Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne

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CRD summary
The authors concluded that at two to four weeks, combination benzoyl peroxide plus salicylic acid had the best profile for treating acne vulgaris; at 10 to 12 weeks, this combination treatment was similar to benzoyl peroxide/clindamycin treatment. Potential limitations with the review process and the uncertain quality of included trials suggest that the authors' conclusions should be treated with caution.

Authors' objectives
To compare the efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin for treating acne vulgaris.

Searching
PubMed was searched from 1987. Search terms were reported but search end dates were not. Food and Drug Administration reviews of new drug applications, posters and unpublished data were also searched.

Study selection
Randomised controlled trials (RCTs) that included at least one treatment arm of 5% benzoyl peroxide (either with or without salicylic acid-based cleanser and toner), or 1% to 1.2% clindamycin, or combination benzoyl peroxide/clindamycin, for acne vulgaris were eligible for inclusion. Eligible trials had to measure treatment efficacy using lesion count and/or percentage reduction in lesion count. Single arm studies, studies with retinoids in all arms, and studies of acne rosacea were excluded.

The primary outcomes were one end point that measured inflammatory lesion count and one end point that measured non-inflammatory lesion count at two to four weeks and/or 10 to 12 weeks.

Approximately a third of included trials used a placebo comparator. The topical medication was applied once or twice a day in the included studies and the length of treatment duration ranged from 2 to 12 weeks. Two trials used split faces to compare two interventions. Most of the combination benzoyl peroxide/clindamycin interventions used 5% benzoyl peroxide/1% clindamycin; one trial used 2.5% benzoyl peroxide/1.2% clindamycin. The included trials were published from 1988 to 2009.

The authors did not report how many reviewers performed the selection.

Assessment of study quality
The criteria used for trial quality assessment included control arms, randomisation procedures, concealment of treatment arm, intention-to-treat analysis, and outcome assessment.

The authors did not report how many reviewers performed the quality assessment.

Data extraction
The numbers of lesions for each outcome were extracted to calculate percentage reduction in lesions. If data were available at one or more treatment end points within the two to four weeks or 10 to 12 weeks periods, then the data for the greater time point were used. Results were separated for 5% benzoyl peroxide with salicylic acid-based cleanser and toner, and for 5% benzoyl peroxide without salicylic acid-based cleanser and toner.

The authors did not report how many reviewers performed the extraction.
Methods of synthesis
Results were pooled by type of topical treatment, calculating weighted mean percentage reductions (WMR%), with
95% confidence intervals (CIs), for lesions and weighted mean percentage reductions in actual lesion counts, using an
intention-to-treat analysis.

Sensitivity analyses were undertaken by calculating the mean actual lesion reduction weighted by the total number of
intention-to-treat participants for each treatment group and end point. All the trials using benzoyl peroxide plus salicylic
acid used the same solubilised formulation of benzoyl peroxide; one other trial used the same solubilised formulation of
benzoyl peroxide without salicylic acid, but was grouped with the benzoyl peroxide plus salicylic acid trials in the
analysis based on the similar formulation.

The meta-analysis was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and
Meta-Analyses) statement from Cochrane guidelines.

Results of the review
Twenty three RCTs were identified for the review. Over 7,309 participants were included; the range for intervention
groups was from 24 to 2,004. There were 10 RCTs for benzoyl peroxide alone (n=824 participants), 14 RCTs for
clindamycin (n=3,143), 15 RCTs for combination benzoyl peroxide/clindamycin (n=1,923), and nine placebo RCTs
(n=1,308). None of the four RCTs (n=210) of benzoyl peroxide plus salicylic acid included a placebo arm. All but one
RCT used an intention-to-treat analysis; in the remaining RCT, follow-up was only continued for 12 weeks with 38 of
65 participants.

Two to four weeks (early time points):
Indirect comparisons showed greater inflammatory acne lesion reduction for benzoyl peroxide plus salicylic acid
((WMR% 55.2, 95% CI 50.7 to 59.7; four RCTs) compared with the other interventions of benzoyl
peroxide/clindamycin (WMR% 40.7, 95% CI 37.2 to 44.2; ten RCTs), benzoyl peroxide alone (WMR% 33.4, 95% CI
29.4 to 37.4%; six RCTs), clindamycin (WMR% 21.5, 95% CI 17.5 to 25.6; five RCTs), or placebo (WMR% 7.3, 95% CI
-3.0 to 17.6; three RCTs).

Non-inflammatory acne lesion reduction was also superior for benzoyl peroxide plus salicylic acid (WMR% 42.7, 95%
CI 39.3 to 46.1; four RCTs) compared with the other interventions of benzoyl peroxide/clindamycin (WMR% 26.2,
95% CI 22.2 to 30.3; ten RCTs), benzoyl peroxide alone (WMR% 19.1, 95% CI 14.1 to 24.2%; six RCTs), clindamycin
(WMR% 10.0%, 95% CI 5.0 to 15.0; five RCTs), and placebo (WMR% 6.7, 95% CI -0.7 to 14.0; three RCTs).

