Author's response to reviews

Title: Efficacy of repeated intrathecal triamcinolone acetonide application in progressive multiple sclerosis patients with spinal symptoms

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Author's response to reviews: see over
Dear ladies and gentlemen,

attached you will find the revised manuscript, entitled

_Efficacy of repeated intrathecal triamcinolone acetonide application in progressive multiple sclerosis patients with spinal symptoms_

for resubmission to your journal „BMC Neurology“ as original article.

All authors have seen and agree with the content of the manuscript and participated in design, execution and analysis of this study and this paper.

We also declare, that we have no conflict of interest in connection with this paper, other than any noted in the covering letter to the editor.

with kindest regards for the authors

Thomas Müller MD
Comments to the reviewer:

This study by Heilwig et al describes the efficacy of repeated intrathecal triamcinolone acetonide application in progressive multiple sclerosis with spinal symptoms. In an open study they assessed the EDSS, Barthel index and somatosensory evoked potentials in 161 hospitalized MS patients before and after treatment. Although the results are positive, there are several concerns. First of all in MS research it is very important to have blind assessment and preferable a placebo control arm. I agree that it is not ethical to perform "placebo lumbar punctures", however the authors could have chosen for a strategy of 1 arm with active treatment and one arm with just follow-up without active treatment with blind assessment by an evaluating physician. A control group is now not available.

We wrote:

Introduction

Nevertheless, there is a need for further results on the usefulness of this treatment. The optimum design would be a placebo controlled arm, but repeat performance of intrathecal saline (placebo) administration under double-blind conditions with the patients’ consent and an approval of an ethical committee is not realistic in clinical practice.

Discussion

However our present study outcomes do not allow any conclusions on the duration of the achieved benefit and the impact of TCA treatment on progression of MS [3]. Therefore there is an urgent need for further confirmatory trials, which additionally address all these issues. A strategy would be to choose one arm with active treatment and one arm with just follow-up without active treatment with blind assessment by an evaluating physician. However we stress concerning long-term steroid therapy and progression of MS, that there are positive outcomes of trials with intravenous methylprednisolone administration in various application rates and dosages on long term disease progression and/or on brain atrophy in secondary-progressive - , respectively relapsing-remitting MS patients [16,21].

2. The treatment given; six times a lumbar puncture with TCA within three weeks is an invasive treatment. Therefore it is important to have results with underline the usefulness of this treatment. By this study I do not believe that we have an adequate answer to this question. Although the authors mention the use of intrathecal methylprednisolone in intractable postherpetic neuralgia referring to the article of Kotani et al in the New Eng J Med 200:343:1514-1519 the correspondence after this publication raised important issues about the safety of this treatment.

Introduction

In recent years, a certain revival of intrathecal methylprednisolone administration took place in the treatment of intractable postherpetic neuralgia and MS with spinal symptoms, both of which turned out to be very effective, but were controversially discussed regarding the safety issues [2,3]. The MS study demonstrated, that six repeat intrathecal TCA injections within three weeks reduced the EDSS score in 31 of 36 progressive MS patients with predominant spinal symptoms. 20 of them entered a follow-up period of 13.1 ± 6.22, 3 - 23 [mean ± SD, range] months with 6.35 ± 3.91, 2 – 15 TCA injections. They received one TCA application on a regular basis in an individually differing frequency every six to twelve weeks. These patients remained stable [3].
The MS study demonstrated, that six repeat intrathecal TCA injections within three weeks reduced the EDSS score in 31 of 36 progressive MS patients with predominant spinal symptoms. 20 of them entered a follow-up period of 13.1 ± 6.22, 3 - 23 [mean ± SD, range] months with 6.35 ± 3.91, 2 – 15 TCA injections. They received one TCA application on a regular basis in an individually differing frequency every six to twelve weeks. These patients remained stable [3].

Introduction

We omitted this comparison throughout the whole MS.

Discussion:

However our present study outcomes do not allow any conclusions on the duration of the achieved benefit and the impact of TCA treatment on progression of MS [3]. Therefore there is an urgent need for further confirmatory trials, which additionally address all these issues. A strategy would be to choose one arm with active treatment and one arm with just follow-up without active treatment with blind assessment by an evaluating physician. However we stress concerning long-term steroid therapy and progression of MS, that there are positive outcomes of trials with intravenous methylprednisolone administration in various application rates and dosages on long term disease progression and/or on brain atrophy in secondary-progressive -, respectively relapsing-remitting MS patients [16,21]. In contrast to studies on intravenous oral steroid treatment, we did not observe the typical side effects of systemic high dosage steroid administration, i.e. edema. This may support previous findings by circumstantial evidence, which report no decrease of endogenous cortisol secretion following intrathecal TCA administration [4].

Minor comments:

abstract: results section advice to mention the period of follow-up

There are no follow-up data in this study. These were demonstrated in a different study with another cohort.


EDSS score and Barthel index improved, walking distance increased, latencies of somatosensory evoked potentials of the median and tibial nerves shortened in all MS patients with serial evaluation (p < 0.0001 for all variables). Side effects were rare, five patients stopped TCA application due to onset of a post lumbar puncture syndrome.
conclusions: the conclusion is not adequate. the authors did not compare their treatment with patients with other treatments

We wrote now:

Our data demonstrate the efficacy and safety of repeated intrathecal TCA application in MS patients with predominant spinal symptoms, which markedly improved. Some MS patients experienced post lumbar puncture syndrome with a frequency within the normal range [11], but typical side effects of systemic high dosage steroid administration did not appear.

Abstract

Repeated intrathecal TCA application improves spinal symptoms, walking distance and SSEP latencies in progressive MS patients. Future trials should evaluate the long-term benefit of this invasive treatment.

method section: was the study retrospective or prospective

We performed scoring with both, EDSS and Barthel index and assessed the walking distance. Then we measured somatosensory evoked potentials (SSEP) in a standardized fashion before start and at the end of the intraspinal TCA treatment within a prospective study design [9]. A technician performed SSEP recordings and measured the walking distance. We blinded the EDSS raters. Retrospectively, we compiled information on patients from their hospital records, i.e. date of birth, sex, duration of disease after diagnosis of MS, dosages of oral baclofen (lioresal®), tolperison (mydocalm®), tizanidin (sirdalud®) on the first and last day of the hospital stay, length of hospitalization in days (tables 1 & 2).

pg 5, What was the reason to stay in bed for at least six hours after intrathecal application of TCA?

Each patient received six intrathecal applications of 40 mg TCA followed by a mandatory stay in bed for at least six hours. This should reduce incidence of lumbar puncture syndrome and hypothetically support the diffusion of TCA in the CSF and the spinal cord [14,15].

in discussion: page 7 our results suggest a certain superiority and so on. see above not investigated and can not be proven also no companion with intravenous administration of methylprednisolone
These statements were omitted

**Comments to the editor:**

Please indicate clearly in the cover letter and the manuscript how the current study differs from and is an advance upon that published in J Neurol Sci 2003, 211:81-84. Please send a copy of this manuscript by e-mail, or by post if that is not possible, so that the referee will be able to view it.

The current study reports SSEP data. The previous study did not.

We report data of 161 MS patients. The other trial only included 36 patients, which were followed up, as described in the article now.

The MS study demonstrated, that six repeat intrathecal TCA injections within three weeks reduced the EDSS score in 31 of 36 progressive MS patients with predominant spinal symptoms. 20 of them entered a follow-up period of 13.1 ± 6.22, 3 - 23 [mean ± SD, range] months with 6.35 ± 3.91, 2 – 15 TCA injections. They received one TCA application on a regular basis in an individually differing frequency every six to twelve weeks. These patients remained stable [3].