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Research Article

Outcomes of Keloid Excision and Intralesional 5-Flurouracil Injection in Adults at the University Teaching Hospital, Lusaka, Zambia

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Abstract

Introduction: Keloid scarring is an abnormal healing response characterized by excessive localized scar tissue growth in response to skin trauma, burns, or infection, for which there is no standard treatment. It is extremely difficult to treat Keloids as surgery alone usually results in recurrence, however the use of Keloid excisions and intralesional injections of 5-fluorouracil has been proven effective worldwide; however, due to paucity of data in the African setting when it comes to the management of keloids and anecdotally, lots of recurrences have been observed. As a result, the purpose of this study was to determine the outcome of Keloid treatment with surgery followed by intralesional 5-FU with a 6-month follow-up at University Teaching Hospitals.

Methods: This was an observational Cohort study on 150 patients simple randomly sampled from the adult hospital at the University Teaching Hospitals. Once the patient had consented the clinician went ahead and performed the excision of smaller lesions of Keloid, under local anaesthesia. There after 5-FU was injected around the lesion 0.5-2ml of 50mg/ml and repeat dose of 5-FU was given weekly until 4 doses of 5-FU were administered. Patients were followed-up monthly using observer scale for 6 months. Ethical approval was granted from the University of Zambia Research Ethics Committee. To test the association and correlations, the chi-square test or Fischer's exact test was carried out for categorical variables and for continuous variables, a t-test was used. Multiple regression was used when considering predictive effects of variables. A p-value of <0.05 at 95% CI was considered significant.

Results: The mean age in this study was 27.5 (6.2) years ranging from 18 to 46 years with nearly half (45.3%) of the study subjects falling between 26 to 35 years age group and 134 (89.3%) of the them were female. The study found that there was a 26.7% incidence rate of keloid recurrence at 6 months while the study identified itchiness (AOR = 2.949, 95% CI: 1.27 - 6.84, p = 0.012), steroid use (AOR = 2.52, 95% CI: 1.11 - 5.74, p = 0.028) and low platelet count (B = 0.001, t = 2.063, p = 0.041) as predictive of keloid recurrence.

Conclusion: The results of this study suggest that treatment of keloids with 5-FU following surgical excision improves the treatment outcomes by 73.3%. The study found that itching with subsequent pain as adverse effect of 5-FU injections, among patients especially in the female population and low platelet count increases the reoccurrence rate of keloids.

Keywords: Keloids; Recurrence; Treatment outcome; 5-Flourouracil; Excision

Introduction

Keloid scarring is an abnormal healing response characterized by excessive localized growth of scar tissue in response to skin trauma burns or infection [1]. As a type of abnormal scarring, it is generally considered to differ from hypertrophic scarring, in that it grows outside the original wound and does not regress with time, as well as displaying microscopic structural differences [2].

There is no acceptable standard treatment in the management of Keloids and it can be challenging for the clinician to choose

which therapy to use for large or recurrent lesions [3]. The condition is notoriously difficult to treat as surgical excision alone usually results in recurrence, occasionally with a more aggressive lesion. In 1999 Fitzpatrick first introduced 5-Flourouracil (5-FU) for the treatment of Keloids [3]. Subsequent investigations have endorsed 5-FU as a viable treatment. As a result, there are many treatment options available, including steroid injection directly into the scar, laser therapy, radiotherapy and combination therapies.

The use of Keloid excision and intralesional injection of 5-Flurouracil has been proven world over to be effective in the management of Keloids [1]. However, there's paucity of data in an African setting when it comes to the management of keloids and anecdotally, lots of recurrences have been observed. This could be as a result of the low usage of combined excision and 5-FU technique that has been applied in most western countries [1].

The standard treatment used is triamcinolone after Keloid excision at the University Teaching hospital (UTH), but it has been observed that there are poor outcomes when triamcinolone is used after Keloid injection. Many studies globally have shown that the use of 5-Flurouracil gives better results. This observation has not been done before in our facility; therefore, we do not know the outcome of our patients. This study was an exploration of the use combined keloid excision and intralesional injection with 5- Fluorouracil in Zambia.

Methods

Study design

A prospective observational cohort study was carried out in the surgical unit of the University Teaching Hospitals in Lusaka, Zambia. Patients were followed prospectively during hospitalization to 6 months after discharge, and data collection was made over a period of 6 months from September 2020 to February 2021.

Participants

The study population consisted of 150 keloid patients consecutively admitted for surgical excision. All patients over 18 years of age with Keloids that were treated with 5-FU following surgical excision and were willing to participate were included in the study. All patients who met this inclusion criterion were systematically sampled by taking every second patient admitted to the surgical units.

