

# Effect of Modafinil Administration on Viability of Random Pattern Skin Flaps on Rats

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## Abstract

**Introduction:** Flaps are routinely done procedures in plastic surgery practice. Distal ischemic necrosis limits the length of a random pattern skin flap that can be raised. Multiple pharmacological interventions have been used to increase flap survival. Modafinil is a non-amphetamine central nervous system stimulant that has anti-ischemic effects. This study is being done to answer the research question "Does Modafinil help in the viability of extended skin flaps?"

**Objective:** Primary objective: To evaluate the quantitative assessment of extended random pattern skin flap survival on the fifth post-operative day after administration of a single dose of modafinil in the immediate pre-operative period and those receiving modafinil in the immediate pre-operative period and for three consecutive days. Secondary objective: To evaluate the histopathological changes in the distal most part of the surviving flap.

**Methods:** The study was conducted in the Plastic Surgery Department at King George's Medical University. A total of 21 rats were included. Group I is the control group. Group II is the group that received a single dose of modafinil preoperatively, and Group III is the group that received one dose preoperatively and three doses postoperatively. On the 5<sup>th</sup> day, the biopsy was taken from the surviving flap edge.

**Results:** Mean surviving flap area was  $9.34 \pm 0.53$  sq. cm in Group I,  $15.21 \pm 1.13$  sq. cm in Group II, and  $17.19 \pm 0.81$  sq. cm in Group III. Inter-group comparison of the surviving flap area showed a significant mean difference with  $P < 0.001$ . The groups receiving modafinil showed mild-to-moderate inflammatory infiltrates as compared to the control group.

**Conclusion:** We have found a significant decrease in the mean necrosed flap area of the extended skin flap area in the group receiving modafinil (14.79 sq.cm in Group II and 12.81 sq.cm in Group III) as compared to the control group (20.66sq.cm).

**Key words:** Modafinil, Random pattern skin flaps on rats, Surviving flap area

## INTRODUCTION

Flaps are routinely done procedures in plastic and reconstructive surgery practice. A random pattern skin flap lacks any significant bias in its vascular pattern and is based on the random blood supply of the subdermal plexus. However, the relative ease of creating a random flap makes them useful almost anywhere on the body. The arterial supply or venous return can get hampered by the

flaps that are raised beyond its normal anatomical territory, and hence, it can undergo necrosis and ischemic changes. Distal ischemic necrosis is a challenge that limits the length of a random pattern skin flap that can be raised.

One of the main fields of research in plastic surgery is to increase the viability of flaps. The surgical techniques to augment the flap viability are surgical delay and vascular delay. These techniques are clinically proven but are time-consuming and require another surgical intervention.

Multiple pharmacological interventions, such as vasodilating and anti-thrombotic drugs, have been used to increase flap survival.<sup>[2]</sup> Modafinil is a non-amphetamine central nervous system stimulant that has anti-ischemic effects on the heart, brain, intestines, and testes. It is well-tolerated, with a low prevalence of adverse effects and a low possibility for

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abuse.<sup>[3]</sup> This study is being done to answer the research question “Does Modafinil help in the viability of extended skin flaps?”

## MATERIALS AND METHODS

This study was conducted in the Plastic and Reconstructive Surgery Department at King George’s Medical University in Lucknow after obtaining Institutional Animal Ethics Committee Clearance. (Approval reference number: 160IAEC/2021). A total of 21 Sprague–Dawley rats weighing 150–350 g were included in the study with seven rats in each group.

- Group I: Control group
- Group II: Modafinil pre-operative group: 25 mg/kg of modafinil was administered on the day of surgery preoperatively
- Group III: Modafinil perioperative group: 25 mg/kg of modafinil was administered preoperatively and for 3 consecutive post-operative days.

The rats were placed at a temperature of 23 +/- 2°C and with a 12:12 h light–dark cycle for a period of 2 weeks of quarantine before the procedure. The rats had access to food and water all the time. Modafinil (Sun Pharma Laboratories’ Modalert 100) was dissolved in normal saline (0.9%) with Tween 80 used as a solvent (<0.5% concentration [v/v]). Modafinil, with a dose 25 mg/kg, was given as per the group protocol either before or after the procedure. The dose of modafinil was decided as per the results of a previous study conducted on rats to check the skin flap survival.<sup>[1]</sup> The rats were anesthetized using 22–24 mg/kg of ketamine hydrochloride intramuscularly + 1–2 mg/kg of xylazine injection intramuscularly + injection atropine 0.02–0.05 mg/kg subcutaneously under all aseptic precautions. The adequacy of anesthesia was checked by noting the loss of limb withdrawal reflexes in the hindlimbs.

