

Comparison between Topical Beta-Sitosterol and Topical Hirudin in Management of Facial Burns

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Abstract

Background: Facial burns are challenging, as the aesthetic outcome is as important as the functional. Topical interventions are currently the cornerstone of treatment of facial burns. Although there is no gold standard agent for the treatment of facial burns, beta-sitosterol is the most commonly used as first line agent.

Recombinant hirudin is an agent derived from medicinal leech and it has anti-thrombotic action, which is thought to have effect on facial burns healing.

Objective: The objective of this study is to compare the effect of beta-sitosterol and hirudin in the management of facial burns regarding the pain, edema, healing time, and aesthetic outcome.

Patients and Methods: A concurrent self-control open label clinical trial was conducted on fifteen patients attending the burn unit at Suez Canal University Hospital with facial burns. Visual Analogue Scale for pain to time, edema, hospitalization time, healing time, scarring by the patient and observer scar assessment scale (POSAS) and final aesthetic outcome.

Expected Outcome: In patients with facial burns, the use of topical hirudin will reduce pain and edema; enhance faster healing and less hospitalization time, less scarring and better final aesthetic outcome.

Conclusion: Topical hirudin use in facial burns is a safe and effective option as it showed statistically significant results regarding wound healing and final scar quality outcome that was better than topical beta-sitosterols. Although its effects regarding pain and edema showed no statically significant difference in comparison to topical beta-sitosterols, it should be considered as an effective safe option in the treatment of facial burns.

Key Words: Topical hirudin – Topical beta-sitosterols – Outcome scar – Healing.

Ethical Committee: The study was approved by the Ethical Committee of Suez Canal University (4781).

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Introduction

Facial burns vary from relatively minor insults to severe debilitating injuries. Over 50% of burn injuries caused by flame, electrical current, steam, hot substances, and chemicals involve the head and neck region [5].

These burns can cause deep damage resulting in lifelong scarring and deformity. Therefore, their treatment is challenging, as the aesthetic outcome is as important as the functional [5,10,11,21,24].

Topical interventions are currently the cornerstone of treatment of facial burns. Moreover, because of the highly vascularized nature of the face as it receives its blood supply directly of the major vessels of the head and neck, exposed dressing by topical agents is used to treat facial burns [6,7,31].

Although there is no gold standard agent for treatment of facial burns, beta-sitosterol oil-based, natural preparations are widely used in Asia and the Middle East. Oils soothe wounds, retain moisture, relieve pain and Beta-sitosterol promotes epithelialization [1,8,14,15].

Other agents like local anticoagulants, heparin and synthetic heparin-based compounds, are multifaceted compounds which improve vascularity as well as having anti-inflammatory, anti-histaminic, anti-serotonin and anti-proteolytic enzyme properties [12,19,23,28,29,30].

There are studies that compare the effect of topical anticoagulants to the other agents used in treatment of burns [9].

Fawzy et al., is one of these studies as it used topical heparin dressing compared to antimicrobi-

al agent for superficial, partial and full thickness burns of face [9].

Fawzy et al., study showed that heparin solution treated patients showed significant less pain, through both VAS and analgesic use [9].

It also showed significant changes regarding edema, which significantly decreased in the topical heparin group and found that the number of healed cases per week in heparin group was significantly more than those in control group. Healing was also done by serial photography and follow-up of the patient till complete healing [9].

Masoud et al., is another comparative study that compared topical heparin solution to silver sulphadiazine in acute burns treatment [20].

Its results are similar to Fawzy et al study regarding pain, edema and healing rate in patients treated with topical heparin [20].

Recombinant hirudin is derived from a class of antithrombotic agents structurally derived from the medicinal leech salivary protein hirudin [12,19,23, 28,29,30].

Some studies suggest that hirudin, when used in the management of thermal injuries of the face, prevents burn extension, limits cutaneous tissue loss, promotes faster healing with fewer contractures, relieves pain, and reduces tissue edema [12,28,29,30].

However, there is no strong evidence supporting these effects due to the poor quality of these articles. Moreover, there is no article, to the best of our knowledge, comparing oils with anticoagulants agents in facial burns [22].

Therefore, this study will compare the effect of application of beta-sitosterol, the most commonly used first line agent, with hirudin regarding edema, pain, hospitalization time, healing, scarring and final aesthetic outcome in cases of facial burns.

Material and Methods

This is a concurrent self-control open label clinical trial conducted on fifteen patients attending the burn unit at Suez Canal University Hospital with facial burns. Visual Analogue Scale for pain to time, edema, hospitalization time, healing time, scarring by the patient and observer scar assessment scale (POSAS) and final aesthetic outcome.

