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Review

Are prostaglandins or calcium channel blockers efficient for free flap salvage? A review of the literature

M. Huby [a,b,*], K. Rem [a,b], V. Moris [c], D. Guillier [c], M. Revol [a,b], S. Cristofari [a,b]

[a] Université Paris Diderot, Sorbonne Paris Cité, 75013 Paris, France
[b] AP–HP, hôpital Saint-Louis, 75010 Paris, France
[c] Service de chirurgie maxillo-faciale – stomatologie – chirurgie plastique réparatrice et esthétique – chirurgie de la main, CHU Dijon Bourgogne, 14, rue Paul-Gaffarel, 21000 Dijon, France

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ABSTRACT

The free flap failure rate is less than 5%. The responsible mechanisms of postoperative secondary ischemia are mostly vascular. The main postoperative complication leading to flap failure is thrombosis. Different strategies have been reported to improve the reliability of flaps and decrease the risk of partial or total necrosis: thus, pharmacologic agents have been studied to reduce the risk of microvascular thrombosis. The aim of this review was to evaluate the effect of calcium channel blockers and prostaglandins on free skin flap survival. A systematic review of the literature was performed to identify articles studying the efficacy of calcium channel blockers and prostaglandins on free flap survival. After full text reading, eleven articles were finally included. Eight articles investigated the role of prostaglandins in free tissue transfers, two in rats subjects, one in rabbits, five in humans. Two articles studied the effect of calcium channel blockers on free flaps, one in rats subjects, one in rabbits. One article studied in different groups the effect of calcium channel blockers and prostaglandins on free flaps in rabbits. Literature regarding the efficacy of calcium channel blockers and prostaglandins to salvage free flap is poor and mainly based on animal models. Nevertheless, studies on prostaglandins showed a slight efficiency of these molecules for free flap salvage. Results are less reliable for calcium channel blockers and dependent on the molecule used. In conclusion, there is a lack of evidence to use them in clinical practice.

1. Introduction

Since 1959 and the first free tissue transfer [1], free skin flap have been more and more used in microvascular reconstructive surgery.

Currently, the failure rate of free flap is less than 5% [2]. The mechanisms responsible of postoperative secondary ischemia are mostly vascular. The main postoperative complication leading to flap failure is thrombosis. Identified risk factors of flap failure can be: irradiated recipient bed, buried flaps, necessity to use vein grafts in the arterial and/or venous microvascular repair [2].

Different strategies have been reported to improve the reliability of flaps and decrease the risk of partial or total necrosis [3]: thus, pharmacologic agents have been studied to reduce the risk of microvascular thrombosis. In particular, calcium channel blockers (CCB) and prostaglandins are frequently studied and described. Some surgical teams use them in per- and postoperative protocol [4].

CCB are known to induce peripheral vasodilatation by relaxation of smooth muscle cells in arteriole. They are divided in three groups: phenylalkylamin (verapamil), dihydropyridin (nimodipine, nitrendipine, nifedipine), benzothiazepin (diltiazem). All these molecules are active on both cardiac and vascular cells, preferentially a cardiac action for verapamil and diltiazem, whereas dihydropyridin have a stronger effect on vascular cells [5]. Primarily used to treat hypertension, it is now also used in Raynaud disease [6].

Prostaglandins are arachidonic acid metabolites. Some of them have a specific function and variously induce vasodilatation and inhibition of platelet aggregation like PGE-1, prostacyclin (PGI-2) [7]. They are used in the treatment of claudication, peripheral arterial occlusive disease or Raynaud syndrome [6].

The aim of this review was to evaluate the effect of calcium channel blockers and prostaglandins on free skin flap survival.

* Corresponding author at: AP–HP, hôpital Saint-Louis, 75010 Paris, France.
E-mail address: marine.huby@hotmail.fr (M. Huby).

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2. Material and methods

A systematic review of the literature was performed on Pubmed using (((free flap) OR free tissue transfer) OR island flap) AND (((((prostacyclin) OR prostaglandin) OR calcium channel blocker) OR verapamil) OR nifedipine).

Ninety-one articles were found. Exclusion criteria were: not related to the subject, non-English-language articles, pedicled flaps or random skin flaps. Twenty articles were identified for full text review. Ten articles were excluded after being read.

One article was included from hand search (Fig. 1).

3. Results

After full text reading, eleven articles were finally included. Eight articles investigated the role of prostaglandins and prostacyclin in free tissue transfer, two in rats subjects, one in rabbits, five in humans. Two articles studied the effect of CCB on free flaps, one in rats subjects, one in rabbits. One article studied in different groups the effect of CCB and prostaglandins on free flaps in rabbits.

