



Effect of Microneedle on Hair Regrowth in Patients with Androgenetic Alopecia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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CMNP 2024;4:e8–e17.

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Abstract

Objective Our objective was to assess the effectiveness and safety of microneedle by comparing microneedle plus 5% topical minoxidil treatment and microneedle alone to 5% topical minoxidil.

Methods We searched databases such as Embase, PubMed, Cochrane library, VIP Database for Chinese Technical Periodicals, Wanfang, and China National Knowledge Infrastructure in relation to literature. The control group received 5% topical minoxidil solution, whereas the treatment group received either microneedle coupled with minoxidil or microneedle alone. The increase in hair count and hair diameter was the main evaluation criterion for assessing hair regrowth. Data were pooled with Stata 15 software.

Results Eight studies with 472 participants were included. Compared with 5% topical minoxidil therapy, microneedle plus minoxidil treatment showed a significant increase in hair count (standard mean difference [SMD]: 15.82, 95% confidence interval [CI]: 12.34, 19.31, $p < 0.05$), but no increase in hair diameter (SMD: -0.21, 95% CI: -2.94, 2.52, $p = 0.879 > 0.05$). The results of subgroup analysis suggested that microneedle plus minoxidil treatment showed a significant increase in hair count whether the depth of microneedle was less than 1 mm (SMD: 1.16, 95% CI: 0.86, 1.42, $p < 0.05$) or more than 1 mm (SMD: 0.52, 95% CI: 0.23, 0.82, $p < 0.05$). In terms of treatment period subgroup, microneedle combined with minoxidil therapy significantly increased hair count and hair diameter than single 5% topical minoxidil, whether in 12-week period (SMD: 1.08, 95% CI: 0.76, 1.39, $p < 0.05$) or 21 to 24 weeks period (SMD: 0.64; 95% CI: 0.35, 0.92, $p < 0.05$).

Conclusion According to this study, the effect of microneedle treatment alone on androgenetic alopecia (AGA) may be limited. However, microneedle plus 5% topical minoxidil treatment had better hair regrowth in hair count and can be considered as an additional therapy option for AGA. Combined with subgroup analysis results, 12-week period and less than 1 mm depth of microneedle penetration were recommended.

Keywords

- ▶ androgenetic alopecia
- ▶ hair regrowth
- ▶ microneedle
- ▶ minoxidil
- ▶ randomized control trial
- ▶ meta-analysis

received
November 2, 2023
accepted after revision
December 22, 2023

DOI <https://doi.org/10.1055/s-0044-1782181>.
ISSN 2096-918X.

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Androgenetic alopecia (AGA), as a highly heritable disease, is featured by gradual scalp hair thinning and alopecia.¹ According to a previous study conducted in China, the incidence of AGA was 11.4%. And associations were stronger in men than in women for AGA.² Its symptoms mainly include the decrease in the diameter and density of the hair in the associated area, the thinning of the hair is observed from vertex in women and from the front hairline in men. Nowadays, people attach more importance to hair and associate it with attraction in both males and females. Even though the medical nature of offending condition is benign, AGA can have damaging psychological consequences.³ Although AGA is very prevalent condition in modern culture, approved therapeutic options and efficient therapies are limited.⁴ At present, among a variety of treatments such as drugs, surgery, nutrition, and laser programs that can be used to treat this chronic disease, the only external treatment recommended by the U.S. Food and Drug Administration is minoxidil.^{5,6} Topical minoxidil is an effective agent with a high benefit–risk ratio. Besides, the clinical effect varies with each individual, so the effectiveness of current treatment methods is not satisfactory. Therefore, it is necessary to seek for alternative treatments or combined therapy to further improve clinical efficacy. At the same time, microneedle, acupuncture and other physical or Chinese medicine methods with fewer adverse reactions for AGA have become a hotspot.

Previous clinical randomized controlled studies demonstrated that microneedle as an enhancer of drug absorption through the skin is an introduced, safe, minimally invasive technique, which has positive therapeutic effects for AGA, particularly when combined with other medications. Microneedle might be a worthy candidate for remedy for AGA.^{7,8} But there is no ample evidence on the effectiveness of microneedle device for AGA at the moment. The efficacy of microneedle therapy for AGA needs powerful evidence of large sample and polycentric clinical tests. The purpose of this study was to further explore the therapeutic effect of microneedle on promoting hair growth and to inform implementation of evidence for clinical decision-making. We also focused on the different effects of these diverse microneedle interventions, namely single microneedle device versus microneedle in combination with topical minoxidil, on the change of hair count and diameter.

Methods

Protocol and Registration

This meta-analysis was registered in PROSPERO (International Prospective Register of Systematic Reviews, identifier CRD 42023412866). According to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement, the findings were reported.⁹

Inclusion Criteria and Exclusion Criteria

The following were the study's inclusion requirements. (1) Subjects were patients clinically diagnosed with II-VI AGA. (2) Patients of treatment group were treated with microneedle

alone or microneedle plus 5% topical minoxidil. Subjects in control group were managed with topical minoxidil alone. (3) Microneedling procedure: Prior to the microneedle treatments, participants were instructed to wash their hair, and they were also told to get their hair trimmed every 6 weeks. The treatment sites were cleaned three times using alcohol or saline wipes before each therapy. Microneedle equipment was linearly passed over the treatment region. The idea's aim was to pinpoint bleeding in the treated area. Then, a gauze pad soaked in saline solution was used to clean the scalp. Minoxidil 5% was used topically in conjunction with microneedle. (4) Efficacy evaluation indexes include hair count and hair diameter, which were measured by a computer and camera-equipped hair microscope equipment. One square inch area on the vertex was selected to accurately recorded hair count and hair diameter. This area's distance from each side, including the glabella anteriorly, the occiput posteriorly, and the tips of both ear helices laterally, was measured and noted. Consequently, the same region could be repeated during the follow-up during the subsequent trials. (5) Randomized controlled trials (RCTs) were included. The following studies were excluded. (1) The use of oral finasteride and other therapeutic drugs that may stimulate hair growth within the past 6 months. (2) Other types of alopecia, anticoagulant drug use, history of bleeding diseases, pregnancy, and active infection at the microneedle site. (3) Letters, books, repeated publication, data not available, data errors, or data not adequate.

