

Natural and synthetic antifibrinolytics in adult cardiac surgery: efficacy, effectiveness and efficiency

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Epsilon-aminocaproic acid and tranexamic acid, two synthetic antifibrinolytics, and aprotinin, an antifibrinolytic derived from bovine lung, are used to reduce excessive bleeding and transfusion of homologous blood products (HBP) after cardiac surgery. This review analyzes the studies on the utilization of antifibrinolytics in adult cardiac surgery according to the epidemiological concepts of efficacy, effectiveness and efficiency. A majority of published studies confirm the efficacy of antifibrinolytics administered prophylactically to reduce postoperative bleeding and transfusion of HBP. More studies are needed, however, to compare antifibrinolytics and determine if any one is superior to the others. Despite their demonstrated efficacy, antifibrinolytics are only one of the options available to diminish the use of HBP. Other blood-saving techniques, surgical expertise, temperature during cardiopulmonary bypass and respect of established transfusion guidelines may modify the effectiveness of antifibrinolytics to the point where antifibrinolytics may not be necessary. At this time, insufficient data have been published to perform a cost vs benefit analysis of the use of antifibrinolytics. This complex analysis takes into account not only direct costs (cost of the drug and of blood products), but also the ensuing effects of treatment such as: length of stay in the operating room, in the intensive care unit and in the hospital; need for surgical re-exploration; treatment of transfusion or drug-related complications, etc. In particu-

lar, the risk of thrombotic complications associated with antifibrinolytics is the subject of an ongoing, unresolved controversy. In conclusion, it is important for each institution to determine if their patient population (or a subset of this population) is likely to benefit from prophylactic treatment with antifibrinolytics, and to confirm that treatment is not associated with an increased incidence of untoward effects, before engaging in the routine use of any of these medications.

Trois antifibrinolytiques sont présentement utilisés en chirurgie cardiaque afin de réduire le saignement postopératoire et la transfusion de produits sanguins homologues (PSH). Il s'agit de l'acide epsilon-aminocaproïque et de l'acide tranexamique, deux antifibrinolytiques de synthèse, ainsi que de l'aprotinine, un antifibrinolytique naturel isolé à partir de poumons de bovins. Cet article fait une revue de l'utilisation des antifibrinolytiques en chirurgie cardiaque de l'adulte en fonction des concepts épidémiologiques fondamentaux que sont l'efficacité expérimentale, l'efficacité clinique et l'efficience. La majorité des études publiées confirme l'efficacité expérimentale des antifibrinolytiques administrés prophylactiquement dans le but de diminuer le saignement postopératoire et la transfusion de PSH. Cependant, les études cherchant à comparer les antifibrinolytiques entre eux sont rares. Seuls d'autres travaux nous permettront d'établir l'efficacité comparée de ces médicaments. Malgré leur efficacité expérimentale, les antifibrinolytiques ne sont qu'une des options à notre disposition pour diminuer le recours à la transfusion. Ainsi, l'efficacité clinique des antifibrinolytiques sera modifiée par l'utilisation des autres technologies visant à minimiser les pertes sanguines et la transfusion, par l'expertise de l'équipe chirurgicale, par la température durant la perfusion extra-corporelle, ainsi que par le respect des indications bien établies de la transfusion. Ainsi, dans un contexte donné, l'utilisation de ces médicaments pourra même s'avérer superflue. Nous ne disposons pas actuellement de données suffisantes pour compléter une analyse coûts/bénéfices des antifibrinolytiques en chirurgie cardiaque de l'adulte. Cette analyse complexe devra tenir compte non seulement des coûts directs (médicaments et produits sanguins), mais aussi

Key words

BLOOD: antifibrinolytics, aprotinin, 6-aminocaproic acid, tranexamic acid;

SURGERY: cardiovascular, cardiopulmonary bypass.

