Topical Cashew Nut Extract (DeBCC©) for the Treatment of Basal Cell Carcinoma: A Randomized Double-blind, Vehicle-Controlled Trial

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ABSTRACT

Objectives. This study aimed to evaluate the efficacy and safety of cashew nut extract (DeBCC©) cream compared with a vehicle cream in the treatment of basal cell carcinomas (BCC), mainly by comparing each group's composite clearance rate, defined by the absence of histopathologic evidence of BCC at the target lesion site.

Methods. A randomized double-blind vehicle-controlled trial was conducted on nineteen patients, who underwent eight weekly topical treatment application sessions of either vehicle or experimental drug. Six weeks post-treatment, they underwent surgical excision of their lesions. A dermatopathologist examined these specimens. Clinical and histopathologic clearances were evaluated.

Results. The clinical clearance rate (67%) of DeBCC was significantly higher compared to vehicle (p=0.003), while the composite clearance rate (33%) was not (p>0.05). The pre-test probability of clinical clearance in concordance with histopathologic clearance (15.79%) suggests that clinical resolution of a BCC lesion may not equate to histopathologic clearance.

Conclusion. This study showed a modest clinical clearance rate but a low composite clearance rate for DeBCC cream. Further studies with bigger sample size that are limited to less aggressive BCC subtypes are needed to strongly establish the efficacy and safety of topical cashew nut extract for BCC treatment.

Key Words: DeBCC, topical cashew nut extract, cashew nut extract, basal cell carcinoma, skin cancer

Introduction

Basal cell carcinoma (BCC) comprises 75% of non-melanoma skin cancers (NMSC) and is the most common malignancy in the world.[1] There is a rising trend in the incidence of BCC because of sun exposure, tanning booth use, the continued depletion of the ozone layer, immunosuppression, and exposure to different carcinogens such as arsenic.[1] Locally, BCC accounts for more than 60% of all skin cancers reported.[2] A nine year retrospective study done at the Philippine General Hospital (PGH) Section of Dermatology yielded 137 cases from 1997 to 2005.[3] This study only included histologically-confirmed BCCs and excluded those seen by other clinics. Although it has a very low mortality rate because it grows slowly and rarely metastasizes, this skin cancer, which commonly develops on the head and neck region, can cause serious disfigurement, functional impairment and places a huge burden on healthcare services worldwide.[4]

The gold standard in the management of BCC is Mohs micrographic surgery with a low recurrence rate of approximately 1%.[1] In the Philippines, there are few dermatologists and surgeons trained in this special technique. Thus, this procedure is only offered in major medical centers in the country. The most common approach to the definitive management of BCC is standard excision with margin control under local anesthesia. The recurrence rate for this technique is 10%.[1,5] However, not all patients accept this option and not all lesions are amenable to excision, such as those in close proximity to vital structures and orifices of the face.[5,6]

Other accepted treatment modalities include electrodessication with curettage, cryosurgery, and radiation therapy. All three are operator-dependent and require much experience for success.[7] Other less accessible options include carbon dioxide laser therapy and photodynamic therapy.

Topical preparations available for use include the chemotherapeutic and cytotoxic agent 5-Fluorouracil (5-FU) and the immunomodulator, Imiquimod. Topical 5% 5-FU has long been used for BCC and its clinical success rate is reported to be 90% with a 5 year recurrence rate of 21%.[1,8] It is not readily available in the Philippines. Imiquimod was recently approved by the US Food and Drug Authority for the treatment of superficial BCC. The reported clearance rate is 75%. Treatment cost is also prohibitive.[9]

Escharotic agents have been used traditionally for warts, nevi and other superficial skin growths, including malignancies. These preparations are composed of caustic corrosive substances that produce a thick coagulated crust or

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eschar, which subsequently heals with varying degrees of scarring.[10] Unfortunately, there is lack of research in this area and most data are anecdotal. With the increasing popularity, acceptability and availability of natural remedies worldwide, increasing numbers of people are choosing plant-based/ natural escharotic agents for various skin conditions. Commonly, patients self-medicate without proper diagnosis and monitoring. Needless to say, a thorough evaluation of the efficacy and safety of such agents is required to ensure rational drug use and the public's safety.

