Efficacy and Safety of Topical Adenosine for Androgenetic Alopecia in Adults: A Systematic Review

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ABSTRACT

Background. Androgenetic alopecia (AGA), also known as pattern hair loss, is the most common type of hair loss in men and women. Due to very limited therapeutic options, search for other effective and safe drugs is necessary.

Objectives. This review aims to evaluate the efficacy and safety of a potential treatment option, topical adenosine, for AGA in male and female adults.

Methods. A search of databases (Cochrane Library, Pubmed Medline, and others) was performed with no time limitations placed. We included human interventional studies published in English involving the use of topical adenosine for AGA in healthy adult males and females. Risk bias assessment was performed using the Cochrane Collaboration criteria.

Results. All four trials in this review, with a total of 260 participants, used 0.75% topical adenosine lotion twice a day for a period of 6-12 months. Comparators were placebo, topical niacinamide, and topical minoxidil. Evaluated parameters include improvement in baldness grading as assessed by dermatologists and investigators, improvement and satisfaction as assessed by participants, anagen growth, thick/thin/vellus hair ratio, and hair density. Two trials found significant improvement with thick hair ratio (>60 or >80 μm) with the use of topical adenosine while two trials showed higher overall participant satisfaction with topical adenosine. Few to no adverse effects were reported with its use.

Conclusion. This is the first systematic review involving topical adenosine for AGA. Topical adenosine may be effective in increasing thick hair ratio and improving the self-perception of hair growth. With minimal to no adverse effects, it may serve as an adjunct or alternative to present treatment options. However, more studies are needed to strengthen these findings.

Key Words: androgenetic alopecia, pattern baldness, baldness, topical adenosine

INTRODUCTION

Androgenetic alopecia (AGA), also known as pattern hair loss, is the most common type of hair loss in men and women. Male pattern hair loss (MPHL) appears as temporal and vertex balding while female pattern hair loss (FPHL) is usually described as mid frontal scalp hair thinning. This disease is familial with a polygenic mode of inheritance.[1]

Currently, there are only two FDA-approved medications for AGA: topical minoxidil and oral finasteride. Minoxidil, however, has adverse effects such as contact dermatitis found in 1.9-5.7% of participants in a phase III trial,[2] as well as facial hypertrichosis, and irritation from propylene glycol. Oral finasteride—an option not approved for women—also has adverse effects (although rare) including decreased libido and erectile dysfunction.[1] Other options for AGA would

Oral presentation at the 19th Dubai World Dermatology and Laser Conference & Exhibition, March 18-20, 2019, Dubai, United Arab Emirates.

E-Poster presented at the 41st Annual Convention of the Philippine Dermatological Society, November 7-9, 2018, Edsa Shangri-La, Mandaluyong City, Philippines.

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have patients resorting to wearing wigs and hairpieces or undergoing very expensive procedures such as laser and hair transplants. Hence, these options leave us with the desire to continue the search for other effective options with fewer adverse effects.

Topical adenosine is an option that may potentially improve AGA. By performing a systematic review, we aim primarily to assess the efficacy of topical adenosine in treating androgenetic alopecia, and as a secondary objective, to assess the presence of any adverse events associated with its use.

MATERIALS AND METHODS

Databases (Cochrane Library, Google Scholar, HERDIN, PROSPERO, Pubmed Medline, Science Direct, and TRIP) were searched using the keywords 'adenosine', 'topical adenosine', and 'androgenetic alopecia' with no time limitations placed. Initial screening was performed based on title and abstract and only human interventional studies using topical adenosine on AGA were included.

The following data were extracted from each study: study design, year, country, sample size, age, sex, race, severity of AGA, dose, and frequency of using topical adenosine and its comparator/placebo, duration and results of treatment, and authors' conclusion. Each study then underwent risk bias assessment using the Cochrane Collaboration criteria.[3]

RESULTS

There was a total of 677 results from the database search. After excluding those that did not meet our criteria as well as the duplicates, four studies remained and were included in this review (Figure 1). Oura et al. (2008) and Iwabuchi et al. (2016) both compared topical adenosine with placebo; Watanabe et al. (2015) compared it with topical niacinamide while Faghihi et al. (2013) compared it with topical minoxidil. These studies underwent a bias risk assessment following the Cochrane Collaboration criteria (Table 1). One study had a low risk of bias, two studies had an unclear risk of bias, while another had a high risk of bias.