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Accepted for publication 1st July, 1994.

des effets associés au traitement tels que: durée de séjour en salle d'opération, aux soins intensifs et à l'hôpital; nécessité d'une ré-exploration pour hémostase; traitement des complications secondaires aux transfusions ou aux médicaments, etc. Plus spécifiquement, le risque de complications thrombotiques secondaires aux antifibrinolytiques fait l'objet d'une controverse non résolue à ce jour. En conclusion, avant de procéder à l'administration routinière de ces médicaments, chaque institution devra déterminer, dans la population chirurgicale qui lui est propre (ou dans un sous-groupe de cette population), l'utilité et l'innocuité des antifibrinolytiques administrés prophylactiquement.

Excessive bleeding after cardiopulmonary bypass (CPB) has always been a major concern of cardiac anaesthetists and surgeons. In an effort to reduce morbidity associated with transfusion of blood products (transmitted infectious diseases, transfusion reactions, etc.) and to answer concerns that the demand for blood and blood products may exceed the supply, many strategies have been explored to diminish the need for transfusion both during and after CPB. Pharmacological intervention with antifibrinolytics to reduce bleeding associated with CPB has received much attention recently.¹⁻³ It has the main advantages of being readily available and easy to administer, of avoiding the use of expensive equipment, and it may be used prophylactically rather than therapeutically in most instances. Nonetheless, administration of antifibrinolytics entails extra costs to the health care system and clinicians have to be confident that these drugs are not only efficacious, but also effective and efficient. The authors review the available knowledge concerning the use of antifibrinolytics in cardiac surgery from an epidemiological point of view.

The basic purpose of clinical epidemiology is to develop and apply rigorous methodology to clinical observations that will lead to valid clinical conclusions.⁴ Before accepting the conclusions of any article, clinicians must be sure that the three basic principles of epidemiology were respected (adapted from M. Cohen⁴). First, the sample chosen must be representative of the population being studied. All persons in the population must have had an equal chance of being chosen. Second, the study was planned so as to minimize systematic and random errors, and the validity of the study must be considered. Systematic error (bias) is that due to all causes other than sampling variability, e.g., error secondary to instrument of measure. Random error (chance) is that due to sampling variability, resulting in characteristics of the sample that are different from those of the population. A high internal validity signifies that the study was well designed and controlled. External validity refers to the general-

izability of the results: are they applicable to other situations? If internal validity is high, generalizability is usually low, because conditions of the study are so strict that they apply only to populations identical to those under study.

Third, studies must be classified as efficacy, effectiveness, or efficiency studies. Efficacy studies try to show that intervention X works in an ideal setting, e.g., the typical randomized trial in a major teaching hospital (institution A). Effectiveness studies try to show how intervention X works in the real world. For example, in institution B, the systematic use of intervention Y may reduce the beneficial effect of intervention X to the point where intervention X (efficacious in the randomized trial conducted in institution A) becomes ineffective. Efficiency studies aim to show what is the best intervention (X, Y, etc.) in terms of cost, personnel, compliance, and the like, given more than one alternative is available. The negative effects of the proposed intervention must be taken into account also when discussing efficiency.

In this article, the authors have analyzed studies on the use of antifibrinolytics in cardiac surgery according to the clinically useful concepts of efficacy, effectiveness and efficiency. While the assumption was made that the studies reviewed respect the first two principles described above, it must be recognized that this premise may not be valid in all cases.

The efficacy of antifibrinolytics in cardiac surgical patients

A number of drugs have been used to decrease blood loss and the use of blood transfusion after cardiac surgery. Recently there has been a renewed interest in antifibrinolytics, an old class of drugs, whether they be synthetic or natural. Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA), two synthetic antifibrinolytics, and aprotinin (Apt), an antifibrinolytic derived from bovine lung, have been used either to diminish or to prevent excessive bleeding associated with cardiac surgery.

