Author's response to reviews

Title: The effectiveness of combined bracing and exercise in adolescent idiopathic scoliosis based on SRS and SOSORT criteria: A prospective study.

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Version: 3 Date: 1 March 2014

Author's response to reviews: see over
We wish to thank the Associate Editor and the reviewers for their contributions to increase the quality of our paper. We provide below a point-by-point answer to your remarks.

**Associate Editor**

The referees have both considered this study as an important study in this field. The short comments from both reviewers should be considered when revising the manuscript. A selection bias may be suspected because only 73/3883 patients were included, but the flow chart gives an excellent view of the selection process. The design of the study does not allow for causal interference and the authors should moderate their arguments and conclusion. The results of this relatively small study with short follow up just supports the results of previous studies. The use of exercises in addition to brace may improve compliance and results but the effect of the combined treatment compared with bracing can not be evaluated in the present study but should be assessed in an RCT.

We completely agree with you.

The authors have designed their study strictly to the accepted criteria, but they should keep in mind that these criteria are consensus based. Therefore, they should broaden their perspective in the discussion. In research it is important that we are not just copying what other have done or are doing but that we critically question common opinion, particularly if this is consensus based. A paragraph in the discussion should question the strict criteria and their evidence. In my opinion it does not make much sense to exclude studies that have included some patients aged 7, 8 or 9 years. By example we found that there were no difference between patients with late-onset juvenile scoliosis (which is a smaller group of patients) and patients with AIS. We studied results at very long term follow up in a much larger cohort of patients (Lange et al and Lange et al) and the influence of compliance in another study (Brox et al.). These studies should be referred to in the discussion. The results strongly support the results of the current study in terms of the effectiveness of bracing and in my opinion it is a reference bias not to include them. Also, the US-trial did not actually fail, but was partly changed to an observational study. This study was recently published in the NEJM and is by far the best study in this field and results indicate that bracing is effective and that compliance is an important aspect of success.

The main aim of the SOSORT and SRS consensuses was to give some rules to make all studies concerning brace efficacy to be comparable to each other. Specifically, the SRS criteria will allow in a short time to have a wide population with the same inclusion and outcome criteria so to perform some meta-studies; the SOSORT criteria in reality are management criteria, specifying what should be the best actual practice in treating patients with braces. That is why the authors designed the study respecting strictly these specific criteria. We agree with you that the mere respect of criteria only based on the fact that all the other do the same can be a great limitation from the researcher point of view, but this was not at all the case. The respect of the proposed criteria aim to enrich the research in the field of conservative treatment of scoliosis. We can specify this by referring to the results by Brox et al and Lange et al and Lange et al.

The text was changed as follows:

...Some previously published papers strongly support the results of the current study in terms of the effectiveness of bracing, but the comparisons are limited by the lack of a complete respect to the SOSORT and SRS criteria. (Brox et al and Lange et al and Lange et al.) This point of view justify the choice of a design of the study strictly respecting these criteria, which have been proposed only by consensus, but aim to make comparable the results obtained by different group of researchers.

I agree that logistic regression should be used to evaluate predictors. This analysis may include up to 7 predictors with success/non-success as the dependent variable. All 73 patients should be included and the following predictors BMI, kyphosis, Cobb, age at baseline, compliance, type of brace, eventually major right thoracic curve or not.

The rules of clinical research methodology may require a regression analysis for all the predictors proposed, but when the authors planned the study, they decided not to analyse predictors because of...
the small size of the sample and the observational design. Surely when the authors will have a bigger sample in the future, the regression logistic analysis will be performed, but in this study all authors agreed not to evaluate predictors.

In general, there are too many tables and figures. Figure 2 and table 3 could be omitted. In table 1 I prefer percentages with no decimals, table 5 too detailed and at least not more than one decimal should be given considering a measurement error of about 4 degrees for Cobb angles.

