Brian L. Erstad

What is the evidence for using hemostatic agents in surgery?

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B. L. Erstad (✉)
Department of Pharmacy Practice
and Science, College of Pharmacy,
Tucson, Arizona 85721–0207, USA
Fax: +1-520-626-7355,
e-mail: erstad@pharmacy.arizona.edu

Abstract The pharmacological methods used to achieve systemic hemostasis have generated much discussion due to concerns of serious adverse effects (e.g., thromboembolic complications) and costs of therapy in addition to efficacy considerations. There are a limited number of well-controlled trials involving pharmacological hemostasis for spine surgery. In the largest double-blinded randomized controlled trial to date involving spine surgery, there was a trend toward reduced homologous transfusion in patients receiving aprotinin, but the only statistically significant result ($p < 0.001$) was a reduction in autologous red cell donations. The findings of this trial are important, since the investigators used a number of restrictive transfusion strategies (e.g., autologous donation, low hematocrit trigger for transfusion, blood-salvaging proce-

dures with the exception of no cell saver) that were not always employed in earlier trials involving hemostatic agents. Smaller studies involving antifibrinolytic agents other than aprotinin have demonstrated reductions in blood loss and transfusion requirements in patients undergoing spine surgery, although the results were not always statistically significant. A very large randomized trial would be required to address comparative medication- and transfusion-related adverse events; such a trial involving patients undergoing cardiac surgery is currently being performed. Additionally, cost-effectiveness analyses are needed to help define the role of these agents based on the data that is available.

Keywords Hemostatics · Antifibrinolytic agents · Hemorrhage

Introduction

Topical, local, regional, and systemic routes of medication administration have been employed for preventing or reducing blood loss and associated transfusion requirements in patients with bleeding diatheses. Examples would include topical fibrin- or thrombin-based products for wound hemostasis, proton pump inhibitor therapy for preventing gastric rebleeding in patients with peptic ulceration, octreotide derivatives for reducing rebleeding in patients with variceal hemorrhage, and the antifibrinolytic agents and desmopressin for systemic hemostasis. The pharmacological methods used to achieve systemic hemostasis have

generated much discussion due to concerns of serious adverse effects (e.g., thromboembolic complications) and costs of therapy in addition to efficacy considerations.

The studies that have been conducted have focused on the operating room, where substantial blood loss can often be anticipated. This paper is intended to provide an overview of the consequences and costs of medications used for systemic hemostasis during spine surgery in light of currently available evidence. Ideally, the efficacy and adverse effects of these agents would be defined by large, well-controlled studies restricted to spine surgery rather than by extrapolation from other surgical procedures. Unfortunately, there are a limited number of such trials involving pharmacological hemostasis in association with

spine surgery. Therefore, potentially applicable information from other investigations of systemic hemostatic agents in the perioperative setting will also be discussed with the caveat that the pathophysiology of bleeding and mechanisms of action of the hemostatic agents may vary depending on the type of surgical procedure being performed.

Evaluating the evidence

When evaluating the studies concerning the benefits and risk of systemic hemostatic agents in the perioperative period, it is important to recognize that there are no standardized levels of evidence or grades of recommendation for ranking the study designs [34]. However, one or more appropriately powered randomized controlled trials (RCTs) are typically considered level I evidence leading to a grade A recommendation using numeric and letter systems [32]. Such trials will be the focus of this review.

The ranking of meta-analyses in hierarchical systems is more controversial, since meta-analyses have been shown to be predictive of large RCT results only 35% of the time [19]. Furthermore, depending on the criteria used for study inclusion in a meta-analysis, the results and conclusions of more than one meta-analysis on a particular topic may conflict. More meta-analyses involving pharmacological forms of hemostasis have pertained to cardiac surgery than any other type of procedure, which is not surprising considering the large number of RCTs of medications that have been conducted in this area.