Objectives of treatment

It must be remembered that the amount of blood shed during and after the operation is only an intermediate outcome. Unfortunately, many studies tend to focus on intermediate outcomes such as bleeding, coagulation profile, platelet count, etc., assuming that any beneficial effect on these will result automatically in a beneficial effect on final outcome. The final outcome to judge the efficacy, effectiveness and efficiency of a drug administered to reduce transfusion is the change in the amount of homologous blood products (HBP) to which patients will be exposed. For example, a drug could produce a small but

important decrease in blood loss, or a beneficial effect on the bleeding time, but not result in decreased transfusions of HBP. The clinical usefulness of such a drug would be questionable.

Epsilon-aminocaproic acid (Amicar®)

Epsilon-aminocaproic acid has been used in cardiac surgery since 1964. The conclusions of the earlier studies may not apply in 1994: from 1964 to the mid-seventies, surgery was performed mainly for congenital heart disease, and the equipment used for CPB produced more fibrinolysis than today. Most of the studies from that period were open and/or uncontrolled.²

Since 1979, several studies have reported a beneficial effect of EACA to treat⁵ or to prevent^{6,7} postoperative bleeding. The prophylactic administration of EACA by DeRossi *et al.* proved efficacious in a study of 350 patients undergoing a variety of surgical procedures.⁷ Blood loss and transfusion of red blood cells decreased in the EACA-treated patients.

Two recent studies demonstrate that EACA may be as efficacious as TA or Apt. Trinh-duc *et al.* could not show any difference in cumulative postoperative blood loss or in HBP requirements between high-dose Apt and EACA,⁸ but this study suffers from the lack of a control group. However, if their conclusions hold true, they might have major financial implications since EACA is much cheaper than high-dose Apt. Postoperative blood loss was reduced similarly by EACA, TA or warm perfusion in a study by Yau *et al.*⁹ In this latter study, requirements for HBP were marginally reduced by TA. Thus, a change in perfusion technique (normothermia vs hypothermia) could obviate the need for any antifibrinolytic medication altogether.

Also, the doses of EACA used by DeRossi *et al.*⁷ (initial dose of 5 g prior to skin incision, followed by an infusion of 1 g · hr⁻¹ for the next 6–8 hr) and by Yau *et al.*⁹ (15 g *iv* at anaesthetic induction) are small relative to the high doses of the other agents that are now being used. The efficacy of higher doses of EACA has not been investigated.

The promotion of an old drug like EACA is difficult. For fear of thrombotic complications, unsubstantiated by controlled studies,^{7,8} many clinicians will hesitate to administer EACA. Studies with EACA have a feeling of "déjà-vu," are less fashionable, and have little chance of being funded by pharmaceutical companies. On the other hand, the drug is cheap, large-scale clinical studies can be conducted at minimal cost, and introduction into everyday practice is readily feasible.

Tranexamic acid (Cyklokapron®)

Tranexamic acid is six to ten times more potent than

EACA¹⁰ and does not suffer from its bad reputation. Identified as an antifibrinolytic in 1964, the prophylactic use of TA to decrease blood loss after CPB was first reported in the late 1980s. Since TA was introduced only recently in cardiac surgery, there are few published reports on its efficacy. Horrow *et al.* reported that prophylactic TA reduced bleeding after cardiac operations (from 750 to 496 ml) in a series of 38 patients.¹¹ A dose of 10 mg · kg⁻¹ was infused prior to skin incision, followed by an infusion of 1 mg · kg⁻¹ · hr⁻¹ for ten hours. The use of packed red blood cells was similar in both groups, but patients receiving TA required less fresh frozen plasma (FFP). Doubling the dose of TA appears to increase its efficacy.¹²

Even higher doses of TA were employed by Karski *et al.*^{13,14} A retrospective chart review on 411 patients showed that 6 g of TA are not more efficacious than 10 g in reducing post-bypass bleeding in the first 24 hr after surgery, but that patients receiving the 10 g bolus required less red blood cells.¹³ Increasing the dose to 20 g achieved minimal increase in blood loss reduction in a prospective study in 146 patients.¹⁴ Transfusion requirements did not differ among groups (TA 10 g vs 20 g vs control) due to the effectiveness of autotransfusion in preserving blood loss.¹⁴ As mentioned previously in a study of 146 patients by Yau *et al.*,⁹ only TA reduced the number of units of packed red blood cells administered to each patient (but not the frequency of platelet, plasma, or cryoprecipitate transfusion) from a mean of three to two units, while postoperative bleeding was reduced similarly by TA, EACA, or warm systemic perfusion (35–37°C).⁹ It is worth noting that, in these three studies,^{9,13,14} postoperative bleeding after hypothermic perfusion (25–29°C) ranged from 1000–1200 ml in the control groups.

