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Journal of Dermatology and Cosmetic Surgery

Research Article

# Safety and Efficacy of Hydrogen Peroxide Topical Solution, 40% (w/w), in Patients with Seborrheic Keratosis: A Follow up Study

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Received: 25 June 2021; Accepted: 18 July 2021; Published: 17 August 2021

Citation of this article: Anto, A., Afshan, G., Vinay, KN., Ravikumar, BC., Nagesha, PC., Rangegowda. (2021) Safety and Efficacy of Hydrogen Peroxide Topical Solution, 40% (w/w), in Patients with Seborrheic Keratosis: A Follow up Study. J Dermatol Cosmetic Surg, 2(1): 10-17.



## Abstract

**Introduction:** Seborrheic keratosis are common benign epidermal tumors developing after middle-age. Approved topical treatments for seborrheic keratosis (SKs) are an unmet need.

**Objective:** To evaluate the safety and efficacy of 40% hydrogen peroxide topical solution (HP40) versus vehicle for the treatment of SKs.

**Methodology:** A total of 50 patients with at least 2 SKs were selected and one lesion on each patient was treated with HP40 and the other with vehicle. Follow up was done at 3, 7 and 15 weeks. At each visit, SKs were graded using the Physician's Lesion Assessment (PLA) scale (0=clear; 1= nearly clear; 2=<1 mm thick; and 3=>1 mm thick). Solution was applied at first visit and at 3 weeks if PLA score was higher than 0.

**Results:** At 15 weeks, significantly more patients treated with HP40 than with vehicle achieved a PLA score of 0 (42% versus 0). Mean PLA score at 15 weeks was 0.82±0.87 in HP40 group and 2.96±0.2 in control group ($p<0.001$). Local skin reaction was only mild burning sensation and resolved within few days.

**Conclusion**: Application of HP40 was well tolerated and effective in the removal of SKs.

**Keywords**: HP40, Hydrogen peroxide, Seborrheic keratosis

**Abbreviations:** HP40: Hydrogen Peroxide 40% solution; SK: Seborrheic Keratosis; PLA: Physician Lesion Assessment Scale; FDA: Food and Drug Administration; mm: Millimeter

## Introduction

Seborrheic keratosis (SKs) are among the most common benign skin lesions [1]. Patients have wide ranges of motivations for treating and/or removing SKs, including embarrassment from the unsightly nature of the lesion, physical irritation or pruritus, and a desire to look younger [2]. Common techniques for SK removal involve cryosurgery, electrosurgery, curettage, or surgical excision. However these procedures are cumbersome. There is, however, a notable lack of well-controlled clinical studies evaluating the efficacy and complication rates of these procedures. Thus, there is a significant and unmet need for a safe, effective, noninvasive, and cosmetically acceptable treatment for this common condition.

Hydrogen peroxide topical solution 40% (w/w) (HP40) is a proprietary formulation of a stabilized, high-concentration hydrogen peroxide (HP) solution that is the first and only US Food and Drug Administration-approved topical treatment for raised SKs. The results of a dose-ranging, phase 2 study demonstrated that topical HP40 was clinically more efficacious than HP 32.5% for treating facial SKs, with both concentrations significantly better than vehicle [3]. this study was done to evaluate the safety and efficacy of HP40 compared with the safety and efficacy of vehicle for the treatment SKs.

## Methodology

A prospective comparative study conducted among 50 seborrheic keratosis patients who attended DVL OPD in Hassan Institute of medical Sciences. Eligible patients were adults >18 years of age with 2 stable, clinically typical, discrete SKs that are more than 2 mm in length and width anywhere on body.

Patients with SKs in intertriginous areas, pedunculated SKs, SKs covered by hair that would interfere with application of the study drug or the study evaluations and Facial SKs on the eyelids or within 5 mm of the orbital rim were excluded from the study [4].

