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The effectiveness of secretomes delivery using microneedling compared to laser-assisted drug delivery for facial skin rejuvenation: a systematic review

A eficácia da administração de secretomas usando microagulhamento ou laser para o rejuvenescimento da pele facial: uma revisão sistemática

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ABSTRACT

This study compared the effectiveness of secretome delivery using microneedling versus laser-assisted drug delivery for facial skin rejuvenation. The review included seven studies that demonstrated that both approaches were effective in delivering secretomes. However, microneedling had a higher patient satisfaction rate and fewer reported adverse events. We concluded that micro needling may be a more patient-friendly and safer option for facial rejuvenation. Further studies with larger sample sizes and extended follow-up periods are needed to confirm these results.

Keywords: Secretome; Laser Therapy; Systematic Review; Skin.

RESUMO

Este estudo comparou a eficácia da administração de secretomas utilizando a técnica de microagulhamento versus a administração assistida por laser para o rejuvenescimento da pele facial. A revisão incluiu sete estudos que demonstraram que ambas as abordagens são efetivas na entrega de secretomas. No entanto, o microagulhamento apresentou uma taxa de satisfação do paciente mais alta e menos eventos adversos relatados. Conclui-se que o microagulhamento pode ser uma opção mais amigável e segura para o rejuvenescimento facial. Estudos adicionais com amostras maiores e períodos de acompanhamento mais longos são necessários para confirmar esses resultados.

Palavras-chave: *Secretoma; Lasers; Revisão Sistemática; Pele.*

Review Article

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INTRODUCTION

Skin aging is a natural process caused by a combination of extrinsic and intrinsic factors, leading to wrinkles, loss of elasticity, and other visible changes.[1,2] One strategy to combat aging is the use of stem cells, such as amniotic membrane stem cells-conditioned medium (AMSC-CM), adipose-derived mesenchymal stem cells (ADMSCs), and human umbilical cord-derived mesenchymal stem cells-conditioned medium (hUC-MSCs-CM).[3,4] To reduce wrinkles and other photoaging-related facial deformities, AMSC-CM, ADMSC-CM, and hUC-MSCs--CM can stimulate dermal collagen production, growth factor, chemokines, dermal fibroblast proliferation and migration, and epidermal keratinocyte migration.[5,6,7]

Several treatments, such as microneedling and laser therapy, can promote skin rejuvenation. The fractional CO_2 and erbium lasers are emerging technologies that show potential for improving skin rejuvenation.[7] The microthermal zone (MTZ) of ablation in the skin facilitates penetration of topical big therapeutic molecules from the surface to the layer of interest while shortening the healing time following laser-induced tissue injury.[8,9] This study aims to compare the effectiveness of secretome delivery using microneedling versus laser-assisted drug delivery (LADD) for facial skin rejuvenation.

METHOD

A systematic review through various stages: (Figure 1)

Search strategy

We conducted a comprehensive investigation in 2023 to explore the efficacy of delivering secretome through microneedling or laser-assisted drug delivery (LADD) therapy for skin rejuvenation. The search utilized keywords such as "SECRETOME", "MESENCHYMAL STEM CELL-CONDITIONED MEDIUM", "AMSC-CM", "ADMSC-CM", "hUC-MSCs-CM", combined with "MICRONEEDLING", and "LASER ASSISTED DRUG DELIVERY", including synonyms. Electronic databases, including Pubmed, Cochrane Central Database, ClinicalTrials.gov, and Mendeley, were consulted from their inception up until June 2023. We assessed the retrieved records systematically using predetermined inclusion and exclusion criteria. Initially, four authors (LPM, MT, RJ, and EK) independently scanned all abstracts to identify relevant studies. In case of discrepancies, the remaining two authors (YK and MT) were involved in the final judgment and eligibility assessment by reviewing the full-text articles. Figure 1 provides a flowchart outlining the literature search strategy, following the Preferred Reporting Items for Systematic Reviews guidelines.

