Author's response to reviews

Title: Revision of a nonunited subtrochanteric femoral fracture around a failed intramedullary nail with the use of RIA products, BMP-7 and hydroxyapatite: A case report

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Version: 3 Date: 23 October 2010

Author's response to reviews: see over
Dear Editor-in-Chief

We thank the editors and reviewers for their hard-work, thorough analysis and comments on this manuscript.

Outlined below is each comment and how we have adjusted the manuscript.

Reply to reviewer 1

Comment 1
‘First of all they along the manuscript they mention a case of an intertrocantheric fracture and only at page 4 they classified this femoral fracture which is a reverse oblique multifragmentary fracture (33.A3.3) please remark this kind of fracture’.

Reply to comment 1
We thank the reviewer for this comment. There appears to be a lack of agreement regarding the definition of a subtrochanteric fracture. It has been defined as a fracture occurring at the level of the lesser trochanter or approximately 5cm below.[2] Classification systems have also included intertrochanteric fractures with distal extension into the subtrochanteric region, such as reverse obliquity intertrochanteric fractures.[2] However, the AO/OTA has classified these type of fractures separately under 31-A3, which have been included in studies and the current case report due to the rare occurrence of a pure subtrochanteric fracture.

Action taken
We have now included the following explanation at the end of paragraph 2 in the manuscript to clarify our classification of this fracture.

This study also highlighted a lack of agreement regarding the definition of a subtrochanteric fracture. It has been defined as a fracture occurring at the level of the lesser trochanter or approximately 5cm below.[2] Classification systems have also included intertrochanteric fractures with distal extension into the subtrochanteric region, such as reverse obliquity intertrochanteric fractures.[2] However, the AO/OTA has classified these type of fractures separately under 31-A3, which have been included in studies and the current case report due to the rare occurrence of a pure subtrochanteric fracture.

Comment 2

‘The Author did not suspect which this non union should be a mistake of the primary surgery as known in the literature (George J. Haidukewych, T. Andrew Israel and Daniel J. Berry J Bone Joint Surg Am. 2001;83:643-650.)’

Furthermore the ruptured nail did not find any explication?

Reply to comment 2

We thank the reviewer for the comment. There is a possibility screw cut out and nonunion with the use of intramedullary nails. This patient was at an increased risk of nonunion due to poor bone quality and complex fracture pattern. In a recent systematic review, pooled analysis of level 1 studies suggested a non-significant lower risk of failure in the IMD (intramedullary device) group when compared to extramedullary devices and no difference in the rate of nonunion.[2] We have
reviewed the literature in the discussion section and there is controversy regarding the best type of implant for fixation of subtrochanteric femoral fractures (underlined). In general, less favourable results and implant failure occur in patients with osteoporotic bone, complex fracture patterns, suboptimal implant positioning, shaft medialisation and varus malreduction for which revision fixation maybe recommended. Our fracture belongs to this high risk group for nonunion and failure of the intramedullary nail.

**Acton taken**

We have cited the paper mentioned by the reviewer (reference number 12) in the first paragraph of the discussion section as shown below:

There has been controversy in the literature regarding the best type of implant for fixation of subtrochanteric femoral fractures.[2] Both intra and extramedullary devices have been advocated for the management of subtrochanteric fractures.[3] Less favourable results and implant failure occur in patients with osteoporotic bone, complex fracture patterns, suboptimal implant positioning, shaft medialisation and varus malreduction for which revision fixation maybe recommended.[1, 2, 5, 12] The biomechanical advantages of IMD are often diminished by suboptimal fracture reduction and false entry point prior to nail insertion.[5] The incidence of neck screw cut out and fracture below the nail was found to be 4% and 3.2% respectively for the TGN nail in a comparison study with the Proximal Femoral Nail (PFN).[13] The PFN was associated with varus malreduction in 7.2% and screw migration resulting in fracture collapse in 8%; however, with a lower incidence of shaft fractures and neck screw cut out incidence, compared to TGN.[13] In a prospective study comparing the success rate of TGN, PFN and DHS for unstable trochanteric fractures, the TGN
group presented with the most failures (4 out of 40) attributed to screw cut out and
nonunion.[6]

**Comment 3**

‘How the Author explain with the revision surgery changing the kind of osteosynthesis which the final good result is done by the combination of RIA autograft, BMP-7 and HA cement and not by a better biomechanically device?’

