THE NOVEL 5-LIPOXYGENASE INHIBITOR (ABT - 761) ATTENUATES CEREBRAL VASOSPASM IN A RABBIT MODEL OF SUBARACHNOID HEMMORHAGE

Marcos Barbosa* Adam Arthur ** Hunter Louis** Richard Polin **
Neal Kassel**

* Serviço de Neurocirurgia, Hospitais da Universidade de Coimbra, Coimbra, Portugal
**Department of Neurological Surgery, UVA, Charlottesville, Virginia, USA

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INTRODUCTION

- Leukotrienes and other eicosanoids, resulting from 5-lipoxygenase activity on arachidonic acid metabolism, have been implicated in the pathogenesis of cerebral VSP after SAH.

- 5-lipoxygenase activity enhanced after SAH. Significant in the pathogenesis of cerebral VSP? Inhibitor should ameliorate experimental VSP.

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INTRODUCTION

- **The present study evaluates the potential therapeutic value of ABT-761, a selective 5-lipoxygenase inhibitor on cerebral vasospasm in an *in vivo* rabbit model of SAH.**

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METHODS

48 male rabbits (3-4 kg) 6 groups (n=8)

GROUP 1 SAH+P

GROUP 2 SAH+D20

GROUP 3 SAH+D30

GROUP 4 C+P

GROUP 5 C+D20

GROUP 6 C+D30

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METHODS

- Anesthetised Intubated
- SAH - 5ml autologous blood into the cisterna magna
- Drug or placebo PO 30 minutes after hemorrhage and repeated 24 hours later.

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METHODS

- 48 hours after CSF was collected from the cisterna magna for ABT-761 concentration determination.
- Animals were sacrified, using the perfusion-fixation method. Basilar artery was removed.
- The cross-sectional areas of basilar artery histological sections were measured by an investigator blinded to the treatment groups of the individual samples.

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Statistical Analysis

- A Kruskal-Wallis one-way analysis of variance was performed on the entire data set of morphometric measurements. Pairwise multiple comparisons *post-hoc* analysis was performed using the Bonferroni-Dunn method.

- Partial correlation coefficients were performed on CSF ABT-761 concentration values by treatment groups.

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RESULTS

- In placebo-treated animals, the average luminal cross-sectional area of the basilar artery was reduced by 68% after SAH compared to controls (*P<.0001)*.

- After SAH the vasospastic response was attenuated in animals treated with 20 and 30 mg/kg representing a 28% and 35% reduction respectively (*P=.0011 and P=.0038)*.

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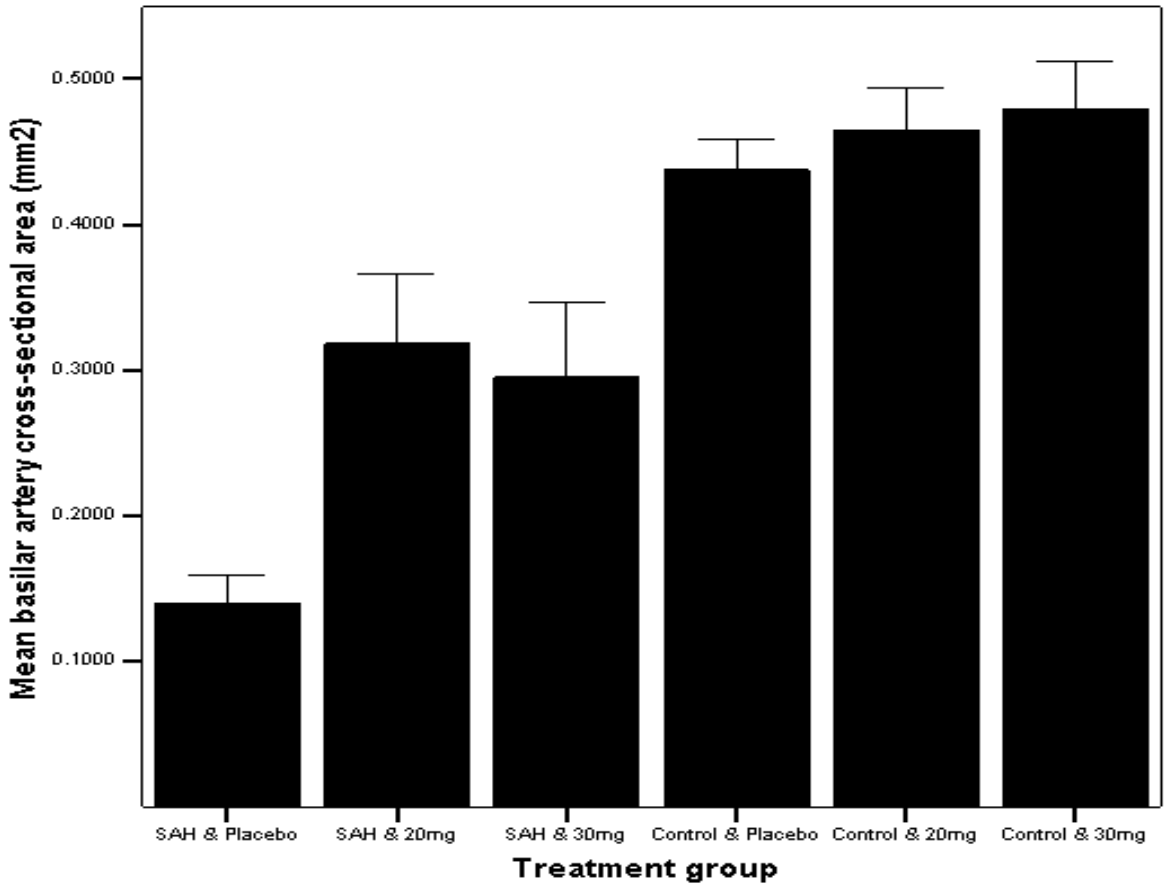