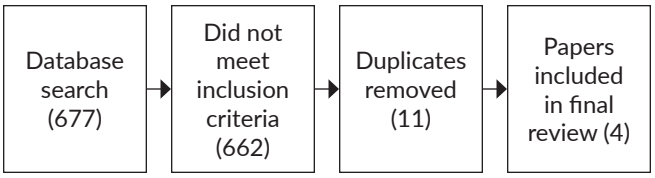

Figure 1. Database search for topical adenosine on AGA.

This review reports a total of 260 adult participants with a mean age of 38.09 years and with varying severities of androgenetic alopecia. The study population was comprised mainly of males (n=233, 89.62%) while only a small portion were females (n=27, 10.38%). The population also had a good combination of races including Japanese (n=128), Caucasian (n=38), and an unspecified race from an Iranian study (n=94). All participants had brown to black hair. Data extracted from the four studies can be found in Table 2.

Topical adenosine vs. placebo

In a double-blind placebo-controlled study,[4] 27 healthy female Japanese participants applied 0.75% adenosine lotion or placebo lotion BID for 12 months. The participants had over stage 1.5 of female pattern hair loss based on a 6-point scale.[5] The efficacy was measured at the 6th and 12th months and this included assessment by dermatologists and investigators, hair parameters from phototrichogram, and self-assessment using a questionnaire.[6]

Table 1. Risk of bias assessment based on Cochrane Collaboration criteria

Bias domain	Source of bias	Oura et al., 2008	Iwabuchi et al., 2016	Watanabe et al., 2015	Faghihi et al. 2013
Selection	**Random sequence generation**	Yes*	Yes*	Yes	Yes*
	Allocation concealment	Not mentioned	Not mentioned	Not mentioned	Not mentioned
Performance	**Blinding of participants and personnel**	Yes	Yes	Yes	Not mentioned
Detection	**Blinding of outcome assessment**	Yes	Not blinded	Yes	Yes
Attrition	**Incomplete outcome data**	Losses to follow-up were disclosed; not included in final analysis	N/A No drop-outs	Losses to follow-up were disclosed; not included in final analysis	Losses to follow-up were disclosed; not included in final analysis
Reporting	**Selective reporting**	All prespecified outcomes were reported	All prespecified outcomes were reported	All prespecified outcomes were reported	All prespecified outcomes were reported
Others	**Other sources of bias**	None	Funded by adenosine manufacturer	Significant differences in vellus-like hair ratio and thick hair ratio at baseline; funded by adenosine manufacturer	Those with allergic reactions or severe complications** were excluded
Judgment	–	Low risk	Unclear risk	Unclear risk	High risk

* *Not described in detail*
** *Hypertrichosis or extensive hair loss*

Table 2. Studies on topical adenosine for androgenetic alopecia

Author, Country, Year	Study Design	Ave. age/ Sex/Race	Exclusion criteria	Dose, frequency, duration	Treatment groups	Type and Severity of AGA
Adenosine vs. Placebo						
Oura et al., Japan, 2008	Double-blind placebo-controlled RCT	38.9 yo/ Japanese F	No systemic illness	3 ml BID x 12 mos.	0.75% adenosine lotion (13) vs. Placebo lotion (14)	FPHL over stage 1.5 (Tajima's classification)
Iwabuchi et al., Japan, 2016	Single-blind placebo-controlled RCT	41.5 yo/ Caucasian/ M (brown to black hair, no blonde)	No systemic illness No minoxidil in past 6 months	3 ml BID x 6 mos.	0.75% adenosine lotion (19) vs. Placebo lotion (19)	Baldness grade 6 (Ishino's classification)
Adenosine vs. Niacinamide						
Watanabe et al., Japan, 2015	Double-blind randomized study *(with placebo-like control)*	41.5 yo/ Japanese/ M (all close to black hair)	No systemic illness No hair dye	3 ml BID x 6 mos.	0.75% adenosine lotion (51) vs. 0.1% niacinamide (placebo-like) lotion (50)	Pattern II or IV hair loss, medium (Ogata's classification)
Adenosine vs. Minoxidil						
Faghihi et al., Iran, 2013	Randomized prospective	30.46 yo/ Race not specified/M	<18 yo No inflammation or infection of scalp No hypersensitivity to minoxidil/adenosine No HTN, CVD	1 ml BID x 6 mos.	0.75% adenosine lotion (53) vs. 5% Minoxidil (41)	MPHL grade II to V (Hamilton-Norwood clinical scale)

