Review article

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CPD

Does topical minoxidil at concentrations higher than 5% provide additional clinical benefit?

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Abstract

Minoxidil solution is used for the treatment of androgenetic alopecia (AGA). Minoxidil 5% solution has been shown to have superior efficacy to minoxidil 2% solution, it is unknown whether concentrations of minoxidil > 5% provide additional clinical benefit. We performed a review of the literature to examine the evidence on the efficacy and safety of higher concentrations of minoxidil in AGA. A search of the PubMed database was performed using the keywords 'minoxidil', 'androgenic alopecia' and 'pattern hair loss'. Relevant articles, including clinical trials, other clinical studies, case series and case reports published in English were considered for review. In addition, relevant references from the bibliography section of the retrieved articles were also reviewed.

Introduction

Minoxidil is the only topical agent approved for the treatment of pattern hair loss (androgenetic alopecia; AGA). Minoxidil is a prodrug. Activation to minoxidil sulfate occurs in the suprabulbar hair follicle outer root sheath and is catalysed by thermostable phenol sulfotransferase (SULT), which has a number of variants. There is considerable interindividual variability in levels of both hepatic SULT2A1 and follicular SULT1A1. Low SULT1A1 activity occurs in approximately 60% of the population and predicts weak hair regrowth.[1,2] These individuals are likely to require higher concentrations of minoxidil lotion to compensate for low SULT1A1 activity.

Minoxidil is poorly soluble in solution and concentrations > 5% tend to be unstable. Crystallization (or powdering) of minoxidil occurs on the scalp when the solvent evaporates.[3] Topical application of minoxidil results in variable systemic absorption depending on various factors, including the vehicle in the formulation, the area of application and skin status (absorption is increased if the scalp is abraded or inflamed). On average, only 1.4% of the active ingredient is systemically absorbed after topical application to the scalp.[4] Percutaneous delivery is further limited by saturation absorption kinetics. Application more frequently than twice daily does not increase minoxidil bioavailability.

Topical formulation

Minoxidil solution consists of inactive ingredients ethanol and propylene glycol, which enhances the solubility of minoxidil. Propylene glycol not only enhances the delivery of the active drug into the hair follicles but is also responsible for the irritation potential attributed to the topical preparation. Propylene glycol-free minoxidil foam consists of stearyl alcohol, cetyl alcohol

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and butylated hydroxytoluene.[4] This formulation has reduced potential for irritation.

Minoxidil gel has also been formulated with polymers such as hydroxypropyl cellulose and hydroxypropyl methylcellulose K4M with the aim of improving efficacy.[5] Newer technology-based formulations, including nanotechnology, have helped form minoxidil formulations loaded on lipid, polymer or inorganic compounds.[6] Microbubbles are shelled with lysozymes, which are anti-infective, and these are then subsequently coated with minoxidil; the resultant compound is then combined with ultrasound waves to guide its delivery precisely into the hair follicle for better results.[7]

Efficacy of topical minoxidil

A systematic review and meta-analysis showed minoxidil solution to be significantly more effective than placebo in promoting total and nonvellus hair growth.[8] Minoxidil is available in different percentages including 1%, 2%, 3%, 5%, 7.5%, 10%, 12.5% and 15%.

A 48-week placebo-controlled randomized, double-blind trial compared with topical minoxidil 5% and 2% in men with AGA (n = 393). In this study, the 5% formulation was significantly better than both the 2% formulation and the placebo for improving nonvellus hair count. Response to treatment was also observed earlier with topical minoxidil 5% than with 2%. Topical minoxidil 5% improved psychosocial perceptions of hair loss among patients. Pruritus and local irritation were greater with topical minoxidil 5%. Systemic effects were not observed with either strength of minoxidil.[9] A study among Japanese men with AGA (n = 300) showed the superiority of topical minoxidil 5% vs. 1%.[10]

Topical minoxidil has been evaluated for response in different strengths from 1% to 15% in AGA. The hair growth with topical minoxidil ranges from 17% to 70%.[11] A study with topical minoxidil 5% formulation (n = 1495 men; 20–40 years of age) in routine clinical practice, reported discontinuation of treatment because of adverse effects (AEs) in only a few patients, but the investigators reported stopping of treatment by many due to fewer effects and an aversion to topical treatment.[12] Topical minoxidil can also be used with finasteride in patients with AGA.[13] Topical minoxidil 0.5% has also been used along with topical tretinoin in AGA for potential additive or synergistic effects for hair regrowth.[14]

In the following section, we review data related to the efficacy of minoxidil at higher strengths.

