Author’s response to reviews

Title: Early wound healing outcomes after regenerative periodontal surgery with Enamel Matrix Derivatives or Guided Tissue Regeneration: A Systematic Review

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Author’s response to reviews:

Rebuttal to peer review of manuscript OHEA-D-19-00022

“Early wound healing outcomes after regenerative periodontal surgery with Enamel Matrix Derivatives or Guided Tissue Regeneration: A Systematic Review”

Mariana Rojas; Lorenzo Marini; Andrea Pilloni; Philipp Sahrmann

We want to thank the reviewers for their precious suggestions and comments.

We feel that they helped to enhance the paper’s quality.

Hereby, we will respond step-by-step to the concerns.

Changed text sections will be highlighted in order to facilitate tracking the changes performed in the revised manuscript.

Reviewer # 1

Comment 1

The authors conducted a review, aiming to compare the early wound healing after regenerative periodontal surgery with either EMD or GTR treatment. The topic is clinically relevant.

Our response: We thank the reviewer for the appreciation of the work conducted for the study.
However, Conclusion was not made solidly based on the data analysis but just with a descriptive analysis. I suggest performing subgroup analysis to distinguish various defect type instead of making an assumptive conclusion.

Our response:

Results of the present review are based on descriptive data for – as we are sure - good and well-described reasons: In order not to compare apples with oranges we decided not to merge data that is – in the way published – incomparable due to considerable heterogeneity. In order to report the results of the few studies fitting to the focused question in the most accurate way we relied on a descriptive report of the results.

In fact, before composing the text, the authors had actually discussed subgroup analysis but in the end decided not to do for good reasons: Splitting the results of 7 heterogeneous studies by performing a sub-analysis – would not help to give a more valid answer.

However, in order to consider the reviewer’s suggestion, the new version of the manuscript contains a separate paragraph in the results section and an according discussion point regarding the addressed issue and two references -81 and 82- were also added. Finally, the conclusion was reformulated considering this point.

Revised text:

Results

Pages 13,14; lines 419-448:

Teeth and defect characteristics at baseline

The studies reported results based on 220 teeth with different intrabony and furcation defects (one defect per tooth). Of these, 97 defects were treated with EMD and 123 defects with GTR technique. In one study [62], degree III furcation-involved defects in mandibular molars were treated and in another study [61] 3-wall, angular intrabony defects in the interproximal area with an intrabony component ≥ 4 mm (measured from the crest to the deepest point of the bony defect) were selected. In one of the studies 2 to 3-wall defects were used [54] while in another [60] advanced intrabony defects (teeth scheduled for extraction) were treated.

Non-contained combined osseous defects in the interproximal area with an intrabony component ≥ 3 mm were treated in two of the studies [58,59]. Finally, in one of the studies [57] different types of intrabony defects (1, 2 and 3 walls) were included and the treatment was assigned accordingly: 1-wall intrabony component 1-3 mm defects were treated with GTR with e-PTFE titanium reinforced membrane (TrM), 1-wall intrabony component 1-5 mm were treated with
GTR (BM + BG) whereas in 2 to 3-wall narrow defects only MB was used. EMD was applied in the defects with a prevalent 3-wall component.

- See Table 5 (Page 14, line 454).

Results

Pages 19,20; lines 774-801:

Healing outcomes associated to treatment characteristics

-Defect morphology

When 2 to 3-wall intrabony defects [56, 57, 61] were evaluated flap dehiscence/membrane exposure was present in 11/42 (26%) sites treated by GTR and in 3/46 (6.5%) of sites treated with EMD. No dehiscence was observed when non-contained intrabony defects were treated with EMD (40 treated defects) [58,59]. However, when GTR procedure was performed in these defects dehiscence/membrane exposure was observed in 9/63 (14%) of the treated sites [57-59].

One study [60] in which advanced intrabony defects in teeth that were scheduled for extraction were assessed, did not report any complication in the healing process of neither group (EMD and GTR).

