# Keloid Disease: Comparison of Treatment with Intralesional Triamcinolone Acetonide, 5-Fluorouracil, Cryotherapy, and their Combination

**ANABA EL** FWACP[1], **COLE-ADEIFE O** FMCP[2], **OAKU IR** MWACP[3]

[1]Department of Medicine, Lagos State University College of Medicine/Lagos State University Teaching Hospital, Lagos, Nigeria.

[2]Department of Medicine, Lagos State University Teaching Hospital, Lagos, Nigeria.

[3]Department of Medicine, General Hospital, Lagos

**Corresponding author:** Ehiaghe L Anaba

Department of Medicine, Lagos State University College of Medicine/ Lagos State University

**Email address**: ehianaba@yahoo.com, **Phone number**: +234 8030495911

**ABSTRACT**

**Background:** Documentation of the efficacy of the modalities of keloid treatment and which of these is the best option is rare. Documentation of the treatment outcomes is also rare. The study aimed to document and compare the treatment outcome of keloid using different modalities of treatment.

**Methods:** This prospective longitudinal study was conducted on 32 patients diagnosed to have keloid. Patients were randomized into 4 different arms of treatment (Intralesional triamcinolone acetonide only [IL TAC 40mg/ml]; IL TAC (0.1ml) plus 5-Fluorouracil (0.9ml); Cryotherapy only; and Cryotherapy plus IL TAC (40mg/ml), and treated every 4 weeks. The size of each keloid was evaluated before and at the end of the study. Data were analyzed using SPSS version 23.0

**Results:** The patients were 53.1% female with a mean ± SD age of 32.47 ± 13.93years and an age range of 16-67 years. The mean ±SD volume of keloid reduced from 3.53±1.56 to 0.29±0.15 with no significant difference in volume reduction when the different modalities of treatment were compared, p=0.869. There were no adverse effects in 50%, while 34% had ulcerations 12.5% had hypopigmentation and 3.1% had hyperpigmentation.

**Conclusion:** All the modalities of treatment were effective in the management of keloid. However, cryotherapy-only results in a faster volume reduction. Two to five sessions of treatment are required for keloid treatment. Ulceration and hypopigmentation should be anticipated in some patients.

**Keywords:** Keloid, Keloid treatment, triamcinolone acetonide, 5-fluorouracil, cryotherapy.

**Maladie Chéloïde : Comparaison du Traitement avec l'Acétonide de Triamcinolone Intralésionnelle, le 5-Fluorouracile, la Cryothérapie et leur Combinaison**

**ABSTRAIT**

**Contexte:** La documentation sur l'efficacité des modalités de traitement des chéloïdes et sur laquelle d'entre elles est la meilleure option est rare. La documentation des résultats du traitement est également rare. L'étude visait à documenter et à comparer les résultats du traitement des chéloïdes en utilisant différentes modalités de traitement.

**Méthodes:** Cette étude longitudinale prospective a été menée sur 32 patients diagnostiqués comme ayant une chéloïde. Les patients ont été randomisés dans 4 bras de traitement différents (acétonide de triamcinolone intralésionnelle uniquement [IL TAC 40 mg/ml] ; IL TAC (0,1 ml) plus 5-fluorouracile (0,9 ml) ; cryothérapie uniquement ; et cryothérapie plus IL TAC (40 mg/ml) , et traité toutes les 4 semaines. La taille de chaque chéloïde a été évaluée avant et à la fin de l'étude. Les données ont été analysées à l'aide de SPSS version 23.0

**Résultats:** Les patients étaient à 53,1 % des femmes avec un âge moyen ± ET de 32,47 ± 13,93 ans et une tranche d'âge de 16 à 67 ans. Le volume moyen ± SD de chéloïde est passé de 3,53 ± 1,56 à 0,29 ± 0,15 sans différence significative de réduction de volume lorsque les différentes modalités de traitement ont été comparées, p = 0,869. Il

n'y avait pas d'effets indésirables chez 50%, tandis que 34% avaient des ulcérations 12,5% avaient une hypopigmentation et 3,1% avaient une hyperpigmentation.

**Conclusion:** Toutes les modalités de traitement ont été efficaces dans la prise en charge des chéloïdes. Cependant, la cryothérapie seule entraîne une réduction de volume plus rapide. Deux à cinq séances de traitement sont nécessaires pour le traitement des chéloïdes. L'ulcération et l'hypopigmentation doivent être anticipées chez certains patients.

