Aprotinin: Effective, but Risky?

The risk associated with aprotinin in cardiac surgery. *Mangano DT, Tudor IC, Dietzel C, for the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation.* N Engl J Med 2006;354:353-365.

Abstract

Background: **The majority of patients undergoing surgical treatment for ST-elevation myocardial infarction receive antifibrinolytic therapy to limit blood loss. This approach appears counterintuitive to the accepted medical treatment of the same condition—namely, fibrinolysis to limit thrombosis. Despite this concern, no independent, large-scale safety assessment has been undertaken.** ***Methods:*** **In this observational study involving 4374 patients undergoing revascularization, we prospectively assessed three agents (aprotinin [1295 patients], aminocaproic acid [883], and tranexamic acid [822]) as compared with no agent (1374 patients) with regard to serious outcomes by propensity and multivariable methods. (Although aprotinin is a serine protease inhibitor, here we use the term antifibrinolytic therapy to include all three agents.)** ***Results:*** **In propensity-adjusted, multivariable logistic regression (C-index, 0.72), use of aprotinin was associated with a doubling in the risk of renal failure requiring dialysis among patients undergoing complex coronary-artery surgery (odds ratio, 2.59; 95 percent confidence interval, 1.36 to 4.95) or primary surgery (odds ratio, 2.34; 95 percent confidence interval, 1.27 to 4.31). Similarly, use of aprotinin in the latter group was associated with a 55 percent increase in the risk of myocardial infarction or heart failure ($P<0.001$) and a 181 percent increase in the risk of stroke or encephalopathy ($P=0.001$). Neither aminocaproic acid nor tranexamic acid was associated with an increased risk of renal, cardiac, or cerebral events. Adjustment according to propensity score for the use of any one of the three agents as compared with no agent yielded nearly identical findings. All the agents reduced blood loss.** ***Conclusions:*** **The association between aprotinin and serious end-organ damage indicates that continued use is not prudent. In contrast, the less expensive generic medications aminocaproic acid and tranexamic acid are safe alternatives. (N Engl J Med 2006;354:353-365); http://content.nejm.org/cgi/content/abstract/354/4/353**

COMMENTS

Intraoperative hyperfibrinolysis contributes to bleeding during orthotopic liver transplantation. Aprotinin, a serine protease inhibitor and an antifibrinolytic drug, has been used with increasing frequency in liver transplantation since a report by Neuhaus in 1989.[1] This topic has been extensively covered; a representative sampling of papers is found in *Liver Transplantation*.[2-6]

Aprotinin has been shown to be effective in decreasing blood loss after liver transplantation, but complications from the use of aprotinin have been reported. Extensive hyperacute venous and arterial intravascular thrombosis with intraoperative thromboemboli have been encountered,[2] although other authors have reported that aprotinin does not have a prothrombic effect.[5] Another review in the field of liver transplantation concluded that aprotinin reduced blood transfusion requirements in adults following orthotopic liver transplantation without increasing thrombotic complications.[7]

This present paper by Mangano et al. from the Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation describes a large study finding that the use of aprotinin in cardiac surgery was associated with double the risk of renal failure requiring dialysis. The study also evaluated aminocaproic acid and tranexamic acid, neither of which was associated with an increase in renal failure. All 3 agents were shown to equally reduce blood loss. The authors pointed out that prior studies using aprotinin were limited in their power to assess the relatively infrequent but serious clinical complications stemming from the use of antifibrinolytic agents. The Mangano study is unique in that it is prospective, international, and multi-institutional, with sufficient power (greater than 800 patients for each group) to address the safety of aprotinin. With >7,500 data entries recorded per patient, the investigators concluded that the use of aprotinin in cardiac surgical patients is associated with an increased risk of death, cardiac events, cerebrovascular events, and renal failure. The incidence of renal failure was 5.5% in patients receiving aprotinin, compared to 1.8% in the control patients and the patients receiving aminocaproic acid and tranexamic acid. The odds ratio of developing renal failure for patients who received aprotinin was 1.89 (95% confidence interval, 1.01 to 3.55, $P = 0.04$), compared to the controls and the patients receiving aminocaproic acid and tranexamic acid.