Finally, in the furcation GIII defects [62], 7/10 (70%) of the GTR treated sites presented membrane exposure while dehiscence was not observed in the EMD group (4 treated sites).

Discussion

Pages 27,28; lines 1051-1081:

With respect to the first point, one of the most notable differences between the studies was the morphology of the defects (Table 5). Although generally in all studies intrabony defects were included, the spectrum ranged from “advanced intrabony defects” (scheduled for extraction) over 3-wall defects, partially non-containing defects and GIII furcation defects. However, a descriptive analysis distinguishes the different types of defects with respect to the individual treatment that was performed.

In fact, the defect morphology –related also with the surgical approach and the biomaterials selected - strongly influences the results of the surgical procedures [11, 57, 81-82]. Clinical success was reported when contained intrabony defects were treated with EMD. In non-contained intrabony defects, GTR procedures are more indicated [11, 81-82] although it has been
observed in a recent study successful clinical results when non-contained intrabony defects were treated with EMD [83].

In the present systematic review, when the 2-3 wall contained intrabony defects were evaluated it was observed flap dehiscence/membrane exposure in 26% of the sites treated by GTR whereas flap dehiscence was observed in only 6.5% of the sites treated with EMD [56, 57, 61]. Instead, in non-contained defects [57-59] 14% of the GTR treated sites showed membrane exposure while no post-surgical complications were observed in the EMD group.

Finally, in the study treating furcation III defects [62], membrane exposure was observed in seven of the ten treated sites (70%). This study was the only one that compared EMD with either GTR or GTR+EMD. When membrane exposure was assessed in the GTR groups 3 (67%, with GTR) and 5 (71%, with GTR+EMD) of 7 sites were find to show such. Although no meta-analysis was performed due to the small power of the published data it seems that EMD as an adjunct to GTR did not provide an additional benefit in the treatment of furcation GIII defects. At the final follow-up, the results also demonstrated that only a partial closure of the furcation entrance was achieved. This finding was in accordance with a previous clinical study [84] which could not be considered in this review since smokers were included.

Within the present systematic review, no relevant differences in the early wound healing results between EMD and GTR surgical treatment in periodontal intrabony defects can be found, although - when a deeper and detailed evaluation of the studies was performed - a tendency for better early healing in the group treated with EMD seems evident. Especially, when the analysis was performed considering different defect types it was observed that both contained and non-contained intrabony defects presented a higher percentage of dehiscence/membrane exposure when GTR treatment was performed. These findings however should be interpreted with care given the heterogeneity and the quality of the studies included. The higher risk in dehiscence/membrane exposure in GTR procedures, however, cannot be interpreted as a general superiority of EMD in the early wound healing of the treatment of intrabony defects. In fact, when only flap dehiscence was analysed the results observed were similar for both treatment groups (12% GTR versus 10.3% EMD treated sites).

Conclusion

Page 30, 1162-1167:

Due to considerable heterogeneity of the published studies a clear beneficial effect of the EMD on the early wound healing after surgical treatment of periodontal intrabony defects cannot be confirmed.
Standardized RCT studies are needed in order to allow for proper comparison of early wound healing after both types of surgical approaches.

Background

Comment 2

lines 122-123: "The use of EMD on the other hand, has been described to have a positive effect on early wound healing." How was this statement made? Did you infer that GTR may not have positive effect on early wound healing?

Our response:

We agree with the reviewer, feeling that the respective statement might be misinterpreted. Therefore, changed the text in order to clarify – based on three references (31,32,33) – that some studies intend a better healing after the use of EMD.

Revised text:

Page 6, lines 127-130:

The use of EMD on the other hand, has been described to have a positive effect on early wound healing. Specifically, EMD has been shown to accelerate reepithelialisation, wound closure, resolution of inflammation, and prolonged blood vessel formation [31-33].

Comment 3

lines 131-132: The definition of null hypothesis should be "no difference" between the two interventions. Please correct this statement based on the definition of null hypothesis.

