

RECOMMENDATIONS

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1. 5-fluorouracil is good tool for treatment and prevention of problematic scars. It is effective, cheap and simple in use with no significant side effect.
2. 5-fluorouracil intra scar injection must not be used in pregnant and in patient with bone marrow depression.
3. Intra marginal excision of keloid give better result than extra marginal excision.
4. A combination of clinical scoring with histological data provided better verification of the overall response to this treatment modality.
5. After surgical incision of keloids, the skin is better closed using interrupted stitches than using continuous intra dermal stitch. The latter causes irritation of the reticular dermis and induces more fibroblastic reaction.
6. Further studies are required to standardize the dose of 5 fluorouracil injection particularly in extensive scars.
7. 5fluorouracil has no role in extensive dermal scar (widened scar).

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PROTOCOL

عولفتم

**CLINICAL AND HISTOPATHOLOGICAL STUDY OF
THE TREATMENT OF PROBLEMATIC SCAR USING
INTRADERMAL INJECTION OF 5-FLUOROURACIL
FOLLOWING SURGICAL EXCISION**

دراسة اكلينيكية وهستوباثولوجية لعلاج الندبات المشوهة باستخدام الحقن الموضعي
لعقار خماسي الفلورو يوراسيل بعد استئصالها جراحيا

Protocol of a thesis submitted
to the Faculty of Medicine
University of Alexandria
In partial fulfillment of the
requirements of the degree of
Master of Surgery

خطة بحث مقدمة
لكلية الطب
جامعة الإسكندرية
إيفاء جزئياً
لشروط الحصول على درجة
الماجستير في الجراحة

by

من

Sherif Ibraheem Hegazy
MBBCh, Alex.
Resident
Alexandria University Hospitals
Department of Surgery
Faculty of Medicine
University of Alexandria
2013

شريف ابراهيم حجازي
بكالوريوس الطب والجراحة ، الإسكندرية
طبيب مقيم
مستشفيات جامعة الإسكندرية
قسم الجراحة
كلية الطب
جامعة الإسكندرية

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SUPERVISORS

المشرفون

Prof. Dr. Raouf Mostafa Gomaa

Professor of Plastic, Reconstructive Surgery,
Faculty of Medicine,
University of Alexandria.

أ.د/ رؤوف مصطفى جمعة

أستاذ جراحة التجميل والاصلاح
كلية الطب
جامعة الإسكندرية

Prof. Dr. Iman Labib Salem

Professor of Plastic, Reconstructive Surgery,
Faculty of Medicine,
University of Alexandria.

أ.د/ ايمان لبيب سالم

أستاذ جراحة التجميل والاصلاح
كلية الطب
جامعة الإسكندرية

Prof. Dr. Layla Kamal Younis

Professor of Pathology,
Faculty of Medicine,
University of Alexandria.

أ.د/ ليلي كمال يونس

استاذ الباثولوجي
كلية الطب
جامعة الإسكندرية





ASSISTANT-RESEARSHER

Haide Abd Almonaem El Ngar

4th the grade student,

Faculty of Medicine,

University of Alexandria.

Mobile phone: 01280069292

E-mail: Haide_120@yahoo.com

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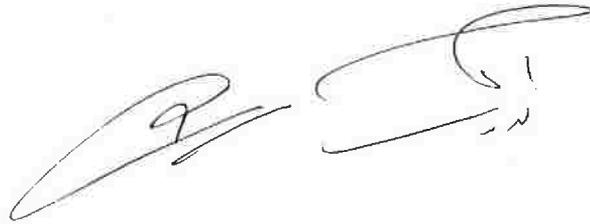
الباحث المساعد

هايدى عبد المنعم النجار

طالب بالفرقة الرابعة

كلية الطب

جامعة الاسكندرية



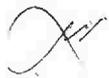
INTRODUCTION

Scars arise after almost every dermal injury (rare exceptions include tattoos, superficial scratches, and hopefully venepunctures). Scars are often considered trivial, but they can be disfiguring and aesthetically unpleasant and sometime cause severe itching, tenderness, pain, sleep disturbance, anxiety, depression, and disruption of daily activities. Other psychosocial sequelae include development of post-traumatic stress reactions, loss of self esteem, and stigmatisation, leading to diminished quality of life.

