Effect of Autologous Fat Grafts In Management of Hypertrophic Scars at Kenyatta National Hospital

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H58/87464/2016

A research dissertation submitted to university of Nairobi in partial fulfillment for the award of master in medicine in plastic reconstructive and aesthetic surgery (MMED PRAS) , University of Nairobi.

Declaration

I hereby declare that this dissertation is my original work and has not been presented elsewhere

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LIST OF ABBREVIATION

AFGs- Autologous Fat Grafts

CM- centimetres

CM2- squared centimetres

DNA- Deoxyribonucleic Acid

ECM- Extracellular Matrix

HTSs- Hypertrophic Scars

IL- Interleukin

KNH – Kenyatta National Hospital

PDGF- Platelet Derived Growth Factor

RCT – Randomized control trial

SGS- Silicone Gel

SPSS- Statistical Package for the Social Sciences

TH- T-Helper

TNF alpha- Tumour Necrosis Factor

VEGF- Vascular Endothelial Growth Factor

5 FU- 5 Fluorouracil

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Summary

Background: Hypertrophic scars are a common global health problem with significant effects on overall quality of life and a huge burden on health care systems. There are numerous treatment modalities for hypertrophic scarring described in literature to date, with silicone gel being the most preferred, however Autologous fat graft (AFGs , henceforth) have also been suggested as an alternative due to their being readily available and cheaper. Despite its possible use in regenerative medicine, few studies have been done to elucidate its effectiveness in treatment of hypertrophic scars.

Study objective: This study therefore evaluated the effectiveness of AFGs in the management of hypertrophic scars.

Study design: Quasi experimental one group pre-test-post - test (non RCT) study design

Setting: Kenyatta National Hospital

Ethical consideration: All data was collected after approval was sought from and granted by the Kenyatta National Hospital / University of Nairobi Ethics Review Committee (KNH/UoN ERC). Informed consent was sought from all the participants.

Methodology: One group of fourty nine (49) adult consenting participants, presenting with hypertrophic scars were recruited. Prior to the administration of the intervention, patient demographic data was collected following which punch biopsies of their wounds were taken for histology. Pain scores were recorded. AFGs were then injected into the hypertrophic scars of the same patients at a dose of 1ml/3.5cm^2 scar area. Scar assessment by a blinded research assistant was done at day 0 and 28. This assessment was guided by the POSAS scale. A punch biopsy was

then collected for histology on day 0 and 28. A structured questionnaire was used to collect the data.

Data management: SPSS (IBM version 21) was used to analyse the data. Tables, graphs and digital photography was used to present the results obtained in the study. The measurements obtained were fed in SPSS from where mean percentages (of the surface area of the scar, vascularity and hyperpigmentation), means (of pain and itchiness scores, height of the scar and pliability scores) and standard deviations were calculated. Age differences were assessed using ANOVA, gender differences as well as group differences using students's 't - test, correlations by cross-tabulations and pearsons correlational test. A p value ≤ 0.05 was considered significant at 95% confidence interval. The findings were represented in tables, line graphs and photomacrographs.

Results: The average age of the participants was 26.20 (18-32) years with the majority being female (76%) as compared to male (24%). In both gender, burns (72%), were the most common causes of scars and in terms of age, the mean age of the scar was >1 year with no gender (p value = 0.907) or age differences (p value = 0.907). The most common scar site was the forearm (16%) and the thigh (16%). The mean surface area of the scar was 39.96% (7 - 100).

There were statistical significant differences between the patients' scores before and after intervention specifically on pain, itch and characteristics of the scar (color, stiffness, thickness and regularity). There were also statistical significant differences between the observers' scores before and after intervention on vascularity, pigmentation, thickness, pliability, surface area and overall opinion of the scar (p value = 0.000).

Conclusion: Findings of our study support that AFGs may be beneficial in the treatment of hypertrophic scars as shown by the improvement of both observer's and patient's scores pre-intervention and post-intervention. Our findings are consistent with existing literature.

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Scar formation is a sequel of the process of wound healing that occurs when body tissues are damaged by a physical injury. A hypertrophic scar (HTS), defined as a visible, elevated scar does not spread into surrounding tissues and often regresses spontaneously (Rabello et al., 2014). These scars are characterized by proliferation of the dermal tissue, with increase in myofibroblasts and an excessive deposition of fibroblast derived extracellular matrix (ECM) proteins and especially collagen, over long periods and by persistent inflammation and fibrosis as suggested by (Atiyeh et al. 2007).

1.1.1 Prevalence of hypertrophic scars

Hypertrophic scars are a frequent complication of burns, trauma, surgical incisions, acne and infections. The incidence of hypertrophic scaring has been seen to be between 40-70% following surgery and up to 91% following burn injury depending on the depth of the wound according to (Bombaro et al. 2003). In our setting, the incidence of burns have been shown to be 27.9 per 1000 persons per year (Wong et al., 2014) and are the most common causes of hypertrophic scars.

Hypertrophic scar formation is a major clinical problem in the industrialized and developing worlds. They result in permanent functional loss and stigma of disfigurement. Systemic, genetic and local factors have been faulted in the formation of hypertrophic scars (Ogawa et al., 2016).

The true burden of hypertrophic scars in Kenya is unknown; however, a study by Bombaro et al. (2003) places it at 30% of all burn wounds in black patients, which are among the commonest causes of morbidity and mortality (Bombaro et al., 2003). Hypertrophic scars further pose a

significant health problem with attendant deleterious effects on quality of life both physically and psychologically by causing pain, pruritus and contractures (Zurada et al., 2006).

Annually, over 1 million people require treatment for burns in the United States, 2 million are injured in motor vehicle accidents, and over 34 million related surgical procedures are performed (Aarabi et al., 2007). Although the incidence of hypertrophic scarring following these types of injuries is not known, it is a common outcome that creates a problem of enormous magnitude. Treatment of these cases is estimated to cost at least 4 billion dollars per annum in the United States of America (Aarabi et al., 2007). The incidence of burns and traumatic injuries is even greater in the developing world (Megan et al., 2017) resulting in a proportionally higher burden of hypertrophic scars.

1.1.2 Management of hypertrophic scars

Numerous methods have been described for the treatment of HTSs; both conservative and surgical, but to date the optimal treatment method has not been established. The most common method used is silicon dressings but due to the long hours required to have the dressing on among other limitations, patient compliance remains an issue (Rabello et al., 2014).

