may be improved by calculating change in Hb or RBC volume, since these reflect the result of both blood loss and transfusion and may be less affected by differences in blood volume.

Effect of epsilon aminocaproic acid on red-cell transfusion requirements in major spinal surgery.

Berenholtz S.M., Pham J.C., Garrett-Mayer E., Atchison C.W., Kostuik J.P., Cohen D.B., Nundy S., Dorman T., Ness P.M., Klag M.J., Pronovost P.J., Kebaish K.M.

Spine. 34 (19) (pp 2096-2103), 2009.

Study Design: Randomized, placebo-controlled trial. Objective: To evaluate the efficacy of epsilon aminocaproic acid (EACA) to reduce the number of red-cell (RBC) transfusions in adult patients undergoing major spinal surgery.

Summary of Background Data: Reconstructive spinal surgery is associated with significant blood loss. The number of studies evaluating the efficacy of EACA in adult patients undergoing spinal surgery remains scarce and limited.

Methods: EACA (100 mg/kg) or placebo was administered to 182 adult patients after the induction of anesthesia followed by an infusion that was continued for 8 hours after surgery. Primary end points included total allogeneic RBC transfusions through postoperative day 8 and postoperative allogeneic plus autologus RBC transfusions through postoperative day 8.

Results: Mean total allogeneic RBC transfusions were not statistically different between the groups (5.9 units EACA vs. 6.9 units placebo; P = 0.17). Mean postoperative RBC transfusions in the EACA group was less (2.0 units vs. 2.8 units placebo; P = 0.03). There was no significant difference in mean estimated intraoperative estimated-blood loss (2938 cc EACA vs. 3273 cc placebo; P = 0.32). Mean intensive care unit length of stay was decreased (EACA: 1.8 days vs. 2.8 days placebo; P = 0.04). The incidence of thromboembolic complications was similar (2.2% EACA vs. 6.6% placebo; P = 0.15).

Conclusion: The difference in total allogeneic RBC transfusions between the groups was not statistically significant. EACA was associated with a 30% (0.8 units) reduction in postoperative RBC transfusions and a 1-day reduction in ICU LOS, without an increased incidence of thromboembolic events. EACA may be considered for patients undergoing major spinal surgery. Larger studies are needed to evaluate the relationship between EACA and total RBC requirements.

The effect of epsilon-aminocaproic acid and aprotinin on fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery: A randomized, double-blind, placebo-controlled, noninferiority trial.

Greilich P.E., Jessen M.E., Satyanarayana N., Whitten C.W., Nuttall G.A., Beckham J.M., Wall M.H., Butterworth J.F.

Anesthesia and Analgesia. 109 (1) (pp 15-24), 2009.

BACKGROUND: Until recently, aprotinin was the only antifibrinolytic drug with a licensed indication in cardiac surgery in the United States. The most popular alternative, epsilon-aminocaproic acid (EACA), has not been adequately compared with aprotinin. We undertook this study to test the hypothesis that EACA, when dosed appropriately, is not inferior to aprotinin at reducing fibrinolysis and blood loss.

METHODS: Seventy-eight patients scheduled for primary, isolated coronary artery bypass graft surgery were

randomly assigned to receive "full Hammersmith" dose aprotinin, high dose EACA (100 mg/kg initial loading dose, 5 g in the pump prime solution, 30 mg * kg * h maintenance infusion) or equal volumes of a saline-placebo in a double-blind trial. Reductions in peak d-dimer formation (a measure of fibrinolysis) and 24-h chest tube drainage (CTD) were the primary end points by which noninferiority of EACA was tested. The noninferiority limit was set at a 30% increase in peak d-dimer formation (a difference of 250 mug/mL) and 24-h CTD (a difference of 350 mL) relative to aprotinin.

RESULTS: The between-group differences (EACA versus aprotinin) in peak d-dimer formation (-3.58 mug/L, 95% CI -203 to 195 mug/L) and 24-h CTD (67 mL, 95% CI -90 to 230 mL) were within the predetermined noninferiority margins (250 mug/mL and 350 mL, respectively) and satisfied the criteria for noninferiority. Compared with saline, significant between-group reductions in peak d-dimer formation were observed using EACA (589 mug/L, 95% CI 399-788 mug/L; P < 0.0001) and aprotinin (585 mug/L, 95% CI 393-778 mug/L; P < 0.0001). Similar reductions in 24 h CTD were also seen using EACA (239 mL, 95% CI 50-415 mL; P < 0.05) and aprotinin (323 mL, 95% CI 105-485 mL; P < 0.05) compared with saline. Plasma EACA levels were maintained well above a target of 260 mug/mL.

CONCLUSIONS: When dosed in a pharmacologically guided manner, EACA is not inferior to aprotinin in reducing fibrinolysis and blood loss in patients undergoing primary, isolated coronary artery bypass surgery.

Efficacy of aminocaproic, tranexamic acids in the control of bleeding during total knee replacement: A randomized clinical trial.

Camarasa M.A., Olle G., Serra-Prat M., Martin A., Sanchez M., Ricos P., Perez A., Opisso L.

British Journal of Anaesthesia. 96 (5) (pp 576-582), 2006.

Background. Risks and costs of allogeneic blood transfusions mandate strategies to reduce blood loss in surgery. The objective of this study was to assess the efficacy of antifibrinolytic treatment in reducing perioperative blood loss during total knee replacement.

