Comparison of the Efficacy of Topical Minoxidil 5% and Adenosine 0.75% Solutions on Male Androgenetic Alopecia and Measuring Patient Satisfaction Rate

Bekijk alvast het aan deze studie gerelateerde haargroeimiddel van Haargroeispecialist:

- Linn Minoxidil 5% (100ml). Geschikt voor mannen met erfelijk haaruitval

Lees ook de voor deze studie relevante artikels van Haargroeispecialist:

- informatie over het populaire haargroeimiddel Minoxidil
- waarom is Adenosine beter voor je dan Minoxidil?
- erfelijke haaruitval bij mannen

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SUMMARY According to the hypothesis on the stimulating effect of adenosine on increasing fibroblast growth factor 7 in dermal papilla cells and its vasorelaxant effect, we performed this study to compare the effect of topical minoxidil 5% and adenosine 0.75% on male pattern androgenetic alopecia. This prospective-randomized study recruited 110 male patients suffering from grade II-V Hamilton androgenetic alopecia. Fifty-five patients received minoxidil 5% (group 1) and adenosine 0.75% (group 2) each. Later, 16 patients were excluded due to allergic reactions or loss to follow up. After 3 and 6 months of treatment, complete and relative recovery rates alongside patient satisfaction rate (faster prevention of primary hair loss and appearance of newly grown hair) were compared between the groups. After 3 months of treatment, relative recovery was achieved in 2.4% and 1.9% of patients in group 1 and group 2, respectively, which was not significantly different (p=0.17). During 6 months, the relative recovery rate did not change either within or between the groups (p=0.99) and after 6 months none of the patients achieved complete recovery. However, the patient satisfaction rate was significantly higher in group 2 (p=0.003). In the light of the results, adenosine has no statistically superiority to minoxidil in the treatment of androgenetic alopecia according to recovery rates. However, the patients were significantly more satisfied with adenosine because of faster prevention of hair loss and appearance of the newly grown hairs. It seems further studies with larger sample size or different drug dosages are required to clarify the findings.

KEY WORDS: androgenetic alopecia, adenosine, minoxidil 5%

INTRODUCTION

Androgenetic alopecia (AGA) or male pattern hair loss is still the imperative cause of alopecia that revealed an obvious tendency to involve half of the population before the age of 50 years (1-5). AGA in general is a hereditary thinning of the scalp hairs by vellus transformation of the terminal hairs due to over repetition of hair growth cycles with shortened anagen phase and miniaturization of the hair follicles

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(3,6,7). Since 1942, when Hamilton first demonstrated that this polygenic inheritance process is mediated mainly by androgen (8), several studies have focused on the hair growth cycle physiology and AGA pathophysiology (2,3,5,9,10). Hair growth cycle is regulated by complex processes, which are the consequences of follicular stem cell and dermal papilla cell (DPC) interactions (9). On the other hand, frontal scalp DPCs are the main target cells of androgen action in AGA (9,10). Androgen binds to the androgen receptors and the complex then activates the responsible genes that control hair growth cycles. Consequently, the duration of anagen phase would be shorter and the follicles become miniaturized and produce fine, shorter and less pigmented vellus hairs that are the characteristics of AGA (2,9). In recent years, quite a lot of studies have focused on various pharmacological approaches such as minoxidil and finasteride to prevent excessive hair loss, promote hair growth and enlarge existing hairs by affecting hair growth cycle in AGA (2,4,9,11-13). Until now, a variety of different direct and indirect effects of minoxidil on hair growth cycle have been studied, such as up-regulating vascular endothelial growth factor (VEGF) expression through development of follicular dermal papilla cell vascularization or its direct effects on the proliferation and survival of DPCs and anti-apoptotic effects on DPCs (11,14,15). Minoxidil is still in the first line of treatment of AGA; however, in recent decade and since 2001 when Li *et al*. (16) reported the correlation between minoxidil and adenosine, scientists have revealed a noticeable tendency to focus on the adenosine characteristics. In this study, we evaluated the effect of topical minoxidil 5% and adenosine 0.75% on recovery of male pattern AGA.