Comparison of different strengths

A randomized, self-comparative clinical trial was performed, enrolling 66 patients with AGA to assess the safety and efficacy of minoxidil 15% solution and compare it with 5% solution. The trial was conducted over a span of 24 weeks, with the participants randomized into two groups: the first group received the 15% formulation and the second group received the 5% formulation. Participants in both groups were directed to apply the given solution to their scalp twice daily. Participants were followed up for 24 weeks and the results were evaluated using subjective assessment of treatment satisfaction by the patient, and objective assessment using the Investigator's Global Assessment (IGA), global scalp photography and phototrichography. A statistically significant difference ($P < 0.005$) was observed between the two groups in terms of hair growth parameters. Minoxidil 15% performed significantly better than the 5% formulation at Weeks 12 and 24. The AEs in both groups were not statistically significant.[15]

A placebo-controlled, double-blind, randomized trial assessing 90 men with AGA over a period of 36 weeks randomized participants into three groups: Group A received minoxidil 5% solution, Group B received minoxidil 10% solution and Group C received placebo. At the end of the 36-week period, the treatment efficacy was evaluated with respect to clinical features and trichoscopic findings. Hair counts in Group A were significantly higher than in the other two groups. Mean ± SD ratio changes in total hair count Groups A, B and C were 0.47 ± 0.26, 0.05 ± 0.13 and 0.01 ± 0.05, respectively for the vertex area, and 0.59 ± 0.64, 0.45 ± 0.74 and − 0.03 ± 0.08, respectively. At the end of the study, the hair pull test was negative for 37% of patients in Group A compared with 37.5% in Group B, while the percentage improvement on global photography was 88.8% vs. 87.5%, respectively. The local AEs (increased initial hair shedding, contact dermatitis and hypertrichosis) were significantly higher in Group B.[16] Unexpectedly, in this study, topical minoxidil 5% was superior to both of the other groups in improving hair regrowth. There was no sexual dysfunction in any of the study groups.[16]

In another study conducted over a duration of 12 weeks, women with pattern hair loss who did not respond to topical minoxidil 5% were treated with topical minoxidil 5%. In contrast to the previous study, at the end of the study, a clinically significant

Table 1 Studies with topical minoxidil with different concentrations.

Reference	Study details	Results
Olsen *et al.*, 2002[9]	Randomized, placebo-controlled. Double-blind trial of minoxidil 5% vs. 2% in men with AGA (n = 393) Efficacy evaluation parameters: scalp target area hair counts, patient and investigator assessment of improvement in scalp coverage	Significantly better efficacy with 5% than 2% formulation or placebo for improving nonvellus hair count. More pruritus and local irritation with topical minoxidil 5%
Tsuboi *et al.*, 2009[10]	Randomized clinical trial of topical minoxidil 5% vs. 1% in AGA (n = 300). Efficacy evaluation parameter: mean change from the baseline in nonvellus hair per cm^2	Topical minoxidil 5% was superior to 1%
Mapar and Omidian, 2007[12]	Minoxidil 5% (n = 1495 men; 20–40 years of age) in routine clinical practice. Evaluation parameters: patients satisfied with the drug and continued treatment, and causes of stopping treatment	Discontinuation due to adverse effects only in a few patients, but stopping of treatment by many due to fewer effects and aversion to topical treatment
Goldust, 2020[15]	Randomized clinical trial in 66 patients with AGA 15% minoxidil solution vs. 5% solution. Efficacy evaluation parameters: participant assessment of treatment satisfaction, Investigator's Global Assessment (IGA), Global scalp photography and phototrichogram	Minoxidil 15% formulation had significantly better efficacy than 5% at weeks 12 and 24. No significant difference in the adverse effects between groups
Ghonemy *et al.*, 2021[16]	Randomized, placebo-controlled, double-blind trial (n = 90 men with AGA) of minoxidil 5% solution, minoxidil 10% solution and placebo. Efficacy evaluation parameters: clinical features (hair count, hair pull test) and trichoscopy	Topical minoxidil 5% was better than the other two groups in improving hair regrowth
McCoy *et al.*, 2016[17]	Topical minoxidil 15% in women with pattern hair loss who did not respond to topical minoxidil 5%. Efficacy evaluation parameters: target area hair counts, improvement in global photographic assessment	Clinically significant response in 60% of patients