**Mots-clés:** Chéloïdes, Traitement des chéloïdes, acétonide de triamcinolone, 5-fluorouracile, cryothérapie

## Introduction

Keloid disease (KD) is a fibroconnective tissue disease arising from inappropriate wound healing with uncontrolled deposition of collagen and ground substance in the dermis due to the overactivity of fibroblasts during wound healing.[1,2] It can occur in any part of the body but typically occurs in areas of a stretch; sternum, arms, shoulders, back, and ear lobes.[3,4] The aetiology of KD is poorly understood but it is observed to follow trauma including surgery, inflammatory disease, burns, and ear piercing; and occurs spontaneously in some individuals.[5,6]

The prevalence of KD ranges from 0.7% to 1.1%.[7–9] Keloid disease occurs mostly in the young; in individuals aged 40 and below with an average age of occurrence of 27-38 years.[5,10,11] Keloidal lesions do not resolve without treatment, and this can be frustrating for both physicians and patients.[1] Typically, patients seek treatment on account of pain, pruritus, dislike of the KD lesions, and embarrassment.[5,12,13] There is currently no permanent cure for KD and recurrence following treatment is a common phenomenon.[1,14] Modalities of treatment of KD are well documented and include; cryotherapy,[15-17] intralesional triamcinolone acetonide injection (IL TAC),[17-19] 5-Fluorouracil (5-FU)[18,20] and their combinations,[20,21] radiotherapy[22] and Lasers.[23] Treatment of KD results in flattening, improvement in pain, and pruritus.[14,19]

Despite the regular treatment of KD in the clinics, documentation of the efficacy of the various modalities of treatment and which of these treatment modalities is the best option is rare. Documentation of treatment outcomes is also rare. The paucity of this data makes it difficult to counsel and advise patients. The objective of this study, therefore, is to document the treatment outcome of keloid treatment using different modalities (Intralesional TAC only [IL TAC 40mg/ml], IL TAC (0.1ml) plus 5-Fluorouracil (0.9ml), Cryotherapy only and Cryotherapy plus IL TAC (40mg/ml). The study also aimed to compare the rate of flattening with the treatment abnormalities and adverse effects following treatment.

## Methods

This prospective longitudinal study was conducted on 32 patients diagnosed to have keloid at the skin clinic of the Lagos State University Teaching Hospital following ethical approval by the hospital's ethical review board (LREC/06/10/1127). The study was explained to the patients: verbal and written informed consents were also obtained from them. The calculated sample size for the study was forty-eight (48) but only 40 patients consented to the study and were studied. Although forty (40) patients were recruited into the study (10 into each arm) only 32 completed the study. The inclusion criteria for the study are written consent; duration of keloid $\geq$ 6 months, treatment naïve patients, and keloids $\leq$5cm in length. Exclusion criteria included; duration of keloid $\leq$ 6 months, treatment for keloid in last 6 months, pregnancy, and keloids $\geq$5cm in length. Irrespective of the number of keloids a patient had, only one was selected per patient for treatment.

The study was conducted over one year (March 2019 to February 2020). Four known and already practiced treatment options in the skin clinic were evaluated: (IL TAC only (40mg/ml),[14,19,24] IL TAC (0.10 of 40mg/ml) plus 5-Fluorouracil (0.9ml of 250mg/5ml),[18,19,24] Cryotherapy (liquid nitrogen) only,[17,21] Cryotherapy plus IL TAC (40mg/ml).[17,21] Ten patients were randomized into each arm of the study by balloting. Each patient blindly chose from a bag containing the treatment options and the chosen treatment option was noted.

Patients were treated every 4 weeks until the keloid flattened out or for a maximum of 5 times (the end point of the study). A 4-week interval was adopted in this study based on the documented treatment

interval of 3-6 weeks in other studies.[19,24] A study proforma was used in documenting the patient's socio-demographic and clinical variables. At each visit, the volume of the keloid was calculated based on the measurement of the length, depth, and height of the keloid. For numbing and pain reduction from the injections, Two millilitres (2mls) of local anesthetic (2% lidocaine plus 1:100,000 adrenaline) was infiltrated around the keloid before the chosen modality of treatment.

For the patients who had injections, this was given intralesionally and spaced 1cm apart using a 27G needle.[19] For cryotherapy, liquid nitrogen was sprayed using a cryogun (0.2mm nozzle) with the formation of an ice ball. Two freeze-thaw cycles of 20 seconds of freezing were done at each contact.[17,25] In addition, at each visit, pain and pruritus were assessed as follows;[17]

- **Pain evaluation**

1– No pain 2– Mild pain
3– Moderate pain 4–Severe pain

- **Pruritus evaluation**

1–No pruritus 2–Mild pruritus
3 – Moderate pruritus
4–Severe pruritus

In addition, adverse effects like pain, hypopigmentation, telangiectasia, and skin atrophy following treatment were also noted. These are known and documented side effects of these treatment modalities.[19,24]

Data were entered into an excel sheet and analyzed using SPSS version 23. Univariate descriptive statistics such as means, medians, frequencies, and proportions are presented. Associations between variables were done using the chi-square test while differences in means were tested using the t-test or Analysis of variance depending on the data.

