Intralesional Cryotherapy to treat exophytic keloids: The Universitas Hospital Bloemfontein Experience.

ABSTRACT

It has been widely reported in literature that keloids, by nature, tend to respond poorly to a wide range of different treatment modalities, in this study we focus mainly on Intralesional Cryotherapy as a promising modality of treatment in the hope of standardizing treatment and prevent recurrences in prone individuals.

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MMED (DERMATOLOGY)

Intralesional Cryotherapy to treat exophytic keloids: The Universitas Hospital Bloemfontein Experience.

By

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Submitted in partial fulfilment of the requirements for the degree

Masters' in Medicine

In the

Department of Dermatology

FACULTY OF HEALTH SCIENCES

UNIVERSITY OF FREE STATE

BLOEMFONTEIN

Supervisors:

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ABBREVIATIONS

ACE: Angiotensin-Converting Enzyme

COX: Cyclooxygenase

H1: Histamine type 1

NSAIDs: Non-Steroidal Anti-inflammatory Drugs

PGE2: Prostaglandin E2

TGF-1: Transforming Growth Factor -1

TNF: Tumor Necrosis Factor.

Contents

ACKNOWLEDGEMENT

My deepest gratitude goes to the following individuals for their contribution towards this project's success:

- Prof's Ncoza Dlova, Anisa Mosam and Dr Frans Maruma- For their constant and unwavering support during the study.
- Mr C. Van Rooyen (Biostatistics) – For his open-door policy and professionalism.

DECLARATION

1. I, Lehlohonolo Makhakhe, declare that the Master's Degree research dissertation that I herewith submit for the MMED degree qualification in Dermatology at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher learning.
2. I, Lehlohonolo Makhakhe, hereby declare that I am aware that the copyright is vested in the University of the Free State.
3. I, Lehlohonolo Makhakhe, hereby declare that all royalties as regards intellectual property that was developed during the course of and in connection with the study at the University of the Free State will accrue to the University.
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5. The study was approved by the Ethics Committee of the Faculty of Health Science of University of Free State.
6. Informed consents were obtained from all the patients included in this study.
7. All the clinical investigations were conducted in accordance with the Declaration of Helsinki principles.

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Lehlohonolo Makhakhe Date

ABSTRACT

The skin is composed of labile cells, which to some extent can regenerate, but in cases of deep and significant damage, healing occurs by secondary intention with subsequent scar formation. Keloids are wound scars that grow beyond the original wound site and are characterized by an overabundance of collagen at the injured site, in a craw like fashion that distinguish them from hypertrophic scars. They result from dermal injury, mostly from trauma, infection and burns, and at times, they occur spontaneously. Keloids commonly occur on the earlobes, back, shoulders and chest and can be a major source of embarrassment and anxiety. These scars can also be painful and itchy. The prevalence of keloids is higher among patients with darker skin especially in Africans and Asians. Treatment options for these scars vary, however, a high recurrence rate after such treatments have been reported. Some modalities have sporadically yielded better outcomes, more so when used in combinations. It is therefore important to find a treatment that is safe, non-toxic and with reduced chances of recurrence in affected individuals. Intralesional cryotherapy is a treatment for keloid scars in which liquid Nitrogen is used to freeze the scar from inside.

This study therefore sought to treat exophytic keloids with intralesional liquid Nitrogen (Cryotherapy) as a deep-freeze from the core of the keloid under local anaesthetic. This adds a newer method of keloid management contributing towards standardizing exophytic keloid management. A prospective case series was conducted among twelve patients attending the Dermatology outpatient department, at Universitas Hospital in Bloemfontein from 1 August 2016 to 01 March 2017. These patients were seen at the initial visit, then at six weeks and six months respectively.

All the subjects were Africans, with 7 (58.3%) being female and 5 (41.7%) male. A third of the patients (4) (33.3%) had more than one site of involvement. Significant reduction in the exophytic keloidal mass post deep-freezing, irrespective of the keloid area, duration, gender and cause was observed among these patients. Two-thirds of these patients were either satisfied or very satisfied with the clinical outcome of the scar at six months.

The use of intralesional cryotherapy for exophytic keloids has potential to become the main modality of treatment in future. Our study had some limitations including a small

sample size, relatively high rate of patients lost to follow up (33.3%) and some unanticipated technical difficulties.

Conflict of interest: None declared

Funding source: None

Key words: Keloids, intralesional cryotherapy

CHAPTER 1

1.0 INTRODUCTION

1.1 Background

The skin is composed of labile cells, which are able to regenerate, but in cases of deep and significant damage, healing occurs by secondary intention with subsequent scar formation. Keloids are characterized by an abundance of collagen at the injured site, in a craw like fashion that distinguish them from hypertrophic scars. They commonly occur on the earlobes, back, shoulders and chest and can be a major source of embarrassment and anxiety. In addition, keloids can be painful and itchy as well and for these reasons, treatment becomes important. Although they can occur spontaneously, keloids largely result from dermal injury mostly from trauma, infection and burns.

Keloids are benign cutaneous lesions that are produced by uncontrolled synthesis and deposition of dermal collagen in predisposed individuals. They commonly occur in the third decade of life but are often found prior to that. Keloids are more common in people of African descent and tend to occur on specific sites on the body, such as the earlobes post piercing, chest, back and shoulders[1].

Apart from occasionally causing itching and local pain, they also cause anxiety and embarrassing disfigurement. Although the mechanisms leading to keloid formation are not yet fully understood, they are a very common occurrence in the general population with very limited data on gender predilection. Younger females have a higher incidence of keloids, because of ear piercing, and the elderly are also at higher risk with sternal keloids due to higher incidence of cardiac surgery[i].

Unlike hypertrophic scars, keloids tend to extend beyond the wound margin and are generally gradual in onset. They seldom resolve spontaneously with very poor response to different forms of treatment. Keloids are uncommon in young children and the elderly, and they are often associated with a degree of family history. It is suggested that familial keloids have an autosomal dominant mode of inheritance with incomplete penetrance and variable expression. Treatment of keloids by cryotherapy leads to cellular hypoxia of individual and targeted fibrotic cells.

1.2 Treatment options for Keloids

The treatment of keloids usually entails surgical excision with adjuvant post-surgical radiation. Surgical excision without adjuvant therapy generally worsens the outcome and recurrence rates are also higher. After surgery, adjuvant drugs that can be used immediately after excision include verapamil, methotrexate, colchicine, zinc and imiquimod.

Other options may include external cryotherapy, topical silicone, pressure application, intralesional bleomycin, Interferon, 5-FluoroUracil (5-FU) and popularly intralesional corticosteroids, imiquimod and laser. Table 1.1 lists the currently available treatment options for hypertrophic scars and keloids. However, in the treatment of keloids, single treatments or combination therapy are often used, resulting in variable outcomes and sometimes recurrences[ii].

Table 1.1: Average Results of Studies Using Various Treatments for Hypertrophic Scars and Keloids[iii]

Treatment	Mean ± SD (95% CI)†	Mean Strength of Study‡
Bleomycin sulphate	0.88 ± 0.12 (0.46 to 1.30)	2.00
Fluorouracil	0.70 ± 0.08 (0.28 to 1.11)	2.30
Triamcinolone acetonide	0.71 ± 0.15 (0.29 to 1.13)	2.75
Excision	0.44 ± 0.16 (0.02 to 0.85)	1.50
Radiation	0.57 ± 0.17 (0.15 to 0.99)	2.00
Interferon gamma	0.38 ± 0.18 (−0.04 to 0.79)	2.00
Pulsed-dye laser +Triamcinolone	0.72 ± 0.29 (0.30 to 1.14)	2.25
Carbon dioxide laser	0.08 ± 0.05 (−0.34 to 0.50)	1.50
Nd: YAG laser + Triamcinolone	0.71 ± 0.17 (0.29 to 1.12)	1.00
Cryotherapy	0.68 ± 0.09 (0.26 to 1.09)	2.00
Pressure	0.73 ± 0.00 (0.31 to 1.15)	1.00
Silicone gel sheeting	0.53 ± 0.11 (0.11 to 0.94)	2.50
Silicone cushion	0.82 ± 0.16 (0.40 to 1.23)	2.00
Pulsed-dye laser	0.70 ± 0.00 (0.28 to 1.12)	2.25
Triamcinolone acetonide	1.00 ± 0.00 (0.58 to 1.42)	1.00

