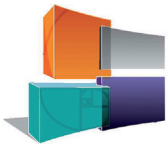
Anaesth Crit Care Pain Med 38 (2019) 665–667



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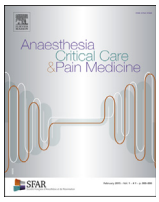

Letter to the Editor

May levosimendan be safe and effective in refractory vasospasm despite adequate treatment with repeated angiography and milrinone infusion after subarachnoid haemorrhage?

Dear Editor,

Despite the recent development of new pharmacological and endovascular treatments, delayed cerebral vasospasm still remains a major cause of disability and mortality after subarachnoid haemorrhage (SAH) [1].

A 55-year-old man was admitted in our intensive care unit for an extensive subarachnoid haemorrhage (SAH) WFNS grade 2 with slight neurologic impairment (Glasgow Coma Scale [GCS] 14/15) despite severe neuroimaging features (Fig. 1A, B). The initial management consisted in an external ventricular drainage and a coiling of an anterior communicating artery aneurysm. The evolution towards intracranial hypertension required a continuous sedation with a therapeutic management guided by brain tissue oxygenation [$PtiO_2$] and advanced haemodynamic monitoring [2]. On the 8th day, a first cerebral vasospasm occurred (Fig. 1C, D), treated by intra-arterial infusion of nimodipine (max. 3 mg) and milrinone (max. 4 mg). Despite an optimal medical treatment, several relapses required repeated endovascular interventions (angioplasty and intra-arterial infusion of vasodilator agents) intravenous infusion of milrinone (up to 2 mcg/kg/min) and magnesium sulfate. A fall in cardiac index was then observed, explained by a severe global heart dysfunction (left ventricular ejection fraction [LVEF] $\leq$ 20% with a restrictive relaxation pattern). A progressive switch from milrinone to levosimendan was performed on the day 14 by a continuous infusion up to 0.2 mcg/kg/min during 24 hours, without an initial bolus (Fig. 2). A significant increase in cardiac index and $PtiO_2$ were observed, with a concomitant decrease in norepinephrine infusion. No significant increase in intracranial pressure occurred. After a progressive weaning from the sedation, neurological status improved daily without recurrence of vasospasm. Patient was discharged from the ICU after 31 days, without significant neurological impairment (GCS 15/15) and complete recovery of ventricular function.

In our observation, we reported a particularly challenging situation (refractory vasospasm complicated by milrinone-associated cardiomyopathy) with no more therapeutic options for the clinician. Although it is not possible without a dedicated study to formally establish a causal link between levosimendan and clinical outcome, at least there are a pathophysiological rationale and a compatible chronology.

As documented by several observational studies, we are prompt to use intravenous milrinone as a first-line therapy for refractory cerebral vasospasm [3,4]. However, the results of this vasodilator and inotropic treatment are neither always satisfactory nor free from adverse effects. With increased combined milrinone and catecholamine use for the treatment of cerebral vasospasm, physicians should be aware of the potential cardiac complications of these agents [5].

In this context, the efficacy of levosimendan has previously been described in the management of both neurogenic stress cardiomyopathy and delayed vasospasm in patients with SAH [6]. Moreover, experimental studies suggest that levosimendan may improve brain oxygenation (or cerebral blood flow) by

https://doi.org/10.1016/j.accpm.2019.07.004
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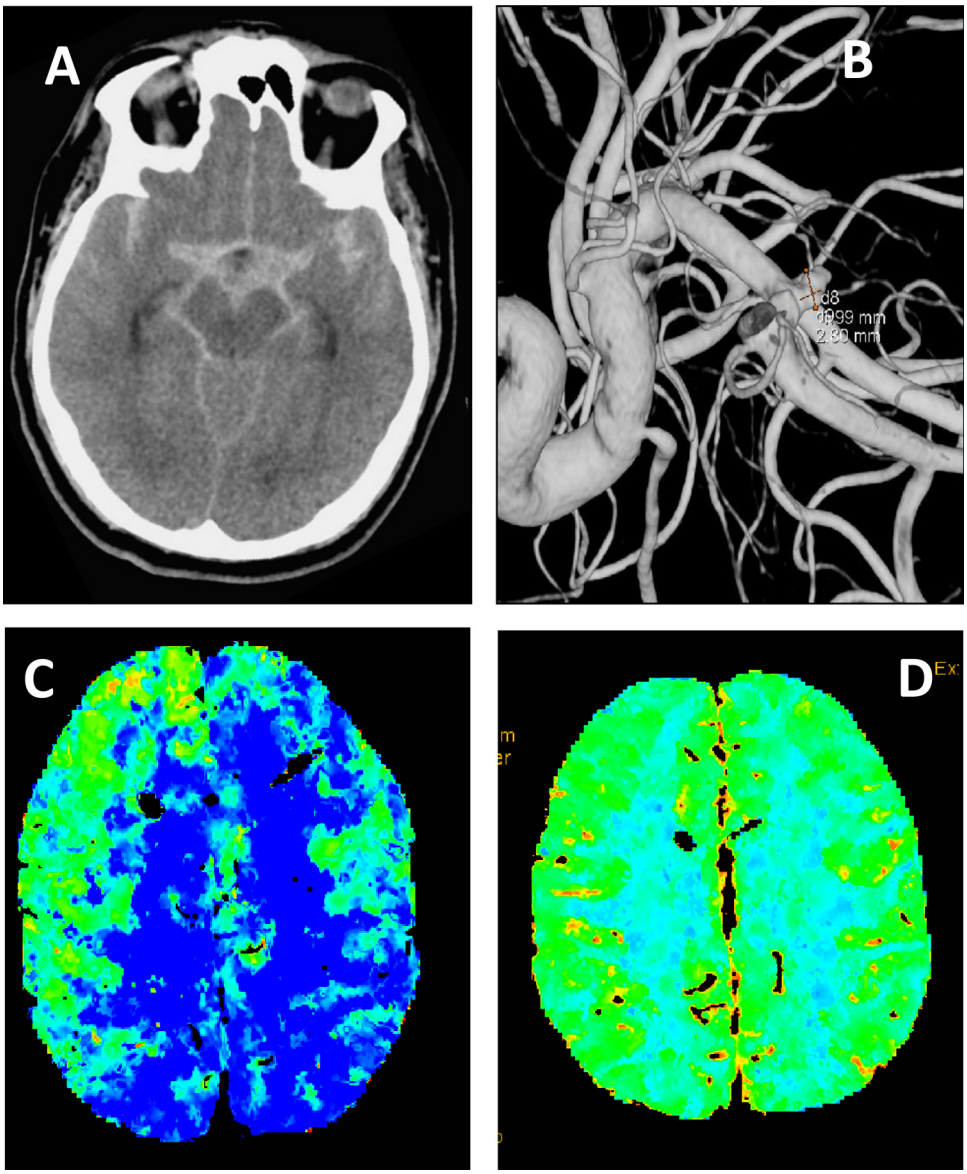