Search Strategy

Databases such as Embase, PubMed, Cochrane library, VIP, Wanfang, and China National Knowledge Infrastructure were systematically searched from their inception to October 7, 2022. We combined free words with medical subject headings phrases related to AGA and microneedle as the search strategy.

Data Extraction and Quality Assessment

Two reviewers evaluated the risk of bias of each study independently, with conflicts resolved by a third reviewer. Duplicates were ruled out first. Secondly, we screened the papers by reading their titles, abstracts, and completed texts in accordance with the inclusion and exclusion requirements. Data were collected by excel. Two researchers extracted data separately, including: first author, country, year of publication, age, sample size, interventions, treatment cycle, depth of microneedle penetration, and the outcome of hair count and diameter, with conflicts resolved by a third reviewer. Two reviewers using Cochrane Collaboration Recommendations assessment tools¹⁰ evaluated the quality of each included articles, with disagreements resolved by a third reviewer. The sources of bias, random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias, were assessed, for each bias domain.

Statistical Analysis

The results were expressed as standard mean differences with their 95% confidence intervals (CIs). Data were calculated using Stata15 software (STATA Corporation, College Station, TX, United States). Heterogeneity of the literature was evaluated

by Cochran's Q and I^2 statistics. Cochran's Q statistic was judged significant, when $p < 0.1$. When I^2 statistics was less than 50%, fixed effect model was performed to meta-analysis; when I^2 was greater than 50%, random effect model was employed. When the number of included trials exceeded 10, publication bias was assessed using funnel plots and quantified by Eger's and Begg's tests. Sensitivity analyses were carried out by one-by-one exclusion. If a sufficient number of trials were included, additional sensitivity analyses were performed.

Results

Research Screening Results

In total, 197 references were retrieved by the electronic searches and 146 references were evaluated after duplicates were removed. Fourteen studies were considered as potentially eligible after screening, and finally, eight^{6-8,11-15} studies were included in the meta-analysis, comprised with 472 participants. ►Fig. 1 illustrated the screening procedure in detail. Cochrane risk bias assessment of included studies presented in ►Fig. 2.

Study Quality and Characteristics

The study and patients fundamental features were displayed in ►Table 1. Two publications (Gita F 2020, Sang ZW 2022) observed the effects of different depths of microneedle

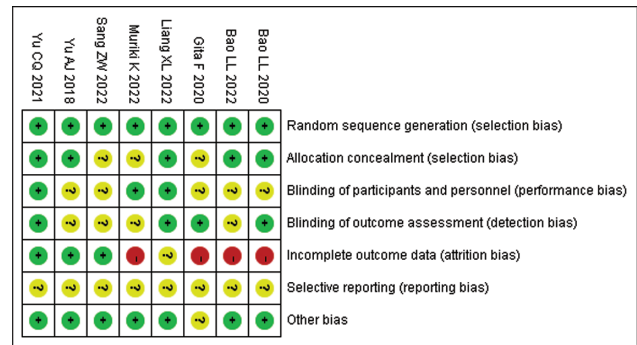


Fig. 2 Cochrane risk bias assessment.

penetration plus 5% topical minoxidil treatment compared with minoxidil alone. Two studies (Bao LL 2020 and Bao LL 2022) included both single microneedle and microneedle combined therapy. The treatment period of the literatures included in our study was 12 to 24 weeks.

Effect of Microneedle Combined with Topical Minoxidil on Androgenetic Alopecia

Hair Count

Seven studies compared the effect of microneedle plus topical minoxidil with minoxidil alone.^{7,8,11-15} In terms of the change

