Author's response to reviews

Title: Does PRP enhance bone-implant integration? A systematic review

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

thank you for giving us the possibility to improve our manuscript, here the requested changes. We hope that now you’ll consider the manuscript improved, interesting for the readers and suitable for publication.

Sincerely
Dr. Elizaveta Kon, corresponding author and co-authors

**Answers to Rudiger Junker**

Introduction:
In my opinion the aims of the current review should be described as:

1.) to analyze effects of PRP related to implant osseo- as well as soft tissue integration as published in clinical studies;

**A:** Done

2.) to identify implant materials for which the additional use of PRP might be associated with superior osseo- and/or soft tissue healing;

**A:** Done

Materials and Methods

1.) In my opinion the current systematic review should concentrate on RCTs (implant material versus implant material + PRP).

**A:** Done, according to the reviewer request we eliminated the comparative studies from the text in order to give more focus on RCTs. However, in order not to lose information, we moved and summarized comparative studies in a table (Table 2).

2.) There is a need for predefined outcome variables for the analysis of these studies.

**A:** It’s not possible to predefine outcomes variables because these studies are not homogeneous (they are actually heterogeneous in terms of material, study designs, outcome measures…) and not all papers evaluated the same variables. This is also the reason why is not possible to attempt a metaanalysis, whereas results have been analysed and categorized in a more qualitative way. In the end, aim of our study is to assess the potential of PRP, not to describe in detail every single study (the reference of every single paper have been reported), which would require a book in the details requested, and we therefore reported the more interesting and significant findings of each study.

Results
The presentation of the findings per type of material as well as per type of surgery (as mentioned above e.g.: sinus lift, periodontal intrabony defects, periodontal furcation defects…) should follow the chosen outcome variables.

**A:** We eliminated comparative studies in order to shorten the text and make it more readable and concise, as requested. The request of deeply detailing all studies goes in the opposite direction of the previous request, and the presentation of detailed and fragmented results as indicated would make the paper unreadable, without adding any further useful information for the purpose of our study. In fact, as previously underlined, aim of our study is to assess the potential of PRP, not to
describe in detail every single study (the reference of every single paper have been reported), which would require a book in the details requested, and we therefore reported the more interesting and significant findings of each study.

Beside RCTs the findings of not RCTs might be briefly mentioned.

A: We moved comparative not randomized papers in a dedicated table (Table 2) with the requested summary of and main findings.

If one aim of the paper is the identification of implant materials for which the additional use of PRP might be associated with superior osseo- and/or soft tissue integration, the results regarding this question should be mentioned in a separate section within the results.

A: Done.

Discussion
In my opinion the discussion could start with repeating and briefly answering the original questions. Thereafter, the current finding could be discussed per type of material as well as per type of surgery (as mentioned above e.g.: sinus lift, periodontal intrabony defects, periodontal furcation defects…). In the moment the discussion nearly only duplicates and summarizes the results.

A: Done, we modified the text as requested.

Conclusion
The conclusions should address the found effects of PRP on:
1) Bone healing
2) Soft tissue healing
3) Implant materials for which the additional use of PRP might be of advantage regarding bone/soft tissue healing.

A: Done, we modified the conclusions section as requested.

Answers to Massimo Innocenti

Please provide a brief discussion of the association between PRP and BMPs;

A: Done, we added a section on this topic in the discussion chapter, as suggested.

Please change “bone implants” in “bone substitutes” in line 71 in the Introduction section, or reformulate the sentence;

A: Done.

Please add in the Discussion section the “step forward” we have made in the last years, by analyze critically the results of the several reported studies.

A: The step forward has been described in the discussion, documenting the augmentation of high quality studies over time.

Answers to Matthias Schulz
The authors could state how the screening was performed. Has any article been read or have the abstracts been screened for exclusion.

A: According to the reviewer request, in “materials and methods” we clarified the research methodology, also adding a dedicated diagram.

The literature examining the paragraphs of Bioactive glasses and Titanium does not fit. The authors should check the numbering of the literature.

A: Our focus was actually to document the possible interaction of PRP with bone-graft, bone-graft substitutes, and all kinds of different possible implants in favouring integration, and we better clarified it in both title and text. Thus, in this view they actually fit and give indications for the use of PRP in the different surgical scenarios, which was our aim. With regard to the number of papers, we performed again the search but we don’t find any additional clinical papers that met our inclusion criteria for bioactive glass and titanium, using the keywords indicated in the materials and methods. If you have some suggestions, it will be our pleasure to insert them in our review.

The question posed in the title is not clearly answered in the conclusion. One option would be to state that a concluding answer to the question is not possible regarding the current literature.

