Author's response to reviews

Title: Outcomes of Total Hip Arthroplasty in Patients with Primary Immune Thrombocytopenia

Authors:

Seung-Jae Lim (limsj70@gmail.com)
In-Kwon Yeo (ikyeo@samsung.com)
Chan-Woo Park (cwpark@samsung.com)
Young-Wan Moon (ywmoon@skku.edu)
Youn-Soo Park (ysp3504@skku.edu)

Version: 3
Date: 23 May 2015

Author's response to reviews: see over
Responses to Reviewers’ Comments

We would like to express our sincere thanks to the reviewers for their constructive and positive comments.

Response to Reviewer #1:
The study is a two to one comparison of outcomes of total hip are the classy in patients with primary immune thrombocytopenia. Overall this is a very well-written manuscript however there are certain concerns that I have.

1.) There is a small number of patients over a long period of enrollment this limited number patients may make it difficult to accurately assess what the outcomes are of this patient population.

Response: Thank you for your excellent comment. We have re-described the limitations of our study in the Discussion section to reflect this comment as shown below:

Page 13, lines 235-239
First, the study is limited by its retrospective nature and by the small number of patients over a long period of enrollment. These limitations might make it difficult to accurately assess what the outcomes are of this patient population. However, these limitations were unavoidable owing to the rarity of ITP and low number of patients treated by THA.

2.) It is questionable whether you can assess outcomes over a ten-year period with multiple implants as over this time. There's been vast amounts of improvements and implant design that have lead to improved outcomes since the initial period of the study.

Response: Thank you for your excellent comment. We have re-described the limitations of our study in the Discussion section to reflect this comment as shown below:

Page 13, lines 241-244
Third, the variety of implants used might have acted as a confounding factor. Nevertheless, our study involves a consecutive series of ITP patients treated using modern cementless components in combination with ceramic-on-ceramic bearings by a single surgeon at a single institution.

3.) I would suggest removing lines 33 to 35.
Response: We have removed -described lines 33 to 35.

4.) The authors list to patient that were diagnosed at the time of preoperative labs. Should these patients really be considered in this study as they have never had symptoms or receive treatments this is solely on the laboratory diagnoses and has never experienced convocations from this disease before.

Response: Thank you for your comments. We have more precisely described the patient population to reflect these comments as shown below:

**Page 6, lines 73-75**

Two of the eleven patients were diagnosed to have ITP as a result of the preoperative hematologic evaluation. The other nine had already been diagnosed to have chronic ITP and had been properly managed by hematologists.

5.) Was there any differences seen and preoperative lab values i.e. hemoglobin platelet count etc.

Response: Thank you for your comment. We have added preoperative lab values in the text to reflect this comment as shown below:

**Page 7-8, lines 101-104**

No significant difference was found between the two groups in preoperative serum hemoglobin level (P > 0.291), but preoperative platelet count was significantly lower in the ITP group (P < 0.001) than that in the non-ITP group.

6.) The authors state that there is no difference and close suction drains however they failed to mention if all the patients had drains or if just some of the patient had drains.

Response: Thank you for your comments. We have added close suction drains to reflect these comments as shown below:

**Page 9, line 127**

Closed suction drains were routinely used.

7.) How did you estimate blood loss as EBL is often in accurate.

Response: Thank you for your excellent comment. We have added estimate blood loss in the text to reflect this comment as shown below:
Page 8-9, lines 124-126

Intra-operative blood loss was estimated by measuring the volume of blood in the suction bottle, by weighing mops and gauze pieces used during surgery and by visual estimation of loss in the operation field.

8.) Authors say that there's no difference and postoperative complications however given the rate of these patients increased bleeding was there any differences and postoperative anticoagulation between the cohorts.

Response: Thank you for your excellent comment. We have re-described the sentences about postoperative anticoagulation to reflect this comment as shown below:

Page 9, lines 132-135

We used a mechanical compression device only without pharmacological thromboprophylaxis for patients in both group because the prevalence of venous thromboembolism in Korean patients without chemoprophylaxis had been reported to be low at that time [15].

In addition numerous other studies in the discussion say that this patient population has increased postoperative complications including pneumonia sepsis etc. however the authors fail to address whether these are increased. If possible I would like to see the authors to see if there was increased readmission rates for the thrombocytopenia cohort.

Response: Thank you for your excellent comments. We have added readmission rates in the text and Table 3 to reflect these comments.

Table 3.

| Re-admission rate (%) | 0  | 0  | 1.000 |

9.) Did any of the patients intraoperatively undergo additional blood management strategies i.e. TXA, fibrin sealant, etc.

Response: Thank you for your comment. We have added hemostatic to reflect this comment as shown below:

Page 9, lines 126-127

Hemostatic, such as tranexamic acid or fibrin sealant, was not used during the study period.
10.) Mention of various blood management strategies in the discussion to reduce the high rate of transfusion in these patients may be worthy for the reader to planned preoperatively if they encounter this patient population.