Methods. A double-blind, randomized and placebo-controlled clinical trial was carried out on 127 patients undergoing total knee replacement. Patients in the study group received tranexamic acid 10 mg kg-1 i.v. just before the tourniquet was deflated and 3 h later, or epsilon-aminocaproic acid 100 mg kg-1 before tourniquet deflation followed by continuous perfusion (1 g h-1) during 3 h. External perioperative blood loss was measured and total blood loss was calculated. The number of patients transfused and number of packed red cell (PRC) units transfused was recorded and possible postoperative thromboembolic complications were investigated.

Results. Total blood loss [mean (SD)] was 1099 ml (535) in the group that received antifibrinolytic agents and 1784 ml (660) in the control group (P <0.001). Five patients (7.5%) in the study group and 23 (38.3%) in the control group (P <0.001) received blood transfusions; the first group received a mean of 0.10 PRC unit per patient and the second, 0.58 (P <0.001). Mean reduction in haemoglobin levels (g dl-1) between preoperative and fifth day postoperative readings was 2.5 (0.9) in the study group and 3.4 (1.2 in the control group (P <0.001). Clinical assessment did not reveal any thromboembolic complications.

Conclusions. Antifibrinolytic agents produce a significant decrease in blood loss in patients undergoing total knee replacement, reflected in a reduction in the number of blood transfusions required.

A double-blind, placebo-controlled trial of epsilon-aminocaproic acid for reducing blood loss in coronary

artery bypass grafting surgery.

Kikura M., Levy J.H., Tanaka K.A., Ramsay J.G.

Journal of the American College of Surgeons. 202 (2) (pp 216-222), 2006.

BACKGROUND: Epsilon-aminocaproic acid is a plasmin inhibitor that potentially reduces perioperative bleeding when administered prophylactically to cardiac surgery patients. To evaluate the efficacy of epsilon-aminocaproic acid, a prospective placebo-controlled trial was conducted in patients undergoing primary coronary artery bypass grafting surgery.

STUDY DESIGN: One hundred patients were randomly assigned to receive either epsilon-aminocaproic acid (100 mg/kg before skin incision followed by 1 g/hour continuous infusion until chest closure, 10 g in cardiopulmonary bypass circuit) or placebo, and the efficacy of epsilon-aminocaproic acid was evaluated by the reduction in postoperative thoracic-drainage volume and in donor-blood transfusion up to postoperative day 12.

RESULTS: Postoperative thoracic-drainage volume was significantly lower in the epsilon-aminocaproic acid group compared with the placebo group (epsilon-aminocaproic acid, 649 +/- 261mL; versus placebo, 940 +/- 626mL; p = 0.003). There were no significant differences between the epsilon-aminocaproic acid and placebo groups in the percentage of patients requiring donor red blood cell transfusions (epsilon-aminocaproic acid, 24%; versus placebo, 18%; p = 0.62) or in the number of units of donor red blood cells transfused (epsilon-aminocaproic acid, 2.2 +/- 0.8 U; versus placebo, 1.9 +/- 0.8 U; p = 0.29). Epsilon-aminocaproic acid did not reduce the risk of donor red blood cell transfusions compared with placebo (odds ratio: 1.2, 95% confidence interval; 0.4 to 3.2, p = 0.63).

CONCLUSIONS: Prophylactic administration of epsilon-aminocaproic acid reduces postoperative thoracic-drainage volume by 30%, but it may not be potent enough to reduce the requirement and the risk for donor blood transfusion in cardiac surgery patients. This information is useful for deciding on a therapy for hemostasis in cardiac surgery.

The efficacy of epsilon-aminocaproic acid and its timing in reducing blood loss in major cardiac coronary bypass surgery: A randomized double-blinded placebo-controlled study.

Gharebaghian M., Eghtesadi-Araghi P.

International Journal of Pharmacology. 2 (1) (pp 131-135), 2006.

It has been shown that in patients undergoing primary minor Coronary Artery Bypass Graft surgery (CABG), epsilon-aminocaproic acid (epsilon-ACA) produces a reduction in chest tube drainage and this effect was similar whether the drug is given prior to incision or following anticoagulation. The aim of this study was to investigate the efficacy of epsilon-ACA and its timing in reducing blood loss in major CABG. In a randomized double-blind study, 60 adult patients undergoing primary CABG requiring equal or more than 4 grafts with extracorporeal circulation were allocated to receive epsilon-ACA either prior to skin incision (bolus 150 mg kg-1, followed by an infusion at 15 mg kg-1 h-1), either prior to skin incision or after heparin, or placebo. All infusions were terminated at the end of cardiopulmonary bypass. Postoperative chest tube drainages (at 6, 12 h and at chest tube removal) were compared. The control group had significantly greater chest tube drainage than either of the two epsilon-ACA groups, at 6 h and chest tube removal times ($p<0.05$). Also there was a significant difference in postoperative chest tube drainages pattern between control and either of the two epsilon-ACA groups ($p<0.05$) but not between two epsilon-ACA groups. Epsilon-ACA effectively reduces blood loss through chest tubes in patients undergoing major CABG and its administration timing has no effects. Considering comparable hemostatic efficacy, it is recommended

administering epsilon-ACA next to anticoagulation.

Aprotinin and epsilon aminocaproic acid are effective in reducing blood loss after primary total hip arthroplasty - A prospective randomized double-blind placebo-controlled study.

Ray M., Hatcher S., Whitehouse S.L., Crawford S., Crawford R.

Journal of Thrombosis and Haemostasis. 3 (7) (pp 1421-1427), 2005.

