The Role of Nicotinamide in Acne Treatment

Running Head: Nicotinamide (Niacinamide) and Acne Treatment

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Abstract

Background: Safe and effective treatment options for acne vulgaris are needed to address side effects and increasing rates of antibiotic resistance from current treatments. Nicotinamide is a vitamin with potent anti-inflammatory properties that could offer a potential treatment option.

Objective: We aim to summarize the relevant literature on the role of nicotinamide in acne vulgaris and discuss the next steps necessary to move this approach into clinical practice.

Methods: We searched PubMed for clinical studies using nicotinamide for treatment of acne vulgaris. We summarized the 10 studies that met our search criteria.

Results: Six of eight studies using topical nicotinamide led to a significant reduction in acne compared to the patient's baseline or performed similarly to another standard-of-care acne treatment. All studies using an oral supplement containing nicotinamide resulted in a significant reduction in acne compared to baseline. No major adverse side effects were noted.

Conclusion: Our review suggests that topical and oral nicotinamide has an unclear effect on acne vulgaris due to the limited nature of the available literature. Additional studies are needed comparing nicotinamide to other first-line acne treatments and evaluating the efficacy and side effect profile of nicotinamide over an extended period of time.

Introduction

Acne vulgaris is an extremely common chronic inflammatory disease of the skin that occurs in approximately 80% of young adults and adolescents, though it can occur in all ages.[1] While the pathogenesis of acne vulgaris is complex, the basic physiology is widely accepted. Hypercornification combined with excess sebum production provokes clogging of the pores.[2] *Propionobacterium acnes* (*P. acnes*) proliferate in this environment and cause an increase in inflammatory cytokines and free fatty acids, which then leads to further irritation.[3] Studies suggest genetic, neuroendocrine, and dietary factors may also contribute to the multifactorial process of acne vulgaris pathogenesis.[4]

Treatments for acne vulgaris target one or more of the steps in pathogenesis and may be administered topically or orally. The most widely used acne treatments are topical formulations. Common examples include retinoids, antibiotics, antibacterial agents, and comedolytic agents.[1] Systemic treatments are used for more severe or resistant forms of acne, including oral isotretinoin, oral antibiotics, and hormonal agents.[5] These treatment modalities are not without their drawbacks. Topical retinoid use may be limited by dryness, erythema, and irritation, while oral isotretinoin treatment is teratogenic and requires routine monitoring of serum lipid profiles and liver function tests.[6] Topical and oral antibiotic overuse and resistance are a growing global concern, both for the effectiveness of acne therapies and for the treatment of infectious diseases.[7,8] Many countries have reported that over 50% of *P. acnes* strains are anti-biotic resistant, particularly to topical macrolides.[9] Regarding the use of hormonal modulators, venous thromboembolism risk remains a concern. For these reasons, alternative treatments have entered the arena of acne care.

Nicotinamide provides potent anti-inflammatory properties without the risk of bacterial resistance and systemic side effects and represents a potential treatment modality for acne vulgaris. Nicotinamide, also known as niacinamide, is a form of vitamin B3, which is an essential water-soluble nutrient present in a variety of foods. Nicotinamide is the amide form of nicotinic acid (niacin) and is identical in vitamin function; however, it does not carry the same vasodilatory, hypolipidemic, and gastrointestinal actions.[10] Furthermore, nicotinamide has demonstrated a low incidence of side effects and toxicity at oral doses up to 3 grams per day for up to five years.[10] Nicotinamide is a precursor for nicotinamide adenine dinucleotide (NAD) and the phosphorylated derivative NADP.[11] NAD provides a substrate for nuclear enzyme poly-ADP-ribose polymerase (PARP-1), which repairs damage from genotoxic stresses, such as UV radiation.[12,13] Having adequate cellular energy and properly functioning PARP-1 is important for a number of skin conditions, for which nicotinamide may have beneficial effects.[14]

Nicotinamide appears to play a number of potential roles in the treatment of acne vulgaris. Draelos et al. demonstrated that 2% topical nicotinamide resulted in a significant reduction in sebum excretion rate in a Japanese study group and decreased casual sebum levels (sebum on the skin surface) in a Caucasian study group over four weeks.[15] In addition, topical nicotinamide helps protect the natural barrier of the skin against infection and may have a bacteriostatic effect on *P. acnes*.[16,17] Lastly, nicotinamide decreases the in vitro secretion of interleukin-8, a cytokine secreted by keratinocytes in response to pathogens (including *P. acnes*), thereby exerting an anti-inflammatory effect through inhibition of leukocyte chemotaxis.[18] Additional anti-inflammatory action may occur via inhibition of lysosomal enzyme release and mast cell degranulation.[17]

Nicotinamide for use in dermatologic ailments has shown promise in clinical studies but has not yet become a standard treatment option. This review examines the potential role of nicotinamide in acne vulgaris, summarizes the relevant published articles, and discusses what studies are needed to move this new approach to such a common ailment into widespread clinical practice.

