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The efficacy and safety of micro-needling combined with tacrolimus *versus* tacrolimus monotherapy for vitiligo treatment: a systematic review and meta-analysis

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Availability of data and materials: All data underlying the findings are fully available.

Abstract

Tacrolimus is a topical immunomodulator that has been used successfully in treating vitiligo; however, recent studies suggested that combining tacrolimus with micro-needling can increase its efficacy. This systematic review aimed to assess the efficacy and safety of micro-needling combined with tacrolimus to treat localized and stable nonsegmental vitiligo. We searched Medline, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). The risk ratio (RR) was used to represent dichotomous outcomes, whereas the odds ratio (OR) was used for adverse events. Three randomized control trials (RCTs) (n=148 participants) were deemed eligible. The pooled effect estimate showed a statistically significant higher re-pigmentation rate in all assessed body areas in favor of treatment with micro-needling combined with tacrolimus (RR=2.02, 95% CI: 1.51-2.70). Nonetheless, no significant difference was found between micro-needling combined with tacrolimus and tacrolimus monotherapy in terms of 5-grade re-pigmentation scale (RR=0.93, 95% CI: 0.53-1.62), histopathological assessment (RR=0.90, 95% CI 0.47-1.75), and adverse events (OR: 1.72, 95% CI: 0.10-29.36). The number of included studies is low, with a relatively low sample size. Micro-needling combined with tacrolimus showed a clinically and statistically substantial improvement in the re-pigmentation of vitiligo sites with acceptable tolerability and safety profile.

Introduction

Vitiligo is an autoimmune disfiguring skin disease that manifests as a non-scaly, amelanotic, chalky-white macule with distinct margins.[1] According to the international consensus, vitiligo is classified into two major classes: nonsegmental vitiligo (NSV) and segmental vitiligo (SV), as they differ in their prognostic implications.[1] Worldwide, vitiligo is a common disease with an estimated prevalence of 0.5-2% in both the adult and pediatric populations.[2] Studies showed that vitiligo burden extends to patients' self-esteem and quality of life.[3,4] Over the years, various treatment modalities have been introduced to treat vitiligo, including topical corticosteroids, topical immunomodulators, phototherapy, surgery, and combined therapy.[1] However, vitiligo appears to be difficult to treat, and satisfactory outcomes are challenging to achieve since treatment options cause some adverse events, carry a recurrence depigmentation rate, and appear to be resisted by some individuals.[5-7]

Combining tacrolimus with micro-needling (Mn) is one of the novel proposed methods to treat localized and stable nonsegmental vitiligo, which is defined as the absence of new lesions or the absence of an increase in the size or number of the current lesions throughout 12 months.[8-11] Although a previous study examined the efficacy of Mn combined with other local therapies,

objective assessment, as well as details about pattern and time of re-pigmentation, were not addressed. Also, published literature lacks a systematic evaluation of the safety of Mn combined with tacrolimus.[12] Thus, we prepared this systematic review and meta-analysis to address this knowledge gap by comprehensively evaluating the efficacy and safety of micro-needling combined with tacrolimus *versus* tacrolimus monotherapy for localized and stable nonsegmental vitiligo.

Materials and Methods

This systematic review was conducted in compliance with a pre-specified protocol registered in PROSPERO (CRD42022375496) and reported in the light of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist.[13]

Eligibility criteria

The eligibility criteria of our systematic review were randomized control trials (RCTs) that compared combined tacrolimus with micro-needling to tacrolimus monotherapy in adults and pediatrics with an established diagnosis of vitiligo. Vitiligo is categorized as local and stable nonsegmental vitiligo, defined as the absence of new lesions or the absence of an increase in the size or number of the existing lesions over 12 months. The pre-specified outcomes were the 5-grade re-pigmentation scale or Physician's Global Assessment (PGA), histopathological assessment, body site re-pigmentation, and adverse events. We excluded trials that included participants with concurrent use of other topical, conventional systemic, or biological therapies.

Search strategy

The systematic search was performed using the Medline, Embase, and CENTRAL databases via Ovid without restriction on language or data. The last search was performed on November 14, 2022, utilizing specific search terms that are provided in the Supplementary Materials. We manually screened the reference list of the included RCTs for any related trials missed during the systematic search.

Study selection and data extraction

Two reviewers performed eligibility screening of titles and abstracts, full-text assessment, and data extraction from eligible trials independently and in duplicate. Any disagreement was resolved by consensus or discussion with the supervising author.