**Results**

Forty (40) patients were recruited into the study but only 32 completed the study giving an attrition rate of 20%. Data analysis is limited to the 32 patients who completed the study. Most of the patients who left the study were those randomized into the cryotherapy alone arm. The patients were 53.1% female with a mean ± SD age of 32.47 ± 13.93years and an age range of 16-67 years. The mean age at the onset of keloid was 27.00 ± 13.88. A family history of keloid was reported as yes, no, and unknown in 28.1%, 68.8%, and 3.1% respectively. Sixty-five percent (65.6%) had previously been treated for keloid but this treatment was not in a dermatology clinic in 87.5% of these.

The mean± SD duration of keloid was 5.40 ± 5.79 years with a range of <1 to >10 years. The duration of keloid was <1 year in 18.8%, 1-5 years in 43.8%, 6-10 years in 21.9%, and >10 years in 15.6%. The main reason for seeking treatment was a dislike for how the keloid looked (68.8%). Keloid followed trauma in 87.5%. Table 1.

**Table 1. Sociodemographic Characteristics of the Patients.**

| SOCIODEMOGRAPHIC CHARACTERISTICS | FREQUENCY (N = 32) N (%) |
|---|---|
| **Age at presentation (years)** | |
| <20 | 6 (18.8) |
| 21-30 | 12 (37.5) |
| 31-40 | 4 (12.5) |
| 41-50 | 6 (18.8) |
| >51-60 | 4 (12.6) |
| **Age at onset (years):** | |
| <10 | 3 (9.4) |
| 11-20 | 10 (31.3) |
| 21-30 | 7 (21.9) |
| 31-40 | 7 (21.9) |
| 41-50 | 3 (9.4) |
| >51-60 | 2 (6.2) |
| ****Reason for seeking treatment:** | |
| Don't like it | 22 (68.8) |
| Pain | 13 (59.1) |
| Itching | 19 (59.4) |
| Size | 14 (43.8) |
| **History of Hypertension/Diabetes:** | |
| No | 27 (84.4) |
| Yes | 5 (15.6) |

