A Retrospective Study on the Safety of Systemic Minoxidil for Hair Loss in the Older Population

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ABSTRACT

Oral or systemic minoxidil has been used off-label for decades to treat androgenetic alopecia (AGA) and other hair loss disorders. Its adverse effects have been reported in the literature to include facial and body hypertrichosis, palpitations, and fluid retention, among others. Most safety studies on low-dose systemic minoxidil for the indication of hair loss have been comprised of the younger population; however, for this retrospective study, we have chosen to look at adverse events in the older population (aged 60 years and above), taking into account the group's possibly higher presence of comorbid conditions and/or intake of other medications.

Among 42 patients, only 19% had experienced adverse events, with facial and body hypertrichosis being the most common. Adverse events were managed successfully by dose reduction, leg elevation, salt restriction, and diuretics, and only 2 had to discontinue minoxidil. No serious adverse events were found in the study. While no diagnostic evaluation is required for healthy patients in this age group, we highly recommend caution when prescribing systemic minoxidil for patients on multiple antihypertensives agents and for those at risk for cardiovascular events.

Keywords: alopecia, androgenetic alopecia, hair loss, minoxidil

INTRODUCTION

Androgenetic alopecia (AGA) is characterized by follicular miniaturization, shortened duration of anagen, and reduced ratio of anagen to telogen. In males, androgens, genetics, oxidative stress, and microinflammation are known to create the classic presentation of male pattern hair loss (MPHL). The same microinflammation and oxidative stress contribute to the etiology of female patten hair loss (FPHL); however, different genes and androgen-independent mechanisms may be at play.[1]

Although a benign medical condition, AGA may inflict a psychological burden that leads to anxiousness, diminished self-esteem, and feelings of stigmatization[2]; for this reason, the search for effective treatment options for AGA is ongoing. Topical minoxidil, with its different forms and concentrations in men and women, and oral finasteride in men have been approved by the United States Food and Drug Administration (US FDA) for use in AGA since 1988 and 1997, respectively.[3,4] Low level laser/light therapy (LLLT) was cleared by the US FDA for male patients with AGA in 2007 and for female patietn with AGA in 2011.[5]

Oral minoxidil, used off-label for treatment of hair disorders, has been tried for various conditions such as AGA, alopecia areata, telogen effluvium, and even scarring alopecias. Most studies used low dose oral minoxidil (LDOM), defined as < 5mg per day,[6] with women needing lower doses (0.25-5.0mg) in general than men (1.25-5.0mg) to show effectiveness.[7] Systematic reviews done in mixed age groups showed that common adverse events (AE) included hypertrichosis, postural hypotension, pedal edema, and palpitations, among others, but it is generally safe and well-tolerated.[7-9] In this study, we aimed to assess its safety and tolerability in the elderly population (≥ 60 years old).

METHODS

This retrospective descriptive study was conducted at DHT Clinic in Bangkok, Thailand, through a review of medical records from 2018 to 2023. While the clinic has been recommending minoxidil tablets for hair disorders since 1995, regulatory constraints stemming from its off-label use and the regrettable loss of records precluded the inclusion of data from this earlier time frame in the current analysis. Patients aged 60 and older at the time of starting systemic minoxidil were identified. All patients were informed of the off-label use of oral or sublingual minoxidil in hair disorders. Inclusion criteria were male/female patients, with or without hair transplant, who took any dose of systemic minoxidil for the duration of at least one month (or shorter if they had intolerable AEs). Patients taking other hair loss drugs and drugs for comorbidities were also included. The following data were recovered from the records: patient demographics, severity of pattern hair loss, indication for use of systemic minoxidil, dose and route of systemic minoxidil, treatment duration, AEs from oral minoxidil, and any withdrawal from treatment.

RESULTS AND DISCUSSION

In this study, data from a total of 42 patients between 2018 to 2023 were included (Table 1). Mean age of participants was 66 years, of which 33 were male (79%) and 9 were female (21%). The most common indications for treatment with systemic minoxidil in this study included male pattern hair loss (n = 33, 79%), female pattern hair loss (n = 7, 16%), and telogen effluvium (n=2, 5%). Among the cases of male pattern baldness, the most common stage was Norwood-Hamilton stage VI (n = 14, 42%). Thirty-one (94%) of the male patients and 1 (11%) female patient underwent hair transplantation. Dosage prescribed ranged from 1-5mg per day (or 0.06mg/kg/day), and only 1 patient was given 10mg/day. The majority took it orally (88%) and the rest took it sublingually (12%). The mean duration of minoxidil intake for all participants was 24 months.