One such escharotic agent is a topical cream prepared from the cashew nut. The oil of the pericarp of the cashew nut contains the toxic substances cardol and anacardic acid.[11] This locally prepared cream was used in several clinical studies involving the treatment of common warts and removal of nevi, with good cosmetic results; some of these studies have also been mentioned in a study on topical cashew nut extract for the treatment of BCC done by Talens et al.[12,13]

Recently, a variant of this locally made cashew nut extract (DeBCC©) has garnered several top international invention awards for its use in the treatment of basal cell carcinoma. This preparation is composed of extract from cashew nut (*Anacardium occidentale),* purified water with steeped/ infused fig tree *(Ficus carica)* leaves/ bark, lemon (*Citrus limon)* extract and talc. Talens et al. reported an open-label prospective case series of 36 patients with BCC on the face that showed 100% clinical remission after a mean of 7 treatment applications of the said drug.[15] The number of treatment applications ranged from 1 to 20 sessions. Topical treatment was applied on the lesions every two weeks, with only mild tingling sensation noted by the patients. Sixteen patients completed the 5-year follow up in the said study, and no clinical recurrences were detected in any of the patients. The main limitation of this study is the lack of post-treatment histopathologic examination to determine presence of residual tumors that may not have been clinically apparent. BCC subtypes specifically the infiltrative and morpheaform patterns have been known for their invasive behavior, spreading contiguously in fascial planes and clinically simulating and masquerading as atrophic scars.[1]

A histologic evaluation of the cashew nut extract's treatment success was therefore warranted to offer this topical preparation confidently as a viable, safe and economical treatment option. This study evaluated the clinical and histologic efficacy and safety of the topical application of cashew nut extract preparation (DeBCC©) in the treatment of BCC compared with a vehicle cream. Specifically, it compared the composite clearance rate of the cashew nut extract treatment with vehicle cream. Composite clearance rate was defined as the proportion of subjects at the 6-week post-treatment visit who were complete responders to the treatment, as proven by absence of clinical and histopathologic evidence of BCC at the target lesion site, or no histologic evidence of BCC despite clinical suspicion of BCC. Secondarily, it compared local skin reactions such as erythema, edema, induration, vesicles, erosion, ulceration, scaling and crusting between the two treatment groups. It also compared visual skin quality such as hypopigmentation, hyperpigmentation, mottled/irregular pigmentation, degree of scarring and atrophy.

Materials and Methods

This was a prospective, randomized, double-blind, vehicle-controlled trial with an interim analysis. The protocol was approved by the National Institutes of Health's Technical and Ethical Review Boards.

Eligibility Criteria

All adult patients seen at and referred to the PGH Out Patient Department, Section of Dermatology, who were diagnosed and confirmed by biopsy to have basal cell carcinoma, were screened for the study. Patients between 18 and 80 years of age entered the study if their lesions had a minimum diameter of 0.5 cm located anywhere in the body, and if they were amenable to surgical excision with marginal control under local anesthesia or Mohs micrographic surgery. Patients referred by other clinics and biopsied elsewhere were required to provide the biopsy slide for review of BCC subtype by the Dermatopathologist-Investigator. The Surgeon-Investigator then assessed if the tumor was amenable to surgical excision or Mohs micrographic surgery. Exclusion criteria included known hypersensitivity to any of the components of the trial drugs, presence of dermatologic conditions in the target site that could be exacerbated by the topical treatment or cause difficulty in the examination, lesions located in areas that would pose unacceptable cosmetic results or surgical complications when the target site is excised (e.g., anogenital region, areas in close proximity to vital structures or orifices of the face), pregnant and lactating women.

Randomization and Intervention

The study protocol was largely based on the methods described by Geisse J et al. on Imiquimod 5% cream for the treatment of superficial basal cell carcinoma.[9] Patients who met the eligibility criteria were invited to join the study. Signed informed consent was obtained. Participants were recruited and randomly allocated to either treatment arm (DeBCC© cream, from RCC Amazing Touch) or vehicle cream, based on a computer generated random number table. The clinical investigators and participants were blinded as to their treatment allocation. On the initiation visit, a baseline template was created for each patient using clear plastic overlay to trace and map the clinically evident tumor margins and local landmarks. Measurement of the

lesions' dimensions (two largest perpendicular diameters and surface area), were also recorded. Participants were asked to return every week over a maximum treatment period of 8 weeks. The cream was applied just enough to cover the lesion. They were instructed to refrain from washing the area for at least 3 hours after the application of the medications. The investigator prescribed rest periods based on the assessment of the lesion site and the evidence of local skin reactions or adverse events that would have made application of the study cream difficult. On every visit, the following local skin reactions were visually assessed using a 4-point scale (0= none, 1= mild, 2= moderate, 3 = severe): erythema, edema/induration, vesicles, erosion, ulceration, scaling, and crusting. Photographic documentation was done at baseline and on each treatment visit. The participants were also asked for other skin reactions like pain or other sensations experienced during treatment and in between sessions. Any other untoward reactions were documented as well. If the lesion was suspected to be infected, the participant received topical antibiotic ointment or oral antibiotics as deemed necessary by the investigator.