** Significant p<0.05*

	Results	Authors' conclusion
	At the 6th month Dermatologists' assessment: • All 'improvement' cases: 39% vs. 21%, p=0.4197 Investigators' assessment: • All 'improvement' cases: 23% vs. 29%, p=1.000 Phototrichogram: • Significant improvement with anagen hair growth rate and thick hair (>80 μm) ratio Self-assessment: • Change in appearance p=0.148 • Change in hair growth p=0.041* • Prevention of hair loss p=0.017* ***At the 12th month*** Dermatologists' assessment • All 'improvement' cases: 85% vs. 36%, p=0.0183* Investigators' assessment: • All 'improvement' cases: 62% vs. 36%, p=0.2568 Phototrichogram: • Significant improvement with anagen hair growth rate and thick hair (>80 μm) ratio Self-assessment: • Change in appearance p=0.048* • Change in hair growth p=0.081 • Prevention of hair loss p=0.036* No adverse effects	Compared to placebo, topical adenosine showed significant improvement via dermatologists', investigators', and self-assessments. Topical adenosine stimulates hair growth and increases thicker hairs.
	Dermatologists' assessment: • Change in baldness grade: -0.35 vs. 0.179, p=0.3955 Phototrichogram: • Change in hair density: 4.9 vs. -3.8 p=0.04* • Change in thick hair (>60 μm) proportion: 5.5 vs. -8.5, p=0.0001* • Change in thin (40-60 μm) hair proportion: -4.1 vs. 1.9, p=0.1113 • Change in vellus (<40 μm) hair proportion: -1.4 vs. 6.6, p=0.0154* No adverse effects	Topical adenosine is effective increasing proportion of thick hairs and may be used as an alternative to minoxidil.
	Dermatologists' assessment: • All "improvement cases" in baldness grade: 48 vs. 38, p=0.0124* Phototrichogram: • Change in thick hair (>60 μm) ratio: 10.4 vs. 6.1, p=0.0331* • Change in thick hair (>80 μm) ratio: 5.1 vs. 2.5, p=0.0268 • Change in vellus hair (<40 μm) ratio: -7.2 vs. -5.9, p=0.5364 • Rate of change in hair density: 2.7 vs. 1 p=0.3789 Self-assessment: • Thickness of hair: 24 vs. 10, p=0.0137* • Overall thickness of hair: 30 vs. 25, p=0.5375 Adverse effects of adenosine: seborrhea and scaling but not causal	Topical adenosine increases thick hair ratio and is not associated with significant adverse events.
	Hair recovery: • Complete recovery: 0 vs. 0 • Relative recovery: 1 vs. 1, p=0.99 Patient satisfaction: • Satisfied: 37 vs. 13, p=0.003* • No change: 16 vs. 22 • Not satisfied: 0 vs. 6 Adverse effects of adenosine: folliculitis and pruritus	Topical adenosine is not statistically superior to minoxidil in terms of recovery rate but adenosine exhibited higher satisfaction rates.

Results showed no significant changes between the adenosine group and placebo group at the 6th month in terms of the dermatologists' (39% vs. 21%, p=0.4197) and investigators' assessments (23% vs. 29%, p=1.0000). In the 12th month, however, significant improvements were seen with the dermatologists' assessment (85% vs. 36%, p=0.0183) but not with the investigators' assessments (62% vs. 36%, p=0.2568).[4]

Based on the graphs presented by the authors, anagen hair growth rate and thick hair (>80 μm) ratio showed significant improvement in the 6th and 12th months. Other parameters such as anagen hair ratio, thin hair (<40 μm) ratio, and hair density did not show significant improvement at either 6th or 12th month.[4]

In terms of self-assessment, participants were satisfied with the prevention of hair loss at both assessment periods. Significant improvement with hair growth at six months (p=0.041) and with the appearance of hair at 12 months (p=0.048) was also perceived by participants. No adverse effects were noted during the entire study period.[4] Overall, compared to placebo, adenosine showed significant improvement via dermatologists' and self-assessments. It also had a significantly positive effect on the anagen hair growth rate and thick hair ratio.