A prospective randomized double-blind placebo-controlled study was undertaken to determine the efficacy and mechanism of action of two antifibrinolytic drugs aprotinin and epsilon aminocaproic acid (EACA) in reducing blood loss in primary unilateral total hip arthroplasty (THA). Aprotinin was administered as a bolus of 2 x 106 kallikrein inhibitor units (KIU) followed by 0.5 x 106 KIU h-1 for 3 h, EACA was given as 10 g over 30 min followed by 5 g over 3 h. The median postoperative blood loss 24 h postoperatively was reduced from 450 mL in the placebo group to 180 mL for aprotinin (60% reduction, P < 0.001) and to 210 mL for EACA (53% reduction, P < 0.01). In this population, there was no reduction in the perioperative transfusion requirements. The mechanism of both drugs was independent of platelets as indicated by flow cytometric measurement of change of their expression of P-selectin, platelet-monocyte aggregates, V/Va and CD40 ligand. There were no thrombotic or infective complications and no adverse events were attributable to use of either drug. Infusion of either aprotinin or EACA at the doses described is a safe and effective means of reducing blood loss after THA. These therapies provide a means of reducing blood loss in THA patients.

Comparison of Epsilon Aminocaproic Acid and Tranexamic Acid in Pediatric Cardiac Surgery.

Chauhan S., Das S.N., Bisoi A., Kale S., Kiran U.

Journal of Cardiothoracic and Vascular Anesthesia. 18 (2) (pp 141-143), 2004.

Objective: This study compared the efficacy of aminocaproic acid and tranexamic acid in reducing postoperative blood loss, as well as blood and blood product requirements in children with cyanotic congenital heart disease. Design: A prospective randomized study.

Setting: Cardiac center of a tertiary care, referral hospital. Participants: One hundred fifty children in the age group of 2 months to 14.5 years with cyanotic congenital heart disease undergoing corrective surgery on cardiopulmonary bypass (CPB).

Interventions: Patients were randomized into 3 groups. Group A was given aminocaproic acid in a dose of 100 mg/kg after anesthetic induction, 100 mg/kg on CPB and 100 mg/kg after protamine. Group T was given tranexamic acid, 10 mg/kg, after anesthetic induction, 10 mg/kg on CPB, and 10 mg/kg after protamine. Group C was the control group.

Main Result: Control group had the longest sternal closure time, maximum blood loss at 24 hours, and maximum requirements of blood and blood products. Among the 2 groups given antifibrinolytics, there was no significant difference in postoperative blood loss, blood and product requirement, and re-exploration rates.

Conclusion: Aminocaproic acid and tranexamic acid are equally effective in reducing postoperative blood loss, as well as blood and blood product requirements in children with cyanotic heart disease undergoing corrective surgery as compared with the control group.

The effect of epsilon aminocaproic acid on blood loss in patients who undergo primary total hip replacement: A pilot study.

Harley B.J., Beaupre L.A., Allyson Jones C., Cinats J.G., Guenther C.R.

Canadian Journal of Surgery. 45 (3) (pp 185-190), 2002.

Objective: To determine if the use of an antifibrinolytic agent (epsilon aminocaproic acid [EACA]) decreased perioperative and postoperative blood loss in patients who underwent total hip arthroplasty (THA).

Design: A prospective, double-blind, randomized, controlled clinical trial. Setting: A university-affiliated tertiary care hospital with a large joint arthroplasty population. Participants: Fifty-five patients who were scheduled for a primary THA.

Method: Patients were randomly assigned to 2 groups to receive either EACA or saline placebo perioperatively. Preoperatively, the groups were similar with respect to gender, mean age, mean hemoglobin level, operative time and prosthesis type. Outcome measures: Blood loss from the start of surgery until the Hemovac drain was removed, and the transfusion rate and hemoglobin levels.

Results: Mean (and standard error) total blood loss for patients receiving EACA was 867 (207) mL and for patients receiving placebo was 1198 (544) mL ($p < 0.025$). Four patients in the EACA group received 7 units of packed red blood cells and 7 patients in the saline group required 12 units.

Conclusions: Patients receiving the placebo sustained greater total blood loss than EACA patients and were more likely to require blood transfusion. In the current climate of concern over blood transfusions during surgery, EACA administration can reduce blood loss and consequently transfusion and transfusion-related risk.

Aprotinin but not epsilon-aminocaproic acid decreases interleukin-10 after cardiac surgery with extracorporeal circulation: randomized, double-blind, placebo-controlled study in patients receiving aprotinin and epsilon-aminocaproic acid.

Greilich P.E., Okada K., Latham P., Kumar R.R., Jessen M.E.

Circulation. 104 (12 Suppl 1) (pp I265-269), 2001.

BACKGROUND: Extracorporeal circulation induces a systemic inflammatory response, which may adversely affect organ function. One manifestation of this response is increased fibrinolysis. Antifibrinolytic drugs such as aprotinin and epsilon-aminocaproic acid have been effective in reducing fibrinolysis and blood loss after extracorporeal circulation; however, the effects of antifibrinolytic drugs on proinflammatory and anti-inflammatory mediators are not known. This study examined the effects of aprotinin and epsilon-aminocaproic acid on plasma levels of proinflammatory [interleukin-6 (IL-6)] and anti-inflammatory [interleukin-10 (IL-10)] cytokines during and after extracorporeal circulation.