Meta-analysis

Data were analyzed using RevMan (Review Manager) version 5.3 (Cochrane Collaboration) and the random-effects model. I^2 and P-value of the Chi^2 test were used to assess statistical heterogeneity. We used a 95% confidence level and a threshold of $P<0.05$. The risk ratio (RR)

was used to represent the dichotomous outcomes: Physician's Global Assessment (PGA), histopathological assessment, and body site re-pigmentation, whereas the odds ratio (OR) was used to represent the dichotomous outcome: adverse events. The data were pooled using the inverse variance weighting method. The ordinal outcomes were dichotomized by performing subgroup analysis as follows: i) Physician's Global Assessment (PGA): 0%, 1-50%, 50-75%, and 75-100%; ii) histopathological assessment: -Ve, weak (+), moderate (++), and strong (+++); iii) re-pigmentation of body sites: face, trunk, extremities, and acral areas; iv) adverse events: pain and itching. The quality of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria.

Risk of bias assessment

Two reviewers performed the risk of bias assessment for the eligible RCTs using the Revised Cochrane Risk of Bias Assessment Tool independently and in duplicate.[14] We sought to assess the potential for publication bias by visual inspection of the funnel plot with RR and standard error when ≥10 studies were available for the analysis, as recommended by the Cochrane Handbook for systematic reviews of interventions. Evidence of publication bias was considered to be present when the funnel plot was not symmetrical.

Results

Figure 1 shows the systematic search and study selection in the present review. The initial search yielded 14 articles, of which six duplicates were excluded. Eventually, only three RCTs were deemed eligible, and all were included in the meta-analysis.[8-10]

Trial characteristics

The three articles included 148 patients. Of these, 74 (50%) patients received Mn combined with tacrolimus, and 74 (50%) patients received tacrolimus monotherapy. The ages of the patients in both groups ranged from 12 years to 60 years. The detailed characteristics are shown in Table 1.

Risk of bias assessment

All three eligible RCTs had an overall low risk of bias (Supplementary Figures A and B illustrate the risk of bias assessment for the included RCTs). However, as the number of included studies in the meta-analysis was less than 10, it was not feasible to assess the funnel plot for the potential of publication bias.

5-grade re-pigmentation scale or Physician's Global Assessment (PGA)

The three RCTs (148 analyzed participants) contributed to the main analysis.[8-10] No significant difference was noted between Mn combined with tacrolimus and tacrolimus monotherapy in

PGA (RR=0.93, 95% CI: 0.53–1.62, *P*=0.79, I^2=68%). The heterogeneity was 68%, indicating considerable variability in the data, which was mostly attributed to the Ebrahim *et al.* trial.[8] Subgroup analysis revealed that applying Mn with tacrolimus showed a significant re-pigmentation rate in the vitiligo sites compared to applying tacrolimus monotherapy, as it showed improvement with a rate of 51% to 100% from the baseline (RR=1.92, 95% CI: 1.32-2.80, P=0.0006, I^2=1%). On the other hand, no significant difference was observed between Mn with tacrolimus and tacrolimus monotherapy in individuals who had only a re-pigmentation rate of 1% to 50% (RR=1.11, 95% CI: 0.52-2.36.1, P=0.78, I^2=36%) and in patients who had poor and no re-pigmentation (RR=0.31, 95% CI: 0.09-1.10, P=0.07, I^2=66%). The re-pigmentation rate was taken after six months of follow-up (Figure 2). The GRADE certainty of evidence was found to be rated as moderate 5-grade re-pigmentation scale (Figure 3).

Histopathological assessment

Two RCTs (108 analyzed participants) contributed to the analysis of histopathological assessment.[8,9] Both Mn combined with tacrolimus and tacrolimus monotherapy showed similar histopathology (RR=0.90, 95% CI: 0.47–1.75, P= 0.76, I^2=67%). Subgroup analysis revealed that treatment with Mn combined with tacrolimus was statistically significantly associated with higher strongly positive stained cells, indicating the presence of more melanoblasts compared to tacrolimus monotherapy (RR=2.11, 95% CI: 1.31-3.93, P<0.002, I^2=0%). Both Mn combined with tacrolimus and tacrolimus monotherapy showed no significant difference in individuals whose biopsies showed moderately positive stained cells (RR=1.67, 95% CI: 0.65-4.28, P<0.29, I^2=0%) and in weakly positive stained cells (RR=0.54, 95% CI: 0.23-1.26, P<0.15, I^2=0%). Finally, the absence of melanoblasts and stained cells had a significantly higher rate in the group that received tacrolimus monotherapy (RR=0.26, 95% CI: 0.11-0.64, P<0.004, I^2=0%) (Figure 4). The GRADE certainty of evidence was found to be rated as moderate for histopathological assessment (Figure 3).