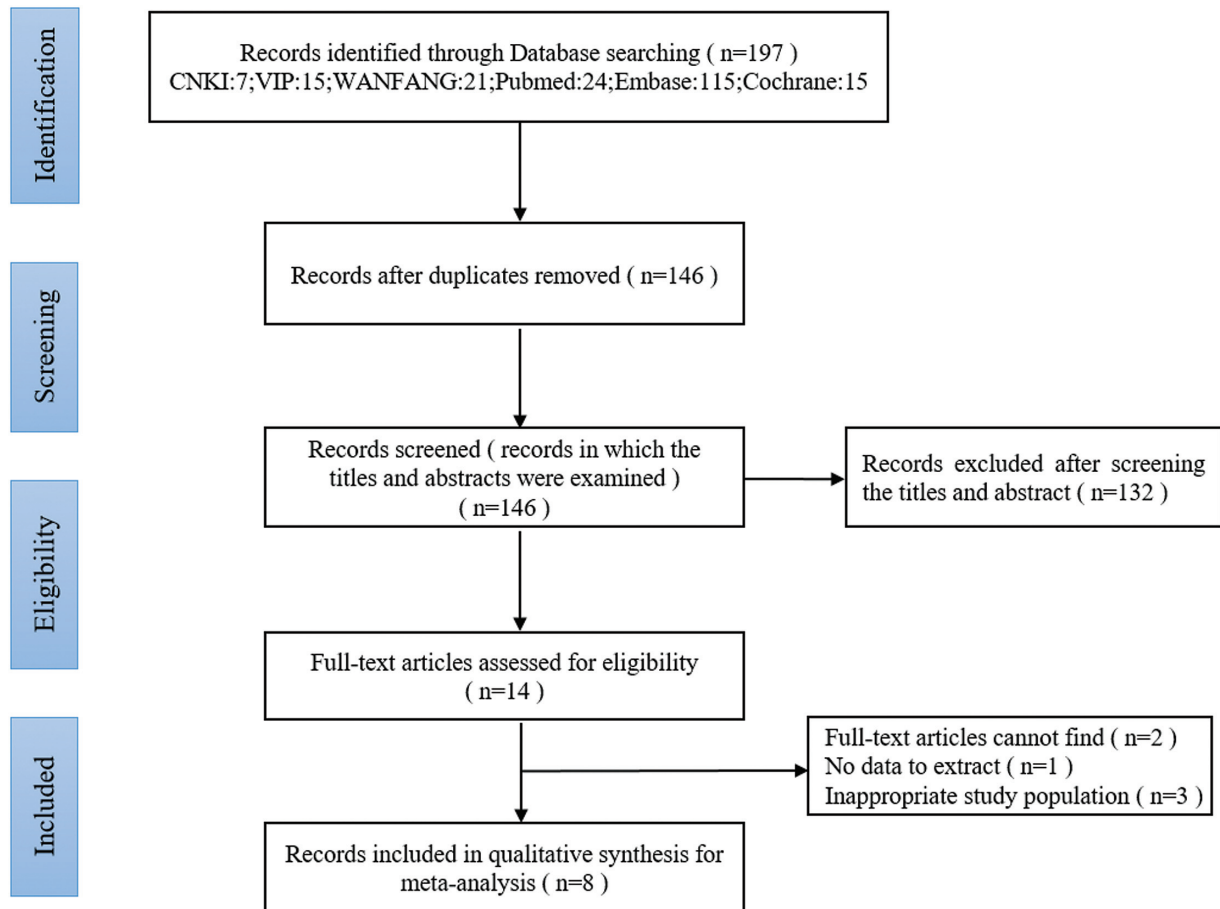


Fig. 1 Article screening flow diagram.

Table 1 Baseline characteristics of the included full-text studies

Study	Location	Study sign	Age (year)	Sample size (n)	Type of interventions	Microneedle penetrating depth	Number of treatments, frequency/duration	Grade of AGA	Duration of intervention	Outcome measure
Yu et al 2021 ⁶	China	RCT	22–50	20	Microneedle vs. Minoxidil	–	Microneedle: once a week	II–VI	16 wk	①②⑤
Faghihi et al 2020 ⁷	Iran	RCT	18–45	59	Minoxidil + Microneedle (1.2 mm) vs. Minoxidil + Microneedle (0.6 mm) vs. Minoxidil	0.6/1.2 mm	Microneedle: once every 2 wk	Male: III–VI; Female: II–III	12 wk	①②④
Yu et al 2018 ⁸	China	RCT	23–45	38	Minoxidil + Microneedle vs. Minoxidil	1.5 mm	Microneedle: five sessions at 4 wk intervals;	III–VI	21 wk	①②③④
Sang et al 2022 ¹⁵	China	RCT	18–50	90	Minoxidil + microneedling (0.5 mm depth) vs. Minoxidil + microneedle (1 mm depth) vs. Minoxidil	0.5/1 mm	Microneedle: twice a week	III–V	12 wk	①②③
Liang et al 2022 ¹¹	China	RCT	18–46	78	Minoxidil + Microneedle vs. Minoxidil	0.7–1 mm	Microneedle: once every 2 wk	Sinclair grad: II–III	24 wk	①③④
Bao et al 2022 ¹⁴	China	RCT	20–60	71	Minoxidil + Microneedle vs. Minoxidil	1–2 mm	Microneedle: once every 3 wk	III–VI	24 wk	①②
Bao et al 2020 ¹²	China	RCT	20–50	56	Minoxidil + Microneedle vs. Minoxidil	1.2–2.5 mm	Microneedle: once every 2 wk	III–VI	24 wk	①②③④
Kumar et al 2018 ¹³	India	RCT	18–40	60	Minoxidil + Microneedle vs. Minoxidil	1.5 mm	Microneedle: weekly for four sessions initially, then once every 2 wk	Norwood–Hamilton grade III–IV	12 wk	①③

Abbreviations: FGF, fibroblast growth factor; PRP, platelet rich plasma; RCT, randomized controlled trials.

Note: ① change in hair count; ② change in hair thickness; ③ subject self-assessment; ④ investigator assessment of hair growth; ⑤ follicular unit density.

of hair count, there was significant heterogeneity in the included literature ($I^2 = 90.5\%$, $p < 0.1$). By sensitivity analysis, we found a high possibility of heterogeneity in Gita F 2020 (► **Supplementary Fig. S1**, available in the online version). The between-group differences in pretreatment hair count in this literature may account for its heterogeneity. After removing this literature, there was no heterogeneity among the remaining literature studies ($I^2 = 0\%$, $p = 0.731 > 0.1$), and the analysis was performed with a fixed-effects model. The pooled mean difference of the change of hair count was 15.82 (95% CI: 12.34, 19.31, $p < 0.05$) (► **Fig. 3**).

We performed subgroup analysis based on microneedle depth and treatment period, respectively. The penetration depth of microneedle was less than 1 mm in four^{8,12-14} studies and more than 1 mm in two^{11,15} studies. With regard to the change of hair count, the pooled standard mean difference estimated by fixed-effects model was 0.52 (95% CI: 0.23, 0.82, $p < 0.05$) and 1.16 (95% CI: 0.86, 1.46, $p < 0.05$) separately (► **Fig. 4**), with no significant heterogeneity between groups in either subgroup.

