PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	PLATELET-RICH THERAPY IN THE TREATMENT OF PATIENTS WITH HIP FRACTURES: A SINGLE CENTRE, PARALLEL GROUP, PARTICIPANT BLINDED, RANDOMISED CONTROLLED TRIAL
AUTHORS	Griffin, Xavier; Achten, Juul; Costa, Matthew; Parsons, Nicholas

VERSION 1 - REVIEW

REVIEWER	Martyn J Parker MD, FRCS(Edinb), Orthopaedic Research Fellow, Peterborough and Stamford Hospital NHS Foundation Trust, Department of Orthopaedics Peterborough City Hospital CBU PO Box 211 Core C Bretton Gate Peterborough PE3 9GZ England Tel 01733 678000 (bleep 1133) Office 01733 677642 Fax 01733 678532 I have no conflict of interest with this study
REVIEW RETURNED	15-Jan-2013

GENERAL COMMENTS	This is an important and relevant randomised trial that should be published in an open access journal. The study has been carefully conducted with full reporting of outcomes. The conclusions reached are accurate and fair. The discussion is also appropriate. The statistical analysis in my opinion seems a little too complicated for such a study. I am not qualified to comment on the appropriateness of all of the tests used. I do not feel the logistic regression analysis contributes little to the conclusion given the limited patient numbers but clearly there are others that feel it is of use. In table 1 there are a few abbreviations that can be omitted or given their definitions (CRF, AMT, NSAI) and I assume the theatre time should be mean time to theatre. These are minor criticisms and I feel the article is suitable for publication in the BMJ.

REVIEWER	Mr. Joseph Alsousou LMSSA Lon, MD , MRCS Ed

	D-Phil Research Fellow in Trauma and Orthopaedic Surgery Nuffield Department of Orthopaedic Rheumatology and Musculoskeletal Sciences (NDORMS) University of Oxford Oxford OX3 9DU
REVIEW RETURNED	30-Jan-2013

THE STUDY	The introduction lack clear explanation of the evidence (in vitro or in vivo animal studies) behind PRP use in osteoportotic bone. Although clinica evidence is lacking in orthopaedic surgery, there is wealth of basic science evidence and evidence in maxillofacial and dental surgery field. This will give the readers a background on PRP possible mechanism of action in osteoporotic or normal bone. The study question is well defined. However, the method lack a clear description of fracture displacement. the study included all fractures but did not elaborate on fracture classifications (Garden , powell, AO,.. etc), which may have had an effect on the fracture reduction and the overall outcome. we can assume that randomisation will equal this effect out between the group in a large sample but we can not see this in this study. The distribution of the fracture classification may vary between the group and this has not been considered in the study. The authors used PRP product but did not clarify the biological component of this product. it is now known that " not all PRP products are in fact PRP". identifying the biological component and classification of the used product will have two advantages: 1. correlate the outcome to the class of PRP (i.e this product may not be effective but another different class product may actually work). 2. inform future research studies about the effect of different PRP products in differnet disorders. Currently, there are three classification systems for PRP : Ehrenfest et al classification (P-PRP, L-PRP, L-PRF and P-PRF) and Mishra et al classification (Type 1-4) and the recently suggested Alsousou et al classification (depends on Leukocytes, activation, Fibrin and preperation method). Quality analysis of the used PRP in this group of patients would have been advantageous and could offer biological information that is otherwise unavailable and may explain the outcome. Did the authors do this analysis? if not, do they have enough information about this product to classify it: Plt count, WBC, fibrin, activation, preperation method ..? Further, the author did not elaborate on the preparation method and activation of PRP. this information is essential for PRP viability. Was Thrombin (allogenic or autologous) used? did they use an alternative to thrombin for activation or was PRP injected into the site without activation. This information is essential when considering the outcome. Did the team carry any assessment of the product delivery to the fracture site? 3ml of the PRP product was injected after removal of one guide wire in the fracture area then the screw was advanced beyond the fracture. did the screw destroy the PRP clot as it advances? did it push the PRP out into the surrounding fracture haematoma? was 3ml PRP enough to cover large fracture area in osteoporotic bone? Did the clot form or did PRP migrate with gravity