**Reply to comment 3**

We thank the reviewer for the comment. In order to give the fracture the best chance of healing in a region of high biomechanical forces we opted to use the condylar blade plate (CBP) together with the combination of RIA autograft, BMP-7 and HA cement. We have discussed the biomechanical advantages of using the CBP in paragraph 3 of the discussion (underlined). We first addressed the biomechanical concept of failure by changing the device to an extramedullary one. The plate is able to target the area below the femoral head that is unlikely to be compromised by the previous fixation. This added advantage was protected by augmenting the bone biology. The combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure. As it is known, bone regeneration requires the presence of a scaffold, which in our case was HA; a source of primary cells with the potential to become bone cells, which in our case was provided by the RIA products from the medullary canal; and in addition bone inducing proteins, which in our case was BMP -7. All these factors have the potential to succeed only in a stable environment which is provided in our case by the CBP.
Action taken

This is now explained in paragraph 4 of the discussion:

In our case we elected to revise the failed TGN device with an extramedullary CBP to provide anatomical reduction and fracture site compression, as bone loss and proximity of the fracture to the femoral neck would not have allowed insertion of a revision nail, to achieve these successfully.[1, 5] Previous literature has confirmed the limited capacity of an IMD to correct the alignment and compress subtrochanteric nonunions to healing in a revision situation, advantages that a CBP can offer.[5, 14] This added advantage was protected by augmenting the bone biology. The combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure.

Comment 4

‘How was the cost for this revision surgery and it was justified by the authors?’

Reply to comment 4

In our case revising the failed fracture in an elderly patient presented us with significant challenges. The lack of bone stock in addition to fragmentation left us with only very few reconstructive options within relatively poor biology. Adding allograft to the osteoporotic and fragmented proximal femoral metaphysis would have been an option, but RIA autograft was considered superior in this revision case as it was easily accessible through the fracture site. Supporting the screw hole up until the subcortical region of the femoral head with HA cement considered an important and relatively cheap option for structural support until bone have had replaced the bone defect. We
agree that the cost of BMP-7 is high, it is however licensed for difficult nonunions when the autograft has failed. In our case we combined autograft and BMP-7 hoping that we provided the patient with the best possible combination of treatment in a single procedure.

**Action taken**

This is explained at the end of the section entitled Revision Surgical Technique and in paragraph 4 of the discussion as follows:

The RIA reamers (Synthes, Inc., West Chester, PA) were used to ream and irrigate the endosteal bone-implant interface and thereafter intramedullary cortico-cancellous reaming autograft was collected following the standard RIA protocol (Figure 3b).

Prior to CBP insertion the femoral neck was filled with injectable HA cement (BoneSourse BVF, Stryker) to fill the void created by the removal of the proximal TGN screw and augment its mechanical strength. The RIA autograft was mixed with the recombinant human rhBMP-7 implant (Stryker Biotech, Hopkinton, MA, USA) and added onto the fracture site.

In our case we elected to revise the failed TGN device with an extramedullary CBP to provide anatomical reduction and fracture site compression, as bone loss and proximity of the fracture to the femoral neck would not have allowed insertion of a revision nail, to achieve these successfully.[1, 5] Previous literature has confirmed the limited capacity of an IMD to correct the alignment and compress subtrochanteric nonunions to healing in a revision situation, advantages that a CBP can offer.[5, 14] This added advantage was protected by augmenting the bone biology. The
combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure.

Comment 5

Finally they are sure which this is the best approach to heal this kind of complications?

Reply to comment 5

In order to give the nonunited fracture the best chance of healing in a region of high biomechanical forces, the use of the condylar blade plate (CBP) together with the combination of RIA autograft, BMP-7 and HA cement was considered to be the best approach.

Action taken

This is explained in paragraph 4 of the discussion as follows:

In our case we elected to revise the failed TGN device with an extramedullary CBP to provide anatomical reduction and fracture site compression, as bone loss and proximity of the fracture to the femoral neck would not have allowed insertion of a revision nail, to achieve these successfully.[1, 5] Previous literature has confirmed the limited capacity of an IMD to correct the alignment and compress subtrochanteric nonunions to healing in a revision situation, advantages that a CBP can offer.[5, 14] This added advantage was protected by augmenting the bone biology. The combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and
to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure.