A prior report by Molenaar et al. has evaluated the influence of aprotinin on the development of renal failure in orthotopic liver transplant recipients.[7] These authors concluded that no higher incidence of postopera-

Abbreviation: DCs, dendritic cells.

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tive renal insufficiency occurred in the group receiving a high dose of aprotinin than in the group receiving a regular dose of aprotinin or the group receiving a placebo. The sample size of the 3 groups together totaled 93 patients. But was this study sufficiently powered to address the safety issue of aprotinin? If the incidence of renal failure were the same in orthotopic liver transplant patients as in patients undergoing cardiac revascularization surgery, it would seem that to adequately power a study to form an accurate conclusion would require between 250 and 400 patients to detect a 4-5% difference in the incidence of renal failure. There have been no studies to date on antifibrinolytic therapy in the field of liver transplantation using a sample size of this magnitude.

In light of the evidence that other agents are effective in reducing blood loss and the increasing indications that renal failure is a major contributor to death following liver transplantation, plus the fact that aminocaproic acid and tranexamic acid are cheaper than aprotinin, maybe it's time that a large, multicenter study is conducted on using these antifibrolytic agents with liver transplantation. A study on tranexamic acid reported in *Liver Transplantation* has revealed that it appears as safe and just as effective as aprotinin[3]; however, this study used a sample size of only 127 patients.

In summary, aprotinin is being used extensively in liver transplantation. Caution should be undertaken with this drug, especially since other cheaper agents are available that appear to be just as effective. To completely settle the merits and risks of aprotinin compared to other antifibrinolytic agents, a large, multicenter study needs to be performed that is sufficiently powered to evaluate the infrequent but serious complications of antifibrinolytic therapy.

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Steroid Use in Liver Transplantation: None, Perioperative, or Full Course

Effect of perioperative steroids on renal function after liver transplantation. *Turner S, Dhamarajah S, Bosomworth M, Bellamy MC, on behalf of Leeds Liver Transplant Group.* Anaesthesia 2006;61:253-259.

Abstract

Subclinical renal dysfunction is thought to occur as a systemic manifestation of ischaemia-reperfusion injury of other organs. Liver transplantation is associated with major ischaemia-reperfusion injury. Thirty-four patients undergoing elective liver transplantation were randomly allocated to receive either saline or 10 $mg.kg^{-1}$ methylprednisolone on induction of anaesthesia. Urine was taken for N-acetyl-β-D-glucosaminidase, creatinine and other markers of tubular function. Serum chemistry was measured for 7 days. Creatinine concentration increased in the saline group but not in the methylprednisolone group ($p < 0.0001$), with the greatest difference on the third postoperative day (mean (SD) 164.8 (135.8) $\mu mol.l^{-1}$ *vs* 88.5 (39.4) $\mu mol.l^{-1}$, respectively). Similar changes were seen in postoperative alanine transferase (865 (739) $U.l^{-1}$ *vs* 517 (608) $U.l^{-1}$, respectively; $p < 0.0001$) on the second postoperative day. Both groups exhibited increases in markers of renal tubular dysfunction and of glomerular permeability. Patients in the saline group sustained more adverse events (8/17 (47%) *vs* 2/17 (12%); $p = 0.02$). The data confirm increased proximal tubular lysosomal turnover, consistent with an increased tubular protein load, following liver transplantation, and suggest that methylprednisolone protects against renal and hepatic dysfunction. (*Anaesthesia 2006;61:253-259.*)

COMMENTS

Administration of a full course of corticosteroids for immunosuppression following liver transplantation has decreased in recent years because of the side effects of steroids, including early recurrence of hepatitis C and impairment of wound healing. There are also unfavorable metabolic consequences of long-term steroid use. Transplant centers are tending toward omitting steroids altogether from their liver transplant immunosuppression protocols when possible.[1] Yet, pretreatment with steroids has been shown beneficial.[2] Does it follow that steroids should be given in the perioperative period for liver transplantation? A study by Kumar et al. showed that steroid therapy given only during the perioperative period is safe and beneficial in kidney transplant recipients.[3]