	out of the area of interest? In the absence of current evidence for application method in this area, the team should have considered assessing this in a small group of patient (i.e with radiopaque dye injection). can the team provide evidence for the validity of the delivery method in this fracture?
RESULTS & CONCLUSIONS	The results are clearly written with regards to the primary outcome. However, the data for the secondary outcome measures was analysed and presented statistically in text despite the large number of loss to follow up for those outcomes (>50%). As a result the power of this analyses was significantly affected. This should have been clearly mentioned and the data from the seconardy outcome measures needed to be treated with caution. was this considered when applyig fisher's test? The authors also included patients who are on anti-platelet therapy. The authors claim that there is no evidence that it can effect the release of gf. This may be true if the platelets or PRP are activated prior to application, which is not explained in the text. However, for non-activated platelet or PRP the use of Aspirin is still controversial and it is not recommended by several authors for it is inhibition of aggregation and clot formation. Furthermore, It is reported in the text that there were no major differences between the two groups co-morbidities. however, in table 1, it is noticeable that a significant number of patient in the treatment group had diabetes 16% comparing to 6.1% in the control group. Did this have an effect on the outcome considering that diabetes can cause platelets dysfunction and alter fracture union ability. did the authors investigate this or analysed the data taking this into account? The sample size calculation was performed depending on available data and orthopaedic surgeons consensus on significant clinical effect. However, there was no consideration to the large variation in treating surgeons experience (11 consultants and 21 trainees). was this considered when deciding the sample size as a factor that may influence the n? if so, this needs to be clearly stated in sample size calculation
GENERAL COMMENTS	I recommend that the authors review the above mentioned points and re-submit for review.

REVIEWER	William S. Pietrzak Clinical Research Biomet, Inc. Warsaw, IN 46580 USA Adjunct Research Professor of Bioengineering Department of Bioengineering University of Illinois at Chicago Chicago, IL 60607 USA My only competing interest is that Biomet markets a PRP system called the GPS. However, I am associated with a separate division of Biomet and have no responsibilities regarding this system.
REVIEW RETURNED	01-Feb-2013

THE STUDY	More information needs to be provided to desctibe the Genesis system used to prepare the PRP. Also, the resulting PRP needs to

	be better characterized, e.g., fold-increase over basline for PRP concentration, means of activiating platelets, etc.
GENERAL COMMENTS	General comments This is a very interesting, well-written paper on an important topic. The authors investigated the effects of using platelet-rich-plasma (PRP) in patients with fractures of the proximal femur treated with closed reduction and screw fixation. As a randomized, controlled clinical study, this is one of the few such studies to investigate this type of autologous therapy. The primary outcome measure was the proportion of patients in each cohort undergoing reoperation for fixation failure within the first year. There were a variety of secondary outcome measures as well. The authors found no significant effect of the use of PRP on the reoperation rate, nor on most of the secondary outcome measures. However, the investigational cohort did have a significantly shorter hospital stay than the control cohort (15 vs. 23 days). The authors concluded that the standard of care, i.e., hip arthroplasty, should remain the procedure of choice for such fractures. This conclusion is easily supported by the Chi square analysis and is the basic message of the paper. However, the authors go into a great deal of other statistical analysis which, to some extent, over-complicates what would otherwise be an elegant, straight-forward paper. They should re-examine the extent of the statistical analysis used to make sure each facet of it is of sufficient benefit to merit its inclusion at the expense of over complicating the paper. Specific comments 1. Make sure ALL abbreviations are defined at first usage. 2. The Participants section of Results and Figure 1 are confusing in accounting for the lost to follow-up (LTF) and Died patients. Is it the case that all lost to follow-up are dead but not all dead are lost to follow-up? In other words, a total of 43 patients died, but 3 patients were revised prior to death, hence, were not lost to follow-up? As such, LTF=40 while died = 43? In particular, Figure 1 is not clear on this and should be self-explanatory without having to read the text. 3. Page 6, line 27. Include the city (Fort Myers) for the location of EmCyte. 4. It is important to note that not all PRPs are creating equal. In particular, what is the platelet concentration above baseline that is created with the Genesis system? How does the PRP creation process affect the integrity of the platelets? How are the platelets activated? If publications exist describing the system and its clinical use, these should be cited. 5. Line 33 in first page of Results. Should “apparently substantial” be changed to “significant” in the statistical sense? 6. Lines 6-18 in second page of Results. If logical regression analysis is used, more detail should be presented about how this was done. As this paragraph is written, it is difficult to understand. 7. Lines 20-29 in second page of Results. Post-operative EQ-5D scores need to be presented.