****Multiple options**

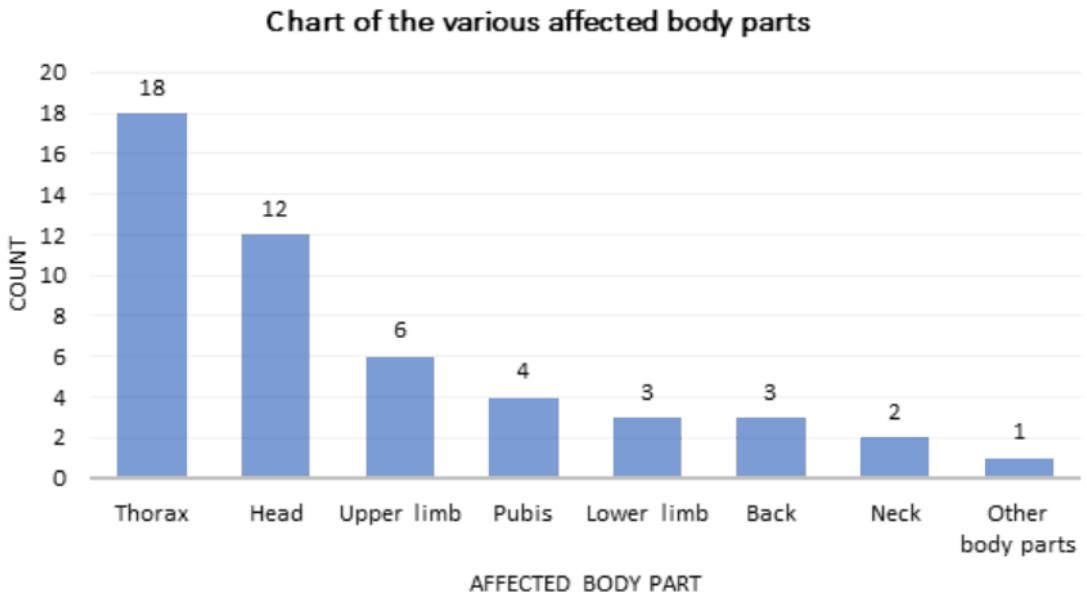



**Figure 1. Bar Chart Showing Site of Keloid Occurrence**

**Table 2. Clinical Characteristics of the Patients.**

| CLINICAL CHARACTERISTICS | FREQUENCY (N = 32) N (%) |
|---|---|
| **Pruritus** | |
| No | 6 (18.8) |
| Yes | 26 (81.2) |
| **Pain** | |
| No | 16 (50.0) |
| Yes | 16 (50.0) |
| **Size of keloid** | |
| Less than 1 cm | 3 (9.4) |
| 1-5cm | 29 (90.6) |
| **Are keloids on visible area:** | |
| No | 6 (18.8) |
| Yes | 26 ((81.2) |
| **Number of keloids:** | |
| 1-5 | 23 (71.8) |
| >6-10 | 9 (28.2) |
| **Pain evaluation:** | |
| 1 | 17 (53.1) |
| 2 | 7 (21.9) |
| 3 | 6 (18.8) |
| 4 | 2 (6.3) |
| **Pruritus evaluation:** | |
| 1 | 10 (31.3) |
| 2 | 10 (31.3) |
| 3 | 7 (21.9) |
| 4 | 5 (15.6) |
| **Adverse effects:** | |
| None | 16 (50.0) |
| Hypopigmentation | 4 (12.5) |
| Ulceration | 11 (34.4) |
| Hyperpigmentation | 1 (3.1) |

Clinical features included pruritus in 18.8%, pain in 50%, and keloid size of 1-5cm in 78.1%. (Table 2). Keloids were located in visible anatomical sites in 81.3%. The most frequent anatomical site of KD occurrence was the trunk. Figure 1.

Following treatment, the mean ±SD volume of keloid reduced from 3.53±1.56 at the first visit to 0.29±0.15 at the fifth visit (endpoint of the study) and 0.00 for the cryotherapy arm at the 4th visit. After the second session, the number of patients returning for treatment declined. A paired sample t-test also showed a significant difference in the volume changes per visit in all the patients. Details are depicted in table 3.

**TABLE 3. Comparison of keloid volume reduction per visit in all the patients**

| STATISTICS | VOLUME OF KELOID PER VISIT | | | | |
|---|---|---|---|---|---|
| | 1st N = 32 | 2nd N = 32 | 3rd N = 29 | 4th N = 20 | 5th N = 7 |
| Mean | 3.53 | 1.74 | 1.06 | 0.74 | 0.29 |
| Standard deviation | 1.56 | 0.995 | 0.54 | 0.46 | 0.15 |
| Minimum | 0.07 | 0.00 | 0.00 | 0.00 | 0.00 |
| Maximum | 24.00 | 6.19 | 4.82 | 3.64 | 1.05 |
| | PAIRED SAMPLE T–TEST[a] | | | | |
| Mean difference | - | 1.79 | 0.82 | 0.66 | 0.41 |
| T-test | - | 2.517 | 3.509 | 4.999 | 2.903 |
| P-value | - | 0.017* | 0.002* | 0.000* | 0.027* |

*a = paired sample for each column is used to test for significant changes from the previous visit*
** = significant at p-level <0.05*

There was no significant difference in volume reduction when the different modalities of treatment were compared. Cryotherapy alone treatment modality was not included in the comparative analysis because all participants that received it did not come for the fifth visit because the volume of KD had reduced to 0.00 by the fourth visit. Figure 2

There were no adverse effects following treatment in 50% of the patients, ulcerations in 34.4%, hypopigmentation in 12.5%, and hyperpigmentation in 3.1%. Atrophy and telangiectasia were not seen in any patient The adverse events of ulceration and hypopigmentation varied based on the treatment modality. Details are shown in figure 3. Within the period of the study, 3 patients in the cryotherapy-only modality of treatment had a recurrence within 6 months of the study (one patient, 2 months after initial flattening). There was no recurrence with the other modalities of treatment within the period of the study.