Thank you for the suggestion, tables have been modified and figures 2 and table 3 omitted.

Please separate discussion from results... and again on page 9, results do not prove but support.

There are some misprints like march (March), patients dropped-out who had (patients who dropped out had), Efficacy (efficacy).

Thank you very much we corrected all your annotation in the text.

Reviewer TB Grivas

Thank you for your comment. The paper was written and submitted well before the BRAIST study was published and presented in Lyon (September 2013): at that point evidence on bracing was questioned much more than now. Anyway, we changed the introduction and discussion and inserted the BRAIST study reference as follows:

Recently a multicenter RCT investigating the role of bracing in AIS patients at risk of curve progression, confirmed brace efficacy. The authors conclude that bracing significantly decreased the progression of high risk curves and that the longer the brace wear the best were the results.

(Effects of Bracing in Adolescents with Idiopathic Scoliosis Stuart L. Weinstein, M.D., Lori A. Dolan, Ph.D., James G. Wright, M.D., M.P.H., and Matthew B. Dobbs, M.D. Previously, a Cochrane review [1] has shown that there is evidence in favor of bracing effectiveness in adolescent idiopathic scoliosis (AIS) treatment. This result is based on a study by Nachemson [2], performed in the name of the Scoliosis Research Society (SRS), where success rates at 4 years were: bracing 74% (95% confidence interval – 95CI: 52-84); observation 34% (95CI: 16-49); and electrical stimulation 33% (95CI 12-60). Due to the design of this study (prospective observational controlled cohort), and its uniqueness, the evidence in favor of bracing was defined as “very low quality”. To increase this quality we would need randomized controlled trials (RCTs); nevertheless, RCTs either in the Netherlands [3-5], and in the US [6] failed, the latter being changed to observational [7], due to the difficulty in recruiting patients; recently, results of an RCT on the SpineCor brace have been presented at the SOSORT Meeting [8].

Reviewer R Adobor

Thank you for your comments. Please see above for a general answer to each of your remarks. You can find below all the answers required.

Major Compulsory Revisions

Authors must provide statistical analysis preferably multiple regression analysis. In cases of statistical significant results, p values and 95% confidential intervals should be provided.

Manuscript needs major language revision and reorganization of the context

A multivariate model, might demonstrate some predictors, but the small sample size and the observational design make the authors to decide not to perform this analysis. In the next years the authors will be able to publish a bigger observational study and surely all predictors will be analysed with the logistic regression analysis, with greater probability to find significant values.

Discretionary Revisions

Figures 2 & 3 could simply be shown as descriptive statistics with mean age and range

As suggested by the associate editor Figure 2 have been omitted and figure 3 have been change in table with mean and range.
General comments
1. Is the question posed by the authors well defined?
Comment: The question posed by the authors could be better defined for easier reading. The research question posed in this study is confusing. Is it the effectivity of the combination of exercise and bracing that is being studied or is it the effectivity of the different types of braces that is being studied or is it the effectivity of combining SRS criteria and SOSORT criteria that is being studied? A more suitable title is suggested: “The effectiveness of combined bracing and exercise in adolescent idiopathic scoliosis based on srs and sosort criteria: A prospective study.

   Thank you very much for title suggestion, indeed the main object of the study was to present the prospective results of the conservative treatment respecting the SOSORT and SRS criteria for results definition. The conservative treatment in agreement with the international guidelines of adolescent idiopathic scoliosis include braces associated to exercises. The text was changed as follows:

Aim of the actual study is to investigate the efficacy of a complete conservative treatment of AIS(brace plus exercises) through an observational study and in the total respect of the SOSORT and SRS criteria.

2. Are the methods appropriate and well described?
Comment: Methods are appropriate but the subjective prescription of brace use according to “clinical needs” is not well defined. The authors described the selection of patients for specific brace type. It will be useful if authors could explain if this selection method has been validated in order to avoid the introduction of bias.