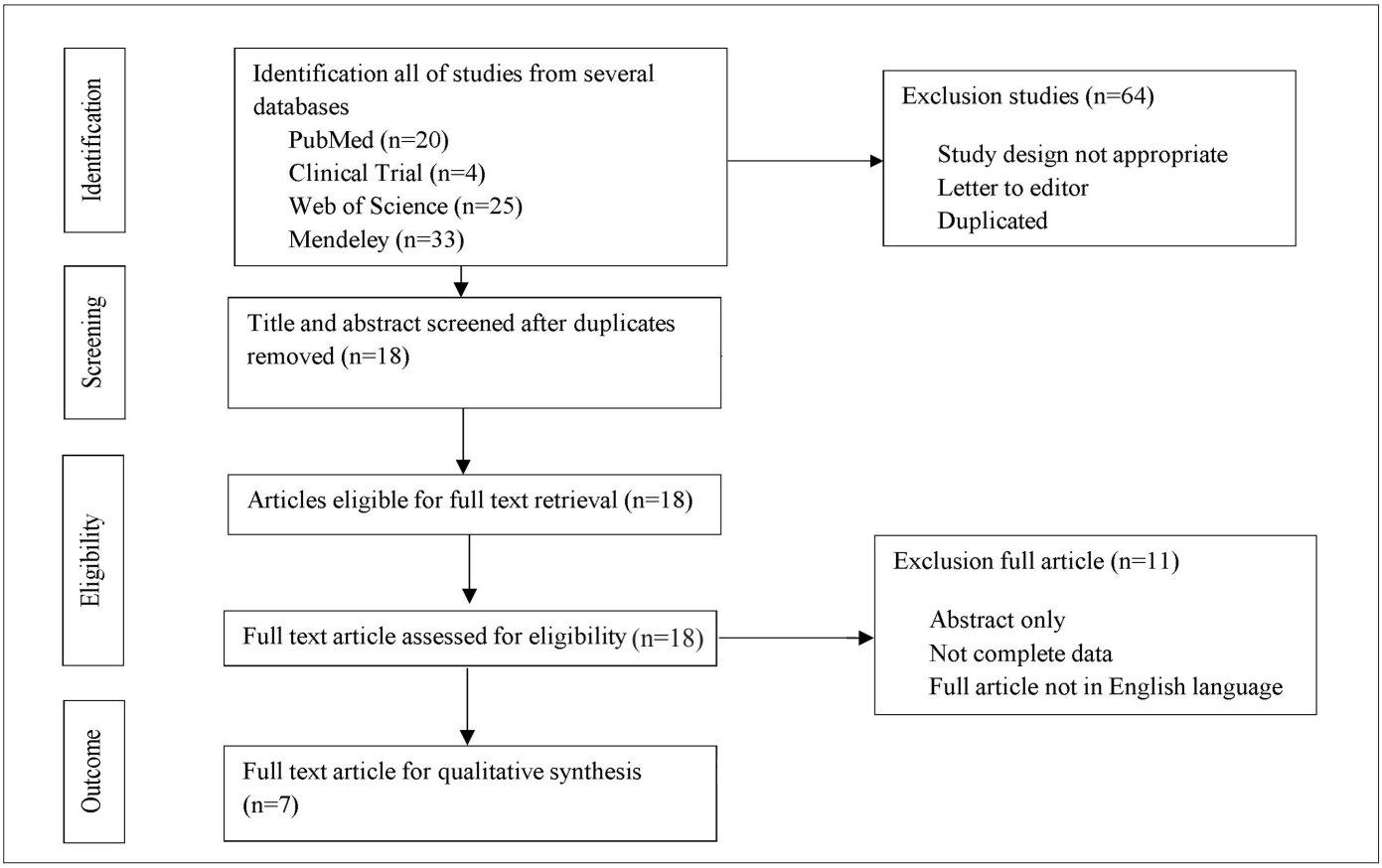

FIGURE 1: The flow diagram of meta-analysis

Selection Criteria

This study included all publications in 2023 that investigated the effectiveness of secretome delivery using microneedling or LADD therapy for skin rejuvenation. The selected publications consisted of original studies, excluding review articles, meta-analyses, epidemiological studies, abstracts only, non-English manuscripts, and editorials.