Methods

We searched PubMed for all articles in English with the following words in the title or abstract: "acne," "nicotinamide," "niacinamide," and "vitamin B3" with no restriction on dates up to October 2016. This search yielded 41 articles. Two reviewers independently determined the eligibility of the studies and performed the methodological quality assessment.

Inclusion Criteria:

- Studies must directly involve subjects with at least mild acne
- Studies must use a human model
- Studies must use topical and/or oral nicotinamide treatments

For each experiment, we determined the degree of acne vulgaris, treatment group regimen, control group regimen, duration of treatment, outcome measures, and results. Treatments containing only nicotinamide are referred to as "single-agent products," whereas treatments containing nicotinamide in addition to other components are referred to as "combination products." Quantitative assessment of acne lesions involved counts of comedones, papules/pustules, and/or cysts. Qualitative assessment of acne lesions was based on the

Physician's Global Evaluation of Inflammatory Acne or modifications of Cook's Acne Grade. The Physician's Global Evaluation of Inflammatory Acne involves rating the change in acne on a scale from "much better" to "worse." Cook's Acne Grade involves rating acne based on how much of the face is involved. We summarized our findings and determined what essential information is missing from the literature, and thus, should be studied before nicotinamide can make its way into standard clinical treatment of acne vulgaris.

Results

Ten articles matched our search criteria; all studies tested the efficacy of nicotinamide on acne vulgaris in humans using either topical or oral therapies. The design and results of the studies are summarized in Tables 1-3. Eight out of the 10 studies demonstrated a significant reduction in acne lesions compared to the patient's baseline acne or similar efficacy to a commonly used treatment for acne vulgaris. Four of the studies used nicotinamide as a single-agent topical product; four of the studies used nicotinamide as a combination topical product; and two of the studies used an oral form of nicotinamide. Outcomes of the available research for each study design are summarized below.

Single-Agent Topical Products

Four studies used nicotinamide as a single-agent topical product (Table 1). Three of the studies randomized patients to treatment with nicotinamide only or clindamycin only; all three studies found that the nicotinamide group had significantly improved acne vulgaris from baseline and that nicotinamide and clindamycin resulted in similar reductions in acne lesions.[19-21] Kaymak and colleagues treated all study participants with only niacinamide and found a

significant improvement in acne vulgaris from baseline.[22] None of the four studies compared nicotinamide to a placebo-treated control group.

Combination Topical Products

Four studies used nicotinamide in a combination topical product (Table 2). Dos et al. and Sardesai et al. directly compared a combination product containing nicotinamide and clindamycin to a clindamycin-only treatment group.[23,24] Both studies demonstrated a significant improvement in acne vulgaris from baseline for both treatment groups, but there was no difference in acne vulgaris when topical nicotinamide and clindamycin were combined.[23,24] Morganti and colleagues randomized patients to receive treatment with emulsions composed of numerous ingredients and either 4% nicotinamide, 1% clindamycin, or neither (emulsion vehicle).[25] The nicotinamide treatment group quantitatively demonstrated a significant improvement in acne vulgaris compared to the emulsion containing clindamycin and the emulsion vehicle.[25] Emanuele compared a nicotinamide treatment group containing 4% nicotinamide, 1% retinol, and 0.5% 7-dehydrocholesterol to the patient's baseline acne.[26] There was a significant improvement in acne vulgaris using this treatment compared to the patient's baseline.[26] It is unclear if the nicotinamide or the other ingredients in the combination product were responsible for the significant improvement.