METHODS AND RESULTS: Seventy-two patients undergoing coronary artery bypass grafting with extracorporeal circulation were randomly assigned in a double-blind study to receive high-dose aprotinin, epsilon-aminocaproic acid, or saline placebo. Plasma levels of IL-6 and IL-10 were measured at 5 time points before, during, and after extracorporeal circulation. In all 3 groups, both IL-6 and IL-10 rose significantly after institution of extracorporeal circulation and remained elevated through the first postoperative day. Compared with saline, aprotinin significantly reduced IL-10 ($P=0.02$) and peak IL-6 ($P=0.02$) after extracorporeal circulation. In contrast, none of the reductions in IL-6 and IL-10 by epsilon-aminocaproic acid achieved statistical significance. Both aprotinin and

epsilon-aminocaproic acid decreased blood loss compared with saline, but there was no significant difference in the number of patients receiving blood products among the treatment groups.

CONCLUSIONS: These data suggest that aprotinin and epsilon-aminocaproic acid differ in their effects on the inflammatory response to extracorporeal circulation. Aprotinin but not epsilon-aminocaproic acid appears to attenuate the rise in the proinflammatory and anti-inflammatory cytokines IL-6 and IL-10. Further studies will be required to determine if these cytokine alterations translate to changes in clinical outcomes.

Postoperative bleeding after coronary revascularization: Comparison between tranexamic acid and epsilon-aminocaproic acid. <Sanguinamento postoperatorio nei pazienti sottoposti a rivascolarizzazione miocardica. Confronto fra acido tranexamico e acido epsilon-amino caproico.>

Maineri P., Covaia G., Realini M., Caccia G., Ucussich E., Luraschi M., Crosta A., Foresti B., Chiaranda M.

Minerva Cardioangiologica. 48 (6) (pp 155-160), 2000.

Background. Microvascular bleeding after Cardiopulmonary bypass (CPB) is mainly due to consumption of clotting factors, platelets damage, and hyperfibrinolysis. Aprotinin, the only antifibrinolytic drug effective in preserving platelets, is no longer available; an alternative regimen based on pure antifibrinolytic drugs has been proposed, since hyperfibrinolysis is known to contribute both to clot lysis and platelet dysfunction. In this study the efficacy of two antifibrinolytic drugs, Tranexamic acid (TA) and epsilon-aminocaproic acid (EACA), was tested in patients undergoing cardiopulmonary bypass (CPB), for primary myocardial revascularization.

Methods. Forty-eight consecutive patients were randomized to receive prophylactically equipotent doses of EACA (group A) or TA (Group B). Platelet count, prothrombin time, fibrin digestion products, blood loss and transfusion requirements recorded after 6 and 24 hours from the end of surgery were compared.

Results. The two groups were comparable for length of CPB and numbers of grafts; no significant difference was observed in the coagulation parameters considered. Blood losses were less in group B (TA) than in group A (EACA), both at 6 and 24 hours after surgery; homologous blood transfused was also less in group B, but no difference was statistically significant. No adverse effect was observed.

Conclusions. In coronary patients, TA and EACA exhibit the same effects on blood loss and requirements after CPB; either drug can be safely used in cardiac surgery.

Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss.

Rao B.H., Saxena N., Chauhan S., Bisoi A.K., Venugopal P.

Indian Journal of Medical Research. 111 (FEB.) (pp 57-61), 2000.

We have studied the efficacy of epsilon aminocaproic acid in reducing postoperative blood loss in infants and children with congenital cyanotic cardiac anomalies undergoing corrective operative procedures. This prospective study was carried out on 170 infants and children randomly divided into two equal groups. Group A acted as the control group and received normal saline as placebo while group B patients received epsilon aminocaproic acid (100 mg/kg body wt) intravenously slowly soon after anaesthetic induction followed by 100 mg/kg in the cardiopulmonary bypass pump at the time of starting of cardiopulmonary bypass and 100 mg/kg after weaning from bypass over a period of 3 h. In group A the time for sternal closure after separation from bypass and administration of protamine was 75.18 +/- 5.5 min and in group B 50.7 +/- 5.2, ($P<0.001$). Blood loss at 24 h in group A was 42.6

+/- 6.9 ml/kg/24 h and in group B 23.7 +/- 5.8 ml/kg/24 h, (P<0.001). The need for packed red cells in group A was 21.8 +/- 7.1 ml/kg/24 h and in group B 10.7 +/- 7.8 ml/kg/24 h, (P<0.001). The need for platelet concentrate in group A was 22.0 +/- 6.7 ml/kg/24 h and group B 6.2 +/- 3.2 ml/kg/24 h, (P<0.001). Fibrin degradation products (split) in group A was 8.2 +/- 0.8 mug/ml, and group B 3.8 +/- 1.3 mug/ml, (P<0.001). Re-exploration rate was also considerably reduced in group B, 5 of 85 (6%) compared to group A, 13 of 85 (15%), (P<0.001). It was found that epsilon aminocaproic acid is effective in reducing postoperative blood loss, packed red cells and plasma product requirements in paediatric patients undergoing corrective surgical procedures for congenital cyanotic heart diseases.

Dosage of epsilon-aminocaproic acid to reduce postoperative blood loss.

Chauhan S., Bisoi A.K., Rao B.H., Rao M.S., Saxena N., Venugopal P.

Asian Cardiovascular and Thoracic Annals. 8 (1) (pp 15-18), 2000.

