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ORIGINAL ARTICLE
Reconstructive

Use of Phosphodiesterase Inhibitors in the Postoperative Period of Skin Flaps: A Systematic Review

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Background: Ischemia-reperfusion injury can occur in several clinical conditions, and it has been widely studied in the context of skin flaps. Vascular distress results in an imbalance between the supply and demand of oxygen to living tissues, and the result of this process is tissue necrosis. Several drugs have been studied to reduce vascular distress of skin flaps and tissue loss.
Methods: The present study performed a systematic review of literature in the main databases (PubMed, Web of Science, LILACS, SciELO, and Cochrane), including articles published in the last 10 years.
Results: It was observed that phosphodiesterase inhibitors, mainly types III and V, have shown promising results in terms of vascularization of the postoperative skin flap, especially when started on the first postoperative day and maintained for 7 days.
Conclusion: New studies with different posology, duration of use, and new drugs are needed to better elucidate the use of this substance to optimize the circulation of skin flaps. *(Plast Reconstr Surg Glob Open 2023; 11:e4978; doi: 10.1097/GOX.0000000000004978; Published online 15 June 2023.)*

INTRODUCTION

Skin flaps are widely used for reconstruction in plastic surgery, but one of their main limitations is vascular distress of the flap and, consequently, necrosis, resulting in loss of tissue. Vascular distress results in ischemia-reperfusion injury, a phenomenon frequently encountered in surgical and clinical conditions that results in loss of anatomical and functional tissue integrity, resulting in formation of free radicals, and increasing morbidity and mortality rates. The reduction in blood flow in the flap can be caused by several factors, which can be anatomical, hemodynamic, and metabolic.[1] In recent years, research has been performed on drugs that could optimize the circulation of skin flaps, such as type V[1–3] phosphodiesterase (PDE) inhibitors, which include tadalafil and sildenafil, and type III, of which the main representative is cilostazol.[4,5] In view of the great divergence in the literature on the optimization of skin flap circulation, this article presents a systematic review of the literature, performed with the main databases currently used. The aim of the study was to verify which drugs have scientific evidence to improve the circulation of skin flaps used in plastic surgery, in addition to defining their dosage and duration of use.

METHODOLOGY

A dual approach was used to design this study. First, a systematic review of the literature was performed to identify possible agents used to optimize flap circulation in plastic surgery. Second, a separate review of the literature was performed with respect to the properties and described the use of each agent, as well as additional clinical and pharmacological considerations to complement the study results.

The present study was carried out through a literature search of scientific articles published in Pubmed, SciELO (Scientific Electronic Library Online), Cochrane, LILACS (Latin American and Caribbean

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Literature on Health Sciences), and Web of Science. Articles published in the last 10 years, and which presented scientific evidence of the use of PDE inhibitors with the aim of improving vascularization in skin flaps were included. The studies used for research were mostly retrospective and experimental studies, excluded studies being case reports, review articles, or meta-analyses. There is currently no review protocol published by Cochrane regarding the use of PDE inhibitors for optimizing circulation in skin flaps.

The search for the descriptors and terms used was carried out by consulting the Medical Subject Headings, through the US National Library of Medicine portal and the Health Sciences Descriptors (DeCS), through the Virtual Health Library portal (BVS). Articles written in English and Portuguese were included. The crosses obeyed the requirements of each base, and descriptors used were: "phosphodiesterase inhibitor," "atorvastatin," "açaí," "flap," and "plastic surgery." The "and" filler was added. Two independent reviewers performed the search, data extraction, and analysis. The articles were selected based on reading titles and abstracts; then, those that did not meet the inclusion criteria were excluded. The divergences among the evaluators were treated in meetings of consensus, with the presence of a third evaluator. The PRISMA declaration methodology for systematic reviews can be seen in Figure 1.

In the second stage, titles and abstracts of publications identified by the electronic search strategy were selected after evaluation of publications with themes relevant to inclusion in the present study. A meta-analysis was not performed due to the heterogeneity of the studies and results found.

Takeaways

Question: Several drugs have been studied in an attempt to reduce the vascular distress of skin flaps and, consequently, tissue loss.

Finding: The present study performed a systematic review of the literature, and it was observed that phosphodiesterase inhibitors, mainly types III and V, have shown promising results in terms of vascularization of the postoperative skin flap.

Meaning: Phosphodiesterase inhibitors could avoid flap necrosis when started on the first postoperative day and maintained for 7 days.

INCLUSION AND EXCLUSION CRITERIA

There were included articles published in the last 10 years, in all languages found, that described or compared the use of intravenous, subcutaneous, and enteral drugs with the aim of optimizing the circulation of skin flaps. Case reports, review articles, meta-analyses, and articles that were not fully available for reading were excluded. Studies that performed only intraoperative application of topical drugs were also excluded.

