

Curitiba, 24th November, 2019.

To Editorial Office
World Journal of Experimental Medicine

Dear Editor,

I am sending you the revised version of the manuscript “**Alendronate disturbs femoral growth due to changes during immunolocalization of TGF- β 1/BMP2 in epiphyseal plate**”. Revisions were made in accordance to reviewer’s comments. Changes were highlighted in the manuscript in order to facilitate the revision. You will see below that I copied the reviewer’s comments before each answer to facilitate the comprehension of this letter.

SPECIFIC COMMENTS TO AUTHORS

COMMENTS INDICATED BY REVIEWER #1

Comments of this reviewer are:

a) “AIM: Verify” Better “Aim: To verify” “On th third day”

Answer: 1 - we changes verify for “to verify”

2- The incorrect term “On th third day” was altered to "on the third day"

b) the “Table-1- Demonstrates median” Better: “Table 1: Median...” The same also for Table 2 and Table 3.

Answer: we corrected the tables legend according to reviewer

c) In addition, avoid the word demonstrates in the legend of figure.

We altered the legend according toreveiwer.. In this section you can see

“Fig. 1 – A - Endochondral ossification on 3rd day on control (a1) and after Alendronate administration (a2). Reveals positivity for TGF- β 1 (brownish color) in proliferative (Chevron arrow), maturation (keys) and hyperplasic stratum of cartilage, while reserve stratum was negative. On other hand the group that received

Alendronate there was an intense positivity for BMP-2 (red color) in reserve stratum (arrow) and proliferative (head of arrow) zones, while maturation (chevron arrows) and hyperplasic stratum (brackets) of cartilage demonstrated positivity for both TGF- β 1 (brown) and BMP-2 (red). B - Endochondral ossification on 12th day. The micrographs b1 reveals the control group, and demonstrates similar pattern for TGF- β 1, but also shows evident presence of BMP-2 in hyperplasic chondrocytes (head of arrows). Micrograph b2 reveals the maintaining of presence of BMP-2 on all stratum of cartilage, at the same time that show an ectopic mineralization (brackets) and decrease of hypertrophic zone of chondrocytes with intense positivity for BMP-2.

d) Maybe showing is better A limitation section in the discussion is needed A section of how this study adds in the existing literature is needed in the discussion.

We added a paragraph as suggested by reviewer.
you can see:

However this cross-sectional study has some limitations. we evaluated the macroscopic , histological and immunohistochemical aspects on 3rd and 12th day of development and few data may be stipulated in the intermediated stages of development of epiphyseal plate. The immunohistochemistry staining identifies proteins present in chondroid matrix or bone matrix, regardless of the time when they were expressed. In addition, this study focused only on epiphyseal plate area and the present results may not be extrapolated to total appendicular or axial bone repair, as well as craniofacial bones since that constitutes are derived from distinct embryological sources and it also demonstrate different functional properties and exhibit differences in protein composition [19]. However this study may give an important information, and it may contribute to the debate over the clinical use of alendronate in earlier stages of bone development.

We hope we have addressed all the reviewers' comments properly.

Yours faithfully,

Allan Fernando Giovanini, PhD