Response: Thank you for your constructive comment. We have re-described the Discussion section to reflect this comment as shown below:

**Page 12-13, lines 211-227**

We believe that this favorable outcome might have resulted from relatively short operative times and thorough perioperative blood management interventions, such as, comprehensive perioperative hematologic evaluations and the adjustment of transfusions according to bleeding risk. The transfusion threshold for pRBCs was hemoglobin levels of 8 g/dL and that for PCs and/or IVIG was platelet count of 80×10⁹/L in the entire perioperative period. We use a mechanical compression device only without pharmacological thromboprophylaxis. These blood management strategies led to excellent immediate postoperative clinical courses and hospital stays similar to those observed in the control group. However, an updated meta-analysis of randomized trials showed that a restrictive transfusion strategy using a hemoglobin transfusion trigger of < 7 g/dL results in a significant reduction in acute coronary syndrome, pulmonary edema, rebleeding, infections, and total mortality, compared with a more liberal strategy [20]. If more restrictive transfusion strategies were used, some of the patients in both groups might not have needed the transfusions following THA. In addition, new cost-effective blood management tools, such as tranexamic acid or fibrin sealant, could be a promising approach to reduce bleeding and consequently lead to lower transfusion rates after total joint arthroplasty in these patient populations [21, 22].

11.) The longest follow-up of these patients was 13 years, was transfusion indications standard for all the time. Or at what time was the current protocol of 8 grams per deciliter initiated.

Response: Thank you for your constructive comments. We have added transfusion indications with referenced to reflect these comments as shown below:

**Page 7, lines 95-99**

During the study period, we used the same transfusion thresholds for both pRBCs and PCs and/or IVIG. Hemoglobin levels of 8 g/dL was the transfusion threshold for pRBCs [12, 13]. Platelet count of more than 80×10⁹/L was the threshold is for the recommended level for PCs.
and/or IVIG administration [14].

**Response to Reviewer #2:**

This is a retrospective case controlled series comparing THA in patients with ITP to those without ITP undergoing THA. Overall the paper is well written and concise and provides the interested reader with some useful information. I would recommend several minor essential revisions.

1. Line 46: I don’t think that it can be stated that more blood loss is “expected in THA than during other surgeries”. I would change to something like “because greater perioperative blood loss may be expected in patients with ITP undergoing THA and because of the additional risk of periprosthetic infection, special….”

   **Response:** Thank you for your kind editing. We have re-describe this sentence to reflect this comment as shown below:

   **Page 5, lines 45-48**

   Furthermore, because greater perioperative blood loss may be expected in patients with ITP undergoing THA and because of the additional risk of periprosthetic infection, special medical management is required to avoid complications in ITP patients managed by THA.

2. Line 51-53: please provide references to support the statements in this sentence.

   **Response:** Thank you for your comment. We have provided references in the text to reflect this comment as shown below:

   **Page 5, lines 51-52**

   Accordingly, questions remain as to whether ITP patients can safely undergo THA, as these patients may be at increased risk of surgical complications and mortality [7, 11].

3. Lines 125-128: specific information was provided as to the threshold for transfusions preoperatively but no information is provided for postoperative transfusion thresholds- please expand on “transfusions were performed based on the results of hematological studies and amounts of blood collected via suction drains”. The threshold for both pRBC and PC should be included.
Response: Thank you for your constructive comments. We have added postoperative transfusion thresholds to reflect these comments as shown below:

Page 9, lines 139-141
The transfusion threshold was hemoglobin levels of 8 g/dL for pRBCs and platelet count of 80×109/L for PCs in the entire postoperative period.

4. Lines 127-128: please provide information on what, if any, chemoprophylaxis was used.
Response: Thank you for your excellent comment. We have re-described the sentences about postoperative anticoagulation to reflect this comment as shown below:
Page 9, lines 132-135
We used a mechanical compression device only without pharmacological thromboprophylaxis for patients in both group because the prevalence of venous thromboembolism in Korean patients without chemoprophylaxis had been reported to be low at that time [15].

5. Lines 168-170: I think that the reader would be interested in the number of patients that developed any wound drainage or superficial wound infection/cellulitis and not just periprosthetic infection. Please also include this data in Table 3.
Response: Thank you for your excellent comments. We have added wound complications in Table 3 to reflect these comments.