INSTRUMENTS AND PROCEDURES FOR DATA COLLECTION

A PICO strategy was used to search the articles, and the explosion was performed using skin flaps: I (intervention) included treatments using PDE inhibitors; C (comparison) included other treatments or a control group; O (outcomes) included studies that resulted in an improvement

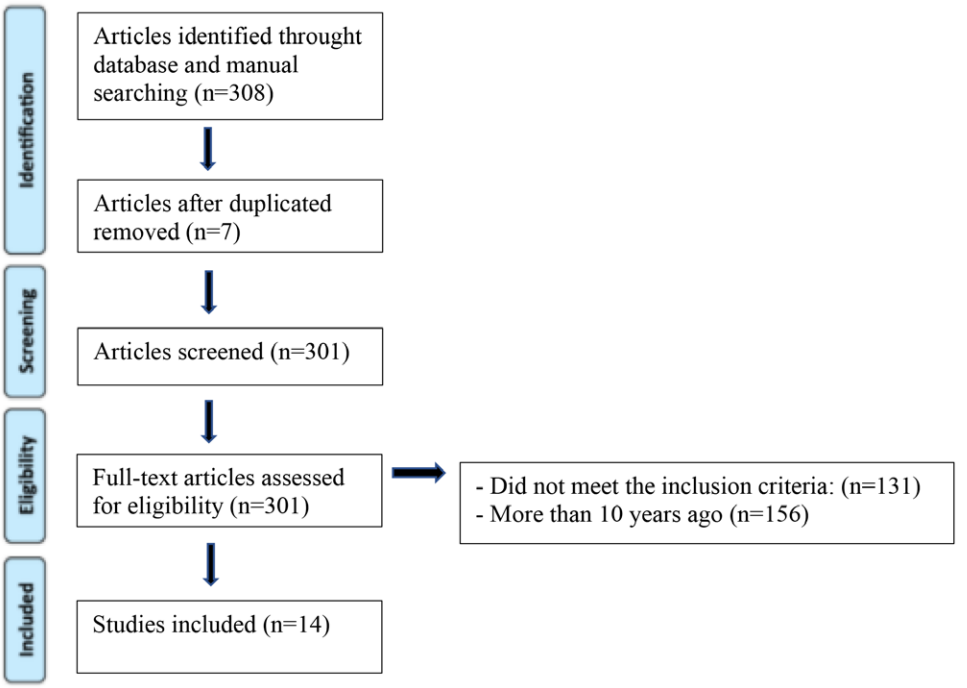

Fig. 1. Flowchart from PRISMA of the selection of studies included in the review.

in the area of vascular distress after treatment with PDE inhibitors. The articles were independently searched by the authors.

RESULTS

A total of 308 articles were found, considering all included databases. Seven articles were repeated, 156 were not published in the last 10 years, and 131 did not meet the inclusion criteria. Thus, the review included 14 articles in the systematic review. These 14 articles, published in the last 10 years, were included in the present study. Articles that used PDE inhibitors in the pre- and/or postoperative period of skin flap surgeries were searched, among which type III (cilostazol) and type V (tadalafil, sildenafil, and vadalafil) of the selective ones, and pentoxifylline in the nonselective class. Despite not including other words besides "PDE inhibitors," other medications that optimize flap circulation were found with these search references and were included in the systematic review. Of the articles studied, 12 were experimental studies with rats and two were with patients, but without a control group. None of the flaps were performed by microsurgery. The mechanisms of action by which these drugs perform their therapeutic effects were investigated, and their efficacies were compared through the present research. Details of each article included in this systematic review can be seen in **table, Supplemental Digital Content 1**, which displays characterization of selected studies, **http://links.lww.com/PRSGO/C607**.

Nonselective Phosphodiesterase Inhibitors

The main representative of this class is pentoxifylline. This medication originated from the extract of theobromine cocoa beans, with the addition of a ketone species, and increases from a ketocaloid species, whose molecular formula is a C13H20N4O3.[6] By blocking membrane-bound PDE, it increases the concentration of cyclic adenosine monophosphate (cAMP). It also inhibits a synthesis of thromboxane and increases the synthesis of prostacyclin. These actions result in reduced platelet aggregation.[7] In the case of its use in optimizing the circulation of skin flaps, pentoxifylline exerts vasodilation in the vascular bed of skeletal muscle, inhibiting PDE and increasing cAMP. This postoperative intervention can be beneficial when used in the postoperative period of surgery for reconstruction with flaps.[7] In the case of its use in optimizing the circulation of skin flaps, pentoxifylline exerts vasodilation in the vascular bed of skeletal muscle, inhibiting PDE and increasing cAMP.[6] It was observed that a dose of 0.1 g of pentoxifylline administered once daily for 7 and 14 days postoperatively ($P < 0.05$) resulted in an improvement in flap circulation, but there was no difference between these groups.[1]