MATERIALS AND METHODS

Study population

This randomized prospective study recruited 110 adult male patients who suffered from grade II to V Hamilton-Norwood clinical scale AGA (1) and were referred to Hair and Skin Disease Clinic of our hospital. The study was approved by the hospital ethics committee, and a written inform consent was obtained from the patients. Age under 18 years and presence of any signs and symptoms of inflammation or infection on the scalp, hypersensitivity to minoxidil/adenosine, and history of hypertension and cardiovascular diseases were considered as exclusion criteria for the study. Also, if any patient was lost to follow up or experienced allergic reaction or severe complication following treatment such as hypertrichosis or extensive hair loss, he was excluded from the study. A total of 110 patients were studied and randomly divided into 2 groups: 55 patients received minoxidil 5% (group 1) and another 55 patients received adenosine 0.75% (group 2). Later, two patients from group 1 and 14 patients from group 2 were excluded from the study due to allergic reaction to the drug or loss to follow up. So, 94 patients, i.e. 53 (56.4%) group 1 and 41 (43.6%) group 2 patients, remained in the study and were included in analysis.

Formulation of the drugs

Minoxidil solution was formulated by dissolving 5% minoxidil in a solution of alcohol 60% vol/vol, propylene glycol, and water and adenosine solution was formulated by dissolving 0.75% adenosine in ultrapure water. Subjects were instructed to apply approximately 1 cc of a lotion topically on the scalp (minoxidil 5% in group 1 and adenosine 0.75% in group 2), twice daily for 6 months.

Hair counting

Macro-photography of scalps was performed at baseline and then at 3 and 6 months of treatment. The photographs were converted into dot maps to determine the entire thinning area and counting all visible terminal hairs at a 1-cm^2 target evaluation site within thinning area of each of the four quadrants of the frontoparietal and occipitoparietal scalp. The three well-trained physicians, who were blinded to treatment, performed all evaluations. The mean ratings of the three investigators represented the evaluated factor.

Recovery scoring

Complete recovery following treatment was defined as returning hair growth in 65% to 100% of the thinning area. Relative recovery was defined as returning hair growth in 30% to 65% of the affected area. Hair growth returning in less than 30% of the thinning area was considered as no recovery or treatment failure.

Patient satisfaction

Patient satisfaction was based on the ability of the drug to prevent primary hair loss faster, stimulate growing more pigmented and thick hair with more similar characteristics of terminal hairs, and prevent hair loss recurrence following treatment discontinuation.

Complications

Folliculitis, pruritus, hair loss and hair casts were considered as major complications of treatment.

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Table 1. Recovery rate and satisfaction among patients with androgenetic alopecia following administration of topical minoxidil 5% and adenosine 0.75%

Characteristic	Minoxidil 5% (group 1)	Adenosine (group 2)	Total	p-value (between groups)
Number of patients	41 (43.60%)	53 (56.40%)	96	
Age (yrs)	46.46±14.28	44.46±15.28	30.46±6.28	0.90
Duration of alopecia	6.24±5.31	6.20±4.97	6.29±5.09	0.97
Complications following treatment	4 (9.5%)	2 (3.8%)		0.17
- pruritus	0	1 (78.95%)	1	
- folliculitis	0	1 (21.05%)	1	
- hair loss	3	0	3	
- hair cast	1	0	1	
Complete recovery rate				-
- after 3 months of treatment	0	0		
- after 6 months of treatment	0	0		
Relative recovery rate	1 (2.4%)	1 (2.4%)	2 (2.12%)	0.99
- after 3 months of treatment				
- after 6 months of treatment	1 (2.4%)	1 (2.4%)	2 (2.12%)	
p-value within group	1 (2.4%)	1 (2.4%)	2 (2.12%)	
Patient satisfaction				0.003
- satisfied	13 (28.4%)	37 (69.8%)		
- not changed	22 (52.4%)	16 (30.4%)		
- dissatisfied	6 (14.6%)	0		

Data are presented as n (%) and mean ± standard deviation.

Statistical analysis

The univariate analysis of continuous variables was performed with the Student's *t* test, and categorical variables were compared using the χ^2-test and Fisher exact test, as appropriate. For statistical analyses, SPSS version 16.0 (SPSS Inc., Chicago, IL) was used. All p values were 2-tailed. A p value of less than 0.05 was considered significant.

RESULTS

The study included 94 patients, 53 (56.4%) group 1 and 41 (43.6%) group 2 patients, mean age 30.46±6.28 years and mean androgenetic alopecia duration 6.22±5.09 years.

At month 3 of treatment

None of 94 patients experienced complete recovery during 3 months. Relative recovery was achieved in 2.4% of group 1 and 1.9% of group 2 patients, with no significant between-group difference (p=0.17). In the other words, 98.1% of group 1 patients and 97.6% group 2 patients had less than 30% of returning hair growth in the thinning area.

At month 6 of treatment

At the end of 6-month treatment, complete and relative recovery did not reveal changes either within or between the groups (p=0.99).

Patient satisfaction rate after 6 months of treatment

The patient satisfaction rate based on faster prevention of primary hair loss and appearance of newly grown hair was significantly higher in the adenosine group (group 2) (p=0.003).