Sample-size considerations

The largest double-blinded RCT to date involving spine surgery was conducted by Lentschener et al. [21]. In that trial, only one patient in the placebo group (none in the aprotinin group) required more than 5 U of red blood cells (RBCs) [21]. Such patients, who lie in the upper tail of a transfusion curve, can hinder the detection of significant differences in bleeding and transfusion requirements between groups. This is illustrated by a multicenter, double-blind RCT involving patients undergoing repeat coronary artery bypass surgery [22]. The statistically significant difference in RBC requirements noted between high- and low-dose aprotinin regimens disappeared (1.6 ± 0.2 U in high dose and 1.6 ± 0.3 U in low dose) when one patient with extensive bleeding was eliminated from the statistical calculations. By assuming that such variation in RBC requirements will not occur, the estimated sample sizes for studies involving systemic hemostatic agents are substantially decreased. For example, in one double-blinded RCT investigating the usefulness of aprotinin for reducing blood loss in orthopedic surgery, it was estimated that only nine patients would be needed in each group to de-

tect a significant difference with 90% power and a significance level of 0.05 [15].

Efficacy of systemic hemostatic agents in spine/orthopedic surgery

In the trial by Lentschener et al. [21], patients undergoing spine surgery were randomized to an aprotinin (2×10^6 KIU loading dose followed by 5×10^5 KIU/h infusion until skin closure) or placebo. This dose of aprotinin, which will be referred to as a high-dose regimen in this paper, has been called a high- or low-dose depending on the investigation, so the clinician needs to consider the actual units administered in any given trial [15, 30]. The sample size in the RCT by Lentschener et al. [21] was calculated from blood-loss data collected at their institution. It was estimated that 72 patients would be needed to find a 30% reduction (80% power, $p < 0.05$) in the baseline transfusion requirement of $2,200 \pm 1,000$ ml using a one-sided analysis. While there was a trend towards reduced RBC requirements in patients receiving homologous transfusions, the only statistically significant result ($p < 0.001$) was a reduction in autologous RBC donations. No fresh frozen plasma was administered in either group. No adverse drug events were attributable to aprotinin. The findings in the trial by Lentschener et al. [21] are important, since the investigators used a number of restrictive transfusion strategies (e.g., autologous donation, low hematocrit trigger for transfusion, blood-salvaging procedures with the exception of no cell saver) that were not always employed in earlier trials involving hemostatic agents. The trial gives clinicians an estimate of the blood-sparing effects of aprotinin beyond these baseline restrictive strategies. Additionally, since the investigators provided a detailed breakdown of transfusion requirements, the data can be compared to that from other investigations that found reductions in allogeneic transfusion when autologous blood was administered.[6].

Assuming that the variation in transfusion requirements, and therefore sample size estimation, is similar to that calculated by Lentschener et al. [21], the number of adequately powered studies involving patients undergoing orthopedic and spine surgeries is quite limited (Table 1). [2, 14, 16, 21, 24, 31]. Based on the findings of two RCTs, desmopressin does not have significant hemostatic activity in association with hip or knee procedures. While it has been postulated that desmopressin may be more useful in patients with preexisting platelet dysfunction, controlled trials substantiating this claim are needed. The antifibrinolytic agent tranexamic acid appears to have some usefulness in reducing blood loss and transfusion requirements in knee arthroplasty, but there are no adequately powered RCTs involving this agent (or the related lysine analogue, aminocaproic acid) in spine surgery. Aprotinin appears to have efficacy in reducing blood loss and trans-

Table 1 Randomized, double-blinded, placebo-controlled trials involving hemostatic medications for orthopedic and spine surgeries^a

Reference	Patients	Dosing regimen	Outcomes
Karnezis et al [16]	92 patients undergoing total hip or knee arthroplasty	Desmopressin 0.3 µg/kg IV during wound closure	No significant differences in blood loss or transfusion requirements
Schott et al [31]	79 patients undergoing total hip replacement	Desmopressin 0.3 µg/kg IV immediately after spinal anesthesia and 6 h later	No significant differences in blood loss or transfusion requirements
Benoni and Fredin [2]	86 patients undergoing knee arthroplasty	Tranexamic acid 10 mg/kg IV before tourniquet deflation	Tranexamic acid significantly reduced total blood loss (730±280 ml versus 1410±480 ml, $p<0.001$) and number of patients receiving red blood cell transfusions (8 versus 24, $p<0.001$)
Hiippala et al [14]	77 patients undergoing knee arthroplasty	Tranexamic acid 15 mg/kg IV before tourniquet deflation plus two more doses of 10 mg/kg IV (one in recovery room and one on ward)	Tranexamic acid significantly reduced total blood loss (689±289 versus 1509±643 ml, $p<0.0001$) and red blood cell requirements (1.0±1.2 versus 3.1±1.6 U, $p<0.0001$)
Lentschener et al [21]	72 patients undergoing posterior lumbar spine fusion	Aprotinin 2×10 ⁶ KIU IV then 5×10 ⁵ KIU/h until skin closure; an additional bolus of 5×10 ⁵ KIU was given for each 3 U of red blood cells administered	Aprotinin significantly reduced blood loss and red blood cell transfusion versus placebo (1935±873 versus 2839±993 ml, respectively, $p=0.007$ and 42 versus 95 U, respectively, $p=0.001$); significant reductions in transfusion limited to autologous (not homologous) donation
Murkin et al [24]	149 patients undergoing unilateral total hip replacement	Aprotinin 5×10 ⁵ KIU IV (low dose); 1×10 ⁶ KIU IV then 2.5×10 ⁵ KIU/h (medium dose); 2×10 ⁶ KIU IV then 5×10 ⁵ KIU/h (high dose) until skin closure	Aprotinin significantly reduced blood loss (1169 ml low dose, 1090 ml medium dose, 1079 ml high dose versus 1408 ml placebo, $p=0.034$, $p=0.005$, $p=0.003$, respectively) and the number of patients transfused (6% with aprotinin versus 15% with placebo, $p=0.03$)