Patients fulfilling the following criteria were included in our study. The study population was 15 patients who have facial burns with the following inclusion criteria: Patients whose age above one year, Patients presenting with facial burns due to any cause and context, patients of both genders and Patients with second and third degree facial burns. This study aims to improve the aesthetic and the

functional outcome of facial burn with the expected outcome that the use of topical hirudin will reduce pain and edema; enhance faster healing and less hospitalization time, less scarring and better final aesthetic outcome.

A predesigned questionnaire that was filled through personal interview was used to collect the following data:

- 1- Socio-demographic characteristics such as age, marital status, level of education, employment state and residency.
- 2- Present History of the patient with detailed history of the burn injury and associated trauma.
- 3- History of any chronic illness e.g., diabetes, hypertension...etc.
- 4- History of any previous operation.

Procedures:

Full history, complete general examination, exclusion of any allergy to local anticoagulants.

Facial burns of each patient were divided in two equal parts: Part A treated with local hirudin (Thrombex cream), and Part B (control) treated with topical beta-sitosterols (MEBO or Penta burn ointment).

In part A, local hirudin (Thrombex cream) was used as exposed dressing in combination with cold saline fomentation and gentle daily cleansing without exposure to heat or sun light with good nutrition, plenty of fluids and rest.

In part B, topical preparations involving beta-sitosterols (MEBO or Penta burn ointment) was used as exposed dressing in combination with cold saline fomentation and gentle daily cleansing without exposure to heat or sun light with good nutrition, plenty of fluids and rest.

Accompanied by general lines of management including head elevation by semi-sitting position, saline fomentation, analgesics to control the pain, and eye care by using artificial tears and any needed antibiotic eye drops.

Daily follow-up of the patients was at early stage until complete healing by visual assessment as a part of our working definition by serial photography, assessment and observation of healing rate in our facility as a subjective method, accompanied by patient and observer scar assessment scale (POSAS) to assess scarring by both patients and observer scales.

Results

The study included 15 participants of mean age 15.13 ± 17.62 years, most of them (66.7%) were females and 66.7% lived in rural areas. None of the included patients were smokers or had facial congenital anomalies.

Most of the patients (60%) had scalds, 33.3% had flame burn and 6.7% had chemical burns. More than half of the patients (66.7%) were deep partial burn and 53.3% were >5% in surface area. mean duration of hospital stay 17.53±8.75 days. Mean outpatient duration was 20.40±8.48 days. 60% of patients reported better healing in the part of facial burn treated by topical Hirudin, 40% of them reported equal results. As mentioned in methods before, healing assessment is done as a part of our working definition by serial photography and daily follow up until complete healing.

Most patients (86.6%) suffered from moderate edema in part of face treated with Beta-sito sterols, only 1 patient suffered from severe edema.

More than 1/2 of patients (66.7%) suffered from moderate edema in part of face treated with topical hirudin, and no one suffered from severe edema. The difference was not statistically significant ($p=0.131$).

All patients (100%) suffered from moderate pain in part of face treated with Beta-sito sterols, 73.3% of patients suffered from moderate pain in part of face treated with topical hirudin and 26.7% of them suffered from mild pain. The difference was statistically significant ($p=0.032$).

Mean colour, stiffness, thickness, skin irregularity & overall POSAS Patient scale were lower in part of face treated with topical hirudin than part treated with Beta-sitosterols, which reflects better response in treatment with topical hirudin than Beta-sitosterols. The difference was statistically significant ($p=0.033, 0.033, 0.48, 0.031$ and 0.023 respectively). There was no statistically significant difference in mean pain or itching.

Mean overall POSAS observer 1,2 and 3 scale were lower in part of face treated with topical hirudin than part treated with Beta-sitosterols, which reflects better response in treatment with topical hirudin than Beta-sitosterols. The difference was statistically significant ($p=0.028, 0.01$) in observer 1 and wasn't statistically significant ($p=0.069$) in observer 2.

Mean average vascularity, pigmentation, thickness, relief, pliability, surface area and overall POSAS observer scale were lower in part of face treated with topical hirudin than part treated with Beta-sitosterols, which reflects better response in treatment with topical hirudin than Beta-sitosterols. The difference was statistically significant ($p=0.032, 0.044, 0.19, 0.032, 0.018, 0.033$ and 0.013 respectively).

Table (1): Comparison between topical beta-sitosterols and topical hirudin regarding POSAS Patient scale (n=15).