Fifty patients satisfying inclusion and exclusion criteria, were recruited irrespective of sex, duration and response of disease to previous therapies. A detailed history of the patient including name, age, sex, occupation, marital status, family history and past history was taken. A thorough clinical examination of patients was done and findings were recorded. Written informed consent was taken from the patients after explaining the procedure in understandable language. In each patient two stable, clinically typical, discrete SKs that are more than 2 mm in length and width were selected. One lesion in each patient was allocated to HP40 group and the other lesion to Vehicle group by simple randomization. The size of the lesions was measured and recorded. For one lesions in each patient Hydrogen peroxide 40% was applied and for the other lesion vehicle was applied. Group 1 consisted of 50 case lesions for which HP40 was applied and Group 2 consisted of 50 control lesions for which Vehicle was applied (Figure 1).

The study medication or vehicle was applied with the use of a single-use, disposable applicator.The treatment solution or vehicle was rubbed onto the 2 SKs by using firm pressure in a circular

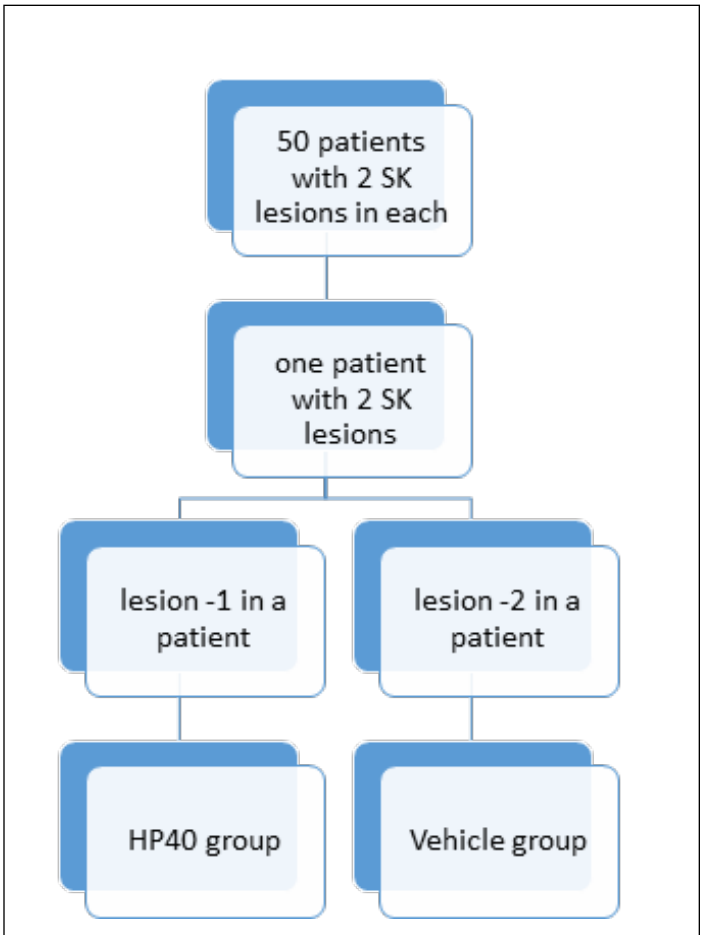



**Figure 1: Flowchart showing selection of patients and allocation of lesions to each group.**

motion for approximately 20 seconds per SK (a total time of 40 seconds for the first round of application to 2 lesions); the application cycle was repeated in the same order up to 3 times. The total time for 4 rounds of applications to 2 SKs was approximately 2 minutes and 40 seconds. Patients were monitored for at least 20 minutes after treatment for adverse events, including local skin reactions. 3 weeks after the first treatment, SKs were assessed and if it's not completely cleared it was re-treated. Assessment was done on 3, 7, 15 weeks. Clinical photographs were taken at beginning of the study, at each follow up visit and after completion of the treatment. Clinical photographs were compared and statistical analysis was done. Clinical Assessment was by using Physician's lesion assessment (PLA) scale with four grades starting from "0" for no visible SKs, "1" for nearly clear SKs, "2" for a thin SK 1 mm or less in depth and "3"for a thick SK more than 1 mm in depth

Institution Ethics Committee approval was obtained before starting the study.

## Results

One lesion in each patient was selected for HP40 and control group respectively in a total of 50 selected patients. 22 patients (44.0%) were females and 28 were males (56%) (p=1). Age group of the patients ranged from 34 – 70 years and mean age of the patients was (57.38±9.05) (p=1) (Table 1).