Excision + Triamcinolone acetonide	0.62 ± 0.30 (0.20 to 1.04	2.00
Excision + Radiation	0.68 ± 0.11 (0.26 to 1.10)	1.80
Fluorouracil + Triamcinolone acetonide	0.70 ± 0.00 (0.28 to 1.12)	3.00
Excision + Pressure (magnetic disks)	0.99 ± 0.00 (0.57 to 1.41)	2.00
Excision + Colchicine	0.69 ± 0.00 (0.27 to 1.11)	3.00
Excision + Imiquimod	1.00 ± 0.00 (0.58 to 1.42)	2.00
Excision + Verapamil hydrochloride	0.78 ± 0.08 (0.36 to 1.20)	2.00
Excision + Verapamil hydrochloride silicone	0.73 ± 0.00 (0.31 to 1.15)	2.00
Carbon dioxide laser + Silicone	0.88 ± 0.00 (0.46 to 1.29)	3.00
Excision + Silicone	0.44 ± 0.49 (0.02 to 0.86)	2.00
Excision + Interferon alfa-2b	0.81 ± 0.00 (0.39 to 1.23)	2.00
Excision + Botulinum toxin	1.00 ± 0.00 (0.58 to 1.42)	1.00

Abbreviation: CI, confidence interval. *No treatment reached statistical significance (P.05). †Data represent percentage improved or percentage without recurrence, depending on the measure reported. ‡The mean strength of the studies was calculated based on a scale from 1 to 3, with 3 being the most consistent, patient-oriented evidence.

A few more poorly documented treatment modalities exists for keloids, however, they utilize the concept of prevention as form of treatment in genetically susceptible individuals. Evidence from recent years has shown variable success with all these modalities used either alone or in combination. Reports of recurrences and individual treatment side effects have also been implicated as obstacles towards a standard treatment protocol.

Some of the complexities in standardizing keloid treatment include:

- Age of the patient
- Area of treatment
- Previous specific treatment
- Infection before and after surgery
- Tension of sutures

- Scars made not following Langers lines
- Vascularity of the keloid
- Keloid versus hypertrophic scar
- Age of the keloid
- Difference in surgical excision techniques.
- Duration of adjuvant treatments
- Different wavelengths with laser
- Duration of follow-ups to exclude recurrences.

Vascular scars tend to do better with freezing. Recurrences tend to increase as time lapses from initial intervention and older keloids tend to be recalcitrant to most treatment modalities due to the aged collagen deposits[iv].

Table 1.2: Various Treatments and the Proposed Mechanisms by Which They Affect Wound Healing and Scar Formation[v].

Treatment	**Mechanism of Action**	**Source**
Excision	Surgical removal of scar	Conway *et al*., 1960
Radiation	Apoptosis of proliferating cells in scar tissue	Watters, 1999
Laser	Induces tissue hypoxia	Alster and Williams, 1995
Cryotherapy	Induces vascular damage	Newsome *et al*., 2006
Triamcinolone acetonide	Inhibits 2-macroblobulin	McCoy *et al*., 1980
Pressure garments	Decreases macroglobulins	Kelly, 2004; Baur *et al*., 1976
Salicylic acid	Inhibits nuclear factor	Edriss and Mueak, 2005
Silicon gel dressing	Increased pressure on wound	Newsome *et al*., 2006
Retinoic acid	Inhibitory effect on DNA synthesis	de Limpens, 1980

Tacrolimus	Inhibits TNF	Kim *et al*., 2001
Imiquimod	Stimulates immune pathways	Atiyeh *et al*., 2005
Antioxidants	Inhibits scar fibroblast proliferation	Phan *et al.*, 2004
Calcipotriol	Inhibits nuclear factor	Mueak, 2005
Zinc	stimulates collagenase	Soderberg *et al*., 1982
Calcium channel blockers	Fibroblast gene expression	Mueak, 2005
Tamoxifen citrate	Decreases the concentration of TGF-1	Mikulec *et al*., 2001
Fluorouracil	Inhibits fibroblast proliferation	Fitzpatrick, 1999
Bleomycin sulphate	Inhibits fibroblasts	Hendricks *et al*., 1993
Interferon	Inhibits collagen synthesis	Jimenez *et al*., 1984
Mitomycin C	Inhibits fibroblast proliferation	Lee, 1994
Botulinum	Toxin Immobilization of surrounding tissues	Gassner, 2003
Silver sulfadiazine	Reduction of bacterial burden	Cho Lee *et al*., 2005
Tranilast	Reduces the stimulatory effect of TGF	Burrell, 2005
Pentoxifylline	Modulates dermal fibroblast	Isseroff, 1993
Hyaluronidase	Decreases inappropriately high concentrations of hyaluronic acid present in hypertrophic scars. It also decreases interstitial fluid viscosity and increase tissue permeability.	Loladze *et al*., 2005
ACE inhibitors	Attenuates scar tissue metabolic activity	Weber, 2000

Relaxin	Modulates synthesis collagen	Amento, 1990
Quercetin	Inhibits proliferation of fibroblasts	Kelly, 2004
Dinoprostone	Restores normal wound repair	Kelly, 2004
Colchicine	Inhibits collagen synthesis	Peacock, 1981
Antihistamines	Blocks H1; inhibits collagen synthesis	Edriss, 2005
D-penicillamine	Inhibits collagen cross-linking	Schorn *et al*., 1979
NSAIDs	Inhibits Nuclear Factor B and / or COX activity	Schorn *et al*., 1979

1.3 Aim

This study therefore aimed to evaluate intralesional cryotherapy as a treatment for exophytic keloids among patients attending the Universitas Academic Hospital, Bloemfontein, Free State Province, South Africa.

1.3.1 Objective

- ✓ To evaluate intralesional deep freezing as a modality of treatment using liquid Nitrogen among African patients seen at Universitas Academic Hospital in a specified preiod.

CHAPTER 2

2.0 METHODOLOGY

2.1 Study Design

A prospective case series was conducted utilizing patients recruited from the Dermatology outpatient clinic of the Universitas Academic Hospital in Bloemfontein, Free State Province, South Africa from 1 August 2016 to 01 March 2017.

2.2 Study setting and sampling

The study was conducted at the Dermatology outpatient clinic of the Universitas Academic Hospital in Bloemfontein, Free State Province, South Africa. The sample size included all the new and follow up patients attending the Dermatology outpatient clinic who were diagnosed with exophytic keloids and consented to the study in writing.

2.3 Inclusion and Exclusion criteria

2.3.1 Inclusion criteria

- The study included all patients who were 12 years and older with exophytic keloids and were seen during the study period.
- The keloids had to be sessile enough to allow for the insertion of the treatment probe.

2.3.2 Exclusion criteria

- All patients with hypertrophic scars
- All keloids (Large multi-lobulated keloids) that were unable to admit the cryo-probe (Figure: 2.1).

Figure;2.1 demonstrates two types of keloids. The keloids on the upper right shoulder, large and multi-lobulated are not suitable for the Cryotherapy probe. The second keloid (Lateral right mid-arm) was ideal for our study, dome shaped, exophytic and unilobular.

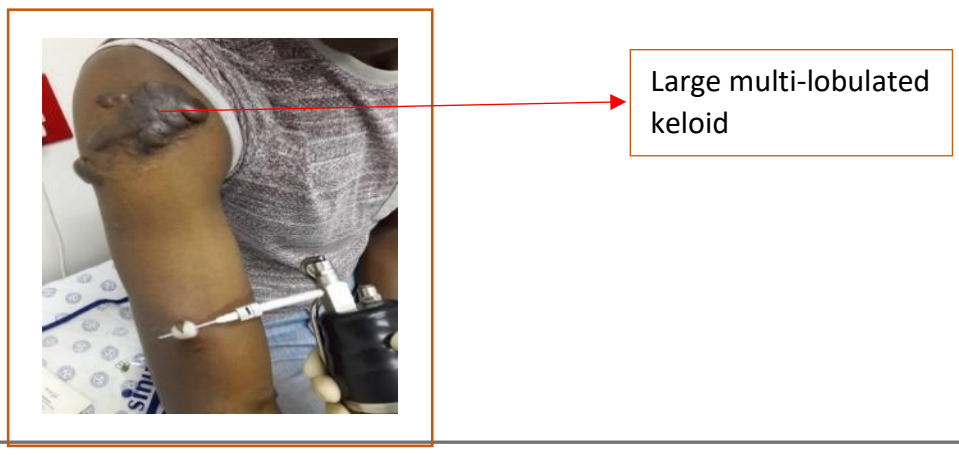

Figure 2.1: Types of keloids

2.4 Assessment of outcome

Assessment of outcome was done through a baseline initial measurement of each keloid's dimensional size, follow-ups at six weeks and at six months respectively. Due to the multi-dimensional nature of the keloids post intralesional cryotherapy, it became impossible to quantify the clinical outcome via measurements. Instead, we relied on pictorial images at baseline, six weeks and six months respectively. As an additional measure, a patient satisfaction scale was included formulated by the author.