The prescription were always based on the international guidelines for the treatment of AIS, and all the Physician working in ISICO Institute work in team and share the same principle for the therapeutical choices. The reviewer can agree that if we want to avoid this bias the only way was to reduce the sample to the patients belonging only to one of the medical doctor. But by doing so the sample would have been smaller and the power of the study less significant, without avoiding completely the subjectivity bias.

The text has been modified as follows:

All the prescriptions were in complete agreement with international guidelines () of AIS and all the physician involved in the study were part of a team sharing all the treatment aim and all the therapeutical choices.

3. Are the data sound?
Comment: The data is sound, but data reporting is complicated.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Comment: The adherence to the relevant standards for reporting and data deposition could have been better.

My suggestion for the authors is to revise the manuscript to better adhere to the standards of reporting.

The introduction should be limited to the specific issue of bracing and exercise in the treatment of adolescent idiopathic patients with scoliosis.

The digression on SRS and SOSORT criteria, is important to make the reader aware about the importance of the respect of these criteria. The main aim of the SOSORT and SRS consensuses was to give some rules to make all studies concerning brace efficacy to be comparable to each other. That is why the authors design the study respecting strictly these specific criteria. Someone should advocate that in research the mere respect of criteria only based on the fact that all the other do the same is a great limitation. In this specific field the respect of the proposed criteria aim to enrich the research in the field of conservative treatment of scoliosis, so we think that is very important to make the reader aware about the meaning of this criteria and their usefulness.

Methods should be limited to the description of the specific methods used in the research.

There is no need for discussion here.
Authors concluded that BMI, thoracic kyphosis, ATR and Cobb angle had statistically significant results on treatment outcome, and failures without reporting the statistical analysis used and no p values were reported.

The analysis of the variance was used to find differences among groups according to the results: worsened, stabilized and improved. We specified this in the results. Since multiple parameters were studied, a multiple regression analysis could be employed to examine the effect of various factors on treatment outcome and failures thereby eliminating confounders.

We already explained the reason why we decided not to perform the regression test.

Correct terminology should be used. Kyphosis was reported as (C7+L3 plumb line distance). Kyphosis is usually measured from T1/T5-T12 according to SRS terminology. The C7+L3 distance is also called Sagittal Index and it was demonstrated that is a reliable index for the clinical evaluation of kyphosis as previously published: Zaina F, Donzelli S, Lusini M, Negrini S. How to measure kyphosis in everyday clinical practice: a reliability study on different methods. *Stud Health Technol Inform*. 2012;176:264-7.

Now the text was changed and this is clearly explained. Thank you.

Worst thoracic ATR is ambiguous.

Thank you, we changed it in the major Thoracic ATR.

Low and high flexibility should be substituted for low and high rigidity. **DONE**

Specific Cobb measure should be used instead of “important Cobb degrees”.

I’m sorry, but in this case “important” was used with the meaning of severe, so I think that it is a misunderstanding due to our language difficulties. So we changed important with severe.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

Comment:

The discussions and the conclusions are not well balanced and not adequately supported by the data. There is ample evidence in the literature including a recent RCT study that bracing according to the SRS criteria is effective in preventing progression and limiting surgery. There is also evidence that the effectiveness of bracing is dependent on compliance and counseling. The effectivity of exercise in reducing curve progression in patients with adolescent idiopathic scoliosis has not been scientifically established yet. The effect of exercise in this study has not been measured objectively. The authors have not differentiated the effect of exercise on the curves from exercise merely increasing compliance or counselling. The study shows good treatment outcome results yet the only conclusion one can draw from it is that bracing is effective in limiting progression and surgery in patients with adolescent idiopathic scoliosis who satisfy SRS and SOSORT criteria. Moreover, exercise is beneficial in patients being braced for AIS.