AFGs have also been suggested as a possible modality of treatment since they secrete cytokines which stimulate the regeneration and synthesis of collagenous fibres, proliferation of blood vessels resuming blood circulation which provides oxygen and nutrition improving the scar texture and appearance (Rabello et al., 2014). Despite their possible use in regenerative medicine, few studies have been done to elucidate its effectiveness in treatment of hypertrophic scars (Rabello et al., 2014). This study therefore aimed to evaluate the effectiveness of AFGs in the treatment of hypertrophic scars. The major complication in use of fat grafting may be related to the procedure or technique themselves, mostly because of physical trauma to underlying structures by the

cannula or other injection device; however, this can easily be by-passed by using blunt cannulas during the Coleman's' technique.

Owing to the possible high burden of HTSs in Kenya attributed to the high incidence of burns and other forms of trauma, findings from this study aimed to assess the effectiveness of AFGs in treatment of HTSs in an attempt to provide an alternative effective treatment modality.

1.2 Literature review

1.2.1 Pathophysiology

Following insults such as burns, trauma and surgical incisions, the epidermis may take up to two weeks to sufficiently regenerate, especially if the insult was a full-thickness wound that penetrated through both the epidermis and the dermis (Tokeo et al., 2015). During this time, it has been shown that intervention with scar development has little to no effect as high collagen levels are required at this early wound healing stage (Tokeo et al., 2015). After this period, new immature stratum corneum allows for very high levels of water loss through the skin. The dehydration that ensues then signals the keratinoctyes to produce cytokines which stimulate the fibroblasts to synthesize and release collagen (Tokeo et al., 2015). The newly formed collagen then rushes to the scar site and is the cause of many undesirable physical and aesthetic properties associated with scarring. Histologically, these hypertrophic scars have normal epidermis and papillary dermis with dermal nodules that are composed of increased numbers of collagen bundles that run in different directions (Tokeo et al., 2015).

Owing to the pathophysiology, modalities that may aid in reducing hypertrophic scar formation therefore tend to center around reducing the dehydration aspect that leads to cytokine release.

Other modalities may also focus around reducing collagen formation to reduce abnormal scarification.

1.2.2 Burden of the scars

These scars are a significant concern for patients and a challenging problem for clinicians because they can be painful, pruritic, erythematous, raised and cosmetically unacceptable. (Rabello et al. 2014) reported that the most common and distressing complications in burn patients who developed HTSs were abnormal appearance (75.2%), pruritus (73.3%) and pain (67.6%). Management of these scars should therefore be one which aids in the alleviation of pain, itchiness and appearance. Up to date, the different management options have been developed and are categorized into two: surgical and non-surgical methods.

1.2.3 Management methods

Surgical management includes excision of the scar with primary closure but this has been noted to increase scar length with a potential of worsening the hypertrophic scar tissue. This has led to preference of non-surgical methods, most of which employ either the use of a pharmacological agent (such as, silicone gel, bleomycin or corticosteroids) while others are more mechanical in nature, such as, pressure garments and laser therapy. Studies have highlighted the advantages and disadvantages of each of the different modalities.

1.2.3.1 Pressure garments

The use of pressure garments was first described in the management of HTSs in 1860 in burn patients (Linares et al., 1993). The mode of action is not well understood but theories include hypoxia, biochemical changes with cellular and collagenous influences. Evidence suggests that pressure controls collagen synthesis by limiting the blood supply, oxygen and nutrients to the scar

tissue (Puzey et al., 2002). This reduces collagen production to the levels found in normal scar tissue more rapidly than the natural maturation process does. Problems with pressure loss from the garments over time and lack of compliance of patients using the garments are among the factors complicating use of pressure garments. (Engrav et al., 2010; Van der Kerckhove et al., 2005).

1.2.3.2 Intra-lesional corticosteroid injections

Intralesional corticosteroid injections have been in use for the management of pathological scars since the mid-1960s and continues to play a major role in the regression of HTSs. It acts by decreasing collagen and glycosaminoglycan synthesis, by reducing the inflammatory process in the wound by decreasing fibroblast proliferation and by increasing hypoxia (Niessen et al., 1999). Response rate varies from 50-100% with a recurrence rate of 9- 50% (Koc et al., 2008). Although relatively effective, corticosteroid injections are associated with significant injection pain, hypopigmentation, skin and subcutaneous fat atrophy, telangiectasis, rebound effect and ineffectiveness. (Roques et al., 2008).

1.2.3.3 Bleomycin

The use of bleomycin was introduced by Bodokh and Brun in 1996 as an alternative treatment for HTSs. Its action is based on being an inhibitor of DNA synthesis. (Bodokh et al., 1996). Local side effects include dermal hypertrophy and hyperpigmentation and systemically, pulmonary fibrosis and hepatotoxicity. Further investigation is required before it can be included in future treatment protocols (Shridharani et al., 2010).

1.2.3.4 Emerging alternative treatment

The use of interferon alpha, beta and gamma increases collagen lysis and in particular inhibit the synthesis of type I and III collagen. However, interferon application is very painful and costly

(Mustoe et al., 2002). The drug 5-florouracil (FU) may be used alone or in combination with corticosteroid injections achieving better results than if each drug was to be used alone (Mustoe et al., 2002).

1.2.3.5 Silicone dressing

Silicone has been widely used since the 1980s and there is good evidence of the efficacy of both silicone gel (Silicone gel) sheets and gel.

Mode of action

Owing to its liquid like gel property, SGS's has the ability to provide improved occlusion and hydration to the wound bed. By doing this, it provides the hydration to the immature forming stratum corneum and by extension, reduces the unwanted dehydration. By doing so, the cells within the stratum corneum will not signal to the keratinocytes in the epidermal skin layer to produce cytokines, which in turn would have signalled fibroblasts to produce excessive amounts of collagen leading to the noted undesirable attributes of a hypertrophic scar (Rabello et al., 2014).

Secondly, the ability of the silicon to transfer tension from the lateral edges of the wound bed to the silicone gel sheet has been shown to reduce the tension caused during scarification which leads to abnormal and keloid scarring. Further, SGS has also been shown to inhibit the body's natural reaction to increase skin capillaries through hyperemia during wound healing (Rabello et al., 2014).This has been reported to reduce the blood supply to the scar site and the exaggeration of the healing process, along with the intensity of the fully formed scar's appearance and physical properties. Finally, through the generation of negatively charged static electric field as a result of friction created between the silicone gel and skin, this static electricity is thought to aid the alignment of collagen cells, thus resulting in the involution of raised scars (Rabello et al., 2014).

