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Original article

Comparison of the effects of different vasoactive and antiplatelet drugs on perforator flap viability. An experimental study

Comparaison des effets des différents agents vasoactifs et antiagrégants sur la viabilité des lambeaux perforateurs. Étude expérimentale

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Abstract

Perforator flaps are very popular in the reconstruction of soft tissue defects. As these flaps generally depend on a single perforator, drugs that increase the perfusion of the flap and/or prevent vascular complications may increase flap survival. In this study, we compared the effects of systemically administered hydralazine (arterial vasodilator via potassium channels), nifedipine (arterial vasodilator via calcium channels), piracetam (antiplatelet and regulator of microcirculation) and alprostadil (vasodilator, antiplatelet, rheological and cytoprotective) on flap survival in a rat epigastric artery perforator flap model. The percentage of necrosis was measured on each flap and evaluated using one-way analysis of variance (Anova). Histopathological analyses were also performed. Mean flap survival area was 3.85 cm^2 in the control group. Mean flap survival area was 4.88 cm^2 in the nifedipine group, 4.69 cm^2 in the hydralazine group, 10.55 cm^2 in the piracetam group and 11.3 cm^2 in the alprostadil group. When compared with the control group, all drugs except hydralazine improved flap survival; piracetam and alprostadil yielded significantly better results than nifedipine. Only the alprostadil group showed signs of improved vascularity in the histological analysis. As far as perforator flap survival is concerned, drugs that regulate the microcirculation by a combination of different antiaggregation mechanisms appear more beneficial than single action vasodilators. Alprostadil, a synthetic PGE-1 analogue, has combined antiplatelet and vasoactive effects that further increase flap survival.

Keywords: Perforator flap; Flap viability; Nifedipine; Piracetam; Hydralazine; Alprostadil

Résumé

L'utilisation des lambeaux perforateurs est très répandue dans la reconstruction des pertes de substance des parties molles. Tous ces lambeaux dépendent généralement d'un seul pédicule perforateur, les substances qui augmentent la perfusion du lambeau et/ou préviennent les complications viscérales peuvent augmenter le taux de survie du lambeau. Dans cette étude, nous avons étudié et comparer les effets des agents suivants utilisés de façon systémique : hydralazine (vasodilatateur artériel via les canaux à potassium), nifedipine (vasodilatateur artériel via les canaux à calcium), piracetam (antiagrégant et régulateur de la microcirculation) et alprostadil (vasodilatateur, antiagrégant, rhéologique et cytoprotecteur) sur la survie du lambeau dans un modèle murin de lambeau perforateur sur l'artère épigastrique inférieure. Sur chaque lambeau nous avons mesuré le pourcentage de nécrose du lambeau et les données ont été évaluées par une analyse de variance à sens unique (Anova). Les examens histopathologiques ont également été pris en compte. La surface moyenne de lambeau survivant était de 3,85 cm^2 dans le groupe témoin. Parmi les groupes étudiés, la surface moyenne de lambeau survivant était de 4,88 cm^2 dans le groupe nifedipine, 4,69 cm^2 dans le groupe

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hydralazine, 10,55 cm^2 dans le groupe piracetam et 11,3 cm^2 dans le groupe alprostadil. Par comparaison avec le groupe témoin, tous les agents sauf l'hydralazine amélioraient la survie du lambeau, le piracetam et l'alprostadil donnaient des résultats significativement meilleurs que la nifedipine. Aux analyses histologiques, seul le groupe alprostadil démontrait une amélioration de la vascularisation. En ce qui concerne la survie des lambeaux, les substances qui régulent la microcirculation par l'intermédiaire de la combinaison de différents mécanismes antiagrégants apparaissent plus efficaces que les vasodilatateurs à action simple. L'alprostadil, un analogue de synthèse de la prostaglandine E1 (PGE-1), a des effets combinés antiagrégants et vasoactifs qui augmentent le plus la survie du lambeau, et il est plus efficace que les antiagrégants ou les vasodilatateurs seuls.

