https://doi.org/10.31925/farmacia.2022.4.16 **ORIGINAL ARTICLE**

EVALUATION OF ANTIPYRETICS USE AND HEAT SENSITIVITY IN PATIENTS WITH MULTIPLE SCLEROSIS AND IT IS IMPACT ON QOL

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Abstract

Multiple sclerosis (MS) is a progressive neurological disorder that leads to disruption of autonomic functions. The specific mechanism of temperature dependence in MS is not fully understood. Between 60% and 80% of MS patients believe that the worsening of symptoms and relapses are due to heat. The use of antipyretics has been shown to reduce heat sensitivity and the risk of relapse in MS patients. The present investigation aimed to assess antipyretic use and heat sensitivity in MS patients and their impact on quality of life. A retrospective cross-sectional chart review study was conducted for all MS patients admitted to King Khalid University Hospital, Riyadh, Saudi Arabia, between June 2015 and December 2018. Demographics and data on MS treatment regimens were collected. Telephone interviews were conducted to collect data on heat sensitivity, prophylaxis techniques and number of relapses. Nearly half of the sample reported heat sensitivity (44%) and only 24% use cooling techniques. The most used antipyretic was paracetamol (46%), followed by non-steroidal anti-inflammatory drugs (NSAIDs) (5%). Interferon use was associated with a higher risk of temperature increase and antipyretic use. The study showed that heat sensitivity is common among MS patients and the risk of relapse is increased. However, only a small number of patients use antipyretics as prophylaxis. MS relapses can be prevented or reduced by avoiding triggers and prophylactic use of antipyretics.

Rezumat

Scleroza multiplă (SM) este o afecțiune neurologică progresivă care conduce la perturbarea funcțiilor autonome. Mecanismul specific al dependenței de temperatură în SM nu este pe deplin înțeles. Între 60% și 80% dintre pacienții cu SM consideră că agravarea simptomelor și apariția recăderilor se datorează căldurii. S-a demonstrat că utilizarea antipireticelor reduce sensibilitatea la căldură și riscul de recidivă la pacienții cu SM. Prezenta cercetare a avut ca scop evaluarea utilizării de antipiretice și a sensibilității la căldură la pacienții cu SM și impactul acestora asupra calității vieții. S-a realizat un studiu retrospectiv asupra pacienților cu SM, internați la Spitalul Universitar King Khalid, Riyadh, Arabia Saudită, în perioada iunie 2015 - decembrie 2018. Au fost colectate date demografice și informații privind regimurile de tratament pentru SM. Au fost efectuate interviuri telefonice pentru a colecta date privind sensibilitatea la căldură, tehnicile de profilaxie și numărul de recidive. Aproape jumătate din eșantion a raportat sensibilitate la căldură (44%) și doar 24% apelează la tehnici de răcire. Cel mai utilizat antipiretic a fost paracetamolul (46%), urmat de antiinflamatoarele nesteroidiene (AINS) (5%). Utilizarea interferonului a fost asociată cu un risc mai mare de creștere a temperaturii și de utilizare a antipireticelor. Studiul a arătat că sensibilitatea la căldură este comună în rândul pacienților cu SM, iar riscul de recidivă este crescut. Cu toate acestea, doar un număr mic de pacienți utilizează antipiretice ca profilaxie. Recidivele de SM pot fi prevenite sau reduse prin evitarea factorilor declanșatori și utilizarea profilactică a antipireticelor.

Keywords: multiple sclerosis, antipyretics, heat sensitivity, quality of life

Introduction

Neurodegeneration, inflammation, and demyelination in the central nervous system (CNS) are hallmarks of multiple sclerosis (MS), a degenerative neurological disease that causes nerve fibers to lose their protective sheaths, causing autonomic systems to malfunction [1]. Four subtypes of multiple sclerosis (MS) have been identified clinically. These include: progressive MS (PS), secondary progressive MS (SPMS), relapsing MS (RRMS) and progressive-relapsing MS (PRMS). More than eighty-five percent of people with RRMS have this type of disease [2], with relapses of new or exacerbated symptoms, which are separated by periods of recovery [3]. However, the condition does not worsen when in remission. Tingling and numbness are the most commonly reported symptoms of RRMS, as well as visual abnormalities, tiredness episodes, and memory loss. About 10% of MS patients have (PPMS), in which the symptoms worsen gradually over time without any early relapses or remissions. Nearly two-thirds of people with RRMS go on to develop secondary-progressive MS, which is a more severe form of the disease [4, 5]. It is important to note that PRMS is an uncommon disease that affects just about 5 percent of people [6, 7].

In early adult life, MS has been documented, typically between the ages of 20- and 40-years. MS is also more common in women than in men (3:1), according to research [8, 9]. MS affects an estimated 2 million people worldwide, however this number could be greater if undiagnosed. Even though MS affects people all over the world, estimations of prevalence is higher in North America and Europe and lesser in Africa and East Asia combined [10, 11]. Prevalence of MS is now more common in Saudi Arabia than in other nearby nations like the United Arab Emirates (UAE), Qatar, and Kuwait (Kuwait). Females, young people, and those with higher levels of education were more likely to be affected [12, 13]. MS can be caused by a variety of reasons, including low vitamin D levels, environmental exposures, such as Epstein-Barr virus infection, and genetic predispositions that have been well documented in the scientific literature [14-16].