In a subgroup analysis based on treatment period, with regard to hair count, the pooled standard mean difference was 1.08 (95% CI: 0.76, 1.39, $p < 0.05$) for 12-week treatment period and 0.64 (95% CI: 0.35, 0.92, $p < 0.05$) for 21 to 24 weeks treatment period (► **Fig. 5**).

Hair Diameter

As to the change of hair diameter, five studies compared microneedle combined with topical minoxidil versus minoxidil alone.^{7,8,12,14,15} The collected literature showed obvious heterogeneity ($I^2 = 62.5\%$, $p = 0.031 < 0.1$). Through

sensitivity analysis (► **Supplementary Fig. S2**, available in the online version), we found Sang ZW 2022 was the heterogeneous source. After removing this literature, there was no heterogeneity among the remaining literature studies ($I^2 = 0\%$, $p = 0.660 > 0.1$). Through fixed-effects model, the merged mean difference was -0.21 (95% CI: $-2.94, 2.52$, $p = 0.879 > 0.05$; ► **Fig. 6**).

Effect of Microneedle Alone on Androgenetic Alopecia

Hair Count and Hair Diameter

In respect of hair count and diameter calculation, three studies compared the difference of curative effects between two monotherapies (microneedle vs. minoxidil). The pooled mean difference of hair count and diameter estimated by fixed-effects model were -9.20 (95% CI: $-19.04, 0.64$, $p = 0.07 > 0.05$, $I^2 = 47.2\%$; ► **Fig. 7A**) and -8.83 (95% CI: $-12.68, -4.99$, $p < 0.05$, $I^2 = 0\%$) (► **Fig. 7B**), respectively, with no significant heterogeneity.

Our findings suggest that single minoxidil treatment was likely superior to microneedle monotherapy, with regard to the increase of hair diameter. In terms of hair count, there was no statistical difference was observed.

Publication Bias

Studies comparing the effects of microneedle plus minoxidil with single minoxidil on hair count and hair diameter were nearly 10. Therefore, we use a funnel graph to detect publication bias. The funnel diagram showed that the left and right asymmetry was not obvious (► **Fig. 8**), which suggested that there was no obvious bias in the study. Additionally, the results of

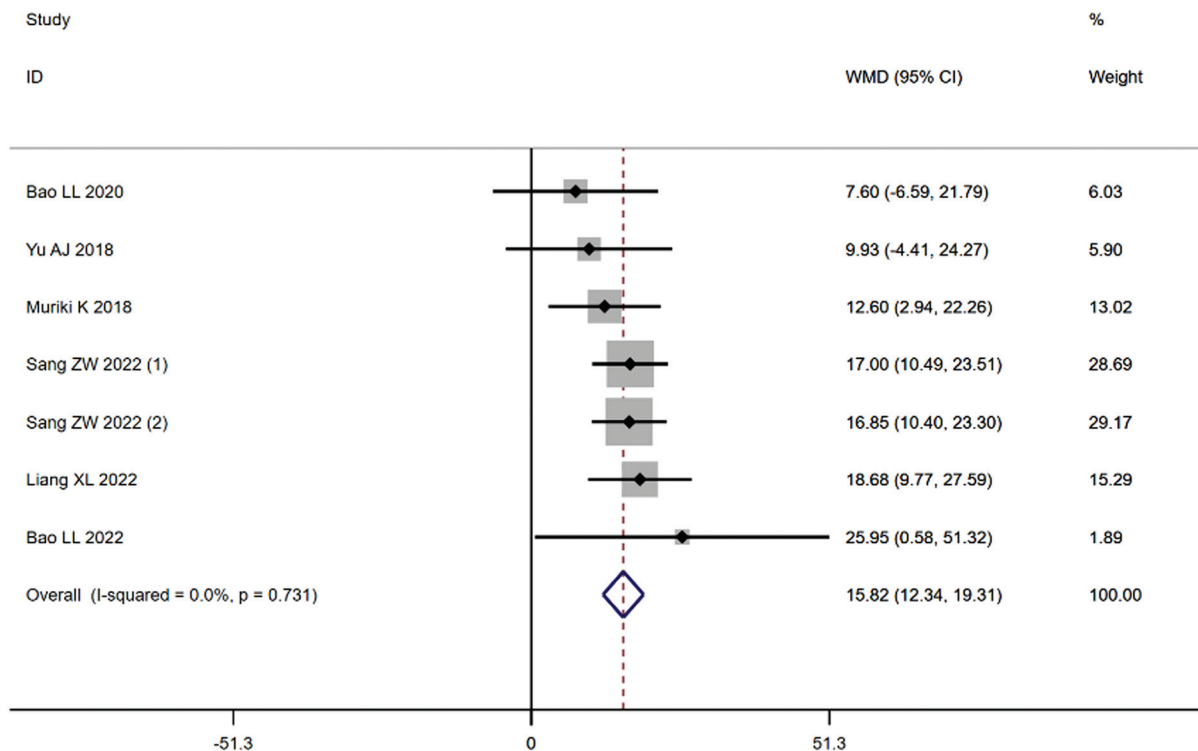


Fig. 3 Forest diagram for effect of microneedle device in combination with 5% topical minoxidil on hair count.

