Author's response to reviews

Title: Biological efficacy of low versus medium dose aspirin after coronary surgery: results from a randomized trial [NCT00262275]

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Author's response to reviews: see over
Dear Sir,

Biological efficacy of low against medium dose aspirin regimen after coronary surgery: results from a randomized trial

Thank you for reviewing our aforementioned manuscript, the comments of each reviewer have been attended to as follows, and each page reference refers to the revised marked version of our manuscript.

Reviewer #1

Minor revisions

1. Were all patients consecutively assessed for eligibility in the study period (2002-2004)?

Yes, this is now stated on page 8 of our revised manuscript.

2. Please provide the platelet count in each group at baseline. If the platelet count was different, please comment on how this could have affected the results.

There were no significant differences in baseline platelet count in both groups: 229 (medium dose) versus 211 (low dose), P=0.23, this has now been added to table 1 of our revised manuscript.

3. Did you use buffered or unbuffered citrate within the collection tubes?

We have phoned the manufacturer, and are informed that the citrate monovettes we use do not contain buffered citrate. The solution is 0.106M trisodium citrate, pH 8.2. However, bearing in mind the buffering capacity of blood and that the anticoagulant is diluted 1/10, we would be certain that the final pH of the PRP will be the same as that of the blood and be well buffered.

4. Did you standardize the number of platelets in PRP before (e.g. at 250/nL) starting the aggregometry measures?
We did not standardise the platelet counts. However PRP platelet counts were checked to make sure they weren't outside of the stipulated ranges for accurate testing on the PAP-4 aggregometer (i.e not below 150 on the post-op morning).

5. I assume that all patients were awake at baseline of the study. Please comment on the rationale to exclude patients being still on the ventilator.

This was to ensure that all patients received 5 full days of antiplatelet medication, and clarified on page 6 of our revised manuscript.

6. Please report on the use of inotropes, nitrates and other vasoactive substances in the study patients, which may also have affected platelet function.

Unfortunately, we did not record the use of the above mentioned variables.

7. In terms of efficacy, clinical outcome data (although the reviewer acknowledges the low power for these endpoints) e.g. rate of myocardial infarction, proven graft occlusion would be extremely interesting to the reading community.

We have not performed this, simply because of the reason stated by the reviewer (low power) as the study was powered on a biological outcome (platelet aggregation).

8. Furthermore, did the dose of aspirin influence chest tube output?

The dose of aspirin would not have affected the chest drain output because aspirin is administered on the first postoperative morning when the chest tubes are removed.

9. This reviewer agrees with the conclusion that low dose aspirin was equally effective to inhibit platelet aggregation as medium dose aspirin. In regard of clinical efficacy, is a 36% or 37% reduction in aggregation worthwhile to be considered clinically effective?

Whilst the percentage aggregation seems modest, this represents the full aspirin effect after 5 days of therapy. The clinical efficacy has been proven by previous meta-analyses of randomised trials.\textsuperscript{1,2}

**Discretionary revisions**

1. Please report on the co-medication of the patients, e.g. unfractionated heparin, NSAID's, prostaglandins, theophyllin etc.

All patients were placed on low molecular weight heparin, and NSAIDs were used in 2 patients in the study (now stated on 6 of our revised manuscript). We did not record the use of prostaglandins or theophyllin.

**Reviewer #2**
Major Compulsory Revisions

1. In the present study clopidogrel therapy was initiated without a loading dose; this may explain the absence of an effect on platelet aggregation observed in the patients treated with clopidogrel; it is well known that without a loading dose it may take up to one week before an steady state of platelet inhibition by clopidogrel is obtained.

In the United Kingdom, a loading dose is only licensed for unstable angina and therefore we did not load the patients (to comply with product licensing). With regards to the normal time to effect, inhibition of platelet aggregation by clopidogrel occurs one hour post dose with a mean percentage inhibition of 48.1% by day 5.\(^3\) This has already been elaborated this in our previous work.\(^4\)

2. Platelet aggregation to ADP is more appropriate method for assessing the inhibition of platelet aggregation by clopidogrel. Did the authors perform this measurement in the patients treated with clopidogrel??

Thank you for this suggestion, we have stated this on page 8 of our manuscript but have now further clarified it. The results have been tabulated in our previous work.\(^4\)

3. Up to 45% of patients show aspirin resistance; have the authors observed any patients with aspirin resistance and was there a difference in incidence between the low an high dose aspirin group?

We have found it difficult to define aspirin resistance. Some authorities have used clinical events despite antiplatelet therapy and others a failure of biological response to antiplatelet therapy. Of the patients with less than 10% response after 5 days on percentage aggregation with collagen, there were 6 in the medium dose and 6 in the low dose aspirin arms, suggesting an equal distribution of poor responders.

4. Given the broad variation in % platelet aggregation and EC50 concentration was the study powered to find a significant difference between the high and low ASA group?

Yes, this was stated on page 7 of our previous manuscript, the sample size calculation was based on 90% power to detect 30% difference.

Thank you for your comments which we believe has strengthened our manuscript.

Kind regards,

Eric Lim
References