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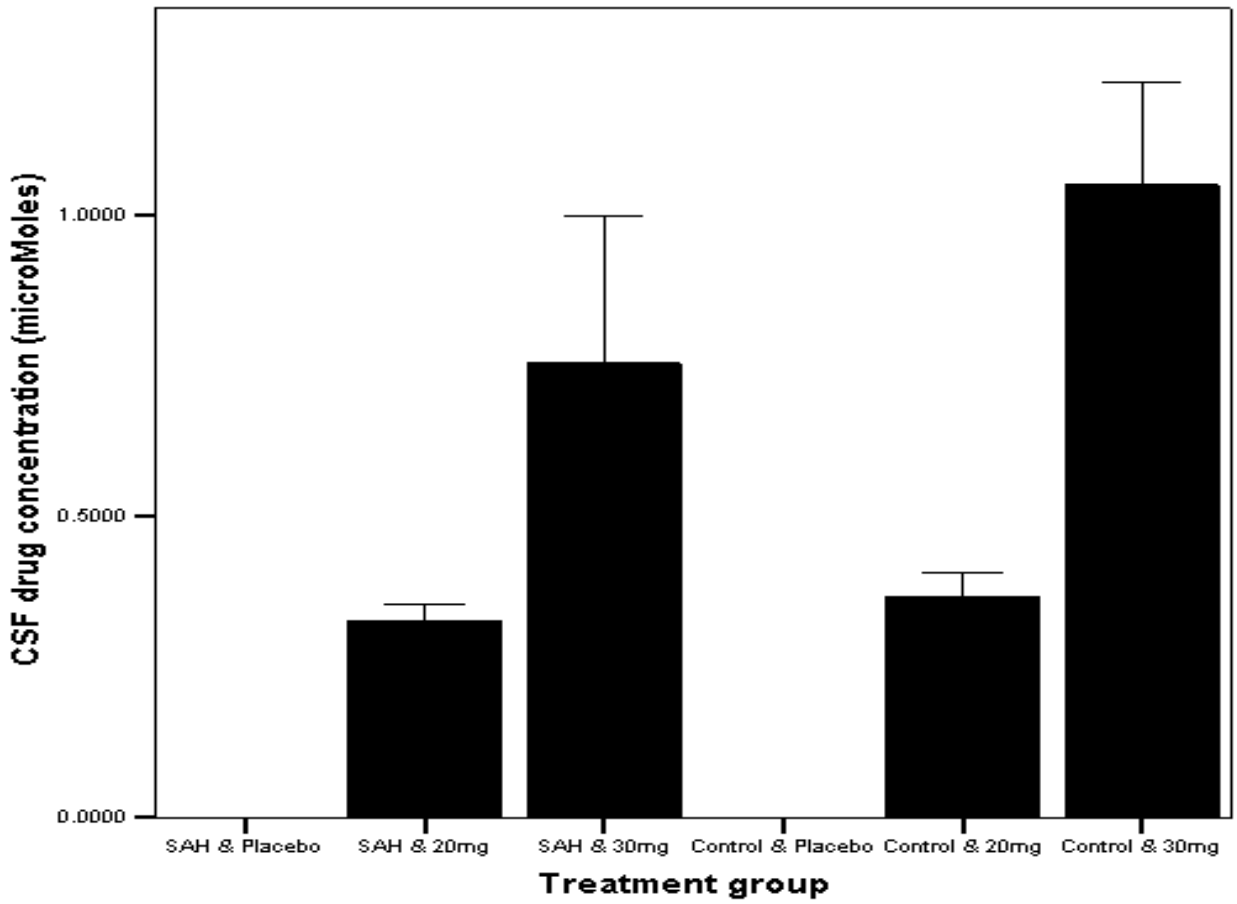