Three interventions (benzoyl peroxide plus salicylic acid, benzoyl peroxide/clindamycin, and benzoyl peroxide) were
more effective for both inflammatory and non-inflammatory lesion reduction when indirectly compared with placebo.

10 to 12 weeks (later time points): The results were less clear cut at later time points.

Inflammatory lesion reductions for the interventions of benzoyl peroxide/clindamycin (WMR% 55.6, 95% CI 53.6 to
57.6; 14 RCTs), benzoyl peroxide plus salicylic acid (WMR% 51.8, 95% CI 43.1 to 60.5; two RCTs), benzoyl peroxide
alone (WMR% 43.7, 95% CI 41.1 to 46.3; ten RCTs) and clindamycin (WMR% 45.9, 95% CI 42.8 to 49.1; 14 RCTs)
were all superior to placebo (WMR% 26.8, 95% CI 21.7 to 31.9; nine RCTs) when compared indirectly. Benzoyl
peroxide/clindamycin had the best profile for inflammatory lesion reduction.

Non-inflammatory lesion reduction for the interventions of benzoyl peroxide plus salicylic acid (WMR% 47.8, 95% CI
40.5 to 55.0; two RCTs), benzoyl peroxide/clindamycin (WMR% 40.3%, 95% CI 37.0 to 43.6; 14 RCTs), clindamycin
(WMR% 32.6, 95% CI 27.9 to 37.4; 14 RCTs) and benzoyl peroxide alone (WMR% 30.9, 95% CI 25.6 to 36.2; 10
RCTs) were all superior to placebo (WMR% 17.0, 95% CI 11.7 to 22.4; nine RCTs) when compared indirectly.
Benzoyl peroxide plus salicylic acid had a better profile than benzoyl peroxide alone and clindamycin; benzoyl
peroxide/clindamycin was superior compared with clindamycin, and benzoyl peroxide plus salicylic acid and benzoyl
peroxide/clindamycin were similar for non-inflammatory lesion reduction.

Results were also reported for actual lesion counts, which were similar but not identical to those for mean percentage.
Authors’ conclusions
At early time points (two to four weeks), combination benzoyl peroxide plus salicylic acid had the best profile. Benzoyl peroxide/clindamycin was only incrementally better than benzoyl peroxide alone, but was superior to clindamycin alone. At later time points (10 to 12 weeks), benzoyl peroxide plus salicylic acid was similar to benzoyl peroxide/clindamycin.

CRD commentary
The review addressed a well-defined question for the interventions, participants and relevant outcomes, but the included studies were not well defined so as to include a relevant comparison group. Unpublished studies were considered, but only one relevant database was searched; it was not clear if any language restrictions were applied, so some relevant studies could have been missed. The authors suggested that publication bias was a possibility. Efforts to reduce error and bias during the review process were not reported.

Trial quality was assessed using suitable criteria, but little relevant data was reported to allow assessment of trial quality. Some relevant trial details were reported, but there were no details on participants; the total number of participants in each trial was not reported, only the total number for each relevant intervention. The authors acknowledged that approximately a third of the included trials only contributed relevant data for one intervention group with no data for a placebo group, since the other interventions in the trials were not eligible for inclusion. The statistical analysis method used was unclear. Indirect comparisons appear to have been used in some trials, when direct comparisons between treatment arms and placebo could have been used. Limited details were provided on the type of analysis performed to pool the treatment arms. Statistical heterogeneity was not assessed, but the authors reported that there was a high level of heterogeneity, which suggested that pooling of the treatment arms may not have been appropriate. There were few trials of benzoyl peroxide/salicylic acid, which was highlighted as one of the most effective interventions.

In view of some potential limitations arising from the review process and uncertainties in the statistical analysis and the quality of included trials, the authors’ conclusions should be treated with caution.

One author disclosed that she had been a consultant for both Obagi and Arcutis and was currently an investigator for Stiefel and a consultant for Galderma (all manufacturers of acne treatments).

Implications of the review for practice and research
Practice: The authors stated that, although the addition of clindamycin to benzoyl peroxide may be more effective than benzoyl peroxide alone, the additional costs and risks should be considered, including antibiotic resistance and availability (over-the-counter versus prescription). Formulation has an effect on product performance. Clindamycin should rarely be used alone giving its inferior performance and the risk of antibiotic resistance. Tolerability and safety end points should be considered.

Research: The authors identified a need for further studies of solubilised benzoyl peroxide to identify the efficacy of its formulation versus its use with salicylic acid. Trials of benzoyl peroxide plus salicylic acid versus benzoyl peroxide/clindamycin at later time points are needed to establish which is superior.

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