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Beneficial effect of botulinum toxin A on secondary ischaemic injury of skin flaps in rats

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Abstract

Botulinum toxin A (BTX-A) protects against primary ischaemia of skin flaps, but its effect on secondary ischaemia is unknown. We induced secondary arterial or venous ischaemia in skin flaps of 32 Wistar rats, and tested the effectiveness of BTX injected subcutaneously 12 hours before the flap was raised. The animals were divided into two groups of 16 (arterial or venous). Eight animals in each group were then treated with saline 1 ml (control), and eight with BTX-A 5 IU (treatment). Ischaemia and necrosis were assessed after five days. There was no significant difference in necrosis between the two treatments in either group, but the amount of ischaemia did differ significantly ($p = 0.031$ in the artetial ishcemia and $p = 0.015$ in the venous ischemia group). BTX helped to salvage poor reperfusion in secondary ischaemia of skin flaps.

Keywords: Botulinum toxin A; secondary ischemia; skin flap; necrosis

Introduction

Today, the success of microsurgical vascular anastomoses, even when done by experienced surgeons, is 90% to 95%. Occlusions, which generally result from technical error or vascular thrombosis, require revision of the anastomosis and restoration of blood flow, but paradoxically, restoration of normal vascular supply can result in secondary ischaemia and lead to devastating complications.

The causes of reperfusion injury are still controversial, although some agreement has been reached through experimental research.[1–3] First, reactive oxygen species have an integral role in the progression of reperfusion injury, and mitochondrial dysfunction is assumed to be its hallmark. Reperfusion injury has been reported to induce the rupture of the outer mitochondrial membrane, which results in the release of cytochrome c into the cytosolic compartment and leads to apoptosis. Lastly, endothelial dysfunction might also promote the development of reperfusion injury.

Various treatments have been proposed, including several drugs, but there is little reported clinical use. Mechanical interventions that might help have also been studied, but we know of no preferred treatment that has been verified clinically.

Numerous studies have shown that botulinum toxin (BTX) can reduce the harmful effects of ischaemic injury,[4,5] but it remains unclear whether botulinum toxin A (BTX-A) can relieve secondary ischaemia. We therefore designed this study to find out.

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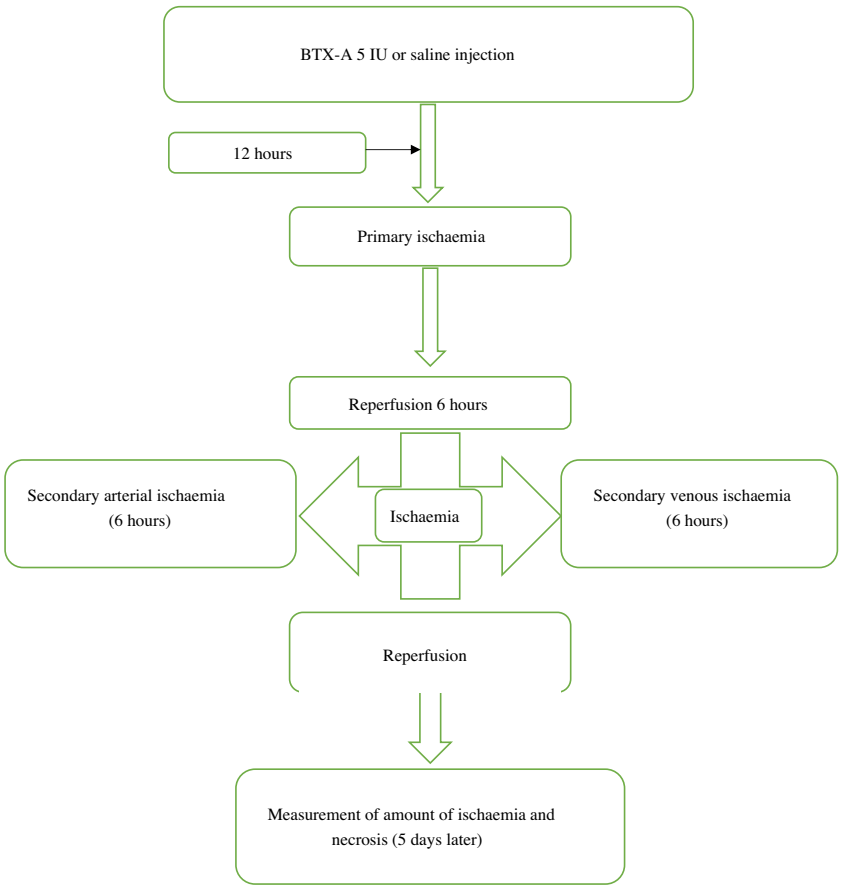

Fig. 1. Experimental protocol.

Material and methods

Animals

Thirty-two Wistar rats (weighing between 210 and 245 g) were kept at room temperature with a 12-hour day/night light cycle. They were allowed free access to drinking water and standard laboratory food. The Institutional Animal Care and Use Committee approved all animal procedures.

Operation

We divided the animals into two groups: arterial and venous (16 in each group), and subdivided both these into treatment and control groups (eight in each). The experimental protocol is described in Fig. 1.

The preconditioned animals were given BTX-A 5 IU or saline 1 ml by subcutaneous injection near the vascular pedicle. The BTX-A agent was made up of BTX-A 5 IU with 0.9% saline 1 ml from a fresh bottle, and the control group was given 0.9% saline 1 ml also from a fresh bottle.

After 12 hours all animals had a flap raised. A $6 \times 3\,cm^2$ skin flap on the epigastric artery was raised to include the panniculus carnosus (as described elsewhere).[6–8] The inferior epigastric artery and vein were separated as they entered the flap and preserved from its caudal portion (Fig. 2), and primary ischaemia was then induced by clamping them for two hours.

Fig. 2. Separation of epigastric artery and vein of the skin flap.

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