



# COMPARISON BETWEEN ADRENALINE AND WITHOUT ADRENALINE SOLUTION ON BLEEDING CONTROL OF SKIN GRAFT DONOR SITE: A RANDOMIZED CONTROLLED TRIAL

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## ABSTRACT

**OBJECTIVE:** To compare the bleeding control of skin graft donor site between normal saline soaked gauze with adrenaline and conventional technique having no adrenaline.

**METHODS:** This open-label randomized control trial was conducted at Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan from October 2020 to March 2021. Seventy-five patients were randomized to interventional (n=36, 48%) and control group (n=39, 52%) through sealed envelopes. Diluted solution was prepared by adding 30cc of Ringer's lactate and 10cc of lignocaine 2%, with 1cc of adrenaline of 1:200000 with 200 ml of normal saline solution. Solution for control group was containing only normal saline. Following the skin harvesting at donor site, a gauze piece soaked with tumescent solution was applied at the donor site wound. Bleeding severity and epithelialization were assessed. Data was recorded in a pre-designed performa and analyzed through SPSS version-25.

**RESULTS:** There was no significant differences in baseline characteristics like age (p=0.823), gender (p=0.984) and nature of injury (p=0.936) among two groups. Severe, moderate and mild bleeding was noted in 20/39 (51.3%), 15/39 (38.5%) and 4/39 (10.3%) cases in control group as compared to 0/36 (0%); 2/36 (5.6%) and 25/36 (69.4%) cases in interventional group respectively (\*\*<0.001). No bleeding was noted in 9/36 (25%) cases of interventional group. Complete epithelialization was observed in 24/36 (66.7%) & 17/39 (43.6%) cases in adrenaline and control groups respectively (p=0.045).

**CONCLUSION:** Application of adrenaline was more effective in bleeding control and early epithelialization at donor site following the skin harvesting as compared to conventional technique.

**Clinical Trials Registry Number:** NCT04590638

**KEYWORDS:** Adrenaline (MeSH); Donor site (Non MeSH); Epinephrine (MeSH), Hemostasis (MeSH); Karachi (Non-MeSH); Pakistan (MeSH); Surgery, Plastic (MeSH); Reconstructive Surgical Procedures (MeSH); Skin-graft (Non-MeSH); Vasoconstrictor Agents (MeSH); Transplant Donor Site (MeSH); Transplantation (MeSH); Tissue Transplantation (MeSH)

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## INTRODUCTION

Skin grafting is one of the most essential procedures in dermatology and reconstructive surgery which is being occasionally performed for reconstruction of the skin damaged in acute or chronic wounds.<sup>1</sup> In 1823, Buenger, a German physician, recognized the first encouraging skin graft by transferring skin to the nose from buttock.<sup>2</sup>

In the previous few years, burn management has considerably enhanced survival along with improving critical care. Though, the existing standard of surgical management of full-thickness burn wounds is still primary excision and auto grafting. The skin harvesting technique creates additional wound at the donor site which also involves clinical management.<sup>3</sup> Donor site management may be exclusively

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challenging in patients where wound healing is possible to be compromised, just as in diabetic or elderly patients.

Extreme bleeding is the primary concerns in skin graft as consequence of skin harvesting which leads to hemodynamic instability and often necessitates allogenic blood transfusion and impacts the surgical plan and restricts the total surface treatable in a single session. Extreme bleeding further lead to a variety of complications including hypotension, anemia, hematoma formation, and insufficient oxygenation of organs, thus worsening patient outcome.<sup>4</sup> It is estimated that blood loss in burn surgery is 196-269 ml per percentage skin grafted and total body surface area excised.<sup>5</sup>

A bloodless surgical field is very essential in reconstructive surgery and as a result, numerous hemostatic techniques including fibrin sealant, thrombin, tourniquets and epinephrine tumescence and have been suggested to address this important subject. Unluckily, surgeons have yet to reach an agreement as to which hemostatic technique is superior. The tumescent technique is simple the practice to subcutaneously inject an adrenaline diluted solution with local anesthetic in order to swollen (tumescent) the tissue and it is being injected till tissues are swollen.<sup>6</sup>