Skin tissue repair results in a broad spectrum of scar types, ranging from a "normal" fine line to a variety of abnormal scars, including widespread scars, atrophic scars, scar contractures, hypertrophic scars, and keloid scars.

Abnormal scars represent failure of the regulatory pathway of fibroblasts proliferation and feedback homeostasis.^(1,2) Some of the proposed mechanisms include altered growth factor regulation, abnormal collagen turnover, familial genetic predisposition, and immune dysfunction.⁽³⁾

The inflammatory phase occurs within minutes after the initial injury, due to the tissue damage, cell death at the site, changes in mechanical tension and release of endogenous antigens and alarmins, such as ADP and ATP. The clotting process occurs to stem the loss of blood and platelets caught in the clot secrete thrombin and fibrin, which further promotes the clotting cascade in addition to the recruitment of inflammatory cells. The inflammatory phase can last for up to days post-injury. Large numbers of neutrophils, polymorphonuclear cells and macrophages enter the wound bed to phagocytose debris and microorganisms found within the injured tissue.⁽⁴⁾



The recruitment of inflammatory cells to the wound is necessary for normal wound healing and induces the release of epidermal growth factor, transforming growth factor- β 1 (TGF β 1) and fibroblast growth factor; these growth factors induce the recruitment, maturation and proliferation of fibroblasts, fibrocytes and myofibroblasts, resulting in the secretion of high levels of collagens and extracellular matrix molecules. During the proliferative stage, tissue granulation starts and the original fibrin clot is replaced with a temporary matrix, composed primarily of collagen, fibronectin and hyaluronic acid, which is slowly replaced by a stronger extracellular matrix in the remodelling phase at later stages.⁽⁴⁾

Keratinocytes proliferate and migrate along the temporary granulated tissue, closing the wound surface and providing additional protection to the wound and laying down laminin and type IV collagen. Endothelial cells promote angiogenesis and reoxygenation of the wound.⁽⁴⁾

During the remodelling stage there is contraction and maturation of the extracellular matrix and this is mediated by myofibroblasts that induce contraction of the wound, and this remodelling process can last for days or from several weeks to up to 1 year, depending on the severity of the wound. During this process, the myofibroblasts initially secrete type III collagen but, as the wound healing progresses, they produce more of the stable type I collagen to reinforce the wound and provide strength to the extracellular matrix. The collagen fibres are then reorganized and crosslinked, increasing fibres strength in the wound.⁽⁴⁾

Although progress has been made in understanding scar pathophysiology, treatment remains unpredictable.⁽⁵⁻⁸⁾ Presently, the response to any accepted scar treatment runs the gamut from minimal to complete.



Treatment can be offered with three courses of action: non-invasive treatment, invasive treatment, and leave alone management.⁽⁹⁾

Non-invasive options include use of compression therapy (such as pressure garments with or without gel sheeting); static and dynamic splints; acrylic casts; masks and clips; application of a variety of oils, lotions, and creams; antihistamine drugs; hydrotherapy; and psychosocial counselling and advice. Silicon sheeting, with or without adhesive, has become popular. Massage therapy is often advocated but lacks evidence of benefit. All the above treatments are empirical. Without proper trials, benefits are difficult to quantify objectively, although even a placebo benefit may be appreciated by patients.⁽⁹⁾

Invasive treatments include surgical excision and resuture. Generally, revision should be considered only if the surgeon thinks that more favourable conditions for wound healing can be provided than on the first occasion (less inflammation, better technique). Intralesional corticosteroid injection is widely used but is prone to complications (fat atrophy, dermal thinning, and pigment changes). Other treatments that have been advocated with variable outcomes include injections of fluorouracil, interferon gamma, and bleomycin, radiotherapy, laser therapy, and cryosurgery.⁽⁹⁾

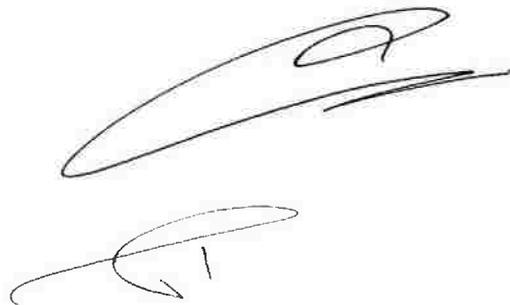
5-Fluorouracil is a fluorinated pyrimidine that acts as an antimetabolic agent. It inhibits thymidylate synthase and interferes with RNA synthesis and function. It has been used in the treatment of a variety of malignancies because of its effects on rapidly proliferating cells.⁽¹⁰⁻¹⁴⁾