Our response:

The reviewer is right and the authors thank for this important clarification. We modified this sentence in the text of the revised manuscript.

Revised text:

Page 6, lines 136-139:

Therefore, this systematic review aimed to compare early wound healing after regenerative periodontal surgery with GTR or EMD application. Our hypothesis was that there is beneficial effect of the EMD respect with GTR on the early wound healing after surgical treatment of periodontal intrabony defects.
Comment 4

line 128: "Adjunct"? Did you compare GTR vs. EMD or GTR vs. GTR+EMD? If you compared the former one, then the EMD is not considered an adjunct.

Our response:

The reviewer is right. We compared GTR vs. EMD. For this reason, the term “adjunct” is not correct in this case. We eliminated this in the main text.

Revised text:

Page 6, lines 134-135:

So far there is no consensus whether the use of EMD may show better early wound healing as compared to GTR.

Methods

Comment 4

lines 155: How about light smokers? Were they also excluded?

Our response:

In fact, light smokers were not included in the present systematic review. We only selected studies with “non-smoker patients” and revised this it in the new inclusion criteria. To clarify this point, the authors decided to add this also in the “exclusion criteria” section. In addition, in the discussion we explain the reason for this decision.

Revised text:

Page 7, lines 161-165:

Exclusion criteria

• Non adult patients;
• Systemic diseases;
• Patients with aggressive periodontitis;
In the present systematic review, we decided to exclude smokers to avoid possible bias considering the fact smoking affects the wound healing process [85]. Indeed, in a recent clinical study [86] in which the impact of smoking status on the clinical outcomes after regenerative surgical procedures were evaluated, the authors concluded that in smoker patients wound healing quality was significantly hampered as when compared to non-smokers. A dose-dependent effect of smoking was observed with respect to the values of PD reduction and CAL gain at 6 months with a tendency to lower values in patients consuming 11-20 cigarettes/day than in smokers from 1 to 10 cigarettes/day. Accordingly, even light smokers were excluded from the present analysis.

Results

Comment 5

line 219: How about the reviewers' agreement on "full text" review?

Our response:

We thank the reviewer for this suggestion. The “full text” review was made for two of the authors (LM and MR) and any disagreement between both reviewers was resolved by discussion with a third reviewer (PS). In order to consider the referee’s critical question, we calculated the agreement in this point and added this information in the main text.

Revised text:

Page 10, lines 231-233:

Finally, seven studies were included [56-62]. Reviewer agreement for title and abstract screening was 92 % and agreement for the full text screening before discussion was 88 %(Table 1).

Comment 6

I will suggest to report the funding sources of each included study since the source of finding may potentially bias the publication outcomes.

Our response:

We appreciate the suggestion of the referee and extracted the regarding information from the studies. We add this information in the results section (Description of the studies - Study
characteristics), in Table 4 and also in a paragraph of the discussion to refer to the potential bias in the outcomes.

Revised text:

Results

Pages 11,12; lines 318-343:

Regarding the funding sources, no according information was given in three of the studies [56, 59, 60]. For two studies [58, 61] no financial or material support was provided by any company. One study [62] reported industrial funding sources (Biora, Basel, Switzerland; Sweden, Padua, Italy and WL Gore, Arizona, USA). One other [57] was partly supported by scientific organisations (Accademia Toscana di Ricerca Odontostomatologica, Florence, Italy and the Periodontal Research fund of the Department of Periodontology of the Eastman Dental Institute, London U.K.

- See table 4 (page 12, line 356)

Discussion

Page 28, lines 1088-1092:

Furthermore, a potential bias regarding the funding sources has to be considered. In concerning this matter there was only one study included that was supported by external companies that sponsored the different biomaterials used for both study groups (EMD and GTR) [62], what rendered the risk for bias rather low.

Discussion

Comment 7

I will suggest to distinguish different type of defects for subgroup discussion, i.e. furcation defect vs. contained defect vs. non-contained defect, since each type of defect is a different entity.