Data Extraction

Two independent authors (MT and LPM) performed the data extraction and quality assessment using a standardized extraction method in an Excel application.

Bias Analysis

We used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) analysis to assess bias in several journals. Table 1 shows that all journals explicitly defined their population, intervention, comparison, and outcome criteria. Although original studies were the most prevalent, some journals exhibited bias in different aspects. One journal displayed biases in participant data, another had bias related to the intervention, one journal had biases due to missing data, and another had biases associated with reporting. Overall, all the included studies received low scores, indicating a risk of bias.

RESULTS

Study selection

Figure 1 provides an overview of the process used to select the studies. Initially, the search identified a total of 82 articles, and after removing duplicates, 18 potentially relevant articles remained. Upon reviewing the titles and abstracts, 64 articles were excluded, resulting in seven studies that met the inclusion criteria. There were no disagreements during the study selection process.

Table 1 presents the characteristics of the seven studies that met the inclusion criteria. These studies encompassed various types, including prospective studies, randomized controlled spit-face studies, and analytical experimental controlled clinical trials. Most cases and studies were conducted in Indonesia, with one study from China. Among the 268 patients included in the studies, 240 were women, while the study by Liang ***et al.*** did not specify the gender of the 28 participants. The studies used microneedling, fractional CO_2 laser, and fractional erbium:YAG laser. The secretomes employed in the studies included AMSC--CM, ADMSCs, and hUC-MSCs-CM.

The effectiveness of included studies

Table 3 shows that microneedling and LADD proved to be effective therapies for delivering secretomes. Microneedling and LADD significantly reduced wrinkles and pore size, improved pigmentation and UV spots, and enhanced moisture and elasticity starting at six weeks.

Adverse events of included studies

Table 2 indicates that both groups experienced adverse events, including erythema, pain, burning sensation, itch, and urticaria. Also, the LADD group reported acne eruption. Microneedling exhibited a higher patient satisfaction rate and lower reported adverse events than the LADD group.

Table 1. ROBINS-I Analysis

Study	Confounding Bias	Participants Bias	Intervention Bias	Missing Data Bias	Outcome Bias	Reporting Bias	Overall Risk Bias
Sari *et al.*, 2021[10]	No	No	No	NI	No	No	Low
Yusharyahya *et al.*, 2023[11]	No	No	Yes	NI	No	Yes	Low
Prakoeswa *et al.*, 2021[12]	No	No	No	NI	No	No	Low
Praharsini *et al.*, 2020[13]	No	Yes	No	NI	No	No	Low
Widianingsih *et al.*, 2019[14]	No	No	No	NI	No	No	Low
Liang *et al.*, 2022[15]	No	No	No	Yes	No	No	Low
Prakoeswa *et al.*, 2018[3]	No	No	No	NI	No	No	Low

Note: Bias analysis showed that all journals have clear population, intervention, comparison, and outcome. These journals were mostly the original study for this research. There were 1 journal with participants' data bias, 1 journal with intervention bias, 1 journal with missing data bias, and 1 journal with reporting bias. All of the included studies have a low score according with overall risk bias.

Table 2. Research characteristics involved in the study and side effects of each study