Recent evidence suggests that 5-fluorouracil selectively blocks collagen synthesis, which may augment its antiscar role.⁽¹⁵⁻¹⁸⁾



Many authors quantify treatment outcome using a visual appearance rating scale. Other outcome measurement options include symptom relief and direct scar size measurement. Qualitative descriptive scales are available for scars but are far from being widely accepted.

In an effort to document objective and reproducible findings, scar volume will be used as our primary outcome measure. In addition, because many of the patients presented with scar-related symptoms as their primary complaint, symptom relief was also used as an outcome measure.

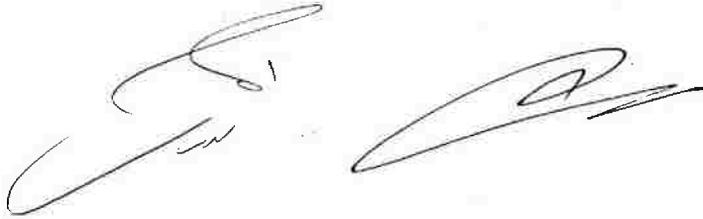


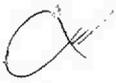


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AIM OF THE WORK

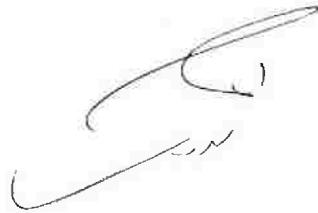
The aim of this work is to evaluate the role of the 5-Fluorouracil in the treatment of problematic scars.





PATIENTS

The 5-Flurouracil will be used for the treatment of (20) patients with problematic scars admitted to the Department of Plastic Surgery at Alexandria Main University Hospital.



METHODS

The 5 Fluorouracil will be used in patients with the following criteria:

- Keloids.
- Extensive dermal scarring.
- Recurrent keloids.
- Scar resistant to management .

Limitations of use:

- Cardiac patient.
- Hepatic patient.
- Patients with depressed bone marrow function.

All patients will be subjected to the following:

- Detailed history taking with stress on history of method and mode of previous trauma.
- Standard Digital Photography.

Management of the problematic scar:

The problematic abnormal scar will be excised extramarginally.

The excised scar will be halved and biopsy will be taken from each one for histopathological examination.

Injection of 5- fluorouracil will be done in the site of half of the scar after healing then every month in the same half for six months.



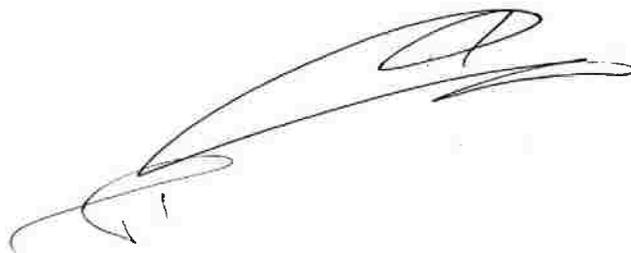
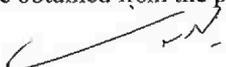
Other incisional biopsies about 2-3 mm will be taken from the site of the already excised halves after 3 months.

Histopathological evaluation:

Skin biopsies will be obtained from patients with problematic scars before and after treatment.

Tissue specimens will be fixed in 10 % solution of formalin, embedded in paraffin and subsequently stained with Hematoxylin-eosin stain for assessment of degree of fibrosis.

The medical ethics will be considered: the patient should be aware of the examination, patient approval should be obtained and informed consent should be obtained from the patient.