A: Done. We changed the conclusion chapter as requested.

Line 74: The term “chemical agents” seems to be a little bit misleading. It should be changed into “mediators”.

A: Done.

In the Methods section, the mesh terms for the search in the PubMed database are listed. The authors used the term “osseointegration”. In the rest of the manuscript the term “osteointegration” is used. The authors should be consistent throughout the review and utilize the same term.

A: Done, we corrected it.

In the Results section, in line 118 to 122, it is stated, that “In particular, RCTs and comparative trials have been analysed. Only papers that compared the results of specific treatments with or without PRP were considered. Those using PRP in all the treated groups and where other factors were the only difference were excluded. All papers documenting PRP augmentation for orthopaedic procedures were described separately to understand the evidence available on its potential in this field.” This should be better inserted in the Methods section as far as it is not describing any results.

A: Done, we moved up the section indicated in “materials and methods”.

Line 164: “from” should be replaced using “by”

A: Done.

Line 284 – 293: The authors should check whether the titanium section is covered by the topic of the review. All other materials/methods that are analyzed in the review are supposed to be bone substitutes or transplants.
A: Our intent is to investigate the role of PRP for osseointegration of all implants, graft, graft-substitutes type, because in orthopaedics we use also metal implants and the integration with the surrounding bone tissue is mandatory for an implant success. Our aim was to explore all forms of PRP use as augmentation procedure for the integration of all possible scenarios found in the common surgical practice. We believe that now our aim was clarified in the manuscript and therefore that all the analysis fits. Also, this extensive analysis may results more comprehensive and useful for the readers.

Line 326: “allogenic”
A: Done.

Line 353: “adding”
A: Done.

The authors could discuss the clinical/paraclinical results separately from the results achieved by histology or other methods.

A: This is not possible because articles are extremely heterogeneous and it would result in an uselessful and full of holes tedious and endless description of data, which is actually not the intent of the study. It’s not possible to categorize outcomes variables because these studies are actually heterogeneous in terms of material, study designs, outcome measures… and not all papers evaluated the same variables. This is also the reason why results have been analysed and categorized in a more qualitative way. In the end, aim of our study is to assess the potential of PRP, not to describe in detail every single study (the reference of every single paper have been reported), which would require a book in the details requested, and we therefore reported the more interesting and significant findings of each study.

Answers to Aaron Nauth

The title and abstract are misleading. The use of the term bone implant is confusing. Most authors do not refer to autologous bone graft as an 'implant'. I think the review is better described as the influence of PRP on bone healing when combined with bone graft or bone graft substitutes.

A: Our systematic review focuses on the role of PRP on favouring the integration of all possible implantable materials in orthopedics (graft, graft-substitutes, and also implants of other kinds). So, according to the reviewer suggestion, we have changed the title and set out the study purpose to better explain our intent and our focus.

The vast majority of the literature cited in this paper is from the oral/maxillofacial literature and the findings are difficult to extrapolate to orthopaedics. Is the review of relevance to this journal?

A: We agree with the reviewer, and it is actually surprising, since also in orthopaedics the implant of such materials is common. In this light, this review is of outmost importance, since it give some clues on the clinical evidence of PRP usefulness for graft, implant and graft substitutes integration, materials that are currently used also in orthopaedics settings. Thus, the exploration of another field helps in extending the view of our field (often different fields progresses remain isolated, which is a barrier to overall progress), and gives some evidences and directions for future studies on the
application of these implants in orthopaedics. We underlined this findings and commented it in the

text, to put this unexpected search results into the proper light.

The authors describe their paper as a systematic review. The Cochrane Collaboration defines a

systematic review as follows: "A systematic review attempts to identify, appraise and synthesize all

the empirical evidence that meets pre-specified eligibility criteria to answer a given research

question. Researchers conducting systematic reviews use explicit methods aimed at minimizing bias,

in order to produce more reliable findings that can be used to inform decision making." I do not

think the manuscript the authors have submitted fulfills these criteria. In fact in the results section

(in the abstract) the authors simply describe the number of papers they found and conclude that

there is 'growing interest". They do not make a substantial attempt to synthesize the data and

provide objective conclusions about the effectiveness of PRP for enhancing bone healing when

combined with bone graft or bone graft substitutes.

A: Our paper is not Cochrane, neither a meta-analysis, which by the way would be impossible due
to the heterogeneity of the studies available. However, it is a systematic review because we have
performed our search following the criteria reported in materials and methods: we have identified
some key words and searched for all papers concerning our intent. Thus, the methodology was
appropriate with respect to our declared intent.