2.5 Ethical considerations

The research protocol for this study was submitted to the Ethics Committee, Faculty of Health Sciences, University of the Free State for approval prior to commencement of the study (HSREC NR 56/2016). Permission to conduct the study and identify suitable patients was also granted by the Head of the department of Dermatology. A consent form was given to the participants in their preferred language. Considering the demographics in Free State, consent forms were offered in three languages, namely, Sesotho, English and Afrikaans. Explanations were offered to any patients who needed further clarification in cases of illiteracy.

This study was conducted with standard professionalism in accordance to the Helsinki Declaration. The study involved an invasive procedure, conducted with caution under sterile conditions to prevent infection. Due to the invasive nature of Intralesional liquid Nitrogen, bleeding was also anticipated, however, every effort was taken to minimise complications.

2.6 Procedural analysis

2.6.1 Patient care

The first step is to identify ideal (exophytic) keloids from hypertrophic scars. An initial diagnosis and correct identification of the specific type of keloid is extremely important. Most keloids tend to be mostly exophytic, but many have a mild endophytic component

as well. The patient will then be evaluated for signs of depression or anxiety disorder as a result of these lesions.

2.6.2 Materials used

Small needle (29G) to localize, large caliber needle (18-20G) for Cryo cylinder admission, liquid nitrogen, alcohol swabs, EMLA topical anaesthetics, lignocaine 2% solution, liquid nitrogen cylinder, gauze and bandage.

2.6.3 Procedure

The procedure was performed only once during the initial visit in a sterile environment. The 29G needle was used to localize the base of the keloid to minimize the normal tissue trauma. EMLA topical anaesthetic was used to numb the site prior to deeper numbing by lignocaine and the larger caliber needle (18-20G) for the actual procedure facilitates a quicker freezing time. It is important to opt for a large bore needle during the procedure. This hastens the procedure, although it leads to more bleeding once the frozen tissue thaws. A well-calculated balance was put in place not to deep freeze the normal adjacent tissue while the endophytic component was also not neglected in terms of treatment with intralesional cryotherapy.

Although the keloid itself tends to be painless (compacted collagen), however, most keloids have a slight endophytic component which can be painful when deeply frozen. A local analgesic (1-2% lignocaine) was therefore used after freezing the keloids. During the procedure, the centre of the keloid was aimed for when the needle was inserted (this leads to a better cosmetic outcome). The end of the needle should go through the keloidal mass all the way out to the other side. Any injury to the normal tissue may potentially cause a hypertrophic scar/keloid to that area eventually, and this must be minimised. Excessive bleeding post cryotherapy is normal, and the patients were adequatetly counselled and reassured. Manual compression for at least 30 minutes to an hour was performed on each patient after the procedure. An antiseptic was used to clean up the area after the procedure. Extra gauzes were given to each patient after the procedure as excessive bleeding always occurs once the frozen tissue thaws. Analgesics and antihistamines were prescribed on a need to basis to the patient, especially during the six-week period post intralesional cryotherapy.

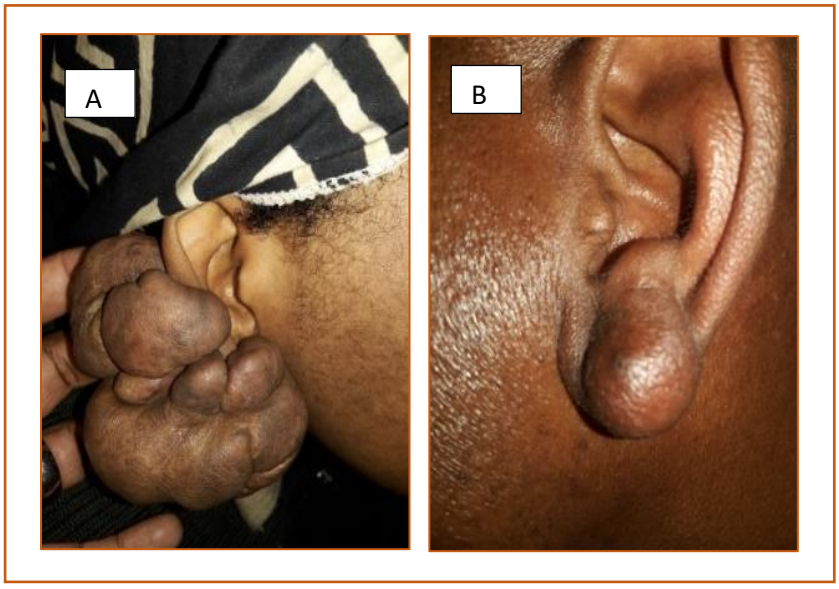

Figure 2.2: A 22 year old African female with a massive, multilobular keloidal mass not ideal for intralesional cryotherapy. B: Patient referred with a diagnosis of earlobe keloid but clinical exam revealed that its an epidermoid cyst which was promptly excised.

It is important to note that only one patient had a family history of keloids and only one patient had actively sought treatment in the past. Figure 2.2 A presents a 22-year-old who was unfortunately not suitable for the study due to the size and multilobular nature of the keloid. She presented with a history of two previous surgical excisions, but the keloid recurred and became bigger each time. She was referred to plastic surgery for re-excision and imiquimod application post- surgery as she would not be suitable for our study owing to the multilobular nature of the mass.

For the actual procedure, a large bore needle is the most preferred because it facilitates a quicker freezing time before the standard cryotherapy bottle freezes over. However, this leads to more bleeding once the ice melts. Smaller bore needles result in extremely slow conduction of ice from the needle to the keloidal tissue.

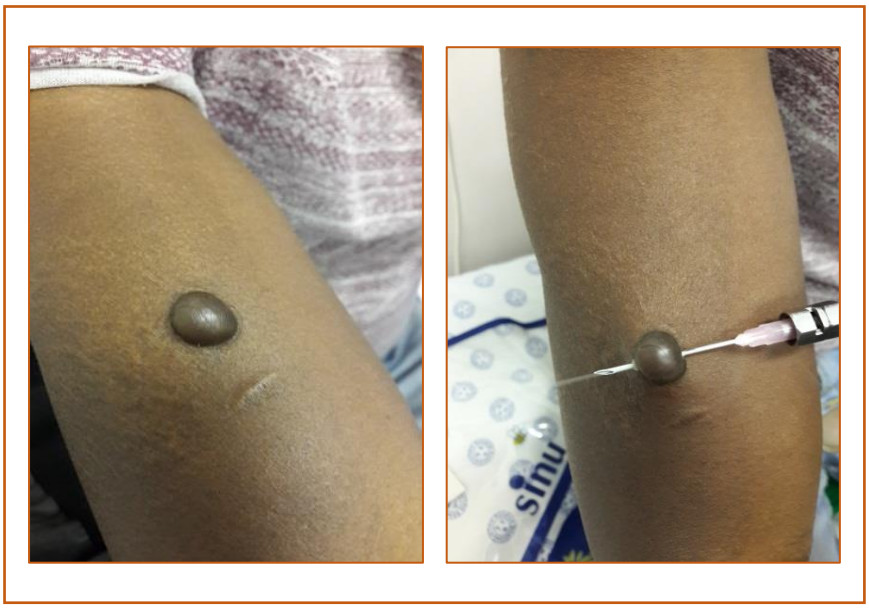

Figure 2.3: Ideal keloids for cryotherapy. Note the needle placed at the centre to ensure symmetry. Pictures taken on Day 0.

The figure above demonstrates a keloid ideal for intralesional cryotherapy. Furthermore, the placement of the needle ensures symmetry and even distribution of the liquid nitrogen during the treatment.

Sequential and pictorial representation of the step-by-step procedure utilized during intralesional cryotherapy treatment is depicted in figure 2.4. The needle was inserted at the center of the keloid to ensure even distribution of the liquid nitrogen. After the keloid was completely frozen, the needle was removed. As anticipated bleeding occurred from the keloid when the freezing melted. The area was aseptically cleaned with alcohol swabs, later dressed in a loose bandage to prevent infection. Care was taken to ensure the bandage was not too tight, to prevent further trauma in an already keloid prone site.

