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Therapeutics

Skin tolerability and efficacy of combination therapy with hydrogen peroxide stabilized cream and adapalene gel in comparison with benzoyl peroxide cream and adapalene gel in common acne. A randomized, investigator-masked, controlled trial

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Summary

Background Combination therapy with antiseptics such as benzoyl peroxide (BP) and topical retinoids is widely used as first-line treatment for acne vulgaris (AV). However, these combinations could have a suboptimal skin tolerability. Recently, a new formulation of hydrogen peroxide (HP) 1% in stabilized cream (Crystacide®; Mipharm, Milan, Italy) became available. A previous clinical study has shown that HP cream monotherapy presents a better skin tolerability in comparison with BP in patients with mild AV.

Objectives To evaluate the tolerability and the efficacy of combination therapy with HP cream and adapalene 0·1% gel in comparison with the combination of BP 4% cream and adapalene 0·1% gel in the treatment of mild to moderate AV.

Methods In a randomized, investigator-blinded trial, 52 patients (mean ± SD age 25 ± 6 years; 19 men and 33 women) with AV were randomly assigned to HP cream and adapalene gel (group HP + A) or to BP cream and adapalene gel (group BP + A), for eight consecutive weeks. Efficacy was assessed by total (TL), inflammatory (IL) and noninflammatory (NL) lesion counts performed at baseline and weeks 4 and 8. Tolerability was assessed by evaluating skin erythema, burning and dryness at weeks 4 and 8.

Results All patients completed the study. At baseline, the mean ± SD numbers of TL, IL and NL were 44 ± 9, 25 ± 7 and 19 ± 6 in group HP + A and 40 ± 9, 21 ± 7 and 19 ± 9 in group BP + A, respectively. At the end of the treatment period, TL, IL and NL were reduced by 93%, 92% and 95%, respectively, in group HP + A and by 88%, 86% and 90%, respectively, in group BP + A. A significantly ($P = 0{\cdot}0025$) greater reduction in NL was observed in group HP + A in comparison with group BP + A. Tolerability was significantly better in group HP + A in comparison with group BP + A ($P = 0{\cdot}02$). Skin dryness and burning sensation were more frequent in group BP + A.

Conclusions The combination of adapalene and HP cream is an effective topical treatment regimen in mild to moderate AV. This combination has shown a better tolerability profile in comparison with the combination of BP and adapalene.

Key words: acne vulgaris, combination therapy, hydrogen peroxide, randomized controlled trial

Acne vulgaris (AV) is a very common disease, affecting 80–85% of teenagers and young adults.[1] The pathology of AV is complex, involving abnormal keratinization, hormonal functions, immune hypersensitivity and

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bacterial growth.[2] The disease is limited to pilosebaceous follicles of the head and upper trunk. *Propionibacterium acnes* is an obligate anaerobic microorganism that plays a pivotal role in the physiopathology of inflammatory AV.[3] Mild papulopustular acne is generally responsive to topical treatment. Oxidative agents such as benzoyl peroxide (BP) have a potent bactericidal activity against *P. acnes*.[4] Topical BP is very effective in the treatment of mild to moderate papulopustular AV. However, its use can cause skin irritation or dryness.[5] BP rapidly decomposes into benzoic acid and hydrogen peroxide (HP), and benzoic acid can be responsible for skin irritation and erythema. Combination therapy with antiseptics such as BP and topical retinoids such as adapalene is widely used as first-line treatment for AV. However, these combinations could have a nonoptimal skin tolerability profile. Recently, a new formulation of HP 1% in stabilized cream became available.[6] A previous clinical study has shown that HP cream presents a better skin tolerability in comparison with BP[7] in patients with mild AV. So far, no clinical data have been available regarding the efficacy and safety profile of this oxidative compound in the treatment of acne in combination with adapalene in comparison with the combination of BP and adapalene.

We aimed to evaluate the efficacy and skin tolerability of combination therapy with HP cream and adapalene 0·1% gel (group HP + A) in comparison with the combination of BP 4% cream and adapalene 0·1% gel (group BP + A) in the treatment of mild to moderate AV.