	8. There was an 8 day (on average) shorter hospital stay for the patients receiving PRP compared to the control patients. It would be interesting for the authors to describe the criteria for patient release from the hospital and speculate on how the various aspects of that criteria could have been influenced by PRP.

VERSION 1 – AUTHOR RESPONSE

GENERAL

2. Make sure ALL abbreviations are defined at first usage.

We have left commonly used abbreviations such as 'UK' without definitions. We are happy to follow editorial style guidance on this point.

3. Throughout, the authors have misspelled 'Whitney' as 'Witney', as in the Mann-Whitney test. Please correct.

Corrected.

INTRODUCTION

4. The introduction lacks clear explanation of the evidence (in vitro or in vivo animal studies) behind PRP use in osteoportotic bone. Although clinical evidence is lacking in orthopaedic surgery, there is wealth of basic science evidence and evidence in maxillofacial and dental surgery field. This will give the readers a background on PRP possible mechanism of action in osteoporotic or normal bone.

We agree that there is substantial evidence available in other fields. However, this was a study focused on the clinical application of PRP in musculoskeletal medicine. The introduction is therefore focused tightly around this field.

5. A null hypothesis is presented - this is out of step with contemporary practice in medical statistics and I would much prefer to see this removed and replaced with the simple research question. A fundamental theoretical dilemma with the null hypothesis testing approach is the fact that the null hypothesis is always false; indeed, with a large enough sample size all effects are statistically significant. On a more practical level, the approach fails to deal adequately with the real-world importance of an effect - we should be concerned primarily with the question of how big the effect (difference) is, rather than whether or not there is an effect. The authors clearly recognise these issues, as they have taken the trouble, admirably, to define a minimum clinically important difference for the primary outcome, and have made inferences with respect to this value. Therefore, it would seem appropriate to remove statements relating to null hypotheses.

We agree with these comments and have rephrased the final paragraph of he introduction appropriately.

METHODS

6. Include the city (Fort Myers) for the location of EmCyte.

Added.

7. The authors refer to an 'EQ-5D score' as one of the secondary outcomes. This is vague, as the

reader has no idea specifically what has been measured here. I assume that they are referring to the EQ5-D index, but the specific method used to convert the profile for the 5 domains to an index and the particular value set used should be cited (e.g. UK value set, time trade off method, or UK value set VAS method). I only realised that it was the index that was being referred to herein, rather than the 100 mm VAS that is also part of the EQ5-D, when I saw the mean values in Table 1. Please add the detail to the Methods, as it is important to those interested in quality of life data.

The reviewer is correct that we have presented EQ-5D index data. We have changed the term ‘EQ-5D score’ to ‘EQ-5D index’ at its first use. Additionally, we have added the population and method used to derive the value set in the Methods.

8. However, the method lacks a clear description of fracture displacement. the study included all fractures but did not elaborate on fracture classifications (Garden , Powell, AO,.. etc), which may have had an effect on the fracture reduction and the overall outcome. We can assume that randomisation will equal this effect out between the group in a large sample but we can not see this in this study. The distribution of the fracture classification may vary between the group and this has not been considered in the study.

We agree that fracture displacement is a crucial possible confounder. Therefore we chose to stratify the allocation sequence by fracture displacement which we report in the details of the sequence generation. We chose to classify fractures by a system described by Parker et al (Ref 12). The proportions of displaced and undisplaced fractures in each group are reported in line 3 of Table 1.

9. The authors used PRP product but did not clarify the biological component of this product. it is now known that " not all PRP products are in fact PRP". Identifying the biological component and classification of the used product will have two advantages: 1. correlate the outcome to the class of PRP (i.e this product may not be effective but another different class product may actually work). 2. Inform future research studies about the effect of different PRP products in differnet disorders. Currently, there are three classification systems for PRP : Ehrenfest et al classification (P-PRP, L-PRP, L-PRF and P-PRF) and Mishra et al classification (Type 1-4) and the recently suggested Alsousou et al classification (depends on Leukocytes, activation, Fibrin and preperation method). Quality analysis of the used PRP in this group of patients would have been advantageous and could offer biological information that is otherwise unavailable and may explain the outcome. Did the authors do this analysis? if not, do they have enough information about this product to classify it: Plt count, WBC, fibrin, activation, preperation method ..?

Further, the author did not elaborate on the preparation method and activation of PRP. This information is essential for PRP viability. Was Thrombin (allogenic or autologous) used? Did they use an alternative to thrombin for activation or was PRP injected into the site without activation. This information is essential when considering the outcome.

