NEW FRONTIERS IN DISEASE ACTIVITY MONITORING AND THERAPY IN THE FIELD OF DERMATOLOGY AND RHEUMATOLOGY

Ph.D. Thesis Booklet

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Budapest

2023

1. INTRODUCTION

1.1. Overview of the topic

1.1.1. What is the topic?

Our main focus is the assessment of the utility of novel disease monitoring and modifying methods in the field of dermatology and rheumatology.

1.1.2. What is the problem to solve?

The progress made in the fields of dermatology and rheumatology necessitates the evaluation of the effectiveness of innovative therapies, while also emphasizing the significance of monitoring disease activity to enable tailored treatment approaches.

1.1.3. What is the importance of the topic?

Dermatological and rheumatological conditions can have a profound impact on patients' quality of life as well as on society as a whole. These conditions often bring about physical discomfort, pain, and visible symptoms, which can lead to significant psychological distress and emotional challenges for patients. Moreover, these conditions impose a financial burden on the healthcare system and society as the long-term management of these conditions often requires ongoing medical care, specialized treatments, and medications.

1.1.4. What would be the impact of our research results?

Through the assessment of the effectiveness of new therapies and the facilitation of widespread adoption of objective disease monitoring systems, the quality of life for patients can be significantly improved. The evaluation of the efficacy of emerging treatments allows healthcare professionals to determine the most suitable interventions for patients, leading to enhanced outcomes and better overall well-being. Additionally, the implementation of objective disease monitoring systems provides clinicians with valuable data on the progression and response to treatment, enabling personalized and timely adjustments to patient care plans.

2. OBJECTIVES

2.1. Investigating the utility of MBDA score for the monitoring of rheumatoid arthritis

Although several studies have evaluated the utility of the MBDA score, and a meta-analysis has been conducted on the correlation of the MBDA score with conventional DAMs; the predictive and discriminative value of the MBDA score was yet to be analyzed in a comprehensive manner. Therefore, our aim was to conduct a systematic review and meta-analysis assessing the predictive and discriminate value of MBDA score besides its correlation with conventional DAMs.

2.2. Investigating the efficacy of PRP in chronic wound management

The effects of PRP on wound healing are heavily investigated, however, the current evidence is inconclusive. Therefore, we aimed to evaluate the efficacy of PRP in chronic wound management.

2.3. Investigating the efficacy of PRP in the treatment of alopecia areata

PRP showed promising results in the treatment of AA, but as there was no systematic evaluation of randomized trials reporting on the therapeutic effect of PRP on AA, we aimed to summarize the latest data on the efficacy of PRP in AA comprehensively.

3. METHODS

Our systematic review and meta-analysis are reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Statement. The Cochrane Handbook's recommendations for Systematic Reviews of Interventions Version 6.1.0 and Cochrane Prognosis Methods Group were followed and the review protocols were registered on PROSPERO (Study I.: CRD42021279474; Study II.: CRD42021287881; Study III.: CRD42021282807).

3.1. Literature search and eligibility criteria

We performed a systematic literature search in five databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Web of Science and Scopus for Study I, and four medical databases, MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, and Web of Science for Study II. and Study III.

Original articles reporting on the performance of the MBDA score's correlation with conventional DAMs, or the predictive and the discriminative value of the MBDA score for radiographic progression, therapy response, remission, and relapse were included for Study I. Randomized clinical trials (RCTs) reporting on patients with chronic wounds treated with PRP, comparing additional PRP treatment with conventional ulcer therapy alone were included for Study II., while RCTs reporting on patients with AA treated with PRP, comparing PRP with TrA or placebo for Study III.

3.2. Study selection and data collection

We used EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA) for the articles' selection. Two independent authors screened the publications separately for the title, abstract, and full text, and disagreements were resolved by a third author.

Two authors independently extracted data into a predefined Excel spreadsheet (Office 365, Microsoft, Redmond, WA, USA), and a third reviewer resolved the discrepancies.