Patients and methods

The study was a randomized, prospective, investigator-masked, 1 : 1 parallel-group trial. Between October 2002 and April 2003, 90 patients were screened. Main inclusion criteria were: male or female aged 15–35 years with mild to moderate AV according to Lehmann *et al.*[8] and defined as: at least 10 and < 50 inflammatory lesions (IL), at least 10 and < 100 noninflammatory lesions (NL) and no more than two nodulocystic lesions. Patients with acne conglobata, severe acne or requiring more than topical treatment were excluded from the study. To qualify for study entry, subjects had to observe an adequate washout period of at least 4 weeks for topical antiacne treatments or oral antibiotics. In total, 52 patients (19 men and 33 women, mean ± SD age 25 ± 6 years) with mild to moderate AV, affecting mainly the face, met inclusion and exclusion criteria and were enrolled in the study, after their informed consent. Enrolled patients were randomized to apply HP cream (Crystacide® 1%; Mipharm, Milan, Italy) once daily in the morning and adapalene gel 0·1% (Differin® gel; Galderma, Italy) once daily in the evening (26 patients) or to apply BP cream (Panoxyl® cream 4%; Stiefel, Italy) in the morning and adapalene gel in the evening (26 patients), for eight consecutive weeks. Randomization was performed using a computer-generated randomization list (Arcus Quickstat, Cambridge, U.K.) with a block of six in a 1 : 1 ratio. No other topical treatments for acne were allowed during the study duration. Efficacy was assessed at each visit (baseline, week 4 and week 8) by counting total lesions (TL), NL and IL. At week 8, a clinical global assessment, in comparison with baseline, was performed using a 0–4 qualitative score: 0, worsening; 1, no improvement; 2, mild improvement; 3, good improvement; 4, very good improvement. Tolerability was assessed at weeks 4 and 8 on a 0–3 qualitative scale (0, poor tolerability; 3, very good tolerability), and erythema, dryness and burning were evaluated using a 0–3 qualitative score: 0, none; 1, mild; 2, moderate; 3, severe. To assure the blinded characteristics of the trial, an investigator unaware of the treatment allocation (F.L.) performed the efficacy and tolerability evaluations.

Statistical methods

A previous controlled trial,[7] conducted in patients with mild acne, has shown that HP cream monotherapy was better tolerated than BP 4% gel. The sample size was calculated on the hypothesis of finding a difference in the skin tolerability score in favour of the HP + adapalene combination of at least 0·8 ± 0·7 points in comparison with the BP + adapalene group. With a power of 95% and a type I error of 0·05, a total of at least 24 patients per treatment arm had to be recruited in the trial. The sample size calculation was performed using the StudySize software ver. 1.07 (CreoStat HB). Fisher's exact test, the Mann–Whitney test and the paired *t*-test were used, when appropriate, to compare clinical study variables. Values are presented as mean ± SD for continuous variables and as median values for ordinal variables. $P < 0·05$ was considered significant.

Study outcomes

The study endpoints were: (i) to assess the skin tolerance by evaluating erythema, dryness and

burning sensation (tolerability score: TS); and (ii) to evaluate the reduction in mean IL, NL and TL (TL = IL + NL) counts in comparison with baseline. Spontaneously reported adverse events were recorded at each scheduled visit. The efficacy and tolerability evaluations were performed on an intention-to-treat basis.

Results

All patients completed the study. Patients' demographic characteristics are summarized in Table 1. At baseline, the two groups were well balanced regarding the AV lesions count. The mean ± SD numbers of TL, IL and NL were 44 ± 9, 25 ± 7 and 19 ± 6 in group HP + A and 40 ± 9, 21 ± 7 and 19 ± 9 in group BP + A, respectively. In comparison with baseline, both combination treatments significantly reduced acne lesions count. At week 8, HP + A treatment reduced the number of TL, IL and NL to 3·2 ± 2, 2·5 ± 1 and 0·7 ± 1, respectively. The BP + A regimen reduced the number of TL, IL and NL to 5·4 ± 2, 3·1 ± 2 and 2·3 ± 2, respectively. At week 8, a significantly ($P = 0·0025$; Mann–Whitney test) greater reduction in NL was observed in group HP + A in comparison with group BP + A (Fig. 1). At week 8, in comparison with baseline the clinical improvement was judged as very good (score 4) in 24 (92%) of 26 patients in group HP + A and in 17 (65%) of 26 in group BP + A ($P = 0·038$; Fisher's exact test). Figure 2 shows the number of patients who complained of mild or moderate erythema, dryness and burning sensation in the two treatment groups during the study. No serious adverse events were recorded during the trial period in either group. No severe cases of erythema, burning or dryness were recorded in either treatment group. Moderate skin burning and dryness sensation were reported more frequently ($P = 0·01$ and $P = 0·0025$; Fisher's exact test) in group BP + A. Moderate erythema was registered in four patients in group BP + A and in none in group HP + A, but this difference was of a borderline statistical significance ($P = 0·055$). The global TS was significantly better in group HP + A [2·8 ± 0·3; median 3; 90% confidence interval (CI) of median 3 to 3] in comparison with group BP + A (1·7 ± 0·6; median 2; 90% CI of median 1 to 2) ($P = 0·02$; Mann–Whitney test).