Our response:

The authors agree with the reviewer and they would have been happy to consider each type of defect as a different entity if data and power would have allowed for it. Regarding this issue, please consider our response to comment 1.
As indicated the authors decided to add a paragraph referring to this point in both the results and in the discussion section.

Comment 8

I will suggest to compare GTR vs. EMD (monotherapy), and GTR vs. GTR+EMD(adjunct) since these two can be totally different subgroup comparisons.

Our response:

This comparison was not made because all the studies compare EMD (monotherapy) with GTR procedures except one study, in which EMD was compared with GTR and GTR +EMD. Even though the authors feel that the data assessed allows for a comprehensive comparison a paragraph in the discussion was added that highlights the results of this study.

Revised text:
Page 27, lines 1069-1075:

Finally, in the study treating furcation III defects [62], membrane exposure was observed in seven of the ten treated sites (70%). This study was the only one that compared EMD with either GTR or GTR+EMD. When membrane exposure was assessed in the GTR groups 3 (67%, with GTR) and 5 (71%, with GTR+EMD) of 7 sites were find to show such. Although no meta-analysis was performed due to the small power of the published data is seems that EMD as an adjunct to GTR did not provide an additional benefit in the treatment of furcation GIII defects.

Comment 9

Your conclusion is solely based on ePTFE membrane. Please state this in your conclusion since nowadays most of the GTR will be done with collagen membranes but not ePTFE membrane.

Our response:

The authors accord with the fact that collagen membranes are first choice in the meantime. In fact, as indicated in Table X, most of the included studies assessed the use of resorbable membranes – what maybe did not catch the referee’s attention.

Therefor we decided to highlight this point ny adding another sentence in the discussion to underline the fact that more than half of the GTR treated sites in the studies included in the present review were with resorbable membranes. Please note also our response to comment 10.

Revised text:
Discussion

Page 25, lines 989-994:

It has been demonstrated that non-resorbable membranes have a higher risk of exposure than resorbable membranes in GTR procedures [74]. In the included studies, no such effect was shown. Of 123 sites treated by GTR, in 71 resorbable membranes were used and in 52 e-PTFE membranes. Surprisingly, flap dehiscence/membrane exposure was present in 30% of the sites treated with resorbable membranes, whereas only in 11.5% sites with non resorbable e-PTFE membranes (Table 6).

Pages 29,30; lines 1131-1143:

Within the present systematic review, no relevant differences in the early wound healing results between EMD and GTR surgical treatment in periodontal intrabony defects can be found, although when a deeper and detailed evaluation of the studies was performed - a tendency for better early healing in the group treated with EMD seems evident. Particularly, when the analysis was performed according the different defect types it was observed that both contained and non-contained intrabony defects presented a higher percentage of dehiscence/membrane exposure when GTR treatment was performed. These findings however should be interpreted with care given the heterogeneity and the quality of the studies included. The higher risk for dehiscence and membrane exposure in GTR procedures should not be interpreted as a beneficial effect of EMD in the early wound healing of the treatment of intrabony defects. In fact, when only flap dehiscence was analysed the results observed were similar for both treatment groups (12% GTR versus 10.3% EMD treated sites).

Conclusion

Page 30, lines 1162-1167:

Due to the considerable heterogeneity of the published studies, a clear beneficial effect of the EMD on the early wound healing outcomes after surgical treatment of periodontal intrabony defects cannot be confirmed.

Standardized RCT studies are needed in order to allow for proper comparison of early wound healing after both types of surgical approaches.

Comment 10
Please comment on the use of dPTFE or collagen membranes on the GTR outcome, since ePTFE is not commonly used for GTR anymore.

Our response:

As mentioned in our response to comment 9, e-PTFE membranes were used in three of the included studies (57,58,61) In one of them (61) 3-wall defects were treated. In the other two studies (57,58), non-contained intrabony defects were treated with e-PTFE titanium reinforce membrane.

