RESEARCH ARTICLE



Duration of effect in treatment of methotrexate intolerance in juvenile idiopathic arthritis using Eye Movement Desensitization and Reprocessing (EMDR) can be improved by Bi-lateral Alternating Stimulation Tactile (BLAST) wristbands

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Abstract

Background Methotrexate (MTX) intolerance in juvenile idiopathic arthritis (JIA) frequently leads to discontinuation due to anticipatory and associative gastrointestinal symptoms. Eye Movement Desensitization and Reprocessing (EMDR) has successfully been used in MTX intolerance, with lasting effects but frequently diminishing efficacy over time. BLAST (bi-lateral alternating stimulation tactile) wristbands utilize a similar process to EMDR. The aim of this study was to determine if utilization of BLAST wristbands could improve and prolong the effect of EMDR on patients with MTX intolerance.

Methods Consecutive patients admitted to the German Center for Pediatric and Adolescent Rheumatology with JIA and signs of MTX intolerance from October 2016 until March 2024 were included in this study. Treatment was performed using an adapted 8 phase EMDR protocol implementing BAST wristbands. Initial patients were treated with EMDR, subsequent patients additionally with BLAST wristbands. Health-related quality of live was determined using the PedsQL. Measurements of MISS (Methotrexate Intolerance Severity Score) and PedsQL were taken at 4 time points: directly before and after (MISS only) treatment, as well as 4 and 12 months after treatment. Changes in MISS and PedsQL were compared using descriptive statistics and repeated measures ANOVA.

Results 87 patients with MTX intolerance were included, 53 in group 1 without BLAST wristbands and 34 in group 2 which were concurrently treated with BLAST wristbands. All patients reported marked improvement of MTX intolerance symptoms (mean MISS score group 1: 15.0 ± 5.5 before treatment, 1.3 ± 1.5 after treatment, group 2: 16.8 ± 5.6 and 2.5 ± 2.5 , respectively). After 4 and 12 months, MISS in group 1 was 8.1 ± 7.1 and 8.7 ± 8.4 , and in group

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2: 7.1 \pm 6.3 and 6.5 \pm 5.7. A repeated measures ANOVA showed a significant difference between the MISS results over time (F(3,114) = 64.6, *p* < 0.001), and also demonstrated a significant difference of the PedsQL results between the two groups over time (F(2,64) = 8.9, *p* < 0.001).

Conclusion Treatment with Eye Movement Desensitization and Reprocessing (EMDR) could present an effective treatment of MTX intolerance, and using BLAST wristbands, further potential improvement is possible.

Keywords Juvenile idiopathic arthritis, Methotrexate, Intolerance, Adverse effects, EMDR

Introduction

Juvenile idiopathic arthritis (JIA) is the leading cause of chronic inflammatory pediatric musculoskeletal disability and represents a diverse group of disorders that share the common symptom of chronic joint inflammation [1]. While the causes of JIA remain unclear, treatment modalities are directed towards symptomatic relief, prevention of joint damage, and maintenance of function. Within the last three decades, various treatment regimens have been adopted, but methotrexate (MTX) remains a mainstay due to its proven efficacy and safety profile [2].

MTX, originally introduced as an antineoplastic agent, was later recognized for its immunomodulatory effects and was thus adopted for the management of several autoimmune disorders, including JIA [3]. However, its clinical utility often faces challenges due to its side effect profile. Notably, up to 50% of JIA patients treated with MTX report adverse reactions, which can range from mild gastrointestinal disturbances to severe hepatotoxicity and hematologic abnormalities [4]. A large number of children develop a pronounced intolerance even at the thought or sight of taking the drug, rendering its continued use almost impossible. The cause of this aversion is not clear, but it is believed to be a mixture of psychological and pharmacological effects [5, 6].

Given this challenge, there is a critical need for innovative approaches to address MTX intolerance in JIA patients. One such promising avenue is the use of psychotherapeutic interventions, particularly Eye Movement Desensitization and Reprocessing (EMDR). EMDR, originally developed for the treatment of post-traumatic stress disorder (PTSD), operates on the premise of reprocessing distressing memories, rendering them less aversive [7]. The methodology involves guiding the patient to recall traumatic memories while subjecting them to bilateral stimulation, usually through guided eye movements. Such an approach has garnered attention for its potential applicability in cases where aversive conditioning to a stimulus, such as a drug, is evident [8].

A previous study has shown the potential of EMDR in this context, which leads to success in reducing the MTX intolerance in almost all cases in a small study of 18 patients. Even though lasting improvement was observed in most patients, positive effects were waning in a part of the patients 6 months after the treatment [9]. One hypothesis states that efficacy of EMDR might be further enhanced by the integration of Bi-lateral Alternating Stimulation Tactile (BLAST) wristbands [10]. These wristbands are a different approach to bilateral stimulation similar to EMDR that can be continued at home, thereby potentially improving its efficacy. Given the complexity of MTX intolerance in JIA and the necessity for alternative interventions, combining EMDR with BLAST wristbands offers a compelling approach that warrants investigation.