Adrenaline (epinephrine) is a catecholamine hormone involved in a human physiology at a broad spectrum level, releasing into the bloodstream following sympathetic nervous system stimulation.<sup>7</sup> First time it was documented in 1997 that a clinically

appropriate concentration of (20 nM) adrenaline is adequate to induce formation of platelet micro aggregates.<sup>8</sup> However, the significance of adrenaline-platelet collaboration in usual hemostasis had been unidentified for a long time till a couple of research groups detected an extended bleeding period to some extent and an impaired thrombin formation in  $\alpha_2$ -AR deficient.<sup>9,10</sup> These clarifications suggested a substantial part of adrenaline in normal hemostatic response. In developed countries, use of adrenaline is now routinely practiced but locally use of adrenaline at donor site is still uncommon and most of the surgeons use normal saline to soak the gauze piece to apply at donor site. To increase the adequacy and appropriateness of adrenaline use in our local settings, we planned to conduct the present study to compare the bleeding control of skin graft donor site between adrenaline and without adrenaline solutions at tertiary care hospital in Karachi, Pakistan.

## METHODS

A randomized control trial was conducted at Department of Plastic and

Reconstructive Surgery in Dr. Ruth K.M. Pfau Civil Hospital, Karachi, Pakistan from October 2020 to March 2021 with the acquiescence of Institutional Review Board (IRB-1627/DUHS/ Approval/ 2020). The trial was registered with ClinicalTrials.gov registry (NCT04590638). The intend to conduct the present study was revealed to patients with associated risks and benefits before inducting them into the study and their rights during the study were also explained to them to take their written consent. There was no monetary incentive for patients for their induction into the study. Patients of any gender of age above 18 years, non-allergic to treatment agents, with normal blood pressure and hemoglobin higher than 10 g/dl, platelets counts  $>150 \times 10^9/L$  with wound at least weeks old were included into the study. Patients with hematological disorders, skin disease and immunocompromised were excluded from this study.

A previously conducted similar study reported that intra-operative bleeding was less than normal in 93.5% and 36% in adrenaline and control group respectively.<sup>11</sup> Using two proportions

sample size calculation approach on WHO sample size calculator at power of 80% and 95% confidence interval, a sample of 10 patients per group is required. Since the calculated sample size was smaller therefore, a sample of at least 30 patients per group will be included into the study. Patients were randomized to interventional (adrenaline) and control group through envelopes and allocation concealment was achieved through sequentially numbered sealed opaque envelopes.<sup>12</sup> Figure 1 presents consort diagram of the current study.

Interventional group received the diluted solution of adrenaline. Diluted solution was prepared by adding 30cc of Ringer's lactate and 10cc of lignocaine 2%, with 1cc of adrenaline of 1:200000 with 200 ml of normal saline solution. Lignocaine was added to reduce the need of general anesthesia. Solution for control group was containing only normal saline. Solution was prepared ten minutes before its application to donor site. Split thickness skin graft of equal dimension and equal thickness of about 10x8 cm harvested from anterior and lateral thigh in both groups. Following the skin harvesting at donor site, a gauze piece soaked with tumescent solution was applied at the donor site wound for 30 minutes. Dressing was done at donor site after removing the soaked gauze.

After 30 minutes applying the soaked gauze at donor site, the apparent bleeding severity was assessed by consultant surgeon which was scored on an ordinal scale of range 0 to 5. The score from 0 to 5 indicated no bleeding, mild bleeding, moderate bleeding, moderate severe bleeding and extreme severe bleeding respectively. Epithelization was also subjectively assessed by the consultant surgeon at 5<sup>th</sup> post-operative day. Using a transparent measuring scale, wound was divided into equal quadrants (each 25%). Epithelialization then measured by subjective clinical assessment of wound by noting decrease in edema and appearance of pink or red new skin. 1=100% wound covered 2=75-100%, 3=50-<75%, 4=25-50%, 5=<25%. The intra and inter observer reliability of subjective assessment shown to be good when performed by experienced surgeons. 100% healing was considered