N.	Study (author, year)	Study Design	Country	Gender (M/F)	Type of Stem Cell	Intervention	Study Duration	Number of Session	Session Interval	2 weeks					
										Erythema	Pain	Burning Sensation	Itch	Urticaria	Acne Eruption
1	Sari *et al.*, 2021[10]	Prospective study	Indonesia	F (60)	AM-SC-CM	Fractional CO_2 and MN	12 weeks	3 sessions	FL: 1 month MN: 2 weeks	N/A	N/A	N/A	N/A	N/A	N/A
2	Yusharyahya *et al.*, 2023[11]	Randomized split-face clinical trial	Indonesia	F (30)	ADMSCs	Fractional CO_2 and MN	6 weeks	3 *sessions*	2 weeks	MN: 0 (0.0%); FL: 2 (6.7%)	MN: 15 (50.0%); FL: 30 (100.0%)	MN: 4 (13.3%); FL: 22 (73.3%)	MN: 1 (3.3%); FL: 2 (6.7%)	N/A	N/A
3	Prakoeswa *et al.*, 2021[12]	One group pre and post-test design model	*Indonesia*	F (60)	AM-SC-CM	*Erbium:YAG and MN*	*8 weeks*	3 *sessions*	4 weeks	N/A	N/A	N/A	N/A	N/A	N/A
4	Praharsini *et al.*, 2020[13]	Controlled split-face	*Indonesia*	F (33)	*AM-SC-CM*	*Erbium:YAG Fractional*	*8 weeks*	3 *sessions*	4 weeks	N/A	N/A	N/A	N/A	1	N/A
5	Widianingsih *et al.*, 2019[14]	Randomized, controlled split-face study	*Indonesia*	F (9)	*AM-SC-CM*	*Erbium:YAG Fractional*	*24 weeks*	3 *sessions*	4 weeks	9 (100%)	7 (77,7%)	N/A	N/A	N/A	2 (22%)
6	Liang *et al.*, 2022[15]	Controlled and prospective study	*China*	PEOPLE (28)	*hUC-MSCs-CM*	*MN*	*10 weeks*	5 *sessions*	2 weeks	1	N/A	N/A	N/A	N/A	N/A
7	Prakoeswa *et al.*, 2018[3]	Analytical experimental controlled clinical trial	*Indonesia*	F (48)	*AM-SC-CM*	*MN*	*8 weeks*	3 *sessions*	2 weeks	1	N/A	N/A	N/A	1	N/A

**N/A: Not available*

Table 3: Results of research interventions

N.	Study	Type of Stem Cell	Intervention	Outcome											
				Wrinkle		Pore Size		Pigmentation		UV Spot		Moisture		Elasticity	
				MN	FL	MN	FL	MN	FL	MN	FL	MN	FL	MN	FL
1	Sari *et al.*, 2021[10]	AM-SC-CM	Fractional CO2 and MN	11.90± 7.345 vs 0.50 (-11-17)	6.73± 2.586 vs. 1.00 (-4-19)	51.20 ±6.723 vs. -2.00 (-9-8)	49.60 ±4.924 vs. 3.50 (-1-10)	N/A	N/A	14.87 ±8.569 vs. 0.00 (-17-9)	7.77± 3.588 vs. 0.00 (-10-8)	N/A	N/A	N/A	N/A
2	Yusharyahya *et al.*, 2023[11]	ADM-SCs	Fractional CO2 and MN	3.50 (9.25) vs. −2.50 (7.00)	2.5 (8.00) vs. −1.00 (9.00)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3	Prakoeswa *et al.*, 2021[12]	AM-SC-CM	Erbium:YAG and MN	Janus 1 vs. 2: p value: 0,216; Janus 1 vs. 3: p value: 0,429; Janus 2 vs. 3: p value: 0,846	Janus 1 vs. 2: p value: 0,043; value: 0,043; Janus 2 vs. 3: p value: 0,000	Janus 1 vs. 2: p value: 0,084; Janus 1 vs. 3: p value: 0,032; Janus 2 vs. 3: p value: 0,029	Janus 1 vs. 2: p value: 0,023; Janus 1 vs. 3: p value: 0,023;	N/A	N/A	Janus 1 vs. 2: p value: 0,38; Janus 1 vs. 3: p value: 0,258; Janus 2 vs. 3: p value: 0,258	Janus 1 vs. 2: p value: 0,04; Janus 1 vs. 3: p value: 0,00; Janus 2 vs. 3: p value: 0,00	N/A	N/A	N/A	N/A
4	Praharsini *et al.*, 202013	AM-SC-CM	Erbium:YAG Fractional	N/A	4.28 ± 0.38 vs. 4.09 ± 0.20	N/A	6.52 ± 0.57 vs. 5.79 ± 0.7	N/A	4.35 ± 1.41 vs. 3.09 ± 0.68	N/A	N/A	N/A	42.2 ± 7.64 vs. 59.1 ± 7.94	N/A	48.2 ±14.1 vs. 61.7 ± 13.1
5	Widianingsih *et al.*, 2019[14]	AM-SC-CM	Erbium:YAG Fractional	N/A	19.7778 ±3.89801 vs. 18.6667 ±4.63681	N/A	48.3333 ±4.21307 vs. 47.1111 ±3.68932	N/A	N/A	N/A	13.1111 ±6.99007 vs. 11.4444 ±4.06544	N/A	N/A	N/A	N/A
6	Liang *et al.*, 2022[15]	hUC-MSCs-CM	MN	17.21 (13.24) vs. 18.18 (13.38)	N/A	23.55 (10.52) vs. 14.05 (6.11)	N/A	23.55 (10.52) vs. 24.40 (10.77)	N/A	24.39 (7.11) vs. 14.47 (5.38)	N/A	2.18 (5.80) vs. 2.07 (6.78)	N/A	0.56 (0.07) vs. 0.57 (0.06)	N/A
7	Prakoeswa *et al.*, 2018[3]	AM-SC-CM	MN	13.92 ± 6.639 vs. 12.13 ± 7.011	N/A	53.17 ± 4.565 vs. 49.63 ± 11.193	N/A	N/A	N/A	17.17 ± 8.646 vs. 14.54 ± 8.748	N/A	N/A	N/A	N/A	N/A

