PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Platelet-rich fibrin/anorganic bovine bone mineral complex as grafting materials in endodontic microsurgery with a large lesion size: study protocol for a randomised controlled trial
AUTHORS	Han, Bing; Wang, Yuhan; Chen, Zhibin; Zheng, Chunyan; Zhang, Zhichun; Liu, Yingyi; Liu, Kaining; Wang, Xiaoyan; Wang, Zuhua

VERSION 1 – REVIEW

REVIEWER	Mancini, Leonardo University of L'Aquila Department of Clinical Medicine Life Health and Environmental Sciences
REVIEW RETURNED	25-Oct-2021

GENERAL COMMENTS	“Platelet-rich fibrin/anorganic bovine bone mineral complex as grafting materials in endodontic microsurgery with a large lesion size: study protocol for a randomised controlled trial” Dear authors, the present manuscript aims to describe the protocol of future randomized clinical trial regarding the possible use of PRF + bone grafts in endodontic microsurgery. The protocol is nicely performed however there are some inconsistencies/imprecisions, which should be clarified, and some data could be presented more in detail. More specifically, the following issues should be addressed. Introduction Line 21 please provide a reference for this sentence “especially lesion size.” Materials and methods Interventions -Line 20 “Prof Kim 29” this is not the right way to cite a manuscript please correct -Line 29 please define the tube type (e.g. with anticoagulant, plain glass tubes….) and PRF typology that you are going to use (e.g. liquid PRF, L-PRF, A-PRF or PRP) -please also specify the protocol of PRF or PRP preparation according to the literature and previously published protocols because that setting is not usual and common. The use of a CBCT is a valid tool evaluating the possible bone regeneration after 1 year of follow up but at the same time seems

	strange that an ethical committee allows overexposing Patients at X-rays without any important reason but only for a follow-up. Please clarify. Discussion Is in line with the study protocol

REVIEWER	John, B KSR College of Dental Sciences
REVIEW RETURNED	14-Nov-2021

GENERAL COMMENTS	It is a well structured study design. It would be good if you could mention the attrition of your sample as a challenge in your study as you have to record your findings at 4 points. So the patients may be lost to follow up at any point which could be a foreseeable challenge.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

Dear authors, the present manuscript aims to describe the protocol of future randomized clinical trial regarding the possible use of PRF + bone grafts in endodontic microsurgery. The protocol is nicely performed however there are some inconsistencies/imprecisions, which should be clarified, and some data could be presented more in detail. More specifically, the following issues should be addressed.

1. Introduction

Line 21 please provide a reference for this sentence "especially lesion size."

Thank you very much for your suggestion. Two references for this sentence have been added as reference 5 and 6 in the manuscript (Page 5). One reference is a related meta-analysis which suggested that regeneration techniques should be applied during endodontic microsurgery with large lesions to improve the outcome[1]. The other reference is a systematic review which pointed out that the type of lesions including the large lesions play an important role in the prognosis of endodontic microsugery[2].

2. Materials and methods

Interventions

-Line 20 "Prof Kim 29" this is not the right way to cite a manuscript please correct

-Line 29 please define the tube type (e.g. with anticoagulant, plain glass tubes….) and PRF typology that you are going to use (e.g. liquid PRF, L-PRF, A-PRF or PRP)

-please also specify the protocol of PRF or PRP preparation according to the literature and previously published protocols because that setting is not usual and common.

The use of a CBCT is a valid tool evaluating the possible bone regeneration after 1 year of follow up but at the same time seems strange that an ethical committee allows overexposing Patients at X-rays without any important reason but only for a follow-up. Please clarify.

Thank you very much. Line 20 "Prof Kim [29]" have been corrected in a right way to cite (Page 8). The details of the tube type and the PRF typology have been added in the manuscript (Page 8). The protocol of PRF preparation have been added in the manuscript (Page 8).

In order to evaluate the outcome of teeth following endodontic microsurgery, there are two radiographic techniques including radiographic 2D (X-ray) and 3D (CBCT) at present. For the radiographic 2D of X-ray, the most succinct and comprehensive classification were Rud's and Molven's radiographic classification of criteria for success[3, 4]. In recent years, "Penn 3D criteria" were established for assessing outcome on CBCT. The CBCT is more sensitive in detecting a radiolucent area and also allows us to view the lesion three-dimensionally. However, till now, the 2D criteria is still not be replaced with the 3D criteria[5]. Both of the 2D and 3D criteria are recommended[6]. In order to get systematic assessment, either 2-dimensional X-rays or 3-dimensional CBCT imaging would be used to evaluate the outcome[7, 8]. According to previous studies, the effective dose for 2D radiographic methods is very low (2~9 μSv), which is comparable to the daily effective dose from surrounding environment (8 μSv)[8-10]. The X-rays at follow-ups (3, 6 and 12 months of follow-up) could provide more comprehensive information of periapical tissue repairment within 1 year after the endodontic microsurgery. These X-rays could not be replaced by CBCT, because CBCT could not be used so frequently. Only CBCT before and 12 months after the surgery would be obtained, which could provide a more sensitive way in detecting the radiolucent area and also allow us to view the lesion three-dimensionally. This protocol had been approved by the Ethics Committee of Peking University School and Hospital of Stomatology (PKUSSIRB-202059179).

3. Discussion

Is in line with the study protocol

According to previous studies, guided tissue regeneration techniques including usage of grafting materials and membrane should be applied in endodontic microsurgery with large lesion size. The best grafting materials are osteoinductive materials due to the presence of growth factors. But the grafting materials used in clinic are osteoconductive materials without growth factors. PRF contains platelets, leukocytes and more than 100 types of growth factors which could promote the proliferation and differentiation of osteoblasts. The innovation of this protocol is achieving osteoinductive effects by combining the liquid PRF with ABBM evenly in endodontic microsurgery. So the PRF/ABBM complex was mainly discussed in the part of Discussion.

Reviewer 2:

It is a well structured study design. It would be good if you could mention the attrition of your sample as a challenge in your study as you have to record your findings at 4 points. So the patients may be lost to follow up at any point which could be a foreseeable challenge.

Thank you very much for your suggestion. The patients have the right to withdraw from this clinical trial without any reason at any point in the trial. Follow-ups will not be affected by the withdrawal. As

mentioned in the "Sample size" of the methods section, a missed follow-up rate of 20% have already been considered in the protocol. Once more than 20% participants withdrawl occur, new participants will be enrolled. In order to successfully complete the study, the study execute time is from June 2021 to December 2024, and the time will be enough.

References

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VERSION 2 – REVIEW

REVIEWER	Mancini, Leonardo University of L'Aquila Department of Clinical Medicine Life Health and Environmental Sciences

REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	Thank you for providing the revised version. from my point of view now the manuscript is acceptable.