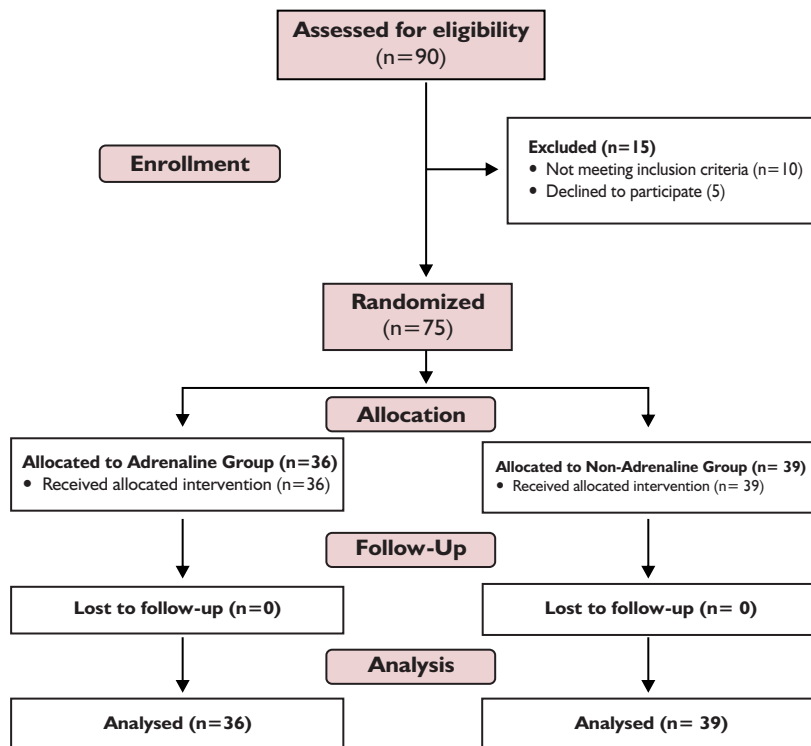


Figure 1: Flow chart showing enrolment of participants, intervention allocation, follow-up, and data analysis

as complete epithelialization whereas 50-75% was considered as partial. Patients' features including age, gender and nature of injury was also recorded in a pre-designed proforma.

Data entry was done into statistical package SPSS version 25 for statistical analysis. Frequency with percentages were calculated for summarizing categorical variables. Numerical variables were expressed as mean ± standard deviation after evaluating supposition of normality with Shapiro-Wilk test. Chi-square or Fisher-exact test was applied to compare patients' features among two treatment groups. Association of study outcomes with treatment groups was also ascertained by applying chi-square or Fisher-exact test. A two-tailed p-value less than 5% level of significance was considered as statistically.

## RESULTS

Total 75 patients were enrolled into the study with almost equal allocation in interventional (adrenaline) group (n=36, 48%) and control group (n=39, 52%). The average age of patients in interventional and control group was 43.25 ± 14.91 years and 42.61 ± 13.51 years respectively. The frequency of

patients with age group = 50 years is 25 (69.4%) and 28 (71.8%) (p=0.823). Gender distribution was almost same between the two groups with 25 (69.4%) males in interventional and 27 (69.2%) males in control group (p=0.984). Nature of injury included road traffic accidents, post burn contracture and abscess with frequency of 15(41.7%), 19(52.8%) and 2(5.6%) in interventional groups respectively. Control group also included patients with road traffic accidents (n=14, 35.9%), post burn contracture (n=22, 56.4%) and abscess (n=3, 7.7%). The nature of wound injury was not significantly unlike between the study groups (p=0.936).

Table I depicts the comparison of participants' characteristics among patients with different bleeding severity. Distribution of age groups = 50 years and > 50 years (p=0.770), gender (p=0.895) and nature of injury (p=0.554) was not significantly dissimilar among patients with different bleeding severity.

Severe, moderate and mild bleeding was noted in 20/39 (51.3%), 15/39 (38.5%) and 4/39 (10.3%) cases in control group as compared to 0/36 (0%); 2/36 (5.6%) and 25/36 (69.4%) cases in interventional group respectively (\*\*<0.001). No bleeding was noted in 9/36 (25%) cases

of interventional group.

Table II displays the association of patients' characteristics with epithelialization status. Patients' age (p=0.302), gender (p=0.616) and nature of injury were not found to be associated with epithelialization status. Complete epithelialization was observed in 24/36 (66.7%) & 17/39 (43.6%) cases in adrenaline and control groups respectively (p=0.045).