It is important to note that not all PRPs are creating equal. In particular, what is the platelet concentration above baseline that is created with the Genesis system? How does the PRP creation process affect the integrity of the platelets? How are the platelets activated? If publications exist describing the system and its clinical use, these should be cited.

More information needs to be provided to describe the Genesis system used to prepare the PRP. Also, the resulting PRP needs to be better characterized, e.g., fold-increase over baseline for PRP concentration, means of activating platelets, etc.

Did the team carry any assessment of the product delivery to the fracture site? 3ml of the PRP product was injected after removal of one guide wire in the fracture area then the screw was

advanced beyond the fracture. Did the screw destroy the PRP clot as it advances? Did it push the PRP out into the surrounding fracture haematoma? Was 3ml PRP enough to cover large fracture area in osteoporotic bone? Did the clot form or did PRP migrate with gravity out of the area of interest? In the absence of current evidence for application method in this area, the team should have considered assessing this in a small group of patient (i.e with radiopaque dye injection). Can the team provide evidence for the validity of the delivery method in this fracture?

We designed this to be a pragmatic trial of a commercially available and licensed PRP product. We agree with the reviewers that 'PRP' describes a range of products with differing biochemical profiles.

We researched our choice of product carefully and chose a system that is commonly used in clinical practice and is supported by in vitro research. We have added two important references that describe the nature and activity of the PRP produced using our system of choice.

We attempted to deliver the PRP to the fracture site as accurately as possible using an image intensifier to position the tip of the introduction needle exactly at the fracture. Such an approach is a common method for delivering bioactive products to fracture sites in trauma surgery. We did not assess the effectiveness of this method further in this pragmatic study.

Finally, we have amended the manuscript to clarify that no thrombin or other activator was added to the PRP.

10. The sample size calculation was performed depending on available data and orthopaedic surgeons consensus on significant clinical effect. However, there was no consideration of the large variation in treating surgeons' experience (11 consultants and 21 trainees). Was this considered when deciding the sample size as a factor that may influence the n? If so, this needs to be clearly stated in sample size calculation.

This was a pragmatic trial. As such we sought to include all operating surgeons that are involved in trauma care in our institution. Whilst such an approach was likely to increase variability in outcome it also increases the generalisability of the results.

11. Line 33 in first page of Results. Should "apparently substantial" be changed to "significant" in the statistical sense?

We specifically chose not to conduct hypothesis tests for differences in baseline characteristics between groups; given that the only difference between the participant groups at baseline was the random treatment allocation, as convention dictates, we have not undertaken formal statistical tests to assess significance. Therefore we deliberately chose not to use the word 'significant' so that a reader might not over-interpret the statement.

12. Lines 6-18 in second page of Results. If logical regression analysis is used, more detail should be presented about how this was done. As this paragraph is written, it is difficult to understand.

The section has been modified to state more explicitly which analyses were undertaken and how the results of the analyses were interpreted.

13. Lines 20-29 in second page of Results. Post-operative EQ-5D scores need to be presented.

The 12 month EQ-5D score for the control group has been added along with the direction of the effect.

14. There was an 8 day (on average) shorter hospital stay for the patients receiving PRP compared to the control patients. It would be interesting for the authors to describe the criteria for patient release from the hospital and speculate on how the various aspects of that criteria could have been influenced by PRP.

Whilst we agree that the difference is interesting we do not have data to explore this finding in greater detail. This was a secondary outcome only and we formed no a priori hypothesis concerning the size and direction of any effect that we might observe. We would prefer not to speculate on this finding without adequate supporting data, but rather report our finding for others to investigate as appropriate.

15. The statistical analysis in my opinion seems a little too complicated for such a study. I am not qualified to comment on the appropriateness of all of the tests used. I do not feel the logistic regression analysis contributes little to the conclusion given the limited patient numbers but clearly there are others that feel it is of use.

However, the authors go into a great deal of other statistical analysis which, to some extent, over-complicates what would otherwise be an elegant, straight-forward paper. They should re-examine the extent of the statistical analysis used to make sure each facet of it is of sufficient benefit to merit its inclusion at the expense of over complicating the paper.