Clinical benefit

A study ascertaining the clinical benefits of silicone gel showed that when applied to hypertrophic scars, pain and itchiness reduced significantly (p=0.04) after 4 weeks, and all pain disappeared after 12 weeks (Rabello et al., 2014). These effects continued until 24 weeks (p=0.04), after which pruritus did not recur. As pertains, redness and elevation of the scar (appearance), scar redness decreased at 4 weeks of treatment, although not significantly (p=0.08). However, after 8 weeks, the redness decreased significantly (p=0.025). The reduction in redness continued until 24 weeks (p=0.033), although it did not completely disappear. Scar elevation showed a concomitant decrease with redness (Similar findings of clinical improvements have been echoed (Rabello et al., 2014) though he reports longer duration for the noted effects. Histologically, reduction in collagen formation and vascularity have been noted as well (Rabello et al., 2014).

Limitations

Although gel sheeting is effective for HTSs treatment, patient compliance may not be satisfactory due to skin reactions to the tape used for fixation, excessive sweating, difficulty in its application and the visibility of the treatment in scars located in visible areas of the face (Rabello et al., 2014).

A study by (Nikkonen et al. 2001) also highlighted other problems documented by patients following use of silicone gel. They included: persistent pruritus (80%), skin breakdown (8%), skin rash (28%), skin maceration (16%), foul smell from the gel (4%), poor durability of the sheet (8%), failure of the sheet to improve hydration of dry scars (52%), poor patient compliance (12%) and poor response of the scar to treatment (24%) of his study population. As a result, the use of AFGs has been suggested.

1.2.3.6 Autologous Fat Graft

Adipose tissue is soft and malleable and is present in the body in large quantities making it the ideal filler for correcting and remodelling profile and volume body defects and is the main source of AFGs.

Mode of action

The cells have angiogenic and anti-apoptotic properties which have effects on wound healing, soft tissue restoration and scar remodelling (Lee et al., 2017). Being mesenchymal stem cells, they coordinate repair response by recruiting other host cells, thus secreting growth factors.

In recent years, many studies have endeavoured to elucidate the underlying mechanism of AFGs in wound healing and repair. These cells not only provide physical support in the injected areas, but also secrete cytokines such as VEGF, PDGF, TGF- beta and IGF-1, (Lee et al., 2017) which are closely connected with regeneration and metabolism. These cytokines may stimulate the regeneration and synthesis of collagen fibres in the recipient areas, thicken the dermis, stimulate endotheliocyte proliferation in blood vessels and hasten the resumption of blood circulation, providing oxygen and nutrition as well as improve scar texture. (Xu et al., 2018).

Actions of cytokine IL-10 are responsible for the inhibiting CD-4 and CD-8, by extension aiding in generation of an anti-inflammatory response according to (Huang et al. 2015).

Autologous fat grafts have also been noted to create a microenvironment following tissue regeneration which encourages nerve release. This encourages neoangiogenesis and increased hydration, and as a result, reduced keratinocyte stimulation and excess collagen deposition.

Clinical benefit

Klinger showed that fat transplantation can be used to cure HTSs. He noted that skin regained the softness, elasticity, colour and thickness of normal skin. Histological analyses identified collagen deposition, thickening of the dermis and blood vessel proliferation, indicating that scar tissue retains ability to become normal skin (Klinger et al., 2013). Similar findings were echoed in 18 patients with post burn hypertrophic scars (Brongo et al., 2012).

Similarly, (Bruno et al. 2013) found that fat transplantation stimulates the regeneration of elastic fibres under scars, enabling disordered collagenous fibres histologically, to regain normal alignment and compactness.

The analgesic effect to the hypertrophic scar from fat grafting has been attributed to scar entrapment release by the cannulas during injection and by release of Brain derived neurotrophic factor (BDNF, henceforth) as evidenced by (Urich et al. 2012) who demonstrated in eighteen out of his twenty patients with hypertrophic scars treated with fat grafting, who had relief of pain following cannula insertion and release of fibrotic tissue. It is worth noting however that just like silicone gel, AFGs have their limitations.

Limitation

Studies have shown that AFGs are closely built-in and niched in the ECM and interconnected to other epithelial cells; hence, when collected within liposuctions, their separation from their niche affects their clinical applications. Similarly, their efficacy has been shown to be reduced when given with local anaesthetics. Additionally, AFGs undergo apoptosis a few days after transplantation making doubtful the implication of patient-associated factors or other epigenetic

factors in regulating the fate of AFGS (Manzini et al., 2020). Despite this, its use has been supported by the successful trials as well as its relative availability.

Autologous fat grafts are easily available with multiple sites present including the lower abdomen, inner arm, and thigh. They are normally harvested using the Coleman's technique and can be injected in multiple sites of the body. It is not immunogenic and according to Piccolo, fat grafting is a procedure that has a short learning curve for surgeons and is a viable option in management of hypertrophic scars (Piccolo et al., 2015). Unlike silicon gels which are expensive to obtain, AFGs also offer a viable cheaper option.

CHAPTER 2: STUDY JUSTIFICATION, SIGNIFICANCE, STUDY QUESTION, HYPOTHESIS, OBJECTIVES

2.1 Justification

There is a heavy burden of hypertrophic scars resulting from different causes and especially burns in our setting, which is noted to be 27.9 per 1000 persons per year (Wong et al., 2014). Individually, these scars are a significant concern for patients and a challenging problem for clinicians because they can be painful, pruritic, erythematous, raised and cosmetically unacceptable. A previous study reported that the most common and distressing complications in burn patients who developed HTSs were abnormal appearance (75.2%), pruritus (73.3%) and pain (67.6%). Hypertrophic scars also have a huge financial and psychological effect on patients. In our local set up, hypertrophic scars lead to straining of meagre resources on our health system by the numerous visits to the hospital and money spent on the various treatment modalities which are not as effective which calls for an innovative way to lessen the burden. There is also paucity of data on the benefits of fat grafts in management of hypertrophic scars. This study therefore aimed to determine the same.

2.2 Study question

What is the effect of autologous fat grafts in hypertrophic scars?

2.3 Null hypothesis

Derived AFGs do not have any effects on hypertrophic scar.

2.4 Objectives

2.4.1 Broad objectives

To assess the effect of autologous fat grafts in management of hypertrophic scars in patients at Kenyatta National Hospital.

2.4.2 Specific objectives

1. To determine the effect of AFGs on pain and pruritus on patients with hypertrophic scars.

2. To determine the effect of AFGS hypertrophic scar appearance.

3. To determine the histological changes on hypertrophic scars after grafting with AFGs.

CHAPTER 3: MATERIALS AND METHODS

3.1 Study design

Quasi experimental (One group pre-test –post - test design) (Non-RCT) study design.