## DISCUSSION

Vasoconstriction is frequently attained during infiltration anesthesia through combining adrenaline with a local anesthetic. Vasoconstriction lessens bleeding, safeguards the surgical field, diminishes the systemic side effects, and extends the interval of local anesthetics. The therapeutic effect of local anesthetics is consequently greatly reliant on the action of the vasoconstrictor administered with it.<sup>13-15</sup> Vasoconstriction influence of adrenaline is difficult, and vasoconstriction strength varies with vessel type: arterioles, sphincters, arteries, precapillary, capillaries, venules, and veins.<sup>16</sup> It is plausible that using a vasoconstrictor adrenaline leads to hindering intraoperative bleeding through short-term obstruction of

**TABLE I: FREQUENCY DISTRIBUTION OF PARTICIPANTS' CHARACTERISTICS AMONG PATIENTS OF DIFFERENT BLEEDING SEVERITY**

Patients features		Bleeding Severity					p-value
		No bleeding n (%)	Mild n (%)	Moderate n (%)	Moderately severe n (%)	extremely severe n (%)	
Age (years)	≤ 50 (n=53)	5 (9.4)	22 (41.5)	11 (20.8)	9 (17)	6(11.3)	0.770
	>50 (n=22)	4 (18.2)	7 (31.8)	6 (27.3)	3 (13.6)	2(9.1)	
Gender	Male (n=52)	5 (9.6)	21 (40.4)	12 (23.1)	8 (15.4)	6(11.5)	0.895
	Female (n=23)	4 (17.4)	8 (34.8)	5 (21.7)	4 (17.4)	2(8.7)	
Nature of injury	Road traffic accident (n=29)	2 (6.9)	15 (51.7)	6 (20.7)	4 (13.8)	2(6.9)	0.554
	Post burn contracture (n=41)	7 (17.1)	11 (26.8)	10 (24.4)	7 (17.1)	6(14.6)	
	Abscess (n=5)	0 (0)	3 (60)	1 (20)	1 (20)	0(0)	
Treatment	With adrenaline (n=36)	9 (25)	25 (69.4)	2 (5.6)	0 (0)	0(0)	**<0.001
	Without adrenaline (n=39)	0 (0)	4 (10.3)	15 (38.5)	12 (30.8)	8(20.5)	

†: Fisher-exact test was reported. \*\*:Significant at p<0.001

vessels that starts bleeding far ahead when the preliminary vasoconstrictor effect has delivered.

The present study investigated the role of adrenaline as hemostatic agent at skin graft donor site. Following the skin harvesting, bleeding at donor site was observed subjectively by the consultant surgeon. In the present study, among Group that received a gauze soaked with tumescent solutions of adrenaline, quarter of the total patients were found to had no bleeding and more than half were observed to have mild bleeding (69.4%) when gauze piece was removed while there was no case of severe bleeding and a small proportions patients had moderate bleeding (5.6%). On the other hand, nearly half of the patients had severe bleeding and 38.5% had moderate bleeding whereas none of the patient was found to have no bleeding and only 10% had mild bleeding. The significant difference in frequency of bleeding severity evidently indicates a superiority of adrenaline as hemostatic agent in contrast to the conventional practice of placing normal saline soaked gauze, which is being followed in our local settings.

Multiple studies are documented in

literature from the West suggesting the use of adrenaline as hemostatic agent in skin harvest procedures. Recently a study was conducted in Singapore to ascertain the effect of adrenaline on skin graft donor site. The researcher marked the donor site into three sections and then each section was randomly infiltrated with a tumescent solution containing no adrenaline, solution containing adrenaline in concentration of 1:500,000 and 1:250,000. The similar bleeding severity scale was used in this study that we used in the present study i.e. bleeding severity was assessed from a scale 0 to 5. It was demonstrated that donor sites that were infiltrated with adrenaline had significantly reduced bleeding score than donor sites infiltrated with solution not containing adrenaline. It was further reported that bleeding control was better for donor sites infiltrated with higher concentration of adrenaline (1:250,000).<sup>17</sup> Fujita et al. and Gümüş et al. Also evaluated the efficacy of adrenaline with tumescent infiltration in burns wound and skin graft donor site and concluded that it was a simple and safe procedure with improved hemostasis effects promoting transfusion-free procedure and brought the advantage of facilitating excision in

burns eschar.<sup>18,19</sup> The supremacy of vasoconstrictor tumescence in bleeding control was proven even in a meta-analysis that aimed to evaluate the effects of vasoconstrictor drugs combined with tumescent solution among patients undergoing skin graft and/or burns debridement. The meta-analysis included 10 relevant trials and their pooled estimate showed that patients receiving vasoconstrictor tumescent were transfused with 1.89 lesser units of red blood cells than patients who did not receive vasoconstrictor tumescent.<sup>20</sup>