Response to treatment was measured as thickness of SK. Mean PLA at 3 weeks in HP40 group is 1.76±0.8 and in control group it was 3 (p<0.001). Mean PLA at 7 weeks in HP40 group was 1.02±0.82 and 2.96±0.2 (p<0.001). Mean PLA at 15 weeks in HP40 group had significantly reduced to 0.82±0.87 and control was 2.96±0.2 (p<0.001) (Table 2, Graph 1). Complete resolution was seen among 21 patients among HP40 group (42%) and none in control group and this was found to be significant (p<0.001).

21 patients in HP40 group had complete resolution by 15 weeks (Figure 2 and 4) and 20 patients almost clear lesions (Figure 3). Whereas in Vehicle group none of the participants achieved completely clear or almost clear lesions at 15 weeks.

Side effects included only mild burning sensation among 6 HP40 group patients (12%) and was not found to be significant (p=0.012). There were no reported recurrences in the study

## Statistical Analysis

Data was entered in Microsoft Excel and SPSS software was used for the analysis. Chi- square test and Mann-Whitney U test was used for analysis.

## Discussion

There are different modalities that had been tried for the treatment of SK in literature, with no standard first line modality of treatment for the same. An extensive medical literature review revealed no prior large randomized controlled trials evaluating drug or procedural treatment options for removal of SKs [5-8]. After up to 2 treatments with 40% hydrogen peroxide topical solution, significant improvements were seen in clearing SKs from the face, trunk, and extremities compared with vehicle. Adverse effects were limited to local skin reactions, which were mostly mild to moderate and self-limited. Only patients treated with HP40 had complete clearance (PLA score of 0) and no patient treated with vehicle met these very rigorous end points. Calculations based on complete clearing (PLA score of 0) of target SK lesions of each patient were used to establish efficacy, but such rigorous methods may not reflect assessment of treatment of SKs in a real-world clinical setting. Patients may self-define treatment success after an aesthetic removal of a raised SK on the basis of what is reflected in the mirror (note the nearly clear lesions in Figure 3) rather than what was measured by a physician using a necessarily stringent

**Table 1: Comparison of parameters in HP40 group and Vehicle group.**

| Parameter | HP40 group | Vehicle group | P value |
|---|---|---|---|
| Number of lesions | 50 | 50 | P<0.001 |
| Males / Females | 28/22 | 28/22 | P=1 |
| Side effects | Mild burning sensation – 6/44 | Nil | P=0.012 |
| PLA at the end of the study | 0.82±0.87 | 2.96±0.2 | P<0.001 |
| Complete resolution | 21 (42%) | Nil | P<0.001 |
| Recurrence | Nil | Nil | - |

**Table 2: Number of cases and controls having PLA scores 0,1,2 and 3 at each follow-up visits.**

| Weeks | HP40 group (50) | Control group(50) |
|---|---|---|
| 3 weeks | PLA 0 -nil<br>PLA 1 - 23<br>PLA 2 - 16<br>PLA 3 - 11 | PLA 0 - 0<br>PLA 1 - 0<br>PLA 2 - 0<br>PLA 3 - 50 |
| 7 weeks | PLA 0 - 13<br>PLA 1 - 26<br>PLA 2 - 8<br>PLA 3 - 3 | PLA 0 - 0<br>PLA 1 - 0<br>PLA 2 - 2<br>PLA 3 - 48 |
| 15 weeks | PLA 0 - 21<br>PLA 1 - 20<br>PLA 2 - 6<br>PLA 3 - 3 | PLA 0 – 0<br>PLA 1 - 0<br>PLA 2 - 2<br>PLA 3 - 48 |