Once the patient had consented the clinician went ahead and performed the excision of smaller lesions of Keloid, sterility was observed and local anaesthesia (Lignocaine) was used. Keloids were excised and sutured using a non-absorbable suture. There after 5-FU was injected around the lesion 0.5-2 ml of 50 mg/ml. The wound was cleaned and dressed. After two weeks the wound was inspected, cleaned and sutures removed, patient were asked to come back after 2 weeks post suture removal, thereafter repeat dose of 5-FU was given weekly for 4 weeks. Monthly follow up using observer scale was done for 6 months.

The variables studied to predict recurrence of keloids included:

Independent variables

- Gender: Male-female
- Age in years
- Presenting complaints: Itching-Pain, duration
- Clinical and biochemical readings: Mean arterial pressure, Pulse, Respiratory rate, Temperature, Haemoglobin, Urea, Creatinine, White cell count, Platelet, Alanine transaminase, and Aspartate aminotransferase.
- Major comorbid illness.

Dependent variable

Keloid recurrence: The observer scar assessment scale was used to categorize the sample into two categories to describe the outcome of keloid treatment; group one had recurrence of keloids and group two had complete healing.

Statistical analysis

Statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL, version 25). All values were expressed as mean ± standard deviation or as frequencies and percentages. Each variable was tested for differences between keloid recurrence and non-recurrence by univariate statistical methods with significance accepted at $p < 0.05$ (Chi squared test, Student's t test or Mann-Whitney test where appropriate). The multivariate analysis included all variables that were significant in the univariate analysis. A pooled multivariate logistic regression analysis was used to test the hypothesis that the study variables used affected the likelihood of keloid recurrence. The model determined the probability of increased keloid recurrence given the independent variables. Stepwise logistic-regression analysis was performed selectively to assess the predictors of keloid recurrence. This analysis resulted in a final prediction model.

This study was approved by the University of Zambia Biomedical Research Ethics Committee and the National Health Research Authority in Lusaka, Zambia.

Results

Participants

The mean age in this study was 27.5 ± 6.2 years ranging from 18 to 46 years with nearly half (45.3%) of the study subjects falling between 26 to 35 years age group and 134 (89.3%) of the them were female.

Clinical characteristics

Regarding the clinical profile of study participants as presented in table 4.2, the majority (77.3%) of the participants presented with complaints of pain which mostly lasted between 6 to 12 hours prior to seeking medical advice. Further, descriptive statistics showed that slightly over a third (34%) of participants were using steroids. Descriptive analysis of clinical and biochemical measurements, the results showed a normally distributed statistics indicating normal average values (Table 1).

Variable	Unit	N (%)	Recurrence	No recurrence	P-value
Age (years)	≤ 25 years	67 (44.7)	19 (28.4)	48 (71.6)	0.907
	26 - 35 years	68 (45.3)	17 (25)	51 (75)	
	≥ 36 years	15 (10)	4 (26.7)	11 (73.3)	
Sex	Male	16 (10.7)	5 (31.3)	11 (68.8)	0.765*
	Female	134 (89.3)	35 (26.1)	99 (73.9)	
Chief complaint	Itchiness	34 (22.7)	15 (44.1)	19 (55.9)	0.014*
	Pain	116 (77.3)	25 (21.6)	91 (78.4)	
Duration of symptoms (hrs)	< 2	37 (24.7)	11 (29.7)	26 (70.3)	0.617
	2 - 6	48 (32)	10 (20.8)	38 (79.2)	
	6 - 12	42 (28)	11 (26.2)	31 (73.8)	
	> 12	23 (15.3)	8 (34.8)	15 (65.2)	
Steroid use	No	99 (66)	20 (20.2)	79 (79.8)	0.019*
	Yes	51 (34)	20 (39.2)	31 (60.8)	
Mean arterial pressure, M (SD)		89.7 ± 6.4	89.7 ± 6	89.8 ± 6.6	0.933
Pulse, M (SD)		80.9 ± 12.6	78.6 ± 13.2	81.7 ± 12.3	0.183
Respiratory rate, M (SD)		15.9 ± 1.8	15.7 ± 2	16 ± 1.7	0.409
Temperature, M (SD)		36.3 ± 0.5	36.3 ± 0.5	36.2 ± 0.5	0.674
Haemoglobin, M (SD)		14.7 ± 1.2	14.7 ± 1.3	14.6 ± 1.2	0.621
Urea, M (SD)		4.4 ± 1.8	4.6 ± 1.8	4.3 ± 1.8	0.425
Creatinine, M (SD)		70.2 ± 10.2	68.1 ± 8.7	71 ± 10.7	0.135
White cell count, M (SD)		5.5 ± 1.4	5.4 ± 1.3	5.5 ± 1.5	0.797
Platelet, M (SD)		319 ± 79.1	293.8 ± 74.3	328.2 ± 79.2	0.018
Alanine transaminase, M (SD)		22.3 ± 6.4	22 ± 6.5	22.4 ± 6.3	0.707
Aspartate aminotransferase, M (SD)		21.2 ± 4.7	20.9 ± 5.3	21.3 ± 4.5	0.627