Turner et al. studied 34 patients receiving liver transplants for the first time. The patients were randomized to receive either saline or methylprednisolone (at 10 mg/kg) on induction of anesthesia. Venovenous bypass was used in all patients, and all patients received dopamine at 2 μg/kg/minute during the perioperative period. The primary outcome variable was serum creatinine, with serum alanine aminotransferase and ad-

verse events (renal failure, graft failure, and death) as secondary outcomes. (This study was reported to have an 80% power to detect a 50% difference between groups at the 5% significance level.) Serum creatinine concentration over the first postoperative week became significantly elevated only in the saline group, peaking on the third postoperative day. Serum alanine aminotransferase peaked at the second postoperative day in both groups, but the elevation in the saline group was significantly greater than in the methylprednisolone group. Adverse events were more frequent in the saline group: 8/17 (47%) compared to 2/17 (12%) in the methylprednisolone group ($P = 0.02$).

A recent report on acute renal failure following liver transplantation with induction therapy used multivariate analysis to reveal an association between acute renal failure and the time to aspartate aminotransferase peak (>20 hours) (odds ratio, 6.35 [1.2-33.6], $P = 0.029$).[4] This suggests that preventing ischemic reperfusion injury to the liver may result in improved renal function. Thus, the improved renal function seen by Turner et al. may be due to the smaller amount of liver damage from ischemic reperfusion injury.

In a recent study by Lladó et al. using no steroids in liver transplantation compared to a full course of steroids in patients receiving basiliximab or cyclosporine, with or without mycophenolate mofetil, there was no difference in the rate or type of rejection, no difference in patient or graft survival, and no difference in overall infections or recurrence of hepatitis C.[1] Metabolic effects of de novo diabetes mellitus were higher in the steroid group. No difference among the groups in the risk of either immediate or long-term renal deficiency was found.[1]

Another factor to consider regarding steroids is their possible influence in avoiding adrenal failure in liver transplant patients. As reviewed in "Liver Transplantation Worldwide" earlier this year,[5] the former routine pairing of steroids with immunosuppressants may have had a role in preventing adrenal insufficiency in many liver transplant recipients. If this turns out to have been the case, then perioperative use of steroids might be recommended for this reason alone.

Eventually, a larger study with increased statistical power needs to be conducted to verify if there are indeed benefits to using steroids in the preoperative period for liver transplant recipients. It appears that a full course of steroids does create increased metabolic complications following liver transplantation, and, conversely, that limiting steroids has no effect on the rejection rate or patient and graft survival. A short, intermediate course may be quite acceptable for preventing acute inflammatory events during the perioperative period. The perioperative course may therefore be the best course to benefit many patients.

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A New Reason for Intraoperative Blood Flow Measurement: Improving Liver Allograft Function

Intraoperative blood flow measurements and liver allograft function: preliminary results. *Gontarczyk GW, Lagiewska B, Pacholczyk M, Trzebicki J, Jureczko L, Kolacz M, et al.* Transplant Proc 2006;38: 234-236.