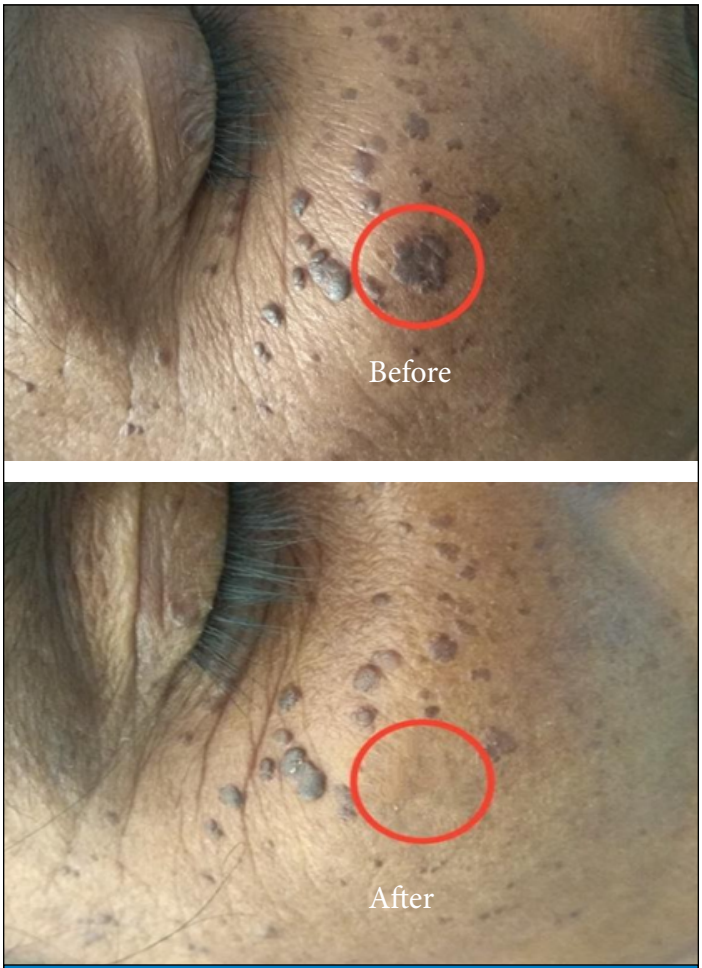
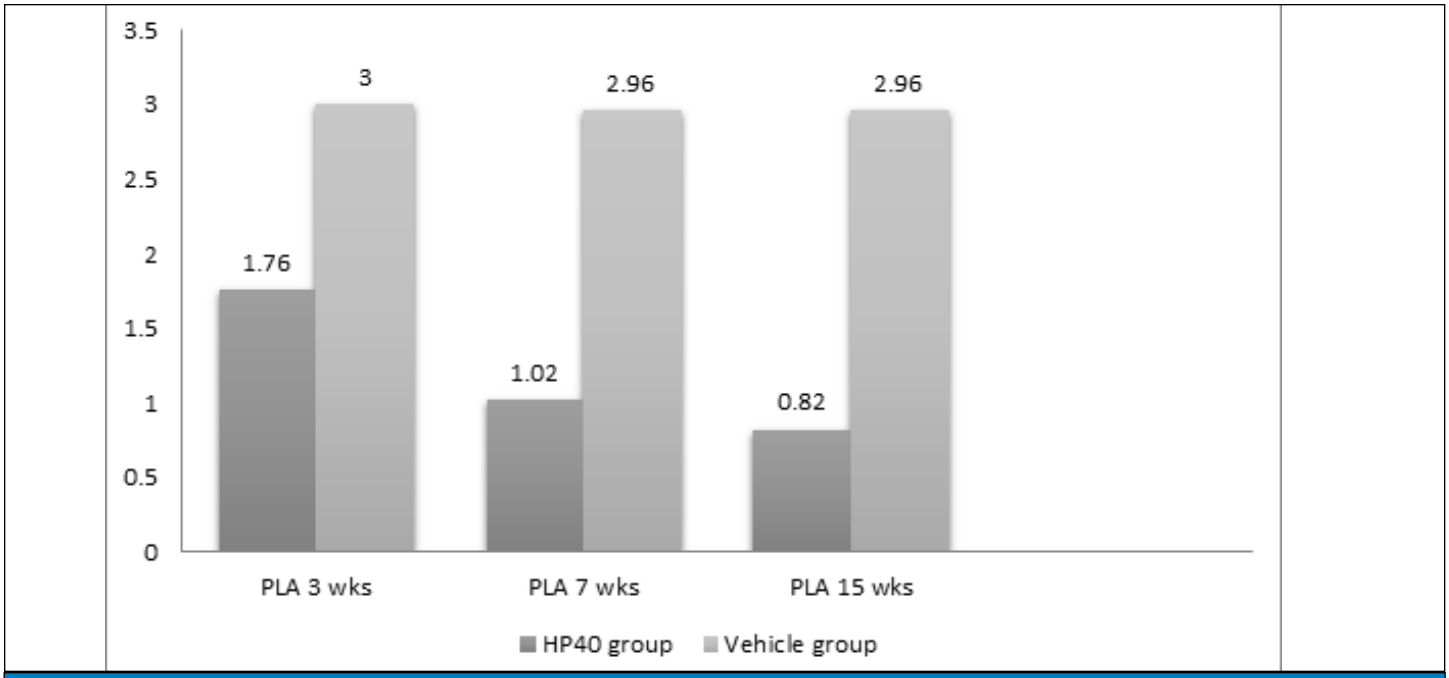