Postoperative blood loss, blood and blood-product requirements, and complications were compared for 3 commonly used doses of epsilon-aminocaproic acid in 150 patients undergoing first-time coronary artery bypass surgery. The patients were randomly assigned to one of 4 groups. Group 1 (n = 30) served as a control, group 2 (n = 30) received a single dose of 150 mg/kg-1 of epsilon-aminocaproic acid after anesthetic induction, group 3 (n = 30) received a loading dose of 150 mg/kg-1 followed by infusion of 1 g/h-1 for 6 hours, and group 4 (n = 60) received doses of 150 mg/kg-1 at induction, on bypass, and after protamine. No patients, including those who had endarterectomies, experienced any complications attributable to epsilon-aminocaproic acid administration. All patients who received epsilon-aminocaproic acid had significantly less bleeding compared to controls. Groups 3 and 4 had the least blood loss and packed-cell requirements.

Hemostatic effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid in primary cardiac surgery.

Casati V., Guzzon D., Oppizzi M., Cossolini M., Torri G., Calori G., Alfieri O.

Annals of Thoracic Surgery. 68 (6) (pp 2252-2257), 1999.

Background. The effects of epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) on bleeding and allogeneic transfusions, and the cost of pharmacological and transfusional treatment were compared to aprotinin (AP).

Methods. We randomized 210 patients subjected to elective cardiac surgery. Of these, 68 patients received EACA (a bolus of 5 g, an infusion of 2 g/h, and 2.5 g in the priming), 72 patients received TA (a bolus of 1 g, an infusion of 400 mg/h, and 500 mg in the priming), and 70 patients received AP (a bolus of 280 mg, an infusion of 70 mg/h, and 280 mg in the priming). Postoperative blood loss and homologous transfusions were collected and the cost of pharmacological treatment and homologous transfusions were calculated.

Results. Bleeding but not allogeneic transfusions was significantly higher in the EACA group (467 +/- 234 versus TA, 311 +/- 231 versus AP, 283 +/- 233; p < 0.001). Costs of pharmacological and transfusional treatment were significantly lower in the TA group ($58.10 +/- $105.10) versus the EACA group ($100.70 +/- $158.60) versus the AP group ($432.60 +/- $118.70) (p < 0.0001).

Conclusions. Compared to AP, TA has the same effects on bleeding and transfusions, but with a significant reduction of costs. Patients treated with EACA showed a significantly higher postoperative bleeding with an

increased trend of transfusion requirement.

Use of E-Aminocaproic acid in the management of aspirin related postoperative bleeding in patients undergoing coronary revascularization.

Rao B.H., Saxena N., Chauhan S., Sashikanth M.

Journal of Anaesthesiology Clinical Pharmacology. 15 (3) (pp 261-264), 1999.

Many of the coronary artery disease patients take aspirin and continue it up to the day of surgery as it has proven beneficial effects in reducing perioperative myocardial infarction and post operative bleeding. E-Aminocaproic acid is an antifibrinolytic agent and reduces the postoperative bleeding. We studied the efficacy of E-Aminocaproic acid with respect to decreased postoperative bleeding in coronary artery disease patients on aspirin therapy. We randomly assigned thirty patients undergoing first time coronary artery revascularization without prior sternotomy requiring cardiopulmonary bypass into two groups. All the patients continued to take aspirin up to the day of surgery. Group I (n - 15) received no E-Aminocaproic acid taken as control group. Group II (n - 15) received E-Aminocaproic acid 100 mg/kg as loading dose after induction of anaesthesia and 1 g/h infusion up to six hour thereafter. No significant difference existed with respect to age, sex, weight, number of grafts, cardiopulmonary bypass time and closure time. Post operative blood loss measured as cumulative chest tube drainage at six, twelve and twenty four hours after shifting the patients to intensive care unit was significantly less in Group II. Blood and blood component requirement was reduced in Group II markedly. None of the patients had perioperative myocardial infarction or cerebrovascular accident. We have concluded prophylactic administration of E-Aminocaproic acid in coronary artery disease patients on aspirin therapy undergoing first time coronary revascularization requiring cardiopulmonary bypass results in significant reduction in post operative blood loss and blood and blood component use.

The effect of prophylactic epsilon-aminocaproic acid on bleeding, transfusions, platelet function, and fibrinolysis during coronary artery bypass grafting.

Troianos C.A., Sypula R.W., Lucas D.M., D'Amico F., Mathie T.B., Desai M., Pasqual R.T., Pellegrini R.V., Newfeld M.L.

Anesthesiology. 91 (2) (pp 430-435), 1999.

Background: Antifibrinolytic medications administered before skin incision decrease bleeding after cardiac surgery. Numerous case reports indicate thrombus formation with administration of epsilon-aminocaproic acid (epsilon- ACA). The purpose of this study was to examine the efficacy of epsilon-ACA administered after heparinization but before cardiopulmonary bypass in reducing bleeding and transfusion requirements after primary coronary artery bypass surgery.

Methods: Seventy-four adult patients undergoing primary coronary artery bypass surgery were randomized to receive 125 mg/kg epsilon-ACA followed by an infusion of 12.5 mg kg-1 h-1 or an equivalent volume of saline. Coagulation studies, thromboelastography, and platelet aggregation tests were performed preoperatively, after bypass, and on the first postoperative day. Mediastinal drainage was recorded during the 24 h after surgery. Homologous blood transfusion triggers were predefined and transfusion amounts were recorded.

Results: One patient was excluded for surgical bleeding and five patients were excluded for transfusion against

predefined criteria. One patient died from a dysrhythmia 2 h postoperatively. Among the remaining 67, the epsilon-ACA group had less mediastinal blood loss during the 24 h after surgery, 529 +/- 241 ml versus 691 +/- 286 ml (mean +/- SD), P < 0.05, despite longer cardiopulmonary bypass times and lower platelet counts, P < 0.05. Platelet aggregation was reduced in both groups following cardiopulmonary bypass but did not differ between groups. Homologous blood transfusion was similar between both groups.