A second study, by Iwabuchi and colleagues,[7] also compared 0.75% adenosine lotion with placebo in a single-blinded 6-month-study with 38 Caucasian male participants. The participants had brown to black hair and on average, presented with a baldness grade of 6 based on the Ishino scale.[8]

Compared with placebo, topical adenosine showed significant improvements in terms of hair density (4.9 vs. -3.8, p=0.04), thick hair proportion (5.5 vs. -8.5, p=0.0001), and vellus hair proportion (-1.4 vs. 6.6, p=0.0154). However, it had no advantage over placebo in improving overall baldness grade. There were also no adverse effects seen, leading the authors to conclude that adenosine may be a useful alternative to minoxidil.[7]

Topical adenosine vs. topical niacinamide

A double-blind randomized study was performed on healthy adult Japanese males with pattern II or IV AGA (Ogata's classification) by Watanabe and colleagues in 2015. In place of a placebo, 0.1% niacinamide lotion was compared against 0.75% adenosine lotion. After six months, there was a significantly higher number of cases showing improved baldness grade among the treatment group compared to the niacinamide group (48 vs. 38, p=0.0124). The treatment group also showed a significant change in thick hair ratio defined as >60 μm (10.4 vs. 6.1, p=0.0331) and in thick hair ratio defined as >80 μm (5.1 vs. 2.5, p=0.0268) compared to the niacinamide group. Through a questionnaire at the end of the study, participants in the treatment group reported satisfaction (24 vs. 10, p=0.0137) in terms of hair thickness; however, no significant difference was seen between the groups in terms of overall satisfaction. While this study observed adverse effects such as scaling and seborrhea, these were not directly attributed to the use of adenosine.[9]

Topical adenosine vs. minoxidil

In this randomized prospective study comparing topical adenosine to the current standard, topical minoxidil, adult males of the unspecified race with male pattern hair loss grade II to V (Hamilton-Norwood) were included.[10] Results showed significant participant satisfaction in the adenosine group compared to the minoxidil group (37 vs. 13, p=0.003) due to the perceived faster prevention of hair loss and favorable appearance of newly grown hairs. There were, however, no significant changes in hair recovery. Adverse effects observed with the use of adenosine include folliculitis and pruritus.[10]

DISCUSSION

There are male and female patterns of AGA, with the male pattern AGA being characterized by androgen hyperactivity and genetic predisposition. Androgens bind to its receptors at the hair bulb, causing an alteration in the dermal papilla during early anagen. These alterations lead to shorter hair, smaller anagen follicles, as well as shorter and delayed anagen phase. The mode of inheritance of MPHL is polygenic with polymorphisms of different genes being linked to premature balding. These include the androgen receptor gene, 5α reductase gene, and two other genes found on chromosomes 3 and 21.[1]

Some authors assume this pathophysiologic model to be the same for females. However, others would consider FPHL to be more complex since the role of androgen in its pathogenesis has not been fully elucidated. In fact, a combination of genetic, hormonal, and environmental factors was thought to be contributory.[11]

Adenosine is a purine nucleoside with a mechanism of action linked to that of minoxidil. A proposed pathway by Marubayashi, Nakaya, Fukui, Li, and Arase involves the stimulation of dermal papilla cells by minoxidil, leading to the activation of the adenosine receptor signal transduction pathway. This pathway allows an increase in intracellular calcium and upregulation of vascular endothelial growth factor (VEGF). Modulation of fibroblast growth factor (FGF-7), keratinocyte growth factor (KGF), and TGF-β are also implicated in the mechanism of action of adenosine.[4,7]