The most recent data presented by Karski *et al.* indicate that 100 mg · kg⁻¹ TA may be the optimal dose to prevent excessive postoperative blood loss in patients undergoing primary CPB without systemic cooling.¹⁵ Of interest, this prospective study on 150 patients did not include a control group and transfusion requirements were not different among the three doses of TA (50, 100, and 150 mg · kg⁻¹).

Thus, at this time, the optimal dose of TA appears to be of the order of 6–10 g, rather than the 1–2 g dose based on estimates of potency. Even so, it remains to be demonstrated that TA offers an advantage over the older and cheaper drug EACA. The main results of the studies on EACA and TA are summarized in Table I.

Aprötinin (Trasylo®)

There is little doubt that high (6 million KIU approximately) and intermediate doses (2 million KIU in the

TABLE 1 Influence of prophylactic EACA or TA on blood losses, percentage of patients transfused, and volume of blood transfused

Author	No. pts	Postoperative blood loss (ml)	% pts transfused	ml or units (U) RBC transfused	
DelRossi ⁷	350†	EACA (12 g)	617 ± 44 ml*	§	2.8 ± 2.0 U*
		C	883 ± 29 ml	§	4.2 ± 2.3 U
Trinh-duc ⁸	56	EACA (18 g)	978 ml#	63%	43 U total
		A	887 ml#	38%	26 U total
Yau ⁹	146**‡	EACA (15 g)	881 ± 64 ml	65%*	2.3 ± 0.3 U
		TA (10 g)	822 ± 42* ml	49%*	2.0 ± 0.2 U*
		C	1113 ± 151 ml	75%	3.0 ± 0.6 U
Horrow ¹¹	38†	TA (1.5 g)	496 ± 228 ml*	0% (FFP)*	275 ± 241 ml
		C	750 ± 314 ml	25% (FFP)	227 ± 324 ml
Karski ¹³	411**‡	TA (6 g)	700 ml*#	45%#	§
		TA (10 g)	600 ml*#	35%*#	§
		EACA (10 g)	700 ml*#	55%#	§
		EACA (15 g)	700 ml*#	50%#	§
		C	950 ml#	60%#	§

* $P < 0.05$. **Retrospective study. †Double-blind study. ‡Non-randomized study. #Data extracted from figure (approximate). §Data not available from the publication.

EACA = epsilon aminocaproic acid (approximate total dose in g); TA = tranexamic acid (approximate total dose in g); A = high dose aprotinin; C = control group; FFP = fresh frozen plasma; RBC = red blood cells.

CPB prime) are efficacious in reducing blood loss and transfusion requirements after CPB in adults (Table II).¹⁶⁻²⁹ The high-dose regimen recommended in the literature¹ is based on theoretical considerations and, surprisingly, dose-ranging studies on the efficacy of Apt in clinical practice have never been conducted. Unfortunately, Apt is an expensive drug (see section on efficacy) and its routine administration in cardiac surgery cannot be implemented without a considerable cost to the health care system.

In an effort to reduce costs, two double-blind, randomized, placebo-controlled studies of Apt 1 million KIU have been conducted in which Apt was administered as an infusion³⁰ or as a bolus in the oxygenator prime* to patients at high risk of being transfused.³¹ The Apt infusion was ineffective but administration of Apt 1 million KIU in the CPB prime reduced both the number of patients receiving FFP and the quantity of FFP transfused to each patient. Two reasons may explain the inefficacy or the limited efficacy of Apt in these studies. The dose may have been insufficient but another important reason which may help explain the discrepancies between the results from different centres was that meticulous surgical haemostasis decreased blood loss to a

level where the efficacy of prophylactic Apt may be difficult to demonstrate.

