Aprotinin use in healthy ASA 1 and 2 children undergoing Posterior Spinal Arthrodesis with Harrington rods for Idiopathic Scoliosis did not result in Renal Insufficiency or Failure…A Retrospective Review

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INTRODUCTION:
Posterior spinal arthrodesis for idiopathic scoliosis, which is associated with large amounts of blood loss that lead to increased morbidity and mortality, often requires blood transfusions. Transfusions increase the risk of transmission of infectious agents (such as human immunodeficiency virus, cytomegalovirus, hepatitis-C virus, hepatitis-B virus, and others) from the infected donor blood as well as the risk of postoperative infections through the suppression of the immune system (1-3). Hemolytic reactions induced by transfusion may be fatal. Therefore, it is crucial to minimize both bleeding and the amount of transfused blood. In 1993, the United States Food and Drug Administration approved the use of aprotinin (serine protease inhibitor) in coronary artery bypass surgery (4). This provoked an interest in the potential use of this drug in other types of surgery. Recently aprotinin has been linked to post-operative renal insufficiency and serious end-organ damage in patients who underwent surgical treatment for ST-elevation myocardial infarction (5). Several clinical trials are being carried out to investigate the role of aprotinin in orthopedic procedures. The purpose of this retrospective study was to determine if aprotinin use was associated with renal dysfunction or failure in patients who underwent posterior spinal arthrodesis and Harrington rod placement for idiopathic scoliosis.

Methods
After Institutional Review Board approval, medical records for 27 children (age 12 to 19 years) who underwent posterior spinal arthrodesis for idiopathic scoliosis between February 2000 to May 2002 were reviewed. Aprotinin was administered to all of these patients to decrease the blood loss. A physician’s note diagnosing the event in the Critical Care Unit progress note, medical unit progress note or on the operating room records was considered a positive finding of an adverse event.
### Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
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<tbody>
<tr>
<td>Age in Month</td>
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<tr>
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<tr>
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<tr>
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<tr>
<td>Duration in minutes</td>
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<td>37.068</td>
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<tr>
<td>Age in years</td>
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<td>12</td>
<td>19</td>
<td>14.65</td>
<td>1.747</td>
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</tbody>
</table>

**RESULTS:**
There was no documented evidence of renal insufficiency or failure in the patient population surveyed for this review.

**DISCUSSION:**
Aprotinin is a naturally occurring serine protease inhibitor that has been shown to reduce blood loss in cardiothoracic and liver surgery (6-10). Aprotinin is nonspecific and inhibits several proteases, such as trypsin, chymotrypsin, cathepsin, elastase, kallikrein, plasmin, protein C, thrombin, and urokinase. Consequently, it has a variety of effects on several organ systems but the mechanism by which it reduces blood loss is not fully understood. It has been postulated that aprotinin reduces bleeding through its effects on fibrinolytic pathways, coagulation pathways, the inflammatory response, and platelet function. It inhibits fibrinolysis, turnover of coagulation factors, and inflammatory cytokine release. In addition, by preserving the adhesive glycoproteins on the platelet membrane, it promotes platelet adhesion (11-15). Taken together, these effects contribute to the pro-hemostatic function of aprotinin. The causes of postoperative renal failure are often multifactorial. Contributing factors are anemia, nephrotoxic antibiotics, decreased renal blood flow and perfusion pressure, and low oxygen saturation in the glomerulus (16)

Aprotinin use in cardiac surgery has been associated with mild elevations in serum creatinine but generally has not been associated with an increase in the risk of acute renal failure. In the presence of angiotensin converting enzyme (ACE) inhibitors, however, aprotinin may contribute to significant reductions in glomerular perfusion pressure (17)

Renal dysfunction following cardiopulmonary bypass (CPB) is well recognized. The extent of perioperative renal impairment ranges from subclinical injury to established renal failure requiring dialysis. Its incidence varies considerably, depending on the definition and criteria used in the different studies. Acute renal failure (ARF) affects 1-5% of patients and remains a major cause of morbidity and mortality. Advanced age and other co-morbidities, including diabetes mellitus and impaired left ventricular function are recognized predisposing factors. The pathophysiology is multifactorial and is thought related to the systemic inflammatory response and renal hypoperfusion secondary to extracorporeal circulation. Non-pulsatile flow during CPB is thought to be an important etiological factor, resulting in renal vasoconstriction and ischemic renal injury. A theoretical reduction in the
incidence and severity of postoperative renal impairment has been proposed by advocating the use of pulsatile flow during CPB, or eliminating CPB, especially in high-risk patients. The current evidence, however, is conflicting. Several large observational studies, including a large proportion of high-risk patients, have demonstrated a significant reduction in the frequency of renal failure in patients undergoing off-pump surgery. As older, sicker patients increasingly constitute the cardiac surgical population, the incidence of postoperative renal injury is likely to increase (18,19).

In their study Kher et al (20) postulated that aprotinin significantly decreased the rise in serum creatinine and apoptosis caused by ischemia-reperfusion. It significantly reduced interleukin 1 and 6 messenger RNA production and showed a trend toward reducing tumor necrosis factor messenger RNA production after ischemia. Aprotinin also significantly reduced caspase 8 activation and showed a trend toward decreasing p38 mitogen-activated protein kinase activation after 1 hour of reperfusion. Their results suggest that aprotinin provides protection from renal ischemia-reperfusion injury. They also suggest that aprotinin may do so by affecting apoptotic signaling and inflammatory cytokine production and is a potential therapeutic measure in clinical situations where renal ischemia-reperfusion injury can be anticipated, provided adequate heparinization is possible. In another study Godfrey et al (21) hypothesized aprotinin is helpful in protecting kidneys from the harmful effects of ischemia.

Because of the smaller number of patients in our review, we cannot conclude that aprotinin is not associated with renal insufficiency in healthy patients undergoing posterior spinal arthrodesis and Harrington rods placements for idiopathic scoliosis. Further review is underway and more focused prospective studies with larger number of patients are needed to implicate aprotonin in causing renal insufficiency post-operatively in healthy patients.

REFERENCES: