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315-321 Lockhart Road,  
Wan Chai, Hong Kong, China

## ESPS Peer-review Report

**Name of Journal:** World Journal of Hepatology

**ESPS Manuscript NO:** 3061

**Title:** Ciclosporin does not attenuate intracranial hypertension in a rats with acute hyperammonemia

**Reviewer code:** 00503536

**Science editor:** Song, Xiu-Xia

**Date sent for review:** 2013-04-06 16:30

**Date reviewed:** 2013-04-13 14:30

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

The manuscript written by Larsen et al. analyzed the effect of ciclosporin on intracranial pressure in rats with hyperammonemia. They also examined cerebral water content and aquaporin-4 expression, and found no favourable effect of ciclosporin on those parameters. The data are inconsistent with in vitro analyses, but may give important information on daily practice. However, there are some concerns that need to be addressed. Major points, 1.The authors administered ciclosporin intrathecally. However, the route of administration is unable to be performed in the clinical setting. Moreover, ciclosporin delivered to brain through blood stream might be more effective than intrathecal administration for increasing the concentration of ciclosporin in the brain. 2.How did the authors determine the dose of ciclosporin? 3.It seems that administration of ciclosporin rather increase the intracranial pressure and brain water content compared with the controls or baseline levels. Based on those data, it could be concluded that ciclosporin might have unfavorable effects on cerebral edema induced by hyperammonemia. The authors should discuss more on that point. Minor point, 1.Are there any data on the effect of ciclosporin on intracranial pressure in humans?



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### ESPS Peer-review Report

**Name of Journal:** World Journal of Hepatology

**ESPS Manuscript NO:** 3061

**Title:** Ciclosporin does not attenuate intracranial hypertension in a rats with acute hyperammonemia

**Reviewer code:** 00020433

**Science editor:** Song, Xiu-Xia

**Date sent for review:** 2013-04-06 16:30

**Date reviewed:** 2013-04-16 00:21

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input checked="" type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

### COMMENTS TO AUTHORS

The main concern about the study is the clinical relevance of this study. Ciclosporin does not cross the blood brain barrier easily. Moreover, ciclosporin is not administered intrathecally in clinical practice. Therefore, how the findings of this study will impact our clinical practice is unclear.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Hepatology

**ESPS Manuscript NO:** 3061

**Title:** Ciclosporin does not attenuate intracranial hypertension in a rats with acute hyperammonemia

**Reviewer code:** 02409324

**Science editor:** Song, Xiu-Xia

**Date sent for review:** 2013-04-06 16:30

**Date reviewed:** 2013-05-01 04:29

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D (Fair)		BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

Larsen and colleagues present a well written paper on the potential brain protective role of ciclosporin in a rat model of acute liver failure. Comments: Referring to "neuroprotection" throughout the manuscript is misleading since neuronal viability was not assessed in this study. Accordingly, statements like "Our present study intended to translate the favourable in vitro results of Cs as a neuroprotectant to an in vivo experiment." are not supported by this investigation. Overall, the introduction can be substantially shortened with concise focus on the potential impact on brain edema. In fact, a more thorough consideration of the potential contribution of cytotoxic vs. vasogenic edema may be more helpful. Abstract: "ciclosporin/vehicle" AND "ammonia/saline" I suggest replacing "/" with "or" to more clearly indicate that separate groups were tested. "Treatment with ciclosporin resulted in relevant tissue concentrations of ciclosporin (>0.2 micromolar) but did NOT reduce intracranial pressure." "Intrathecal administration of ciclosporin does not attenuate intracranial hypertension or brain edema in rats with portacaval anastomosis and hyperammonemia." Please clarify that this is only true in the used model and at 4 hours. Introduction: "The cerebral edema seen during hyperammonemia is predominantly cytotoxic,..." If this was true, then a net change in brain water content/global ICP would not be expected. Accordingly, the primary aims of the study "that Cs would attenuate ICH, preserve normal brain water content" would not be expected (as echoed by the negative results). I suggest abbreviating "intrathecally" with "i.th." or similar since "it." is easily confused with the pronoun "it". Methods: "The vehicle-treated groups were given a vehicle composed of ethanol, ricinus oil and saline in an equivalent volume following the same procedure." Please clarify that this is the appropriate vehicle for cyclosporine. Please clarify at what time points blood gases and physiological parameters were



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recorded. Considering the length of this experiment, a single measurement (at unknown time point) in ventilated and drug treated animals is insufficient. Statistics: Was the data normally distributed? Given the multigroup design, the use of t-Test was inappropriate and the AQP data requires reanalysis correcting for multiple comparisons. Results: PaO<sub>2</sub> and MAP appear rather high. In my experience, it is impossible to attain PaO<sub>2</sub> of >100mmHg unless oxygen is supplemented. What were the ventilation parameters? ICP appears low. Are these physiological values? Could there have been a CSF-leak? Please define "pp" and "\*" in Table1. Reporting a correlation between increased ICP and brain water content is trivial. I am confused by Figure1. This does not seem to reflect the ICP measurements mentioned in the abstract and results sections. Figures 3A&B should be combined into a single figure.



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## ESPS Peer-review Report

**Name of Journal:** World Journal of Hepatology

**ESPS Manuscript NO:** 3061

**Title:** Ciclosporin does not attenuate intracranial hypertension in a rats with acute hyperammonemia

**Reviewer code:** 00054001

**Science editor:** Song, Xiu-Xia

**Date sent for review:** 2013-04-06 16:30

**Date reviewed:** 2013-05-08 21:06

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

The authors describe in this manuscript the impact of intrathecal ciclosporin administration on intracranial pressure under the condition of intracranial hypertension (ICH) caused by hyperammonemia. The authors speculated that ciclosporin decreases intracranial pressure due to down-regulation of aquaporin-4 because ciclosporin has been reported to prevent ammonia-mediated astrocyte swelling that was considered to have a pivotal role of ICH caused by hyperammonemia. However, results of this study showed that ciclosporin did not have any beneficial effects on ICH caused by hyperammonemia. This manuscript was well organized and well written. My only concern is the following. Do the authors have ideas of other alternatives than ciclosporin? I think the authors should refer to that in Discussion session.