Oral Nicotinamide Products

Two studies involving oral nicotinamide therapy for acne vulgaris matched our search criteria (Table 3). Niren et al. used a combination product containing nicotinamide, zinc, copper, and folic acid and demonstrated a significant improvement in acne vulgaris compared to acne prior to treatment.[27] There was no difference in acne lesions when an oral antibiotic (name not stated in primary article) was combined with the nicotinamide combination product. Shalita et al.

used a combination product containing nicotinamide, azelaic acid, zinc, pyridoxine, copper, and folic acid and showed a significant improvement in acne vulgaris compared to acne prior to treatment.[28] Participants in this study were permitted to continue their regular acne regimens during the study; therefore, it is unclear if the treatment was responsible for the improvement in acne vulgaris. In both studies, the individual components of each combination product were not tested separately; therefore, it is unclear if nicotinamide itself contributed to the improvement in acne vulgaris. There were no studies that tested the effect of oral nicotinamide on acne vulgaris as a single-agent.

Side Effects

No major adverse side effects were noted by any of the studies. Minor side effects for nicotinamide topical treatments included itching, burning, mild dermatitis, and greasy skin. These side effects were also experienced by patients in the "other topical treatment" groups with no significant difference in frequency or severity between groups in any of the topical studies. No side effects were experienced by patients taking oral nicotinamide formulations.

Discussion

Acne vulgaris remains a prevalent problem, and the need persists for new safe and effective treatment options. Current modalities carry significant risks, including antibiotic resistance and systemic interactions.[9] Unpleasant side effects, such as dry, irritated skin with topical retinoids or mandatory routine laboratory monitoring with oral isotretinoin, are not only concerning, but they limit compliance for many patients. Topical and oral forms of nicotinamide represent a possible treatment alternative for acne vulgaris, but the benefit of these products is

unclear. Our literature review suggests that a limited series of studies demonstrate that topical nicotinamide treatments have a significant effect on reducing acne vulgaris with minimal side effects. Four of these studies also showed that topical nicotinamide reduced acne lesions similarly to topical clindamycin, thereby implying that nicotinamide could potentially be used as a treatment alternative to clindamycin. However, two of the eight topical studies showed that nicotinamide did not demonstrate a reduction in acne lesions when added to clindamycin treatment. The benefit of oral nicotinamide is further unclear because nicotinamide has only been tested as a combination product and not by itself.

The authors opine that there are several study design limitations that need to be addressed in order to determine if nicotinamide is a potential treatment option for acne vulgaris in the clinical setting. The current literature would benefit from additional studies using an adequate control group, expanding comparisons of nicotinamide with other standard-of-care acne vulgaris treatments, lengthening treatment endpoints, objectifying outcome measures, and establishing a long-term side effect profile.

Control Groups

Six of the 10 studies examined combination treatments without including a treatment group consisting of only nicotinamide. This design makes it difficult to determine what product within the combination treatment is responsible for the effect on acne vulgaris. In addition, only one study prospectively randomized patients to a control group that received treatment with a gel containing the active treatment or a vehicle gel (gel that does not contain active treatment); including such a control group would clarify if the improvement was due to time or the treatment itself.[25]

Additional Treatment Groups

The American Academy of Dermatology's treatment algorithm for acne vulgaris recommends first line treatment for mild acne with benzoyl peroxide, topical retinoid, or topical combination therapy (benzoyl peroxide + antibiotic, retinoid + benzoyl peroxide, or retinoid + benzoyl peroxide + antibiotic).[4] These agents are often used in the treatment of moderate acne vulgaris as well. Therefore, there is a need to compare the effects of nicotinamide to these first-line products in single treatment and combination treatment forms. No topical studies compared nicotinamide to benzoyl peroxide or used a nicotinamide-benzoyl peroxide combination product. One topical nicotinamide combination product included retinol but did not directly compare nicotinamide by itself to a retinoid gel or a vehicle gel. None of the oral nicotinamide studies compared nicotinamide to systemic antibiotics alone or to oral isotretinoin.

The optimal concentrations, doses, and treatment regimens have yet to be determined for topical and oral nicotinamide treatments. Topical nicotinamide gel has shown positive effects on acne vulgaris at 4% and 5% concentrations. Oral nicotinamide has been used successfully to treat acne vulgaris at 600 mg and 750 mg nicotinamide one to four times daily.[27] Further studies are needed to directly compare different amounts of nicotinamide to obtain a clinical standard for acne vulgaris treatment.