ETHICS OF RESEARCH

Research on human or human products:

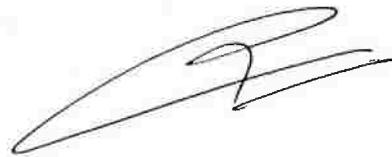
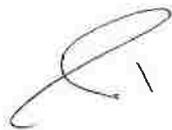
- Prospective study: informed consent will be taken from patients. In case of incompetent patients the informed consent will be taken from the guardians.
- Retrospective study: confidentiality of records will be considered.
- DNA/genomic material: informed consent for DNA / genomic test and for research will be taken from patients. No further test will be carried out except with further approval of committee and patients. If the samples will travel outside Egypt the researcher will be responsible for transportation and security approval.
- All drugs used in the research are approved by the Egyptian Ministry of Health.

Research on animal:

- The animal species are appropriate for the test.
- After test, if animal will suffer, it will be euthanized and properly disposed.
- After operation, it will have a proper postoperative care.

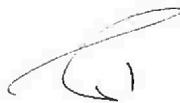
RESULTS

Data will be collected, tabulated and statistically analyzed using suitable statistical tests.

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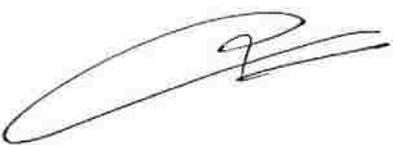
DISCUSSION

The results of this study will be discussed in view of achievement of the aim, and will be compared with other works in the literature.



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ARABIC SUMMERY

المخلص العربي

تحدث الندبات الجلدية نتيجة مضاعفات أثناء الشام الجروح ما بعد أنواع مختلفة من الاصابات. بالإضافة إلى الأسباب التجميلية، قد تكون الندبات حاكة وقد تحد من نطاق الحركة. بعض المرضى وجروح معينة هم أكثر عرضة لتكوين هذه الندبات. سبب هذه الندبات غير معروف. وقد اقترحت عدة نظريات، رغم أن أيا منها لم يتم اثباته

علاج هذه الندبات صعب للغاية. وقد وجدت علاجات متعددة في الماضي مع درجات متفاوتة من النجاح. وقد ثبت استجابة الندبات للعلاج ببلصغط، والحقن الموضعي للكورتيزون، والعلاج الكيميائي والإشعاع، والسيليكون الموضعي، وحمض الريتونيك والعلاج بالليزر. ولكن حتى الآن لا توجد طريقة العلاج المقبولة عالميا والتي ينتج عنه اختفاء الندبات.

وكان الهدف من هذا العمل تقييم فعالية الحقن الموضعي من عقار خماسي فلورويوراسيل. دواء العلاج الكيميائي، على الندبات الجراحية

شملت هذه الدراسة 20 مريضا مقسمة إلى ثلاث مجموعات على حسب نوع الندبات .

- المجموعة 1: تشمل (9) من المرضى الذين تم استئصال الندبات التغلظية المخلييه جراحيا (the keloid) وعلاجها بعد ذلك عن طريق الحقن الموضعي لعقار خماسي الفلورويوراسيل على الفترات الخاصة وفقا للبروتوكول المقترح.
- المجموعة 2: تشمل (8) من المرضى الذين تم استئصال الندبات التضخمية جراحيا (hypertrophic scars) وعلاجها بعد ذلك عن طريق الحقن الموضعي لعقار خماسي الفلورويوراسيل على الفترات الخاصة وفقا للبروتوكول المقترح .

- المجموعة 3: تشمل (3) من المرضى الذين تم استئصال الندبات العريضة (widened scars) جراحيا وعلاجها بعد ذلك عن طريق الحقن الموضعي لعقار خماسي الفلورويوراسيل على الفترات الخاصة وفقا للبروتوكول المقترح.

واستند التحليل النهائي على المقارنات بين نصف الجرح الذي تم حقنه بعقار خماسي الفلورويوراسيل ونصف الجرح الذي لم يتم حقنه في نفس المريض. تم تقييم الاستجابة للعلاج بعد تتبع عشرة أشهر تتبعا اكلينيكيًا وبأثولوجيا عن طريق ت.حالي الانسجه

التقييم الاكلينيكي للعلاج يعتمد على 4 علامات وأعراض اكلينيكيه من الندبات التي شملت سمك، مرونة، الأوعية الدموية وتصبغ ندبة الناتجة عن ذلك. ويقدر التأثير الكلي على تحسين هذه النتائج ومتدرج كما يلي (جيد) (تم تحسين 3 أو 4 من هذه العلامات والأعراض) (المتوسط) (إذا تم التحسن في اثنين من هذه الاعراض) و (الضعيف) (إن لم يحدث أي تحسن أو حدث تحسن في واحد فقط من هذه الأعراض). تم جدولة النتيجة وتم تحليلها إحصائيا.

