Author's response to reviews

Title: Manual therapy followed by specific active exercises versus a placebo followed by specific active exercises on the improvement of functional disability in patients with chronic non specific low back pain: a randomized controlled trial

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Author's response to reviews: see over
General comments

We thank the reviewers for the constructive remarks. As suggested by reviewer 1, we performed new statistical analyses. We also use an alpha level of 0.025 to make inference about the two main outcomes (i.e., pain and function). This work was performed by Dr. P. Ballabeni who also read the manuscript and participated actively to its correction. Therefore, we suggest that Dr. Ballabeni is included as coauthor of this study.

With the new statistical analyses, the effect of manual therapy, followed immediately by active exercises, was confirmed. Moreover, this therapy combined with active exercises might also improve the pain (p=0.032, alphal = 0.025).

We have accepted almost all the comments of the reviewers and highlighted the corrections in yellow. We believe that the changes have improved the quality of this manuscript.

Finally, the results section has been described more in details. This is specially the case for the Shirado results, which are also briefly commented in the discussion section (lines 333-337).

Reviewer 1

1) Abstract
   a) In the new statistical analysis, which is certainly more appropriate and powerful, the treatment effect on pain is actually the effect of manual therapy and not of baseline differences between treatment groups. Therefore, the conclusions are more easy to understand
   b) Short term has been replaced by immediate.

2) We agree with the reviewer that the randomization should be described more thoroughly. A new paragraph was therefore added in the new manuscript (lines 128 to 133):
   “Following the initial evaluation visit, patients were randomly assigned to their treatment group. Concealment allocation was performed by using a randomized table of numbers [38], from which every four consecutive numbers were retained. Individual index cards with the corresponding number were folded and placed in consecutively numbered, sealed opaque envelopes. Even numbers were allocated to the manual therapy (MT) group and odd numbers to the sham therapy group (ST)”

3) Sample size calculation. We have added a new paragraph on the sample size calculation (lines 114-118):
   ”Before the study, calculated the sample size needed to detect a predicted effect of an ODI score difference of 5.5 with a SD of 10 [22, 37]. We predicted that 52 patients per group were needed to reach a power of 0.8 with a type I error probability of 5%. During the experimental phase, we had problems with patient recruitment and were forced, for financial reasons, to stop the patients’ recruitments before the target sample size was reached.”

4) Chapter on statistical analysis was re-written and the use of the new significance threshold for the two outcomes was described (lines 238-239)

5) The term “Time effect” has been reserved to the main effect analysis.

6) As suggested by the reviewer, we used a different method for longitudinal analysis (linear mixed models). The method section has been totally rewritten (lines 229-236) :
“The effect of treatment (MT + AE vs. ST + AE), time and the treatment-time interaction on the six outcome variables pain intensity (VAS-pain (average 48-hour pain)), ODI, FABQ-Wk, FABQ-PA, Sorensen and Shirado, evaluated, after the 8th therapeutic session, and at 3 and 6 months after the end of treatment, were estimated by means of random coefficient linear mixed models. The outcomes’ baseline values (measure before treatment) were entered as a covariate to adjust for baseline differences between treatments. First, the analysis was performed with the interaction. When the effect was not significant, the analysis was repeated without the interaction.”

7) The statistics for the immediate pain analyses has been performed by using a mixed model. The Methods section has been rewritten accordingly (lines 223-229):

“The effect of intervention (MT vs. ST), time and the intervention-time interaction on the immediate effect of the intervention (VAS-pain (immediate effect)) at each time point (pain after minus pain before) was analysed by means of random coefficient linear mixed models. In these models, the effects of the independent variables are allowed to vary between subjects. In other words, subjects were allowed to have their individual slopes for the outcome over time. To control for potential bias due to regression to the mean, pain measured before each therapeutic session was entered in the model as time-varying covariate.”

8) The reviewer suggests replacing Figure 2 by a table. As suggested we removed figure 2. However, the figure 3 of the old manuscript reported pain results (immediate and through the 8-wk treatments). We think that a new table will present the same results twice (i.e., those of figure 3 of the old version). For this reason, we kept this figure 3 (Figure 2 in the new version) with a new comment (lines 558-560):

“Manual therapy induced a greater immediate effect (i.e. difference between after and before) than sham therapy.”

