Author's response to reviews

Title: The treatment of medial tibial stress syndrome in athletes; a randomized clinical trial

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Author's response to reviews: see over
Reviewer's report

**Title:** The treatment of medial tibial stress syndrome in athletes; a randomized clinical trial

**Version:** 1  **Date:** 6 September 2011

**Reviewer number:** 2

**Reviewer's report:**
1. Is the question posed by the authors new and well defined? Yes.
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work? Yes.
3. Are the data sound and well controlled? Yes.
4. Does the manuscript adhere to the relevant standards for reporting and data deposition? Yes.
5. Are the discussion and conclusions well balanced and adequately supported by the data? Yes.
6. Do the title and abstract accurately convey what has been found? Yes.
7. Is the writing acceptable? Yes

**Problems with the paper:**

a) Introduction: Make more clear that the etiology is still uncertain. I do not agree that the findings in imaging (DEXA, HR-CT) related to osteopenia in the painful part of the tibia lead us to anywhere other than a hypothesis. It is no proof. And I do not agree that it is feasible to deduct a therapy regimen from these findings.

*We agree that no proof is available that MTSS is caused by bone overload. We think that arguments are available for the bone overload theory (osteopenia as described on high—resolution CT images and the decrease in bone density in MTSS patients compared to athletic controls). To obtain proof for the bone overload theory histological material should be obtained. This is however hard to accomplish since in the Netherlands not many MTSS patients end up being operated.*

*We adjusted the text so that it is more clear that we think that arguments for bone overload exists and that the etiology of bone overload is a theory:*

Recently, different imaging techniques have demonstrated that the tibial cortex is *probably* involved in MTSS. With dual energy x-ray absorptiometry (DEXA) scanning Magnusson et al. showed that decreased bone density was present in the symptomatic part of the tibia [6]. High resolution computer tomography (CT) scans revealed osteopenia in the involved tibial cortex [7]. **However, histological studies are needed in which the bone overload theory is confirmed. Until then, bone overload as a cause of MTSS remains a hypothesis.** (line 54-59)

What imaging data were availabe when you chose an individual for inclusion in the study?

*No imaging was used routinely in this study. When we were unsure if the complaints were caused by MTSS or a stress fracture an x-ray was performed. If a fracture line was seen, the patient was excluded. All patients had complaints for more than three weeks (with a mean duration of complaints of 178-214 days in the three treatment groups). In this way, the chance of seeing a fracture line if the patients did indeed have a stress fracture was high.*
When unsure if the complaints were caused by MTSS or chronic compartment syndrome, compartment pressure measurements were performed.

We did not perform imaging in all patients. The reason for this was that the leading definition of MTSS by Yates and White (2004) defines MTSS on clinical grounds and not on imaging. Furthermore, imaging modalities such as MRI and bone scans have the disadvantage that often asymptomatic controls have abnormalities on scans as well (Bergman et al., AJR 2004; Drubach et al., J Nucl Med 2001). Moreover, MRI studies showed that not all MTSS patient showed abnormalities on the scans (Aoki et al., Clin Orthop Rel Res 2004; Fredericson et al., Am J Sports Med 1995).

Where imaging parameters different before and and at conclusion of the study?

We did not perform imaging at conclusion of the study.

Who funded the study?

No funding was received to conduct the study.

b) Methods: How many patients with suspected MTSS were excluded from the study because of stress fracture or CECS? How were these diagnoses confirmed?

Three patients were excluded because a high suspicion of a stress fracture was raised. The length of palpation pain along the tibia was less than 5 centimetres and imaging revealed a fracture line.

One patient was excluded because the complaints were not along the posteromedial border of the tibia, but in the calf. The patient was referred for intracompartmental pressure measurement, and the pressures found were increased.

Figure 1 shows the flow of the patients through the study, and in the figure a box is included stating why patients were excluded from the study.

Please address exclusion criteria more extensively than in Table 1.

In table 1 we added more exclusion criteria based on imaging:

Focal pain on palpation of the posteromedial tibia or stress fracture present on x-ray

Clinical suspicion of exercise induced compartment syndrome or increased intra-compartmental pressure

I did not find your primary endpoint anywhere: time to complete a running program (able to run 18 minutes with high intensity)

We agree with the reviewer that this was not stated clear enough. We adjusted the text to:

Primary outcome: the number of days from inclusion to the completion of phase six of the running schedule (being able to run 18 consecutive minutes outdoors at a speed in which speech becomes difficult) was used as primary outcome measurement. (line 205-207)
c) Intake:
You write that your non validated test has used in previous studies, I assume with you as lead author.
What I miss, in the discussion, how the running test in the current study fared in comparison with the pneumatic leg brace (Ref: #32) and shockwave therapy (Ref: #33). Please discuss the results, at least you administered the same test! (though not validated, but there is none)

We agree with the reviewer that it is a problem in MTSS studies that no validated outcome measure exists.

We agree that we did not discuss and compared the results of the running test in this study with other studies in which the running test was use. We added:

Prior to the start of treatment a running test was performed. The running test, although not validated, was used in previous studies on MTSS [32,33]. The results of the running tests in these studies were more or less comparable to the findings in this study. For the future, the running test should be validated. (line 283-286)

d) Compliance.
I find your way out of the compliance dilemma fascinating. However, there was no direct supervision of the athletes doing the exercises. Personally I am convinced that when i a study hardly anybody will admit I did not follow the prescription at al. This remains a major weak point in the study design, and I am honestly surprised it passed your ethical committee.