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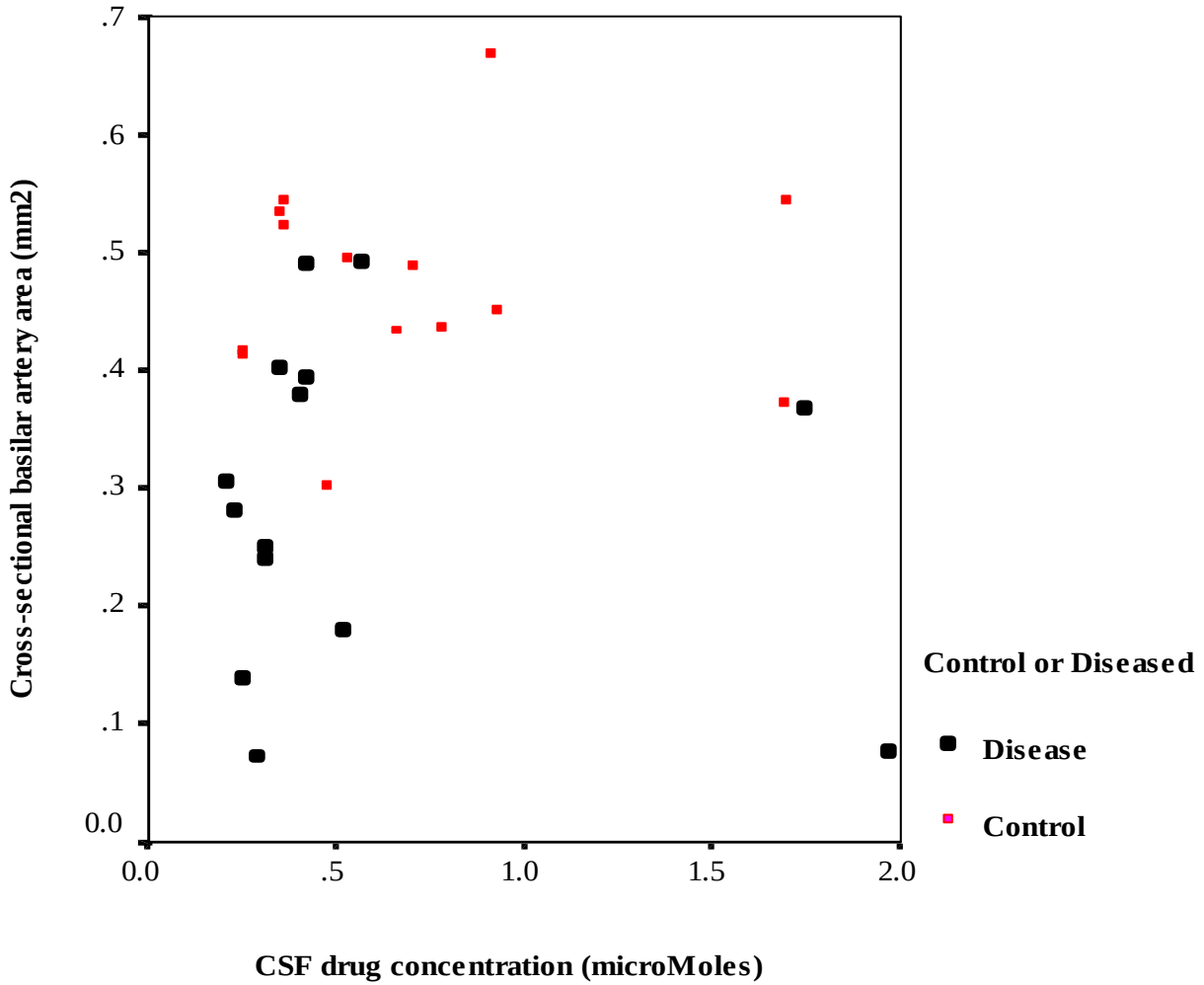

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DISCUSSION

- The greater degree of variability in drug concentration among control animals may indicate a trend towards variable drug utilization in the SAH animals than in Control animals.

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DISCUSSION

- Vasospasm is a major complication after SAH
- Difficulties in prevention and treatment
- Pathogenesis still unclear, likely to be multifactorial, with inflammatory processes involved

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DISCUSSION

- Leukotrienes are inflammatory mediators with cerebral vasoconstrictor properties
- Production is elevated in SAH
- CSF levels correlate with vasospasm

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DISCUSSION

- ABT-761 is a second-generation, potent and selective inhibitor of leukotriene formation both in vivo and in vitro

- Able to prevent experimental VSP, by attenuating the vascular effects of the 5-lipoxygenase products of arachidonic acid metabolism

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CONCLUSION

- Established the potential utility of a specific leukotriene inhibitor for the treatment of experimental VSP
- Indirect evidence for a role of inflammation in the pathogenesis of cerebral vasospam
- Primate studies are needed to clarify whether 5-lipoxygenase inhibition has a potential role in the treatment of clinical cerebral vasospasm