Similarly, a lack of efficacy of prophylactic high-dose Apt in elective aortocoronary bypass grafting has been reported by Boldt *et al.*³² Blood losses until the first postoperative day in their patients treated by haemofiltration alone during bypass (390 ± 230 ml) were not different from those in whom high dose Apt and haemofiltration were used (260 ± 160 ml).³² It must be noted, however, that the lowest rectal temperature during bypass was $34.1 \pm 0.5^\circ\text{C}$. As in the study by Yau *et al.* on the effect of warm surgery, EACA and TA on postoperative bleeding,⁹ the influence of temperature during CPB may be important to the point where the beneficial effects of high doses of Apt on platelet function, postoperative blood losses and transfusion of HBP are negated by normothermic CPB (nasopharyngeal temperature $>34^\circ\text{C}$).³³ These three recent studies^{9,32,33} emphasize the importance of considering perfusion temperature when evaluating the efficacy of antifibrinolytics.

Aspirin therapy is associated with increased bleeding and transfusion requirements and more frequent surgical reexploration after coronary artery bypass surgery. Nonetheless, several surgeons will hesitate to interrupt aspirin therapy before the operation, for fear of reactivating anginal symptoms. In these circumstances, high-dose Apt decreases both blood loss and prevalence of transfusion.^{34,35} However, low-dose Apt (2 million KIU in the pump prime) or TA (10 g *iv* prior to skin incision) may be as efficacious as high-dose Apt.³⁶

Studies comparing Apt with synthetic antifibrinolytics

*Hardy JF, Bélisle S, Perrault J, Carrier M, Robitaille D.

Aprotinin 1 million KIU in the CPB circuit reduces the transfusion of fresh frozen plasma in high risk cardiac surgical patients. Presented at the 15th Annual Meeting of the Society of Cardiovascular Anesthesiologists, April 1993, San Diego, California.

TABLE II Influence of prophylactic aprotinin on blood losses, percentage of patients transfused, and volume of blood transfused

Author	No. pts		Postoperative blood loss ml or g of haemoglobin	% pts transfused	ml or units (U) RBC transfused
Royston ¹⁶	22*	A	286 ± 48 ml	36%	§
		C	1509 ± 388 ml	100%	§
van Oeveren ¹⁷	22	A	357 ml	§	§
		C	674 ml	§	§
Alajmo ¹⁸	34	A	486 ± 47 ml	§	213 ± 85 ml
		C	830 ± 117 ml	§	409 ± 140 ml
Bidstrup ¹⁹	80†	A	309 ± 133 ml	20%	§
		C	573 ± 166 ml	95%	§
Dietrich ²⁰	152‡	A	761 ± 51 ml	58%	1015 ± 113 ml
	317¶	C	1070 ± 43 ml	82%	1783 ± 100 ml
Fraedrich ²¹	80†	A	652 ± 382 ml	§	242 ± 359 ml
		C	1204 ± 705 ml	§	937 ± 843 ml
Wildevuur ²²	28†	a	14 ± 3 g	§	§
		C	64 ± 6 g	§	§
Dietrich ²³	40†	A	738 ± 411 ml	37%	163 ± 308 ml
		C	1431 ± 760 ml	75%	838 ± 963 ml
van Oeveren ²⁴	60†	A	17 ± 9 g	38%	§
		C	37 ± 12 g	68%	§
		a	19 ± 9 g	38%	§
Blauhut ²⁵	26‡	A	§	15%	§
		C	§	62%	§
Harder ²⁶	80†	A	559 ± 109 ml	31.5%	§
		C	911 ± 170 ml	57.2%	§
Havel ²⁷	22	A	610 ± 310 ml	§	§
		C	1000 ± 440 ml	§	§
Carrel ²⁸	23†	a	430 ± 130 ml	§	205 ± 125 ml
	30	C	915 ± 270 ml	§	880 ± 220 ml
Schönberger ²⁹	200**	A	684 ± 57 ml (IMA)	22%	0.5 ± 0.2 U
		A	1055 ± 80 ml (BIMA)	22%	0.6 ± 0.2 U
		C	1237 ± 93 ml (IMA)	58%	1.6 ± 0.3 U
		C	1404 ± 135 ml (BIMA)	52%	2.5 ± 0.7 U