Mots clés : Lambeau perforateur ; Viabilité du lambeau ; Nifedipine ; Piracetam ; Hydralazine ; Alprostadil

1. Introduction

Perforator flaps were first described by Koshima in 1989 and their use has increased since then [1,2]. They can be designed as free or pedicled flaps [3]. Pedicled perforator flaps provide most of the advantages of free perforator flaps without requiring microvascular anastomosis [4,5]. As these flaps usually hinge on a single perforator, drugs that improve the vascularity and/or prevent vascular complications may prove instrumental in flap viability.

In this study, we aimed to compare the effects of systemically administered hydralazine (arterial vasodilator via potassium channels), nifedipine (arterial vasodilator via calcium channels), piracetam (antiplatelet and regulator of microcirculation) and alprostadil (vasodilator, antiplatelet, rheological and cytoprotective) on the survival of a rat epigastric artery perforator flap model.

2. Material and methods

This study was conducted after the approval of our institute's ethics committee and in accordance with its guidelines. Sixty male Sprague Dawley rats, weighing between 215–312 grams were used. The number of animals required was determined using power analysis software (Gpower 3.1, Dusseldorf University, Germany). All procedures were performed under general anesthesia induced by intraperitoneal ketamine HCL (75 mg/kg) and intramuscular xylazine (0.2 mL/kg). A surgical microscope (316, OPMI-99, Zeiss, Germany) and standard microvascular instruments were used. The anterior abdominal wall was shaved, prepped and draped. Each animal was secured to the operating tray in a supine position and the surgical procedure was performed as described previously [5]. A symmetrical 6 × 6 cm rectangular flap was planned. The tip of the xiphoid marked the midpoint of the cranial margin of the flap and the other margins were drawn accordingly. The flap was based on the second left cranial perforator vessel of the left rectus abdominis muscle, which is located cranial to the virtual umbilicus.

Following incision of the skin and the panniculus carnosus, the flap was elevated in a lateral to medial fashion, exposing the perforators, which entered the panniculus carnosus after piercing the rectus abdominis muscles. All vessels supplying the skin paddle other than the designated perforator were cauterized. The perforator was isolated using microforceps and adventitia scissors but the dissection did not extend into the rectus muscle (Fig. 1). Afterwards, the flaps were sutured back in place using 4-0 non-absorbable sutures and each animal was returned to its individual cage with free access to food and water. Acetaminophen was administered intraperitoneally at 50 mg/kg for postoperative analgesia. Three animals died of anesthesia complications and another seven ate their flaps—-they were consequently excluded from the study.

2.1. Experimental design

Rats were divided into five groups of 10. For 7 days, 10 mg/kg nifedipine, 2.5 mg/kg hydralazine, 1 g/kg piracetam, and 4 mcg/kg alprostadil solutions were administered intraperitoneally to the respective groups. The control group received no injections. On the seventh postoperative day, all rats were sacrificed, and histopathological and planimetric analyses were performed. All drug dosages were calculated according to the World Health Organization formula for converting human dosages to animal dosages:

$$\text{human dosage (mg/kg)} = \text{animal dosage (mg/kg)} \ (\times)\text{animal Km/human Km.}$$

2.2. Planimetric analysis

Photos of the flaps were taken by a digital camera. Necrotic and viable flap areas were measured quantitatively using photo

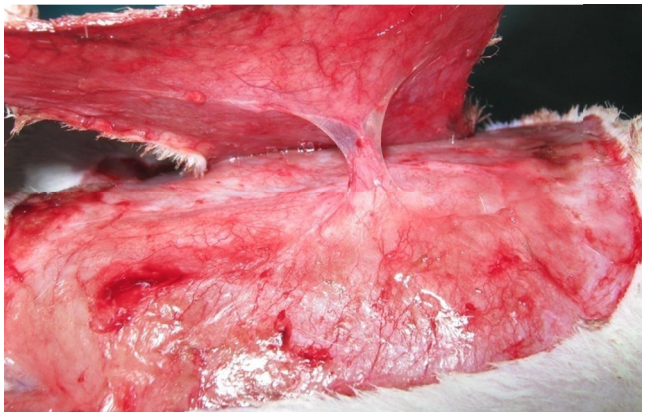

Fig. 1. Design of the flap showing left second cranial perforator.