Re-pigmentation of body sites

Two RCTs (108 analyzed participants) reported data on the re-pigmentation of body sites.[8,9] Overall, administration of Mn combined with tacrolimus showed superior re-pigmentation rates when compared to tacrolimus monotherapy in all assessed body sites with overall low heterogenicity (RR=2.02, 95% CI: 1.51-2.70, P<0.00004, I^2=24%). Subgroup analysis also showed that Mn combined with tacrolimus had statistically significant higher re-pigmentation rates compared to tacrolimus monotherapy in the face (RR=1.54, 95% CI: 1.15-2.05, P=0.003, I^2=0%), trunk (RR=2.11, 95% CI: 1.27-3.51, P=0.004, I^2=0%), extremities (RR=2.78, 95% CI: 1.63-4.74, P=0.0002, I^2=0%), and acral areas (RR=12.45, 95% CI: 1.67-92.64, P=0.01, I^2=0%)

(Figure 5). The GRADE certainty of evidence was found to be rated as moderate for re-pigmentation of body sites (Figure 3).

Adverse events

Two RCTs (108 analyzed participants) reported this outcome.[8,9] Both studies showed that both Mn combined with tacrolimus and tacrolimus monotherapy are tolerable, and no major adverse events were reported, such as scarring or koebnerization (OR: 1.72, 95% CI: 0.10-29.36, P=0.71, I^2=82%). Subgroup analysis showed that combined Mn with tacrolimus was significantly associated with more painful treatment (OR: 28.58, 95% CI: 3.66-223.6, P=0.001, I^2=0%); however, the pain was reported to be mild in both studies. Tacrolimus monotherapy was more associated with a mild burning sensation or itchiness, but no significant difference was noted (OR: 0.17, 95% CI: 0.01-2.17, P=0.17, I^2=64%) (Figure 6). The GRADE certainty of evidence was found to be rated as low for adverse events (Figure 3).

Discussion

This comparative systematic review and meta-analysis compared the efficacy and safety of micro-needling combined with tacrolimus *versus* tacrolimus monotherapy for treating localized and stable nonsegmental vitiligo. The pooled effect estimate showed a statistically significant higher re-pigmentation rate in all assessed body areas in favor of treatment with Mn combined with tacrolimus. Nonetheless, no significant difference was found between Mn combined with tacrolimus and tacrolimus monotherapy with respect to the 5-grade re-pigmentation scale and histopathological assessment. In terms of adverse events, both treatments were safe to use and tolerable, with no major adverse events reported.

The finding of our review showed that 44.6% of those who received Mn combined with tacrolimus achieved an excellent re-pigmentation rate (75-100%) on PGA. Our finding is inconsistent with previous studies: Korobko *et al.*[15] reported an excellent re-pigmentation rate of only 4.5%; Mina *et al.*[16] of 16%; and Ibrahim *et al.*[17] of 32%. This variation could be attributed to several factors, such as the difference in the dose of the treatment. Mina *et al.*[16] and Ibrahim *et al.*[17] have only used the lowest concentration (0.03%) of tacrolimus, whereas the used concentration in two of our studies was (0.1%). Also, Korobko *et al.*[15] trial recorded the response in a three-month follow-up, while in our study the response was measured after six months. Even though our study showed that there is no significant difference in achieving 1-50% re-pigmentation rate on PGA between combined Mn with tacrolimus (25.67%) *versus* tacrolimus monotherapy (22.9%), the failure rate in inducing re-pigmentation was 16.2% and 43.24% respectively, which highlights the importance of adopting a multi-modal approach

when treating vitiligo. In addition, histopathological assessment is another assessment tool that has offered an objective method to evaluate the re-pigmentation rate. In our review, more than half of the patients who received Mn with tacrolimus (59.25%) had very strongly positive (+++) results, which was consistent with other studies.[16,17]