After completing the eight treatment sessions or once the lesions became clinically imperceptible, the participants were scheduled for a post-treatment excision biopsy at least six weeks hence. Both treatment arms underwent excision after the prescribed treatment period. Prior to surgery, visual skin quality assessment of the lesion site and surrounding area was done using the 4 point scale (0= none, 1= mild, 2= moderate, 3 = severe) on the following parameters: hypopigmentation, hyperpigmentation, mottled/irregular pigmentation, degree of scarring, atrophy.

Surgical excision was guided by the baseline template and photographs taken at the initiation visit. For tumors that were still clinically evident, surgical excision was done with a 3 to 4 mm margin around the original lesion margins, as seen on the baseline template. For tumors that were no longer clinically evident, a 1 to 2 mm margin based on the baseline template was done. The 12 o' clock position of the lesion was marked with a suture by the surgeon. For the histopathologic examination, three gross sections of 2 mm each were taken in either direction from the center. These were level sectioned to achieve representative sections at 1 mm interval. The remainders of the specimen were serially sectioned at 3 mm interval to the tips of the elliptical excision specimen and stained by hematoxylin and eosin for evaluation by a single blinded dermatopathologist.

Materials

Materials for this study were provided by RCC Amazing Touch, a local company that has come up with the formulation for DeBCC Cream. The treatment cream for this study was made from the exact formulation and ingredients as the DeBCC Cream. Its ingredients included extract from pericarp of cashew nut (Anacardium occidentale, Linn.), purified water, and talc.

The vehicle cream, composed of purified water and talc, were provided by the same company. Both formulations, which were similar in appearance, were separately placed in identical plastic containers. Containers that held the treatment creams were placed in a jar labelled as A. Containers that held the vehicle creams were placed in a separate jar labelled as B.

Whenever a new participant was enrolled in the study, the investigator referred to the allocation list for the treatment assignment. Dispensing of the assigned cream was done by the same investigator who randomized the participant to either the treatment or vehicle group.

Sample size

The sample size was calculated accepting a power of 90%, two-sided alpha of 0.025, using the formula for computing the difference between two proportions, with an interim analysis. The projected success rate of cashew nut extract cream was set at 70% and the assumed clearance rate for placebo was 10%, assuming a conservative clearance rate similar to that of Imiquimod. The sample size computed for each arm was 17 participants, amounting to a total of 34 participants.

This interim analysis was done after recruiting a total of 19 participants, with one drop-out. Due to difficulties in recruiting the required number of participants, this study was terminated after conducting the interim analysis.

Data processing and analysis

An intention-to-treat analysis was performed. The difference between complete composite clearance rates of the two treatment groups was computed using the Fisher's exact test. Concordance between clinical assessments and histological results was evaluated; the positive and negative predictive values, sensitivity and specificity for clinical assessment of tumor clearance were computed post hoc. Differences in the intensity of each local skin reaction that occurred during the treatment period were compared between the treatment groups using Repeated Measures test. Wilcoxon test was the initial test of choice for the secondary outcomes; however, on reevaluation, Repeated Measures test was used for analyzing the said data. Mean scores were used to study the local skin reactions that were visually documented at baseline and before surgery. The data processing was done through SPSS and SAS software.

Results

Figure 1 shows that out of 105 patients with histologically-proven basal cell carcinoma (BCC) from July 2007 to July 2010, a total of 19 patients were recruited into the study. Of these, 9 participants were assigned to the experimental group and 10 participants were assigned to the

vehicle group. All of the participants underwent 8 weekly treatment application sessions. One participant in the experimental group withdrew from the study due to distance and the inconvenience of frequent follow-up. Two patients from the experimental group who appeared to have a clinical clearance of their BCC within weeks after all treatment applications were both lost to follow-up for two years but came back with lesions on the same location as their previous tumors. Both underwent surgery. A total 18 participants finished the entire study duration, with the last participant undergoing the post-treatment surgery on October 2010. Follow-up rate based on McNemar's test was adequate, with p = 0.67 in the worst scenario, and p = 0.56 in the best scenario.

Table 1 shows the baseline characteristics of the participants.