Mechanism of Action

Oral minoxidil was originally used to treat refractory hypertension; however, when taken for more than two weeks, patients experienced hypertrichosis. This subsequently led to

Table 1. Characteristics of Study Participants

	Male (n=33)	Female (n=9)
Mean age	66.2 years	65.8 years
Country of Origin	East Asian 1 (3%) Southeast Asia 19 (58%) South Africa 1 (3%) Caucasian (Australia) 1 (3%) Caucasian (USA, Canada) 8 (24%) Caucasian (Europe) 3 (9%)	Southeast Asia 8 (89%) Southern Asia 1 (11%)
Mean dose of systemic minoxidil	4.8 mg (0.06 mg/kg/day)	2.75 mg (0.03 mg/kg/day)
Diagnosis of hair disorder	Male pattern baldness (100%): NH class III (n=3, 9.1%) NH class III vertex (n=2, 6.1%) NH class IV (n=4, 12.1%) NH class V (n=10, 30.3%) NH class VI (n=14, 42.4%)	Female pattern baldness (78%): Ludwig II (n=6, 67%) Ludwig III (n=1, 11%) Telogen effluvium (n=2, 22%)
Mean duration of systemic minoxidil	27.5 months	5.86 months
Route of systemic minoxidil		
Oral	29	8
Sublingual	4	1
Use of other hair loss drugs*		
F	19	1
S	0	3
K	0	1
TM	1	0
F + TM	4	0
F + D + TM	1	0
F + S + TM + K	1	0
S + K	0	2
K + TM	0	1
No medications other than oral/sublingual minoxidil	7	1
Participants with comorbid conditions		
Any comorbid conditions	19 (58%)	4 (44%)
Hypertension	9	2
Dyslipidemia	7	3
Endocrine disorders		
Diabetes	4	2
Hypothyroidism	1	0
Cardiac rhythm disorder (Atrial fibrillation, heart block)	2	0
Dermatological disorders (psoriasis)	1	0
Musculoskeletal disorders (Gout)	1	0
Psychiatric/psychological disorders (sleep disorder, depression)	2	0

*F = oral finasteride 1-1.25mg/day, D = oral dutasteride 0.5mg/week, S = spironolactone 25-50mg/day, K = ketoconazole 2% shampoo 2-3 times a week, TM = topical minoxidil 5% foam/solution/lotion

**ARB = angiotensin-receptor blocker, CCB = calcium channel blocker, SARI = serotonin reuptake inhibitor, GLP-1 receptor agonist = glucagon-like peptide-1 receptor agonist, SGLT-2 inhibitor = sodium-glucose co-transporter 2 (SGLT2) inhibitor

development of minoxidil solution, which gained FDA approval in 1988 for alopecia. Minoxidil is activated into minoxidil sulfate by the sulfotransferase enzyme found in hair follicles. It has a few characteristics and mechanisms of action hypothesized to be responsible for hair growth; namely, vasodilation, anti-inflammatory properties, and Wnt/β-catenin signaling.[10]

Minoxidil opens adenosine triphosphate (ATP)-sensitive potassium channels, causing smooth muscle relaxation in blood vessels.[11] This resulting vasodilation was suggested to aid in increasing blood and nutrient supply to the hair follicles while anti-inflammatory properties were attributed to its ability to inhibit interleukin-1α and prostacyclin. Minoxidil was also shown to stimulate release of vascular endothelial growth factor (VEGF), which is linked to β-catenin signaling pathway.[12] Activation of the β-catenin signaling activity in dermal papilla cells by minoxidil has been suggested to lead to extension of anagen phase.[10]

Effectiveness

Sharma and colleagues reported clinical improvement with use of oral minoxidil 0.25-5.0mg once or twice daily in 61-100% of AGA cases and in 18-82.4% of alopecia areata cases. Success was also seen in female pattern hair loss and chronic telogen effluvium among others.[7] According to Jimenez-Cauhe and colleagues, a clinical response was seen in 70-100% of the patients using 0.25-5.0mg oral minoxidil.[8]

Adverse Events

A multicenter study showed that approximately one-fifth of participants (20.6%) taking minoxidil experienced AEs, while the majority (79.4%) did not. The most common AEs were hypertrichosis (15.1%), lightheadedness (1.7%), and fluid retention (1.3%).[9] Other reviews demonstrate similar results; hypertrichosis was the most commonly observed AE with 24% of the patients being affected. Other AEs included pedal edema (2%), heart rate alterations (1.3%), and postural hypotension (1.1%).[7,8] Additionally, intake of oral minoxidil should be cautiously monitored in patients with renal failure and hepatic impairment; the drug is contraindicated in cases of drug hypersensitivity and those with history of pheochromocytoma.[7]