Generally, both Mn with tacrolimus and tacrolimus monotherapy are well-tolerated and demonstrate an acceptable safety profile. No major adverse events were reported, such as scarring or koebnerization. Subgroup analysis showed that combined micro-needling with tacrolimus was significantly associated with more painful treatment than tacrolimus monotherapy; however, most of the reported adverse events are rated mild in severity, with no discontinuation throughout the treatment's course. Likewise, four trials showed that both Mn and tacrolimus had no serious adverse effects, and permanent discontinuation has never occurred.[18-21] A Mild transient burning sensation was reported after applying tacrolimus ointment to the perioral area and eyelids. Also, a vasodilation reaction after applying tacrolimus on the face was associated with patients who ingested variable and even small amounts of alcohol during the treatment course, and avoidance of such a reaction was done by discontinuing alcohol intake.[18] Perioral dermatitis was reported only in one patient after tacrolimus usage. Moreover, the application of tacrolimus could be limited to small lesion areas, as some patients expressed their dissatisfaction with the greasy texture of the ointment and the difficulty of applying it in hair-covered areas.[19] Finally, the usage of tacrolimus after ultraviolet B (UVB) plays a role in preventing phototherapy-induced erythema by inhibiting the early inflammation process.[20]

Mn has offered not only a good option to use in the multi-modality approach but also a good alternative to surgical grafting to treat stable, localized, and refractory vitiligo lesions.[22,23] Mn mechanism of action could rely on the trauma-induced micro-inflammation that was discussed earlier that resembles the normal wound healing process. Other hypotheses suggested that Mn also works by causing melanocytic autoinoculation, as the mechanical trauma will stimulate melanocyte migration from the surrounding pigmented areas.[8] Also, a mechanical migration of melanocytes from the pigmented area is possible, as melanocytes can physically move with the needle; therefore, they can assist the re-pigmentation process by providing reservoirs for melanogenesis.[21] The effectiveness of combining Mn with a topical treatment like tacrolimus may stem from the inflammatory response triggered by this combination. This response can lead to a multicellular infiltration that may counteract the effects of melanocyte-toxic T cells. Furthermore, this immunomodulation can facilitate the establishment of migrating melanocytes.[21]

Limitations

We acknowledge that our review has some limitations. First, the number of included studies is low as a result of the novelty of the used technique. Second, the sample size provided by the included RCTs is relatively low, which limited our conclusions.

Conclusions

Micro-needling is one of the most innovative modalities to treat localized and stable nonsegmental vitiligo. This study revealed that combining Mn with tacrolimus has significantly higher re-pigmentation rates in all assessed body areas when compared to tacrolimus monotherapy. Nevertheless, no significant difference was found between Mn combined with tacrolimus and tacrolimus monotherapy with respect to the 5-grade re-pigmentation scale and histopathological assessment. No major adverse events were reported, and discontinuation through the treatment course has never occurred, suggesting that Mn combined with tacrolimus is a safe and well-tolerated therapeutic alternative. Further well-designed studies with a larger sample and longer follow-up periods are required to examine the stability of the re-pigmented area and to assess further outcomes, such as the needed number of sessions and the regimen with the best response.

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Table 1. Characteristics of the included studies.

Summary statistics		Number of studies: 3 RCTs; total number of participants: 148; assignment: Mn with tacrolimus (n=74), tacrolimus monotherapy (n=74); range of participant's age: 12-60; treatment duration: 6 months		
Measured outcomes		5-grade re-pigmentation scale	5-grade re-pigmentation scale	5-grade re-pigmentation scale
		Histopathological Assessment	Histopathological Assessment	
		Body sites re-pigmentation	Body sites re-pigmentation	
		Adverse events	Adverse events	
Size of treated skin (cm^2)		5-15	5-15	NR
Treatment details	**Duration**	6 months	6 months	6 months
	Tacrolimus route	Ointment	Ointment	Ointment
	Tacrolimus dose (%)	0.10%	0.10%	0.03%
	Mn size (mm)	1.5-2	0.5-2	0.5
Previous vitiligo treatment	**Tacrolimus monotherapy**	No (56.7%) Yes (43.3%)	No (41.7%) Yes (58.3%)	NR
	Mn with Tacrolimus	No (53.3%) Yes: (46.7%)	No (54.2%) Yes (45.8%)	NR
Affected site	**Tacrolimus monotherapy**	Face (33.3%) Trunk (26.7%) Extremities (33.3%) Acral areas (6.7%)	Trunk (29.2%) Knee and Elbow (20.8%) Leg (29.2%) Acral part (20.8%)	Lower limb (55%) Upper limbs (20%) Trunk (25%)
	Mn with Tacrolimus	Face (23.3%) Trunk (33.3%) Extremities (33.3%) Acral areas (10%)	Trunk (20.8%) Knee and Elbow (25%) Leg (37.5%) Acral part (16.7%)	Lower limb (45%) Upper limbs (25%) Trunk (30%)
Mean age	**Tacrolimus monotherapy**	36.87	35.2	26.35
	Mn with Tacrolimus	36.52	36.8	26.35

