Author's response to reviews

Title: Vasodilative effects of prostaglandin E1 derivate on arteries of nerve roots in a canine model of a chronically compressed cauda equina

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Response to reviewers

Reviewer Dr. Setsuro Komiya

Thank you very much.

Reviewer Dr. Makoto Fukusaki

Thank you for your comments.

Background
Q1
The hypothesis of this work is weak.

A1
Thank you for your suggestion. We have changed the introduction. PGE1 leads to vasodilation in both arterioles and venules (reference #6). Because the blood vessels on the cauda equina dilate during NIC during myeloscopic observation of lumbar spinal canal stenosis, microcirculatory disturbance of vessels on the cauda equina may an important role of NIC (reference #7). In addition, dilation of vessels is observed after administration of Lipo PGE1 in patients with lumbar spinal stenosis undergoing a myeloscopic examination (reference #8). However, even if vasodilatory effects are achieved in both arteries and veins, this would lead to blood stasis, which may subsequently induce a reduction of blood flow. In the experimental study of the porcine cauda equina compression, blood flow in veins on spinal nerve is stopped by the lower compression pressure compared with the one in arteries (reference #4). Therefore, it is important to investigate not only a change in the diameter of blood vessels but also a change in the blood flow in both arteries and veins in the same model. The aim of this study was to assess the effect of a PGE1 derivate on nerve blood flow in both arteries and veins in a chronic cauda equina compression canine.
model.
(page 4 line 5~P5 line 1)

Methods

Q2

One week after the initial surgeries, OP-1206 alpha-CD was administered orally and study was conducted.

How much was OP-1206 alpha CD absorbed through stomach via a silicon catheter?

How long is the half-life of OP-1206 alpha CD?

How did you decide the dose of OP-1206 alpha CD in this study?

A2

Thank you for your comments.

Ninety to 95% of the OP-1206 alpha-CD is absorbed through stomach in a rat, and the half-life of this drug is 7 hours (reference #14).

There are no data regarding absorption rates in a canine model. In the clinical setting, oral therapy with 15 to 30µg per day OP1206 alpha-CD is used for an adult patient. In rat studies (reference #15,16), oral administration of 30-300µg/kg OP-1206 alpha-CD has been used; however, these concentrations are higher than those used in the clinical setting. In a rat model, the blood concentration of OP1206 alpha-CD is approximately 2 to 2.5% of the total amount of drug administered. In a previous canine model, 3-30 ng/kg/min OP-1206 alpha-CD was administered intravenously (reference #17).

According to the clinical setting, 30µg was chosen orally in this study. Because the mean weight of dogs in this study was 11.1 kg, 3µg/kg OP-1206 alpha-CD was chosen as the best dose.

We have added the information in the methods section. (page 7 last line ~ page 8 line 10)
Results

Q3
The authors should show the changes in diameter of blood vessels, blood flow velocity and blood flow index in sham operation model, too.

Q5
Although the administration of OP-1206 CD gradually caused the arterial dilation and the increase in arterial blood flow in the nerve roots, the author needs to observe the same indices in vehicle and sham models.

A3 and A5
Thank you for your important suggestion.
We agree with the need to investigate these three measurements in a sham-operated model for academic reasons. However, ethical restrictions, especially with big animals such as those used in a canine model, are strict. Because only patients with cauda equina compression receive treatment in the clinical situation, we did not perform a sham operation in dogs without this disorder in order to prevent sacrificing a large number of canines in this study.
In addition, in our previous studies using the same measurement system, blood vessels in the naïve and sham of canine models did not react after administration of vehicle. Therefore, we only investigated a cauda equina compression model with treatment in this study.

Q4
The author should display the value of vessels diameter, blood flow velocity and blood flow volume index on the table in either group.

A4
Thank you for your suggestion. However, the data would be repeated, therefore, we would like to show figures to be easy to see the progress of changes in each measurement.
Discussion

Q6
You cannot discuss about NIC because you have no data in walking function of your study.

A6
Thank you for your comment.
We agree with your comment and have changed “According to our results in this study and previous clinical reports” to “According to the previous studies”. (Page 15, line 13~line 14)

Q7
PGE1 can change the arterial blood flow in the nerve roots due to primary and secondary effects according to Fukuda H et al paper. The author needs to add the conclusion section in this study.

A7
Thank you for your suggestion.
We have added this point in the discussion section. (P 15 line 1~line 5)