*Reoperations. **Retrospective study. †Double-blind study. ‡Non-randomized study. §Data not available from the publication. ¶Historic controls. IMA = unilateral internal mammary artery bypass grafting; BIMA = bilateral IMA; RBC = red blood cells; A = high-dose aprotinin; C = control group; a = 2 million KIU in cardiopulmonary bypass prime only.

Blood losses were significantly reduced by A or a when compared to C.

(Adapted from Hardy JF, Desroches J. Natural and synthetic antifibrinolytics in cardiac surgery, *Can J Anaesth* 1992; 39: 353-65).

have begun to appear recently. Apart from the published study by Trinh-duc *et al.* comparing high doses of Apt with EACA that was discussed previously,⁸ a few other comparative studies have been published in abstract form. Isetta *et al.* compared Apt with TA in 108 patients undergoing CPB.³⁷ Infusion of intermediate doses of Apt (500,000 KIU after induction, followed by an infusion of 500,000 KIU · hr⁻¹ until the end of CPB) did not offer any advantage over low-dose TA (15 mg · kg⁻¹ before the injection of heparin prior to CPB and 15 mg · kg⁻¹ after injection of protamine). Both treatments reduced blood loss and transfusions. Hamilton *et al.* compared high-dose Apt with TA 10 g *iv* prior to skin incision in 24 patients undergoing repeat open heart surgery.³⁸ Chest tube drainage and transfusion requirements were similar in both groups. Murkin compared blood loss and

requirements for red blood cells in patients undergoing repeat sternotomy who received either high-dose Apt, low-dose Apt (2 million KIU in the pump prime), or TA (10 g *iv* prior to skin incision).³⁹ He concluded that high-dose Apt and TA were equally effective in this patient population whereas low-dose Apt did not prove to be beneficial. It remains unclear why low-dose Apt was not efficacious in reoperative procedures³⁹ but of benefit in aspirin-treated patients.³⁶

Unfortunately, as in the report by Trinh-duc *et al.*,⁸ the studies by Hamilton³⁸ and by Murkin^{36,39} suffer from the lack of a control group. Another major limitation of these studies³⁶⁻³⁹ is the small number of patients enrolled. Given the inherent and important variability of postoperative blood loss and of transfusion requirements, considerably more patients will be required before the

results of similar studies can be interpreted with an acceptable degree of confidence.

Thus, in general, high doses of Apt (6 million KIU) are efficacious. Very low doses (1 million KIU) may not suffice, especially if bleeding is already low. Overall, intermediate doses (2 million KIU in the pump prime) have proved to be as effective as the high-dose regimen (Table II). Finally, a different and interesting approach to the use of Apt in open heart operations has been proposed by Tatar *et al.*⁴⁰ Topical application of Apt 1 million KIU in the pericardial cavity reduces postoperative chest drainage and transfusion of HBP. The advantages of this approach include the use of a small, relatively inexpensive dose and, possibly, the lack of systemic effect since Apt could not be detected in the patients' blood.

Should we be using these drugs, i.e., are antifibrinolytics effective?

As one can see from the previous discussion of the efficacy of antifibrinolytics to decrease blood loss and transfusion requirements in cardiac surgical patients, there is no simple answer to this question. Studies from different centres have produced a sum of data that tend to demonstrate that drugs administered prophylactically will reduce excessive bleeding effectively in the first 24 hr after cardiac surgery. Excessive bleeding could, tentatively, be defined as chest drainage of >600–800 ml. At the present time, there is no definitive data to prove that any one of the available antifibrinolytics (EACA, TA, or Apt) is superior to the others in this respect.