^a Studies with enrollment of more than 70 subjects

fusion requirements when administered in association with hip replacement and spine surgery, particularly with higher-dose regimens, but only one RCT is available to substantiate each of these proposed uses.

There are three smaller prospective studies that have investigated the efficacy of antifibrinolytics in spine surgery. Two studies ($n=59$ and $n=40$) involving children undergoing posterior spinal fusion for scoliosis have demonstrated reductions in blood loss and transfusion requirements with either aminocaproic acid or tranexamic acid [10, 26]. In the other study involving 60 adult patients undergoing sequential anterior and posterior spine fusions were randomized (but not blinded) to receive either aprotinin, aminocaproic acid, or a control group [35]. Both aprotinin and aminocaproic acid led to reduced blood loss and transfusion requirements compared to the control group, but the reduction with aminocaproic acid was only statistically significant in the former study.

Efficacy of systemic hemostatic agents in other types of surgery

Although it is more problematic to extrapolate the efficacy of systemic hemostatic agents from hepatic or cardiac surgery to spine surgery, there are some general themes that are consistent across investigations. Of the larger studies

involving hepatic resection or transplantation, two double-blinded RCTs ($n=97$ and $n=137$) involving aprotinin found statistically significant reductions in blood loss and transfusion requirements [20, 28], and a third RCT with a somewhat smaller sample size ($n=80$) found trends toward benefits with aprotinin [11]. A fourth double-blinded RCT ($n=132$) comparing tranexamic acid and aminocaproic acid to placebo found reductions in transfusion requirements with both lysine analogues compared to placebo, but the results were only statistically significant for tranexamic acid [7].

Numerous double-blinded RCTs, particularly with aprotinin, have been conducted in cardiac surgery. Several meta-analyses have also been conducted in attempt to compare the efficacy of desmopressin and the various antifibrinolytic agents [9]. While the *lack* of evidence supporting the use of desmopressin during cardiac surgery is quite consistent, possible efficacy differences between the antifibrinolytic agents is less apparent. Underlying the drive for the numerous RCTs and meta-analytic comparisons is the substantial cost differences between aprotinin and the other hemostatic agents. Given the increasing controversy concerning the place of meta-analysis in evidence-based classification systems, it is not surprising that the meta-analyses in the cardiac surgery area have not resolved the discussion of the preferred hemostatic agent. To the contrary, a 3-year multicenter RCT comparing antifibrinolytic

agents is currently being conducted in Canada with an anticipated enrollment of approximately 3,000 patients [29]. The desired enrollment indicates the perceived (as well as calculated) number of patients needed to definitively answer efficacy questions concerning the antifibrinolytic agents.

There have been four randomized trials (all conducted prior to 1987) involving the lysine analogues for preventing blood loss after prostatectomy or thyroid surgery. The first double-blinded RCT involving 92 patients undergoing transvesical prostatectomy found significant reductions ($p < 0.02$) in blood loss in patients starting tranexamic acid the morning of surgery and continuing for 4 days [12]. A second unblinded RCT allocated 100 patients to receive tranexamic acid for 3 weeks after prostatectomy or endoscopic bladder tumor resection and also found significant reductions in blood loss in the tranexamic group ($p < 0.01$). [23] Additionally, one of two small ($n=46$ and $n=54$) double-blinded RCTs involving aminocaproic acid in patients undergoing prostatectomy found a significant reduction in blood loss [18, 33]. A double-blinded RCT involving 76 patients undergoing thyroid surgery found no significant reduction in blood loss with tranexamic acid [1]. None of these trials involving the lysine analogues investigated reductions in transfusion requirements.

