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Original Article

Tadalafil significantly reduces ischemia reperfusion injury in skin island flaps

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ABSTRACT

Introduction: Numerous pharmacological agents have been used to enhance the viability of flaps. Ischemia reperfusion (I/R) injury is an unwanted, sometimes devastating complication in reconstructive microsurgery. Tadalafil, a specific inhibitor of phosphodiesterase type 5 is mainly used for erectile dysfunction, and acts on vascular smooth muscles, platelets and leukocytes. Herein, the protective and therapeutical effect of tadalafil in I/R injury in rat skin flap model is evaluated. **Materials and Methods:** Sixty epigastric island flaps were used to create I/R model in 60 Wistar rats (non-ischemic group, ischemic group, medication group). Biochemical markers including total nitrite, malondialdehyde (MDA) and myeloperoxidase (MPO) were analysed. Necrosis rates were calculated and histopathologic evaluation was carried out. **Results:** MDA, MPO and total nitrite values were found elevated in the ischemic group, however there was an evident drop in the medication group. Histological results revealed that early inflammatory findings (oedema, neutrophil infiltration, necrosis rate) were observed lower with tadalafil administration. Moreover, statistical significance ($P < 0.05$) was recorded. **Conclusions:** We conclude that tadalafil has beneficial effects on epigastric island flaps against I/R injury.

KEY WORDS

Free radicals; ischemia; island flap; reperfusion injury; tadalafil

INTRODUCTION

Ischemia reperfusion (I/R) injury can be devastating during flap reconstruction. Some described metabolic alterations such as capillary narrowing, leukocyte sequestration, neutrophil infiltration, dysfunction of endothelium, end-organ membrane dysfunction and enzymatic defects of mediators take place in I/R injury.[1] Free oxygen radicals play key role in reperfused tissues, thus causing detrimental effects[2].

Tadalafil is a competitive and potent inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE-5).[3] PDE-5 specifically inhibits nitric oxide (NO)/GMP pathway in vascular smooth muscles inducing vasodilatation and in platelets inhibiting aggregation.[4] Among PDE-5 inhibitors like silenafil, verdenafil, tadalafil, udenafil, avanafil, tadalafil has longest half-life.

There is little data existing in flap surgery field for PDE-5 inhibitors. In this experimental study, local response to

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the reperfused skin flap with systemic administration of tadalafil is investigated.

MATERIALS AND METHODS

This study was performed under the guidelines for the care and use of laboratory animals and approved by Animal Ethics Committee of Ankara Training and Research Hospital.

Sixty Wistar rats (ratus norvergicus) ranging between 300 g and 380 g (343 g mean) were used in this study. Ketamine hydrochloride (HCl) and xylazine HCl were injected intramuscular for anesthesia. Tadalafil tablets (20 mg) were dissolved in 20 cc water. This solution was given enterally (5 mg/kg) with nasogastric catheter according to the weight of the rat (1.7 mg mean). Sixty rats were divided into 3 groups as non-ischemic, ischemic and medication groups. Each group was divided into 2 sub-groups (n = 10) (sub-groups a and b). The animals were randomly distributed. Superficial epigastric island flaps (7 cm × 4 cm) were elevated from the epigastric area according to the experimental model described by Petry *et al*.[5] [Figure 1]. Acland V3 clamps for pedicle clamping were used to induce complete flap ischemia. For reperfusion at the end of the ischemia the clamps were removed from the pedicle and the vascular flow observed with microscobic examination.

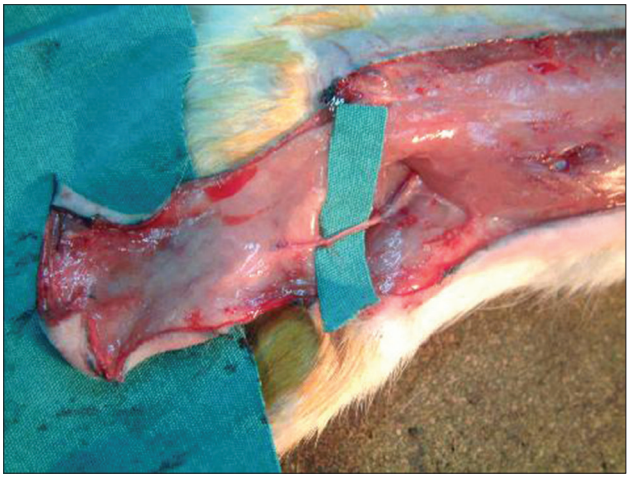

Figure 1: Epigastic island flap elevated on superficial epigastic artery and vein according to the model described by Petry *et al*