POSAS Patient scale	Beta-sitosterols n=15	Topical hirudin n=15	95% Confidence interval		Test value•	p-value	Sig.
			Lower	Upper			
Pain	5.60±2.03	5.20±1.74	-1.0135	1.8135	0.580	0.567	NS
Itching	4.93±1.94	4.20±2.14	-7.9782	2.2644	0.980	0.335	NS
Colour	4.73±1.83	3.27±1.75	.12666	2.80667	2.242	0.033	S
Stiffness	5.33±2.16	3.73±1.71	.14285	3.05715	2.249	0.033	S
Thickness	4.67±1.91	3.27±1.79	0.1310	2.78690	2.068	0.048	S
Skin irregularity	4.47±1.64	3.27±1.22	.11731	2.28269	2.270	0.031	S
Overall	6.87±2.03	5.20±1.74	.25219	3.08114	2.414	0.023	S

•: Independent t-test.

p-value >0.05: Non-significant (NS). p-value <0.05: Significant (S). p-value <0.01: Highly significant (HS).

Table (2): Comparison between topical beta-sitosterols and topical hirudin regarding average opinion POSAS observer scale (n=15).

Average POSAS observer scale	Beta-sitosterols n=15	Topical hirudin n=15	95% Confidence interval		Test value•	p-value	Sig.
			Lower	Upper			
Vascularity	6.00±2.26	4.33±1.73	.12666	2.80667	2.258	0.032	S
Pigmentation	5.93±2.43	4.23±1.96	0.1310	2.78690	2.108	0.044	S
Thickness	4.91±2.05	3.28±1.48	.29531	2.97136	2.501	0.019	S
Relief	5.98±2.26	4.32±1.72	.15419	3.16581	2.258	0.032	S
Pliability	5.31±1.96	3.73±1.46	.28649	2.87351	2.502	0.018	S
Surface area	4.69 ±1.71	3.44±1.31	.10815	2.38518	2.243	0.033	S
Overall	6.28±2.48	4.01±1.72	.51342	4.01991	2.648	0.013	S

•: Independent t-test.

p-value >0.05: Non-significant (NS). p-value <0.05: Significant (S). p-value <0.01: Highly significant (HS).

Case (1):

1- A three-year-old male patient presented with flame burn of face, with no inhalational injury. This deep partial and full thickness of face was divided into 2 halves: On the right topical beta-sitosterol was used, while topical hirudin was used on the left.



Fig. (1): Patient at time of presentation.
(1-A): Portrait view.



Fig. (2): Patient one week after burn with faster healing on the left side on which topical hirudin is used.
(2-A): Portrait view.



Fig. (2): Patient one week after burn with faster healing on the left side on which topical hirudin is used.
(2-B): Close-up right lateral view.



Fig. (2): Patient one week after burn with faster healing on the left side on which topical hirudin is used.
(2-C): Close-up left lateral view.

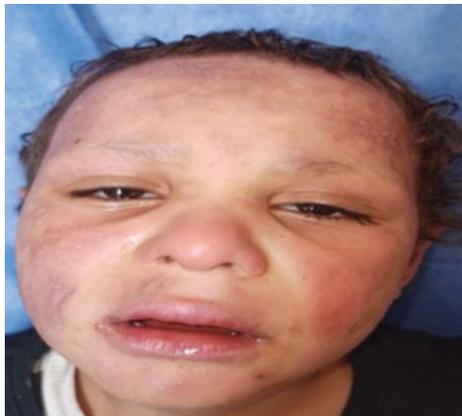


Fig. (3): Patient 4 months after burn with better scar outcome on the left side on which topical hirudin is used.
(3-A): Portrait view.



Fig. (3): Patient 4 months after burn with better scar outcome on the left side on which topical hirudin is used.
(3-B): General right lateral view.

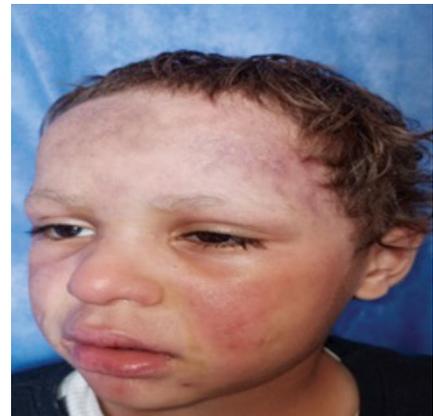


Fig. (3): Patient 4 months after burn with better scar outcome on the left side on which topical hirudin is used.
(3-C): General left lateral view.

Case (2):

2- A three-year-old female patient presented with scald burn on left side of face of deep partial and full thickness degrees. On the upper part, topical hirudin was used and topical beta-sitosterol was used on the lower part.