Gender	**Female**	35	20	13
	Male	25	28	7
Number of participants	**Tacrolimus monotherapy**	30	24	20
	Mn with Tacrolimus	30	24	20
Study arms		Mn with Tacrolimus Mn monotherapy Tacrolimus monotherapy	Mn with Tacrolimus Tacrolimus monotherapy	Tacrolimus monotherapy Mn with Tacrolimus Mn monotherapy Tacrolimus under occlusion
Study, year		**Ebrahim, 2020**	**Ebrahim, 2021**	**Esmat, 2021**

Figure 1. study flow diagram.

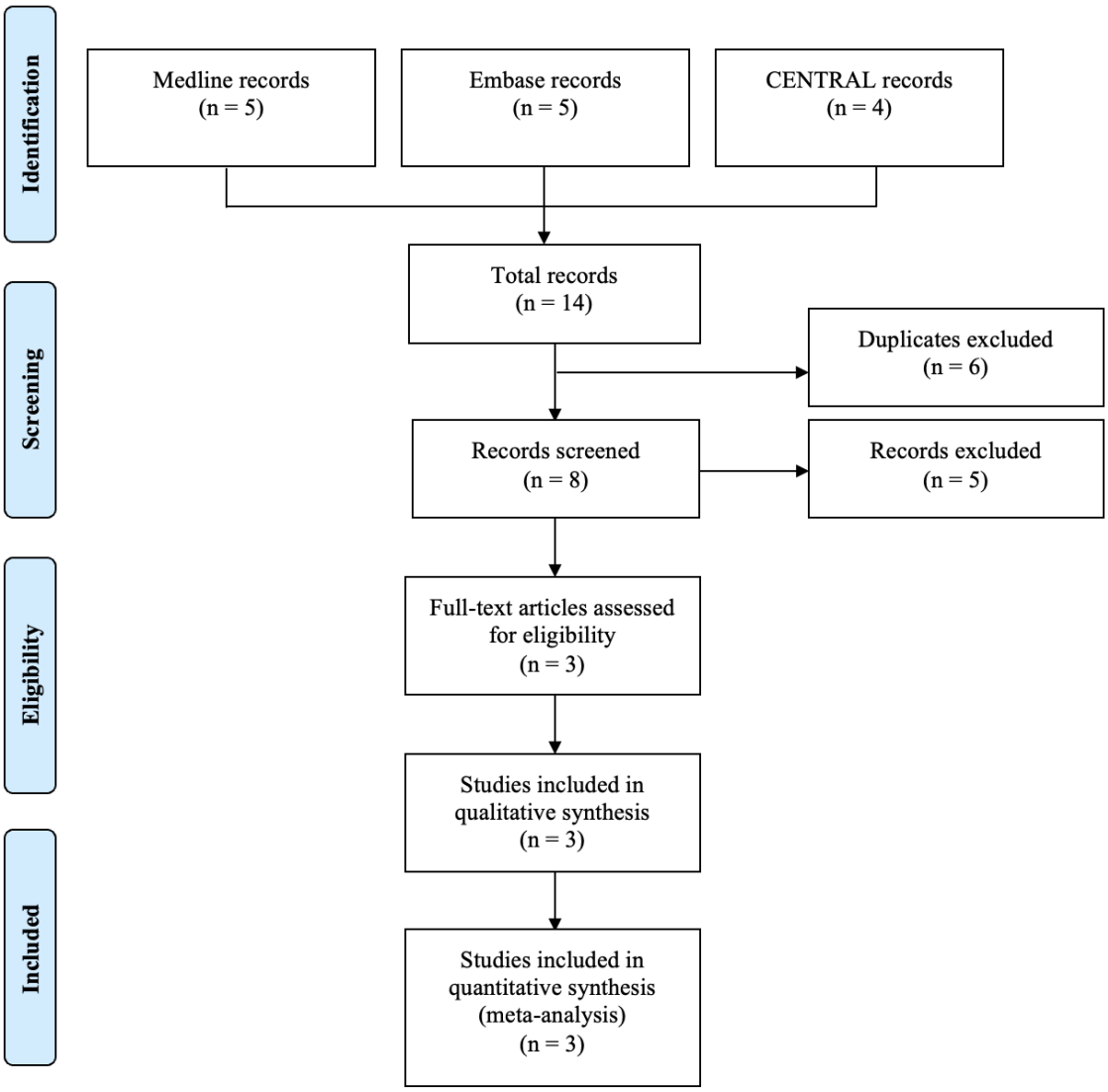
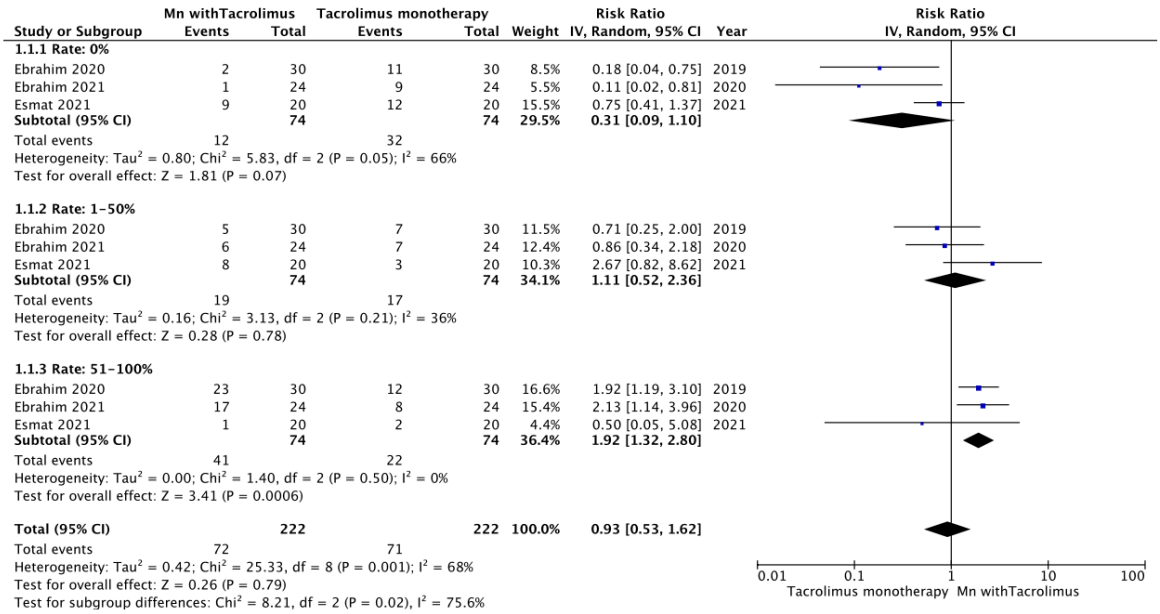