Study Length

Only one topical study tested treatment groups for to an endpoint of 12 weeks.[25] The other topical studies all used endpoints ranging from six to eight weeks. Clindamycin was used as a comparison group in six out of the eight topical studies; however, the topical form of this antibiotic is effective at reducing acne lesions over an 8-12-week period.[29] Combination products consisting of clindamycin and benzoyl peroxide have shown significant treatment benefit over an 11-week period, while topical retinoids have shown benefit over a 12-week period.[30-32]

Additional studies with endpoints of at least 12 weeks for nicotinamide treatment are needed to determine the true efficacy of topical nicotinamide treatment compared to these agents.

Both oral nicotinamide treatments were tested for eight weeks and compared to baseline.[27,28] However, most systemic antibiotics and oral isotretinoin treatments are given over a course of three to six months.[33,34] Future studies involving oral nicotinamide treatments should consider expanding their treatment course to further establish long-term effects on acne vulgaris treatment. Additional studies are needed for both oral and topical treatments that detail efficacy following cessation of treatment.

Outcome Measures

Eight of the 10 studies used quantitative outcome measures, but there was little consistency in the outcome measures used (number of lesions, scarring, etc.). Although no universal grading scale can be recommended, using a quantitative grading scale that includes the numbers and type of acne lesions, disease severity, and scarring can help objectively guide treatment over time and compare results between treatment options.[4] Improvement in erythema and reduction in sebum production are additional outcome measures that could help define responses to nicotinamide treatment.[35]

Side Effect Profile

In this review, no major adverse effects were noted by patients receiving treatment with nicotinamide; however, longer term studies are needed to adequately profile side effects of nicotinamide for both topical and oral agents. Although most patients experience minimal side effects at topical concentrations less than 6% and oral doses less than 3 g/day, potential severe side effects at high doses include elevation of liver enzymes, nausea, heartburn, and flushing.[10]

Future Applications

Nicotinamide has shown promise not only in the realm of treating acute acne vulgaris, but also with respect to complications of acne, including pigmentation changes. Recent studies have demonstrated that nicotinamide has significant skin lightening effects through the inhibition of melanosome transfer from melanocytes to keratinocytes.[36] This mechanism of action could benefit patients being treated for acne who are predisposed to post-inflammatory hyperpigmentation, but future studies are needed. Furthermore, nicotinamide may not cause sun-sensitivity that is associated with other lightening agents used to treat post-inflammatory hyperpigmentation. Rather, nicotinamide potentially prevents photoimmunosuppression and photocarcinogenesis.[14] These benefits make it a possible adjunct therapy to existing photosensitizing acne treatments, such as the tetracycline antibiotics or retinoids. Uses of nicotinamide should continue to be explored through randomized controlled clinical trials as it has the potential to benefit dermatologic care for multiple indications.

Limitations of this Review

Our study has several limitations. First, as this is a review article, there is a potential for publication bias. If only positive studies are published, the review of the literature will be overwhelmingly positive. This is an inherent problem for all review articles and could very well be a factor in this review. However, there has been increasing awareness of this issue, and many studies with negative results are being published in high impact journals. Secondly, our review did not limit our included studies to only double-blinded randomized-controlled trials due to the lack of such studies in the literature. Therefore, the results reported in the studies are more subject to biases and less clearly due to the effects of nicotinamide. However, the findings by multiple studies that nicotinamide had an equivalent effect as clindamycin certainly supports

more thorough investigation into the treatment potential of nicotinamide. Lastly, because only 10 studies met our selection criteria and most of the studies were relatively small, we may simply not have enough power to demonstrate real differences between nicotinamide and clindamycin. This further highlights the need for large, double-blinded, randomized-controlled clinical trials.

Conclusion

Nicotinamide is an inexpensive, over-the-counter, water-soluble vitamin with a well-established safety profile. Limited studies have suggested that it is effective in treating acne vulgaris, but additional evidence is necessary before nicotinamide can be considered an alternative or adjunct to current acne vulgaris treatment regimens. Additional randomized controlled clinical trials are needed comparing nicotinamide to other first-line acne treatments and evaluating the efficacy and the side effect profile of nicotinamide over an extended period of time.

Abbreviations

g, grams; mg, milligrams; mcg, micrograms; *Propionobacterium acnes, P. acnes*; NAD, nicotinamide adenine dinucleotide; NADP, Nicotinamide adenine dinucleotide phosphate; PARP-1, poly-ADP-ribose polymerase-1

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Table 1: Overview of topical studies that use nicotinamide as a single-agent treatment.

