Format for ANSWERING REVIEWERS

December 16, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6581-review.doc).

Title: Current and future medical therapeutic strategies for the functional repair of spinal cord injury

Author: Tevfik Yılmaz ,Erkan Kaptanoğlu

Name of Journal: *World Journal of Orthopedics*

ESPS Manuscript NO: 6581

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

(1) Reviewer 1

'A systematic review' (Page 5 2nd paragraph) was corrected as 'In a systematic review'.

Sentence starting with ' by considering' was revised as '' A lot of pharmacological treatment methods have been studying in considering the pathophysiological mechanisms in SCI. There methods are mentional in the following''

Conclusion part was shortened . and last sentence of conclusion was removed.

(2) Reviewer 2

What is the aim of your review

This article reviews current evidence for early surgical decompression and nonsurgical treatment options including pharmachological and cellular therapy as the treatment choices for SCI.

Introduction chapter to outline current evidence on this topic and aim of your review. This will help the reader to get a coincice "take home message" of your review

Currently, the management of patients with acute SCI includes pharmacological agents, surgical intervention, and cellular therapies.There is no still a commonly accepted pharmacological agent that is used in the treatment of SCI. But some clinical studies have been done to reveal an effective agent. The timing of surgery is another controversial issue among the authors. However studies about the cellular therapies give hope for future. Various clinical studies using pharmacological agents, cellular therapies and surgical intervention for SCI are discussed and summarised in this review.

Table including most significant papers (a selection of 5 paper out of 128 provided) should be provided

We added table5

Can author provide diagrams/pictures of pathophysiology of spinal cord injury and corticosteroids mechanism of action (theories)?

We added table 3 and figure 2

Case examples with radiographs are always appreciated.

(3) Reviewer 3

You need to add some diagrams to explain the pathophysiology and mechanisms of action of drugs

We added table 3 and figure1, 2

You need to be more critical of the evidence and suggest how future trials can tackle these problems to provide useful information minor language changes improve the abstract - the colleagues I showed it to said they would not read this article if they read that abstract.

A number of study on surgical timing suggest that early surgical intervention is safe and feasible and that it can improve clinical and neurological outcomes and reduce health care costs, minimize the secondary damage caused by compression of the spinal cord after trauma. Various clinical studies using pharmacological agents, cellular therapies and surgical intervention for SCI are discussed and summarised in this review

Need to improve english grammar. This is too general – please be more specific with what you intend to review in this paper. I wouldn't read this article if I read this abstract in its current form.

Spinal cord injury leads to social and psychological problems in patients and requires costly treatment and care. In recent years, various pharmacological agents have been tested for acute spinal cord injury (SCI). Large scale, prospective, randomized, controlled clinical trials have failed to demonstrate marked neurological benefit in contrast to their success in the laboratory. Today, the most important problem is ineffectivess of nonsurgical treatment choices in human SCI that showed neuroprotective effects in animal studies. Recently attempted cellular therapy and trasplantations are promising. A better understanding of the pathophysiology of spinal cord injury started in early 1980's. Researches had been dealing with neuroprotection in 1980s and the first half of 1990s, and regeneration studies have started in the second half of the 1990's. A number of study on surgical timing suggest that early surgical intervention is safe and feasible and that it can improve clinical and neurological outcomes and reduce health care costs, minimize the secondary damage caused by compression of the spinal cord after trauma. This article reviews current evidence for early surgical decompression and nonsurgical treatment options, including pharmachological and cellular therapy, as the treatment choices for SCI. Değiştirilecek eklenecek

Do you have a diagram to demonstrate this ischaemic penumbra around the injured cord – this would help

We added Figure 1 and The area around irreversible injury is the ischemic penumbra. If the ischemia exceeds beyond critical level, infarct area expands and irreversible injury occurs. Function can be restored in case of regenerated blood flow before the beginning of injury

You should explain that there is a difference between those with a static neurological picture and those with a progressive deficit – you could bring in the ASIA score here

We added Table 2 and. The patients in the early surgery group showed 83.3% improvement in ASIA score, whereas ASIA score of 26.6% patients in late surgery group improved.

Please be more critical of the literature here – what is the evidence type (RCT, observational studies/systematic review – of so of what type of trials)

In a randomized controlled study (RCT) done by Cengiz et all, postoperative ASIA score significantly increased in the early surgery group and late surgery group compared to pre-operative ASIA score. In addition to this finding the post-operative ASIA score of the early surgery group was significantly better than late surgery group. Cadotte et all. suggested early surgery is safe and strongly recommended in patients without lifethreatening polytrauma and without major medical co-morbidities according to findings in class II and class III studies. Urgent surgical decompression should be carried out in patients with deteriorating neurology.RCT ve literature eklendi

You should mention the relevance of a p-value and the point about multiple post-hoc analyses in NASCIS II

Improvement in the motor function was statistically significant at 6 months and even after 1 year in the MP group compared with the controls (17.2 and 12.0 points improvement respectively, p=.030)

You should also mention a new trial in Canada which is tryting to address this – multicntre basd in Toronto

Any trial data?

Cethrin: This agent facilitated axonal growth and promoted functional recovery in a Mouse model. The researchers observed an early neurological improvement and reduced apoptosis rates.

You devote a large section of your paper to drugs that are rarely used. I agree they should be mentioned, but the emphasis for readers should be balanced

We removed Since TRH has a very short half-life, more stable analogs have been developed and The aforementioned useful behavioral and non-behavioral results were seen in paradigms of estrogen pretreatment (or treatment at the time of injury).

You should also mention about avaoidance of complications – as these affect outcome in SCI e.g. bowel management, avoidance of autonomic problems etc

No complications were seen in early surgery group, whereas three cases of respiratory failure and one case of sepsis wre seen in the late surgery group[37]. It was reported that early surgery results in reduced LOS, less secondary complications, early mobilization, and transfer to rehabilitation and should be considered in all SCI patients.

In addition, another level-2b evidence study suggested that with compared to surgical intervention from 72 h to 5 days after thoracolumbar SCI, stabilization of spinal and cord surgical decompression in than 8 h would result in better neurological outcome, shorter duration of hospitalization, shorter duration of stay in the intensive care unit, and lower frequency of secondary complications. [37]

You need some diagrams as these concepts are difficult to grasp with text alone

We added figures and tables (figure 1,2 ;table 1, 2, 3, 4, 5)

You need to mention how future trials should assess outcome in SCI – what do we measure to assess success? Then go on to talk about challenges in data acquisition

The high quality of the trials and the intense scrutiny of their design and interpretation of outcome measures are playing a critical role in shaping the next generation of trials. We propose the following recommendations for the researcers for future trials: statistical power needed for clinical trials; injury severity and timing of experimental therapy administration; appropriate clinical trial outcome measures; and prospective clinical trial design. These recommendations will be helpful for the SCI community in its further clinical evaluation of novel therapies[130].

Measuring the success of Walking Index for Spinal Cord Injury might be used, which was revised recently, represents an international attempt to make a complex, valid, and reliable device for assessing walking independent of burden of care[131]. Later, a multinational collaboration, led by the Toronto SCI team and several centers in Canada, US, and Europe developed a novel outcome measure to quantitatively assess hand and upper-extremity function in tetraplegic patients (the Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) outcome measure. There are two important parameters in the development of new outcome measures which one establishs the psychometric properties and other provides insights into functional and neurological impairment[132].

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Orthopedics*.

Sincerely yours,

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