3.3. Quality assessment

The risk of bias assessment was carried out by using the Quality In Prognosis Studies (QUIPS) tool for Study I. and the revised tool for assessing the risk of bias (RoB 2) for Study II. and III. To assess the quality of the evidence for Study II. and Study II., we followed the recommendation of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup and used GRADEPro Guideline Development Tool for visualization.

3.4. Data synthesis and analysis

The statistical analyses were performed with R (R Core Team 2022, v4.2.1). Forest plots were used to graphically summarize the results. Random-effects meta-analyses were performed on the different datasets as we anticipated considerable between-study heterogeneity.

For dichotomous outcomes the odds ratio (OR) with 95% confidence interval (CI) was used for the effect measure; to calculate the OR, the total number of patients in each group and those with the event of interest were extracted from each study. Raw data from the selected studies were pooled using a random effect model with the Mantel-Haenszel method. For the pooled results exact Mantel-Haenszel method (no continuity correction) was used to handle zero cell counts. At individual studies zero cell count problem was adjusted by treatment arm continuity correction. In case of continuous outcomes, mean difference (MD) and standardized mean difference (SMD) with 95% CI were calculated as effect size. In case of correlations, the correlations retrieved from the studies belonged to three categories: Pearson's correlation coefficient (c.c.), Spearman's c.c. and those that the type of c.c. was not mentioned in the article. For the meta-analyses, Fisher's z-transformation was carried out on the collected c.c.-s, which were then retransformed for the reporting of the results.

Between-study heterogeneity was described by the Higgins & Thompson's I^2 statistics.

4. RESULTS

4.1. Study I.

4.1.1. MBDA score for the assessment of disease activity

Six study groups of five publications with a total of 667 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP (COR = 0.45, CI: 0.28-0.59; I^2 = 71.0%). Assessing the correlations of baseline MBDA scores with baseline DAS28-ESR, a moderate correlation was found based on the results of two publications with a total of 127 subjects (COR = 0.55, CI: 0.19-0.78; I^2 = 0.0%).

Six study groups of four publications with a total of 287 subjects revealed a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP (COR = 0.44, CI: 0.28-0.57; I^2 = 70.0%). The only study investigating the correlations of follow-up MBDA scores with follow-up DAS28-ESR found a moderate correlation (COR=0.49, CI: 0.22-0.69) between MBDA score and DAS28-ESR.

Ten study groups of six articles with a total of 698 subjects demonstrated a moderate correlation between the change in MBDA score and the change of DAS28-CRP (COR = 0.40, CI: 0.32-0.48; I^2 = 19.0%). Seven study groups of six articles with a total of 543 subjects exhibited a moderate correlation between the change of MBDA score and the change of DAS28-ESR (COR = 0.56, CI: 0.51-0.60; I^2 = 71.0%).

4.1.2. MBDA score for the assessment of radiographic progression

When evaluating the predictive value of MBDA score for radiographic progression, three studies with a total of 481 subjects showed that the odds of radiographic progression are significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) (OR = 1.03, CI: 1.02-1.05; I^2 = 10.0%). In contrast, the odds of progression for patients with a high baseline DAS28-CRP were not significantly higher than for patients with a low baseline DAS28-CRP (OR = 1.12, CI: 0.91-1.37; I^2 = 0.0%).

4.2. Study II.

4.2.1. Complete closure

Thirty-three study groups of 29 RCTs with a total of 2,198 wounds showed that the odds for complete closure were significantly higher in the PRP group than in the control group (OR=5.32; CI: 3.37; 8.40; I^2=58%).