Conclusions: Prophylactic administration of epsilon-ACA after heparinization but before cardiopulmonary bypass is of minimal benefit for reducing blood loss postoperatively in patients undergoing primary coronary artery bypass grafting.

The effect of coagulation protection with combination of epsilon aminocaproic acid and plasma saver in open-heart surgery.

Liu Y.C., Tsai T.P.

Acta anaesthesiologica Sinica. 36 (3) (pp 149-154), 1998.

BACKGROUND: Bleeding remains a major complication and a major determinant in the prognosis of open-heart surgery. Coagulopathy related to cardiopulmonary bypass (CPB) seems to be the culprit. Since homologous blood transfusion in many occasions is not only responsible for mobidity and mortality but also increases medical costs. Therefore, the application of autologous blood transfusion including components such as PRBC, FFP and platelets concentrate is inevitable and comes in its stead. To reduce the use of homologous plasma and platelets transfusion in open-heart surgery, we designed a study to utilize the combination of autologous platelet rich plasma (PRP) and epsilon aminocaproic acid (EACA) to evaluate its effects on blood loss and blood component transfusion in open-heart patients.

METHODS: Sixty patients who received elective cardiac surgery were randomly divided into 3 groups: 1. Control group; 2. EACA group (150 mg/kg, i.v. before CPB); 3. PRP-EACA group (PRP 10 ml/kg harvested with a plasma saver followed by i.v. EACA 150 mg/kg). Anesthesia was uniform in all patients. Coagulation profile was evaluated by thromboelastography (TEG) during the operation. Blood loss during operation and the amount of drainage from the chest tubes in the postoperative period were recorded and compared between groups.

RESULTS: Patients who were given EACA injection before CPB saw less blood loss perioperatively and received less transfusion of blood components. TEG analysis showed that patients who received EACA injection had a better coagulation profile and the platelet function was also better after CPB. However, no additive effect can be attained from combination of autologous PRP transfusion and EACA injection.

CONCLUSIONS: With Pre-CPB EACA as protection, reduction of both blood loss and blood transfusion could be realized in open-heart surgery.

Prophylactic tranexamic acid and epsilon-aminocaproic acid for primary myocardial revascularization.

Hardy J.-F., Belisle S., Dupont C., Harel F., Robitaille D., Roy M., Gagnon L.

Annals of Thoracic Surgery. 65 (2) (pp 371-376), 1998.

Background. The efficacy of prophylactic epsilon-aminocaproic acid and tranexamic acid to reduce transfusions after primary myocardial revascularization was evaluated in a teaching hospital context.

Methods. Patients (n = 134) received either epsilon-aminocaproic acid (15-g bolus + infusion of 1 g/h), high-dose

tranexamic acid (10-g bolus + placebo infusion), or normal saline solution in a double-blind fashion. Anticoagulation and conduct of cardiopulmonary bypass were standardized.

Results. Tranexamic acid and epsilon-aminocaproic acid produced a significant reduction in postoperative blood loss compared with placebo (median loss, 438 mL, 538 mL, and 700 mL, respectively). Transfusion of red cells was similar in all three groups. Nonetheless, the percentage of patients receiving hemostatic blood products was significantly decreased in the epsilon-aminocaproic acid group compared with the placebo group (20% versus 43%; p = 0.03). Both tranexamic acid and epsilon-aminocaproic acid significantly decreased total exposure to allogeneic blood products compared with placebo (p = 0.01 and P = 0.05, respectively), and this reduction was clinically important (median exposure, 2,2, and 7.5 units, respectively). Fibrinolysis was inhibited significantly in both treatment groups.

Conclusions. We conclude that either high-dose tranexamic acid or epsilon-aminocaproic acid effectively reduces transfusions in patients undergoing primary, elective myocardial revascularization.

Tranexamic acid reduces bleeding after cardiopulmonary bypass when compared to epsilon aminocaproic acid and placebo.

Pinosky M.L., Kennedy D.J., Fishman R.L., Reeves S.T., Alpert C.C., Ecklund J., Kribbs S., Spinale F.G., Kratz J.M., Crawford R., Gravlee G.P., Dorman B.H.

Journal of Cardiac Surgery. 12 (5) (pp 330-338), 1997.

Perioperative bleeding following coronary artery bypass grafting (CABG) is associated with increased blood product usage. Although aprotonin is effective in reducing perioperative blood loss, excessive cost prohibits routine utilization. Epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are inexpensive antifibrinolytic agents, which, when given prophylactically, may reduce blood loss. The present study was undertaken to compare the efficacy of TA and EACA in reducing perioperative blood loss. Methods: The study population consisted of first-time CABG patients. Patients were allocated in a prospective double-blind fashion: (1) group EACA (loading dose 150 mg/kg, continuous infusion 10 mg/kg per hour for 6 hours, N = 20); (2) group TA (loading dose 15 mg/kg, continuous infusion 1 mg/kg per hour for 6 hours, N = 20); (3) control group (infusion of normal saline for 6 hours, N = 19). Results: Treatment groups were similar preoperatively. No significant difference in intraoperative blood loss or perioperative use of blood products was noted. D-dimer concentration was elevated in the control group compared to the EACA and TA groups (p < 0.05). Group TA had less postoperative blood loss than the EACA and control groups at 6 and 12 hours postoperatively (p < 0.05). TA had reduced total blood loss (600 +/- 49 mL) postoperatively compared to EACA (961 +/- 148 mL) and control (1060 +/- 127mL, p < 0.05). Conclusion: TA and EACA effectively inhibited fibrinolytic activity intraoperatively and throughout the first 24 hours postoperatively. TA was more effective in reducing blood loss postoperatively following CABG. This suggests that TA may be beneficial as an effective and inexpensive antifibrinolytic in first-time CABG patients.