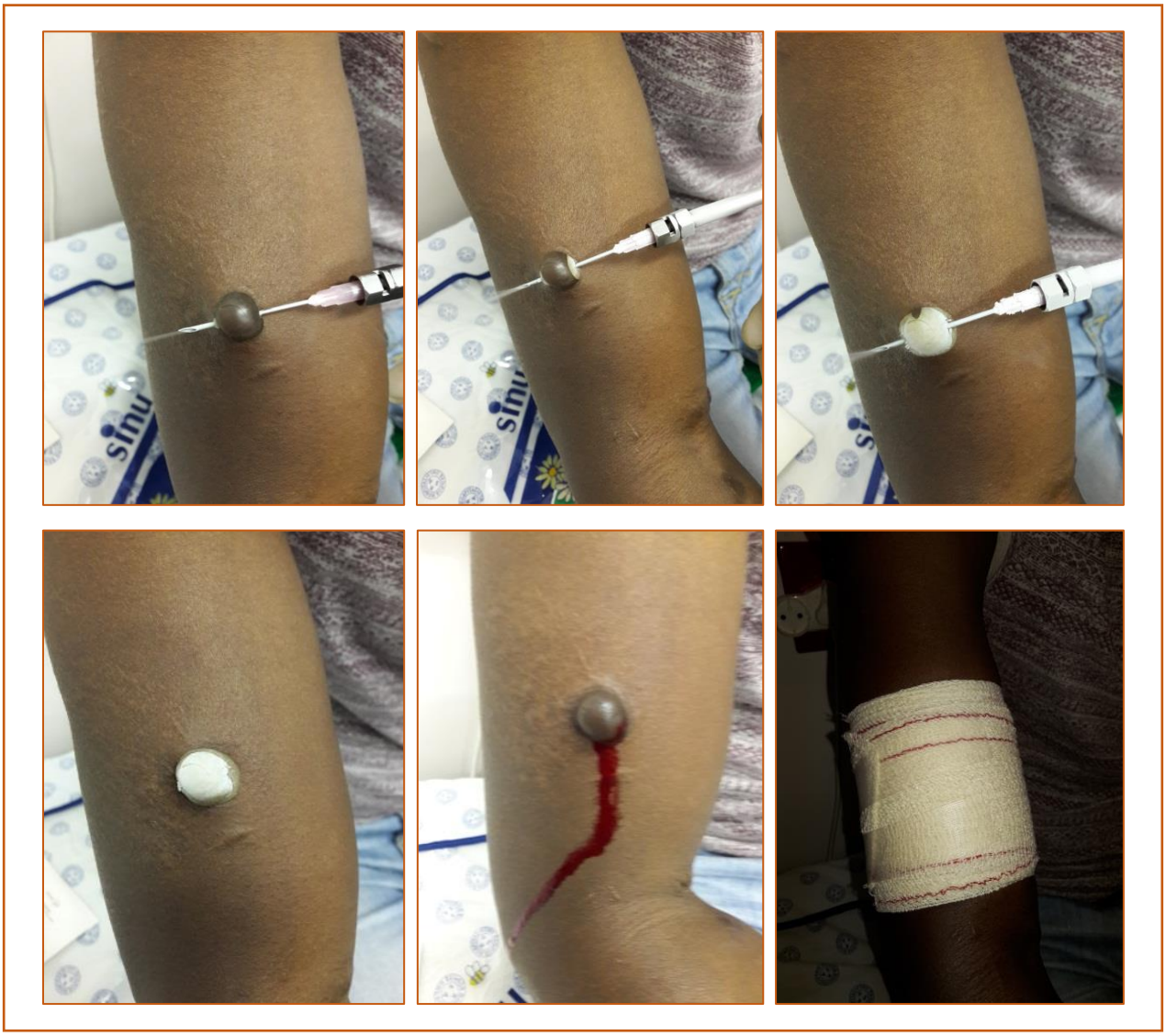

Figure 2.4: Chronology of intralesional cryotherapy treatment of same patient in 4.3 from deep-freezing to bleeding, as a result of the melting.

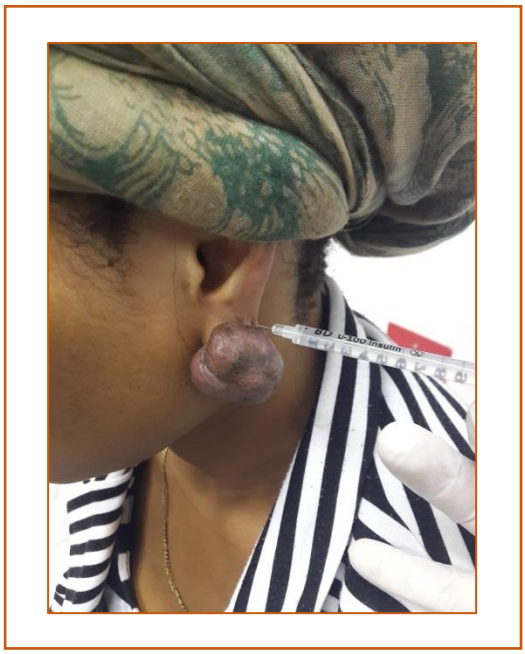

Figure 2.5: Note the usage of an Insulin needle (29G) to minimise further skin trauma in a high-risk individual and at a high-risk area. It may have been even better to apply EMLA cream only to numb the adjacent sites.

CHAPTER 3

3.0 RESULTS AND DISCUSSION

3.1 Demographics

Table 3.1 gives an overview of the demographics and clinical history of the participants. Twelve participants were recruited for this study and all were Africans, attending the Dermatology outpatient at Universitas Hospital in Bloemfontein. Of these, 7 (58.3%) were female and 5 (41.7%) were male. Participants ages ranged from 14 to 60 years (mean age was 26.8 years). The age of the keloids treated ranged from 10 months to 50 years (mean age in months was 85.3). Of the total number, 6 had symptom of itch, 1 patient had pain, 1 had both itching and pain and the rest (4) had no symptoms. Only one patient had a positive family history of Keloids.

Four subjects had more than one area of involvement, however, only one keloid per patient was allowed and subjected to treatment in the study. Nine (75%) of the 12 patients had ear lobe involvement, and of those, 8 (88.9%) were due to ear piercing and 1 (11.1%) was due to contact allergy to nickel. The cause of keloids in the remaining patients were acne vulgaris 1 (0.83%) trauma was the cause in 2 (1.66%). 1 (0.83%) patient had an arthropod bite related keloid, but a more cosmetically worrying keloid secondary due to ear piercing.

Only one subject had a positive family history, admitting that a distant relative also suffered from keloids. 2 (1.66%) patients had comorbidities (60-year-old female with diabetes mellitus and hypertension and a 30-year-old male with HIV infection). Both patients with chronic ailments were on treatment and well controlled. Post screening none of the patients displayed any underlying primary or secondary psychological affectation, although 4 admitted to feeling self-conscious due to keloids.

It is worth noting that although 5 patients had more than one site of involvement, (Figure 3.1), only one keloid per patient was treated as part of the study.

Table 3.1: Demographics and Characteristics of study participants

Age (years)	Gender	Previous Treatment	Duration (months)	Symptom	Co-Morbidities	Family History	Other Sites Involved
17	F	No	48	None	None	None	N
30	F	No	24	Occasional itching.	None	None	N
17	M	No	60	None	None	Yes	Y
14	M	No	24	None	None	None	Y
37	F	No	24	Itching.	None	None	N
17	M	No	48	Pain, itch	None	None	N
23	F	No	24	None	None	None	Y
30	M	No	60	Itch	HIV+	None	Y
35	M	No	36	Itch	None	None	Y
60	F	No	600	Occasional itching	Hypertension and Diabetes	None	N
15	F	No	36	Pain	None	None	N
27	F	No	10	Itch.	None	None	N

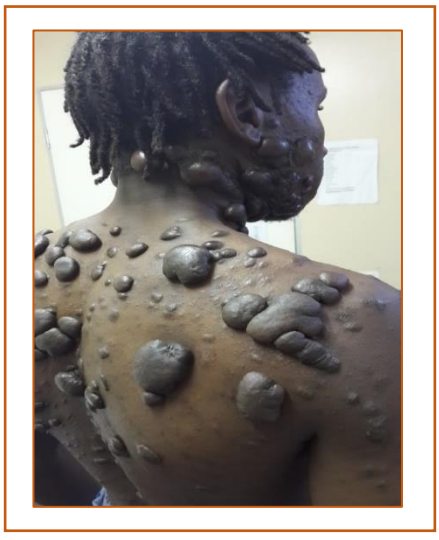

Figure 3.1 Multiple Keloids secondary to previous Acne Vulgaris.