Therefore, the authors add a paragraph in the discussion to clarify this point.

Revised text:

Page 25, lines 980-998:

It has been demonstrated that non-resorbable membranes have a higher risk of exposure than resorbable membranes in GTR procedures [74]. In the included studies, no such effect was shown. Of 123 sites treated by GTR, in 71 resorbable membranes were used and in 52 e-PTFE membranes. Surprisingly, flap dehiscence/membrane exposure was present in 30% of the sites treated with resorbable membranes, whereas only in 11.5% sites with non resorbable e-PTFE membranes (Table 6).

Regarding this point, it is important to underline that in the selected studies 20 of the 52 treated sites were 3-wall contained intrabony defects. Studies [11, 81-82] show a good prognosis when these defect types are treated with others surgical approaches or with resorbable membranes.

Comment 11

lines 600-602: how did you define "early wound healing"?

Our response:

Healing itself takes place following a well-organized chronology of biological events that are crucial for the quality of the final repair of wounded tissues. Wound closure has been recognized to be crucial for periodontal wound healing, especially following regenerative procedures. As it has been reported that the first postoperative week appears to be critical for the maintenance of wound stability, wound healing should be monitored early.

Although periodontal wound healing is not completed before 2-3 weeks it is important to underline that haemostatic and inflammatory phases and re-epithelization begins at 24 hours after tissue injury.
Therefore, the authors define “early wound healing” as the healing during the first post-surgical week.

A paragraph in the discussion was added indicating this definition of “early”.

Moreover, in our revision, we decided to include studies in which the outcomes were assessed in terms of early wound healing during the time period of one to six weeks. We added this information in the revised text.

Revised text:

Materials and methods

Page 7, lines 166-167:

The outcome was assessed in terms of early wound healing during the time period of one to six weeks.

Discussion

Page 21, lines 861-863:

Wound closure is one of the most important factors in obtaining successful clinical results, especially in regeneration procedures [18]. With this regard, the first post-operative week has been considered critical for the maintenance of wound stability [19].

Reviewer # 2

Comment 1

In this systematic review, the early wound healing outcomes after two periodontal regenerative procedures have been assessed. In particular guided tissue regeneration (GTR) and application of enamel matrix derivatives (EMD) have been considered.

The topic of this review is very interesting. Clinical trials usually assess medium and long-term outcomes of the surgical procedures, however the critical biological as well as clinical aspects that occurs during the first few weeks after surgery and that guide healing towards a regenerative rather than a reparative pattern are poorly investigated.

Our response: We thank the reviewer for the appreciation of the work conducted for the study.
Comment 2

The major issue of the manuscript regards the heterogeneity of the GTR treatments included in the study. Authors included regenerative procedures performed with both resorbable and unresorbable membranes, with the graft of bone substitutes or with the membrane alone (without graft), and even membrane + EMD. Thus it is not clear, what is the factor that the authors think can affect the early wound healing (the membrane, the graft,…?). No data are reported about healing outcomes associated to the use of grafting materials (presence/absence, composition…).

Our response:

We agree with the reviewer regarding the problem of the high heterogeneity of the included studies. For this reason, only a descriptive analysis could be performed without drawing false conclusions.

Defect morphology and different GTR techniques are two aspects that present a wide range of heterogeneity.

However, in order to involve the referee’s suggestion, we added a short section in the discussion section

Revised text:

Discussion

Page 25, lines 989-994

Biomaterials

It has been demonstrated that non-resorbable membranes have a higher risk of exposure than resorbable membranes in GTR procedures [74]. In the included studies, no such effect was shown. Of 123 GTR treated sites, 71 were treated with resorbable membranes while 52 with e-PTFE membranes. Surprisingly, flap dehiscence/membrane exposure was present in 30% of the sites treated with resorbable membranes, whereas only in 11.5% sites with non resorbable e-PTFE membranes (Table 6).