3.2 Study area

This study was carried out at Kenyatta National Hospital, a 2000-bed facility that serves as a tertiary referral centre as well as a teaching hospital for the University of Nairobi. The specific sites were in the Plastic Surgery clinic and ward 4D where the participants were recruited from. The procedures were carried out in the Kenyatta National Hospital Burns theatre. The collected histology samples were processed and read in the University of Nairobi Histology and Pathology laboratory.

3.3 Study population

The study population were male and female adults above eighteen years with hypertrophic scars presenting at KNH requiring specialized plastic surgery treatment.

3.4 Sample size

Sample size was calculated using the sample size formula for a dependent t-test as suggested by (Cohen et al 1988). In this formula:

$N= [Z\alpha +Z\beta]^2 \sigma/ \delta$

Where: N = total sample size

$Z\alpha$ and $Z\beta$ are alpha and beta levels, taken as 1.96 (for p = 0.05) and 1.28 (for power =0.8)

Δ = hypothesized difference is 9%. The assumption that 90% of the patients and not 99% as suggested by Piccolo et al (2015) might benefit bring the difference to 9.

σ = Hypothesized standard deviation of difference taken as 20, suggesting that the benefits might range from 80% – 90%, since the intervention might not work in some individuals.

Specifically in our setting, this may be due to external factors such as unknown chronic illnesses, or factors encountered in the home environment which might affect the overall effectiveness of the intervention unlike what (Piccolo et al. 2015) reported in where all patients were hospitalized and monitored.

Therefore:

$(1.96 + 1.28) * 20/9 = 7^2 = 49$

Therefore, a total of 49 participants were recruited.

3.5 Selection criteria

3.5.1 Inclusion criteria

This study included participants who met the following criteria:

1. Patients who had a small painful and retractile scars less than 10cm2 which will enable infiltration of autologous fat grafts with local anaesthesia
2. Patients with hypertrophic scars with any aetiological factors like burns, post-surgery and trauma related.
3. All adult consenting participants with hypertrophic scars over 18 years of age.

3.5.2 Exclusion criteria

The exclusion criteria included patients with:

1. Keloids

2. Participants with known allergy to adrenaline, lignocaine and general anesthetic drugs
3. Patients with conditions altering wound healing such as Diabetes Mellitus and Connective Tissue Disease.

3.6 Data collection procedure

A pre-study training program was done for all involved personnel (principal investigator / operating surgeon and research assistants) to ensure standardized method of AFGs harvesting, processing and re-injecting and collecting data. This training was conducted under supervision of the study supervisors.

During the main study, the participants were selected using systematic random sampling where the patients were selected in intervals of 3, in this case the 1^{st}, 4^{th}, 7^{th}, and so on, until the sample size was derived. The experiment was then carefully explained to them after which they were presented with a consent form to sign. Once the participants had consented to the study, they were requested to fill in a questionnaire collecting information on their demographics as well as pain scores. After this, they received their treatment thereafter and follow up assessment after 0 and 28 days using a data collection tool (Appendix III) by two trained independent research assistants. These assistants were selected from a pool of postgraduate students pursuing plastic surgery and with at least 2 years of research background. Perioperative data was collected by the principle researcher using standard tool (Appendix II).The clinical changes were assessed with the help of the POSAS scale. The POSAS consists of an Observer and a Patient Scale and includes a comprehensive list of items, based on clinically relevant scar characteristics. The observer scored six items: vascularization, pigmentation, thickness, surface roughness, pliability, and surface area. The patient scored six items: pain, pruritus, color, thickness, relief, and pliability. All included items are scored on the same polytomous 10-point scale, in which a score of 1 is given when the

scar characteristic is comparable to ‘normal skin’ and a score of 10 reflects the ‘worst imaginable scar’. All items were summed to give a total scar score, and therefore, a higher score represents a poorer scar quality

The following steps were carried out in succession during the administration of the intervention.

3.6.1 Harvesting of AFG

The Coleman’s technique was used to harvest the AFG. The Coleman technique entails fat harvesting with a blunt-tipped 3 mm cannula using a standard 10 mL Leur-Lok syringe with 2 mL of negative pressure space in the barrel of the syringe providing low-level suction. Harvest sites include the lower abdomen, flanks, inner and outer thighs, plus other sites such as the gluteal and sub mental areas. Tumescent fluid used was 0.5 % lidocaine -1;200,000 epinephrine injected into the subcutaneous fat using a 10 cc syringe connected to a 3mm cannula introduced into the subcutaneous tissues. Cross tunnelling was done followed by syringe aspiration technique using long atraumatic cannula to harvest the lipoaspirate.

3.6.2 Injection of lipoaspirate

Aliquots of the rich autologous fat grafts layer was injected into a hypertrophic scar base at a dose of 1ml per 3.5cm2 of scar area using a 3mm cannula.

3.6.3 Anaesthesia

Regional anaesthesia with sedation was preferred where applicable and general anaesthesia was used for those cases who demanded it.

3.6.4 Analgesia

Standard analgesia was NSAIDs in combination with paracetamol. Opioid analgesics was added where there was breakthrough pain.

3.6.5 Antibiotic use

Prophylaxis: The preoperative dose of antibiotics was administered within one hour of the procedure.

3.6.6 Dressing materials

All wounds had petrolatum gauze impregnated with 10% chlorhexidine an antiseptic combined with plain absorbent gauze and a tertiary dressing to secure it in form of a crepe bandage or cotton gauze roll.

3.6.7 Scar assessment

In determining the effect of the AFG on hypertrophic scars, changes in pain and itchiness around the scar were observed post intervention using POSAS scale. Similarly, scar quality and quality of life were assessed both pre - and post - intervention using quality of life assessment scale. To determine the changes in the scar quality, biopsies of the wound were taken before the intervention and 28 days, after, which, they were processed for light microscopy and staining to observe for changes in the epithelial thickness, vascularity, collagen type density and dermal hyperplasia.

3.7 Data analysis

The measurements obtained were fed in SPSS (Statistical Package of Social Sciences SPSS version 21.0) from where percentages (of the surface area of the healing wound, vascularity and hyperpigmentation), means (of pain and itchiness scores, height of the scar and pliability scores) and standard deviations were calculated. Statistical significant differences based on age, on the different variables observed, were then analyzed using the one way ANOVA, whereas gender differences were analyzed using the Students T test. Correlation between the both pliability and age to causation of the scar were analyzed using the cross tabulations, following which the degree

of correlation were assessed using Pearson correlational test. A p value ≤ 0.05 was considered significant at 95% confidence interval. The findings were represented in tables, line graphs and photo macrographs.