Reduction of bleeding after heart operations through the prophylactic use of epsilon-aminocaproic acid.

Salm T.J.V., Kaur S., Lancey R.A., Okike O.N., Pezzella A.T., Stahl R.F., Leone L., Li J.-M., Valeri C.R., Michelson A.D.

Journal of Thoracic and Cardiovascular Surgery. 112 (4) (pp 1098-1107), 1996.

Excessive postoperative bleeding after heart operations continues to be a source of morbidity. This prospective double-blind study evaluated epsilonaminocaproic acid as an agent to reduce postoperative bleeding and investigated its mode of action. One hundred three patients were randomly assigned to receive either 30 gm epsilon-aminocaproic acid (51 patients) or an equivalent volume of placebo (52 patients). In a subset of these patients (14 epsilon-aminocaproic acid, 12 placebo), tests of platelet function and fibrinolysis were performed. Results: By multivariate analysis, three factors were associated with decreased blood loss in the first 24 hours after operation: epsilon-aminocaproic acid versus placebo (647 ml versus 839 ml, p = 0.004), surgeon 1 versus all other surgeons (582 ml versus 978 ml, p = 0.002), and no intraaortic balloon versus intraaortic balloon pump use (664 ml versus 1410 ml, p = 0.02). No significant differences in platelet function could be demonstrated between the two groups. Inhibited fibrinolysis, as reflected by less depression of the euglobulin clot lysis and no rise in D- dimer levels, was significant in the epsilon-aminocaproic acid group compared with the placebo group. Conclusion: The intraoperative use of epsilon- aminocaproic acid reduces postoperative cardiac surgical bleeding.

Changes in coagulation patterns, blood loss and blood use after cardiopulmonary bypass: Aprotinin vs tranexamic acid vs epsilon aminocaproic acid.

Menichetti A., Tritapepe L., Ruvolo G., Speziale G., Cogliati A., Di Giovanni C., Pacilli M., Criniti A.

Journal of Cardiovascular Surgery. 37 (4) (pp 401-407), 1996.

Cardiopulmonary bypass (CPB) increases risk of postoperative bleeding and need for transfusion. The aim of this study was to evaluate the effects of aprotinin, epsilon aminocaproic acid and tranexamic acid on coagulation patterns and need for banked blood transfusion. Ninety-six consecutive patients who underwent coronary artery bypass surgery were randomly assigned to 4 groups (24 patients each). The following parametrs were monitored before, during and after CPB: activated letting time, hemoglobin, prothrombin time, activated prothromboplastin time, fibrinogen, antithrombin III, xDP, Factor VIII, Thrombin-Antithrombin Complex and plasminogen. Analysis of postoperative bleeding and need for transfusion showed that the aprotinin group had significantly lower mediastinal bleeding. Transfused patients were 2, 4, 12 and 18 respectively in the aprotinin, epsilon aminocaproic acid, tranexamic acid and placebo treated group. In conclusion the use of protease inhibitors significantly reduces postoperative bleeding and transfusion. The aprotinin-treated group had the lower need for transfusion.

The effect of low-dose epsilon-aminocaproic acid on patients following coronary artery bypass surgery.

Montesano R.M., Gustafson P.A., Palanzo D.A., Manley N.J., Sadr F.S.

Perfusion. 11 (1) (pp 53-56), 1996.

The effect of low-dose epsilon-aminocaproic acid (EACA) on the postoperative course of 46 patients was studied. Patients undergoing coronary artery bypass grafting were randomly selected in two groups. Group 1 (20 patients) received 5 g EACA upon initiation of cardiopulmonary bypass (CPB). Group 2 (26 patients) received no antifibrinolytic drugs prior to CPB. Neither group received antifibrinolytic drugs after CPB. There was no significant difference between the two groups' blood usage on CPB: 0.65 units in Group 1 and 0.60 units in Group 2. After CPB, blood usage significantly differed: 2.2 +/- 1.7 (SD) units in Group 1 and 3.9 +/- 3.0 units in Group 2 (p = 0.033). Significant difference was also demonstrated in postoperative blood loss in the first 24 hours: 1610 +/- 531 ml in Group 1 versus 2025 +/- 804 ml in Group 2 (p = 0.043). Pre-CPB administration of low-dose EACA significantly

decreases blood loss and blood usage in the postoperative period.

Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requirements in patients undergoing first-time coronary artery bypass grafting: A randomized, prospective, double-blind study.

Daily P.O., Lamphere J.A., Dembitsky W.P., Adamson R.M., Dans N.F., Metzdorff M.T., Mark J.B.D., Ciaburri D., Gundry S.R., Miller D.C.

Journal of Thoracic and Cardiovascular Surgery. 108 (1) (pp 99-108), 1994.