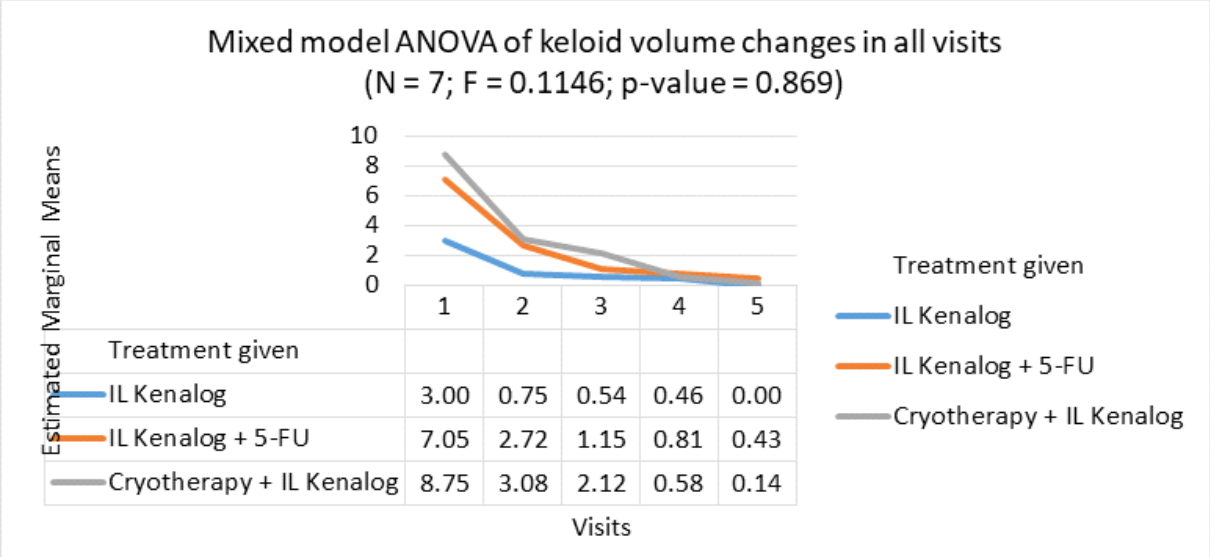
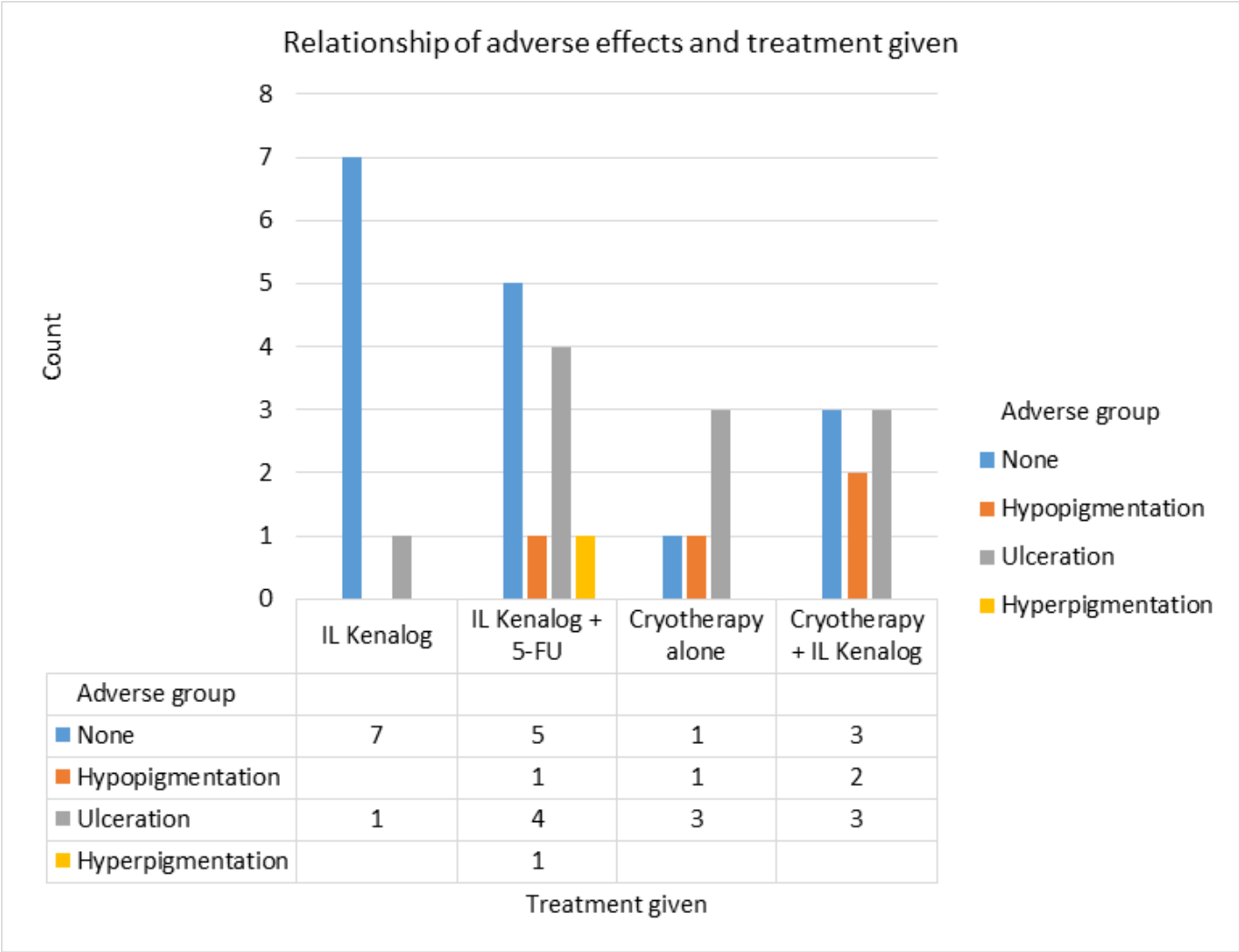