The rat is placed supine. The drug is injected in the lower left quadrant of the abdomen intraperitoneally. The tip of the needle is to enter the skin at an angle of 20–45° so as to avoid injury to the intestine or the urinary bladder. The rat is laid prone, and the limbs are restrained. A Modified McFarlane’s flap is marked on the dorsum of the rat of size 10 × 3 cm measured by a paper scale. The flap was

raised on the dorsum of the rat with a cranial base and was sutured back with 3–0 nylon. Neosporin ointment was applied over the suture site. On the 5<sup>th</sup> postoperative day, the surviving flap is measured using a paper scale. The area is calculated by measuring the length and width of the flap using a paper scale. The mean flap necrosis was calculated by comparing the surviving flap area with the flap area on the day of the procedure. On the 5<sup>th</sup> postoperative day, a tissue biopsy was taken for histopathological examination of the flap edges. Hematoxylin and eosin (H and E) staining is used for histopathological study, which is done under ×200 magnification.

## Statistical Analysis

Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean and Standard deviation. Quantitative variables were compared using a one-way analysis of variance with *post hoc* Tukey’s test among groups. A *P* < 0.05 was considered statistically significant. The data were entered into MS Excel spreadsheet and analysis was done using Statistical Package for Social Sciences version 23.0.

## RESULTS

On the 5<sup>th</sup> post-operative day, before taking the biopsy, a subjective assessment of the flap was done. The color, temperature, and turgor of the skin were assessed. The viable part of the flap was pink in color, warm and soft-to-touch. The necrotic part of the flap was brown-black in color, cold and hard-to-touch.

In our study, the mean surviving flap area was 9.34 ± 0.53 sq. cm in Group I, 15.21 ± 1.13 sq. cm in Group II, and 17.19 ± 0.81 sq. cm in Group III. In our study, the groups receiving modafinil showed mild-to-moderate inflammatory infiltrates as compared to the control group which showed prominent acute inflammation.

In our study, we have found a significant decrease in the mean necrosed flap area of the extended skin flap area in the group receiving modafinil (14.79 sq.cm) as compared to the control group (20.66 sq.cm). Furthermore, the group receiving modafinil perioperatively had a mean necrosed flap area of 12.81 sq.cm as compared to the

**Table 1: The mean surviving and the mean necrosed flap areas in each group on the 5<sup>th</sup> post-operative day**

Parameters	Group I		Group II		Group III		Total		P-value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Surviving flap area (sq.cm)	9.34	0.53	15.21	1.13	17.19	0.81	13.91	3.51	<0.001
Necrosed flap area (sq.cm)	20.66	0.53	14.79	1.13	12.81	0.81	16.09	3.51	<0.001

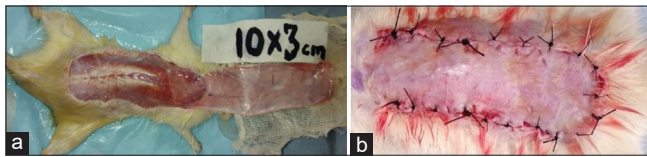
SD: Standard deviation

group that received modafinil as a single pre-operative dose (14.79 sq.cm).

Intergroup comparison of the surviving flap area and necrosed flap area showed a significant mean difference with  $P < 0.001$ . The necrosis of the groups receiving modafinil was less as compared to the control group [Figures 1-5 and Table 1].