9) Table 2 of the old manuscript has been replaced by three tables, i.e. table 2 (with the means of the outcomes) and table 3 (with the statistical results for primary outcomes) and Table 4 (statistical results for secondary outcomes). With the new statistical analyses, which includes the baseline as a covariate, the terms are no more confusing (i.e., the term “treatment” represents really the treatment effect)

10) The results have been presented separately for the primary and secondary outcomes (tables 3 and 4)

11) Discussion
   a) The discussion has been changed according to the new analyses.
   b) Heterogeneity (see lines 347-348) and small sample size (see lines 349-350)
   c) As suggested we added a sentence as follows (lines 345-346):
      “Moreover, one additional limitation is that the therapist, providing the sham ultrasound, could be blinded to the sham (i.e. could not know that the ultrasound were not efficient).”
   d) The reviewer suggested adding that “the specific effects of manual therapy regimen may not be isolated because the non specific effects of the sham therapy ultrasound may be different from the non specific effects of manipulation regimen”. We totally agree that this suggestion is pertinent. However, we did not correct the manuscript because we believe that this rationale could be generalized to many interventions studies. Consequently, to our opinion, this rationale could be included into the “general knowledge” of controlled studies.

12) Conclusion
a) The immediate effect has been confirmed
b) The results of the primary outcomes have been discussed.
c) Preliminary results (pilot study). This rationale has been discussed in the conclusion

2) Reviewer 2

The third sentence (“Mainly, risk factors…”) was rewritten as follows (lines 64-66):
“Moreover, psycho-social, physical and behavioral components play an important role in the occurrence of chronic non specific low back pain (CNSLBP)”

The reviewer suggested adding that other models are also available. The sentence has been corrected accordingly (lines 68-70):
“Several CNSLBP Models have been conceptualized in order to select better appropriate conservative treatments (e.g., Biomedical Model of health; Biopsychosocial Model of Disability [8])”.

Last sentence (line 72): evidences was corrected by evidence

Line 74: system was added to central nervous

Line 76: studies was corrected by study

Line 77: Enhance/increase was corrected by inappropriate

Lines 80-82 were rewritten as follows:
” Unfortunately, this strategy may be difficult to initiate due to fear that movements would induce more pain and/or injury [15].

Lines 83-85 were described more in details:
“In fact, CNSLBP patients would tend to show signs of negative anticipation, poor pain tolerance and low level of exercise/activity achievement and outcome when asked to exercise [16-20]”

Line 86: changed RCT observed was replaced by randomized controlled trials reported

Last line: “as well” was removed

2.1 Subjects: Last line 106 was changed by : the usual medication can be continued

Page 10 (lines 189-191), the sentence was replaced by:
“At the end of the 8 therapeutic sessions, no particular recommendations were given to patients but to continue their exercises if desired. This issue was not investigated at the 3- and 6-month evaluation visits”

Statistical analysis: power analysis was performed (see lines 11-118)

Details on the lost of the follow-up were added (lines 356-358).

Discussion (p14 of the old manuscript) has been replaced by the following sentence (lines 315-316):
“The reported analgesic effect of manual therapy (i.e., the immediate effect) may allow the patient to perform better/more accurate active exercises.”
Discussion p15, second paragraph of the old manuscript “this should be confirmed”. With the new statistical analyses, we did not find any changes in FABQ-wk, this sentence in no more valid and has been removed.

Discussion p15, last sentence of the old manuscript. The following sentence “Therefore, they were not optimal to isolate any effect” was removed (line 348)

Next line the following sentence in the old manuscript “the number of patients was not important but comparable...” was reformulated in the new manuscript (line 350). The word “Inconvenience” has been replaced, as suggested, by “limitation” (line 351)

Discussion p 16 The word Type II error was removed and the sentence was reformulated as follows (lines 353-355):

“Nonetheless, further studies with a larger number of patients are obviously needed in order to assess the exact role of fear avoidance in this therapy.”

P 16 of the old manuscript. The sentence “Data of all patients were integrated into the study analysis” was replaced by (lines 356-357)

“All data available from patients, even if they dropped out of the study”