We agree that many methods of studying adherence to treatment exist. A 2003 WHO report stated that no gold standard for assessing adherence exists (WHO 2003). In our opinion self-reported adherence can be used to assess adherence as well. Kallings et al. showed that 16% of the people reported non-adherence. (Kallings et al., J Phys Act Health 2009). That is why we think most people will be honest about adherence. We can’t know for sure if nobody who said adhered to the treatment protocol really performed the advised treatment, but based on the Kallings et al. study, we like to think so.

e) Power analysis:
I find it ridiculous to calculate a power based on studies reporting a maximum recovery time of ten to twenty days.
This makes the whole sample size calculation close to worthless. And with it your statistics.
What about a pilot study from your institutions? This would have provided more sound data.

We agree very much with the reviewer. The power calculation was based on 10-20 days to recovery. Unfortunately, when we started this study, only randomized studies in which these short times to recovery were described, were available. That is why we had no choice but base our power calculation on these figures. During the study, the study by Rompe et al. appeared (Rompe et al., Am J Sports Med 2010) and data from our other studies (Moen et al., J Royal Army Med Corps 2010; Moen...
et al., Br J Sports Med 2011) started to come in. That is when we realized that a time to recovery of 10-20 days was far from what we were seeing. In the discussion we tried to explain this process:

At the start of the study, based on the available information from military studies [1,9,10], we assumed that 22 athletes per treatment group were needed to find a clinically relevant reduction of 50% in time to recovery, i.e. from 17 days to 8-9 days, with alpha set on 0.05 and a power of 0.8. However, recent studies [12,32,33] indicated that a time to recovery of 60-100 days is likely to be more realistic in athletes with MTSS. The current study was therefore able to detect a large effect of the interventions. For future studies, with the data from these studies and the data from this study a more precise power analysis could be possible [12,32,33].

In retrospect, this power analysis was not worth much. That was why in the discussion we stated that the present study can be used for an adequate power analysis in the future. We agree with the reviewer that it would have been better to have started a pilot study first. Unfortunately, that was not the case.

f) Discussion: Be even more critical.
Your study (as many before on this topic) has major flaws:
No validated outcome measure

We agree that this a major weakness in treatment studies on MTSS in general. Currently, we are developing a validated outcome score to improve the quality of treatment studies in the future.

In the text we added:

The development of validated outcome measures is a priority in this research field to increase the quality of treatment studies on MTSS. (line 289-290)

Diagnosis based on subjective criteria only

The diagnosis of MTSS was based on the widely used definition of Yates and White (Am J Sports Med 2004). According to them no imaging is needed to diagnose an athlete with MTSS. There is no accepted gold standard used to make the diagnosis. This is a common problem in many injuries in sports medicine research and part of a wider debate. In our pragmatic approach we chose for a clinical exam based diagnosis.

When a suspicion of stress fracture or compartment syndrome was raised, the athletes was excluded. In this way we think the chance that athletes with another diagnosis than MTSS were included was small.

Questionable sample size and power calculation

We agree that the power analysis in retrospect was not accurate as it was based on times to recovery that did not apply to the group in the final study. As stated above, at the time of designing our study, no other randomized controlled trials were available to use for power calculation. In the discussion we think we were critical in explaining the (in retrospect) flaw in power calculation:

One of the weakness of this study is the power analysis used. At the start of the study, based on the available information from military studies [1,9,10], we assumed that 22 athletes per treatment group were needed to find a clinically relevant reduction of 50% in time to recovery, i.e. from 17 days to 8-9 days, with alpha set on 0.05 and a power of 0.8. However, recent studies [12,32,33] indicated
that a time to recovery of 60-100 days is likely to be more realistic in athletes with MTSS. The current study was therefore able to detect a large effect of the interventions. For future studies, with the data from these studies and the data from this study a more precise power analysis could be possible [12,32,33]. (line 326-333)

Questionable assessment of compliance

We agree that other ways to assess compliance could have been used, but think that our chosen method is a valid possibility as well. In the discussion, we think we were critical of the used method stating:

Self-reported adherence to the treatment was used to quantify compliance. This method of quantifying adherence carries a potential risk of bias, including social desirability [34]. (line 313-314)

No superior result of any of your treatment measures

We can admit that we hoped that one of the treatment options would have been superior compared to the other. Unfortunately that was not the case. However, we do not consider this a major flaw. The medical literature has been plagued by publication bias in the past and the fact that no treatment is superior is also clinically relevant.

So what does your study add to our knowledge? Nothing, unfortunately.

We feel that this comment is a little harsh. Even negative findings contribute to the increasing knowledge base on the subject of MTSS. We think that our study provides insight in the recovery pattern of athletes. In the previous literature (in military populations) a short time to recovery was described. We showed that the time to recovery (at least in athletes) is much longer. Also we think that with the data from this study, in the future, more adequate power analysis can be calculated.

I do not find it adequate to recommend a running program to treat MTSS. Without a resting control group you cannot suggest to treat MTSS with a graded running program alone (page 13, line 296)

We agree, and that is why we changed the text to:

No significant differences between the groups for primary and secondary outcome measures were found. Therefore, if MTSS is treated with a running program, no large additional effect of the two interventions can be expected. It should however, be noted that a graded running program has not been compared with a control group that rested in any study. (line 302-305)

Table 3:
Baseline
How many patients had bilateral MTSS? Did you exclude bilateral MTSS? Or count as two cases?

77-96% of the athletes in the treatment groups had bilateral complaints. We did not exclude athletes with bilateral complaints and they were counted as one case. For centimetres of palpation pain we
noted the leg with the greatest length of palpation pain. For all other parameters, for example days with complaints, the moment when the first symptoms were noted, in any leg, was described.

In table 3 we changed; “both legs” to “bilateral”.

**Level of interest:** An article whose findings are important to those with closely related research interests  
**Quality of written English:** Acceptable  
**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.