Figure 2. Forest plot of 5-grade re-pigmentation scale or Physician's Global Assessment (PGA).



Mn, micro-needling; CI, confidence interval; IV, inverse variance.

Figure 3. Grading of recommendations assessment, development, and evaluation (GRADE) evidence profile.

Microneedling and tacrolimus compared to Tacrolimus monotherapy for [health problem]
Bibliography: . [Intervention] for [health problem]. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With Tacrolimus monotherapy	With Microneedling and tacrolimus	Relative effect (95% CI)	Risk with Tacrolimus monotherapy	Risk difference with Microneedling and tacrolimus
5-Grade Re-pigmentation Rate or Physician's Global Assessment (PGA)											
148 (3 RCTs)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate	70/74 (94.6%)	72/74 (97.3%)	**RR 0.93** (0.53 to 1.62)	946 per 1,000	**66 fewer per 1,000** (from 445 fewer to 586 more)
Histopathological Assessment											
108 (2 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate	54/54 (100.0%)	54/54 (100.0%)	**RR 0.90** (0.47 to 1.75)	1,000 per 1,000	**100 fewer per 1,000** (from 530 fewer to 750 more)
Body sites re-pigmentation											
108 (2 RCTs)	not serious	not serious	not serious	serious[c]	none	⨁⨁⨁◯ Moderate	52/54 (96.3%)	118/54 (218.5%)	**RR 2.02** (1.51 to 2.70)	963 per 1,000	**982 more per 1,000** (from 491 more to 1,000 more)
Adverse events											
108 (2 RCTs)	not serious	serious[d]	not serious	serious[e]	none	⨁⨁◯◯ Low	20/54 (37.0%)	24/54 (44.4%)	**OR 1.72** (0.10 to 29.36)	370 per 1,000	**133 more per 1,000** (from 315 fewer to 575 more)