Author (Year)	Acne Severity	Nicotinamide Treatment Group	Other Treatment Group	Control	Treatment Duration (Application)	Outcome Measure	Nicotinamide Group versus Control Group	Nicotinamide Group versus "Other" Treatment Group
Shahmoradi (2013)[19]	Mild/ Moderate	5% nicotinamide gel	2% clindamycin gel	Baseline	8 weeks (BID)	Quantitative Assessment	+	0
Khodaeiani (2013)[20]	Moderate	4% nicotinamide gel	1% clindamycin gel	Baseline	8 weeks (BID)	Quantitative and Qualitative Assessments	+	0
Shalita (1995)[21]	Moderate	4% nicotinamide gel	1% clindamycin gel	Baseline	8 weeks (BID)	Quantitative and Qualitative Assessments	+	0
Kaymak (2008)[22]	Mild/ Moderate	4% niacinamide gel	N/A	Baseline	8 weeks (NS)	Quantitative Assessment	+	N/A

Abbreviations: N/A, not applicable; BID, twice daily; NS, not stated; %, percent. Baseline refers to the patient's acne prior to treatment.

Significance is referred to the nicotinamide treatment group compared to the control group and the "other treatment group": "+" $P<0.05$ (Statistically significant improvement in acne), "0" $P>0.05$ (Non-statistically significant improvement in acne).

Table 2: Overview of topical studies that use nicotinamide in a combination product treatment.

Author (Year)	Acne Severity	Nicotinamide Treatment Group	Other Treatment Group	Control	Treatment Duration (Application)	Outcome Measure	Nicotinamide versus Control group	Nicotinamide versus "Other" treatment group
Dos (2003)[23]	Moderate	4% nicotinamide gel and 1% clindamycin phosphate gel	1% clindamycin phosphate gel	N/A	6 weeks (BID)	Quantitative Assessment	+	0
Sardesai (2003)[24]	Inflammatory	4% nicotinamide gel and 1% clindamycin gel	1% clindamycin gel	N/A	8 weeks (NS)	Qualitative Assessment	+	0
Morganti (2011)[25]	Inflammatory	4% nicotinamide-phospholipidic emulsion	1% clindamycin emulsion	Emulsion without nicotinamide or clindamycin	12 weeks (QD)	Quantitative Assessment	+	+
Emanuele (2012)[26]	Inflammatory	4% nicotinamide, 1% retinol, 0.5% 7-dehydrocholesterol	N/A	Baseline	45 days (BID)	Qualitative Assessment	+	N/A

Abbreviations: N/A, not applicable; NS, not stated; BID, twice daily; QD, once daily; %, percent. Baseline refers to the patient's acne prior to treatment.

Significance is referred to the nicotinamide treatment group compared to the control group and the "other" treatment group: "+" $P<0.05$ (Statistically significant improvement in acne), "0" $P>0.05$ (Non-statistically significant improvement in acne).

Table 3: Overview of oral studies that use nicotinamide.

Author (Year)	Acne Severity	Nicotinamide Treatment Group	Other Treatment Group	Control	Treatment Duration (Application)	Outcome Measure	Nicotinamide Group versus Control Group	Nicotinamide Group versus "Other" Treatment Group
Niren (2006)[27]	Moderate	Oral Nicomide (nicotinamide 750mg, zinc 25mg, copper 1.5mg, folic acid 500mcg)	Oral Nicomide Plus Oral antibiotic	Baseline	8 weeks (1-3 times daily)	Qualitative	+	0
Shalita (2012)[28]	Moderate	Oral NicAzel (nicotinamide 600mg, azelaic acid 5mg, zinc 10mg, pyridoxine 5mg, copper 1.5mg, folic acid 500mcg)	N/A	Baseline*	8 weeks (1-4 times daily)	Qualitative	+	N/A

Abbreviations: N/A, not applicable; mg, milligram; mcg, microgram. Baseline refers to the patient's acne prior to treatment.

* Refers to patients allowed to continue any previous acne regimens.

Significance is referred to the nicotinamide treatment group compared to the control group and the "other treatment group": "+" $P<0.05$ (Statistically significant improvement in acne), "0" $P>0.05$ (Non-statistically significant improvement in acne).