Fig. (1): Patient at time of presentation.
(1-A): Close-up lateral view.



Fig. (2): Patient two weeks after burn.
(2-A): Close-up lateral view.



Fig. (3): Patient one month after burn with faster healing on the upper part.
(3-A): Close-up lateral view.



Fig. (4): Patient 4 months after burn with better scar outcome on the upper part on which topical hirudin is used.
(4-A): Close-up lateral view.

Discussion

Patients with facial burns are real challenge for the clinician as not only the function should be restored, but also the aesthetic needs as well [5,10,11,21,24].

There is variety of lines for management of face burns. The corner stone in the treatment is essentially topical [1,8,14,15].

Although there is no gold standard agent for treatment of facial burns, beta-sitosterol oil-based, natural preparations are widely used in Asia and the Middle East and are considered as the gold standard. Moist exposed burn ointment (MEBO) enhances wound healing by moisture retention but

also other studies showed that it affects cytokines related to wound epithelialization [1,8,14,15].

Recently the role of local anticoagulants, including diluted topical heparin and the recombinant forms like recombinant hirudin, have been proved effective in the treatment of burns particularly facial burns [12,19,23,28,29,30].

Our study aimed at comparing the effects of topical recombinant hirudin and topical beta-sitosterols in facial burns treatment on a population of 15 burns patients. To the best of our knowledge, this is the first study to study such comparison.

To assure objectivity, we used Patient and observer scar assessment scale (POSAS) for burn

scars evaluation. In addition to objectivity, it is the only score that includes both the patient and observer scales [4].

The age range of our study was from 1 year to 45 years with mean age of 15.13 ± 17.62 years, which differs from the mean age of the studies we are comparing to, as most study populations of these studies were adults [9,13,18,20,30].

Regarding pain assessment, we used both visual analogue scale (VAS) and Patient and observer scar assessment scale (POSAS) in our study.

Patient and observer scar assessment scale (POSAS) showed no statistically significant difference in mean pain or itching as shown in Table (1).

This statically insignificant difference can be related to that most of our patients were children below 5 years; the VAS was more convenient for them. In addition, POSAS is for already healed wounds not active wounds.

Fawzy et al., used topical heparin dressing compared to antimicrobial agent for superficial, partial and full thickness burns of face. They used visual analogue scale (VAS) only for pain assessment [9].

Fawzy et al., study showed that heparin solution treated patients showed significant less pain, through both VAS and analgesic use [9].

Fawzy et al., study differs from our study in the design. As our patients had both products on the wound, the assessment of pain was less precise. Fawzy et al., used concurrent independent controls, therefore, the pain judgment was more precise. Another factor is the age of the patients. In our study, the majority of our cases were children. On the contrary, the majority of Fawzy et al., patients were adults who could express and evaluate pain more precisely. The use of analgesics is not a valid factor in our study as the patients had both products at the same wound [9].

Regarding pain, Masoud et al., a comparative study showed that topical heparin solution (H group) significantly decreased the requirement of analgesics (doses and numbers) compared to conventional treatment (C group) with silver sulphadiazine in acute burns. Furthermore, heparin showed less pain than the conventional treatment as assessed by visual analogue scale (VAS) [20].

The major difference between both studies and ours is the use of beta-sitosterol instead of the antimicrobial. This would explain the less significant differences as beta-sitosterol was proven to have significantly more analgesic effect than antimicrobial. Another factor might be due to the site of ap-

plication: It was limited to the face in our study, while the whole body was included in the other studies [1,20].

In our study, most patients (86.6%) suffered from moderate edema in the part treated with beta-sitosterols versus two-thirds (66.7%) in the hirudin part. Only one patient suffered from severe edema in the beta-sitosterols part versus zero in the hirudin part. Nevertheless, this difference was not statistically significant. It differs from Fawzy et al., Masoud et al., and Venakatachalapathy et al., studies.

These studies showed significant changes regarding edema, which significantly decreased in the topical heparin group [9,20,30].

The difference between these studies and our study can be related to that we compared to beta-sitosterol, which already has anti-edema effect. It is also may be due to the use of both topical agents on the same wound with possible cross-over from both sides at the contact part.

Our study showed that about two-thirds of the patients reported better healing in the part treated by topical hirudin than parts treated by beta-sitosterol, which was a significant difference. Healing assessment in our study was done using serial photography and daily follow-up until complete healing.

Similarly, Fawzy et al., also found that the number of healed cases per week in heparin group was significantly more than those in control group. Healing was also done by serial photography and follow-up of the patient till complete healing [9].

Consistent with our study, Masoud et al., study, serial photographs and follow up of Heparin group patients revealed significant early healing [20].