Topical minoxidil can also have some systemic absorption and may also cause hypertrichosis in areas not in contact with the solution. This effect was found to be dose-dependent; its incidence was higher with use of 5% minoxidil solution compared to lower concentrations. Spontaneous resolution was reported to be fastest on the face and arms after stopping for 1-3 months, followed by legs after stopping for 4-5 months.[13]

Table 2 lists the AEs seen in our study. Only 5 out of the 33 male participants (15%) and 3 out of the 9 female participants (33%) experienced AEs. In men, the most common AE was facial and body hypertrichosis (6%, n = 2), followed by upper eyelid swelling, palpitations, and leg swelling (with 1 event each). In women, the most frequent AEs were facial/body hypertrichosis (22%, n = 2), upper eyelid swelling (n = 2), and palpitations (n = 1). AEs seemed to occur more in women in our study which is consistent with another published study that reported that 20.1% of women experienced hypertrichosis with 1.11mg/day of minoxidil vs. only 5.8% of men on 2.6mg/day of minoxidil.[9] Furthermore, in our study, AEs (7 vs 1) seemed to occur more often among those taking minoxidil orally versus sublingually (Table 3).

Table 2. Adverse Events (AEs) in Male and Female Participants

	Male (n=33)	Female (n=9)	Total
Patients without any AEs	28 (85%)	6 (67%)	34 (81%)
Patients with any AEs	5 (15%)	3 (33%)	8 (19%)
Adverse events*	5	5	10
Facial or body hypertrichosis	2 (6%)	2 (22%)	4 (9.5%)
Upper eyelid swelling	1 (3%)	2 (22%)	3 (7.1%)
Palpitations	1 (3%)	1 (11%)	2 (4.8%)
Leg swelling	1 (3%)	0	1 (2.4%)

**There was more than one adverse event in some participants.*

Table 3. Routes of Administration, Duration and Presence/Absence of Comorbid Conditions in Patients With and Without Adverse Events (AEs)

Patients	Route		Duration		Comorbid Conditions	
	Oral	SL	< 6 mos	≥ 6 mos	Without	With
With any AE (n=8)	7 (5-10mg)	1 (5mg)	3	5	3	5
Without AE (n=34)	30 (1-5mg)	4 (5mg)	12	22	15	19

**SL = sublingual*

Systemic Minoxidil for the Older Population

Clinicians should be aware of possible drug interactions and AE risks in older patients as they tend to develop more comorbid medical conditions and are more likely to be on other medications.[14] Among the male participants in the study, 58% had medical conditions including hypertension, dyslipidemia, diabetes, cardiac rhythm disorders (with pacemaker), thyroid disorder, dermatological disorder, and gout. Among female participants, 44% had medical conditions

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such as hypertension, dyslipidemia, diabetes, and anemia (Table 2). Prior to starting hair loss medications, the patients were already on the following drugs to treat these disorders: anti-hypertensives, cholesterol-lowering agents, anti-diabetic drugs, and sedatives among others. The most commonly taken drugs by both male and female participants were anti-hypertensives (26%) followed by cholesterol-lowering agents (21%).

Polypharmacy is defined as taking 5 or more medications. Patients taking 5 drugs were found in an observational study to be almost four times more likely to be hospitalized for adverse drug events.[14] Hence, physicians must perform careful review of the drug chart when planning to prescribe another drug such as minoxidil. In particular, caution should be taken when combining systemic minoxidil with cardiovascular medications in vulnerable populations. This is because minoxidil's vasodilatory properties can persist up to 72 hours, potentially causing sodium and fluid retention that can lead to more serious cardiovascular AEs.[13] One study involving patients with preexisting hypertension and/or arrythmias found that those taking 3 more antihypertensives had a higher risk of experiencing more than one AE, such as light-headedness and generalized weakness. In another group of 10 patients with varying arrythmias (atrial fibrillation, supraventricular extrasystole, sinus tachycardia, etc.) and cardiac procedures done (e.g., cardiac ablation and pacemaker insertion), only 1 experienced an AE (periorbital and pedal edema). No other patient experienced a cardiovascular AE or any other AE.[15]

In our study, we observed only 3 cases of polypharmacy, none of whom experienced any AEs with minoxidil intake. However, due to the small study size, it is difficult to infer whether the presence of comorbid conditions or polypharmacy increases the risk of having AEs (Table 3).