**Figure 2: HP40 group - Patient number 31, before and after treatment.**

scale in clinical trials [9,10].

To better understand treatment outcome at the individual level, comparison was done between two lesions of same patient one treated with HP40 and other with vehicle solution. By this individual variations between patients were avoided. As expected, a higher mean per-patient percentage of treated lesions with a PLA score of 0 (clear) or a PLA score of 1 or lower (clear or nearly clear) was observed with HP40 versus with vehicle, with the overall rates being 42% versus 0 and 40% versus 0, respectively. HP40 provides a novel, standardized, noninvasive, and elegant topical method to treat SKs that affords both patients and practitioners an alternative to the currently used destructive/ablative modalities with narrow therapeutic windows. The reasons given by patients for avoiding SK treatment include the fear of scarring, permanent hypopigmentation, and treatment-related pain and discomfort [2]. Adverse effects in our study was transient and had resolved by the end of the study. Mild burning sensation only occurred in 12% of lesions treated with HP40 and there was no reported scarring, erythema, scaling or pigmentary changes associated with the treatment. Overall, HP40 was extremely well tolerated, with less incidence of adverse effects not significantly higher than vehicle. The mechanism of action of HP40 for the treatment of SK has not been fully elucidated. However, HP at various concentrations has been studied across numerous industries [11-14]. It is considered that with penetration of the proprietary HP40 solution into the SK lesion, HP may act not only through its direct oxidation of organic tissues, generation of reactive oxygen species, and local lipid peroxidation but also through generation of local concentrations of oxygen that are toxic to SK cells [15-18]. Recent *ex vivo* skin implant studies of neonatal foreskin suggest that HP40 leads to less cytotoxicity and greater melanocyte viability than with liquid nitrogen [19]. Ongoing studies are investigating the safety and efficacy of HP40 in darker skin types as well as the explicit assessment of patient satisfaction with treatment results. Future evaluations of HP40 compared with traditional destructive procedures (eg, cryosurgery) may have clinical utility.

Baumann et al. [20] in 2018 compared results from 2 identical, randomized, double-blind,placebo-controlled, phase 3 studies on Safety and efficacy of hydrogen peroxide topical solution, 40%