Comment 6
‘The figures need to be cut in a better way.’

Reply to comment 6 and action taken
We thank the reviewer for this comment. The figures have now been improved.

Reply to reviewer 2
Comment 1
‘Did the authors pre-operatively plan to use the combination of RIA autograft, BMP-7 and HA cement for the treatment of this subtrochanteric non-union?’

Reply to comment 1
Yes, in order to give the fracture the best chance of healing in a region of high biomechanical forces we opted to use the condylar blade plate (CBP) together with the combination of RIA autograft, BMP-7 and HA cement. Our approach was the combination of the three components necessary for bone regeneration. The cell source from the RIA reamings, the substitute HA for the structural support and the growth factor BMP-7. In addition mechanical stability was achieved with the CBP.

Action taken
This is explained in paragraph 4 of the discussion as follows:
In our case we elected to revise the failed TGN device with an extramedullary CBP to provide anatomical reduction and fracture site compression, as bone loss and
proximity of the fracture to the femoral neck would not have allowed insertion of a revision nail, to achieve these successfully.[1, 5] Previous literature has confirmed the limited capacity of an IMD to correct the alignment and compress subtrochanteric nonunions to healing in a revision situation, advantages that a CBP can offer.[5, 14] This added advantage was protected by augmenting the bone biology. The combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure.

**Comment 2**

If the answer to the above question was yes, why was this necessary? Could one, or a combination of two, of the above treatments have been used? In particular could RIA and HA cement or BMP-7 and HA cement been used in combination only??

**Reply to comment 2**

We agree to an extent with the comment, it was however considered important to combine the three elements of osteogenesis together, namely the HA scaffold, the RIA cell source and the osteogenic stimulus BMP-7. RIA aspirate contains mesenchymal stem cells known to differentiate toward the osteogenic lineage under the appropriate stimuli. BMP-7 was used as it has previously been used with success in randomized human nonunion studies[9] and experimental healing of metaphyseal bone defects to augment bone healing.[17] There would have been lack of an osteogenic stimulus if RIA and HA cement were used alone without BMP-7,. The injected HA cement was required to provide temporary mechanical support to the subchondral zone of the femoral head, after removal of the proximal TGN screw as
the CBP blade did not reach this zone. It was important to use the combination of the three to provide the best chance of fracture union in this area of high biomechanical forces.

**Action taken**

This is explained in paragraphs 4 and 5 of the discussion as follows:

In our case we elected to revise the failed TGN device with an extramedullary CBP to provide anatomical reduction and fracture site compression, as bone loss and proximity of the fracture to the femoral neck would not have allowed insertion of a revision nail, to achieve these successfully.[1, 5] Previous literature has confirmed the limited capacity of an IMD to correct the alignment and compress subtrochanteric nonunions to healing in a revision situation, advantages that a CBP can offer.[5, 14] This added advantage was protected by augmenting the bone biology. The combination of RIA autograft, BMP-7 and HA cement was used due to bone loss and to restore the medial column to prevent cyclical loading of the plate on the tension side of the femur and potentially implant failure.

The gold standard method of enhancing bone healing in non-united fractures is autologous bone graft.[7] however, it has been associated with donor site morbidity and limited availability.[7] The RIA system has been developed originally as a simultaneous reaming and aspiration system to reduce the intramedullary pressure, heat generation, and possibly fat embolism.[15] In addition, it has been recently reported that RIA aspirate contains mesenchymal stem cells[16] known to differentiate toward the osteogenic lineage under the appropriate stimuli.[10, 17]
Comment 3

Where there other possible aetiological factors for non-union, eg smoking etc?

Reply to comment 3

We had no such a predisposing factor as smoking to explain the nonunion. We believe that failure of the intramedullary device was attributed primarily to osteoporosis and the configuration of the original fracture. The weakened bone from osteoporosis and fracture fragmentation required all bone regeneration components to recover structural and biological integrity during revision surgery.

We hope that the above replies to the reviewer comments satisfy the requirements, if not please let us know. In anticipation of your response.

Yours sincerely,

Christopher Tzioupis
Pavlos Panteliadis
Zakareya Gamie
Eleftherios Tsiridis