In Group I (non-ischemic group, n = 20), the elevated flaps were immediately re-adapted to the epigastric area without any intervention. The half of the animals (n = 10) was sacrificed after 12 h (Group I a). The rest was sacrificed after 7 days (Group I b). In Group II (ischemic group, n = 20), the pedicles of the flaps (superficial epigastric artery and vein) were clamped for 12 h to achieve global ischemia and subsequently reperfused. The half of the animals (n = 10) was sacrificed after 12 h of reperfusion (Group II a). The rest was sacrificed 7 days later (Group II b). In Group III (medication group, n = 20), the same protocol was applied like in the Group II, but at the 30th min of the reperfusion, a single dose of 5 mg/kg of tadalafil was administered enterally. The half of the animals (n = 10) was sacrificed after 12 h of reperfusion (Group III a). In the rest of the animals (Group III b), 5 mg/kg tadalafil were administered daily and at the 7th day they were sacrificed. Sub-groups a

Table 1: Total nitrite, MDA, MPO values for groups Ia, IIa, IIIa.

Group		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean*
Ia	Total Nitrite (nmol/mg)	0,13	0,05	0,06	0,04	0,36	0,09	0,08	0,07	0,09	0,21	0,11
	MDA (nmol/ mg)	0,29	0,25	0,28	0,2	0,76	0,31	0,22	0,34	0,29	0,23	0,31
	MPO (mU/ mg)	17,63	6,94	14,01	36,66	36,22	20,34	23,47	19,34	22,14	19,43	21,61
IIa	Total Nitrite (nmol/mg)	0,18	0,49	0,12	0,35	0,28	0,12	0,47	0,32	0,29	0,36	0,29
	MDA (nmol/ mg)	0,63	1,38	1,03	1,22	0,49	0,88	0,91	0,78	0,67	0,82	0,88
	MPO (mU/ mg)	67,86	92,03	26,09	61,54	99,67	135,82	78,45	83,79	92,58	68,32	80,61
IIIa	Total Nitrite (nmol/mg)	0,29	0,19	0,23	0,16	0,12	0,19	0,08	0,11	0,16	0,17	0,17
	MDA (nmol/ mg)	0,33	0,21	0,50	0,31	0,25	0,40	0,37	0,29	0,41	0,34	0,34
	MPO (mU/ mg)	21,91	32,34	40,05	41,01	47,24	37,64	37,11	29,56	32,78	40,89	36,05

Table 2: Total nitrite, MDA, MPO values for groups Ib, IIb, IIIb

Group		*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*Mean*
Ib	Total Nitrite (nmol/mg)	0,07	0,06	0,07	0,04	0,17	0,13	0,12	0,11	0,14	0,08	0,09
	MDA (nmol/ mg)	0,29	0,16	0,16	0,14	0,34	0,21	0,25	0,41	0,15	0,22	0,23
	MPO (mU/ mg)	14,78	2,70	17,43	11,86	41,74	43,69	19,32	22,47	21,55	30,14	22,56
IIb	Total Nitrite (nmol/mg)	0,48	0,39	0,45	0,37	0,40	0,57	0,41	0,90	1,06	0,85	0,58
	MDA (nmol/ mg)	0,64	0,46	1,03	0,71	0,24	0,56	0,83	0,85	0,60	0,72	0,66
	MPO (mU/ mg)	40,71	135,39	124,06	167,66	244,55	271,96	182,71	169,82	122,19	243,96	170,30
IIIb	Total Nitrite (nmol/mg)	0,18	0,30	0,14	0,17	0,65	0,11	0,37	0,27	0,19	0,22	0,26
	MDA (nmol/ mg)	0,20	0,23	0,22	0,45	0,27	0,18	0,23	0,44	0,27	0,15	0,26
	MPO (mU/ mg)	54,11	110,34	63,22	92,78	96,73	88,44	121,98	61,49	41,40	59,48	78,99