Selective Phosphodiesterase Inhibitors

The main representatives are PDE inhibitors types III and V. Tadalafil is an active and potent inhibitor of cyclic guanosine monophosphate of PDE type V (PDE-V). PDE-V specifically inhibits the nitric oxide (NO)/GMP pathway in smooth muscle vessels inducing vasodilation and increased plaque. Among PDE-V inhibitors, such as sildenafil, verdenafil, tadalafil, udenafil, and avanafil, tadalafil has the longest half-life.[2] There are four PDE-V inhibitors (sildenafil, vardenafil, tadalafil, and udenafil) on the market, and the half-life of each drug is 4, 4–5, 17.5, and 12 hours, respectively.[3]

Of the type III PDE inhibitors, cilostazol is the most common representative. This drug is used in clinical practice for the treatment of intermittent claudication. Degradation of intracellular cAMP is inhibited because of the inhibition of the enzyme PDE, and the increased concentration of cAMP in muscle cells of the cases inhibits the release of intracellular calcium and causes vasodilation.[8]

Both tadalafil (10 mg/d daily) and sildenafil (10 mg/kg daily) had beneficial effects in optimizing skin flap circulation when started in the immediate postoperative period, with greater influx of neutrophils, and increased mononuclear population in the seventh day ($P < 0.05$). However, on the 14th day, these differences were observed only in the tadalafil group ($P < 0.05$).[2] Most initial studies show beneficial effects in the first 7 operative days,[3,5] but there is evidence that these drugs can be started preoperatively, at a dosage of 5 mg/kg per day in the 7 days before surgery.[1] No discrepancies were observed in the results that do not concern the use of drugs of the same class and type. The only difference between PDE-V inhibitors would be the half-life of each one, which is variable.[9]

It was observed that the use of 2% nitroglycerin applied topically every 8 hours, starting on the day of surgery and maintained for 7 days postoperatively, when combined with the use of sildenafil 100/mg, presented better results compared with the use of sildenafil alone.[5]

In addition to PDE inhibitors, there are several plant polyphenols that exert important effects on the cardiovascular system and may be potential natural sources for new drugs in the treatment of cardiovascular and metabolic diseases.[4] The functional açaí (Euterpe olerace) has gained great popularity due to its significant importance of polyphenols, which potently promote antioxidant effects and endothelium-dependent vasodilators, increasing the bioavailability of NO in cells and endothelium.[6] It was observed in studies with rats that açaí extract can be used in the postoperative period of skin flaps to reduce the chances of necrosis, and that its use has synergistic effects on the circulation of the flap as well as cilostazol.[6]

Atorvastatin is also a drug that has been shown to have an effect on the vascularization of skin flaps in the postoperative period in isolation, and both nitroglycerin and the action of U-74389G, an antioxidant drug, showed synergistic effects of action with sildenafil, through the reduction of lymphocyte concentration and edema. An experimental study with 45 rats performed a comparison between the use of sildenafil 10 mg/kg and atorvastatin 10 mg/kg, in the optimization of flap circulation. Both medications were separated after 12 hours and digital images after 7 days.[7] In both groups, there was an improvement in the circulation of the flaps.[7]

In the study that combined the use of sildenafil and U-74389G, a significant reduction ($P < 0.05$) was observed in the concentrations of lymphocytes and polymorphonuclear leukocytes, as well as in the appearance of edema after histopathological evaluation of the ischemic tissue, showing that the synergistic action of U-74389G and sildenafil appears protective and promising in cases of ischemic flap injuries during tissue reconstruction surgery.[8] U-74389G is a chemical compound of the lazaroid class, and they are synthetic aminoacids, without glucocorticoid and mineralocorticoid activity, exerting a lipid membrane with peroxidation action and functioning as oxygen-free radical protectors.[8]

Regarding the time of use of these drugs for the potential effect of flap optimization, vascularization was observed, with evidence of a single dose in the postoperative period,[10] treatment for 3 days,[11] and studies highlighting the importance of using them for 7 days after performing the procedure.[12] Some studies on the use of medications may even improve flap circulation in smokers.[11,13] By administering PDE-V inhibition twice daily, animals exposed to nicotine show a reduction of more than 50% in skin flap necrosis when compared with the nicotine control group, in a statistically significant way.[10] Even with the dosage of 5 mg/d of tadalafil for 3 postoperative days, with the first dose after the procedure, a protective effect of flap necrosis was observed in smokers.[14]