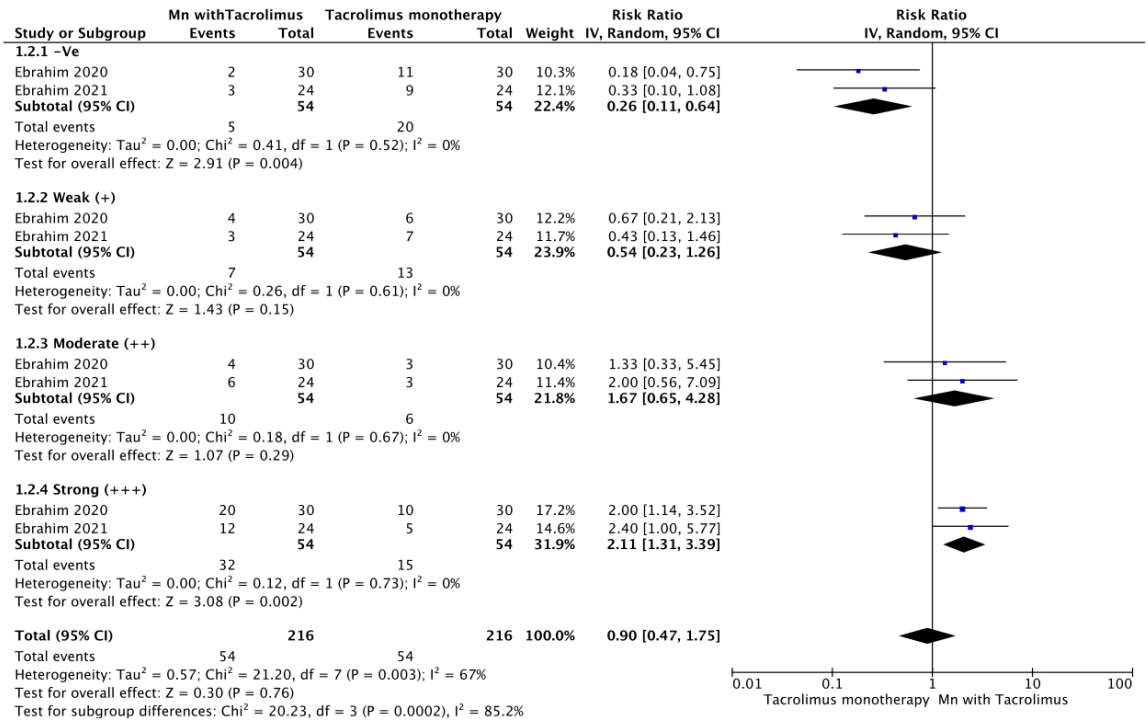
CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio

Explanations

a. small sample size
b. small sample size
c. small sample size
d. Each subgroup favors different arm
e. small sample size