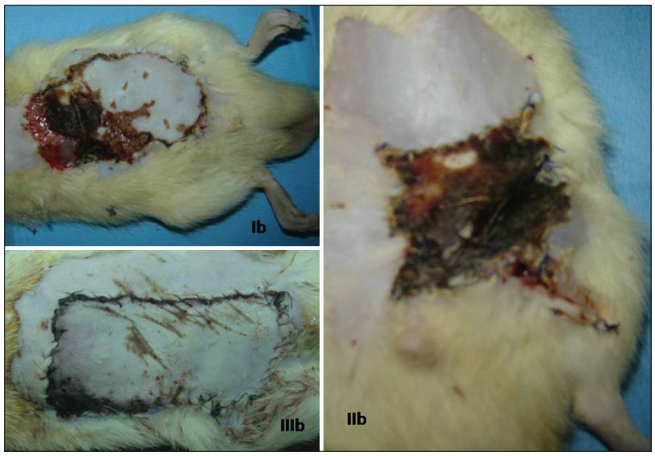

Figure 2: A sample of flaps among the animals. I b, II b, and III b show the status of flaps sacrificed on the 7th day after reperfusion. Please note that the animals numbered as 2, 6, and 1 represent these flaps, respectively

and b were observed for 24 h and 7 days, respectively.

The tissue samples (4 cm × 1 cm in size) obtained from the flaps in all of the sub-groups were freezed via liquid nitrogen to analyze malondialdehyde (MDA), total nitrite and myeloperoxidase (MPO) levels. The flaps in Group I b , II b and III b were digitally photographed at the 7th day. After the transfer of the photographs to the computer, total flap areas, and necrotic areas were marked and calculated via software (AutoCAD, Autodesk Inc., San Rafael, CA, USA). The specimens were obtained from the mid-portion of the flaps (4 cm × 1 cm in dimensions) and stained with H and E. Neutrofil infiltration, edema, necrosis, neovascularization and fibrosis rates were assessed by the same patholog. For the statistical analysis, Wilcoxon signed rank test was used via SPSS 11.0 for Windows Release (Microsoft Corporation, USA) and *P* value below 0.05 was accepted as statistically significant. The biochemical and statistical analysis were carried out between the Groups I a and II a, II a and III a, I b and II b, and II b and III b.

RESULTS

No complications were noted during the study.

The mean MDA, MPO, and total nitrite values were found elevated in the ischemic group (Group II a and II b), but there was an evident drop in the medication group (Group III a and III b). Tables 1 and 2 show total nitrite, MDA and MPO values for sub-groups a and b, respectively. At the 7th day, necrotic areas could be clearly assessed macroscopically. Figure 2 shows a sample among the flaps in Groups I b, II b, and III b. Mean necrosis rates among the flaps were 13.2%, 43.2%, and 19.9% in Group I b, Group II b, and Group III b, respectively [Table 3].

Statistically significant difference was calculated between the groups and clearly documented on Table 4. In this manner, all but one of the results was observed as statistically significant ($P < 0.05$). The p-score for MDA between the Group I a and II a was calculated as 0.445 which was not accepted as significant.

Histological results [Table 5] revealed that early inflammatory findings (oedema, neutrophil infiltration, necrosis rate) were significantly higher in

Table 3: Necrosis rates of the flaps in percentages

Rat number	*Group Ib (Non-ischemic group)*	*Group IIb (Ischemic group)*	*Group IIIb (Medication group)*
1	9	29	9
2	27	57	15
3	11	42	22
4	0	32	13
5	12	46	20
6	17	74	16
7	13	28	25
8	19	36	19
9	10	61	26
10	14	27	34
Mean	13,2 (%)	43,2 (%)	19,9 (%)

Table 4: Calculated p-scores for biochemical markers between the groups. (MDA: malondialdehyde, MPO: myeloperoxidase)

	Total nitrite	*MDA*	*MPO*
p-score between group Ia-IIa	0.017	0.445	0.005
p-score between group IIa-IIIa	0.028	0.005	0.007
p-score between group Ib-IIb	0.005	0.007	0.005
p-score between group IIb-IIIb	0.007	0.007	0.007

ischemic group (Group II a and II b) [Figure 3]. On the other hand, these findings were observed lower with tadalafil administration (Group III a and III b) [Figure 4].

DISCUSSION

Reconstructive microsurgery includes mandatory ischemic periods. Whatever the reason is, ischemia causes tissue hypoxia and triggers anaerobic metabolism. At the time of the reperfusion of the tissue, some proinflammatory substances are secreted.

