Aprotinin use in cardiac surgery, 2006

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Cardiac surgeons face many challenges with a changing patient population. Bleeding is a major risk for death during cardiac surgery, and the use of blood products is a predictor of short-term morbidity (e.g. renal failure) and long-term mortality and morbidity [1, 2]. Many strategies have been have been explored to help reverse the effects of cardiopulmonary bypass – its effects on clotting factors and platelets – and of antiplatelet agents. Aprotinin was first reported to reduce blood loss and the need for transfusion in not only coronary bypass surgery (CABG) but also high-risk cases [3].

Considerable publicity surrounded the recent publication in the *New England Journal of Medicine* of an observational study entitled "The risk associated with aprotinin in cardiac surgery" authored by Mangano and colleagues [4]. This was followed some time later by limited correspondence [5-7]. Somewhat surprisingly, there was a wealth of interest shown by the lay press and law firms in many countries, no doubt engendered by the venomous press release surrounding the article's publication (http://www.iref.org/ accessed July 1, 2006).

The report was based on data collected from the McSpi database, with information being collected on some 7500 data elements from the period 1996-2000 from 5436 patients. The study aims were to assess the safety of 'the use of either serine protease inhibitors or lysine analogues in patients with acute coronary syndromes presenting for coronary artery surgery (sic)'. As a guide to how the study was conducted, the authors have provided a CONSORT flow diagram. (The CONSORT Group provides guidelines and a checklist for reporting randomised controlled trials [8].) From the original 5436 patients, some 4374 were analysed. Exclusions from the analysis included incomplete data, did not undergo cardiopulmonary bypass or did not undergo treatment. A further 691 were unable to be included due to use of multiple antifibrinolytic agents, no validation of drug dose or type or received an inadequate dose of antifibrinolytic agent. The final comparison examined the use of the lysine analogues epsilon amino caproic acid and tranexamic acid and the serine protease inhibitor aprotinin compared to a 'control' group who received no drug. Each of these drugs has been utilised as part of blood conservation programmes for over 20 years where they are available. All have been subjected to numerous studies but aprotinin is the only agent licensed in many countries for use in cardiac surgery for reduction of blood transfusion.

Allocation of treatment was not controlled by the study protocol, which used a recruitment method favouring low volume units. The control group received no therapy. Complex statistics – multi-variable logistic regression and propensity scoring – were employed to control for the lack of randomisation. The authors concluded, based on their data, that aprotinin was associated with serious end organ damage, namely increased risk of renal failure, requiring dialysis in both complex and primary surgery, in primary but not complex surgery an increase risk of myocardial infarction or heart failure, stroke or encephalopathy. Neither of the lysine analogues was associated with an increased risk of these events.

Readers will ask why this report differs from hundreds of previously published articles, including several meta-analyses, and why there is little comment about these divergent results. Levi showed in 1999 a reduction in mortality [9] and both Henry in a Cochrane Review [10] and Sedrakyan [11] (CABG only) demonstrated reductions in stroke, bleeding and reoperations for bleeding. None of these analyses showed increases in renal impairment or myocardial infarction. All showed reductions in return to theatre for bleeding. The Cochrane review noted the lack of safety data on EACA and TA [10] and further commented that none of these drugs appeared to have any major side effects. No comment about the multitude of studies with differing views is made by the authors. Sedrakyan has offered further comments re some possible explanations of this difference [12].

In examining this report, many inconsistencies are evident. Not all drugs were available in all countries during the time frame of the data collection. Not all drugs were licensed for the use for which they had been administered. What was the basis for use of each of the drugs? It is clear from

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the tables that there were large variations in the patient characteristics (co-variates) of each group. Patients in the treated groups had higher occurrences of hepatic dysfunction, renal dysfunction, pulmonary disease and diabetes. In an earlier report from the same group, significant inter-country differences were noted. This does not appear to have been included in the analysis [13]. Some 691 patients were excluded from the analysis for inadequate dosing, multiple drugs or no validation of drug type or dose. A safety study is based on an intention to treat policy and as such these would be included. An earlier report indicated that the mortality in this excluded subset was 7.2% (50/691 deaths) as compared with 2.6% in this study [14]. The endpoints are composite, making further analysis difficult. An intention to treat policy would include most of these.

Mangano used propensity scores to match each group. This method relies on collected or observed co-variates to produce a score which can be included in an analysis. It is considered, when done appropriately, to be a useful alternative to a randomised controlled trial, especially when that may be difficult or expensive to perform. However, any statistical adjustment in an observational study relies on a lack of hidden bias. Failure to account for treatment selection bias can result in biased estimation of the true treatment effect. This may be confounded by provider and subject preferences. The subjects in each group may differ systematically, being sicker or healthier. The limitations of this method can be seen in this study, as a number of confounders are evident.

Transfusion practices vary enormously from centre to centre. Despite numerous consensus statements and guidelines and despite a lack of evidence supporting transfusion, patients continue to be exposed to the significant risks of blood replacement. Blood products remain a scarce resource the world over. And in many countries about 20% of blood is used in cardiac surgery. In many centres over 50% of patients receive no transfusion. The Australian National Database Report for 2004-2005 shows that 42.1% of patients received red cell transfusion [15]. Other data indicate that 10-20% of patients receive about 80% of blood products. A high risk for transfusion group can be identified and therapies to reduce their exposure can be more appropriately delivered. These will likely include advanced age, preoperative anaemia, small body size (red cell mass) non-CABG, urgent operations, preoperative antithrombotic agents, acquired or congenital clotting disorders and multiple comorbidities. Aprotinin has been shown to be highly effective at transfusion reduction [11]. No data on transfusions are given in this manuscript apart from a comment re fresh frozen plasma and red cell transfusion increasing the risk of the renal composite outcome.

Renal dysfunction after cardiac surgery is a constant concern. The need for dialysis increases mortality significantly. In a previous publication from the same group, they indicated a rate of 7.7% for renal dysfunction, with 1.4% overall requiring dialysis [16]. This study reports a rate of 8% for the composite renal outcome in the aprotinin group. Why there is such a lower rate in the no drug group is not clear. The STS has reported a rate of 3.53% in their study of over 500,000 patients for new dialysis [17]. No comment was made on the lack of association of aprotinin with renal dysfunction from the same group reporting on more than 800 patients having aortic surgery with deep hypothermic circulatory arrest [18].

The recommendations of Mangano cannot be sustained by this publication. There are no data on transfusion effects of each of the drugs. No authority has recommended withdrawal of aprotinin. The cardiac surgical team should weigh up the potential harmful effects of withholding aprotinin in high-risk patients as part of a planned strategy for blood conservation, with abundant evidence of safety data against a single observational study with significantly flawed methodology. The results of studies such as the BART study being conducted in Canada are eagerly awaited as these are powered to look at relatively infrequent events such as renal dialysis and myocardial infarction in a high transfusion risk group.

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