Fukuoka et al. conducted a study in Japan to evaluate the effectiveness of tumescent injection in bleeding control at donor site in split thickness skin graft. The researchers randomly assigned the patients in to two groups and both the groups received adrenaline in from of subcutaneous injections and soaked gauze. The author reported that both methods have sufficient hemostatic effect and post-operative pain and healing time was also not different between the two groups.<sup>6</sup> In one of the way, findings of this study can be interpreted in way that despite of the tumescent technique, when both the groups received adrenaline hemostatic effect and other success parameters were not significantly different and there was satisfactorily bleeding control in both the groups which further raises the importance of adrenaline as hemostatic agent. Apart from plastic reconstruction studies, effectiveness of adrenaline in controlling blood loss was also evident in other procedures including total knee arthroplasty,<sup>21</sup> endoscopic sinus surgery<sup>22</sup> and hair transplantation.<sup>23</sup>

In the present study the comparison was also made between adrenaline and without adrenaline soaked gauze in terms of epithelialization. Among adrenaline group, donor site was completely epithelialized in more than half of the patients (66.7%) whereas not even half of the patients were found to have donor site with complete epithelialize (43.6%) among control group which was a significant difference. P Gacto and his co-workers conducted a similar study and reported that almost all of donor sites were epithelialized on post-operating first week (98.5%) while epithelialization rate in control group was 71% with a

**TABLE II: ASSOCIATION OF PATIENTS' CHARACTERISTICS WITH EPITHELIALIZATION STATUS**

Patients characteristics		Epithelialization status		p-value
		Partly	Complete	
Age (years)	≤ 50 (n=53)	22 (41.5)	31 (58.5)	0.302
	> 50 (n=22)	12 (54.5)	10 (45.5)	
Gender	Male (n=52)	25 (48.1)	27 (51.9)	0.616
	Female (n=23)	9 (39.1)	14 (60.9)	
Nature of injury	Road traffic accident (n=29)	11 (37.9)	18 (62.1)	0.230
	Post burn contracture (n=41)	19 (46.3)	22 (53.7)	
	Abscess (n=5)	4 (80)	1 (20)	
Treatment	With adrenaline (n=36)	12 (33.3)	24 (66.7)	*0.045
	Without adrenaline (n=39)	22 (56.4)	17 (43.6)	

†: Fisher-exact test was reported, \*Significant at p<0.05

statistically significant difference.<sup>11</sup> The effects of epinephrine on wound healing was studied in an animal study that compared wound healing between those receiving lidocaine infiltration and lidocaine with adrenaline infiltration. On histopathological reports it was evident that there was extensive bleeding even on 7<sup>th</sup> post-operative day and on 14<sup>th</sup> post-operative day, there was incomplete epithelialization. While in adrenaline group, there was incomplete epithelialization on 7<sup>th</sup> post-operative day that was completed till 14<sup>th</sup> post-operative day.<sup>24</sup> The obvious reason for early epithelialization in adrenaline is less severity of bleeding which enables epithelialization at faster rate than control group.

The current study was although a randomized control trial but there were few loopholes in planning of this study. The current study did not analyze the post-operative pain, time to graft take, post-operative complications and patient satisfaction which could further contribute in changing the view-point of reconstructive surgeons in our local settings and hence making improved practice. We proposed a future study in reconstructive surgery to overcome the limitations of the existing study.

## CONCLUSION

The present study confirmed that application of adrenaline was effective in bleeding control and early epithelialization at donor site following the skin harvesting as compared to conventional technique of placing normal saline soaked gauze, which is being in our local settings.

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### AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**MA:** Conception & study design, drafting the manuscript, approval of the final version to be published

**HA & FAA:** Analysis and interpretation of data, critical review, approval of the final version to be published

**FA:** Acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

**UA & ST:** Acquisition of data, drafting the manuscript, critical review, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

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Authors declared no conflict of interest

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The data that support the findings of this study are available from the corresponding author upon reasonable request.



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