Table 1. Baseline characteristics of patients (N= 19)

Characteristics	Experimental Group (DeBCC) (n=9)	Vehicle Group (n=10)
Sex: Male	2	5
Female	7	5
Age (years)	Range: 55-72	Range: 34-76
	Mean: 62	Mean: 59.8
	Median: 58.5	Median: 55
	Mode: 56, 64, 67	Mode: 66
Duration of lesion (months)	Range: 12 – 300	Range: 29 – 120
	Mean: 70	Mean: 55.9
	Median: 156	Median: 74.5
	Mode: 60	Mode: 36
Location of lesion	Forehead	Infraorbital
	Supraorbital	Nasal
	Nasal	Perinasal
	Infranasal	Labial
	Perinasal	Mandibular
Widest diameter (cm)	Range: 0.8 – 2.6	Range: 0.4 – 2.5
	Mean:1.8	Mean: 1.2
	Median: 1.7	Median: 1.45
	Mode: 2; 2.2	Mode: 1
Histologic subtype:		
Nodular	3	8
Morpheaform	1	0
Mixed:	5	2
Micronodular and nodular	3	1
Superficial and nodular	1	0
Nodular and infiltrative	1	0
Nodular and morpheaform	0	1

More females than males enrolled in the study. The ages of all participants ranged from 34 to 72 years. The mean age was 60 years. The duration of the lesions prior to consultation ranged from 12 – 300 months, with a mode of 36 months. All lesions were located on the face, with a mean diameter of 1.53cm. The most common histologic subtype of BCC included in the study was nodular (11/19), followed by mixed type— micronodular & nodular/ nodular & morpheaform/ superficial & nodular/ nodular & infiltrative (7/19) and lastly, morpheaform (1/19).

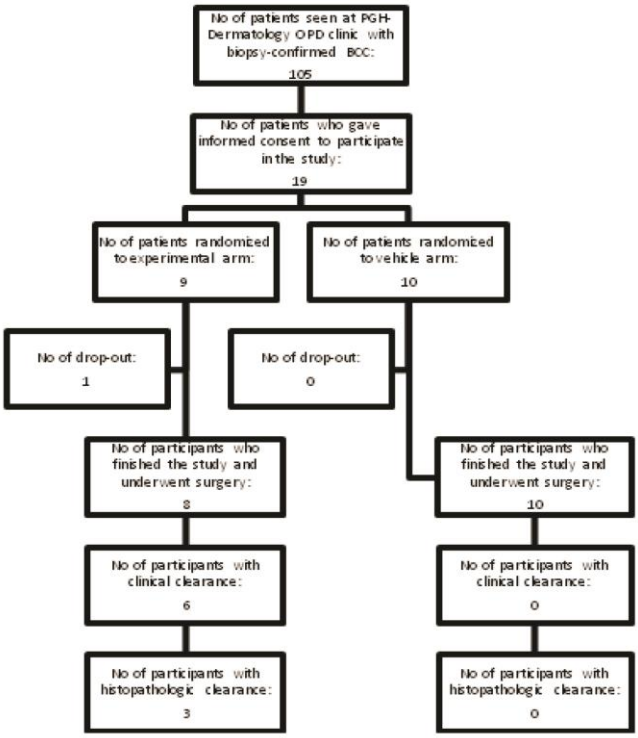


Figure 1. Participant flow

On one hand, six participants (6/9) in the experimental group were noted to have clinical clearance of the lesions after completing the treatment applications. This clinical clearance was statistically significant (p value = 0.003). On the other hand, only three participants in the experimental group (3/9) were noted to have both clinical and histopathological clearance of BCC. The computed composite clearance rate, defined as either both clinical and histopathological clearance, or histopathological clearance alone, was not statistically significant (p value= 0.087). The subtypes that resulted to a composite clearance of the BCC after treatment were the nodular and mixed (superficial & nodular; micronodular & nodular). No participant in the vehicle group had clinical or histopathological clearance of their BCC. The relative risk reduction (RRR) was 33% (CI 95% CI: -45, 58%) for DeBCC.

Table 2 shows the number of patients who achieved clinical tumor clearance and composite tumor clearance.