DISCUSSION

The use of skin flaps is widely used in the reconstruction of defects after tumor ressection, inflammatory lesions, injuries caused by radiotherapy, and trauma. One of the biggest concerns in the postoperative period of skin flaps is their vascularization, with the most distal point presenting a greater risk of vascular distress.[9] Ischemia/reperfusion injury has several consequences, such as narrowing, leukocyte sequestration, neutrophilic infiltration, endothelium dysfunction, target organ membrane dysfunction, and enzymatic disruption in the arrangement of inflammatory mediators.[2] Tissue reperfusion triggers the release of many proinflammatory cytokines.[10]

It is known that initially PDE inhibitors were used for the treatment of sexual impotence and pulmonary hypertension, but over the years, other applications have been verified for this important class of drugs, among which the use in skin flaps can be used to optimize its vascularization.[1] The dose of sildenafil or tadalafil used in most studies was 5 mg/kg daily.[2,11] There are studies that applied tadalafil 10 mg/d in a single daily dose on the day of the procedure and on the next two subsequent days, resulting in three doses in total, and were successful in reducing flap necrosis rates.[3]

On the other hand, another study with groups comparing 10 mg/kg of sildenafil, 10 mg/kg of tadalafil, and 10 mg/kg of vardenafil, administered 2 days before and 2 days after flap surgery, showed that although there were rates of minor necrosis compared with the control group, there was no statistically significant difference ($P = 0.077$).[9] The common side effects of tadalafil include headaches, dyspepsia, myalgia, rhinitis, and flushing.[14]

Cilostazol is a potent selective inhibitor of PDE type III that increases cAMP, decreasing intracellular calcium in muscle cells, causing cellular relaxation and vasodilation, in addition to promoting inhibition of platelet activation and aggregation, reducing thrombosis.[6] Optimization in the circulation of the flaps was observed with the use of cilostazol 30 mg/kg, orally, twice a day, 7 days before, and 7 days after surgery.[6] No signs of flap ischemia or necrosis were also observed using cilostazol 30 mg/kg twice a day, starting immediately after surgery and continuing for 7 days, without using it in the preoperative period.[13] When the same dose is not given for 7 days in the preoperative period, this demonstrates that it will result in higher rates of flap necrosis compared with the groups in which it was presented during the operative period for 14 days, not only in the preoperative period.[4]

Although most studies demonstrate a beneficial effect of these medications on the circulation of flaps, there was no consensus regarding the dose and time of use in the pre- or postoperative period, with use ranging from 1 week preoperatively,[12] to 1 week postoperative.[2] Thus, it is necessary to perform studies to define a protocol for the use of these drugs in skin flap surgery.

Another class of drugs that has shown beneficial effects on flap circulation is atorvastatin. This medication is an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase, the key enzyme in the biosynthesis of cholesterol in the liver and responsible for catalyzing the reduction of 3-hydroxy-3-methylglutaryl-CoA to mevalonate. Particularly, the Rac protein pathway and an endothelial NO synthase have been shown to be related to reactive species production and subsequent ischemia/reperfusion injury.[7] Although there is evidence that this medication optimizes flap circulation, there were no differences in the images after 7 days compared with the experimental group that received sildenafil alone.[7] It is possible that this lack of statistically significant difference between the groups was due to the administration of a single dose of these medications intraoperatively. In addition, the study was performed only in rats, which partially compromises its conclusions. More studies using these drugs would be important in an attempt to verify whether they have similar beneficial effects, since atorvastatin is a lower cost medication and results in fewer systemic side effects, such as hypotension and headache, often seen with the use of inhibitors of PDE.

Açaí, widely explored for its nutrients in the food industry, also showed that it does not affect the circulation of properties mainly due to its antioxidant and vasodilatory action[6]; however, an isolated article of these components of studies was found in the present systematic review, and therefore, more studies must be performed so that new consensus is established. The dose used was 100 mg/kg, once a day, 30 days before surgery, and 7 days after surgery.[6]

Although there are articles showing the improvement of flap circulation in smokers with the use of PDE inhibitors,[13,15] these results should be interpreted with caution, since in practice we observe catastrophic results in skin flaps, even in

clinical patients who are previously healthy and nonsmokers. The orientation to stop smoking 4 weeks before and after the procedure should prevail in clinical-surgical practice.

CONCLUSIONS

The vascularization of skin flaps in the postoperative period remains the main challenge in this class of surgery. Several medications have been proposed in an attempt to reduce vascular distress and optimize flap circulation. The use of PDE inhibitors for a period of 5–7 days after surgery has shown beneficial effects in optimizing flap circulation. Although there is a considerable number of studies evidenced in this systematic review, most of them are in rats, and it is essential to perform new studies in humans to define treatment time and doses to create specific protocols for this purpose.

REGISTRATION AND PROTOCOL

The present review was not registered, and a protocol was not prepared. More studies should be done until protocols about the use of PDE inhibitors after skin flaps can be written.

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DISCLOSURES

The authors have no financial interest to declare in relation to the content of this article.

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