As part of the revision process, we have carefully re-examined all the analysis presented in this manuscript. Almost all the reported analyses were pre-specified in the trial protocol; therefore we have taken the view that we should report all such analyses. In addition we have also reported a competing risks analysis as we felt that this methodology might answer the important question of whether the difference in the risk of death between groups was an important influence on revision risk. This methodology was included in the trial statistical analysis plan after advice from the trial data monitoring and steering committees. We feel that the scope and complexity of the reported statistical analysis is appropriate in what is overall a relatively short and focused manuscript. We accept the reviewers' comments and would be happy to accept editorial board style guidance.

RESULTS

16. The results are clearly written with regards to the primary outcome. However, the data for the secondary outcome measures was analysed and presented statistically in text despite the large number of loss to follow up for those outcomes (>50%). As a result the power of this analyses was significantly affected. This should have been clearly mentioned and the data from the secondary outcome measures needed to be treated with caution. Was this considered when applying fisher's test?

We anticipated that the collection of outcome might be difficult in this population. This was one of the reasons that we chose revision as our primary outcome measure as it is more easily determined than many other measures such as patient-reported measures. The reviewer is right that we experienced substantial loss to follow-up for our main secondary measure (EQ-5D) due to factors such as death, new onset dementia/confusion, patient fatigue and increasing general ill-health. We have reported this openly in the flow diagram and in the first section of the results.
We have not discussed post-hoc power analyses since these are less helpful than the consideration of the CIs; the sample size was not predicated on the secondary measures and we would only ever use these measures to support the finding from a primary outcome or generate putative hypotheses.

17. Furthermore, It is reported in the text that there were no major differences between the two groups co-morbidities. However, in table 1, it is noticeable that a significant number of patient in the treatment group had diabetes 16% comparing to 6.1% in the control group. Did this have an effect on the

outcome considering that diabetes can cause platelets dysfunction and alter fracture union ability. Did the authors investigate this or analysed the data taking this into account?

We randomly allocated all our participants to treatment arms and checked for the influence of important baseline characteristics (including diabetes) on outcomes through regression analyses. Diabetes was not found to be a significant predictor variable. As mentioned previously we did not perform hypothesis tests for any of the baseline characteristics in line with convention.

18. The Participants section of Results and Figure 1 are confusing in accounting for the lost to follow-up (LTF) and Died patients. Is it the case that all lost to follow-up are dead but not all dead are lost to follow-up? In other words, a total of 43 patients died, but 3 patients were revised prior to death, hence, were not lost to follow-up? As such, LTF=40 while died = 43? In particular, Figure 1 is not clear on this and should be self-explanatory without having to read the text.

We agree with the reviewer that this is difficult to present clearly. We made the decision that any revision, including those in participants who subsequently died prior to final follow-up would be included in the analysis. This occurred in 3 cases, which he have made explicit in the text. Therefore, the reviewer is quite right that LTF was 40, hence 160 participants were available for the final analysis. We do agree that the CONSORT flow diagram is difficult to interpret without the accompanying text. We have therefore added explanatory notes in the figure legend.

19. You present a point estimate for Number Needed to Treat for benefit of 18; I think that if you are going to present the point estimate then a presentation of the uncertainty is warranted via a confidence interval. I assume that this has not been done because it will be very wide and will extend from harm, through infinity, to benefit. Nonetheless, I feel that it is warranted. (See, e.g., Altman D.G. Confidence intervals for the number needed to treat (1998) British Medical Journal, 317 (7168), pp. 1309-1312.) With a quick analysis of your data in Table 3, I make the 95% CI for the NNT for benefit of 18 to be: 11 (Harm) to infinity to 5 (Benefit), consistent with the presentation recommended in Altman's article, above.

On balance we have removed the NNT and left CIs as an alternative means to present the data.

20. The authors have modeled the EQ5-D index data using a standard t-test. I am not disputing the authors' claim that the residuals were approximately normally distributed, but often EQ5-D index data are grossly non-normal, semi-continuous, with spikes at certain values. As such they often require non-standard treatment in the analysis. Was the variance uniform as well as the distribution being approximately normal?

We concur with the reviewer. It is also our experience that the EQ-5D score is often not well approximated by the Normal distribution. However, in this frail population the distributional properties of the measure are often very good – due in part at least to the lack of any marked ceiling effects. Diagnostic plots of residuals showed good agreement with normal approximation theory and no evidence of heteroscedasticity. Therefore we chose to use the t-test and linear regression analysis for reporting EQ-5D outcomes for this study, for reasons of optimality. Although in general we would not see this as setting a precedent, and would always recommend that assumptions be checked carefully when analyzing this measure.