When subgrouping was based on ulcer etiologies, the odds for complete closure were significantly higher in the PRP group than in the control group, both in diabetic foot ulcers (OR=2.26; CI: 1.50; 3.41; I^2=12.0%) as well as venous leg ulcers (OR=8.02; CI: 3.63; 17.71; I^2=10.0%). The test for subgroup difference showed a significant difference between the two groups (χ^2=9.88; df=1; p=0.002), the odds for complete closure were significantly higher in venous ulcers than in the diabetic foot ulcers treated with PRP.

Subgrouping based on the way of the application of PRP showed similar results. The odds for complete closure were significantly higher both in the topically applied (OR=4.74; CI: 2.87; 7.83; I^2=60%) and injected (OR=9.42; CI: 3.32; 26.76; I^2=0%) PRP groups than in the control group, with no significant subgroup difference (χ^2=2.34; df=1; p=0.126).

The odds for complete closure were significantly higher in the PRP group than in the control group in the short (OR=6.03; CI: 3.21; 11.33; I^2=47%), medium (OR=3.38; CI: 1.15; 9.89; I^2=73%), and long (OR=8.24; CI: 1.66; 40.87; I^2=0%) follow-up categories as well with no significant subgroup differences (χ^2=2.50; df=3; p=0.476).

4.2.2. Reduction of wound area

Pooled SMDs from 18 study groups of 16 RCTs with a total of 1,062 wounds showed a significant difference between the post-treatment wound size of the PRP and the control groups (SMD = -1.21, CI: -1.74; -0.68; I^2 = 92.5%), the PRP group showing greater improvement (see Figure 7).

Subgrouping based on ulcer etiology, application method, and follow-up length showed similar results. The post-treatment wound size was

significantly smaller in the PRP group than in the control group in diabetic (SMD = -0.68, CI: -1.31; -0.06; I^2 =93.64%), venous (SMD = -1.26, CI: -2.28; -0.24; I^2=90.76%), topically applied (SMD = -0.94, CI: -1.43;-0.46; I^2=91.26%), and injected (SMD =-1.03, CI: -1.79;-0.26; I^2 =86.63%) subgroups, as well as in the short follow-up subgroup (SMD = -1.00, CI: -1.64;-0.35; I^2 = 89.41%). However, the difference between the PRP and the control groups was not significant in the medium (SMD = -1.38, CI: -2.96; 0.19; I^2 = 54.51%), and long (SMD = -0.63, CI: -1.64; 0.37; I^2 = 93.88%) follow-up groups. No significant subgroup differences were recorded.

4.3. Study III.

4.3.1. Reduction of SALT score

Two studies evaluated the post-treatment SALT score 12 weeks after the first treatment session, one study 16 weeks after the first treatment session, and one at multiple timepoints: weeks 3, 6, 9, 12, and 24. We used the SALT score of the 12th-week evaluation of this study for our meta-analytical calculations. Pooled MDs from four RCTs with a total of 201 subjects did not show a significant difference in mean change in SALT scores between the PRP and TrA groups (MD = - 2.04, CI: -4.72-0.65; I^2 = 80.4%, p = 0.14).

5. CONCLUSION

5.1. Study I.

The utilization of the MBDA score in the management of RA patients holds significant value, serving as a valuable tool for monitoring disease activity and predicting radiological progression. However, to further enhance our understanding of the utility of the MBDA score and the specific contributions of individual biomarkers in disease activity monitoring, additional studies are warranted. These future investigations will provide valuable insights and contribute to the ongoing advancement of RA patient care.

5.2. Study II.

PRP has demonstrated both safety and efficacy as a modality for promoting wound healing. Its integration into clinical practice has the potential to transform it into a widely utilized and valuable tool. By leveraging the benefits of PRP, patients' quality of life can be enhanced while simultaneously reducing the healthcare burden associated with wound management.

5.3. Study III.

PRP offers a promising alternative as a topical steroid-free treatment option for AA. While no significant difference was observed between PRP and conventional treatment (TrA), it is imperative to conduct further high-quality RCTs to better evaluate the efficacy of PRP and enhance the strength of the existing evidence.

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