## DISCUSSION

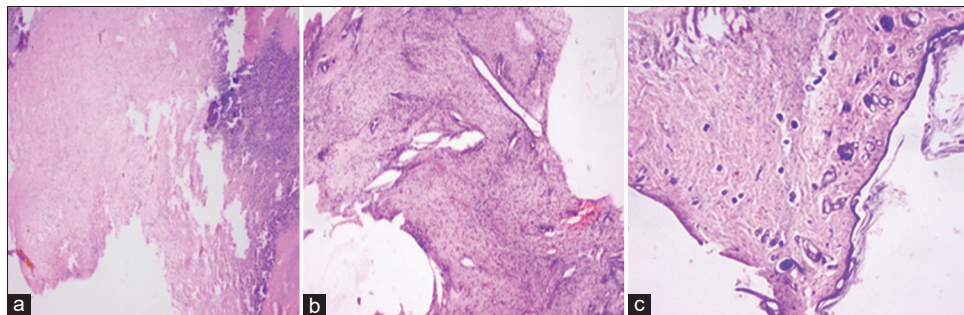
The techniques of skin flaps are well established, and they vary according to the location of the wound and the



**Figure 1:** (a) A modified McFarlane's flap is raised on the dorsum of the rat. (b) The flap is sutured back to the dorsum of the rat using 3-0 Nylon sutures



**Figure 2:** (a): Group I (b): Group II (c): Group III. Flap changes were noted on the 5<sup>th</sup> post-operative day. (a) Group I is the control group. (b) Group II received modafinil preoperatively. (c) Group III received modafinil perioperatively

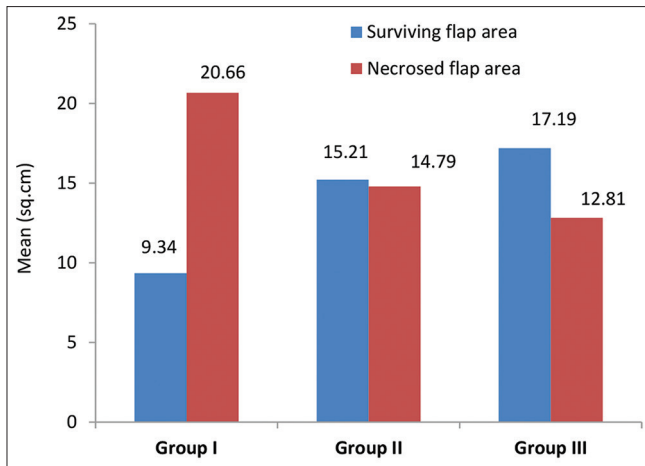


**Figure 3:** Histopathological studies (using H and E staining under  $\times 200$  magnification) of the effect of modafinil on the surviving flap edges: (a) Control group: The section indicates large areas of necrosis with dense acute inflammation with predominantly polymorphs. (b) Modafinil pre-operative group: The section shows dense collagenization with focal mild to moderate inflammatory cell infiltrates. (c) Modafinil perioperative group: The section shows dense collagenization and minimal inflammatory cell infiltrates

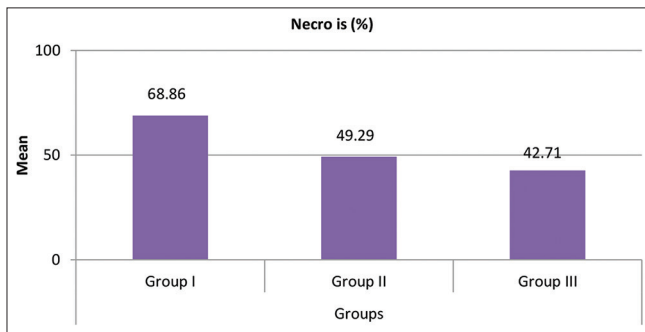
extension of the defect.<sup>[4]</sup> The most feared complication of a skin flap is a significant area of necrosis, causing the failure of the surgical procedure. The estimated frequency of necrosis of skin flaps varies between 2% and 20%.<sup>[4]</sup> Treatment of flap failure can be costly and time-consuming and may require prolonged hospitalization. Surgical and pharmacological interventions can be done to augment flap viability. Surgical interventions such as vascular delay, surgical delay, and modifying the flap design by converting the random-pattern skin flap to an axial-pattern skin flap can be done.<sup>[5]</sup>