Our response:

On the other hand, the healing outcomes associated with the use of grafting materials were not reported because were used only in one study [57] in 11 out of 123 intrabony defects. The authors therefore consider any further conclusions on this issue critical.
Furthermore, in one study (60), EMD is associated to the membrane. It is not clear if data of sites treated with this combination of biomaterials have been assigned to the EMD or to the GTR group.

Our response: In the study in which EMD was associated with the membrane, the authors included this treated defects in the GTR group since the use of the barrier (membrane) is the bases of the RTG treatment. If the reviewer considers it necessary, we can add this clarification in the text.

Comment 3

Conclusion. Since comparative analysis has not been performed between groups, it is not possible to state "there might be a potential beneficial effect of the EMD on the early wound healing outcomes after surgical treatment of periodontal intrabony defects." Results do not support this conclusion.

Our response:

True! The authors thank the reviewer for this valuable comment. The authors discussed this point together and feel that due to the heterogeneity of the included studies and, consequently, the impossibility of performing a comparative statistical analysis, the conclusion should be altered. Therefore, the conclusion was modified.

Revised text:

Page 30, lines 1162-1167:

Conclusion

Due to the considerable heterogeneity of the published studies, a clear beneficial effect of the EMD on the early wound healing outcomes after surgical treatment of periodontal intrabony defects cannot be confirmed.

Standardized RCT studies are needed in order to allow for proper comparison of early wound healing after both types of surgical approaches.

Minor issues

Comment 4

Table 4: It has been reported "bioreorbable membrane (BM) and collagen membrane (CM)". Collagen membranes are resorbable. What is the difference between CM and BM?.
Our response:

Since no other BMs were assessed we adapted the wording in the table 4 and in the table 6. “CM” was replaced by “BM”.

Revised text:

Page 12,13. Table 4:

V. Iorio-Siciliano
et al.
2014 [57]
EMD + DBBM vs BM + DBBM

Page 47. Table 6:

V. Iorio-Siciliano
et al.
2014 [57]
DBBM + BM

Comment 5

Page 13, line 279. "…angular intrabony defects in the interproximal area ≥4 mm were selected…". Please clarify the concept. Do the authors mean ≥4 mm of intrabony component?

Our response:

Yes, and the author want to thank the referee.

In fact, this value refers to the infrabony component of the defects. We added an according clarification in the revised main text. In addition, we clarified the same point in the second part of the sentence where we also refered to the infrabony component of the defects.

Revised text:

Page 13,14; lines 423-440:
In another study [61] 3-wall, angular intrabony defects in the interproximal area with an infrabony component ≥ 4 mm (measured from the crest to the deepest point of the bony defect) were selected. In one of the studies 2 to 3-wall defects were used [54] while in another [60] advanced intrabony defects (teeth scheduled for extraction) were treated.

Comment 6
Page 18 Defect morphology: please, describe this data separately for GTR and EMD groups.
Our response:
The authors thank the reviewer for this suggestion. This information was now added.
Revised text:
Pages 19, 20; lines 775-801:
-Defect morphology
When 2 to 3-wall intrabony defects [56, 57, 61] were evaluated flap dehiscence/membrane exposure was present in 11/42 (26%) sites treated by GTR and in 3/46 (6.5%) of sites treated with EMD. No dehiscence was observed when non-contained intrabony defects were treated with EMD (40 treated defects) [58, 59]. However, when GTR procedure was performed in these defects dehiscence/membrane exposure was observed in 9/63 (14%) of the treated sites [57-59].

One study [60] in which advanced intrabony defects in teeth that were scheduled for extraction were assessed, did not report any complication in the healing process of neither group (EMD and GTR).

Finally, in the furcation GIII defects [62], 7/10 (70%) of the GTR treated sites presented membrane exposure while dehiscence was not observed in the EMD group (4 treated sites).

Comment 7
Page 20, line 436: Please, remove ":" after findings and add the punctuation mark.
Our response:
We modified this in the main text accordingly.
Revised text:
Page 22, lines 884-886:
Due to a strong heterogeneity a meta-analysis could not be performed, but a descriptive data analysis revealed clinically relevant findings.