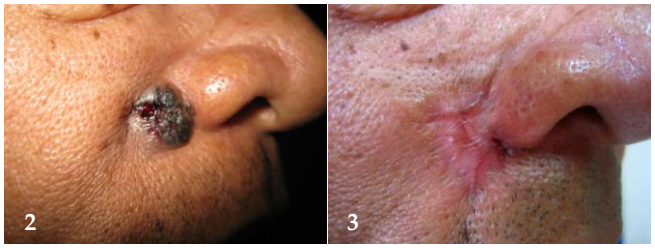
Table 2. Clinical and composite clearance

	Clinical	Histological
Treatment	6/9	3/9
Vehicle	0/10	0/10

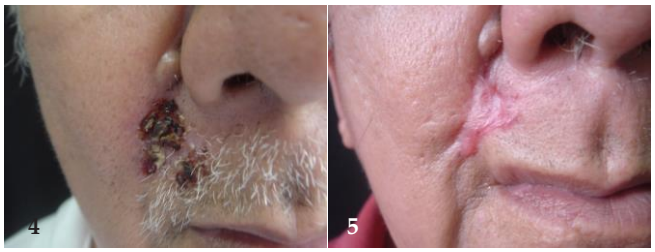
Composite clearance is defined as either both clinical and histopathological clearance, or histopathological clearance alone.

Figures 2 to 5 show photos of two patients in the treatment group. The patient shown in Figures 2 to 3

obtained only clinical tumor clearance of nodular BCC after treatment. On the other hand, the patient shown in Figures 4 to 5 obtained composite tumor clearance of ulcerated BCC after treatment.

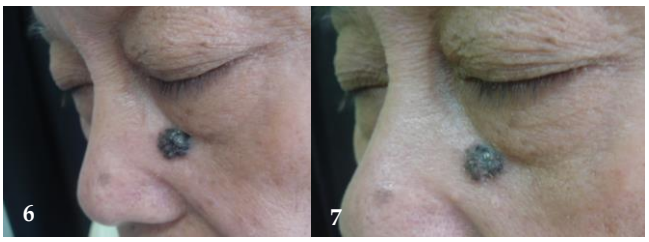


Figures 2 and 3. Before (2) and after (3) photos of patient in treatment group. Post-treatment, he was clinically assessed to have tumor clearance. Post-surgery histopathological result of the scar-like lesion revealed the same nodular BCC seen pre-treatment.



Figures 4 and 5. Before (4) and after (5) photos of a patient with ulcerated BCC in treatment group. Post-treatment, he was clinically assessed to have tumor clearance. Post-surgery histopathological result of the lesional site revealed a scar.

Figures 6 to 7 show a patient in the vehicle group. The BCC lesion remains unchanged when comparing the two photos taken before and after treatment.



Figures 6 and 7. Before (6) and after (7) photos of a patient in the vehicle group.

Post-hoc analysis was done, computing for concordance between the clinical assessments and histological results, that showed a positive predictive value (PPV) of 50% and negative predictive value (NPV) of 100%. The PPV means that only half of the BCC lesions, which were clinically assessed to have a tumor clearance, were proven to have tumor clearance based on histopathology. The NPV means that all of the BCC lesions, which were clinically assessed to have no tumor clearance, were also proven to have no clearance of BCC based on histopathology. The sensitivity of clinical assessment in detecting a tumor clearance was 100% and specificity was 81.25%. In other words, in terms of sensitivity, clinical clearance of BCC corresponded to a histopathologic clearance of BCC lesions post-treatment 100% of the time. Meanwhile, in terms of specificity, absence of clinical clearance of BCC corresponded to absence of histopathologic clearance of BCC only 81.25% of the time. The pre-test probability of the clinical assessments in concordance with the histological results was 15.79%. This means that based on the results of this study, clinical tumor clearance was not highly reflective of a histopathologic clearance.

The secondary outcomes in the study included local skin reactions shown in Table 3.

Table 3. Skin reactions and adverse events

Secondary Outcomes	DeBCC group	Vehicle group	p-value based on the Test of Repeated Measures
	Means of scores for all patients at every visit, using the 4 point scale : (0= none, 1= mild, 2= moderate, 3 = severe)		
Erythema	1.553	0.038	0.006
Edema	0.918	0.312	0.004
Bleeding	1.820	0.162	<0.001
Vesicles	0	0	-
Pain	2.252	0.262	<0.001
Tingling	1.092	0.276	0.266
Burning	2.014	0.150	<0.001
Pruritus	0.173	0.338	0.924
Headache	0.060	0.100	0.395
Malaise	0	0.075	0.036

The mean scores of these local reactions, namely erythema, edema, and bleeding, were higher in the experimental group. Higher mean scores for the symptoms of pain, tingling, burning, and throbbing, were also seen in the experimental group. The vehicle group had higher mean scores for pruritus and headache. Other symptoms, such as cool sensation, fever, myalgia, fatigue and malaise, were noted in the placebo group alone. Among these values, erythema ($p = 0.006$), edema ($p = 0.004$), pain ($p < 0.001$), burning ($p < 0.001$), and bleeding ($p < 0.001$) showed significantly higher scores in the experimental group.