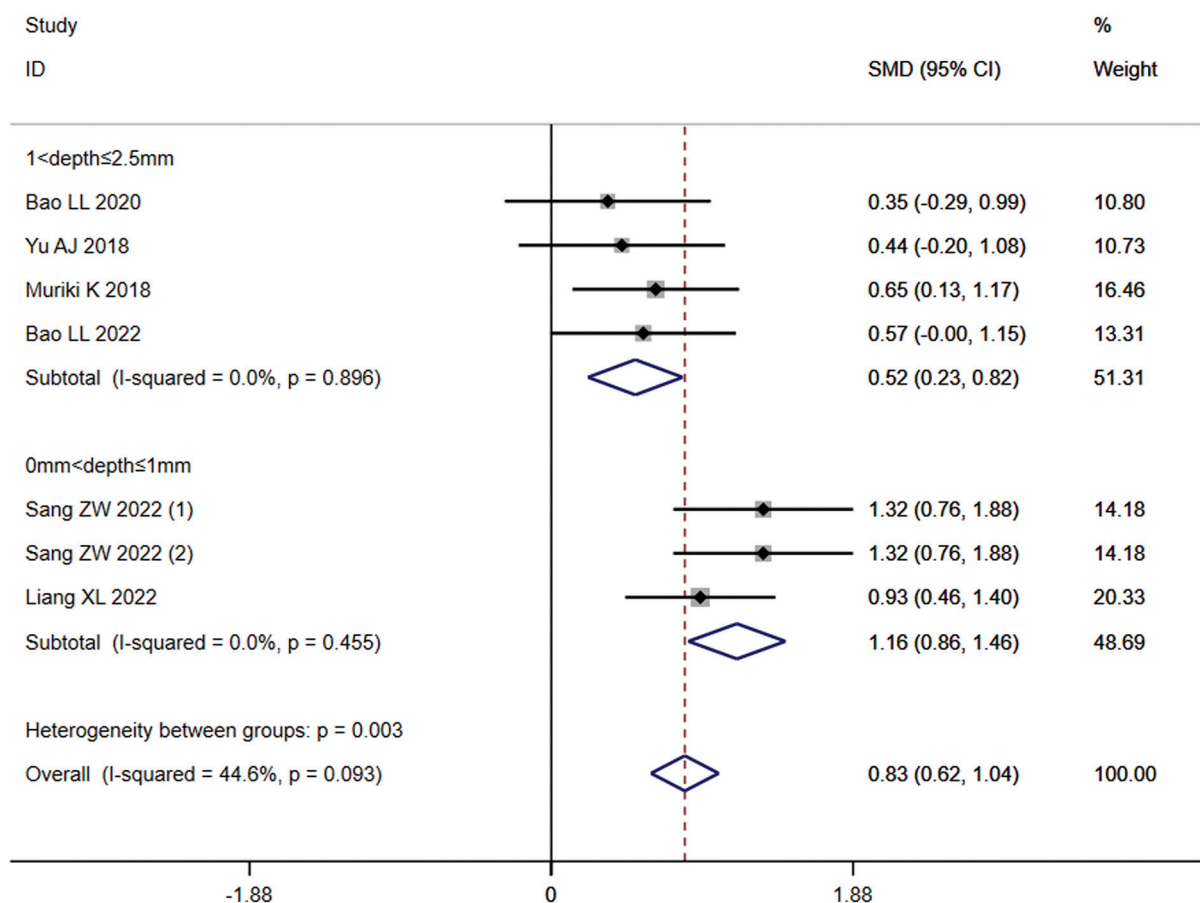


Fig. 4 Forest plot for the effect of microneedle plus 5% topical minoxidil subgroup, with regards to the depth of penetration.

Begg's test do not statistically indicate publication bias ($p > 0.05$, –Supplementary Fig. S3, available in the online version).

Safety Analysis

A total of eight studies had detected the adverse events during treatment,^{6–8,11–15} of which seven studies reported the adverse events in detail.^{6–8,11,12,14,15} No serious adverse reactions occurred in both groups. The main adverse reactions symptoms were slight erythema, scale, and pruritus at the acupuncture site, which were well tolerated by all patients and improved after symptomatic treatment.

Discussion

AGA is spurred on by a physiological chain of events that includes the interaction of heredity, the hair follicle cells' reaction to androgens, microinflammation, lifestyle, and environmental variables.¹⁶ Currently, minoxidil and finasteride for AGA and minoxidil for female AGA still are the treatment options with the highest level of evidence as the available treatments were not ideal and may linked to serious negative effects.¹⁷ Besides, how to treat minoxidil nonresponders remains a problem.¹⁸ Multiple causes of AGA may be the reason why finasteride or minoxidil alone cannot produce good outcomes always.

We assessed the impact of the microneedle technique on hair regeneration for AGA through inclusion in eight RCTs with 472 participants. The following findings were drawn from our data. (1) For microneedle plus 5% topical minoxidil on AGA, we reported two indicators of the promotion of hair regrowth, including hair count and diameter. In particular, microneedle combined with 5% topical minoxidil resulted in a significant rise in hair count when compared to minoxidil alone, but with an insignificant improvement in hair diameter. (ii) With regard to hair count, subgroup analysis of microneedle combined with 5% minoxidil versus single minoxidil shown 12-week treatment period was superior to 21 to 24 weeks, and microneedle depth less than 1 mm was better than 1 mm depth of microneedle. (iii) For microneedle-alone treatment on hair regrowth for AGA, microneedle showed no statistical difference in hair count, compared to minoxidil alone. Additionally, minoxidil alone treatment was observed better hair diameter rise than single microneedle.

