Author's response to reviews

Title: The impact of administration of tranexamic acid in reducing the use of red blood cells and other blood products in cardiac surgery.

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Author's response to reviews: see over
Papworth Hospital, March 23, 2006.

We are pleased that both reviewers agree that this manuscript is an article of importance in its field. We thank both reviewers for their useful comments and are herewith answering them and describing how the manuscript has been modified when appropriate.

We definitely recognise the importance of Dr Mangano publication, but would like to emphasize that our manuscript was submitted to BioMedcentral before this paper was published in the NEJM. While we recognise the importance of this paper, to incorporate it in our introduction and discussion warrants a total rewriting of our manuscript, as well as the addition of new analysis as suggested by Dr Cassidi. We feel however that our manuscript in its present form delivers the intended message and that the readers will certainly be able to amalgamate the information we present with the ones presented by Dr Mangano, and many others papers and commentaries published in the last few weeks.

**Answer to Dr M Ereth comments.**

**Major compulsory revisions:**

1. We understand that Dr Ereth wishes us to delineate the impact of CPB duration on the results. This information is already incorporated in the manuscript as we report that “This analysis also showed that the odds of being returned to theatre were higher if the patients were male, were older, had a lower BMI, had a higher EuroSCORE, had a longer bypass time, had an emergency operation or had a combined operation (Table 5).” This information is also reported in table 5. We also report that bypass time was incorporated in the final multivariate model for predicting red blood cell transfusion, predicting return to theatre and length of stay in theatre.

Further detailed information added to the manuscript would lengthen it considerably, as we would then logically have to incorporate more details in relation to all the other co-variates linked to a higher rate of transfusion or return for bleeding (i.e. age, BMI, Euroscore, priority, surgery type, combined surgery, surgeon, sex, etc.).

For information, we are herewith detailing the duration of CPB (in minutes) for all patients, and patients operated for CABG surgery only:

<table>
<thead>
<tr>
<th></th>
<th>All – with Tranexamic Acid</th>
<th>All without tranexamic Acid</th>
<th>CABG with TXA</th>
<th>CABG without TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean</strong></td>
<td>76</td>
<td>77</td>
<td>71</td>
<td>70</td>
</tr>
<tr>
<td><strong>Median</strong></td>
<td>72</td>
<td>73</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td><strong>Percentile 25</strong></td>
<td>59</td>
<td>59</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td><strong>Percentile 75</strong></td>
<td>89</td>
<td>88</td>
<td>82</td>
<td>82</td>
</tr>
</tbody>
</table>
We also refer to CPB time in the last paragraph of the paper stating that the observed difference in CPB duration was clinically insignificant.

2. As requested, we have clarified the use of cryoprecipitate in the manuscript, by adding in the method section - under outcome of interest – point c: Whether or not a patient received any transfusions (including RBC, FFP, platelets and cryoprecipitate).

A total of 27 patients received cryoprecipitate, out of 4191 patients studied. In the group receiving tranexamic acid, 0.54% received a transfusion of cryoprecipitate; while cryoprecipitate was transfused in 1.08% of the patients not given tranexamic acid. All patients receiving cryoprecipitate were also administered FFPs.

3. As explained above, Dr Mangano paper was published after our submission was posted.

4. We agree that this is indeed a legitimate criticism, and have therefore commented further in our discussion, recognising this important point. “…A legitimate criticism of this paper could be that patients returned to theatre for an obvious surgical reason should have been excluded from the analysis. We elected not to do so as to record accurately and without bias the cause of return is difficult and likely to be inaccurate due to the inherent bias of the operator in the absence of a neutral adjudicator. It may also be that patients with more intra-operative blood loss are more likely to return later as the surgeon will have had greater difficulties in ensuring correct haemostasis…”

Minor essential revisions:

We could not eliminate bias in patients selected for TXA therapy, as this was an observational study. It is correct to assume that, in light of current published evidence, better care currently include the use of TXA and that not using it is incorrect…. So TXA may simply be a surrogate marker of those professionals delivering a better standard of care overall. We have modified the last paragraph to clarify this further:

While this observational study lacks characteristics inherent to a well conducted randomised, double blinded, placebo controlled trial, it adds to the wealth of knowledge already available by studying the effect of a therapy in a large group of patients subjected to a normal clinical pathway. We used multivariate logistic regression in order to minimise a selection bias on treatment allocation….