**Figure 2. Comparison of Volume Reduction by the Different Modalities of Treatment.**




| Adverse group | IL Kenalog | IL Kenalog + 5-FU | Cryotherapy alone | Cryotherapy + IL Kenalog |
|---|---|---|---|---|
| None | 7 | 5 | 1 | 3 |
| Hypopigmentation | | 1 | 1 | 2 |
| Ulceration | 1 | 4 | 3 | 3 |
| Hyperpigmentation | | 1 | | |

**Figure 3. Adverse Effect Based on the Treatment Modalities**

## Discussion

Keloid disease, a fibroconnective tissue disease arising from inappropriate wound healing typically does not resolve without treatment.[1] Patients present to the clinic for treatment on account of pain, pruritus, dislike for the lesions, or embarrassment.[5,12,13] Different modalities of treatment are offered based on the patient's presentation, available treatment modality, cost, and expertise of the therapist.[14,19,25]

The most common reason for seeking treatment in this study was dislike for the lesion. Apart from the cosmetic effect of these lesions, most of the patients in this study had lesions in visible anatomic sites (chest and face). This could cause embarrassment especially if friends and colleagues asked questions. Dislike for KD lesions has been reported as a reason for seeking treatment.[5,12,13] The other reasons for seeking treatments were pain, pruritus, and the size of the lesions. These reasons have been reported in other studies of KD.[5,13,19] Due to the expansive nature of the KD lesions with pressure on the nerves and the release of cytokines, the lesions tend to be pruritic and painful.

All the modalities of treatment resulted in a significant volume reduction (mean volume reduction from 3.53 $cm^3$ to 0.29 $cm^3$) in consonance with what has been reported following the treatment of KD using the different treatment modalities.[2,14,17,19,24.25] These treatments lead to a resolution of KD due to a decrease in fibroblast proliferation and collagen synthesis, degeneration of collagen, anti-angiogenesis, vasoconstriction, and necrosis of the keloid tissue by vascular damage.[17] The number of sessions required for volume reduction ranged from 2 to 5 with almost all the patients experiencing a flattening by the fifth visit. This rate of volume reduction following treatment is similar to that reported in other studies of KD treatment.[13,17,18]

There was no significant difference in volume reduction when the different modalities were compared. Thus, the four modalities of treatment are equally effective in the treatment of KD. Conclusions from comparative studies of different modalities of treatment differ. Zhang et al similar to this study report no difference in volume reduction[14] while other authors reported a better volume reduction with combination therapies.[1,19,21]

The rate of volume reduction differed. Cryotherapy-only was noted to result in a faster volume reduction followed by IL TAC only, then cryotherapy plus IL TAC, and then IL TAC plus 5-FU. This observation can be translated into clinical practice when patients are being advised on the choice of a modality of therapy. The endpoint of KD treatment is usually volume reduction with flattening of the lesions as seen in this study.[10,13,14,19] Srivastava et al in contrast reported a faster resolution of KD with the combination of IL TAC plus 5-FU contrary to our study in which this modality was the slowest.[19]

There was a significant reduction of the intensity of pain and pruritus to their complete resolution following treatment in the patients who had presented with these symptoms as reported in other studies.[19]

Half of the patients had adverse effects from the treatment. This was mostly ulceration from cryotherapy and 5-FU. These modalities of treatment work by causing tissue necrosis, blistering, ulceration, and healing leading to the resolution of KD.[17,19,26] Thus, ulcers are known sequelae of these modalities.[19] Like this study, ulcers following the use of 5-FU and cryotherapy have been reported in KD patients.[19] There was a high attrition from the cryotherapy-only arm of the study. The authors opine that the adverse effects of ulceration and pain associated with cryotherapy may be partly responsible for this attrition.