Thank you for these interesting annotation, it is not possible to measure exercise objectively, as compliance to exercises can not be verified or demonstrate, we specify this argue in the discussion. All patients were treated according to a specific protocol used in our Institute which associate exercises to brace treatment, so the results concern the efficacy of brace associated with exercises.

6. Are limitations of the work clearly stated?

Comment: The authors have clearly stated the strengths of the study but unfortunately limitations of the work have not clearly been stated. The subjective selection of brace treatment according to “clinical needs” is clearly a limitation in the present study.

The prescription of the brace type and dose have to be personalized according to the specific clinical needs of each patients and must be decided by experts in the treatment of AIS in agreement
with his specific experience. The patients included into the study were treated in the same Institute specialized in the treatment of spine pathologies. All MD involved have a high grade of experience and work in the same team thus sharing with all the colleagues the same strategies for brace treatment. This team work can also guarantee a good uniformity. All experts involved into the study strictly follow the actual international guidelines cited below:

- **It is recommended that braces are worn full time or no less than 18 hours per day at the beginning of treatment, unless otherwise justified in the opinion of a clinician specialized in conservative treatment of spinal deformities (SoR: B) (SoE: IV) [145, 160]**

- **Since there is a “dose-response” to treatment, it is recommended that the hours of bracing per day are in proportion with the severity of deformity, the age of the patient, the stage, aim and overall results of treatment, and the achievable compliance (SoR: B) (SoE: IV) [145, 160]**

- **It is recommended that each treating team provide the brace that they know best and are most prepared to manage: due to the actual knowledge, there is no brace that can be recommended over the others (SoR: C) (SoE: IV) [134, 138, 139, 141, 145]**

Secondly the inclusion of several parameters (several types of braces and lack of description of exercise and dosage) is a limitation that needs to be addressed. The lack of use of a regression analysis on the effect of the multiple braces and different types of exercise and other factors on the outcome measure is certainly a limitation in the study that needs to be addressed.

We added a little digression in the discussion as reported below. The inclusion of different brace type and the association with exercise can be interpreted as a limitation of the study, because of the effects of confounders. However the scientific literature is not yet able to demonstrate what is the best brace for scoliosis treatment, and it is not yet possible to objectively measure the effects of exercises. In addition the study was done in a everyday clinical setting and not in experimental setting. Another possible limitation is that the treatment management was done by different specialists; according to their personal experience and the specific clinical need of patients. Though all patients included into the study were treated in the same Institute specialized in the treatment of spine pathologies. All specialists involved have a high grade of experience and work in the same team thus sharing with all the colleagues the same strategies for brace treatment. All experts involved into the study strictly follow the actual international guidelines. All these aspect can contribute to a good uniformity.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Comment: The authors have clearly acknowledged previous work upon which they have built the present research.

8. Do the title and abstract accurately convey what has been found?

Comment: The title and the abstract needs to be revised according to suggestions in this review. The abstract needs to be rewritten and better formed and composed to function as an autonomous text for easier reading.

9. Is the writing acceptable?

Comment: The style and form of writing needs to be greatly improved. I suggest that authors seek assistance from a native English speaker or a professional scientific editor for language editing. This manuscript is not ready for publication in its present form. This reviewer will be willing to assist in further review of this manuscript and get it ready for publication in “Scoliosis” after a major review of this manuscript has been performed.

Specific comments

Abstract
Background Context
A Cochrane review suggests that, while waiting for RCTs results, studies according to the SRS criteria are tools to obtain evidence on the effectiveness of bracing for adolescent idiopathic scoliosis (AIS).
Comment: An RCT result on effectiveness of bracing has recently been published. Authors should consider referring to this article: Effects of Bracing in Adolescents with Idiopathic Scoliosis. Stuart L. Weinstein, M.D., Lori A. Dolan, Ph.D., James G. Wright, M.D., M.P.H., and Matthew B. Dobbs, M.D. N Engl J Med 2013; 369:1512-1521 October 17, 2013

DONE

Purpose
Authors wrote “Present prospective results of bracing plus exercises, completely following the SRS and SOSORT criteria.
Comment: Consider: To present prospective results of bracing plus exercises, based on SRS and SOSORT criteria.