As for the reduction of transfusion, it is less clear if pharmacological treatment is effective. This lack of effect may result, in part, from suboptimal transfusion habits. Excessive and inappropriate transfusion in a number of American hospitals has been shown to result from non-compliance with national consensus recommendations.⁴¹ Application of these recommendations at the institutional level should result in decreases of perioperative blood component use, and should be implemented before pharmacological prophylaxis.

Exposure to HBP was determined in relationship to postoperative chest drainage in 3022 patients from the data bank of the Department of Anesthesia of the Montreal Heart Institute. The figure shows that patients bleeding up to 1000 ml after CPB receive an average of six units of HBP or less during their hospital stay. These patients represent 72% of the total population (2188/3022). As postoperative bleeding increases >1000 ml, the number of units transfused also increases. It is conceivable that the first group of patients could be managed conservatively by methods such as predonation of autologous blood, reinfusion of shed mediastinal blood and intraoperative autotransfusion. On the other hand, the

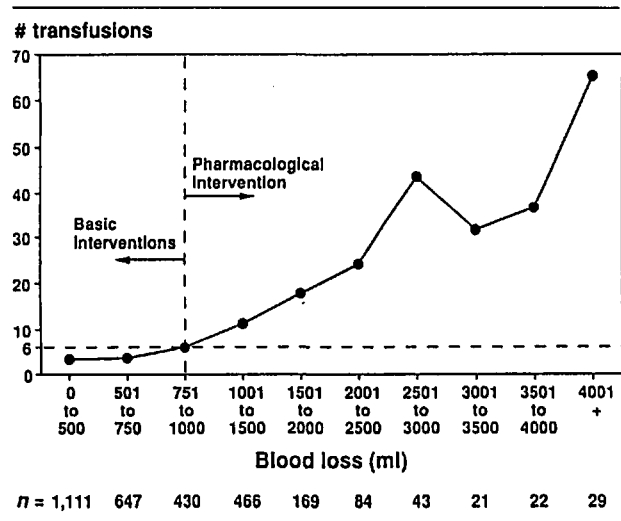


FIGURE Mean exposure to homologous blood products (units) as a function of postoperative mediastinal drainage, from 3032 adult cardiac operations performed with cardiopulmonary bypass at the Montreal Heart Institute in 1991 and 1992. Patients bleeding ≤ 1000 ml were exposed to fewer than six units on average.

28% of patients likely to receive > six units of HBP would probably benefit the most from pharmacological prophylaxis. While this approach suggests that patients undergoing cardiac surgery may be subdivided into two groups according to postoperative bleeding and the use of blood products, there remains to be found a method (laboratory, demographic or other) of identifying to which group a given patient belongs before surgery.

Cost vs benefit analysis (efficiency)

This is a complex issue that takes into account not only direct costs (cost of the drug and of blood products), but also the ensuing effects of the treatment such as: length of stay in the operating room, in the intensive care unit and in the hospital, need for surgical re-exploration, treatment of transfusion or drug-related complications, etc.

The issue of cost is especially relevant with Apt, an expensive drug. At the present time, the cost of high-dose Apt (6 million KIU) treatment is approximately \$930/CDN (a vial of 500,000 KIU costs \$77.50 CDN at our institution). Routine use of Apt alone would entail an expense of more than 2.5% of the annual budget of the Montreal Heart Institute. On the other hand, drugs like EACA and TA are relatively inexpensive and could be used extensively, with less impact on the hospital's budget. The prophylactic administration of synthetic antifibrinolytics requires up to 20 g of EACA or 10 g *iv* of TA which costs \$89 CDN and \$247 CDN per patient respectively. If proved effective at the institutional level, the use of intermediate (2 million KIU in the CPB prime)

or low (1 million KIU in the pericardial cavity) doses of Apt would be competitive from an economic standpoint.