Microneedle, as a least invasive technique, was initially applied to improve transdermal drug delivery. Drugs can enter the skin through reversible microchannels created on the skin by a microneedle array device and have a promoting effects locally or penetrate the capillary networks of the dermis, with fewer negative effects compared with systemic administration.¹⁹ Using an electrodynamic microneedle to

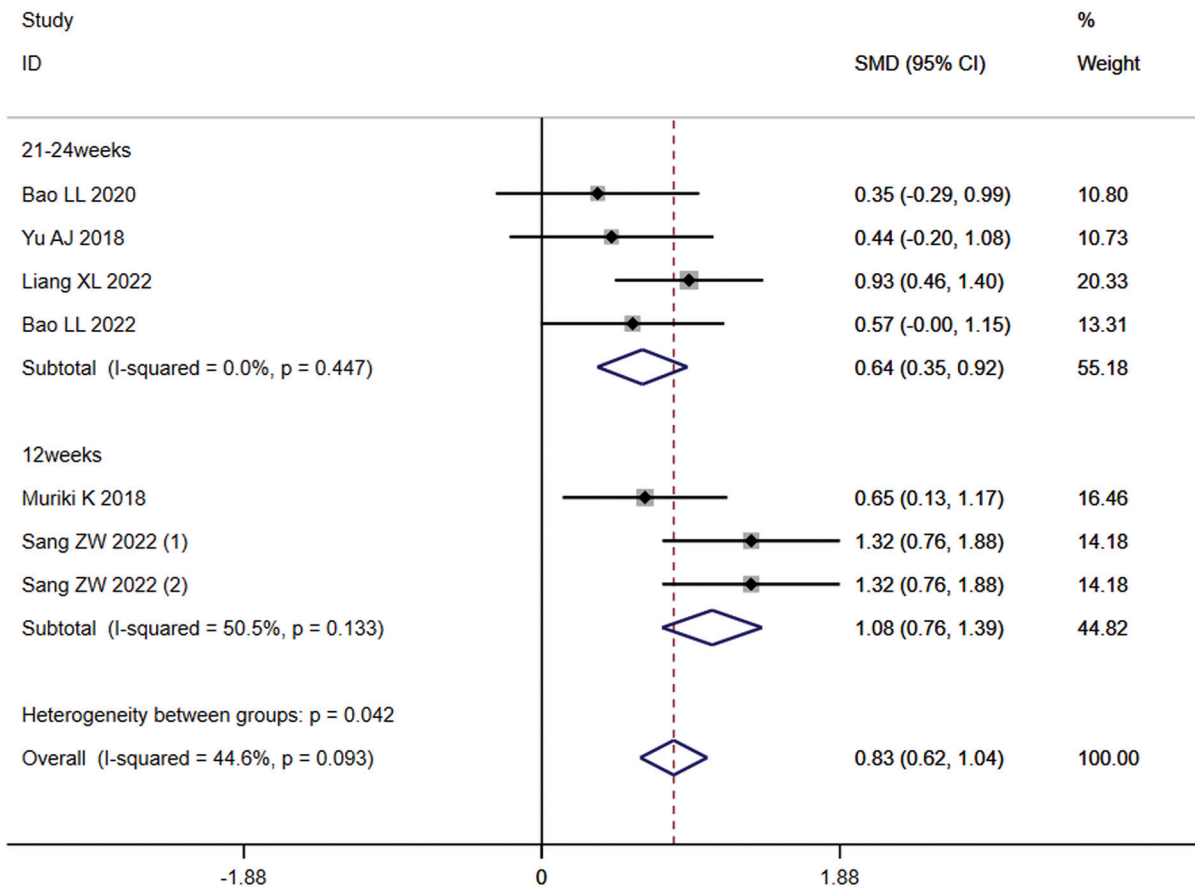


Fig. 5 Forest plot for the effect of microneedle plus 5% topical minoxidil subgroup, with regards to the treatment cycle.