Adverse effects of systemic hemostatic agents

A major concern with all systemic hemostatic medications, and one of the reasons for increasing the sample size of clinical trials, is the possibility of adverse effects. Of concern with all systemic hemostatic medications is the potential for thrombotic complications, and isolated case reports of such complications exist [25, 37]. However, a cause-and-effect relationship based on isolated case reports is not possible, and for each of these reports, there are other large series of patients in which no thrombotic complications were found [3].

Aprotinin has the advantage in that it has been studied in a large number of RCTs in cardiac surgery, but other hemostatic medications such as the lysine analogues have been available for many years. For example, a double-blinded RCT evaluating the safety of aminocaproic acid in association with prostatectomy was published in 1966; no evidence of serious adverse effects such as thromboembolic complications were found in the 259 patients randomized to the treatment group [36].

Aprotinin has some unique concerns related to the bovine source of the product, in particular reports of anaphylaxis upon reexposure that have been documented in a multicenter, prospective, observational study [8]. Adverse-effect concerns with the use of systemic hemostatic medications must be balanced with possible transfusion-related reactions and infectious diseases that are avoided by reductions in blood requirements. A very large RCT would

be required to address comparative medication, and transfusion-related adverse events considering safety concerns have not been resolved by previous investigations [17]. Hopefully, the Canadian trial that is in progress will address some of the adverse effects as well as efficacy concerns [29].

Economic considerations

Until the efficacy and adverse-effect concerns are resolved through further trials, clinicians must reconcile the costs and consequences of hemostatic medications and blood transfusion. This is where formal economic analyses have a role. Unfortunately, only one large multicenter, double-blinded study has compared antifibrinolytic agents with a prospectively implemented economic analysis [3]. In that trial, aprotinin was significantly more effective than aminocaproic acid in reducing blood loss, but transfusion rates between the two medications was similar. Therefore, aminocaproic acid was the less costly agent in the analysis that not only considered medication costs but transfusion and operating room costs as well.

Given the high cost of aprotinin, the other antifibrinolytic agents would always demonstrate economic superiority if transfusion requirements were similar and there were no significant differences in other efficacy or adverse effect measures. However, if aprotinin decreases transfusion requirements to a greater degree than other agents without a concomitant increase in adverse effects, as has been demonstrated in a number of trials discussed in this paper, economic analyses could define the relative cost-effectiveness of the agents. Similarly, a systematic review of the antifibrinolytic agents by the Cochrane collaboration found a reduced need for reoperation in patients receiving aprotinin compared to control (RR=0.4, 95% CI=0.25–0.66) [13]. Again, this could have important implications in a cost-effectiveness analysis. Depending on the comparative decrease in transfused blood or reexploration rates, the analysis could define the point at which aprotinin might be a preferred product despite its higher purchase cost.

One way to improve the cost-effectiveness of all systemic hemostatic medications is to restrict their use to patients at high risk for bleeding and transfusion. Recent studies evaluating factors predictive of allogeneic transfusion in association with spine surgery have helped to define high-risk patient and institutional factors [5, 27, 38]. Some of the factors that have been significantly predictive increased allogeneic transfusion in at least two of these recent studies include increasing age, female gender, comorbidities or complications, and low preoperative hemoglobin concentrations. The cost-effectiveness of hemostatic medications can also be improved by knowledge of commercially available formulations. Such knowledge may allow for cost-reduction measures such as dose

rounding by product size when using weight-based dosing regimens or decreased product wastage associated with canceled procedures by diluting the agent in an intravenous solution immediately prior to use.

Conclusions

The vast majority of RCTs involving hemostatic agents have been conducted in the operating room, particularly in

patients undergoing coronary artery bypass surgery. There is a limited amount of high-level evidence supporting the use of systemic hemostatic agents for noncardiac surgery. Large RCTs are needed to answer concerns not only related to efficacy but also toxicity. Additionally, cost-effectiveness analyses are needed to help define the role of these agents based on the data that is available.

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