Hypopigmentation was observed more in the patients who had cryotherapy. This hypopigmentation is due to a combination of factors. A decrease in the number of melanocytes, decreased melanosome synthesis, melanocyte separation by oedema, and a consequent block in melanin transfer to keratinocytes.[17,26-28] Repigmentation usually follows the migration of melanocytes from the surrounding skin into the hypopigmented area.[27] Hypopigmentation following cryotherapy and IL TAC has similarly been reported in KD patients following treatment.[25]

Telangiectasia and atrophy were not seen in the patients contrary to that reported in other studies.[19] Anticipated adverse events following the use of IL TAC include atrophy and telangiectasia.[19] This is due to the anti-collagen effect of steroids with a consequent thinning of vascular walls and loss of dermal collagen.[17,19] The authors opine that the size of the keloids and the number of IL TAC (5 in number) deployed in this study may not have been enough to result in telangiectasia and atrophy. Further studies are required to explore the relationship between the number of injections and the occurrence of telangiectasia. Although atrophy was not reported in this study, Perdanasari et al from their study opine that a combination of IL TAC with 5-FU mitigates atrophy from treatment.[24] Recurrence of keloid was noted in only the patients on the cryotherapy-only arm contrary to reports from other studies where IL TAC is implicated in recurrence.[19-21] Keloids are known to reoccur following treatment but the combination of different treatment modalities is reported to reduce the incidence.[19-21] Increasingly, comparative studies of different modalities of treatment and varying techniques of therapy are being conducted due to difficulty in the treatment of keloids.[15,16,19,22,24,29]

This study was limited by several factors. These included the number of patients who consented to the study, the longitudinal nature of the study with resultant patient dropout, and the side effects of treatment, especially with the cryotherapy-only modality.

In conclusion, Intralesional TAC only [IL TAC 40mg/ml], IL TAC (0.1ml) plus 5-Fluorouracil (0.9ml), Cryotherapy only, and Cryotherapy plus IL TAC (40mg/ml) are equally effective in the management of keloid. However, cryotherapy-only results in a faster volume reduction. Ulceration and hypopigmentation should be anticipated in some. Any modality of treatment available in the clinic can be used in the treatment of keloid but the speed of resolution of KD and the post-treatment side effects depend on the modality of treatment.