DONE

Patient Sample
Authors wrote “Out of 3,883 patients at their first evaluation, according to SRS inclusion criteria (AIS, age 10 years or older; Risser test 0-2; Cobb degrees 25-40°; no prior treatment; less than one year postmenarchal)73 patients (60 females) have been included, age 12 years 10 months ± 17 months”.
Comment: Statement is ambiguous; consider: 73 patients (60 females), with an average age of 12 years 10 months ± 17 months, who satisfied SRS criteria were included out of 3,883 patients at their first evaluation.

Changed as you suggested, thank you!
There is no need to elaborate on the SRS criteria in the abstract.

Outcome Measures
Physiological measures. SRS (unchanged; worsened 6° or more; over 45° at the end of treatment; surgically treated) and rate of improvement (6° or more).
Comment: Consider: Cobb angle at the end of treatment according to SRS criteria: (unchanged; worsened 6° or more, over 45° and surgically treated, and rate of improvement of 6° or more).

Methods
Braces (Sibilla, Lyon, Sforzesco, SpineCor) and prescription hours (18-23 hours/day) have been individually defined according to clinical needs; weaning was gradual after Risser 3; all patients performed exercises; SOSORT management criteria were respected
Comment: The prescription of brace wear according to clinical needs introduces subjectivity that could lead to bias. The concept of “clinical needs” needs to be explained.
Also, statement is not clear: Consider: Braces (Sibilla, Lyon, Sforzesco, SpineCor) were prescribed for 18-23 hours/day) according to individual clinical needs. (according to severity of Cobb angles if that is the case.) Weaning was gradual after Risser 3. All patients performed exercises and were managed according to SOSORT criteria.

Analyses.
Authors wrote: ” Intent-to-treat: including all patients, and efficacy, with only end-of-treatment patients
Comments: Statement is not clear. Consider: Results in all patients were analysed according to intent--to--treat at the end of the treatment.
Authors wrote: ”Median reported compliance in 3 years 4 months ± 20 months of treatment: 99.1% (22.2-109.2%). Overall, of the 7 (9.6%) patient worsened, 1 (1.4%) progressed beyond 45° and was fused; 46 patients (49.3%) improved. Intent-to-treat: failures were 11 (15.1%); at start, they had statistically significant low BMI and kyphosis, and high thoracic ATR and °Cobb. Drop-outs showed reduced compliance and years of treatment: they discontinued
therapy with 22.7° (range 16-35°) scoliosis at Risser 1.3±1 stage”

Comment: Statement is ambiguous and disorganized. Consider: Overall, 46 patients (49.3%) improved. Seven patients (9.6%) worsened of which 1 patient progressed beyond 45° and was fused. Median compliance was 3 years 4 months ± 20 months: 99.1% (22.2-109.2%)

Employing intent-to-treat analysis, there were failures in 11 patients (15.1%). At start, these patients had statistically significant low BMI and kyphosis, high thoracic rotation and (higher) Cobb angles. Drop-outs showed reduced compliance and years of treatment. Average magnitude of scoliosis at discontinuation was 22.7° (range 16-35°) and Risser 1.3±1.

Conclusions
Authors wrote “This study confirms according to the SRS criteria the efficacy of conservative treatment respecting SOSORT criteria. According to an Intent-to-Treat analysis, the rate of failure increased from 1.4% (Efficacy Analysis) to 15.1%.

Comment: Statement is ambiguous: Consider: Bracing in patients with adolescent idiopathic scoliosis who satisfy SRS criteria is effective in reducing progression. Combining bracing with exercise according to SOSORT criteria increases efficacy.

Thank you for your suggestions, abstract have been changed.