The study was conducted to compare the effect of a single pre-operative dose of modafinil and perioperative modafinil administration on the viability of the extended skin flap area in rats. Although the exact mechanism of action of modafinil remains unclear, *in vitro* studies have shown that modafinil binds to the dopamine reuptake pump, thus preventing the reuptake of dopamine. 100–200 mg/day of morning dosage is prescribed. At higher doses, it may slightly induce its own metabolism possibly by actions of inducing CYP450A4. The half-life is 10–12 h.<sup>[3]</sup> Modafinil is well absorbed. Following oral administration, it reaches peak plasma concentration between 2 and 4 h.<sup>[5,6]</sup> It is well-tolerated. It has a low prevalence of adverse effects and low abuse potential. Clinical studies suggest that modafinil does not have the abuse potential of amphetamine and methylphenidate.<sup>[4]</sup> The common adverse effects are headaches, nausea, rhinitis, nervousness, diarrhea, insomnia, and anxiety. High doses of modafinil may induce psychosis in rare cases.

Random pattern skin flaps survive with a wide base of dimension  $4 \times 10$ cm (McFarlane's flap). In McFarlane's *et al.* study, the original dimensions were 4 cm across the base and 10 cm in length (i.e., 1:2.5 ratio), and the scapulae were the base of the flap. In the original study, the authors noted necrosis of 25–50% of the flap length. Camargo *et al.* observed that the McFarlane flap group showed necrosis in 3% of the total area of the flap, whereas the modified



**Figure 4:** Chart depicting the mean surviving and the mean necrosed flap areas in each group on the 5<sup>th</sup> post-operative day



**Figure 5:** Chart depicting the percentage of necrosis in each group. (Group I: Control group, Group II: Modafinil pre-operative group, and Group III: Modafinil perioperative group)

McFarlane flap group showed necrosis in 37% of the total area of the flap.<sup>[2]</sup> Thus, the more appropriate flap is the modified McFarlane flap for experimental studies on the viability of skin flaps.

Few experimental studies have been done on rats to evaluate the anti-ischemic properties of modafinil on testes, intestines, and skin flaps. Han *et al.* noted that in a model of atherosclerosis, modafinil suppressed the secretion of proinflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$  and promoted the secretion of anti-inflammatory cytokines such as IL-4 and IL-10.<sup>[7]</sup> Modafinil has an immunomodulatory effect. Yousefi-Manesh *et al.* noted that in testicular ischemia-reperfusion models of rats, modafinil ameliorated inflammation and oxidative stress.<sup>[5]</sup> Dejban *et al.* noted in rat colon that modafinil has a protective effect on injuries induced by acetic acid via inhibition of inflammatory cascade and mediation of NO pathway.<sup>[8]</sup> Various experiments have suggested that modafinil causes the downregulation of inflammatory cytokines and further oxidative damage.<sup>[9]</sup>

Several studies have shown modafinil has an inhibitory

effect on the production of reactive oxygen species that has a protective role in neurodegenerative diseases, coronary artery ischemia, and reperfusion injury. Arrmin *et al.*, in their study, stated that modafinil increases skin flap survival mediated by the nitric oxide pathway and K ATP channels.<sup>[1]</sup> The effective dose of modafinil in their study was 25 mg/kg in a rat. The human equivalent dose for a 60 kg man would be approximately 240 mg.<sup>[10]</sup> In our study, the group receiving modafinil showed mild to moderate inflammatory infiltrates, and the control group showed prominent acute inflammation. The findings in our study are consistent with the findings in other studies that evaluated the histological effects of modafinil.<sup>[5]</sup> Binnenmars *et al.* reported a patient who experienced polymorphic non-sustained ventricular tachycardia related to modafinil treatment for narcolepsy.<sup>[11]</sup> Thus, the patients should be evaluated for any cardiac symptoms after starting on modafinil, and the drug should be stopped if necessary.<sup>[12-14]</sup>

### Limitations

This is an experimental study and the limitations of an experimental study are applicable here. Here, we have injected the drug intraperitoneally in rats. The drug is available in tablet form and the effect of oral administration of the drug on extended flaps is to be ascertained.

### CONCLUSION

We have found a significant decrease in the mean necrosed flap area of the extended skin flap area in the group receiving modafinil (14.79 sq.cm) as compared to the control group (20.66 sq.cm). Furthermore, the group receiving modafinil perioperatively had a mean necrosed flap area of (12.81 sq.cm) as compared to the group receiving modafinil as a single pre-operative dose (14.79 sq.cm). Thus, modafinil may be considered an adjuvant treatment in cases of failing flaps.

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