Fig. 1. Initial CT scan showing a diffuse haemorrhagic pattern involving the ventricular system classified grade IV in the Fisher Scale (A) secondary to the rupture of a 3 mm aneurysm of the anterior communicating artery (B). Secondary CT scan with perfusion sequences showing vasospasm in anterior cerebrals arteries (Tmax sequences: C) without constituted ischemia (cerebral blood volume sequences: D).

multiple pharmacological pathways including an increase of myofilaments contraction by a calcium-sensitisation of troponin C; a systemic and cerebral vasodilation by an opening of ATP-dependent potassium channels in vascular smooth muscles [7]. On the other hand, no study has previously compared two inotropic agents to reduce vasospasm after failure of adequate management using optimisation of cerebral haemodynamics and repeated endovascular management.

In conclusion, the present case suggests the pharmacodynamics properties of levosimendan may be beneficial if dealing with refractory vasospasm when conventional treatment and milrinone infusion have failed. However, clinical trials are required to determine the indications for Levosimendan to prevent or treat delayed cerebral vasospasm after SAH.

Human and animal rights

The authors declare that the work described has been carried out in accordance with the Declaration of Helsinki of the World Medical Association revised in 2013 for experiments involving humans as well as in accordance with the EU Directive 2010/63/EU for animal experiments.

Informed consent and patient details

The authors declare that this report does not contain any personal information that could lead to the identification of the patient(s).

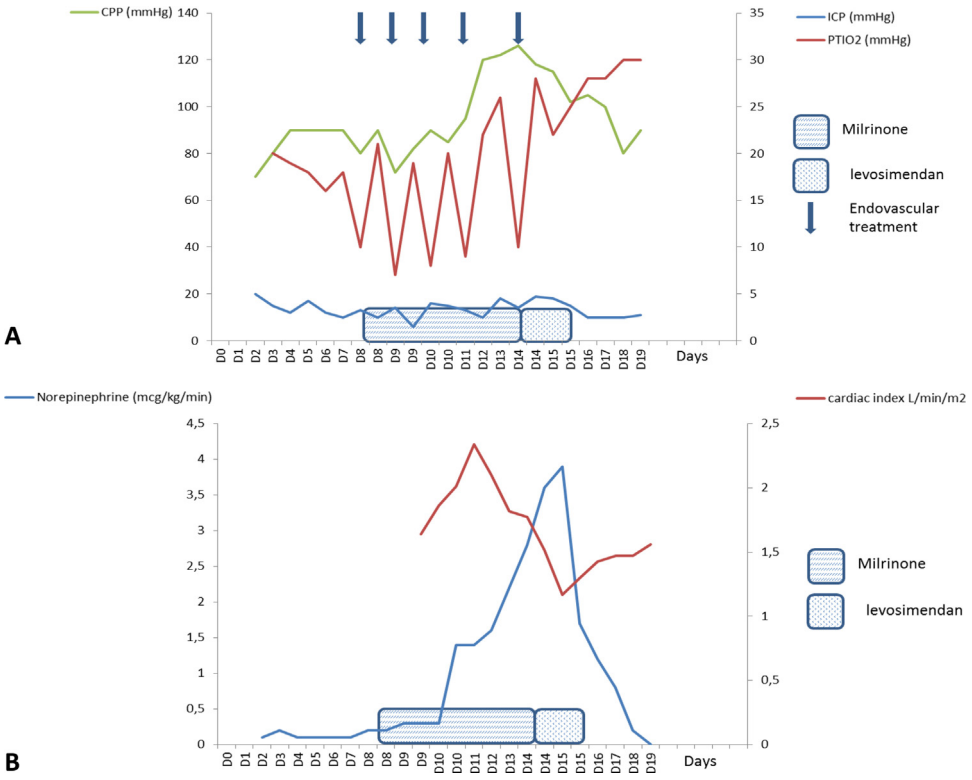

Fig. 2. Evolution of the brain tissue oxygenation ($PTiO_2$), cerebral perfusion pressure (CPP) and doses of norepinephrine over time.

The authors declare that they obtained a written informed consent from the patients and/or volunteers included in the article. The authors also confirm that the personal details of the patients and/or volunteers have been removed.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

This work did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

All authors attest that they meet the current International Committee of Medical Journal Editors (ICMJE) criteria for Authorship.

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Available online 16 July 2019