In this study, we examined the efficacy of EMDR using tactile bilateral stimulation with BLAST wristbands in managing MTX intolerance in JIA patients, potentially offering a novel solution to a longstanding challenge. We compare data collected prior to the introduction to BLAST armbands with patient data acquired after the introduction of the armbands.

Methods

Consecutive patients admitted to the German Center for Pediatric and Adolescent Rheumatology from October 2016 until March 2023 for planned EMDR treatment were included in this study (Table 1). Inclusion criteria were (1) diagnosis of JIA according to ILAR criteria [1], (2) age between 8 and 17 years, (3) symptoms of MTX intolerance as determined by the Methotrexate Intolerance Severity Score (MISS) questionnaire, previously developed and validated in JIA [4] and (4) necessity of MTX treatment for at least 6 more months as determined by the treating physician. All patients had inactive disease on MTX prior to EMDR treatment. The MISS consists of four domains: abdominal pain, nausea, vomiting and behavioral symptoms, assessing symptoms after MTX administration, anticipatory and associative symptoms. The behavioral symptoms domain includes restlessness, irritability and refusal of MTX, which develop in response to MTX-induced gastrointestinal symptoms and anticipation thereof. A patient could score 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms) or 3 (severe symptoms) points on each item. MTX intolerance was defined as ≥ 6 points, including at least one anticipatory, associative or behavioral symptom [3].

The standard 8 phase EMDR protocol was adapted for the treatment of MTX intolerance. Treatment started with a structured psychosocial and medical history.

	Table 1	Baseline demographic	data of the	patient cohorts
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Characteristics	Without BLAST wristband N=53	With BLAST wristband N=34
Gender, female	44 (83%)	27 (79%)
Age, mean±SD	13,6±3,6 years	12,8±3, years
JIA subtype		
Oligoarticular, persistent	10 (19%)	9 (26%)
Oligoarticular, extended	21 (40%)	10 (29%)
Polyarticular, rheumatoid-factor	10 (19%)	7 (21%)
Delvarticular resumpted factor	1 (20/)	
positive	1 (2%)	-
Psoriatic arthritis	5 (9%)	2 (6%)
Enthesitis-related arthritis	7 (21%)	7 (21%)
Systemic arthritis	2 (4%)	-
Undifferentiated arthritis	3 (6%)	3 (9%)
Disease characteristics		
ANA positive	72%	73%
HLA-B27 positive	13%	19%

Subsequently, five sessions lasting 60 min each were held over a time period of 10-12 days, concluding with an application of MTX in a clinical setting. Patients without BLAST wristbands were then given instructions how to self-apply EMDR by bilateral tapping of their shoulders at home.

The initial 53 patients were treated with EMDR only, using bilateral eye movement as stimulation, as previously published for the first 18 patients, and were retained as control group [9]. Patients were advised for

at home continuation of the treatment to use tapping on the shoulders to substitute for the eye movements. Subsequent patients were treated with EMDR using bilateral tactile stimulation with BLAST wristbands throughout. These patients were then given instructions on how to use BLAST wristbands at home, substituting for the shoulder tapping.

Health-related quality of live was determined using the PedsQL. Measurements of MISS and PedsQL were taken at 4 time points: directly before and after (MISS only) treatment, as well as 4 and 12 months after treatment. MISS scores and PedsQL scores were investigated using descriptive statistics, mean MISS scores were calculated after testing for normality using the Shapiro-Wilk test. Changes in MISS and PedsQL were compared using and repeated measures ANOVA.

Results

87 patients with JIA and MTX intolerance [mean MISS at inclusion: 15.7 ± 5.6] were included, 53 in group 1 without BLAST wristbands and 34 in group 2, concurrently treated with BLAST wristbands. Directly after treatment, all patients reported marked improvement of MTX intolerance symptoms [group 1: mean MISS from 15.0 ± 5.5 to 1.3 ± 1.5 , group 2: from 16.8 ± 5.6 to 2.5 ± 2.5].

Both groups showed a mean increase of MISS scores at 4 months [BLAST group: 8.1 ± 7.1 , control group: 7.1 ± 6.3], and 12 months [BLAST group: 8.7 ± 8.4 , control group: 6.5 ± 5.7]. A repeated measures ANOVA, however, showed a significant difference between the MISS results over time (F(3,114)=64.6, p=<0.001) (Fig. 1).

Estimated Marginal Means of MISS Treatment 20 with MTX Intolerance Severity Score (MISS) BLAST armbands 0 15 10 5 0 before after treatment 4 months 12 months treatment Time

Error bars: 95% CI

Fig. 1 Mean MISS scores of the two cohorts prior to, directly after and four months after EMDR treatment

a significant difference of the PedsQL results between the

two groups over time (F(2,64) = 8.9, p = < 0.001).

The results of our study demonstrate potential benefits of combining EMDR with BLAST wristbands to manage MTX intolerance in JIA patients. This tactile EMDR approach with the goal of continuation of therapy at home shows a significant further reduction in intolerance scores compared to EMDR alone, demonstrating added benefit of the BLAST wristbands in the patients' ability to tolerate MTX therapy. Quality of life, which has already been proven to significantly improve with EMDR treatment, was enhanced even more with BLAST wristbands than without this additional treatment.