Table 1: Distribution of study subjects according to Keloid recurrence.
*Fisher's Exact Test; M: Mean; SD: Standard Deviation; N: Frequency; %: Percentage

Incidence of keloid recurrence

Using the observer scar assessment scale to categorize the sample into two categories to describe the outcome of keloid treatment with 5-Flouroucil injection following surgical excision, the study found that there was a 26.7% incidence rate of keloid recurrence (Figure 1).

Figure 1: The incidence of Keloid recurrence among the study population.

Evolution

Cross-tabulations of association between socio-demographics and recurrence of keloids were performed and the results showed a general trend towards complete keloid resolution; however, when a chi-square statistic was applied to determine the measure of significant associations, it was observed that there were no statistically significant differences between the groups ($p > 0.05$). Further, cross-tabulations of association between clinical factors and recurrence of keloids were performed and the results a general poor association between the groups. However, participants who mainly complained of itchiness (44.1%) were more prone to keloid recurrence when compared to participants who mainly complained of pain (21.6%): the chi-square statistic showed this to be statistically significant ($\chi2 = 6.847$, $p = 0.014$) (Table 1).

Furthermore, the cross tubulation between steroid use and recurrence showed that 39.2% of participants on steroids (intralesional Triamcinolone injection) tended to experience keloid recurrence compared to 20.2% of participants who were not on steroids (intralesional Triamcinolone injection). The chi-square statistic showed this to be statistically significant ($\chi2 = 6.223$, $p = 0.019$). However, an independent-samples t-test comparing the mean platelet counts of participants who had keloid recurrence and participants who did not have a recurrence found a significant difference between the means of the two groups ($t = -2.386$, $p < 0.018$). The mean platelet count of participants with keloid recurrence was significantly lower (293.8 ± 74.3) than the mean platelet counts of participants with no recurrence (328.2 ± 79.2) (Table 1).

A logistic regression was completed to determine the relationship between the participants' clinical characteristics (i.e., presenting complaint, steroid use and duration of symptoms) and keloid recurrence. There was no significant association between duration of symptoms and keloid recurrence. However, participants who presented with itching were about three times more likely than those complaining of pain to have recurrence of keloids (AOR: 2.949, 95% CI: 1.27 - 6.84, $p = 0.012$). Also, participants who were using steroids were about three times more likely to have keloid recurrence than those who were not using steroids (AOR: 2.52, 95% CI: 1.11 - 5.74, $p = 0.028$) (Table 2).

Variable	Unit	Adj. Odds Ratios	95% CI	p-value
Chief complaint	Pain	ref.	1	
	Itching	2.949	1.271 - 6.841	0.012
Steroid use	No	ref.	1	
	Yes	2.52	1.106 - 5.74	0.028
Duration of symptoms	< 2	ref.	1	
	2 - 6	1.126	0.383 - 3.315	0.829
	6 - 12	0.99	0.353 - 2.776	0.985
	> 12	0.942	0.289 - 3.074	0.921

Table 2: Logistic regression of clinical characteristics on Keloid recurrence.
*CI : Confidence Interval.

A multiple linear regression was carried out to ascertain the extent to which MAP, pulse, respiratory rate, temperature, haemoglobin, urea, creatinine, white cell count, platelet count, ALT and AST can predict keloid recurrence. The regression model predicted 28.9% of the variance. The model was not suitable for predicting the outcome ($F = 1.146$, $df = 11$, $p = 0.331$). However, participants' platelet count was the only predictor of keloid recurrence. Participants with low platelet count had 0.001 chance of developing a recurrence than their counterparts with higher platelet count ($p = 0.041$) (Table 3).