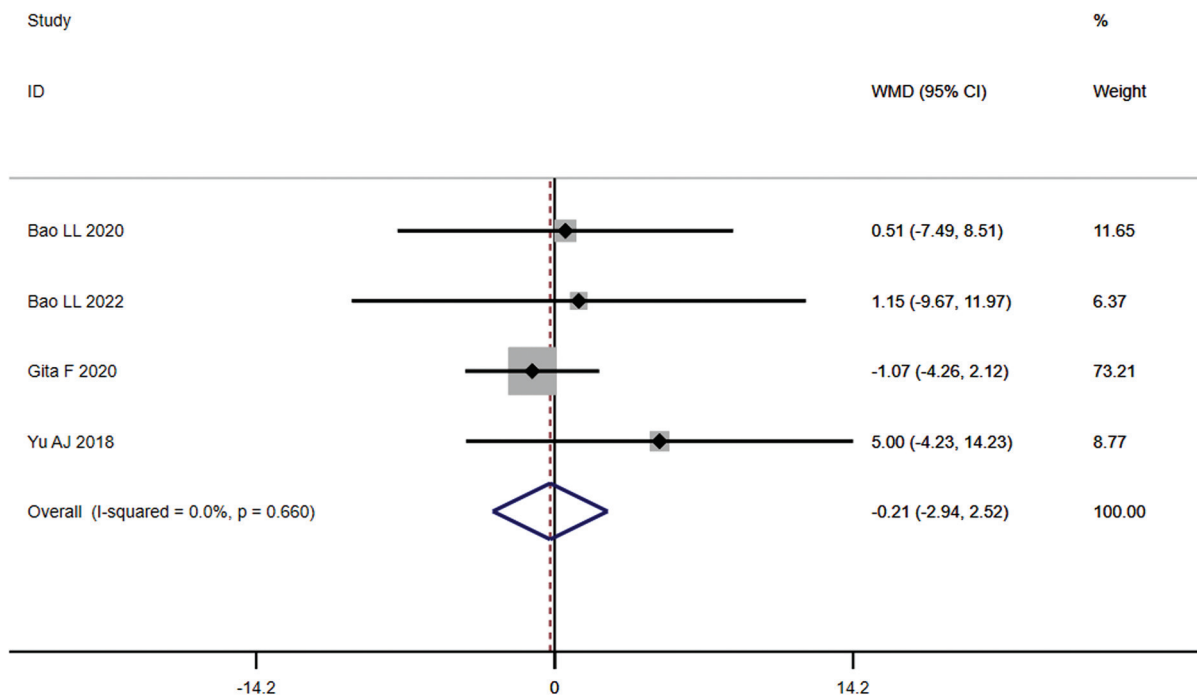
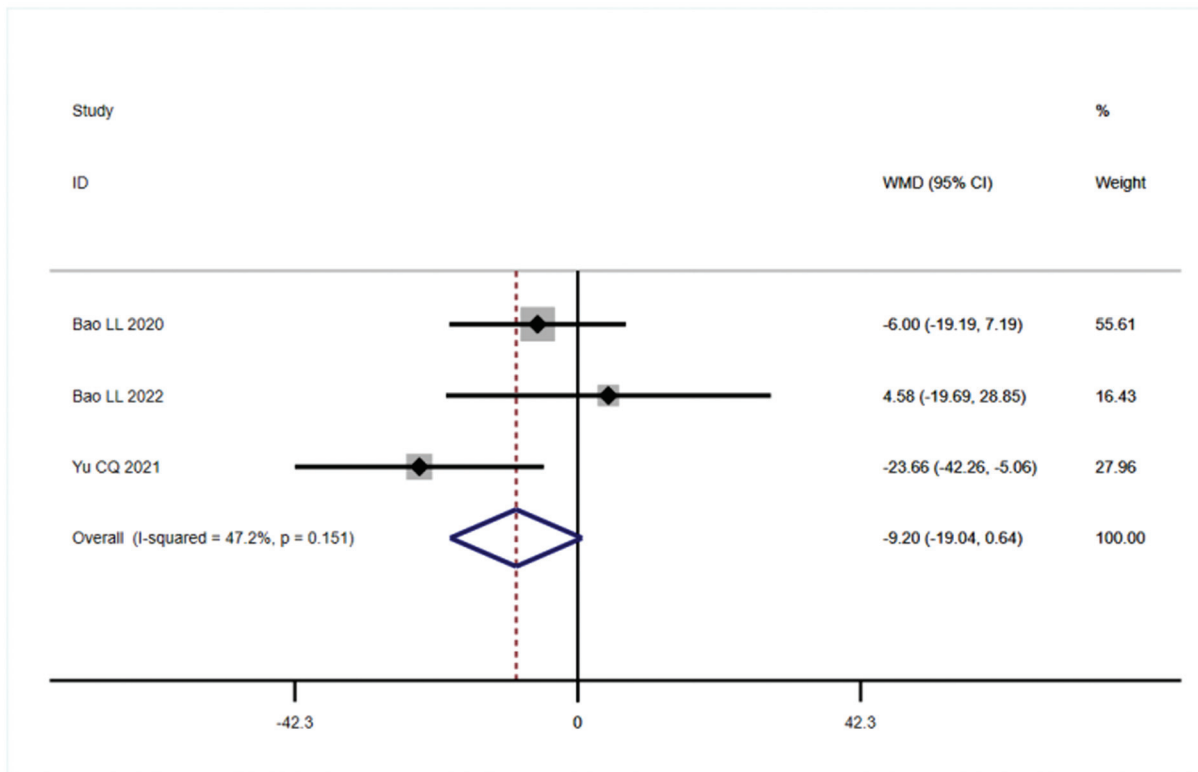


Fig. 6 Forest diagram for effect of microneedle plus 5% topical minoxidil on hair diameter.