Based on economic concerns alone, it appears illogical to administer an expensive drug like Apt (6 million KIU) to low-risk primary procedures, when less expensive alternatives (such as retransfusion of shed mediastinal blood) have already demonstrated their efficacy. Also, in first-time procedures, the beneficial effect of the drug on consumption of blood products is likely to be small when surgical blood loss is already minimal^{31,32} and/or when transfusion practice does not follow established guidelines. Application of these guidelines should result in considerable decreases of perioperative blood component use and reduce costs.

Reduced operating times, less need for work after regular hours, and shorter stays in the intensive care unit may still justify the short-term cost of a drug like Apt. However, the appropriate data must become available to substantiate a beneficial effect of the drug on these variables. Similarly, data demonstrating the beneficial effect of Apt on transfusion-related complications must also become available to justify the cost of the drug in the long term. While the initial low cost of synthetic antifibrinolytics is attractive,³⁸ data on the financial consequences of potential side effects must ensure that these do not outweigh the initial economies.

Finally, while antifibrinolytics may be useful, manipulation of haemostasis is a two-edged sword. The risk of thrombotic complications is controversial, probably small, but exists. Thrombotic complications affecting cerebral, cardiac or renal function will cause severe morbidity, if not mortality, to the patient and entail considerable expense for the health care system. Two recent studies suggest that, under certain circumstances, the use of Apt⁴² or TA⁴³ may be associated with an increased incidence of postoperative myocardial infarction, but both studies failed to achieve statistical significance. Still, these results are of concern because they indicate that use of antifibrinolytics may be associated with deleterious effects on the myocardium when anticoagulation is inadequate⁴⁴ (as in the study by Cosgrove *et al.*⁴²) or when the drug is used routinely after, rather than before, CPB (as in the study by Ovrum *et al.*⁴³). Also, use of Apt in elderly patients undergoing operations on the thoracic or thoraco-abdominal aorta using CPB and profound hypothermic circulatory arrest is associated with an increased risk of postoperative renal dysfunction and failure, and of death.⁴⁵ On the other hand, in a magnetic resonance imaging study examining saphenous vein graft patency after aortocoronary bypass grafting, Bidstrup *et al.* failed to demonstrate an adverse effect of Apt in patients undergoing first-time myocardial revascularization.⁴⁶ Similarly,

an adverse effect of Apt on early vein graft patency rates was not demonstrated in a study of 216 patients assessed by ultrafast computed tomography,⁴⁷ or in a study of 45 patients undergoing coronary angiography after coronary bypass operation.⁴⁸ Data on the safety and efficacy of Apt therapy in 41 cardiac centres in the United Kingdom show that the use of Apt in cardiac surgical patients at high risk for excessive bleeding is associated with a low incidence of adverse events.⁴⁹ It remains to be demonstrated whether topical application of Apt (or synthetic antifibrinolytics) will avoid thrombotic complications completely.

Again, the inappropriate use of potent drugs like antifibrinolytics is likely to be associated with major complications. More studies are required to define exactly which patients should receive which drug, at what dosage and under what conditions. Failure to respect the limits of drug usage established by these studies risks swinging the pendulum from generalized, routine use of antifibrinolytics to overt rejection of a useful therapeutic modality for fear of (unwarranted) complications.

Conclusion

A majority of published studies confirms the efficacy of antifibrinolytics administered prophylactically to reduce postoperative bleeding and transfusion of HBP. More studies are needed to compare antifibrinolytics and determine if any drug is superior. Despite their proved efficacy, antifibrinolytics are only one of the options available to reduce the use of HBP.⁵⁰ The expertise of the surgeon, normothermic CPB and strict adherence to established transfusion guidelines may blunt the effectiveness of antifibrinolytics to the point where antifibrinolytics may not be necessary. Under certain circumstances, manipulation of haemostasis may be associated with complications. It is important therefore for each institution to determine if their patient population (or a subset of this population) is likely to benefit from prophylactic treatment with antifibrinolytics, and to confirm that treatment is not associated with an increased incidence of untoward effects, before engaging in the routine use of any of these medications.

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