Discussion

Keloids are fibro-proliferative disorders very notorious for recurrence. By the definition of the study recurrence means any extension of the scar beyond original surgical wound and any elevation of scar from normal surrounding skin. Surgical removal alone as a therapy has an overall recurrence rate range from 40-100% [4]. Adding adjuvant therapies will reduce recurrence after excision. Most commonly used adjuvant is Intralesional triamcinolone

Variable	B	Std. Error	t	p-value
Platelet	0.001	0	2.063	0.041
Mean arterial pressure	0.003	0.006	0.459	0.647
Pulse	0.005	0.003	1.806	0.073
Respiratory rate	0.02	0.021	0.965	0.336
Temperature	-0.053	0.071	-0.751	0.454
Haemoglobin	-0.02	0.03	-0.654	0.514
Urea	-0.019	0.022	-0.897	0.371
Creatinine	0.005	0.004	1.452	0.149
White cell count	0.011	0.026	0.436	0.663
Alanine transaminase	0.003	0.006	0.457	0.648
Aspartate aminotransferase	0.004	0.008	0.471	0.638

Table 3: Linear regression of clinical parameters on Keloid recurrence.

B = Regression Coefficient, t = T-Test Statistic.

which combined with surgery have a recurrence rate of 40-50%; [5] however, in this study patients were given intralesional 5-Flouroucil immediately postoperatively and later on after wounds were healed. In our current study, recurrence rates are documented as 26.7% which is better than surgical excision alone and comparable to other adjuvants [6]. Also, our findings were better than Kontochristopoulus., *et al*. [7] who investigated the effects of intralesional 5-FU in 20 patients with keloid lesions on various locations including the chest, back, extremities, and earlobes. The study administered weekly intralesional injections of 0.2-0.4 ml/cm2 of 50 mg/ml 5-FU over an average of seven sessions and found that 40% of patients had good improvement, and 5% had excellent improvement while at 52-week follow-up, 47% demonstrated reoccurrence.

The treatment outcome of these patients gave a good outcome in 73.3% of participants. Poor results as judged by recurrence occurred in 26.7% of patients [7]. The good outcome observed in our patients was similar to reported success rates 76 to 100% with post-surgical irradiation in other studies [8,9]. In a study by Gupta and Kalra [10], nearly 51.7 percent of patients showed excellent flattening, and nearly 70% reported reduced itching, pain, and discharge. After following patients for 3 to 6 months, no recurrences occurred [10]. Congruent to our findings, the effects of excision followed by intralesional injection of 5-FU were studied by Haurani., *et al*. [11] in 32 patients with keloid lesions and 21 patients with hypertrophic scars enrolled in a 5-FU intralesional treatment protocol of 50 mg/ml administered every 2-4 weeks with a total dose of 500 mg after keloids were excised 2 weeks before the treatment began. At 1-year follow-up, 27% of patients reported fair or good improvement, 63% showed excellent improvement, and 19% showed recurrence of lesions [11].

With regards to reoccurrence, Wilson [12] demonstrated the lowest rate of 3.75% which may have been due to the combination of previous excision with 5-FU as well as botulism toxin similar to our findings although ours had a higher rate. This contrasts with the high rate of recurrence reported by Kontochristopoulus., *et al*. [7] who reported a recurrence rate of 47%, which may be a result of the longer follow-up time period used in this study. Most studies conducted like ours used very short follow-up times (*one year), which is not long enough to draw any conclusions about recurrence. Consequently, most studies have reported a very low recurrence rate, and others have reported no recurrence at all. Additionally, the existence of an unintended inclusion bias cannot be excluded, as study protocols may favour patients who produce positive results.

The age of our study participants ranged from 18 to 46 years. forty-five percent of the study subjects were aged 26 to 35 years. Our age group falls in the age range known to be the age group of peak incidences as reported in other studies [13,14]. These particular age groups are very susceptible to forming keloids, and they may also seek treatment more because of increased consciousness of their body image. Our study showed a significant female preponderance similar to a study by Chike-Obi., *et al*. [15] on the pathogenesis, clinical features and management of keloids, who also reported slight female-sided gender distribution. However, Olabanji and Oladele [6] reported an equal distribution which they considered a fairly consistent pattern. Increase in female number in our study may be because of the common practice of ear piercing in this region and increased cosmetic concerns in females. Female patients had a tendency to recurrence incongruent with the findings of other studies [16-18], though the difference was not significant.

Pain and itching have been associated with poor treatment outcomes in previous studies [19,20] and in this study itching was predictive poor outcomes. This could because pain and itching are among the frequently reported symptoms of keloid disease [21] and are often associated with impairment. However, Brown., *et al*.