3.8 Data and safety monitoring

There were no severe adverse events expected in this study since autologous ASCs were not manipulated and were injected promptly after harvesting. Fat graft is routinely used in plastic surgery in combination or separately for cosmetic and reconstructive purposes and has been well tolerated. Some participants required general anaesthesia so as to enable safe harvesting of the fat. No severe adverse events to the DSMB were noted.

These include any adverse event that:

i. results in death

ii. is life threatening, or places the participant at immediate risk of death from the event as it occurred

iii. requires or prolongs hospitalization

iv. causes persistent or significant disability or incapacity

v. is another condition which investigators judge to represent significant hazards

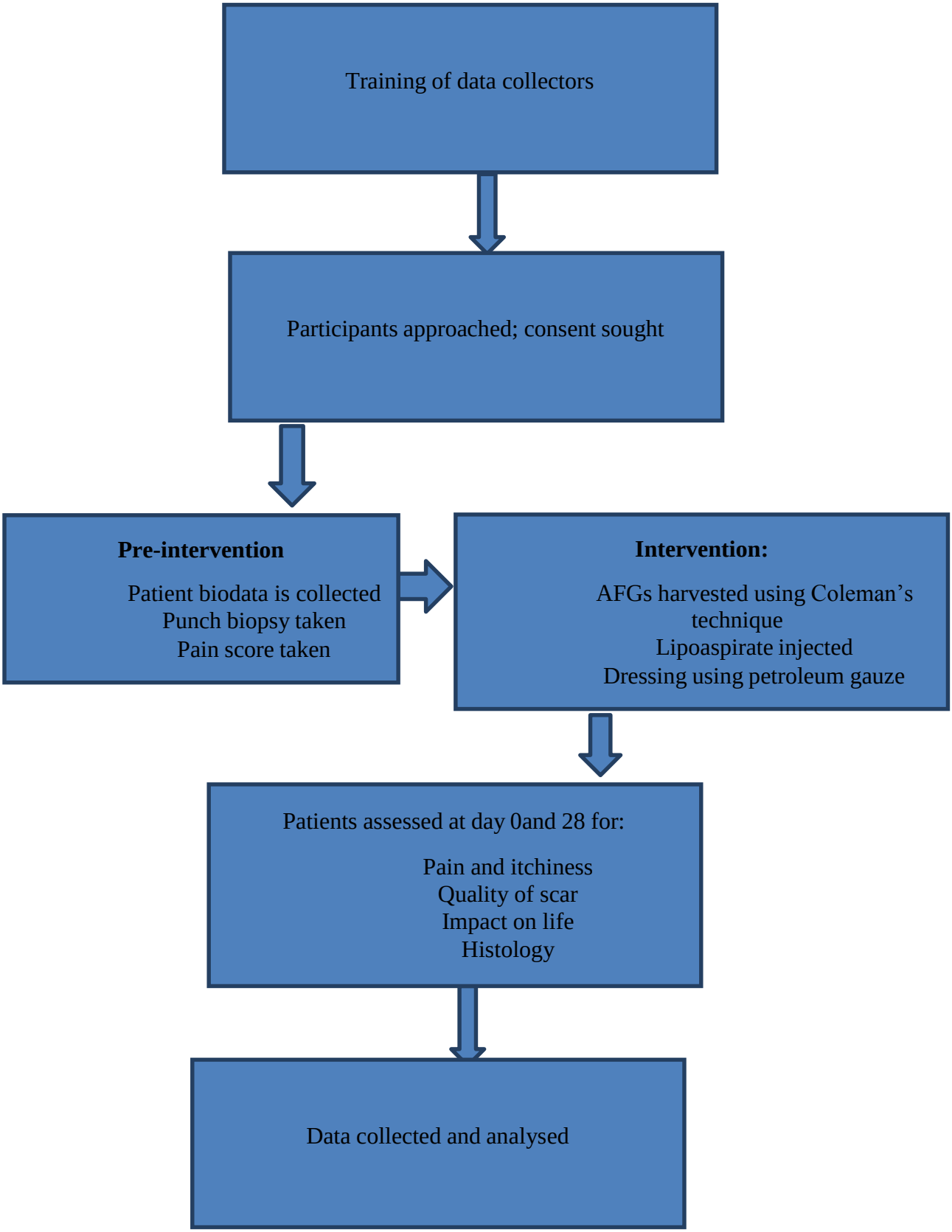
All hospitalizations from expected causes are reported in the quarterly report to the DSMB.

3.8 Ethical consideration

All data was collected after the approval of the Kenyatta National Hospital / University of Nairobi Ethics Review Committee (KNH / UoN ERC) and procedures conformed to the World Medical Association Declaration of Helsinki. Informed consent was sought from all the

participants. Non-participation did not affect such a participants' care in the hospital. Participation in this study would not attract extra cost to the medical care of the participants. Participants' hospital file number would be included into the data sheet to facilitate easy tracing and capture missed information during data collection.

A flow chart summarizing data collection procedure is as follows:



CHAPTER 4: RESULTS

4.1 Demographics

The average age of the participants was 26.20 (18-32) years, with majority being between the age group, 30-32 years. In the study, most participants were female (76%) as compared to male.

4.2 Description of scars

The most common cause of scars was burns (72%), followed by surgery (16%), then trauma (12%). The mean age of the scar was >1 year (44%), followed by 10-12 months (32%) and 6-9 months (24%). The most common scar site was the forearm (16%) and the thigh (16%) while the least was chin (4%), hand (4%) and cheek (4%) (Table 1). There was no associated gender or age differences noted in all the above parameters (p value >0.05).

Table 1: Table summarizing scar site

Table summarizing scar Site	
Forearm	**16.0**
Hand	4.0
Thorax	8.0
Abdomen	8.0
Trunk	8.0
Thigh	**16.0**
Leg	12.0
Foot	12.0
Chin	4.0
Cheek	4.0

The most common involved site was the right (36%) and left (36%). Anterior, posterior and centre involvement was 4%, 8% and 16%. The mean surface area of the scar was 39.96% (7 - 100). The

distribution based on gender and age was not statistically different (p value >0.05). The mean AFG injected was 11.88mm (2-30mm).

4.3 Analysis of the scores (pre and post analysis) of the patient and observer

4.3.1 Determining change in pain, pruritus and hypertrophic scar appearance – Analysis scores of the patients

There were statistical significant differences between the patients' scores pre - and post - intervention in terms of pain, pruritus and appearance of the hypertrophic scar. There were however no statistical significant differences noted on gender, while it was noted amongst the different age groups as tabulated below (Table 2).