Visual skin quality assessment at baseline and post-treatment (presurgery) in the experimental group showed that the mean score for hyperpigmentation decreased after all the treatment application sessions. However, in this group, the scores of hypopigmentation, scarring, atrophy and telangiectasia increased. In the placebo group, mottling/irregular pigmentation scores increased, while scarring scores decreased after all the treatment applications. For those with clinical clearance, visual skin quality at the

end of treatment period showed a decrease in hyperpigmentation and mottling/irregular pigmentation; and an increase in telangiectasia, scarring, atrophy, and erythema.

Discussion and Analysis

This study corroborates the findings of Talens et al. that the escharotic agent DeBCC can produce clinical clearance of BCC tumors. While their study reported a 100% clinical remission, ours had a modest result of 67%. This lower clinical clearance rate may be due to the fact that we limited our treatment applications to a maximum of 8 sessions while the previous study performed up to 20 treatment sessions before achieving clinical clearance. It is possible that extending the sessions might improve the results. However, for ethical reasons, we opted to limit our trial period to the average number of treatment applications based on their previous study to avoid delay in providing the definitive surgical management.

This trial also confirms our suspicion that clinical clearance may not correlate with histopathologic clearance as shown by a low composite clearance rate of 33% for the treatment group and a pre-test probability of 15.79%. These findings point to serious issues in using topical medications for malignancies. Firstly, can this topical treatment be offered only for less aggressive subtypes of BCC such as superficial or nodular BCC, or restricted to superficial BCC alone, as in the case of Imiquimod? Post-hoc analysis revealed that the histologic types of treatment failures were the nodular, nodular & micro nodular, pigmented & nodular, pigmented, nodular & morpheaform, nodular & infiltrative subtypes. The histologic subtypes that had tumor clearance were the nodular and ulcerated types. Unfortunately, this study could not evaluate outcomes in relation to histologic subtype due to the uneven distribution of subtypes; also, the BCC subtypes in our population were not complete as we had no superficial subtype in our sample population. Secondly, if this modality is offered, is there a clinical parameter that can be used to determine which among the treated lesions are truly cleared? For example, can a dermatoscope, which is a simple handheld magnifying tool used to assess morphologic features of common skin tumors, be utilized to assess tumor clearance and guide the clinician in continuing or discontinuing treatment applications?

Local skin reactions were more intense in the experimental group. This is expected since the medication is an escharotic agent. Nonetheless, all participants endured these reactions well, with none withdrawing from the study due to intolerable skin reactions.

The visual skin quality of those with clinical clearance showed acceptable cosmetic results. This is probably the reason why some patients who experienced clinical remission were initially lost to follow-up, returning for surgery only when their lesions recurred.

The low patient recruitment despite financial support for the transportation and surgical expenses probably implies low acceptability among patients for this procedure. Many of those eligible for the study opted to have surgery done right away rather than wait for a 3-month delay. Some patients did not agree to go through the multiple treatment application sessions. However, for those who prefer non-invasive approaches, this procedure may be an option in the future.

The RRR of 33% favors the trial drug but the confidence interval (CI 95%: -4%, 58%) shows that this study is still inconclusive, probably due to the small sample size.

Conclusion and Recommendations

This vehicle-controlled study showed a modest clinical clearance rate but a low composite clearance rate for DeBCC cream after 8 weekly treatments. Intense local skin reactions were observed but these were all bearable. For those with clinical clearance, visual skin quality at the end of treatment period showed acceptable cosmetic results.

Currently, the use of topical cashew nut extract cream as an efficacious treatment for basal cell carcinoma is still in need of sufficient evidence. Further studies are needed to establish efficacy and safety of this topical cashew oil preparation. In particular, a multicenter study would be ideal for a larger population catchment and better follow up among participants. We also recommend limiting the trials to less aggressive subtypes such as nodular and superficial BCC and to determine the relationship of histologic subtype on the outcomes. We also recommend using Moh's micrographic surgery as the definitive mode of management for both treatment arms and extending the number of treatment applications beyond eight sessions. Using dermoscopy findings as clinical guide to treatment may also be explored.

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