*N/A: Not available

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Table 4: The comparison of microneedling with laser therapy

Comparison	Microneedling	LADD
Type of treatment	Non-laser-based treatment	Laser-based treatment
Technique	Uses a device with tiny needles to create microinjury for providing skin access to topical drugs	Uses a laser to create microthermal zone for providing skin access to topical drugs
Targeted	Wrinkle, fine lines, acne scars, overall skin rejuvenation	Wrinkle, fine lines, age spots, acne scars
Recovery time	Minimal downtime, some redness and mild swelling	Several days to a week for redness and peeling
Pain/discomfort	May cause mild to moderate discomfort during the treatment	May cause discomfort during and after the treatment
Effectiveness	Effective, but may require several treatments for best results	Highly effective, noticeable, results in a few weeks
Cost	Less expensive to laser therapy	Expensive

The comparison of microneedling and laser therapy

Table 4 reveals that LADD was slightly more effective than microneedling in facial skin rejuvenation, although the difference was not statistically significant. Microneedling demonstrated fewer adverse events and lower costs compared to LADD.

DISCUSSION

Microneedling and LADD procedures have been used in cosmetic dermatology for several goals, including skin aging therapy. Both methods successfully construct vertical microtunnels into the dermis, allowing transdermal topical drug delivery.[6-8]

LADD is widely known for its capacity to increase collagen formation and remodeling, allowing photoaged skin's aberrant collagen fibers to rearrange as needed while microneedle creates microinjury and generates a regulated skin injury with little epidermal damage, which stimulates the dermal wound healing cascade (inflammation, proliferation, and remodeling).[1,2,6]

Mild erythema, localized edema, and skin peeling are the most frequent and anticipated adverse events of microneedling and typically resolve within 48 to 72 hours.[6] Compared to microneedling, LADD had more unfavorable effects, such as longer erythema, discomfort, burning sensation, and itch. In light of these findings, dermatologists can select between Microneedling and LADD to distribute secretome, given that LADD may not be available in every clinic due to high costs, while microneedling may be available in all settings. Microneedling is a beneficial option over more invasive procedures such as laser skin resurfacing and deep chemical peeling due to its quick post--treatment recovery, low adverse events profile, and remarkable clinical results.[2,5-7] To improve the therapeutic effect further, the AMSC-CM, ADMSCs, and hUC-MSCs- CM are delivered through laser channels. These cells exert their anti-wrinkle effects by upregulating procollagen type I production and inhibiting matrix metalloproteinase 1 (MMP- 1) secretion, which is responsible for the degradation of collagen fibers. The current study breaks down the skin barrier.[4,5]

CONCLUSION

Microneedling and laser-assisted drug delivery are effective methods for delivering secretomes for skin rejuvenation. However, microneedling may be a more patient-friendly and safer option. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings. ●

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