A



B

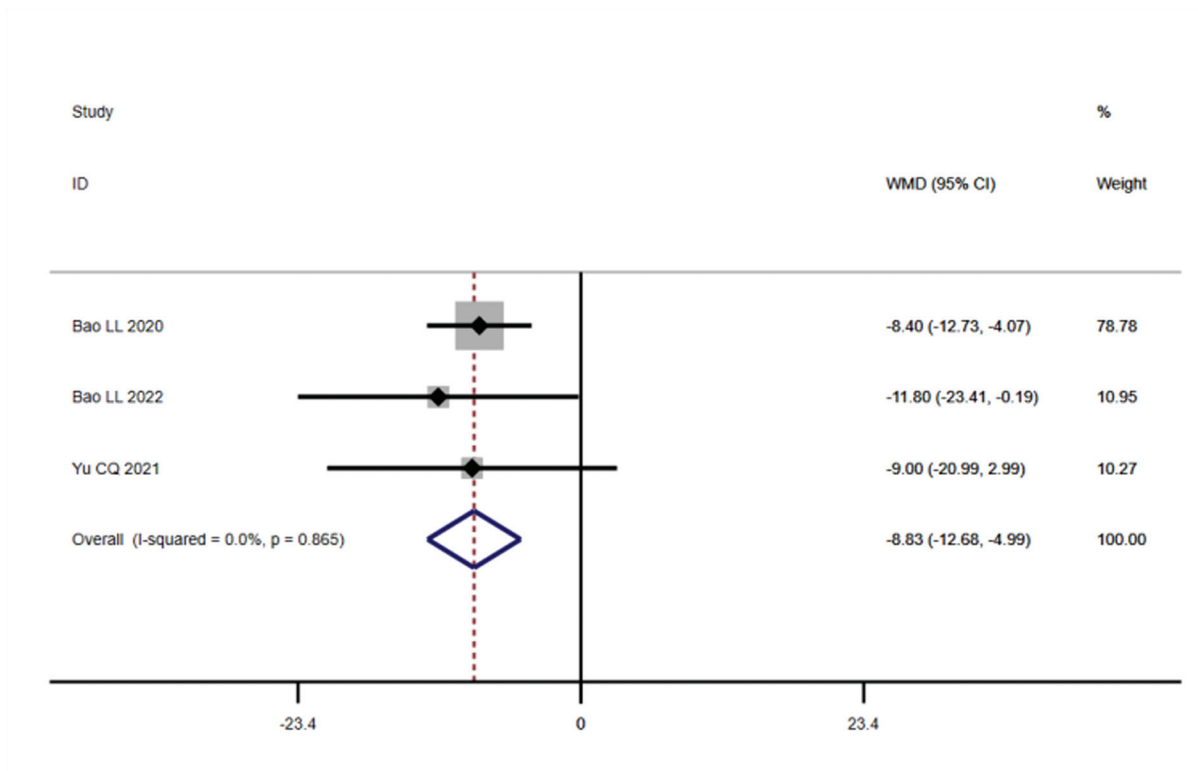


Fig. 7 Forest diagram for effects of microneedle alone on hair regrowth: hair count (A) and hair diameter (B).

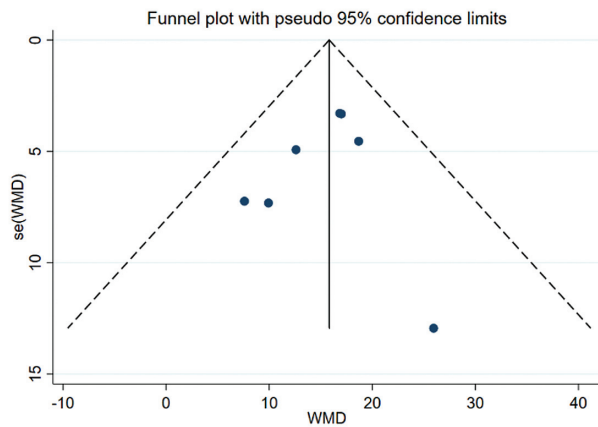


Fig. 8 The funnel plots representing no obvious publication bias: the effects of microneedle combined 5% topical minoxidil on hair regrowth of hair count.

treat AGA can considerably speed up the rate of minoxidil's percutaneous absorption. As the latest studies revealed it's hair regrowth effect, its important role in the hair loss treatment have caught public attention.^{20–23} The combination of microneedle and topical minoxidil can produce a synergistic effect on hair regrowth and is worth promoting for clinical application.

In addition, microneedle also encourages hair growth in a variety of other ways. The hair follicle has been identified as a target for AGA, and a crucial penetration pathway of percutaneous absorption.²⁴ Therefore, microneedle device is a potential option for reaching hair follicles by piercing the skin and distributing drugs straight into dermal layers.²⁵ Microneedle can also induce collagen formation, neovascularization, and growth factor production of treated areas.²³ A recent experiment on AGA mouse model highlighted the close association between boosting perifollicular angiogenesis and the awakening of hair follicle stem cells.²⁶ According to a pilot investigation, microneedle also improved minoxidil response through upregulating follicular sulfotransferase enzymes to faster hair regrowth.²⁷ Therefore, individuals who are not satisfied with traditional managements perhaps obtain better response from microneedle. This meta-analysis imply that, contrast with single minoxidil, microneedle applied with minoxidil had definite advantage of hair regeneration, whether in terms of hair count or hair diameter calculation. The efficacy of microneedle applied individually is weaker than alone minoxidil. We speculated that in the early stages of treatment microneedle enhanced hair regrowth potentially mainly through promoting transdermal delivery of minoxidil. The effectiveness of utilizing microneedles alone may surpass that of minoxidil as the treatment cycle extends. In general, perifollicular angiogenesis, upregulating follicular sulfotransferase enzymes, awakening of hair follicle stem cells, neovascularization, growth factor production, and various unknown kinds of ways play synergistic effect on hair regeneration.

We would like to make it clear that microneedle is distinct from traditional needling. The microneedle device is repeatedly, sequentially, and in several directions across the scalp while

applying strong pressure, until little bleeding sites are seen. Microneedles vary in lengths ranging from 0.5 to 3 mm, although 1.5 mm is the size most often used on AGA patients.²⁸ The microneedle array device can generate substantial reversible microholes. And the treatment outcome may vary depending on the depth of the microneedles. In our study, we found that less than 1 mm depth of microneedle penetration showed better rise in hair count than the others. The optimal treatment depth of microneedling still needs to be evaluated from a combination of multiple indicators of hair regrowth and long-term effects after further literature expansion.

Microneedle provides an easy technique that is economical, well-tolerated, and has therapeutic advantages. At the microneedle device applied site, just erythema, red and swollen were observed. In this trial, no severe side effects were found. In addition, a 5 weeks period experiment of microneedle over mice *in vivo* showed no statistical change of inflammation and other biomarkers of immunity, infection, after repeated microneedle arrays were inserted into mouse skin.²⁹ Therefore, the application of microneedles in AGA can be well accepted by patients with AGA.

Conclusion

This study indicated microneedle device applied in combination with 5% topical minoxidil is better in hair regrowth, comparing with single 5% topical minoxidil and microneedle alone. However, with scarce literature on microneedle for AGA at present, a few other limitations of this research should be addressed, such as no follow-up data, different treatment cycle, and microneedle depth of the included papers. The optimal depth, interval, frequency, and cycle of microneedle therapy need more favorable evidence to be determined.

CRedit Authorship Contribution Statement

Chunyan Xu: Conceptualization, project administration, data curation, formal analysis, writing-original draft, and writing-review and editing. Xingwu Duan: Project administration, supervision, and writing-review and editing. Qiang Yin: Data curation, formal analysis, and writing-review and editing. Keshuai Liu: Data curation, formal analysis, and writing-review and editing.

Funding

This work was supported by the National Natural Science Foundation (8207151023).

Conflict of Interest

The authors declare no conflict of interest.

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