I/R injury has various consequences like capillary narrowing, leukocyte sequestration, neutrophil infiltration, dysfunction of endotel, end-organ membrane dysfunction and enzymatic defects in the arrangement of inflammatory mediators.[1] Reperfusion of the tissues, in addition, triggers many cytokines.[1,5] Proinflammatory substances like histamine, platelet activating factor (PAF), leukotriene B4, tumour necrosis factor, tromboxane A2 and interleukin-1 are sequestrated from the environment of the damaged tissues and have negative effects on ischemic area.[6] Complement system is one of the major casquade in I/R injury and the end products C3a and C5b-9 cause variable inflammatory consequences.[7]

The protection mechanisms against I/R injury are multifactorial

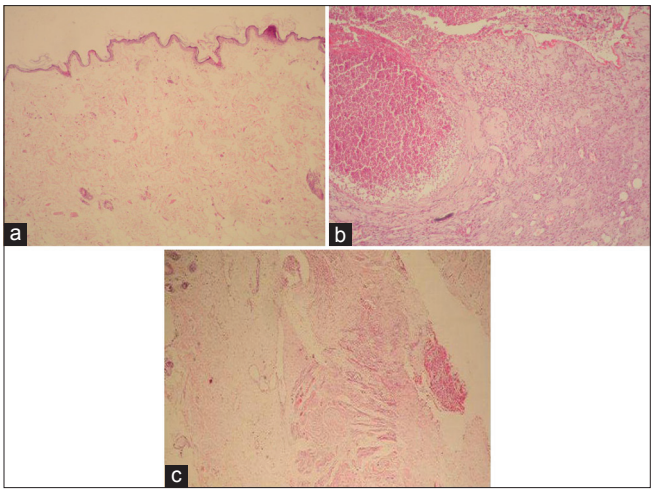

Figure 3: Oedema, neutrophil infiltration, and necrosis rate can be seen on (a) (H and E, ×10), where these findings are observed quite significant on (b) (H and E, ×20). (c) (H and E, ×10) demonstrates evident decrease in these findings

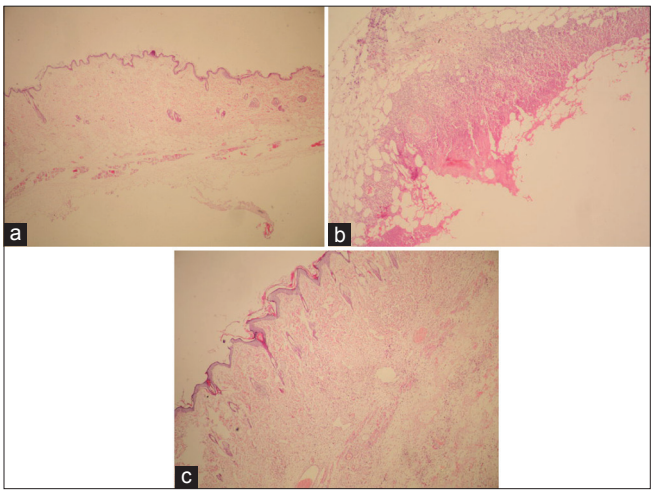

Figure 4: Oedema, neutrophil infiltration, necrosis rate and fibrosis are observed few, but neovascularization can be seen significant on (a). However, (b) reveals the opposite findings with Ib. On the other hand, (c) indicates evident decrease in oedema, neutrophil infiltration, necrosis rate and fibrosis, but quite increase in neovascularization

and still have not been clearly identified. Unlike cytokines, NO, which is secreted from endothel, is a well-known protective mediator against I/R injury.[8] Physiological regulation of vascular tonus, inhibition of platelet aggregation, prevention of leukocyte adhesion, scavenging free radicals, maintenance of vascular permeability, prevention of smooth muscle proliferation, supporting immune defence and regeneration of endothelia are the main described roles of NO.[9] Ischemic conditions, however, cause NO to yield a free radical, peroxynitrite. This mechanism, paradoxically, explains why nitric oxidase synthetase inhibitors have protective effect on the injury.[10] MDA is marker of tissue

Table 5: The comparison of the histological scores among three groups

Histological findings	*Group Ia (Non-ischemic grup)*	*Group IIa (Ischemic group)*	*Group IIIa (Medication group)*
Oedema	++	++++	++
Neutrophil infiltration	+	++++	++
Necrosis rate	+	+++	++
(+: Lowest ++: Lower +++: Medium ++++: High)			
Histological findings	*Group Ib (Non-ischemic grup)*	*Group IIb (Ischemic group)*	*Group IIIb (Medication group)*
Oedema	++	++++	++
Neutrophil infiltration	+	++++	++
Necrosis rate	+	+++	++
Fibrosis	+	+++	++
Neovascularization	++++	+	+++
(+: Lowest ++: Lower +++: Medium ++++: High)			

injury and formed during lipid peroxidation.[11] Few studies revealed that PDE-5 inhibitors had decreased MDA levels in different experimental organ systems in rats.[11-13] MPO is a characteristic constituent of neutrophil granules and is widely used as a marker of tissue invasion and neutrophil sequestration.[14]