Question (in pairs – pre and post test respectively.)		**Mode**	**Mean**	**Sig.**	**Gender differences (p value**	**Age group differences (p value)**
Pair 1	Has the scar been painful the past few weeks? (Pre) Has the scar been painful the past few weeks?(Post)	6 2	6.52 2.72	.007	0.972 0.948	0.003 0.106
Pair 2	Has the scar been itching the past few weeks? (Pre) Has the scar been itching the past few weeks?(Post)	8 1	6.56 2.48	.000	0.474 0.982	0.015 0.106

Pair 3	Is the scar colour different from the colour of your normal skin at present?(Pre) Is the scar colour different from the colour of your normal skin at present?(Post)	7 3	6.52 4.04	.001	0.424 0.809	0.028 0.013
Pair 4	Is the stiffness of the scar different from your normal skin at present?(Pre) Is the stiffness of the scar different from your normal skin at present?(Post)	8 3	6.92 3.48	.000	0.915 0.740	0.006 0.001
Pair 5	Is the thickness of the scar different from your normal skin at present?(Pre) Is the thickness of the scar different from your normal skin at present?(Post)	7 3	6.52 4.04	.000	0.615 0.762	0.039 0.008
Pair 6	Is the scar more irregular than your normal skin at present?(Pre) Is the scar more irregular than your normal skin at present?(Post)	6 4	5.96 4.32	.015	0.834 0.672	0.028 0.012
Pair 7	What is your overall opinion of the scar compared to normal skin? What is your overall opinion of the scar compared to normal skin?	7 4	6.60 4.12	.000	0.500 0.852	0.010 0.006

Table 2: Table summarizing results of paired T test as well as an Independent T test (gender differences) and Anova (age group differences on the questions asked to patients.

In the cases where the statistical significance was noted, most times it was noted between age group pairs, 18-20 and 21-23, 18-20 and 23-23, 18-20 and 24-26 and 18-20 and 30-32. The respective p values are tabulated below (Table 3).

Age grouping	18-20 and 21-23	18-20 and 24-26	18-20 and 27-29	18 – 20 and 30-32
Painful (Pretest)	0.032	-	0.003	0.005
Itch (Pre-test)	0.048	0.028	0.015	0.007
Color (Pretest)	0.047	-	0.024	0.020
Color (Post test)	-	0.020	0.010	0.014
Stiffness (Pre-test)	0.017	0.018	0.009	0.002
Stiffness (Post-test)	0.004	0.002	0.001	0.001
Thickness (Pretest)	-	-	-	0.019
Thickness (Posttest)	0.056	0.024	0.005	0.007
Irregular (Pre-test)	0.040	-	-	-
Irregular (post-test)	0.019	0.024	0.010	0.007
Opinion (pre-test)	0.030		0.021	0.005
Opinion (post-test)	0.013	0.011	0.003	0.006

Table 3: Table summarizing results of Tukey test assessing differences noted on age groupings.

4.3.2 Changes noted on the scar - Analysis of the scores (pre and post analysis) of the observer

There was statistical significant differences between the observers' scores. There was however no statistical significant differences noted on gender, while it was noted amongst some age groups as tabulated below (Table 4). The noted changes were also observed physically (Figure 1 & 2).

	Paired T test value	Mode	Mean	Significance	Gender differences (p value	Age group differences (p value)
Pair 1	Vascularity (Pre) Vascularity (Post)	9 5	8.04 4.76	.000	0.264 0.902	0.327 0.957
Pair 2	Pigmentation(Pre) – Pigmentation (Post)	8 4	7.72 4.44	.000	0.559 0.863	0.597 0.992
Pair 3	Thickness (Pre) Thickness(Post)	8 4	7.48 4.24	.000	0.542 0.245	0.557 0.589
Pair 4	Relief (Pre) Relief (Post)	7 4	6.84 4.28	.000	0.988 0.786	0.651 0.790
Pair 5	Pliability (Pre) Pliability (Post)	8 3	7.80 3.40	.000	0.362 0.206	0.464 0.510

Pair 6	Surface Area (Pre) Surface Area (Post)	5 4	6.36 4.20	.000	0.957 0.568	**0.013** 0.538
Pair 7	Overall Opinion (Pre) Overall Opinion (Post)	8 4	7.42 4.28	.000	0.221 0.381	0.406 0.648

Table 4: Table summarizing results of paired T test as well as Independent T test (gender differences) and Anova (age group differences on the scores of the observer.

Tukey test revealed significant differences between the age groups: 18-21 and 21-23 (p value = 0.043) and between 21-23 and 30-32 (p value = 0.032).

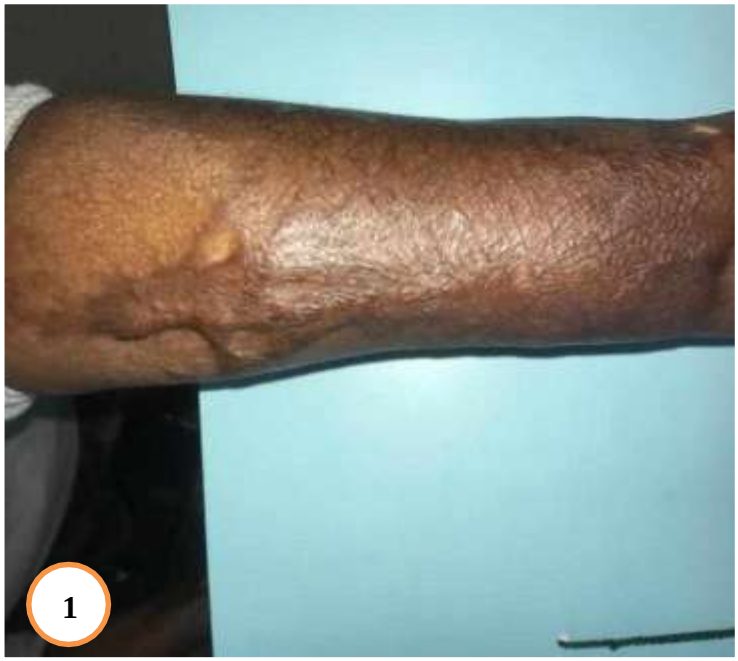


Figure 1: Figure showing hypertrophic scar pre-intervention

Figure 2: Figure showing hypertrophic scar after intervention

4.4 Histological changes noted after AFG administration.

The epidermis was noted to be majorly classified as class 2 on day 0 (50%) and class 3 on day 28 (60%) (p value = 0.034). Similarly, the inflammatory cells were noted to be at grade 1 on day 0 (100%) and grade 3 on day 28 (60%) (p value = 0.001). The vessel density was noted to be at 3 per HPF (66.7%) on day 0 while it was 5 per HPF on day 28 (50%) (p value = 0.020). The vein density was also noted at 3 per HPF (50%) on day 0 and 5 per HPF (75%) on day 28 (p value = 0.012). Collagen bundles were majorly thin (41.7%) on day 0 and thick on day 28 (60%) (p value = 0.011). The fibres were also majorly horizontal (32%) on day 0 and vertical (100%) on day 28 (p value = 0.018). The dermal hyperplasia was majorly at 4 per HPF (25%) and 7 per HPF (25%) on day 0 and 6 (60%) on day 28 (p value = 0.048).