The database search yielded 4 trials with different risks of bias. All studies, except for one, used 3 ml of 0.75% topical adenosine twice a day for six or 12 months, which allowed for better comparison across studies. Most of the studies lasted for 12 months except for that of Oura and colleagues who acknowledged that their shorter study period (six months) could have easily affected their results.[4] Meanwhile, in the study by Watanabe and colleagues, there was an unclear reason for the ethical disapproval of placebo which

Table 3. Significant results from different parameters across studies

Methods	Parameters	Oura et al., 2008	Iwabuchi et al., 2016	Watanabe et al., 2015	Faghihi et al., 2013
		Adenosine vs. Placebo 3 ml x 12 mos	Adenosine vs. Placebo 3 ml x 6 mos	Adenosine vs. Niacinamide 3 ml x 6 mos	Adenosine vs. Minoxidil 1 ml x 6 mos
Dermatologist/investigator assessment	Baldness scales	Y	N	Y	N
Phototrichogram	Anagen hair growth rate	Y	–	–	–
	Hair density	N	Y	N	–
	Thick hair ratio (>80 μm)	Y	–	Y	–
	Thick hair ratio (>60 μm)	–	Y	Y	–
	Thin hair ratio (40-60 μm)	–	N	–	–
	Vellus hair ratio (<40 μm)	N	Y	N	–
Self-assessment questionnaire	Overall satisfaction	Y	–	N	Y
Adverse effects of adenosine	Adverse effects of adenosine	None	None	Seborrhea, scaling	Pruritus, folliculitis

Y – Yes. Significant changes were observed between topical adenosine and comparator.
N – No. No significant changes were observed between topical adenosine and comparator.
Dash (–) – Parameter was not tested in the study.

compelled the authors to use topical niacinamide instead.[9] Niacinamide, an antioxidant and inflammatory agent, affects hair growth indirectly. It converts to nicotinamide adenine dinucleotide (NAD) which fuels rapidly proliferating tissues such as the hair follicle.[12]

The studies measured efficacy and safety parameters using different methods. Nevertheless, results across the studies are analyzed and presented in Table 3. Two out of four studies showed significant improvement via grading scales by dermatologists or investigators and thus makes for an equivocal result in terms of improvement in baldness grades. On the other hand, three studies measured improvements in thick hair proportion (>60 or >80 μm) and all found significant improvements in the adenosine group compared to placebo and niacinamide.

With regard to self-assessment, the different questionnaires used made cohesive analysis challenging. Two out of three studies showed significant overall improvement via self-assessment, specifically with the perception of hair thickness, new growth, and prevention of hair loss. Furthermore, the few adverse effects reported in two of the studies which included seborrhea, scaling, pruritus, and folliculitis, showed that adenosine may be a safe treatment option for AGA.

Topical adenosine is not widely available in the Philippines. It is, nonetheless, marketed as a shampoo and scalp treatment under a Japanese cosmetic brand and costs higher than the minoxidil solution. Despite these issues with cost and availability, topical adenosine may still be a treatment option for AGA due to its few adverse effects.

Strengths

This is the first systematic review on the use of topical adenosine for patients with AGA. The studies included both Asian and Caucasian participants which can allow us to perceive any existing difference in the response to medication. The studies also used the same concentration of adenosine, permitting a more uniform interstudy comparison. In addition, the use of both subjective and objective parameters provides a more holistic assessment of the efficacy and safety of adenosine.

Limitations

There are few studies available and among the participants, only 10% were females. Some of the studies had shorter follow-up periods as well as different dosages and frequency than others. The limited availability and higher cost of adenosine may also be a factor in the number of existing trials.

CONCLUSION

The use of topical adenosine may increase the thick hair ratio and improve the self-perception of hair growth. It has few to no adverse effects and may serve as an adjunct or alternative to minoxidil. With the limited yield from the database search, more trials are required with a higher number of female participants. In addition, the dose, frequency, and duration of the effect of adenosine have yet to be established or identified. A minimum follow-up period of six months should most likely be used to observe if therapeutic effects will be sustained.

Statement of Authorship

All authors participated in data collection and analysis, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This paper was funded by the authors.

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