response was observed in 60% of the participants (Table 1).[17]

A comparative study between minoxidil 2% and 5% formulations demonstrated that minoxidil has a dose–response effect that results in plateauing of its clinical efficacy after a certain threshold. According to this report, minoxidil can start following this curve from 7.5% concentrations as it is insoluble in water and its maximum solubility in propylene glycol is 7.5%, after which it easily crystallizes. Thus, higher concentrations do not lead to significant differences in the desired therapeutic effect.[18]

Prognostic factors, treatment duration and adverse effects

Factors increasing responsiveness to topical minoxidil therapy include younger age (< 40 years), early initiation of treatment (< 10 years' duration of hair loss), smaller area of involvement (< 100 mm) and increased number of terminal or indeterminate (intermediate) hairs before initiation of treatment.

Usually at least 4 months of continuous therapy with minoxidil topical solution is required for response; however, treatment should be continued for up to a year before labelling the condition unresponsive.

More AEs may be seen with higher percentage formulations, due to the requirement for higher concentration of propylene glycol to achieve solution. These include hypertrichosis, contact dermatitis (allergic/irritant) and early telogen shedding. Rarely, the treatment may be associated with headache, breathlessness, palpitations and tachycardia.

Conclusion

While most studies reported superior efficacy of higher concentrations of minoxidil, some authors did not find better efficacy but did find an increased propensity to local irritation with higher concentrations. Differences in study settings, patients and duration of follow-up might explain the diversity in the reported results. Further controlled trials with larger sample sizes and longer follow-up durations are necessary to delineate the optimal concentration of minoxidil for treating pattern hair loss.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethics statement

Ethics approval not applicable. The patient provided informed consent for publication of their case details and images.

Data availability

Data are available on request from the corresponding author.

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CPD questions

Learning objective

To demonstrate up-to-date knowledge about minoxidil and its use for hair growth.

Question 1

What is monilethrix of the scalp?

(a) A hair-shaft disorder.
(b) Type of scarring alopecia.
(c) Type of alopecia areata.
(d) Type of chronic telogen effluvium.
(e) Condition with overgrowth of hair follicles.

Question 2

Which of the following is the US Food and Drug Administration (FDA)-approved indication for use of topical minoxidil?

(a) Alopecia areata.
(b) Androgenetic alopecia.
(c) Frontal fibrosing alopecia.
(d) Monilethrix.
(e) Chronic telogen effluvium.

Question 3

What is suggested if a patient is allergic to propylene glycol (PG), used as vehicle in minoxidil preparation?

(a) Do not use minoxidil.
(b) Continue the preparation without any additional treatment.
(c) Continue treatment with same preparation and counsel the patient.
(d) Stop the treatment and restart after 1 week.
(e) Use minoxidil with a PG-free formula.

Question 4

How would you treat a patient with persistence of allergic response after using a minoxidil preparation free from likely allergens?

(a) Stop the current preparation and replace with other minoxidil preparation.
(b) Continue the current preparation without any additional treatment.
(c) Continue treatment with same preparation and counsel the patient.
(d) Stop the treatment and restart after 1 week.
(e) Do not use any minoxidil preparation.

Question 5

Which of the following factors affects the absorption of topical minoxidil?

(a) Vehicle in the preparation.
(b) Area of application.
(c) Skin status.
(d) Frequency of application.
(e) Time of application.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures.
- Reflect on the article.
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions.
- Complete the required evaluation component of the activity.

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

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