CHAPTER 5: DISCUSSION AND CONCLUSION

For scar treatment, where medical and surgical therapies seem to be ineffective especially in the long term, autologous fat graft has proven to be a new chance to repair tissue damages. Autologous fat grafting has been shown to bear the ability to regenerate and remodel surrounding tissues.

5.1 Demographics

Most of the participants in our study were female by gender and 26 years old. Additionally, the most common cause of scars in both genders was burns (88.3%, 68.4% for males and females respectively). Our findings mirrored that from the Chinese populace where hypertrophic scars were noted mostly among females (Cecilia et al., 2005). In their study, however, most scars were from surgery. Our study however agreed with findings of a review by Lee et al. (2017) where burns were shown to be the major cause of hypertrophic scars in most studies.

5.2 Description of the scar

Our findings on the mean age at presentation was lower than that of (Klinger et al. 2013) in Italy (38.3 years), and in Netherlands (Delavary et al., 2012) (37.4 years), but similar to a study by (David et al. 1995) where younger patients were noted to have more scars owing to constant muscular tension. However, when considering that most scars from our setting were from burns, the findings are discrepant from current literature. This is because it is expected that the most affected age groups by burns are the young and elderly. Children are affected mostly due to their curiosity and desire to experiment which is matched neither by their capacity to understand the potential of danger nor by their ability to respond. In the elderly, their susceptibility arises from age-related deterioration of judgment and coordination, alterations in cognition and balance secondary to medication use, and the pathophysiologic consequences of the physical insults of

injury (Peck et al., 2011). In our case therefore, the reason for the higher number of middle aged patients, presenting with burns associated scars may be due to the high alcohol intake, which has been shown to be the leading cause of burns in this age group (74%) and which was the major cause of burns in our findings. The increased alcohol intake may therefore predispose to increased risk of burns and subsequent hypertrophic scar, mostly among the males. Additionally, alcohol intake has increased due to the mental and socio-economic effects brought about by COVID - 19 (Ramalho et al., 2020).

On the cause of the scars, our findings were similar to current literature in that burns were the commonest cause as demonstrated in a review by (Lee et al. 2017). This might be due to an increase in inter-partner violence, especially for women and increased alcohol intake among males owing to the lockdown and mental health changes brought about by the covid 19 pandemic as mentioned.

The mean age of the scar was >1 year (44%) and the most common scar site was the forearm (16%) and the thigh (16%). Our findings are consistent with literature which suggests that certain anatomical regions such as the deltoid region are more vulnerable to scar formation due to their high skin tension (David et al., 1995).

5.3 Differences on the pre and post intervention scores on patient assessment

5.3.1 Determining change in pain, pruritus and hypertrophic scar appearance -Analysis scores of the patients

Findings of our study showed that there were statistical significant differences between the patients' pre and post intervention scores. There were however no statistical significant differences based on gender, while it was noted amongst different age groups. The differences noted in the pre - and post - intervention scores were similar to those reported by (Klinger et al. 2013), (Bruno et al. 2013) and (Brongo et al. 2012). The changes observed might be due to the healing properties

of fat grafts as noted and subsequent reduction in the associated factors assessed on the POSAS score.

As concerns the age group differences, the younger age group (18-21) reported higher satisfaction as compared to all other age groups. Younger groups reported better scores than the older groups possibly due to their increased perception of their cosmetic appearance as compared to older age groups. As such, it is possible that they were more satisfied with the outcomes. The higher post satisfaction scores noted in our study may be linked to the histology observed pre and post intervention.

5.3.2Differences on the pre and post intervention scores on observer assessment

There were statistical significant differences between the observers' scores with better scores being reported post intervention. Our findings mirrored that of (Klinger et al. 2013). There were no statistical significant differences based on gender, while it was noted amongst the 18-21 and 21-23 (p value = 0.043) and between 21-23 and 30-32 (p value = 0.032). Better scores were recorded in younger groups possibly due to more attention being paid on their cosmetic appearances as compared to older age groups. This might possibly translate to better satisfaction scores as witnessed.

5.4 Histological findings

Histologically, an increase in fibroblasts, connective tissue deposition as well as vascularity was observed. Our findings mirrored that of (Klinger et al. 2013), where he reported improvement in skin elasticity, texture and thickness in three patients with hemifacial hypertrophic scars and keloids secondary to severe burns. In their study, histological examinations by punch biopsies

before and after fat grafting demonstrated new collagen deposition, local hypervascularity and dermal hyperplasia.

The changes noted on histology may be due to the effects of the fat graft cells. They have been postulated to have angiogenic and antiapoptotic properties which have effects on wound healing, soft-tissue restoration and scar remodelling. The precise mechanism by fat graft that leads to tissue improvement is still unclear. These results may be achieved through mesenchymal stem cells rather than adipocyte-derived products, stromal growth factors, hormones, tissue macrophages components, or all these. The exact role of stem cells in the scars release process remains to be determined. Probably, at the basis of tissue remodelling process, there is the local action of cytokines, growth factors, angiogenic factors, enzymes, and cellular component contained in lipoaspirate leading to the formation of the noted new blood vessels with fibrotic tissue remodelling and a new inflammatory response (Klinger et al., 2013).

The improvement in skin elasticity, texture and thickness as mentioned therefore might explain the higher post intervention scores observed in our setting and others as well.

5.6 Limitation of the study

One of the limitations of this study was an issue with long term follow up of the patients as we only followed up the patients for a month.

5.7 Conclusion

General improvement of all parameters confirms autologous fat grafting therapeutic effect, especially in the treatment of hypertrophic scars.

5.8 Recommendations

We recommend conducting the study for a longer period of time so as to observe the effects of autologous fat grafts for a longer period of time. We also recommend a larger sample size so as to obtain more data.