3.2 Area of involvement chart

The area of involvement of the keloids is shown in Figure 3.2. Of the 12 patients recruited in this study, an overwhelming majority of 9 (75%) of cases were found to have ear lobe involvement, 4 (33%) of which had both ears affected. 2 patients (16.7%) had keloids on other body areas.

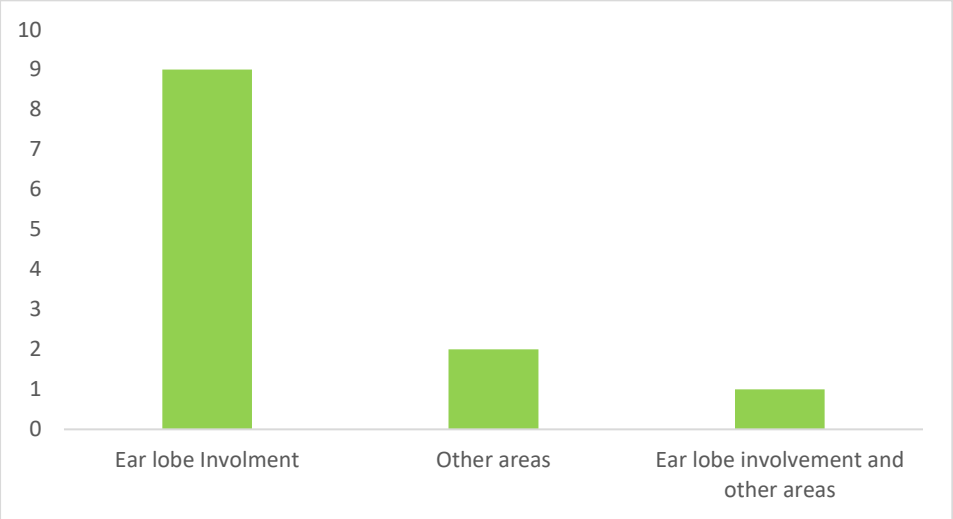

Figure 3.2: Area of Involvement

3.3 Causes of keloids

Majority of the keloids were caused by ear piercing (66.7%), followed by trauma (16.7%). Other causes include arthropod bite, allergic reactions and acne vulgaris (Figure 3.3).

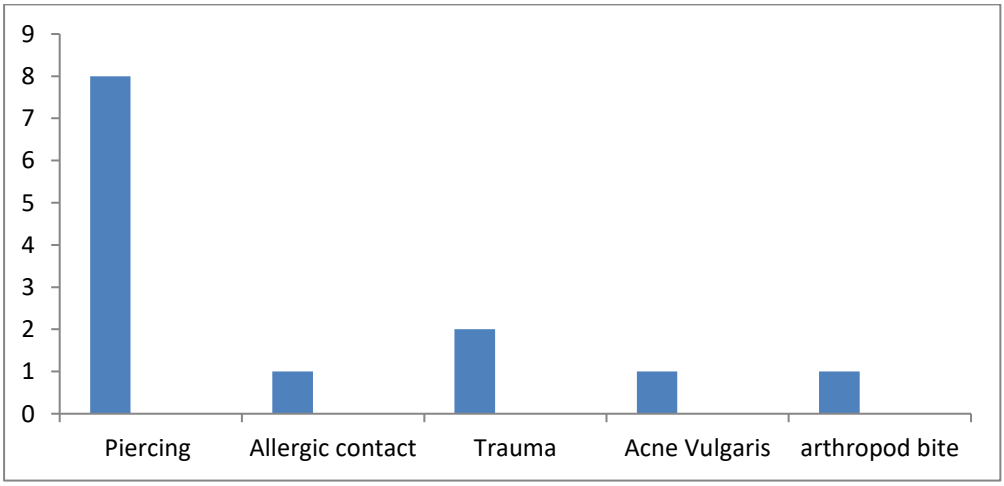

Figure 3.3: Various causes of keloids

3.4 Patient Satisfaction scale

The results indicate that the majority of respondents were either satisfied or very satisfied with the clinical outcome of the treatment at six months follow up. A mean average of 80% at 6 months was observed. Bigger keloids and those of longer duration showed poorer responses compared to smaller keloids less than 2 years duration, 2 patients were lost to follow up and were not included in the scale.

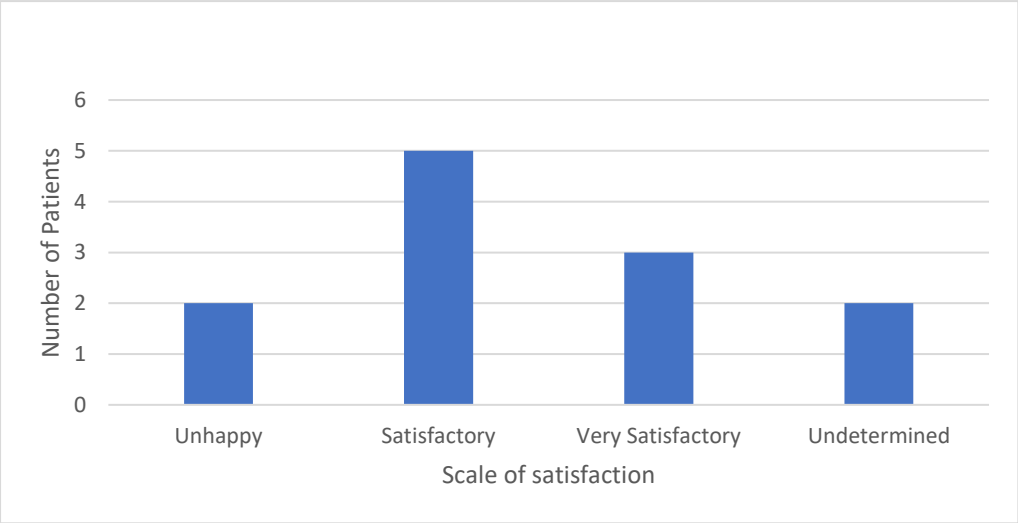

Figure 3.4: Patient satisfaction scale

3.5 Post-treatment outcomes

Figure 3.5 demonstrates complete removal of keloid describe site by intralesional cryotherapy. The resultant post cryotherapy depigmentation and hyperpigmentation of the keloid resolved at 6 weeks and at 6 months respectively. Figure 3.5 shows more than a 50% reduction in the keloid size at 6 months post-treatment.

The percentage reduction in keloid size post-treatment for all patients is shown in Table 3.2. A significant amount of 10 (83.3%) patients had more than 60% keloid reduction at 6 weeks post-treatment, 2 (16.6%) of which presented with complete clearance. At 6 months post-treatment, the outcomes remained the same for all patients. Only 2 (16.6%) patients were lost to follow-up at the 6 months review.