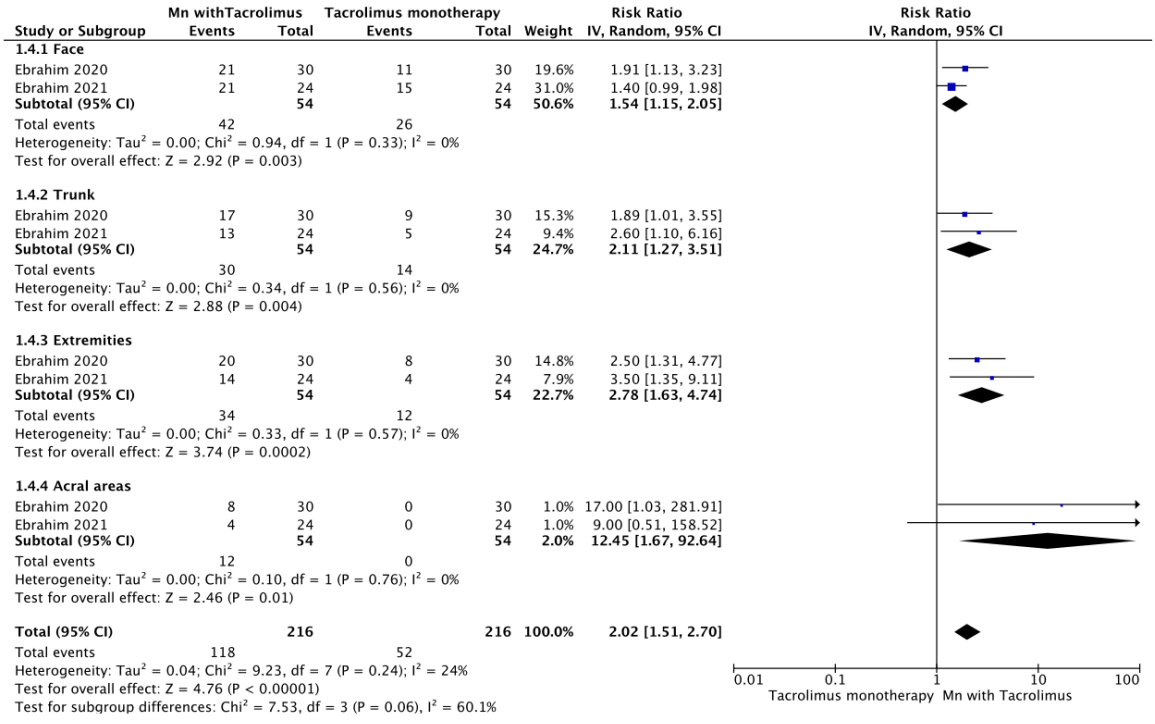
CI, confidence interval; RCT, randomized controlled trial; RR, risk ratio; OR, odds ratio.

Figure 4. Forest plot of histopathological assessment.



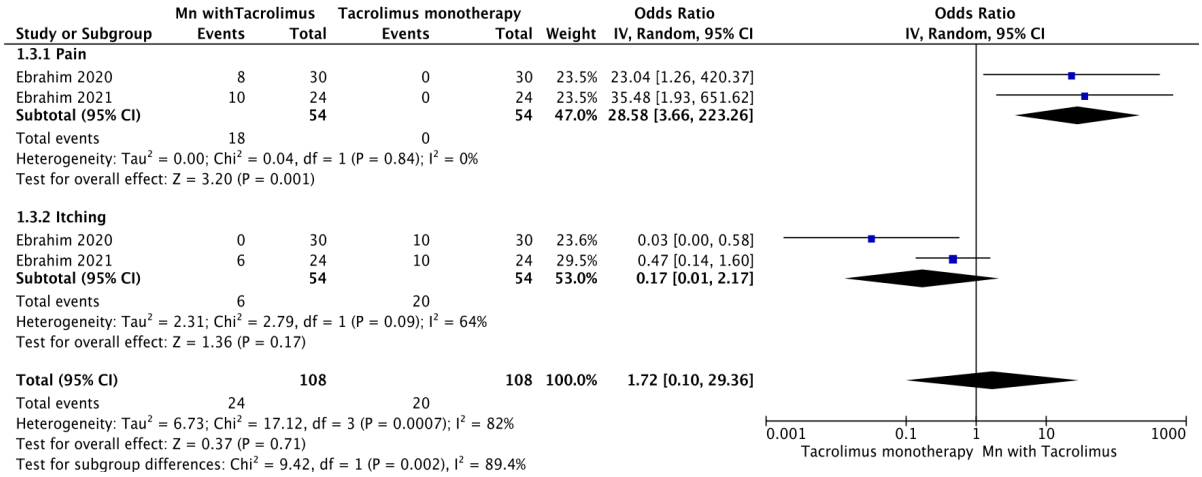
Mn, micro-needling; -Ve, negative; CI, confidence interval; IV, inverse variance.

Figure 5. Forest plot of re-pigmentation of body sites.



Mn, micro-needling; CI, confidence interval; IV, inverse variance.

Figure 6. Forest plot of adverse events.



Mn, micro-needling; CI, confidence interval; IV, inverse variance.

Online Supplementary Material:

Supplementary Figure A. *Risk of bias graph.*

Supplementary Figure B. *Risk of bias summary.*