The prophylactic use of aprotinin has recently been reported to be associated with a significant decrease in blood loss in patients undergoing cardiopulmonary bypass procedures. One of the primary effects of aprotinin is prevention of plasmin degradation of platelet function. Because aprotinin is commercially unavailable in the United States at this time, we evaluated epsilon-aminocaproic acid with respect to decreased perioperative blood loss. We prospectively randomized 40 patients undergoing first-time coronary artery bypass grafting without prior sternotomy into two groups: one group (n = 21) received prophylactic and preincision epsilon-aminocaproic acid and the other (n = 19) received a placebo. No significant differences existed between patient groups with respect to age, body surface area, cardiopulmonary bypass time, and aortic crossclamp time. Cumulative blood loss at 4, 8, 12, and 24 hours after chest closure was significantly less in the epsilon-aminocaproic acid group (426 +/- 242 ml versus 634 +/- 224 ml, p = 0.002, at 12 hours). Only one patient receiving epsilon-aminocaproic acid was given blood or blood components compared to five patients in the placebo group (p < 0.02). D- dimers and fibrin split products were significantly less prevalent in the epsilon-aminocaproic acid group (at 4 hours: 0/20 versus 7/16, p < 0.002 and 5/20 versus 12/19, p < 0.05, respectively). None of the patients had a perioperative myocardial infarction or cerebrovascular accident. The prophylactic administration of epsilon-aminocaproic acid results in a significant decrease in blood loss in patients undergoing first-time coronary artery bypass grafting, and blood transfusion requirements are significantly less. It may be important to administer epsilon-aminocaproic acid before skin incision to be optimally effective.

Decreased postoperative drainage with addition of epsilon-aminocaproic acid before cardiopulmonary bypass.

Arom K.V., Emery R.W., Hammon Jr. J.W., Lawler Jr. M.R., Strong M.D.

Annals of Thoracic Surgery. 57 (5) (pp 1108-1113), 1994.

Desmopressin (DDAVP, 0.3 mug/kg) has been used routinely after cardiopulmonary bypass, particularly in patients having antiplatelet therapy. Recently epsilon-aminocaproic acid (single dose of 5 g) given before cardiopulmonary bypass has been added to the protocol. One hundred consecutive patients taking desmopressin and epsilon-aminocaproic acid (group A) and another 100 taking desmopressin alone (group B) were analyzed. There was no difference among these two groups in patient age, sex, preoperative history of bleeding and drug consumption, or number of patients for elective, urgent, emergent, redo, and reoperation for bleeding. Results of routine preoperative coagulation studies were within normal limits in both groups. Preoperative hemoglobin level was 13.5 g/dL in group A and 13.8 g/dL in group B (p = 0.12). Estimated blood loss in the operating room was 513 mL for group A and 587 mL for group B (p = 0.07). The total chest drainage at the end of 24 hours was 492 mL in group A and 746 mL in group B (p = 0.0001). Amicar given before cardiopulmonary bypass does not lessen

operating room blood loss, but significantly decreases postoperative chest drainage. Group B patients received more fresh frozen plasma (60 U versus 4 U), more platelets (130 U versus 16 U), and more cryoprecipitate (118 U versus 10 U) than group A patients. Adding epsilon-aminocaproic acid could save $206.18 in blood product use per patient, compared with the expense of $24.12 per patient for E- aminocaproic acid administration.

＜海外における臨床試験等＞
１）上記試験はすべて海外試験であった。

＜日本における臨床試験等※＞
１）追加すべき事項なし

※ICH-GCP 準拠の臨床試験については、その旨記載すること。

（２）Peer-reviewed journal の総説、メタ・アナリシス等の報告状況

１）追加すべき事項なし

（３）教科書等への標準的治療としての記載状況

＜海外における教科書等＞
１）追加すべき事項なし

＜日本における教科書等＞
１）追加すべき事項なし

（４）学会又は組織等の診療ガイドラインへの記載状況

＜海外におけるガイドライン等＞
１）追加すべき事項なし

＜日本におけるガイドライン等＞
１）追加すべき事項なし

（５）要望内容に係る本邦での臨床試験成績及び臨床使用実態（上記（１）以外）について

１）追加すべき事項なし

（６）上記の（１）から（５）を踏まえた要望の妥当性について

＜要望効能・効果について＞
既に海外で発売されている有効成分が同一の製品の効能・効果に基づけば、要望された効能・効果、“繊維素溶解に伴う著しい出血に対する止血促進”は妥当と考える。しかしながら国内患者に対するデータもないことから、要望され

た効能・効果が本邦において適切かどうかは判断できない。

＜要望用法・用量について＞
既に海外で発売されている有効成分が同一の製品の用法・用量に基づけば、要望された用法・用量、“4 から 5 g を最初の 1 時間静注、続いて 1 時間当たり 1g を静注、止血が得られるまで約 8 時間継続する”は妥当と考える。しかしながら国内患者に対するデータもないことから、要望された用法・用量が本邦において適切かどうかは判断できない。

＜臨床的位置づけについて＞
類似した効能を有する薬剤としては、
ⅰ．凝固系促進薬：フィトナジオン、メナテトレノン、
ⅱ．線溶系抑制薬：トラネキサム酸、カルバゾクロム、トロンビン
が挙げられ、特に、トラネキサム酸は、アミノカプロン酸と同様の機序により繊維素溶解を阻害し止血促進作用を示すため、 アミノカプロン酸の代替薬になり得ると考えられる。

以上を総合的に判断すると、本剤の医療上の必要性は必ずしも高いとは言えないと考える。

4．実施すべき試験の種類とその方法案

国内では剤型を問わず未承認の薬剤であり、新有効成分として必要な非臨床試験、臨床試験等のデータはなく、更に承認取得のためには国内での臨床試験等のデータが必要となる。国内での開発を進めるに当たっては、日本人で至適用量、有効性、安全性を検討するための大規模な臨床試験が必要であると考える。

5．備考

＜その他＞

6．参考文献一覧