Table 1. Patients' demographic characteristics at baseline

	Group HP + A	Group BP + A	*P*-value
Subjects	26	26	
Men/women	9/17	10/16	
Age (mean ± SD, years)	25 ± 7	25 ± 6	NS
Lesion counts (mean ± SD)			
Total	44 ± 9	40 ± 9	NS
Inflammatory	25 ± 7	21 ± 7	NS
Noninflammatory	19 ± 6	19 ± 9	NS

NS, Not significant.

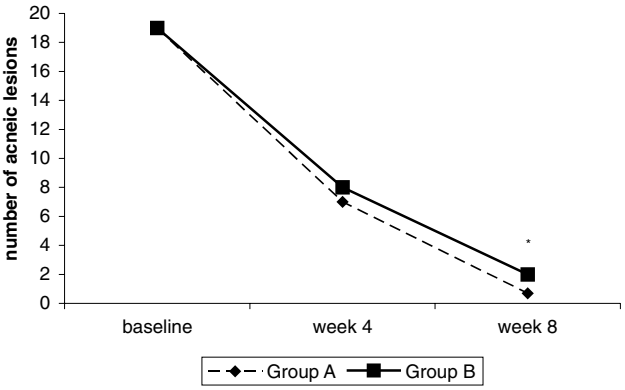

Figure 1. Evolution of noninflammatory lesions count during treatment. Group A, hydrogen peroxide 1% in stabilized cream + adapalene 0·1% gel; group B, benzoyl peroxide 4% cream + adapalene 0·1% gel. *$P = 0·0025$, Fisher's exact test.

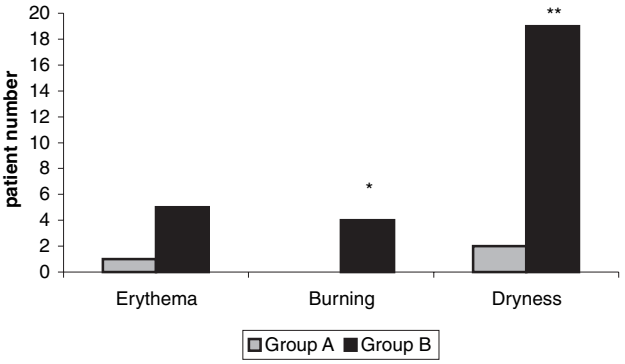

Figure 2. Tolerability evaluation: patients with mild and/or moderate symptoms during study period. Group A, hydrogen peroxide 1% in stabilized cream + adapalene 0·1% gel; group B, benzoyl peroxide 4% cream + adapalene 0·1% gel. *$P = 0·01$; **$P = 0·0025$, Fisher's exact test.

Discussion

Combination therapy with antiseptics such as BP and topical retinoids is widely used as first-line treatment for mild to moderate AV. The antimicrobial and comedolytic actions of BP were considered a cornerstone of early acne treatment.[9] Good skin tolerability is the crucial factor for patient compliance. BP and retinoids may produce a low to moderate grade irritant

dermatitis.[10] BP rapidly decomposes into benzoic acid and HP, and benzoic acid can be responsible for skin irritation and erythema. Adapalene gel is an effective and well-tolerated topical retinoid.[11] The combination of adapalene and BP has been shown to be an effective topical treatment for mild to moderate acne.[12] However, the concomitant use of these two products could be associated with an increased incidence of facial dryness and erythema.[13] Our study has demonstrated that the combination of adapalene gel and HP cream is an effective topical treatment regimen in patients with mild to moderate AV. The combination of HP and adapalene was at least as effective as the combination of BP and adapalene in reducing TL and IL. Furthermore, at the end of the treatment period, HP and adapalene induced a greater reduction in NL in comparison with BP and adapalene. The combination of HP and adapalene has shown a good skin tolerability, with a better tolerability profile in comparison with the combination of adapalene and BP, with a lower incidence of skin burning sensation and dryness.

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