Comment 8

Page 20: It is not clear why the frequency of membrane exposure (28%) in GTR group is higher than the frequency of dehiscence (12%). In fact in discussion it has been reported: "if a membrane exposure is present, it means that a dehiscence of the flap has also occurred". It should be highlighted that percentage of dehiscence and membrane exposure have been computed from data of different manuscripts, and this data should be commented.

Our response:

The authors agree with the reviewer with the fact that this point needs clarification. The authors report the results of the studies exactly as mentioned in each one of them. Two of the studies refer to “dehiscence” (57,61) and five studies to “membrane exposure” (56,58,59,60,62). The statement "if a membrane exposure is present, it means that a dehiscence of the flap has also occurred" was the explanation of the authors to make a join analysis of both phenomena (dehiscence and membrane exposure) which in our opinion could be more useful when describing the results. Accordingly, we added an explication on this issue and clarified, that all dehiscencies represented likewise membrane exposures.

Revised text:

Pages 22,23; lines 887-910:

First, the data suggest that there is no relevant difference in the early wound healing outcomes between the two treatments evaluated, since flap dehiscence was observed in the 12% of the GTR treated sites and in the 10.3% of the EMD treated sites [57,61]. Second, other parameters as suppuration, abscess and allergic reactions were not reported in any of the studies. Swelling was reported in one study [59] but without a difference between the two treatment groups. However, membrane exposure was observed in the 28.8% of the GTR treated sites in 5 studies [56, 58, 59, 60, 62]. While this finding was reported in a considerable number of times, the control group using EMD did not show such undesired wound healings. In our reading the phenomenon “membrane exposition” is strictly related to flap dehiscence. A flap dehiscence may not necessarily result always in a membrane exposure but if a membrane exposure is present, it means that a dehiscence of the flap has also occurred. Therefore, this parameter should not be considered separately. Moreover, none of the studies included reported both parameters. Dehiscence was evaluated in only two of the studies [57, 61] while membrane exposure in five of them [56, 58, 59, 60, 62]. Therefore, an analysis of both parameters together could be useful.
Comment 9

Page 21, line 451-452. "minimal amount (3.1%) in the EMD treated sites whereas flap dehiscence/membrane exposure was observed in the 22% of GTR…". These data (3.1% and 22%) are not reported in the results. Please, report them.

Our response:

The reviewer is right and we thank the referee for this input.

We add a paragraph with this information in the results section (early wound healing outcomes) of the main text.

Revised text: page 19, lines 767-770:

When flap dehiscence and membrane exposure were evaluated together it was observed that flap dehiscence was registered only 3.1% in the EMD treated sites whereas flap dehiscence/membrane exposure was observed in the 22% of defects treated with GTR.

Comment 10

Page 21, line 472: "during the first first post-surgical…"

Our response: the reviewer is right. We corrected the mistake in the main text.

Revised text:

Page 24, line 933:

Suturing is one of the most important factors related to wound stability [67], especially during the first post-surgical weeks

Comment 11

Page 22, line 490: please, add "of the" after (5/39).

Our response:

We corrected the text.

Revised text:

Page 24, line 964:
In one study [61] the first evaluation was made at 5 days and, at this time, a wound dehiscence could be observed in the 14% (5/39) of the treated sites.

Comment 12

Page 24, line 530: "with antibiotic administration In fact…" Please, add the punctuation mark after "administration".

Our response:

We added the punctuation mark in the main text.

Revised text:

page 26, line 1026:

“…were not more frequent than in the studies with antibiotic administration. In fact,…”

Comment 13

Page 24, line 542: "especially considered: First, the already mentioned...". Please change First, with first.

Our response:

Thanks, we changed the text accordingly.

Revised text:

Page 26, line 1038:

“Two important aspects related with the included studies should be especially considered: first, the already mentioned…”