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The effects of epinephrine and dobutamine on skin flap viability in rats: A randomized double-blind placebo-controlled study

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KEYWORDS
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Summary *Background:* Intraoperative reduction in arterial pressure may cause hypoperfusion of skin flaps, which may increase the risk of flap failure. There is no international consensus regarding the use of vasoactive or inotropic agents to restore or maintain flap perfusion.

The purpose of this study was to evaluate the effects of the intraoperative administration of epinephrine and dobutamine on axial-pattern skin flap survival in rats.

Methods: Fifty-four Sprague Dawley rats were randomized into three groups ($n = 18$). A tubed axial-pattern skin flap was performed. Animals were randomized to receive an intraperitoneal injection of epinephrine 0.1 mg/kg, dobutamine 0.3 mg/kg, or saline (0.5 ml). The rats were euthanized after 7 days and the viable area of the flap was compared between the groups using a digital imaging and computer software.

Results: Seven rats/flaps were excluded from the study due to autocannibalism ($n = 3$), postoperative tracheal obstruction ($n = 2$), anesthesia-induced respiratory arrest ($n = 1$), and abnormal behavior requiring euthanization ($n = 1$). The mean flap survival was 46% ± 9% in the saline group ($n = 17$), 41% ± 9% in the epinephrine group ($n = 14$) ($p = 0.088$ compared to the saline group), and 54% ± 9% in the dobutamine group ($n = 16$) ($p = 0.02$ compared to the saline group and $p = 0.001$ compared to the epinephrine group).

Conclusions: Intraoperative intraperitoneal injection of dobutamine improves skin flap survival in rats, whereas intraperitoneal epinephrine tends to decrease skin flap survival.

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Introduction

Skin flaps are widely used in plastic surgery when reconstructing skin and soft tissue defects. Partial or complete flap necrosis remains a significant problem. The primary causes of flap necrosis are insufficient arterial blood flow and/or venous congestion, which decrease blood flow through the flap.[1] Hypoperfusion of the flap and vital organs can occur in response to intraoperative reduction in arterial blood pressure.[2] Reduction of arterial blood pressure is a common side effect to general anesthesia, particularly in connection to the anesthetic induction.[3] Severe arterial hypotension has been reported to occur in 9% of patients undergoing general anesthesia with intravenous (i.v.) anesthetic drugs (e.g., propofol).[4] Maintenance of adequate peri- and postoperative perfusion is important for vital organs as well as skin flaps.

Systemic arterial blood pressure is often thought to reflect skin flap blood flow. However, the main determinants of blood flow are cardiac output and systemic vascular resistance (SVR).[1,5] The four determinants of cardiac output are: heart rate, contractility, preload, and afterload.[6] Reduced systemic arterial pressure can be corrected with fluid therapy and reduction of the anesthetic agent/minimum alveolar concentration (MAC) depending on the anesthetic depth. The use of vasoactive agents, such as dobutamine or epinephrine, may be required to restore and maintain cardiac output and systemic perfusion. These two drugs are used clinically and considered as first- or second-line options in head and neck free tissue transfer.[7]

Epinephrine is an inotropic agent, which acts as a nonselective adrenergic-receptor agonist. It increases cardiac output by increasing heart rate (chronotropic effect) and contractility (inotropic effect). Due to epinephrine's vasoconstrictive effect, the afterload and SVR also increase. The net result is an increase in arterial blood pressure but at the expense of decreased blood flow to the skin and vital organs.[2,8] Dobutamine is predominantly a β1-receptor agonist with a dose-dependent effect on the cardiovascular system. It has a direct effect on the heart with both chronotropic and inotropic effects. Dobutamine lowers SVR (i.e., causes vasodilation) via stimulation of β2-receptors and does not affect the arterial blood pressure significantly. Overall, these effects increase the blood flow to the skin and vital organs.[2,9,10]

However, in free flap surgery, epinephrine has also been shown to decrease blood flow by 10% and dobutamine to increase blood flow by up to 15% compared to the baseline in control tissue.[8] It remains to be seen if these changes in blood flow have any clinical influence on skin flap viability. Epinephrine and dobutamine have pharmacological effects that are beneficial to maintaining adequate systemic perfusion. However, the vasoconstrictive effects of epinephrine may be detrimental for skin flaps. The aim of this study was to evaluate the effects of epinephrine and dobutamine on axial-pattern skin flap viability in rats.

Methods

Sample size

The sample size required for detecting a 20% difference between intervention groups at an 80% power and a significance level of 0.05 was 16 animals per group. This calculation was based on the standard deviation (3.37 cm^2) of the flap model and difference in skin blood flow for epinephrine and dobutamine.[11] In the case of unexpected mortality, an additional two rats were assigned to each group.

Animals

Fifty-four male Sprague Dawley rats weighing 295 ± 13 g were used in this study. Only males were used in this study in order to avoid gender-related differences. The rats were acclimatized for 7 days in UNO Type IV cages (UNO Roestvaststall B.V., Zevenaar, the Netherlands) in groups of four rats per cage. Postoperatively, the rats were individually housed in UNO Type III cages (UNO Roestvaststall B.V., Zevenaar, the Netherlands). Animals were maintained on a normal 12-h day/night cycle at 21 °C with a relative humidity of 45–55%. The rats were fed a standard diet and water *ad libitum*.

Randomization, doses, and blinding

Each rat was weighed and block-randomized with a computer software (Graphpad Software, Inc., La Jolla, CA, USA) into one of the following perioperative interventions: epinephrine 0.1 mg/kg (SAD, Copenhagen, Denmark), dobutamine 0.3 mg/kg (Dobutrex) (PharmaCoDane, Herlev, Denmark), or isotonic saline (0.5 ml) were injected intraperitoneally (i.p.) blinded to the surgeons. The rats were assigned a unique identification number blinded to the investigators. The randomization protocol ensured that both surgeons operated the same number of rats in each group.

Surgical procedure

Two surgeons performed the procedures (CWK and RMI). All rats were anesthetized by a subcutaneous injection of fentanyl 236 μg/kg (VetaPharma Limited, Leeds, UK), fluanisone 7.5 mg/kg (VetaPharma Limited, Leeds, UK), and midazolam 3.75 mg/kg (Hameln Pharmaceuticals GMBH, Hameln, Germany). The dorsum of the rat was shaved using an electric clipper and prepped with ethanol. Epinephrine, dobutamine, or saline was injected i.p. according to the randomization.

A modified McFarlane skin flap was constructed in each rat: A 2.0 × 7.0-cm distally based rectangular flap was drawn with a cranial triangular area on the dorsum of the rat. A transparent template was used to ensure all flaps had similar dimensions. The flap extended 7 cm cranially from the point where the paired gluteal muscles met closest in the midline.[12] An incision was made and the flap was elevated including the panniculus carnosus. The triangular area was included in the flap. The donor site was closed under the flap using 4/0 sutures (Ethicon, Johnson & Johnson Intl., Somerville, NJ, USA). A tubed flap was made by suturing the lateral edges of the flap together with 4/0 sutures. Subsequently, the tubed flap was attached to the donor site (Figure 1). The sutures were placed approximately 1 cm apart. Elizabethan collars were attached to