Complications

Four group 1 patients (9.8%) and two group 2 patients (3.8%) experienced mild complications during treatment. One patient in group 1 suffered from hair cast and another three patients suffered from increased hair loss. Of the two group 2 patients, one patient suffered from folliculitis and pruritus each. Details are shown in Table 1.

DISCUSSION

Despite the low success rate and speculative mechanism of minoxidil in returning normal hair

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growth cycle and promoting hair growth, it is still the first-line treatment for AGA. Minoxidil is an adenosine triphosphate (ATP) sensitive potassium channel opener that demonstrated some effects on hair growth cycle through different mechanisms like up-regulating VEGF expression, stimulating DPC proliferation, increasing DPC survival and preventing DPC apoptosis and death (11,14). Expression of VEGF mRNA in DPCs varies among different phases of normal hair growth cycle, with extreme expression in anagen phase, which results in improving dermal papilla vascularization. There is strong evidence that minoxidil also has effects on improving dermal papilla vascularization by overexpression of the VEGF mRNA and resembling anagen phase alongside opening potassium channels (11,15,17). However, Li *et al*. (16) suggest that minoxidil has no direct effect on hair growth and its effect is perhaps mediated by adenosine as activation of adenosine receptors in cultured DPCs, thus possibly regulating minoxidil-induced production of VEGF. Adenosine is an endogenous molecule that regulates tissue function *via* binding to and activating one of the four G-protein receptors, A1, A2A, A2B and A3 (18). Since the first discovery of the practical effect of adenosine on the cardiac function, adenosine has been investigated in many studies, which have revealed that it is able to regulate all body organ systems sufficiently (18-21). In this regard, Lino *et al*. (20) demonstrated that adenosine could stimulate hair growth *via* up-regulating fibroblast growth factor 7 (FGF-7) in DPCs. Furthermore, Oura *et al*. (22) confirmed the role of adenosine in stimulation of hair growth and thickening of hair shafts in hair growth cycle anagen phase and stated that adenosine is useful for treating female pattern hair loss as well as androgenetic male alopecia. Another interesting finding by Hwang *et al*. (21) in 2012 showed the growth of DPCs and lengthening of the anagen phase by increasing the cysteine level *via* fibroblast growth factors 2 and 7 in an organ culture of mouse vibrissae hair follicles.

In this study, the application of adenosine 0.75% solution just once daily showed an equivalent treatment effect to that of 5% minoxidil applied once daily in terms of changes in total recovered area by newly grown terminal hairs. After 3 months of treatment, relative recovery, i.e. hair growth returning in 30% to 65% of the thinning area, was not significantly different between the groups (p=0.17). In the next 3 months, at the end of month 6, the relative recovery rate did not change either within or between the groups (p=0.99) and none of 94 patients achieved complete recovery during 6 months of treatment. Despite no between-group difference according to recovery rate detected by the investigator, the patient satisfaction rate was significantly higher in the adenosine group (p=0.003), based on faster prevention of primary hair loss and appearance of newly grown hairs. These results show that minoxidil and adenosine have the same effect on recovery of hair loss in AGA and there is no superiority regarding treatment of AGA by adenosine. However, according to the patient satisfaction rate, adenosine is superior as the first-choice treatment for AGA due to faster prevention of hair loss and favorable appearance of newly grown hairs. Regardless of differences between the groups, none of the recovery rates achieved in this study was satisfactory enough. It seems to be related to some reasons like insufficient application of solution by patients or inadequate dosage of minoxidil and adenosine administered, as in the study reported by Oura *et al*. (22), the patients applied 3 cc of lotions twice daily for 12 months, which is much greater dosage used over a longer treatment period. Another factor that seems to have influenced the results is monotherapy. Future studies may reveal that utilizing a combination of minoxidil and adenosine just like a combination of minoxidil and finasteride can improve and return hair growth with more pigmented, thickened, terminal hairs. On the other hand, in the present study, the patients were followed up for up to 6 months, which was a shorter period than the follow up reported from the studies that achieved better results. It could easily affect the result of the study; for instance, in the study by Oura *et al*. (22), hair appearance improved from 0 in month 6 to 30% in month 12 in adenosine group by dermatologist assessment, and from 15% in month 6 to 23% in month 12 by investigator assessment.

CONCLUSION

The conclusion, the present study interestingly showed that topical application of a solution with 0.75% adenosine had the same effects to minoxidil 5% in the regulation of hair growth cycle and recovery of hair loss. According to the patient satisfaction rate, adenosine was superior to minoxidil in the treatment of AGA because it could prevent hair loss faster and stimulate hair growth more desirably.

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