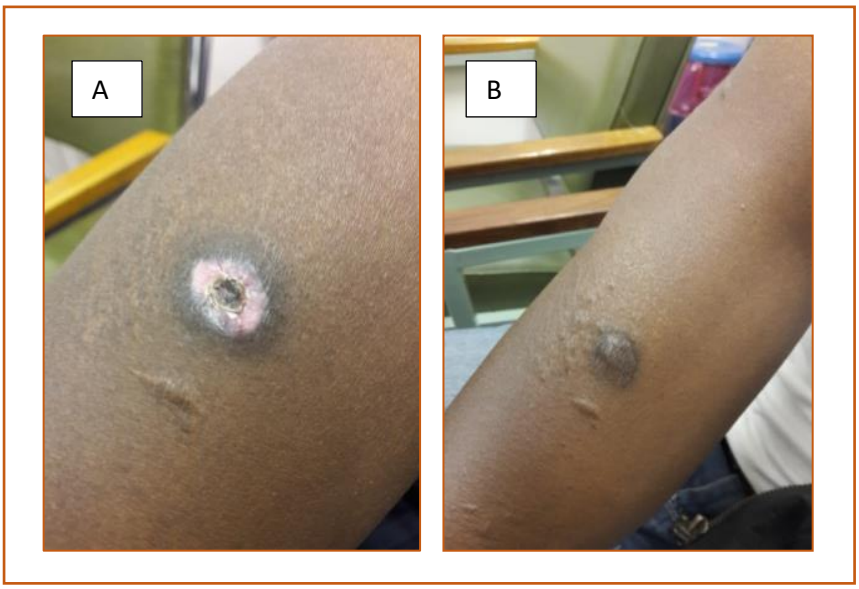

Figure 3.5: Post-treatment keloid on the left arm at A: 6 weeks and B: 6 months

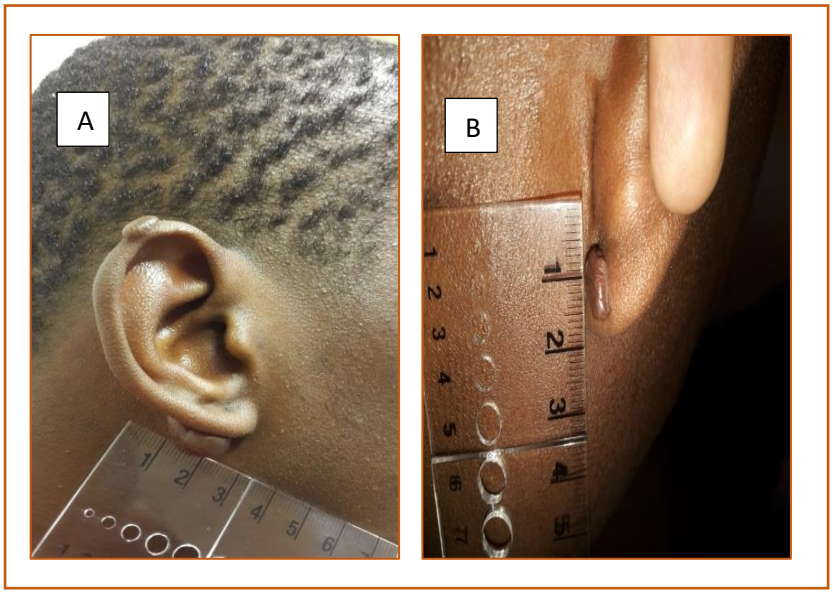

Figure 3.6: a: Keloid initially measuring 1.8cm X 1.2 cm, and b: Keloid measuring 0.7cm X 0.4cm at six months post intralesional deep freezing.

Table 3.2: Post-treatment outcomes

Initial Size (cm)	6/52 Follow Up	6/12 Follow Up
1.1 X 1.0	90% Reduction	Same
3.0 X 1.8	70% Reduction	Lost to follow up
3.2 X 3.5	40% Reduction	Same
2.9 X 2.1	60% Reduction	Same
3.2 X 1.0	60% Reduction	Lost to follow up
1.8 X 1.2	100% reduction	Same
1.0 X 1.0	95% Reduction	Same
1.2 X 1.1	95% Reduction	Same
1.0 X1.2	100% Reduction	Same
5.0 X 2.5	30% Reduction	Same
1.8 X 1.2	75% Reduction	Same
3.1 X 2.2	70% Reduction.	Same

3.6 Discussion

It has been extensively reported in the literature that keloids, by nature, tend to respond poorly to a wide range of different treatment modalities. There have been very few reported cases documenting spontaneous keloid resolution. Some of the symptoms and complications of keloids include local irritation, itching and occasionally pain. Above symptoms tend to be more pronounced with newer and growing keloids. Apart from the symptoms, keloids have been shown to affect the quality of life, causing considerable embarrassment and self-consciousness of those afflicted[vi].

Keloids are benign dermal fibroproliferative tumors with no malignant potential. The first description of abnormal scar formation in the form of keloids was recorded by Smith papyrus regarding surgical techniques in Egypt around 1700 BC. The term *keloid*, meaning "crab claw," was first coined by Alibert in 1806, in an attempt to illustrate the way the lesions expand laterally from the original scar into normal

tissue. Since that time, physicians have attempted to characterize normal scars, hypertrophic scars, and keloids.

Keloids are found only in humans and occur in 5-15% of wounds when hypertrophic scars are also included. They tend to affect both sexes equally, although a higher incidence exists in women, possibly secondary to the fact that women tend to engage in more cosmetic procedures than men, ear piercing as the main example. The frequency of keloids in individuals with highly pigmented i.e Fitzepatrick photoskintype V and VI is 15 times higher than in persons with less pigmented skin[vii]. The average age at onset is 10-30 years. Senior citizens at the extremes of age rarely develop keloids. Patients with darker skin tend to be more prone to keloid formation. Studies are ongoing to try and ascertain conclusively which genes are associated with keloids formation. Multiple patho-mechanisms have been described in keloid formation and studies are ongoing to try and target certain aspects of wound healing. A number of therapeutic modalities are linked with high rate of recurrences and none have been shown to be more superior however combination therapies show some promise.

3.7 Study findings

- ✓ All keloids treated showed improvement towards a desired clinical outcome and cosmetic appeal.
- ✓ At six weeks, most treated lesions were still centrally inflamed or depigmented, and had a characteristic hyperpigmented halo on the periphery.
- ✓ Both the Clinician and patient satisfaction were more pronounced on smaller keloids (2- 5cm and unilobular) than larger ones.
- ✓ At six weeks, the trajectory became clear as to whether the keloid will completely flatten out or not when re-examined at six months.
- ✓ All treated lesions healed with post inflammatory hyperpigmentation and therefore it is crucial to warn and counsel the patients about this.
- ✓ Cryotherapy was done only once on day 0, baseline and never repeated.
- ✓ Pain was reported by all participants a few hours post the procedure and pruritus locally on sites, a few days later.

- ✓ Keloids larger than 5 cm diameter tended to freeze up the cryotherapy cylinder at the hinge, making it difficult to continue with the procedure in such cases.
- ✓ Duration of prolonged and uninterrupted freezing was a major factor causing the freezing up of the hinges.

3.8 Limitations of the study

Several limitations were observed during the study. The duration of the study was only one year, thus making it difficult to comment on the recurrence rate of keloids as per their typical nature. A third of the patients (4) (33.3%) were lost to follow up despite all efforts to have them honour their clinic follow-up dates.

Furthermore, objective measurement of the outcome after the intervention proved problematic as some keloids retained their size diameters but clinically flattened (Figure 3.7). The figure below demonstrates the difficulty in objective and standardised measurement of keloid. The keloid nodule on the left jaw retained the same diameter but was markedly flatter.

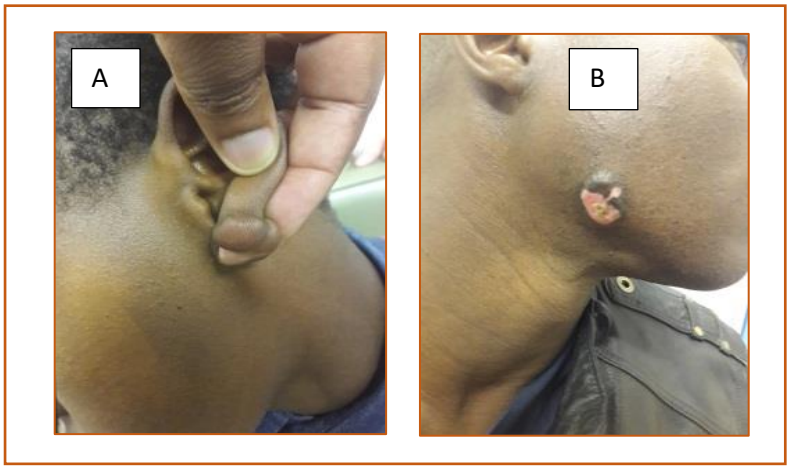

Figure 3.7: Limitation in the standardized measurement of the keloid post-treatment

Several technical difficulties were also encountered during the procedure. Some of these limitations are being presented in pictorial format.

Not all cryotherapy cylinders allow for a needle placing through which to undertake the procedure, when it could be used, the single Cylinder utilized in our study tended to freeze up easily and impede effective freezing of more than one keloid at a time. (Figure 3.9). Only ideal, unilobular (dome shaped) keloids in a horizontal plane can be treated in this way.

Figure 3.8: Freezing of the cryotherapy bottle during the procedure

Another limitation that was observed during the procedure was that the needle was sometimes not long enough especially for the larger keloids. This made it difficult and impossible to freeze the keloid in one treatment. Figure 3.9 a, b, c and d gives a pictorial illustration of such difficulty. Even the longest needle was unable to run through the entire length of the large keloid. This led to a less desirable compensatory manoeuvre of only partially treating the keloidal mass.