**Graph 1: Graph comparing mean PLA in HP40 group and Vehicle group.**

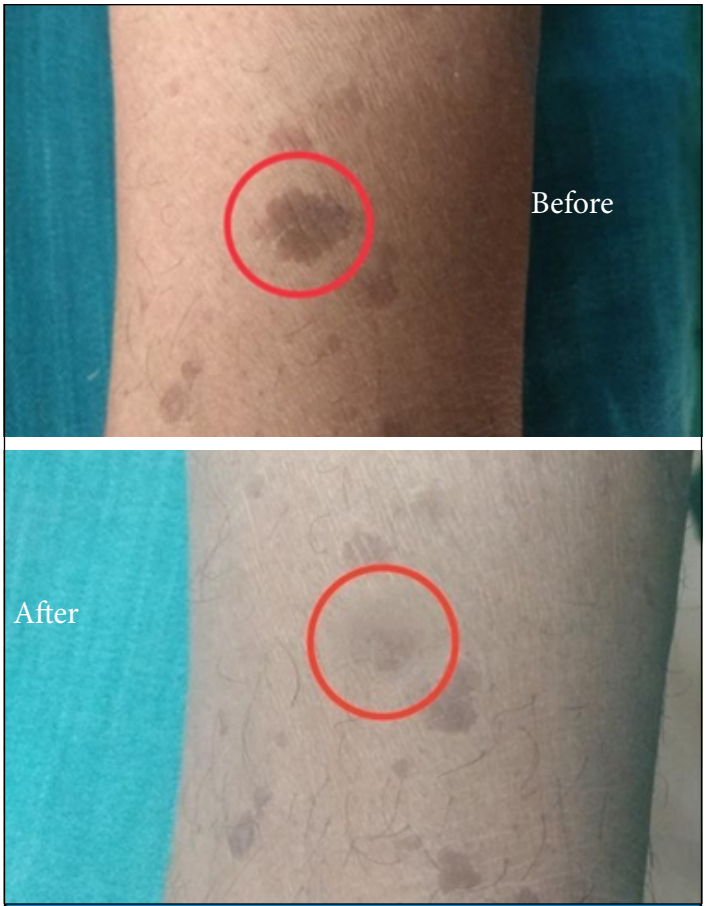



**Figure 3: HP40 group - Patient number 8, before and after treatment.**

(w/w),in patients with seborrheic keratosis: A total of 937 patients with 4 SKs each were randomized 1:1 to HP40 or vehicle and treated. Those with no significant response were treated again after 3 weeks and were followed up. 30% patients in HP40 group had complete clearance of SK and 51% had nearly complete clearance versus 1% and 7% in vehicle group. In our study it was 40% and 42% in HP40 group as compared to 0 in vehicle group. Side effects were mild and subsided before the completion of study. Application of HP40 was found to be well tolerated and effective in the removal of SKs (Table 3).

Smith et al. [21] compared two randomized controlled studies in 2018 for site specific response of hydrogen peroxide 40% to SKs and found that SK clearance with HP40 was highest among SKs on the face and lowest among SKs on the extremities. Dyspigmentation rates were lowest among SKs treated on the face. Anatomic location of SK was found to be a predictor of both treatment response and risk of dyspigmentation with HP40 application. In our study site wise comparison was not done and dyspigmentation was not observed among the participants after HP40 or vehicle. This would be due to variation in skin types (Table 3).

DuBois et al. [3] conducted a study in 2014 on 119 patients to study dose response profile of high concentration hydrogen peroxide on SKs on face. Greater magnitude of effect was seen with

**Table 3: Comparison of parameters in each studies with our study.**

| | Baumann et al. [20] | Smith et al. [21] | DuBois et al. [3] | Stephanie Kao et al. [19] | This study |
|---|---|---|---|---|---|
| Number of cases vs controls | Study 1<br>223 vs 227<br>Study 2<br>244 vs 243 | 467 vs 470 | 39 vs 39 vs 41 | Ex vivo evaluation of cytotoxicity | 50 vs 50 |
| Study between | HP40 vs Vehicle | HP40 vs Vehicle | HP40 vs HP32.5 vs Vehicle | HP 40 vsCryotherapy | HP40 vs Vehicle |
| Site of lesions | 4 lesions ( atleast 1 on face & 1 on trunk / extremity) | 4 lesions ( atleast 1 on face & 1 on trunk / extremity) | Single face lesion | -- | Anywhere on body |
| Improvement | Mean per-patient % of clear or near clear SKs<br>Study 1 – 47% vs 10%<br>Study 2 – 54% vs 5% | Clear or near clear :<br>65% vs 10% - facial<br>46% vs 5% - Trunk<br>38% vs 9% - extremities | Clear or near clear :<br>HP40 – 68%<br>HP32.5 – 62%<br>Vehicle – 5% | -- | Mean PLA score of 0.82 in HP40 vs 2.96 in Vehicle group |
| Side effects | Mild – erythema, scaling, hyperpigmentation | Delayed adverse effects like dyspigmentationand scaring were low and least reported for facial SKs | Mild and transient – erythema, edema, stinging | Less pigmentary alteration with HP40 compared to Cryotherapy | Transient mild burning |