Reperfusion of the ischemic tissues causes release of various free radicals containing superoxide (O_2^-), hydrogen peroxide, hydroxyl radical ions,[14,15] which trigger the inflammatory mediators. For this reason, studies are mainly focused on antioxidant therapy in I/R injury. In this manner, O_2 - dismutase, catalase, desferroxamine, U74006F (inhibitor of lipid peroxidation), and histamine, PAF, leukotriene B4, tromboxane A2 inhibitors were successfully used to struggle with I/R injury.[15-19]

Not only was the entire concern focused on substance inhibition therapy but also few studies aimed to decrease the leucosyte-endothel relationship. In this manner, monoclonal antibodies against selectins (selectin P, selectin L, selectin E), endothelial intercellular adhesion molecule and beta 2 glycoprotein (cluster of differentiation molecule number 18) (CD 18) were used.[20-23] In a study, montelukast, a selective cysteinyl leukotriene 1 receptor antagonist was found protective in a rat skin I/R injury model.[24] Moreover, caffeic acid phenethyl ester, melatonin, simvastatin, lidocaine were successfully used to alter I/R injury.[24-27]

Apart from the pharmacological agents, ischemic preconditioning is a planned intervention against I/R injury. This method is mainly composed of manually applied short ischemic periods with subsequent reperfusion of tissues.[5] Ischemic preconditioning was first described for myocardium, but numerous organ studies followed this.[28-33] Like ischemic preconditioning, graded cold application gives a tolerance to the tissue against I/R injury.[34]

PDE are a superfamily of enzymes that have multiple roles on numerous pathways. PDE was first isolated by Uzunov and Weiss at rat brain tissue in 1972.[35] Later then, selective blockage of different PDEs was shown.

Tadalafil, specific inhibitor of PDE-5, is an oral pharmacological agent that is mainly used for erectile dysfunction.[3] Among the other PDE-5 inhibitors, tadalafil has the longest half-life time with 36 h.

In the literature, there are many reports for PDE-5 on different organ systems. The main use of PDE-5 inhibitors is for erectile dysfunction,[36] but they are also still being successfully used for pulmonary arterial hypertension.[37] Tadalafil, like the prototype PDE-5 inhibitor sildenafil, has some common actions on platelets, endothel, vision, brain circulation.[38-43] Unlike sildenafil, tadalafil has lower side effects, especially on vision.[42]

There are few studies about tadalafil on flap experiments in surgical literature. In a study, local injection of tadalafil augmented the survival of axial-pattern skin flaps in rats, but the analysis was not documented biochemically.[44] In another study, tissue response to local and systemic (orogastric) administration of sildenafil citrate was evaluated in dorsal skin flaps in rats. According to this study, systemic administration apparently decreased the ratio of necrosis of the flaps with regard to local administration.[45] Moreover, another study with systemic usage of tadalafil increased random pattern flap survival, but could not achieve a statistical significance.[46]

In our study, the epigastric island flap was chosen since it simulates microsurgical free tissue transfer, closely.[47] This model has been widely used in various experimental models on I/R injury and skin flap survival.[14,24,25,27] In Group III, a single dose of tadalafil was administered to the animals at the 30th min of the reperfusion, because once the flaps are reperfused, mean free radical blood level is settled in certain time. It is clearly demonstrated that tadalafil decreased the negative effects of I/R injury via well-known actions on vascular smooth muscles, platelets and leukocytes. The biochemical markers (total nitrite, MDA, MPO) and necrosis rates were significantly increased in ischemic group. Systemic administration of tadalafil in our study established the proposed blood-level in Group III; so that the biochemical markers were statistically lowered. Moreover, it was statistically significant that tadalafil administration decreased necrosis rates of the flaps in Group III.

More complex actions have to take place in the alteration of free oxygen radicals. Tadalafil possibly acts on these mechanisms. Although this is not clearly understood and demonstrated, more researches are needed to prove this hypothesis. As a consequence, this study proved that tadalafil reduced the I/R injury in rat skin experimental model. However, further clinical studies will manage the benefits of tadalafil in various models, and these results may ensue in the future that tadalafil can be used as a potent inhibitor of I/R injury.

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