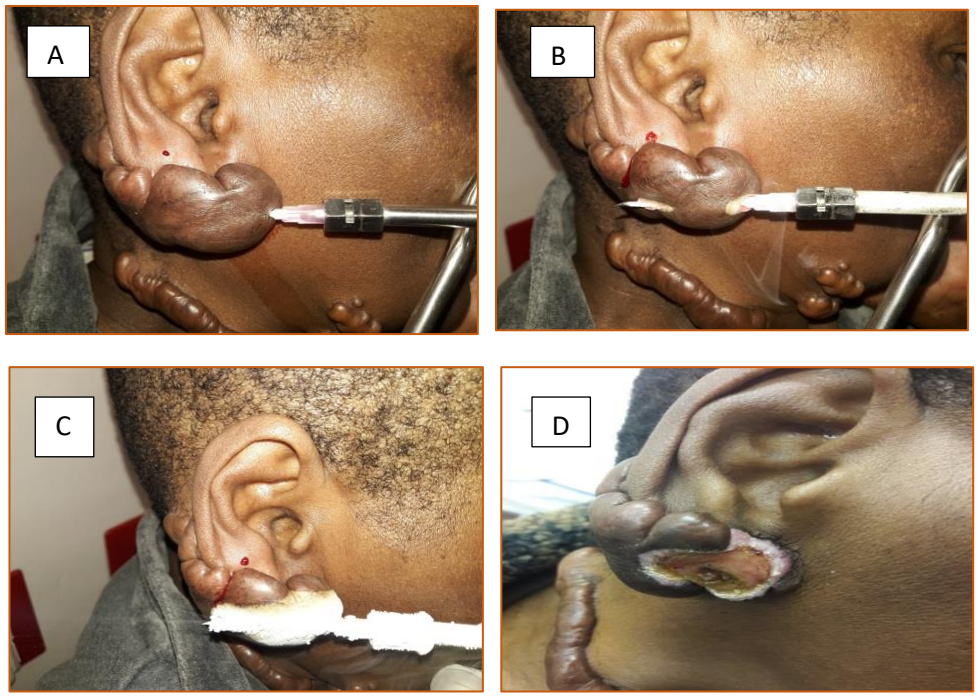

Figure 3.9

A and B: Illustration of limitations of the cryotherapy methods.

C and D: Partially frozen portion of the large keloid leading to only a fraction of the keloid being treated at six weeks.

Another limitation that was observed during the procedure was the inability of the needle to withstand the drop in temperature. This led to the needle freezing and sometimes breaking within the keloids. Figure 3.10 gives a good illustration of this limitation. Figure 3.10 (A, B and C) shows the needle breaking off inside the keloids due to its inability to withstand the excessive freezing intensity. Figure 3.10 (D) illustrates how the needle had to be manually removed with forceps during the procedure. This limitation was mainly observed during the procedure for larger keloids and care must at all times be taken not to further traumatise the site.

Figure 3.10: Needles freezing up and breaking off within the keloids.

During the procedure, it was also observed that the Cryotherapy bottle froze before the completion of the treatment on the keloid (Figure 3.11 a). This resulted in the inability of the cryotherapy bottle to discharge the liquid nitrogen in the keloid. Even though steps such as rinsing the lid of the bottle was undertaken, the device was unable to discharge the liquid nitrogen (Figure 3.11 b). After the bottle was left to stand and thaw, it suddenly started to discharge the liquid nitrogen without being handled (Figure 3.11 c).

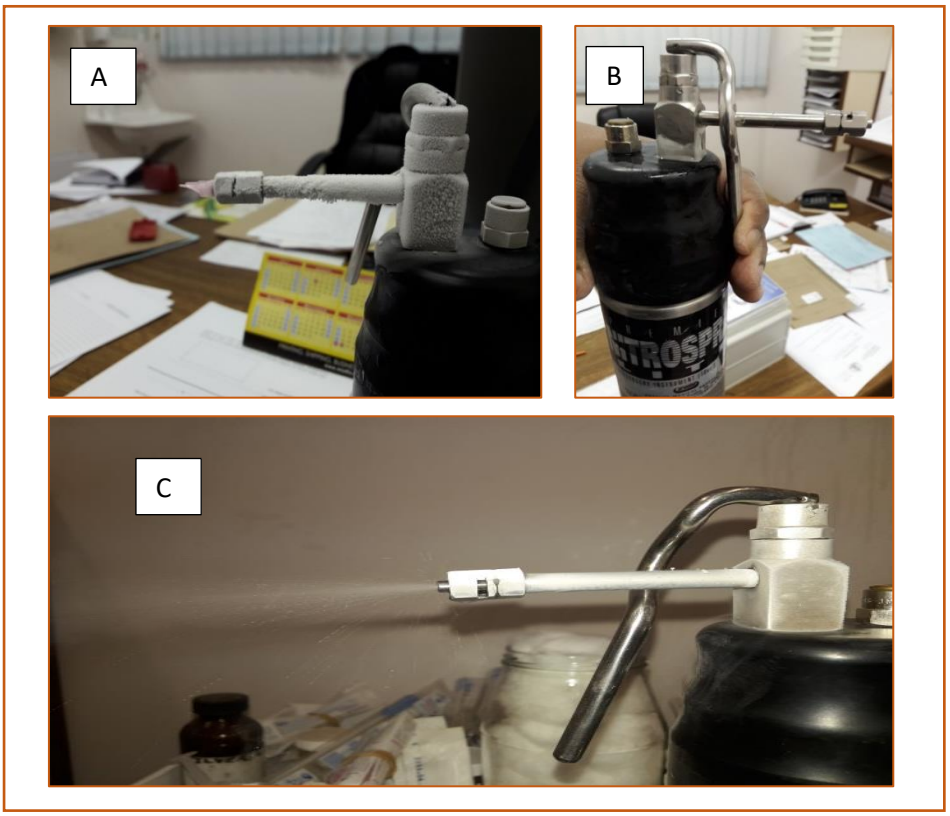

Figure 3.11: Malfunctioning of the crytotherapy bottle during the procedure.

3.9 Conclusion

Intralesional cryotherapy as treatment of exophytic keloids has been shown to result in cosmetic improvement and reduction of symptoms like itching and pain. This is an avenue that is worth exploring in an attempt to find a more desirable, and consistent method to at least reduce the size of the keloids. Perhaps also add topical modalities to augment the primary effects and further reduce chances of recurrence.

3.10 Recommendations

Based on the findings of this study, the following recommendations have been considered:

- A more formal and perhaps multi-centered study should be undertaken as a follow up of this pilot project, with more study volunteers.
- It would be ideal to conduct the same study with a more durable cryotherapy cylinder to ensure coverage of larger keloids and enable treatment of more keloids at a time.
- This study should be published and presented to companies who produce cryo bottles, in the hope of having them create more durable bottles designed specifically for keloid treatment.
- It would be ideal to follow up a cohort of patients on this modality of treatment, for a longer period in an attempt to also review recurrence rates in the long run.
- Transportation and other related financial incentives should be considered to ensure better patient compliance.
- Objective measurements for multidimensional keloids would assist.

CHAPTER 4

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5.0 ANNEXURE

5.1 CONSENT TO PARTICIPATE IN RESEARCH

Title of the study: Intralesional Cryotherapy to treat exophytic keloids: The Universitas Hospital Bloemfontein experience.

You are hereby requested to take part in the study as informed by:

……

Should the need arise, you may contact Dr L. Makhakhe at 051 405 3759 any time if you have questions about the research or if you are injured as a result of the research. You may contact the Secretariat of the Ethics Committee of the Faculty of Health Sciences, UFS at telephone number (051) 401 7795 if you have questions about your rights as a research subject.

Your participation in this research is voluntary, and you will not be penalized or lose benefits if you refuse to participate or decide to terminate **participation**. If you agree to participate, you will be given a signed copy of this document as well as the ***participant*** information sheet, which is a written summary of the research. Furthermore, you may be required to come in on a regular basis to evaluate the effects of therapy on your condition. This study will be kept confidential and only relevant parties will be given the result outcome.

I, _____

declare that:

The research study, including the above information has been verbally explained to me. I understand what my involvement in the study means and I voluntarily agree to ***participate***. I am fully aware of the possible complications, which include local infection, recurrences and, in rare cases, nerve injury.

We have since learned of a newer method with no current clinical trials as an option to treating keloids. This new method is easy, cost effective and promising as a game changer in managing certain types of keloids.

The study will be conducted at the Dermatology clinic from 1 March to 30 September 2016. Patients will receive consent forms. To date, we have not been very active in treating these types of keloids because of the low yield with treatment modalities, even when these modalities were used in combination.

The study population is everyone that fits the criteria, visiting our clinic for help. On average we see about one or two such patients per month.

We will localize (make numb) the skin around the keloid with the smallest of needles and then insert a bigger needle on the keloid and freeze from the core of the keloid. The procedure of freezing is painless, ice crystals destroy fibrotic cells and thus shrink the nodule. Small bleeding from the needle insertion site is expected, but usually well managed via compression for a few minutes.

We will not have a control method as this is experimental study to seek better treatment outcome. We will minimise complications such as infections by working in under a sterile condition.