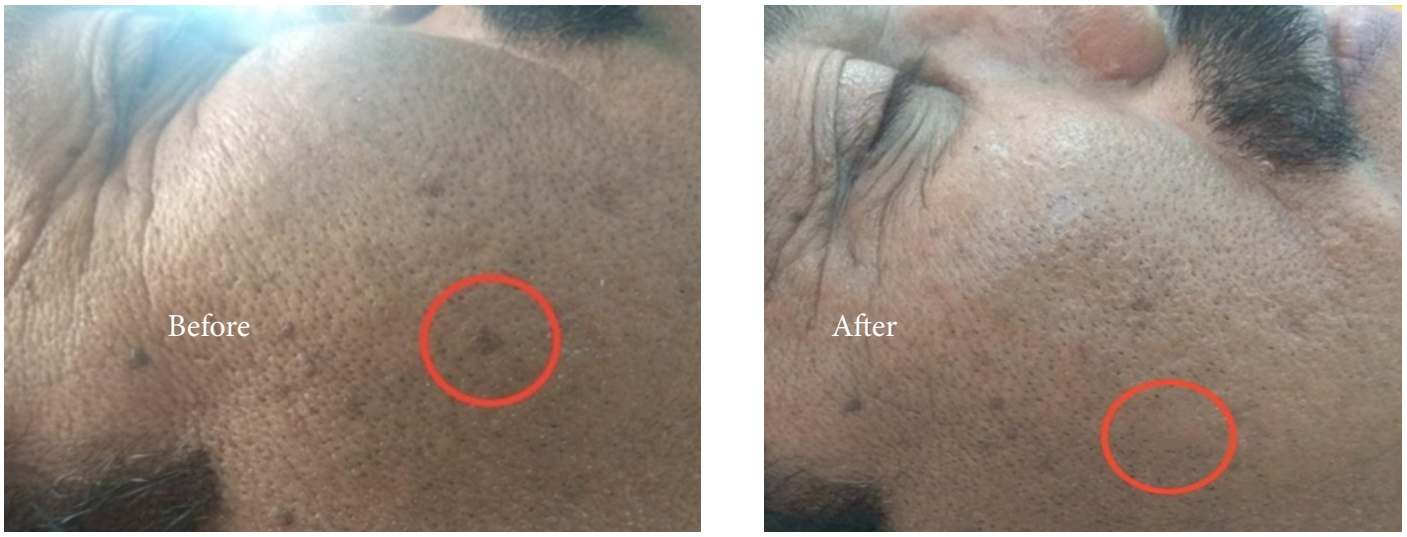



**Figure 4: HP40 group – patient number 19, before and after treatment.**

the 40% concentration than the 32.5% concentration. Hydrogen peroxide solution had a favorable safety and tolerability profile at both concentrations. In our study 40% solution was used and found to be efficacious and with low adverse effects (Table 3).

Stephanie Kao et al. [19] in 2018 conducted a study comparing cytotoxicity and melanocyte viability after 40% hydrogen peroxide and cryosurgery on SKs and found that HP40 might be less caustic option for SK removal that reduces the risk of post treatment pigmentary alterations (Table 3).

## Limitations

The number of treatment sessions for each lesion in these studies was limited by protocol design to 2, and the optimal number of treatment sessions to clear all lesions was not evaluated. Fitzpatrick skin type of patients were not taken in to consideration. It is likely that even greater efficacy would be achieved if more than 2 HP40 treatment sessions were applied. Factors influencing treatment failure were not evaluated. Other limitations are small sample size and shorter term of follow-up.

## Conclusion

Though there are different modalities in treating SK most are with less efficacy and side effects like pigmentary changes and permanent scaring. The current results demonstrate that HP40, which is a proprietary, stabilized, high-concentration HP-based topical solution, effectively treats SKs of the face, trunk, and extremities, with a low risk of inducing pigmentary changes and scarring.

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