Table 3.
<table>
<thead>
<tr>
<th>Complications</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound hematoma</td>
<td>0</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
</tr>
</tbody>
</table>

6. Lines 218-220: the authors hint at the modern approach to blood management by mentioning the recent adoption of tranexamic acid in perioperative blood management. It would also be helpful to know, since the threshold for transfusion has steadily risen over the past decade, whether those ITP patients that received a transfusion postoperatively perhaps would have been treated differently now. We commonly accept a postoperative hgb of 7-8 g/dL if the patient is otherwise asymptomatic. I wonder if some of these patients were transfused then but might
currently not require a transfusion? The threshold for transfusion postoperatively as suggested above (#3) will help the reader to evaluate if these patients would be as likely to require transfusion following THA today. In other words, it may be that there was a lower threshold to transfuse during the study period and that with more current strategies (like the use of tranexamic acid) and a higher threshold to transfuse that some or many of the study patients (and controls) may not have needed the transfusions.

7. Lines 223-230: Please edit as necessary to reflect the above changes.

Response: Thank you for your insightful and constructive comments. We have re-described the Discussion section to reflect these comments as shown below:

Page 12-13, lines 211-227

We believe that this favorable outcome might have resulted from relatively short operative times and thorough perioperative blood management interventions, such as, comprehensive perioperative hematologic evaluations and the adjustment of transfusions according to bleeding risk. The transfusion threshold for pRBCs was hemoglobin levels of 8 g/dL and that for PCs and/or IVIG was platelet count of 80×10⁹/L in the entire perioperative period. We use a mechanical compression device only without pharmacological thromboprophylaxis. These blood management strategies led to excellent immediate postoperative clinical courses and hospital stays similar to those observed in the control group. However, an updated meta-analysis of randomized trials showed that a restrictive transfusion strategy using a hemoglobin transfusion trigger of < 7 g/dL results in a significant reduction in acute coronary syndrome, pulmonary edema, rebleeding, infections, and total mortality, compared with a more liberal strategy [20]. If more restrictive transfusion strategies were used, some of the patients in both groups might not have needed the transfusions following THA. In addition, new cost-effective blood management tools, such as tranexamic acid or fibrin sealant, could be a promising approach to reduce bleeding and consequently lead to lower transfusion rates after total joint arthroplasty in these patient populations [21, 22].

Response to Reviewer #3:

1. Is the question posed by the authors well defined? Yes
2. Are the methods appropriate and well described? Yes
3. Are the data sound? No, because no clear data, numbers too small
4. Do the figures appear to be genuine, i.e. without evidence of manipulation? Yes
5. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes
6. Are the discussion and conclusions well balanced and adequately supported by the data? No, too many different implants for a very small number of patients.
7. Are limitations of the work clearly stated? Yes
8. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? Yes
9. Do the title and abstract accurately convey what has been found? Yes
10. Is the writing acceptable? Yes

Response: Thank you for your excellent comments. We have re-described the limitations of our study in the Discussion section to reflect these comments as shown below:

**Page 13-14, lines 235-246**

Several limitations of the present study warrant consideration. First, the study is limited by its retrospective nature and by the small number of patients over a long period of enrollment. These limitations might make it difficult to accurately assess what the outcomes are of this patient population. However, these limitations were unavoidable owing to the rarity of ITP and low number of patients treated by THA. Second, follow-up durations varied widely, for example, although all patients were followed for a minimum of 2 years some were followed for as much as 13 years, and the average follow-up was 7.1 years. Third, the variety of implants used might have acted as a confounding factor. Nevertheless, our study involves a consecutive series of ITP patients treated using modern cementless components in combination with ceramic-on-ceramic bearings by a single surgeon at a single institution. Fourth, new blood management strategies, such as tranexamic acid or fibrin sealant, and more restrictive blood transfusion strategies have not been used during the study period.

Response to Editorial request:
1. Please include name of institutional review board that approved your study.
Response: Thank you for your comment. We have re-described the sentence to reflect this comment as shown below:

Page 6, lines 59
After obtaining approval from the Institutional Review Board of Samsung Medical Center,

2. Please include list of abbreviations.
Response: Thank you for your comment. We have described list of abbreviations to reflect this comment as shown below:

Page 14-15
Abbreviations
ALT: Alanine aminotransferase
ASA: American society of anesthesiologists
AST: Aspartate aminotransferase
AVN: Avascular necrosis of the femoral head
BUN: Blood urea nitrogen
CMV: Cytomegalovirus
EBV: Epstein-Barr virus
FFP: Fresh frozen plasma
GGT: Gamma-glutamyl transpeptidase
HIV: Human immunodeficiency virus
Hb: Hemoglobin
ITP: Immune thrombocytopenia
IVIG: Intravenous immunoglobulin
LDH: Llactate dehydrogenase
OA: Osteoarthritis
PC: Platelet concentrate
PLT: Platelet
pRBC: Packed red blood cell
THA: Total hip arthroplasty
TSH: Thyroid stimulating hormone
We hope that we have addressed each of your concerns, and we would be happy to make any further changes that you deem necessary.