Author’s response to reviews

Title: The COMT-polymorphism is not associated with the incidence of acute kidney injury after cardiac surgery - a prospective cohort study

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Author’s response to reviews:

Dear Prof. Dr. De Caestecker,

Thank you very much for the detailed assessment of our manuscript entitled, “The COMT-polymorphism is not associated with the incidence of acute kidney injury after cardiac surgery - a prospective cohort study.” and the helpful comments raised by the reviewers. We hope that we sufficiently addressed all reviewers’ comments and hope that the manuscript is now suitable for publication.

Here our point-by-point responses to the reviewers’ comments:

Reviewer N°1: Mark De Caestecker

1) We revised the following text passages:

Abstract paragraph 3:

We enrolled 150 patients between April and December 2014. No significant differences were found for demography, comorbidities, or operative strategy according to the underlying COMT genotype. AKI occurred in 35 patients (23.5%) of the total cohort, and no differences were evident between the COMT genotypes (20.5% Met/Met, 24.7% Val/Met, 25.0% Val/Val,
There were also no differences in the post-operative period, including ICU or in-hospital stay.

Methods page 7 lines 7-10:

“The primary endpoint was defined as the development of AKI within the first 48 hours after surgery according to the most recent recommendations by KDIGO [5] as increase in serum creatinine (SCr) ≥0.3 mg/dl within 48hrs or increase in SCr ≥1.5 times baseline or reduction of urine volume <0.5 ml/kg/h for at least 6 hrs.”

Discussion page 12 lines 5-21:

“Data on varying risk for AKI dependent on the COMT genotype is conflicting. Especially two recent publications are showing associations between COMT and AKI or renal damage respectively. In the early first work paper it has been shown that the Val/Val phenotype of the COMT enzyme is associated with AKI [4]. This was explained be a decreased catecholamine degradation in association with shock caused by the COMT polymorphism[4]. In a second more recent attempt the same group could not reproduce that association in a second cohort [7]. Instead they describe elevation of renal stress markers without a consecutive AKI. In a retrospective approach, another group could not show an association between COMT genotype and RIFLE-AKI after cardiac surgery [4, 6, 7].

While all papers used the RIFLE classification for AKI definition, we used the latest definition by the Kidney Disease Improving Global Outcome (KDIGO) published in 2012 [4-7]. The authors stated that the RIFLE classification might be more robust for AKI diagnosis after cardiac surgery, but latest papers show that the KDIGO definition with its strict 0.3ml/dl within 48hrs definition has an impact on short- and longterm outcome [18, 19, 26-30]. Even slight changes in serum creatinine are associated with al significant increase of early postoperative mortality [27]. Higher longterm mortality and rehospitalisation rates after cardiac surgery are associated with mild AKI [18, 26].”

2) We performed some additional analyses regarding cardiac dysfunction and did not find any meaningful and significant association of the COMT genotype, cardiac dysfunction and the occurrence of postoperative AKI.

<table>
<thead>
<tr>
<th></th>
<th>Met/Met</th>
<th>Val/Met</th>
<th>Val/Val</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal cardiac function</td>
<td>4/21 (26.3%)</td>
<td>12/50 (24.0%)</td>
<td>5/9 (55.6%)</td>
</tr>
<tr>
<td>Cardiac dysfunction</td>
<td>5/23 (21.7%)</td>
<td>6/23 (26.1%)</td>
<td>3/23 (13.0%)</td>
</tr>
</tbody>
</table>

Also in logistic regression analyses, cardiac dysfunction was not associated with the incidence of AKI neither in univariate (OR 0.7, 95% CI 0.33 – 1.51, p=0.4), nor in multivariate modelling (OR 0.70, 95% CI 0.31- 1.57, p=0.4) adjusting for COMT genotype and also including the interaction of COMT genotype and cardiac dysfunction. However, a potential clinically existent relation might be missed in our analyses due to limited statistical power.
Reviewer № 2: Kathleen Liu

1) and 2) all events of AKI were based on calculations using SCr (as according to KDIGO definitions). We did not use urine output to determine the occurrence of AKI, as these were recorded during clinical routine and thus frequently were not detailed enough to make precise estimations for the short timeframes (i.e., 6 and 12 hours).

3) We analysed the incidence of any AKI during hospital stay including the SCr rise within 5 days (Table 2). We did not observe any differences between the COMT genotypes regarding any AKI during hospital stay.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All patients</th>
<th>Met/Met (n=44)</th>
<th>Val/Met (n=73)</th>
<th>Val/Val (n=32)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI during hospital stay, n (%)</td>
<td>45 (30.2)</td>
<td>11 (25.0)</td>
<td>24 (32.9)</td>
<td>10 (31.3)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

4) Thank you for this remark and we apologize for that mistake. According to the comments of the reviewer 1 we rewrote that paragraph and changed the remaining mistake.

5) See 4

6) We rephrased the mentioned sentence:

"i.e. colloidal infusions have been avoided in the last years in exchange for crystalline solutions"

7) We corrected the sentence as well.

“AKI has been in focus of research in the recent years.”

Best Regards

Mehmet Oezkur