3.1. Prostaglandins

All results of the included studies describing prostaglandins effects on free flap survival are reported in Table 1.

Three articles studied the effect of prostaglandins in cold ischemia conditions.

Lindner et al. studied different drugs, which might increase tissue survival after four days of ex vivo storage at 4°C in phosphate-buffered Ringer solution at pH 7.8 [8]. They used superficial epigastric flaps of rats transplanted to the contralateral side after four days. The first group flaps were stored without drug treatment ($n = 10$). In group II, animals received two different doses of PGE-1 through the right carotid artery before flap harvest ($n = 10$) or before flap harvest anastomosis ($n = 10$). At low dose of PGE-1, no flap survived. At high dose of intra-arterial PGE-1, 20% of flaps survived if animals received the drug before flap harvest, 10% if they received PGE-1 before flap harvest and anastomosis. This slight benefit of PGE-1 in flap survival was not significant. This study was not able to prove a benefit of prostaglandins in free flap survival.

Knight et al. and Lepore et al. used the same model of epigastric free flap in rabbits. The free flaps were ex vivo stored at 25°C in saline-moistened gauze in a sealed sterile container for 21 hours and then revascularized by microvascular anastomoses to the contralateral side [9,10]. Knight et al. compared both in vivo systemic and local injection of physiologic serum in control group and prostaglandins after reperfusion. They used an intra-arterial infusion of PGI2 through a distal femoral arterial catheter for 30 min after anastomoses with two bolus doses injected intravenously in 14 rabbits. The mean percentage of surviving area in rabbits epigastric skin flaps one week after ischemia was 68% ($P < 0.025$) with the PGI2 infusion vs. 39.9% in control group ($n = 18$). In Lepore et al. study, their model focused on in vivo local pre- and post-reperfusion injection of prostaglandins compared to physiologic serum. They infused PGI2 intra-arterialy through a distal femoral arterial catheter one minute before the arterial clamp was released after arterial and venous anastomoses and continued the perfusion for 40 minutes. The percentage area of flap

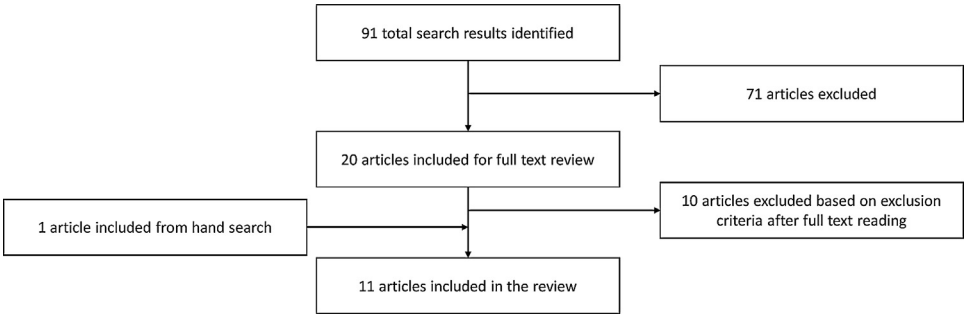

Fig. 1. Flow diagram of systematic literature search.

Table 1
Characteristic of included studies about prostaglandins effect on free flaps survival.

Study	Subject of the study	Ischemia	Systemic/local injection	Pre/per/postoperative injection	Drug administrated	Efficacy on flap survival	Limits of the study
Lindner 1986	Rat	Cold	Systemic	Pre + per + postoperative	PGE-1	Not significant	Small number of subject (10)
Frick 1993	Rat	Warm	Local + systemic	Peroperative	Iloprost, cicaprost	Yes	Small number of subject (≤ 10)
Knight 1991	Rabbit	Cold	Local + systemic	Peroperative	Prostacyclin	Yes	Small number of subject (10)
Lepore 1994	Rabbit	Cold	Local	Peroperative	Prostacyclin	Yes	Small number of subject ($n = 18$)
Gateley 1996	Human	Warm	Systemic	Per + postoperative	PGE-1	Yes	Two case reports
Renaud 1996	Human	Warm	Local + systemic	Per + postoperative	Iloprost + urokinase	Yes	One case report, mix of drugs
Hataya 1999	Human	Warm	Local	Per + postoperative	PGE-1 + heparin	Yes	One case report, association of PGE-1 + heparin
Rodríguez Vegas 2007	Human	Cold + warm	Systemic	Per + postoperative	PGE-1 + heparin	Yes	No control group, association of PGE-1 + heparin
Riva 2012	Human	Warm	Systemic	Postoperative	PGE-1	No	Retrospective study

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