DISCUSSION

21. The authors also included patients who are on anti-platelet therapy. The authors claim that there is no evidence that it can effect the release of gf. This may be true if the platelets or PRP are

activated prior to application, which is not explained in the text. However, for non-activated platelet or PRP the use of Aspirin is still controversial and it is not recommended by several authors for it is inhibition of aggregation and clot formation.

We agree some authors advise not to use PRP in patients taking aspirin. We have made our inclusion of patients taking aspirin explicit to the reader in table 1 and the discussion. To our knowledge there is no evidence that the efficacy of PRP is reduced by concurrent aspirin use. Given that aspirin is such a common medication in this population, and the lack of evidence for its effect on PRP efficacy, we felt it important to include this subgroup in order that the trial be as pragmatic as possible.

TABLES

22. In table 1 there are a few abbreviations that can be omitted or given their definitions (CRF, AMT, NSAI) and I assume the theatre time should be mean time to theatre.

Corrected.

VERSION 2 – REVIEW

REVIEWER	Mr. Joseph Alsousou LMSSA Lon, MD , MRCS Ed D-Phil Research Fellow in Trauma and Orthopaedic Surgery Nuffield Department of Orthopaedic Rheumatology and Musculoskeletal Sciences (NDORMS) University of Oxford Oxford OX3 9DU
REVIEW RETURNED	15-May-2013

THE STUDY	PRP classification systems are essential and the authors need to add this to the paper with the relevant references.
RESULTS & CONCLUSIONS	The authors states that “We researched our choice of product carefully and chose a system that is commonly used in clinical practice and is supported by in vitro research. We have added two important references that describe the nature and activity of the PRP produced using our system of choice” The references describe the product; however I think it is essential that the authors mention some of the biological componenet of this product and it is classification. i.e platelet concentration, white cell concentration. The classification systems are mentioned my previous review (Mishra or Ehrenfest). This is imperative in any PRP clinical research. I suggest adding a sentence with the class of this product.
GENERAL COMMENTS	Thanks to all the authors for amending the manuscript and the detailed reply. Although the paper focus is on clinical application, the introduction still lack the motivation to the study in this particular problem. The beif introduction gives the reader the impression that this is new treatment so let’s try it in hip fractures. I still think that a brief introduction into the effect of PRP on bone with supporting references is required. In reply to the reviewers concern regarding PRP product preparation: The authors states that “We researched our choice of product carefully and chose a system that is commonly used in clinical practice and is supported by in vitro research. We have added two

	important references that describe the nature and activity of the PRP produced using our system of choice” The references describe the product; however I think it is essential that the authors mention some of the biological componenet of this product and it is classification. i.e platelet concentration, white cell concentration. The classification systems are mentioned my previous review (Mishra or Ehrenfest). This is imperative in any PRP clinical research. I suggest adding a sentence with the class of this product. Although this is a pragmatic trial, the delivery method is not a routine pragmatic technique. I still have concerns regarding the delivery method which has not been validated for this particular fracture in any previous study. Can the authors supply evidence or reference of using this delivery method in this fracture? With regards to the higher number of diabetic patients in the treatment group (16% vs. 6.1%): The authors reply “We randomly allocated all our participants to treatment arms and checked for the influence of important baseline characteristics (including diabetes) on outcomes through regression analyses.” But in the manuscript the regression analysis performed was adjusted for sex, fracture displacement, dementia and age. There is no mention of other factors such as diabetes. How was the number of diabetic patients checked in the regression analysis? please clarify in the text

VERSION 2 – AUTHOR RESPONSE

1. PRP classification systems are essential and the authors need to add this to the paper with the relevant references.
We have added the classification of the PRP using Mishra et al classification system.

2. I still think that a brief introduction into the effect of PRP on bone with supporting references is required.
The authors believe that the introduction is succinct and sufficient, building towards the research question. We are prepared to lengthen it if the editor feels it is required.

3. I still have concerns regarding the delivery method which has not been validated for this particular fracture in any previous study.
We believe that we have sufficiently described our technique for other surgeons to reproduce it. We did not conduct any testing of the procedure as we believe that although it is not commonly employed in these fractures it is used elsewhere for the delivery of bioactive products to fracture sites.

4. Regression analysis to account for the higher number of diabetic patients in the treatment group (16% vs. 6.1%).
We have added an additional line in the results to make this more explicit.