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APPENDICES

APPENDIX I: PERIOPERATIVE DATA COLLECTION SHEET

(Fill out the form and Tick in the applicable/appropriate box **clearly**)

1. Study No…….
2. Age (years): ……..
3. Gender: Male Female
4. Cause of hypertrophic scar

Burns	Trauma
Infection	Surgery

5. Age of Scar

0-3 months	10-12 months
4-6 months	>1 year
6-9 months	

6. Scar site

Arm	Posterior trunk
Forearm	Thigh
Hand	Leg
Thorax	Foot
Abdomen	Scalp
SacraL	

Surface area table

Surface area of HTs	**Amount of AFGs Injected**

Hospital in-patient Number

Study Number

Histological Assessment Parameters

Histological scar assessment parameters will be charted serially at day 0 and 28 as follows.

Diagnostic Criteria	**Results**
Epidermis Morphology	
Inflammatory Cells	
Blood Vessels	
1. Type	
2. Density	
Collagen Bundles	
1. Type	
Dermal Hyperplasia	

POSAS Patient scale

The Patient and Observer Scar Assessment Scale: v2.0/z/EN

Date of examination:

Observer:

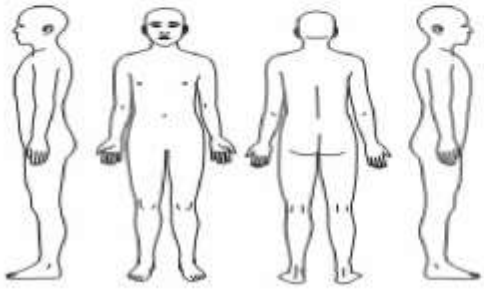
Location:

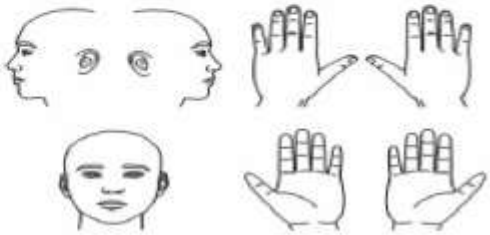
Research / study:

Name of patient:

Date of birth:

Identification number:





1 = no, not at all — yes, very much = 10

	1	2	3	4	5	6	7	8	9	10
HAS THE SCAR BEEN PAINFUL THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○
HAS THE SCAR BEEN ITCHING THE PAST FEW WEEKS?	○	○	○	○	○	○	○	○	○	○

1 = no, as normal skin — yes, very different = 10

	1	2	3	4	5	6	7	8	9	10
IS THE SCAR COLOR DIFFERENT FROM THE COLOR OF YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE STIFFNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE THICKNESS OF THE SCAR DIFFERENT FROM YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○
IS THE SCAR MORE IRREGULAR THAN YOUR NORMAL SKIN AT PRESENT?	○	○	○	○	○	○	○	○	○	○

1 = as normal skin — very different = 10

	1	2	3	4	5	6	7	8	9	10
WHAT IS YOUR OVERALL OPINION OF THE SCAR COMPARED TO NORMAL SKIN?	○	○	○	○	○	○	○	○	○	○

[illegible]

POSAS Observer scale

The Patient and Observer Scar Assessment Scale v 2.0 / EN

Date of examination:

Observer:

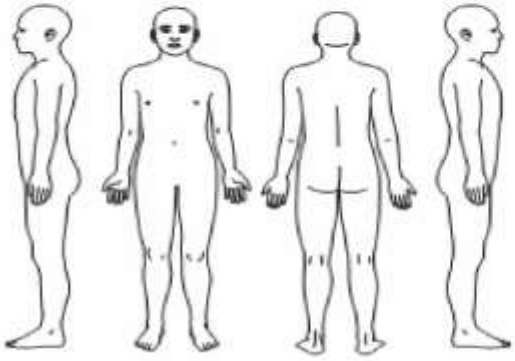
Location:

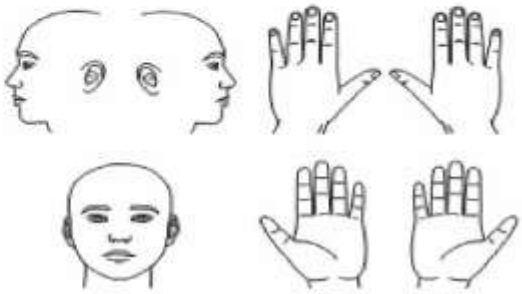
Research / study:

Name of patient:

Date of birth:

Identification number:





	1 = normal skin								worst scar imaginable = 10	
PARAMETER	1	2	3	4	5	6	7	8	9	10	**CATEGORY**
VASCULARITY	○	○	○	○	○	○	○	○	○	○	PALE | PINK | RED | PURPLE | MIX
PIGMENTATION	○	○	○	○	○	○	○	○	○	○	HYPO | HYPER | MIX
THICKNESS	○	○	○	○	○	○	○	○	○	○	THICKER | THINNER
RELIEF	○	○	○	○	○	○	○	○	○	○	MORE | LESS | MIX
PLIABILITY	○	○	○	○	○	○	○	○	○	○	SUPPLE | STIFF | MIX
SURFACE AREA	○	○	○	○	○	○	○	○	○	○	EXPANSION | CONTRACTION | MIX
OVERALL OPINION	○	○	○	○	○	○	○	○	○	○	

Explanation

The observer scale of the POSAS consists of six items (vascularity, pigmentation, thickness, relief, pliability and surface area).
All items are scored on a scale ranging from 1 ("like normal skin") to 10 ("worst scar imaginable").
The sum of the six items results in a total score of the POSAS observer scale. Categories boxes are added for each item. Furthermore, an overall opinion is scored on a scale ranging from 1 to 10.
All parameters should preferably be compared to normal skin on a comparable anatomic location.

Explanatory notes on the items:

- **VASCULARITY** Presence of vessels in scar tissue assessed by the amount of redness, tested by the amount of blood return after blanching with a piece of Plexiglas
- **PIGMENTATION** Brownish coloration of the scar by pigment (melanin); apply Plexiglas to the skin with moderate pressure to eliminate the effect of vascularity
- **THICKNESS** Average distance between the subcutical-dermal border and the epidermal surface of the scar
- **RELIEF** The extent to which surface irregularities are present (preferably compared with adjacent normal skin)
- **PLIABILITY** Suppleness of the scar tested by wrinkling the scar between the thumb and index finger
- **SURFACE AREA** Surface area of the scar in relation to the original wound area

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