[22] found less pain and itching complaints and minimal correlations with treatment outcome and Prabhu., *et al*. [23] also in their study to compare the efficacy of weekly intralesional injections of 50 mg/ml 5-FU versus 40 mg/ml TAC (control) in 30 patients with keloids for 4 weeks, found pruritus and pain was present in the 5-FU group but this distinction was not statistically significant. The differences between keloids and other scar types can be explained by their respective severity, which is generally less than keloids. In a prospective study, Nanda., *et al*. [24] used pure 5-FU to treat keloids and found no evidence for hypopigmentation or telangiectasias. Further evaluation of 5-FU is warranted due to its reduced side effect profile. By reducing the steroid component and utilizing a 9:1 ratio, such as Fitzpatrick, [25] adverse effects may be minimized.

There are a number of clinical studies on the efficacy of 5-FU in keloid treatment that revealed promising results [7,26,27] Fitzpatrick [25] was the first to publish an anecdotal report of a vast experience with 5-FU, although there are no quantitative data or control group presented. Fitzpatrick said that adding triamcinolone to 5-FU injections would not have any additional therapeutic effect, but it may reduce the risk of erythema caused by pure 5-FU injections [25]. Recently, a prospective study revealed that 5-FU had a significant improvement in efficacy over triamcinolone [26]. However, patient follow-up in our study was limited to 24 weeks, which is inadequate because keloids can recur from months to years after treatment.

There is a broad range of reported dosing intervals, from several injections per week to once a month. Outcome in the use of intralesional 5-FU with steroids after excision was predictable, with fewer than a quarter of the patients eventually having good results in terms of non-recurrence in size in our population. This contrasts a 64 to 100% complete flattening reported in other studies [9,28]. This is probably because our patients present with more mature lesions which are associated with poorer response as many of our patients however, often reported improvement in symptoms especially pruritus after treatment. The use of steroids gave poor result in 39.2% of cases and it was established to increase the likelihood of recurrence by two-fold in our population. Another factor in our study that correlated significantly to treatment outcome was patients' platelet count. Our findings showed that a reduction in platelet count accounted for 0.1% increase in the likelihood in Keloid recurrence. However, to the best of our knowledge, our study was the only one to have assessed the association of biochemical parameters and Keloid treatment outcomes.

5-FU drug toxicity is usually seen with intravenous dosing and primarily involves adverse haematologic effects such as anaemia, thrombocytopenia, and leukopenia [29]. No systemic side effects following injection were observed in any of the patients in our study. The study reported adverse effects of erythema, itching and significant pain at the injection site. These were generally transient or easily manageable.

Our study had several limitations. All patients were recruited from an academic hospital, possibly resulting in a selection bias towards patients with a relatively high burden of disease. This could limit the generalizability of the current results to the entire keloid patient population. On the other hand, the patients from the present study represent those who seek treatment from a medical specialist. The sample was evenly distributed on sex, age groups, and other clinical characteristics. Although the sample size in our study was not large enough to draw definitive conclusions for some of the studied variables, the findings are important due to the paucity of systematic studies about this topic. Further research is necessary to support the data.

Conclusion

The results of this study suggested that treatment of keloids with 5-FU following surgical excision improved the treatment outcomes by 73.3%. However, the study found that itching with subsequent pain as adverse effect of 5-FU injections among patients especially in the female population and low platelet count increases the reoccurrence rate of keloids. Combined treatment of surgical excision and post-surgical 5-Fu injections showed good or satisfactory outcome however, the study proposes that further studies be conducted to assess the success rate of a single treatment regimen with surgical excision and 5-FU and also to compared the efficacy of 5-FU and other adjuvant therapies.

Key Messages

Research has shown that recurrence rate is high with TAC globally; however, Radiotherapy cannot sustain all patients as the facilities are inadequate to care for the ever-increasing number of patients that need radiotherapy services for oncology.

Treatment of keloids with 5-FU following surgical excision improves the treatment outcomes by 73.3%.

Outcome in the use of intralesional 5-FU with after Keloid excision is predictable, with fewer than a quarter of the patients eventually having good results in terms of non-recurrence in size.

The supporting basic scientific data, and anecdotal observations warrant closer investigation in order to formulate best therapy options in the management of keloids.

Competing Interests

The authors declare no competing interest.

Authors' Contributions

All authors (RMB, JG, and CN) designed and are responsible for the reported research. RMB conducted analysis and prepared the initial manuscript. JG and CN coordinated and provided general advice. All authors have contributed significantly to the interpretation of the data, to the revision of the manuscript and to the approval of the final version to be submitted.

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