Diagnostic Tests Prior to Starting Systemic Minoxidil

Prior to starting systemic minoxidil, history, physical examination, and vital signs must be obtained or performed as with any other patient. As there are no specific guidelines regarding diagnostic evaluation for hair loss patients before minoxidil is prescribed, tests should be requested on a case-to-case basis depending on the patient's personal and family medical history. In an open-label study by Panchaprateep and colleagues, a small portion (10-23%) of their 30 AGA patients had underlying diseases such as diabetes, dyslipidemia, hypertension, and metabolic syndrome. After 24 weeks of oral minoxidil (5mg) intake, they found that complete blood count, blood urea nitrogen, creatinine, and electrolytes were normal, although some patients had slight increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Initial response to oral minoxidil included a small decrease in blood pressure and pulse rate, and orthostatic hypotension; however, after 24 weeks, blood pressure and pulse rate showed insignificant changes compared to baseline. Abnormal EKG findings (premature ventricular contraction and new T wave inversion) were observed in 20% of the patients, but these were reportedly asymptomatic and non-ischemic. The study concluded that oral minoxidil is generally safe in healthy subjects but should not be prescribed to an elderly patient with increased risk of the following: myocardial infarction (MI), heart failure, chronic renal failure, or severe hypertension.[16]

In a multicenter study of LDOM for treatment of alopecia in patients with a history of hypertension by Jimenez-Cauhe and colleagues, EKG was not routinely ordered, and most patients were not required to see a cardiologist prior to starting LDOM. However, baseline EKG, BP monitoring, and consultation with cardiologist were recommended as a special precaution for patients with a personal history of postural hypotension, syncope, uncontrolled hypertension, and arrhythmia; those using 3 or more antihypertensive drugs; and those being treated with the alpha-blocker doxazosin. Furthermore, the authors do not recommend LDOM to patients with a history of or an increased risk of MI, chronic heart failure with reduced ejection fraction, severe valvular disease, pericardial disorders, and advanced renal disease. Consultation with a cardiologist prior to LDOM use was highly advised in these groups.[15]

Prior to consultation at our clinic, patients with cardiovascular disorders, especially those with cardiac rhythm disorders, were already being seen by internists and/or cardiologists. They were subsequently cleared by their attending physicians to proceed with minoxidil intake and had regular follow-up consultations, blood pressure monitoring, and necessary blood tests/EKG. While no serious AEs were observed thereafter in our study, we still advise that a careful evaluation of patient risk for serious AEs should be done prior to starting minoxidil for patients with hair loss. For healthy patients with low risk, performing diagnostic tests are not necessary prior to starting LDOM. For those with moderate to high risk of serious AEs, we are echoing the conclusion made by Panchaprateep et al and Jimenez-Cauhe et al that caution should be exercised when starting LDOM in these patients and that consultation with a cardiologist is highly advised.

Management of Adverse Events

Most AEs resolved upon reduction of dose and/or frequency of minoxidil intake and changing route of administration from oral to sublingual. In instances where hypertrichosis remained unresolved, women opted to shave, while the men demonstrated a higher tolerance for it. Leg edema seen in this study was managed by advising decreased salt intake, leg elevation, and addition of furosemide 20mg once a day. Out of the 8 subjects who experienced AEs, 2 (25%)—a male and a female—discontinued taking systemic minoxidil due to intolerability of palpitation and upper eyelid swelling. One of them switched to topical minoxidil and did not exhibit recurrence of palpitations. Although not observed in this study, patients with risk of or a personal history of postural hypotension may be advised to take minoxidil before bedtime as a preventive measure.[15] Gradual titration until target dose is reached may also be done to monitor appearance of AEs.

Limitations

This is a retrospective chart review involving a relatively small population. While this study showed there is a less

incidence of hypertrichosis (9.5%) in patients ≥ 60 years old compared to other studies (24%),[8] it is also likely that this is due to certain study limitations. The lower incidence of hypertrichosis may be explained first by the small number of subjects and second by the mostly male population who may not find facial or body hypertrichosis a reportable problem.

CONCLUSION

The majority of our subjects did not experience any AEs while taking systemic minoxidil. Those who did had facial and body hypertrichosis, upper eyelid swelling, palpitations, and leg swelling; these led to discontinuation of medication in one-fourth of participants with AEs. We recommend using a low dose of oral or sublingual minoxidil with gradual titration up to 5mg a day depending on the patient's tolerance. Oral and sublingual minoxidil can be considered safe for the elderly population (60 years old and over), and routine diagnostic tests are not necessary for healthy patients. While no significant AEs were noted in this study, we advise exercising caution when prescribing minoxidil to individuals with a predisposition to serious AEs. For future research, we recommend increasing the sample size and incorporating data on the timing of AE onset and resolution.

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