In addition, it demonstrated that heparin significantly decreased the time required to prepare a burn wound for grafting [20].

The results of Venakatachalapathy et al., study regarding healing is also consistent with our study. It showed significantly better healing in the heparin group and documented the appearance of new skin that was generally better in the heparin group patients. They referred this to the effect of heparin accelerating collagen production and deposition in the early phase. In the second phase, it decelerated and reabsorbed collagen.

This would tend to inhibit fibrin accumulation and scar formation. These had led to faster healing and better quality of scars in the heparin group [30].

Faster healing rate of heparin was also referred to its effect in the revascularization of ischemic tissue. This improved the quality and greater quantity of vascular granulation tissue that were noteworthy, consistent, and earlier post-burn features [30].

The similar effects of both topical heparin and topical hirudin in faster wound healing could be related to the anticoagulant effect of both products. This helps washing away the already formed thrombi and prevention of formation of new thrombi, consequently improving wound vascularity and healing.

Manzoor et al., randomized controlled clinical trial compared topical conventional treatments (including Polymyxin B sulphate, Bacitracin Zinc and Sulphadiazine 1% cream) with topical heparin treatment in partial thickness burn patients in the whole body [18].

Similar to our study, Manzoor et al., showed significantly faster healing in the topical heparin group. Healing assessment was also done by serial photography and daily follow-up till complete healing.

This study found that heparin therapy was associated with faster healing of the partial thickness burns, as evidenced by the wound size, number of wounds healed, or days needed to heal. This effect was also associated with less skin discoloration, pseudo-eschar formation and skin allergy [18].

In Manzoor et al., the significant effect of heparin in wound healing was explained by its chemotactic effect on endothelial cells, with resultant stimulation of neovascularization and improvement of blood circulation subjacent to the burn. In partial thickness burns, the deeper layers of skin develop ischemic injury due to vasoconstriction mediated by local generation of compounds, such as thromboxane and possibly by vascular thrombosis within dermis [18]. Heparin has been shown to increase survival of deeper layers of skin through its vasodilator and anti-thrombin effects, which prevents formation of new thrombi, and helps wash away the already formed thrombi [18].

Our study showed significant lower mean color, stiffness, thickness, skin irregularity and overall POSAS Patient scale in part of face treated with topical hirudin as shown in Table (1). Moreover, the overall POSAS observer 1, 2 and 3 scale means were similarly significantly lower in part of face treated with topical hirudin.

In addition, the mean average vascularity, pigmentation, thickness, relief, pliability, surface area and overall POSAS observer scale were significantly lower in part treated with topical hirudin as shown in Table (2).

Similar findings were noted at Masoud et al., study. Although scar assessment was done using scar parameters of Vancouver scar scale and not POSAS as in our study, results were significantly better in the heparin group. Vascularity, thickness, pliability, and pigmentation were recorded and revealed hypertrophic scarring in 10% of patients in heparin group versus 20% in control group. In addition, serial photographs revealed early healing and less scar related complications in the heparin group [20].

Our study results were consistent with Venkatachalapathy et al., study. The appearance of new skin was significantly better in the heparin group with significantly better quality of the outcome scar.

These effects were related to the heparin effect in the early phase that initially accelerated collagen production and deposition. In the second phase, it decelerated and reabsorbs collagen, which would tend to inhibit fibrin accumulation and scar formation [30].

Study limitations:

Our study limitations include the relatively low population (15 patients) and most of the study population was below 10 years with mean age of 15.13 ± 17.62 years.

Our study designs made it difficult to judge pain and edema as patients had both products on the wound site with possible crossover of products from both sides on the contact part.

Our healing assessment was done by subjective methods including serial photography and daily follow-up by our work place physicians, which could be sometimes biased and did not provide the proper-blinded assessment.

Our study lacks sure methods of scar assessment. These include Spectrophotometer that quantifies scar color, pigmentation and vascularity objectively and ultrasonography, which evaluates scar thickness.

Conclusion:

Topical hirudin use in facial burns is effective as it showed statistically significant results regarding wound healing and final scar quality outcome compared to topical beta-sitosterols.

Topical hirudin and topical heparin solution have significant effects on burn wound healing and final scar quality.

On the other hand, topical hirudin showed less significant results regarding pain and insig-

nificant results regarding edema compared to beta-sitosterols.

Topical heparin solution as mentioned in the previous studies has remarkable effect on pain and edema compared to conventional topical anti-microbial agents.

Data management:

The obtained data was coded, filtered, entered and processed on a personal computer using Statistical Package of Social Science (SPSS version 22).

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