EMDR on its own has shown promise in various therapeutic settings, especially where trauma or adverse psychological reactions are involved [11, 12]. Its efficacy in PTSD treatment suggests the methodology's ability to help patients reprocess distressing memories, making them less aversive. It is likely that a similar mechanism is at play with MTX intolerance. Children, after repeated experiences with MTX's adverse effects, may associate the drug with a traumatic or aversive reaction, leading to an anticipatory response even before the drug is administered. EMDR, by addressing the initial experiences and the conditioned response, may attenuate the aversive nature of the memory or anticipation.

Instead of the traditional EMDR with bilateral eye movement stimulation, we implemented EMDR with tactile stimulation, using BLAST wristbands. The BLAST wristbands might provoke a greater effect and hold a higher appeal for further usage at home. Paulsen suggested that tactile bilateral stimulation might, in some cases, be more effective than visual or auditory bilateral stimulation, especially where dissociation or severe trauma is concerned [13]. Using BLAST wristbands, the exact same kind of stimulation is used in the EMDR therapy sessions, in the self-exercises at home and in the situation while taking the MTX.

Comparing our findings with existing literature, Bulatović et al. highlighted the high prevalence of MTX intolerance in JIA, with many patients developing an aversion to the drug over time [4]. While alternative therapeutic approaches and drugs are explored, our study presents a non-pharmacological approach to address the psychological aspect of the intolerance, which, as van Dijkhuizen et al. suggest, may play a significant role in the intolerance observed [14].

EMDR is based on the Adaptive Information Processing Method which states that, when experiences are processed in a healthy way, multiple elements of the experience such as thoughts, images, emotions and sensations are stored in our memory and helpful associations are forged with stored experiences and reactions in memory. In the case of a disturbing or traumatic event, dysfunctional coping mechanisms can negatively affect this information processing. This can possibly lead to



Fig. 2 Summary PedsQL scores of the two cohorts prior to, four months and 12 months after EMDR treatment

flashback looks of negative experience memories which leads to an imbalance of emotions.

EMDR can be an effective treatment of traumatic stress disorder in adults and children [15–17] Benefits of this treatment have been demonstrated in the treatment of other kinds of dysfunctional memories and inefficient information processing of further adverse life experiences [18, 19]. We have already shown that EMDR is effective in treating MTX intolerance, strengthening the theory that MTX intolerance is based on dysfunctional or incomplete information processing evoked by e.g. strong negative feelings or adverse anticipation of side effects in line with taking MTX [9]. Patients have experienced MTX-related adverse effects or might have been told of the possibility of these occurring, and thus anticipate them in the future, with regular weekly re-enforcements and virtually no chance for escape [4, 20].

EMDR enables the processing of dysfunctional and traumatic memories, using an intensive recall combined with bilateral stimulation usually evoked by eye movement to dissolve the memories by reprocessing them (13). As a result, affective distress is relieved, negative beliefs are reformulated, and physiological arousal is reduced. Unprocessed memory content and dysfunctional experiences and memories are reprocessed several times in order to enable healthy information processing [21]. Bilateral stimulation by eye movement is supposed to counteract the ,frozen information, enabling dissolution of traumatic memories, neutralization of the negative affect and reduction of physiological arousal [22].

Our results should be interpreted in light of several limitations. The sample size of our study, though significant, is still limited. Larger-scale studies may provide a more comprehensive understanding of the approach's efficacy. In addition, the long-term effects of this combined intervention remain unknown. Follow-ups extending beyond 12 months might give insight into the sustained benefits or potential drawbacks of the approach. Considering individual variability, the mean intolerance score reduction was approx. 50%, but individual responses varied. Some participants might have benefited more from the intervention than others. Further analysis and possibly subgroup categorization might provide insights into which JIA patients stand to benefit the most from this combined approach. Another potential avenue for exploration is the role of other therapeutic interventions in conjunction with EMDR using BLAST. Cognitive Behavioral Therapy (CBT), for instance, has shown promise in managing chronic pain and could potentially offer an additional layer of support for these patients, addressing both the psychological aversion and the physical discomfort associated with MTX (8).

Conclusion

In conclusion, our findings underscore the potential of an integrated EMDR and BLAST wristband approach in managing MTX intolerance in JIA patients. Given the significant impact of JIA on pediatric populations and the central role of MTX in its management, solutions like these can enhance the quality of life for these patients, allowing them to benefit from a potentially effective treatment without the psychological distress associated with its administration.

Abbreviations

BLAST Bi-Lateral Alternating Stimulation T (wristbands)

EMDR Eye Movement Desensitization and Reprocessing

JIA Juvenile Idiopathic Arthritis

MTX Methotrexate

MISS Methotrexate Intolerance Severity Score (MISS)

Author contributions

LH, BE and BH designed the study, recruited the patients and performed the statistical analysis, LH and BE performed the EMDR treatment on the patients. JPH participated in the design and coordination of the study and helped draft the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval

The study was approved by the Ethics Committee of the Medical Faculty, Ludwig-Maximilians University Munich, Germany (Nr. 23–0456).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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