Abstract

Introduction: **Our previous studies showed a correlation of intraoperative renal allograft blood flow and immediate functions. A similar relation is not well established for liver transplantation. The aim of this study was to assess the relation between hepatic blood flow on revascularization and immediate liver graft function (IF).** ***Methods:*** **Studies evaluating arterial and portal flow in newly transplanted livers were started in May 2004. Total hepatic artery and portal vein blood flow were assessed in 15 liver transplant recipients. Parenchymal flow was also recorded. Measurements were taken at 30 and 120 minutes after simultaneous arterial/portal reperfusion. Flow results were correlated with IF.** ***Results:*** **Mean arterial blood flow (ABF) was 16.3 mL/min/100 g in both measurements. Portal flow was reduced from 168 to 127 mL/min/100 g from the first to the second measurement. Mean parenchymal flow (PF) did not alter over time (29.1 and 30.4 mL/min/100 g, respectively). Among recorded flow results we observed a significant correlation between PF with IF measured as: bile volume ($R = 0.36$ to 0.62; $P < .05$), serum AST ($R = -0.4$ to -0.68; $P < .05$), and ALT level ($R = -0.2$ to -0.71; $P < .05$), bilirubin level as well as INR ($R = -0.39$ to -0.61; $P < .05$) assayed daily for 14 days. Similar observations were made between ABF and INR, hiatal parenchymal flow, and ALT as well as INR.** ***Conclusions:*** **These preliminary results suggest hepatic blood flow may be a reliable predictor of graft viability and function. Of the variables measured, portal blood flow seems to be the most valuable indicator of liver function. (*Transplant Proc 2006;38:234-236.*)**

COMMENTS

In 1988, intraoperative blood flow volume measurement was found to be reproducible and stable for assessing hepatic circulation in normal anesthetized patients.[1] Normal hepatic arterial flow was measured as 267.3 ± 21.2 mL/min, and portal venous flow as 746.4 ± 41.3 mL/min. Temporary occlusion of the portal vein resulted in a significant increase in the hepatic arterial flow (23.6 ± 4.3 mL/min), whereas temporary occlusion of the hepatic artery did not significantly alter the portal venous flow.[1]

Since then, particular uses for intraoperative blood flow volume measurement applicable to liver transplantation have been found. In 1992, Henderson et al. showed that in a liver transplant patient, the intraoperative mean portal flow was 1,808 ± 929 mL/min, markedly higher than in normal patients, and the hepatic artery flow was reduced.[2] When the portal flow was reduced by 50%, the hepatic artery flow increased from 322 ± 228 to 419 ± 27 mL/min, indicating an intact hepatic arterial buffer response.[2] In 1997 Rasmussen et al., after using an intraoperative flow meter to identify 6 patients out of 70 having vascular abnormalities, declared that intraoperative measurement was a necessity in liver transplantation.[3] Today, some centers use intraoperative flow meters in all liver patients, and other programs have never used them.

In 2002, Lin et al. reported that routine use of intraoperative flow measurements could predict subsequent hepatic artery thrombosis. In 198 patients studied by Lin, there were 13 (6.6%) that developed hepatic artery thrombosis. The mean hepatic artery flow in the patients who developed hepatic artery thrombosis was 262 mL/min, significantly lower than the flow of 436 mL/min in those that did not develop hepatic artery thrombosis ($P = 0.0036$). The risk of hepatic artery thrombosis was found to increase by a factor of 6 when the hepatic artery flow rate was less than 200 mL/min.[4] However, there was extensive overlap of the intraoperative hepatic artery flow rates between those that developed hepatic artery thrombosis and those that did not.[4] Molmenti et al. in 2002 reported in *Liver Transplantation* that patients developing hepatic artery strictures had lower intraoperative hepatic flow volumes, both arterial and portal flow, than those who did not develop strictures.[5] Others have shown the usefulness of intraoperative flow measurements for assessing arterial and venous functioning in split liver and living donor livers.[6,7]

This present paper by Gontarczyk et al., instead of determining anatomical abnormalities from the flow measurements, assessed the relationship between perioperative hepatic blood flow and immediate liver graft function. These investigators converted both the arterial flow and portal flow to flow per hundred grams of liver tissue. Significant correlation was found between hepatic blood flow and immediate function in terms of bile volume (ratio = 0.36 + 0.62; $P < 0.05$) and serum alanine aminotransferase ($R = -0.2$ to -0.71; $P < 0.05$). Overall, the most reliable predictor of early graft function was the portal blood flow. As the authors point out, their number of patients was small, and the further evaluation on the immediate graft function using intraoperative flow meter is needed.

The likelihood that this latest study will influence those programs not using intraoperative flows to start is probably not high, since the flow measurement does not indicate what should be done to improve immediate graft function. Programs already using intraoperative flow measurement now have an additional purpose for doing so.