ونتيجة هذا العمل أفضل من مثيلاتها من الدراسات المماثلة. وأظهر تقييم النتائج الإجمالية للمرضى في العمل الحالي استجابة جيدة في 75% من المرضى متوسط الاستجابة في 10% وضعف الاستجابة في ال 15% الباقية في النصف الذي تم حقنه. في النصف الذي لم يتم حقنه. الدراسات أظهرت 40% من المرضى ضعف الاستجابة 25% ومتوسط في حين أظهرت 35% من المرضى استجابة جيدة.

واعتمد التقييم الهيستوباثولوجي على فحص العينات التي تم الحصول عليها من نصف الجرح الذي تم حقنه ونصف الجرح الذي لم يتم حقنه قبل وبعد علاج الندبه وقد وجد في الندبات التغلظية المخلييه ألياف الكولاجين، التي هي كبيرة بشكل غير طبيعي، كثيفة، واسعة، ورتبت بشكل عشوائي. تم العثور على عدد قليل من الخلايا الليفية والعديد من الأوعية الدموية الصغيرة التي شكلت حديثا. في المقابل وجد في الندبات التضخمية الكولاجين وهو يتحفظ بالشكل العقدي، مع سمك منتظم إلى حد ما من الألياف مع مواز لها محور طويل إلى البشرة. وشهدت الخلايا الليفية بعدد أكثر من الندبات التغلظية المخلييه

وأظهرت الندبات الواسعه مصنوعة من ألياف الكولاجين بالتوازي مع البشرة. و لا يشبه الياف الكولاجين الموجوده في الندبات التغلظيه او التضخمييه.

الدراسه باستخدامالمجهر الضوئي ودراسة هيكلية فانقة منالأجزاء من الندبات التي تم حقنها باستخدام عقار خماسي الفلورويوراسيل أظهرت تحسنا ملحوظا. الفحص باستخدام صبغة (H & E) أظهرت انخفاض سمك الندبة، وانخفاض حجم حزام الكولاجين، والتفتت والتمزق من ألياف الكولاجين. وقد تقلص الأوعية الدموية بشكل ملحوظ بعد العلاج.

وأظهر فحص الأنسجة من الندبات الواسعة لافرق ملحوظ بين النصفين الذي تم حقنه و الذي لم يتم حقنه باستخدام العقار. وقد تطابقت النتائج الهيستوباسولوجيه مع النتائج الاكلينيكيه في هذه الدراسات.

الملخص العربي

لجنة الإشراف

.....
أ.د./ رؤوف مصطفى جمعه
أستاذ جراحة التجميل والإصلاح
كلية الطب
جامعة الإسكندرية

.....
أ.د./ إيمان نبيب سالم
أستاذ جراحة التجميل والإصلاح
كلية الطب
جامعة الإسكندرية

.....
أ.د./ ليلى كمال يونس
أستاذ الباثولوجى
كلية الطب
جامعة الإسكندرية

دراسة إكلينيكية وهيستوباثولوجية لعلاج الندبات المشوهة باستخدام الحقن الموضعي لعقار
خماسي الفلورويوراسيل بعد استئصالها جراحيا

مقدمة من

شريف إبراهيم حجازى

بكالوريوس الطب والجراحة - جامعة الإسكندرية، 2008

للحصول على درجة

الماجستير

فى

الجراحة

موافقون

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لجنة المناقشة والحكم على الرسالة

أ.د / إيمان لبيب سالم
أستاذ جراحة التجميل والإصلاح
كلية الطب
جامعة الإسكندرية

أ.د / نادر جمعه المليجي
أستاذ جراحة التجميل والإصلاح
كلية الطب
جامعة طنطا

أ.د / ناصر أحمد غزلان
أستاذ جراحة التجميل والإصلاح
كلية الطب
جامعة الإسكندرية



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رسالة علمية

مقدمة إلى كلية الطب - جامعة الإسكندرية
إستيفاء للدراسات المقررة للحصول على درجة

الماجستير

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2015