_____ _____

Signature of **Participant** Date

_____ _____

Signature of Witness Date
(Where applicable)

_____ _____

Signature of Translator Date
(Where applicable)

5.2 Tumello ya ho nka karolo diphuputsong tsa rona

<u>Lebitso la diphuputso tsa rona:</u> Tshebediso ya sehatsetsi ho fokotsa maqeba a itseng bakuding ba Kliniki ya letlalo, Universitas Annex, Mangaung, Bloemfontein.

O kuptjwa ho nka karolo diphuputsong tsa rona, ditaba kaofela o di hlaloseditswe ke:

……

Ha ho ka hlokahala, o ka fumana ngaka Makhakhe ho 051 405 3759 nako efe kapa efe ha dipotso di ka ba teng. O ka nto bua le rona ha o ka utlwa bohloko ka nako eo diphuputso di etswa. O lokollehile ho bua le ba ditokelo lefapheng mohaleng o latelang: 051 401 7795.

Tumellano ya ho nka karolo ha se qobello, mme ha ho kahlolo ha o ka se rate ho nka karolo, kapa hona ho fetola monahano ha o ile wa nka karolo. Ha o ka nka karolo, o tla fumana tokomane eo o tla e tekena, mme re tla kopa ho o bona ha nako e ntse e ya, ho bona hore dintho ntse di tsamaya jwang.

Taba tsohle ke lekunutu la rona le ba lefapha la bophelo. Ke dumela ho nka karolo, le hore ha ke a qobellwa ho fumana thuso ka mokgwa ona. Ke hlaloseditswe hore mathata a tshwaetso, le ho utlwa bohloko ha methapo ho ka etsahala.

_____ _____

Ho Tekena mokudi Letsatsi

_____ _____

Ho Tekena ya pakang Letsatsi
(Ha ho hlokahala)

_____ _____

Ho tekena motoloki Letsatsi
(Ha ho hlokahala)

5.3 TOESTEMMING OM AAN NAVORSINSING DEEL TE NEEM

<u>Die titel van die studie</u>: Die gebruik van intralesionale diep vries deur vloeibare stikstof om eksofitiese keloide te behandel in pasiente wat die dermatologie kliniek by Universitas Hospitaal Annex, Bloemfontein, besoek.

U word hierdeur versoek om aan die studie deel te neem soos ingelig deur:

……

Sou dit nodig wees, kan u Dr L. Makhakhe enige tyd kontak by 051 405 3759, indien u vrae het oor die navorsing of indien u beseer is as gevolg van die navorsing. U mag die Sekretaris van die Etiese komitee van die Fakulteit van Gesondheidswetenskappe, UFS kontak by telefoon nommer 051 401 7795 indien u vrae het oor u regte as ‘n deelnemer aan die navorsing studie.

U deelname in hierdie navorsing is vrywillig en u sal nie gepenaliseer word of voordele verloor indien u weier om aan die studie deel te neem of besluit om u deelname te beëindig nie. Indien u instem om deel te neem sal u ‘n getekende afskrif van hierdie dokument sowel as die deelnemer inligtingstuk, wat ‘n opsomming is van die navorsing studie, ontvang. Verder mag dit van u verwag word om gereeld na die kliniek te kom om die effek van die behandeling op u toestand te evalueer. Hierdie studie sal vertroulik gehou word en die resultate sal slegs aan belanghebbende partye bekend gemaak word.

Ek, _____

Verklaar dat:

Die navorsing studie, insluitend die bogaande inligting, mondelings aan my verduidelik is. Ek verstaan wat my betrokkenheid in die studie behels en ek stem vrywillig in om deel te neem. Ek is ten volle bewus van die moontlike komplikasies, wat plaaslike infeksie, reoccurences en selde senuwee besering in te sluit.

_____ _____

Handtekening van die Datum

Deelnemer

_____ _____

Handtekening van die Datum

Getuie (Indien toepaslik)

_____ _____

Handtekening van die Datum

Tolk (Indien toepaslik)

5.4 PARTICIPANT INFORMATION LEAFLET AND ASSENT FORM

TITLE OF THE RESEARCH PROJECT: Intralesional Cryotherapy to treat exophytic keloids: The Universitas Hospital Bloemfontein Experience.

RESEARCHERS NAME(S): Dr L. Makhakhe

ADDRESS: National Hospital, Corner of Roth and Willow str, Bloemfontein

CONTACT NUMBER: 072 675 3020

What is RESEARCH?

Research is something we do to find new knowledge about the way things (and people) work. We use research projects or studies to help us find out more about disease or illness and better ways of helping or treating them.

What is this research project all about?

This research is about a new method that we can use to remove the overgrowth on your skin. This method has been shown to have better treatment outcomes than the currently used methods for removing overgrowth. The method involves freezing the overgrowth on the skin with a cold bottle so that it shrinks over time.

Why have I been invited to take part in this research project?

You have been invited because we will like to help you reduce or completely remove the overgrowth on your skin. Once we have worked on the overgrowth, you will look even more beautiful.

Who is doing the research?

I am Dr Makhakhe, I work for the Department of Health.

What will happen to me in this study?

I will make your overgrown skin numb, and use a bottle filled with gas to make the overgrowth very cold. It will not be painful and takes about 15 minutes to complete. You will be given pain medication afterwards to take home, just in case you experience pain.

Can anything bad happen to me?

Nothing serious can happen to you. However, the area where we freeze can become infected, swollen and uncomfortable. There may be pain afterwards and we may need to repeat the procedure on follow up.

Can anything good happen to me?

Yes, the overgrowth is expected to become smaller and smaller as time goes.

Will anyone know I am in the study?

Not just anyone, just the people working with us at the Clinic, and other people who will need to know how our bottle freezing worked on your overgrowth.

Who can I talk to about the study? *Myself, Dr Makhakhe at the Clinic at 051 405 2324 and the Ethics Committee at 051 401 7795*

What if I do not want to do this?

You will not be forced in any way to do anything that you are not happy with. This is to help you, but if you are unhappy to take part, then no one will be angry at you.

Do you understand this research study and are you willing to take part in it?

YES NO

Has the researcher answered all your questions?

YES NO

Do you understand that you can pull out of the study at any time?

YES NO

_____ _____

Signature of Child Date

5.5 INLIGTINGSTUK EN TOESTEMMINGSVORM VIR DEELNEMERS

TITEL VAN NAVORSINGSPROJEK: The use of intralesional deep freezing with liquid Nitrogen to treat exophytic keloids in patients attending the dermatology clinic at Universitas Hospital Annex, Bloemfontein.

NAVORSER(S): Dr L. Makhakhe

ADRES: National Hospital, Corner of Roth and Willow str, Bloemfontein

KONTAKNOMMER: 072 675 3020

Wat is navorsing?*Dit gaan oor keloids (harder (Knoppe)) wat dikkering is.*

Waaroor gaan hierdie navorsingsprojek?

Ons vries die knop vel met koue gas bottlels sodat die knop kan krimp met verloop van tyd.

Hoekom vra julle my om aan hierdie navorsingsprojek deel te neem?

Hulle het knoppe op die vel.

Wie doen die navorsing?

Ek, Dr Makhakhe, wat werk vir die Department van Gesondheid.

Wat sal in hierdie studie met my gebeur?

Di knop kaan weg gaan na tyd perk.

Kan enigiets fout gaan?

Ja, jy kan as die knop rooi en warm word met swelling en ongemaklik is Dan kaan dit n gogga wees by die knop. Daar kan pyn daarna wees na die proses. Maar ons kaan pyn medikasie gee.

Watter goeie dinge kan in die studie met my gebeur?

Ja, die knoppe kaan heel te maal weg gaan.

Sal enigiemand weet ek neem deel?

Nee, dis privaat tussen dokter en patient.

Met wie kan ek oor die studie praat? *Myself, Dr Makhakhe by 051 405 2324 en Etiek commettee by 051 401 7795*

Wat gebeur as ek nie wil deelneem nie?

Niemand sal jou dwing. Dis vry willig.

Verstaan jy hierdie navorsingstudie, en wil jy daaraan deelneem?

JA NEE

Het die navorser ál jou vrae beantwoord?

JA NEE

Verstaan jy dat jy kan ophou deelneem net wanneer jy wil?

JA NEE

_____ _____

Handtekening van kind Datum

5.6 PATIENT SATISFACTION SCALE

Compared to your initial presentation, how satisfied are you with your overall treatment at 6 months?

Patient	Unhappy	Satisfied	Very satisfied	Undetermined
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				