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Another Dendritic Cell Enters the Transplant Story

Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. *Ochando JC, Homma C, Yang Y, Hidalgo A, Garin A, Tacke F, et al.* Nat Immunol 2006 Apr 23;[Epub ahead of print].

Abstract

The induction of alloantigen-specific unresponsiveness remains an elusive goal in organ transplantation. Here we identify plasmacytoid dendritic cells (pDCs) as phagocytic antigen-presenting cells essential for tolerance to vascularized cardiac allografts. Tolerizing pDCs acquired alloantigen in the allograft and then moved through the blood to home to peripheral lymph nodes. In the lymph node, alloantigen-presenting pDCs induced the generation of $CCR4^+CD4^+CD25^+Foxp3^+$ regulatory T cells (T_{reg} cells). Depletion of pDCs or prevention of pDC lymph node homing inhibited peripheral

T_{reg} cell development and tolerance induction, whereas adoptive transfer of tolerized pDCs induced T_{reg} cell development and prolonged graft survival. Thus, alloantigen-presenting pDCs home to the lymph nodes in tolerogenic conditions, where they mediate alloantigen-specific T_{reg} cell development and allograft tolerance. (*Nat Immunol 2006 Apr 23;[Epub ahead of print]*)

COMMENTS

How can tolerance be induced to foreign transplant antigens? The answer to this question continues to elude researchers in clinical transplantation. Dendritic cells (DCs) have been emerging with a major role in the unfolding story of immunity to antigens. A recent paper by Morelli and Thomson discusses the presentation of foreign antigens by immature DCs to T cells as a leading theory for the induction of tolerance.[1]

DCs are known to exist in various subtypes, and the precise subpopulations have not always been clearly identified. Two models for the generation of functionally distinct DC subtypes have been reviewed by Shortman and Liu.[2] The functional plasticity model proposes that all DCs belong to a single hematopoietic lineage, the different subtypes of DCs generated by local environmental influences on a relatively mature but plastic end-product cell.[2] The specialized lineage model proposes that the different subtypes of DCs derive from early divergences in the developmental pathway, producing several distinct hematopoietic sublineages.[2] These divergences lead to Langerhan DCs, interstitial DCs, DC1 or myeloid DCs, and DC2 or plasmacytoid DCs.[2]

In studying precursors for the DC subtypes, particular functional bases and surface markers are found to be associated with each subtype. Precursors to DC1 cells express Toll-like receptors 1, 2, 4, 5 and 8, and precursors to DC2 cells express Toll-like receptors 7 and 9. Precursors to DC1 produce tumor-necrosis factor-α and interleukin 6 to stimuli, where precursors to DC2 produce interferon-α and interferon-β when stimulated. Precursors to DC1 express the surface markers CD11c, CD11b, CD14, and CD45RO. In contrast, precursors to DC2 cells do not express CD11c or CD11b, but express CD45RA.[2]

In this present paper, Ochando et al. have identified plasmacytoid DCs as alloantigen-presenting cells that mediate tolerance to vascularized allografts. The authors explain how plasmacytoid DCs take up foreign antigen by phagocytosis, home to the peripheral lymph nodes (not to the spleen) and induce the generation of regulatory T cells in the peripheral lymph nodes, producing tolerance. In this tolerogenic regimen of donor-specific transfusion, plus the monoclonal antibody to CD40L, plasmacytoid DCs are seen to be influential in the induction of tolerance.

So in the novel that is the quest for transplant tolerance, a new protagonist has entered the story in the form of the plasmacytoid DC. Among the confusing collection of DC subtypes, the plasmacytoid DC, until now rarely mentioned, is becoming prominent. The plasmacytoid DCs are seen to have a function similar to immature DCs in taking up antigen and presenting it to T cells. In the model of Ochando et al., plasmacytoid DCs induce tolerance, but the authors point out that additional models employing plasmacytoid DCs need to be studied. We look forward to the next chapter of this story.

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James D. Perkins, MD, Special Editor
University of Washington Medical Center
Seattle, WA