Author’s response to reviews

Title: Bryophyllum pinnatum enhances the inhibitory effect of atosiban and nifedipine on human myometrial contractility: an in vitro study

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Author’s response to reviews:

From:

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To:

BMC Complementary and Alternative Medicine

Zurich, 19th of September 2019

Dear Sir or Madam
Please find enclosed the revised version of our manuscript entitled “Bryophyllum pinnatum enhances the inhibitory effect of atosiban and nifedipine on human myometrial contractility in vitro” by Stefanie Santos, Christian Haslinger, Mónica Mennet, Ursula von Mandach, Matthias Hamburger and myself.

We have revised the paper according to the reviewers’ suggestions and the changed text is highlighted in yellow. We are grateful for the feedback and suggestions, which we believe have markedly contributed to improve our manuscript. Please see below point-by-point response to the Reviewers’ comments. The order and content of the declarations was changed and complemented in accordance to the journal requirements.

We hope that the new version of our manuscript is adequate for publication at BMC Complementary and Alternative Medicine and hope that a quick acceptance of the paper will be possible.

Yours sincerely,

Dr. Ana Paula Simões-Wüst

Point-by-point response

Thomas Monsees (Reviewer 1): A well planned and written manuscript which findings might have clinical relevance.

Background p 4, line 79: Authors should include reasons why a recent randomized trial using this plant extract (BPJ) was discontinued early.

Answer: Done (see p. 4, lines 87-90)

Discussion p 12, last paragraph: Authors should discuss what might be the reason that BPJ increases the frequency of contractions whereas other tocolytics do not?

Answer: Now we are investigating the signalling pathways that are involved in the mechanism of action of Bryophyllum press juice and start to have some hypothesis that would explain the increase of frequency in the myograph model. In the revised version of the present manuscript this is shortly mentioned (see p. 16, lines 371-377).

Also, can authors refer to previous plant analysis to indicate possible components of BPJ that might induce uterine contractions?

Answer: (see p. 16, lines 366-371).
Carsten Gründemann (Reviewer 2): In the context of obstetrics, the authors investigated the influence of Bryophyllum pinnatum extracts alone or in combination with common clinical-used synthetic drugs on contractility by using primary myometrium biopsies.

The topic of the manuscript is clinical relevant, the experimental setting is straight forward designed and the article is well and concisely written but needs further revision before its acceptance.

The authors have to revise as follow:

1.) Please include the votum identification number and approval date from the local ethics committee into the design section.

Answer: Done (see p. 6, lines 126-127).

2.) Please combine the two paragraphs "Combination of BPJ and atosiban/nifedipine" in the methods section.

Answer: Done (see p. 7, line 152 - p. 8, line 168).

3.) Please demonstrate with experiments in an additional readout system that the contraction capacities of the myometrium biopsies are not mediated through reduction in viability.

Answer: We had previously shown that BPJ does not affect myometrial cell viability using an additional, independent readout and at concentrations markedly higher than those used in the present work (see reference 33 from the revised version). Indeed, the proof that BPJ does not affect myometrial cell viability when used in combination with atosiban or with nifedipine was missing in the previous version. The revised version comprises cell viability tests performed with myometrium cells treated with the same concentrations as in the combination experiments, with 2x and 4x those same concentrations during 24 h. Moreover, we show with fluorescence microscopy that the cells are not undergoing apoptosis (methods on p. 9, line 203 – p. 10, line 240; results on p. 13, line 306 – p. 14, line 329 and on Fig. 5; discussion on p. 14, lines 329-330).

4.) To strengthen the main conclusion of the manuscript it is necessary to demonstrate that BPJ alone and in combination with atosiban and/or nifedipine has dose-dependent activity on your actual experimental read out. Please provide these additional data in combined figures.

Answer: Previous work (reference 24 of the revised version) showed that BPJ has a concentration-dependent effect on the strength of myometrial contractility. We thank the Reviewer for this suggestion of showing as well the dose-dependency of the combined
treatments. These new data are now shown – side-by-side with those of BPJ and control – in Figure 3 and indeed resulted in a marked improvement of our manuscript.