## References


1. U d-Din S, Bayat A. Strategic Management of Keloid Disease in Ethnic Skin: a Structured Approach Supported by the Emerging literature. Brit. J. Dermatol. 2013;169 s3:71–81.
2. Wong T-S, Li J Z-H, Chen S, Chan J Y-W, Gao W. The Efficacy of Triamcinolone Acetonide in Keloid Treatment: a Systematic Review and Meta-analysis. Frontiers in Medicine 2016:5:8pgs.
3. Reinholz M, Poetschke J, Schwaiger H, Epple A, Ruzicka T, Gauglitz GG. The Dermatology Life Quality Index as a Means to Assess Life Quality in Patients with Different Scar Types. J Eur Acad Dermatol Venereol. 2015;29:2112-9.
4. Ogawa R, Okai K, Tokumura F, Mori K, Ohmori Y, Huang C, Hyakusoku H, Akaishi S. The Relationship between Skin Stretching/contraction and Pathologic Scarring: The Important Role of Mechanical Forces in Keloid Generation The Int. J. Tissue. Repair Regeneration. 2012;20:149-157
5. Bijlard E, Kouwenberg CAE, Timman R, Hovius SER, Busschbach JJV, Mureau MAM. Burden of Keloid Disease: A Cross-sectional Health-related Quality of Life Assessment. Acta Derm Venereol 2017; 97: 225–229.
6. Fijałkowska M, Kasielska A, Antoszewski B, Variety of Complications after Auricle Piercing. Int. J. Dermatol. 2014;53:952–955.
7. Akinboro AO, Mejiuni AD, Akinlade MO, Audu BM, Ayodele OE. Spectrum of Skin Diseases Presented at LAUTECH Teaching Hospital, Osogbo, Southwest Nigeria. Int. J. Dermatol. 2015;54: 443–450.
8. Henshaw EB, Olasode OA. Skin Diseases in Nigeria: the Calabar Experience. Int. J. Dermatol. 2015;54:319–326.
9. Dlova NC, Mankahla A, Madala N, Grobler A, Tsoka-Gwegweni J, Hift RJ. The Spectrum of Skin Diseases in a Black Population in Durban, KwaZulu-Natal, South Africa Int. J. Dermatol. 2015;54:279–285.
10. Walliczek U, Engel S, Weiss C, Aderhold C, Lippert C, Wenzel A, Hörmann K, Schultz JD. Clinical Outcome and Quality of Life after a Multimodal Therapy Approach to Ear Keloids. JAMA Facial Plast Surg. 2015;17:333-9.
11. Belie O, Ugburo AO, Mofikoya BO. Demographic and clinical characteristics of keloids in an urban center in Sub-Sahara Africa. Niger J Clin Pract 2019;22:1049-1054
12. Olaitan P B. Keloids: Assessment of Effects and Psychosocial- impacts on Subjects in a Black African population. Indian J Dermatol Venereol Leprol 2009;75:368-72.
13. Anaba EL, Akwara I, Johnson O. A Prospective Study of Pattern of Keloid and Number of Intralesional Triamcinolone Acetonide Injections in a Community Based Dermatology Clinic in Lagos, Nigeria. Int. J.Res. Dermatol. 2019;5:760-764
14. Zhang Z, Cheng L, Wang R, Cen Y, Li Z. Effects and safety of triamcinolone acetonide-controlled common therapy in keloid treatment: a Bayesian network meta-analysis. Ther Clin Risk Manag. 2018;14:973-980
15. Bijlard E, Timman R, Verduijn GM, Niessen FB, van Neck JW, Busschbach JJV, Mureau MAM. Intralesional Cryotherapy Versus Excision and Corticosteroids or Brachytherapy for keloid Treatment: Study Protocol for a Randomised Controlled trial. Trials 2013, 14:439.
16. Abdel-Meguid AM, Weshahy AH, Sayed DS, Refaiy AEM, Awad SMI. Intralesional vs. Contact Cryosurgery in Treatment of Keloids: a Clinical and Immunohistochemical Study. Int. J. Dermatol. 2015;54:468–475
17. Lee HJ, Jang YJ. Recent Understandings of Biology, Prophylaxis and Treatment Strategies for Hypertrophic Scars and Keloids. Int. J. Mol. Sci. 2018;711: 19pgs.
18. Coppola MM, Salzillo R, Segreto F, Persichetti P. Triamcinolone Acetonide Intralesional Injection for the Treatment of Keloid Scars: Patient Selection and Perspectives. Clin. Cosm & Invest. Dermatol. 2018;11:387–396.
19. Srivastava S, Patil A, Prakash C, Kumari H. Comparison of Intralesional Triamcinolone Acetonide, 5-Fluorouracil, and their Combination in Treatment of Keloids. World J

Plast Surg 2018;7:212-219.

20. Bijlard E, Steltenpool S, Niessen FB. Intralesional 5-Fluorouracil in Keloid Treatment: A Systematic Review Acta Derm Venereol 2015; 95:778–782.
21. Boutli-Kasapidou F, Tsakiri A, Anagnostou E, Mourellou O. Hypertrophic and Keloidal Scars: an Approach to Polytherapy. Int. J. Dermatol. 2005;44:324–327
22. Bischof M, Krempien R, Debus J, Treiber M. Postoperative Electron Beam Radiotherapy for Keloids: Objective Findings and Patient Satisfaction in Self-assessment. Int. J. Dermatol. 2007;46:971–975.
23. Bouzari N, Davis SC, Nouri K. Laser Treatment of Keloids and Hypertrophic Scars. Int. J. Dermatol. 2007;46:80 –88.
24. Perdanasari AT, Lazzeri D, Su W, Xi W, Zheng Z, Ke L, Min P, Feng S, Zhang Y, Persichetti P. Recent Developments in the Use of Intralesional Injections Keloid Treatment. Arch Plast Surg 2014;41:620-629.
25. O'Boyle CP, Shayan-Arani H, Hamada MW. Intralesional Cryotherapy for Hypertrophic Scars and keloids: a Review. Scars, Burns & Healing. 2017;3: 1–9.
26. Vachiramon V, Thadanipon K. Postinflammatory Hypopigmentation. Clin. and Exper. Dermatol. 2011;36:708–714.
27. Gage AA, Meenaghan MA, Natiella JR, Greene GW Jr. Sensitivity of Pigmented Mucosa and Skin to Freezing Injury. Cryobiology 1979; 16: 348–61
28. Burge SM, Bristol M, Millard PR, Dawber RP. Pigment Changes in Human Skin after Cryotherapy. Cryobiology 1986; 23: 422–32.
29. Kaushal V, Kumar S, Brar BK, Singh A. Comparative evaluation of therapeutic efficacy and safety of intralesional triamcinolone acetonide injection vs intralesional radiofrequency with intralesional triamcinolone acetonide in treatment of keloids. Dermatol Ther. 2020;33:e13919.