Answer to Dr Valter Cassidi comments.

General considerations:

1. As discussed above, our study was submitted before the Mangano manuscript was published, hence the reasons why we are not referring to it. We considered your suggestion to incorporate this paper in our introduction and discussion, but concluded
that this would require to rewrite entirely the introduction and discussion, without affecting the results and message we intended to deliver.

2. We considered a propensity analysis (before the Mangano publication) but after discussion with our professional statisticians, elected not to follow that route. The number of co-variates required to conduct such an analysis is well above what was collected in our 4191 patients, and the time and expense well above the means of our small unit.

3. We elected to concentrate on exposure to transfusion and amount transfused, as these are the important clinical endpoints. Reporting the amount of postoperative blood loss would in our opinion not bring any more valuable information to the paper, and may distract a reader from the fact that what matters for the patient and for health-economics are (1) return to theatre and (2) transfusion. For the reviewer benefit, we are herewith listing the blood loss (uncorrected for weight) for the studied population:

<table>
<thead>
<tr>
<th></th>
<th>All with TXA</th>
<th>All without TXA</th>
<th>Without return and TXA</th>
<th>Without return and no TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>621</td>
<td>819</td>
<td>531</td>
<td>559</td>
</tr>
<tr>
<td>Median</td>
<td>450</td>
<td>575</td>
<td>425</td>
<td>550</td>
</tr>
<tr>
<td>P25</td>
<td>325</td>
<td>375</td>
<td>325</td>
<td>375</td>
</tr>
<tr>
<td>P75</td>
<td>675</td>
<td>875</td>
<td>625</td>
<td>775</td>
</tr>
</tbody>
</table>

4. We unfortunately did not collect any information on perioperative MI and/or acute renal failure – and don’t have accurate data in our database at present.

Major compulsory revisions:

1. Dr Cassidi points out a major shortcoming in the institutional guidelines used at the time of the data collection. To avoid any reader to be puzzled, and as our guidelines were not more precise, we have changed the sentence to:

For example, our institute guidelines state that we should administer tranexamic acid at a dose of 2g intravenously for any cardiac operation that involves use of cardiopulmonary bypass and where aprotinin is not administered.

2. We have renumbered the references as indicated.

3. We agree that aspirin is generally thought to be associated with increased bleeding, but we were not surprised that aspirin has in fact no effect on postoperative transfusion. Please refer to “Aspirin and Mortality from Coronary Bypass Surgery” Mangano et al; NEJM 2002; 347: 1309-1317 – or “Effect of aspirin in coronary artery bypass grafting” Vuylsteke et al, J Cardiothorac Vasc Anesth 1997; 11: 831-4 – for previous data published from our institution. To discuss aspirin and bleeding would prolong the discussion even further, despite this not being our primary aim.
4. We agree that a poor adherence by some to the institutional protocol may explain why surgeons and anaesthetists impact on the transfusion rate. We are reporting compliance of anaesthetists in table 1 and chose not to discuss extensively the reasons behind the lack of compliance – as the author is probably well aware, this would fill up many thesis!

5. The fact that the anaesthetist is not ‘significant’ (sic) in the multivariate model is likely to be due to the fact that operator (surgeon) ability is more likely to account for a good operation. It could also be a statistical trick, hence our detailed stepwise statistical analysis.

6. We agree that we could rewrite the whole discussion in light of the paper published by Mangano. It may also be important to highlight the papers published since the reviewers posted his comments… We believe that the main message of the paper, as well as the ensuing discussion, is still accurate without referring to Mangano work.

7. We have added a reference to the paper of Dowd et al in our discussion, as it is indeed a landmark paper in relation to attempts to identify the best dose of TXA. We are however unable to discuss further TXA pharmacokinetic as this would lengthen even more our discussion, and was not the primary aim of our study.

8. As explained in the introduction, the 20% of patients did not receive TXA for no obvious reason, except that the operator either forgot, elected or neglected to administer it.

9. Reference list has been amended accordingly.

10. We have removed the p-value (NS) as it is indeed illogical to have one at that point.