The central nervous system may be affected in different ways by MS, so each patient will have different symptoms [17]. However, some common symptoms include incontinence symptoms, altered sensation, muscular changes, sexual disabilities, constipation, and pain. Other symptoms include cognitive impairment and visual changes, as well as fatigue as a common symptom of MS. In addition to fatigue and other symptoms, one of the significant common factors that can lead to a reduction in quality of life (QOL) in MS patients is the temperature or Uhthoff's phenomenon [18, 19]. QOL deficits in MS patients are also caused by this important component [20, 21]. When prostaglandin concentrations rise in certain brain regions, it causes an increase in body temperature. This alters the activation level of nerves in the hypothalamus that regulate body temperature, and it is treated with anti-pyretic drugs [22]. It has been known since the late 19th century that antipyretic drugs like NSAIDs, aspirin, and acetaminophen, which block the cyclooxygenase enzyme and lower PGE (2) levels in the hypothalamus, are routinely prescribed for people with fever [22, 23]. Antipyretic drugs have been shown to reduce the number of relapses caused by MS and to improve patients' quality of life, although this finding needs to be confirmed by more study. In present investigation, we aim to study the effectiveness of NSAID and other antipyretic medication in terms of MS-related relapse reduction and to compare the effectiveness of NSAID and other antipyretic medication in terms of MS-related QOL improvement in patients.

Materials and Methods

A cross sectional retrospective chart review study for all MS patients were seen at King Khalid University Hospital, Riyadh, Saudi Arabia between June 2015 and December 2018. Demographics and MS treatment regimens data were collected. A questionnaire was prepared and a phone-based interview was conducted to the 117 enrolled participants fulfilling the criteria to collect data regarding heat sensitivity, prophylaxis techniques, and number of relapses. IRB Approval was obtained prior starting the study. Participants were eligible for the study provided they were at least 18 years old and had been diagnosed with multiple sclerosis by a physician. Before beginning the survey, participants were asked to confirm their agreement by the "I agree" for the survey. Patients with incomplete medical file or declined to participate in the survey were excluded from the study sample.

Data collection

The data was directly collected and entered as individuals demographic characteristics (age and gender), MS type, comorbidities if any, preventive measures taken, medication use (both prescribed and OTC), exposure to sun, hot bath or doing some exercise and sensitivity towards warm temperature. All responses to the surveys were kept strictly confidential, and no identifiable information was collected in any way, shape, or form. Questionnaire completion and privacy concerns were discussed. The completion of the questionnaire was interpreted as an agreement to participate in the research. The health status was checked by utilizing the questionnaire on patients' general well-being and ability to function in everyday life. We used the questionnaire to assess co-morbidities. The questionnaire determines if the co-morbidity limits activities and whether treatment is received. In our study, all listed conditions were summed to determine an estimate of the number of co-morbidities each participant reported. The following comorbidities were determined: diabetes, diabetes insipidus, developmental disorders, hypo-thyroidism, hyperthyroidism, anxiety, hypohidrosis/ anhidrosis, fibromyalgia and any other comorbidities. Participants were then categorized as having: none, one or more, co-morbidities. Participants were grouped, based on their summary score.

The patients were categorized as *per* the MS type ad PPRM: Primary Progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; PRMS: Progressive-relapsing multiple sclerosis. We used a researcher-generated list of disease modifying drugs (DMDs) and common MS drugs. We asked for specific details including past and current use and duration of use. For the purpose of analysis, participants were categorized according to whether they currently took antipyretics for MS.

We explored participants' exposure to sun. After sun exposure or taking a hot bath or doing some exercise, is your condition get relapse? yes or no. If yes, then worsening of symptoms. To identify whether there is any method to control it, the participations were asked if they are experiencing any worsening of symptoms after sun exposure or taking a hot bath or doing some exercise, is there any medications or intervention? In order to understand the impact of warm temperature

on the participants, they were asked if they experience any of the following symptoms: feeling hot or sweating in moderately warm temperature, feeling fatigue during warm weather or nausea, vomiting, or dizziness in response to warm weather? To compare between the participants' level of heat sensitivity they were asked: On a scale of 1 to 5, how would you rate the sensitivity of warm temperature? 1 (mild), 2, 3, 4 and 5 (severe).

Statistical analysis

Descriptive statistics such as percentage, mean and standard deviation (SD) were used to describe MS patients' demographic data, illness information, and reported problems for each level. Inferential statistics were applied to determine differences in MS patients when grouped according to demographic variables and illness information. Independent t-test was utilized to test the significance of differences between nominal variables (*i.e.* gender) and one-way ANOVA to test significant differences. Multiple linear regression was carried out to identify which variables were significantly associated with the quality of life of MS patients. The independent variables were age, sex, duration of illness, and on treatment or not on treatment. The Statistical Package for Social Sciences (SPSS) version 21.0 was used for data analysis. The significance level was predetermined at $p < 0.05$ for all tests.

Results and Discussion

117 patients were included in this study, in which 67% of them are females and the average age was 39.5 years answered the questionnaires with a response rate of 100%. Almost half of the sample reported heat sensitivity (44%) and only 24% follow cooling techniques. The main course of the disease was RRMS, remission state (75.21%). In relation to comorbidities (Table I), three participants had epilepsy (2.56%), four participants had depression (3.41%), neurogenic bladder disorder in three participants (2.56%), two participants with migraine and anxiety (1.70%), and one participant had both anxiety-depression (0.85%). One hundred two participants (87.17%) were not having comorbidities. Seventy-six participants (64.95%) reported sensitivity to sun exposure, with no difference between men and women ($p < 0.001$). Among them (68.42%) participants were sensitive to elevated temperatures, 1.31% were sensitive to exercise and 2.63% participants were sensitive to elevated temperature along with exercise and 27.63% participants were sensitive to both including elevated temperatures and exercise.

The participants (24.78%) received interventions to the sensitivity to sun exposure. The participants received both non-pharmacological (shower and cold temperatures) and pharmacological intervention to the above sensitivity (Table II). The most used pharmacological intervention as antipyretic was paracetamol (46%) followed by ibuprofen and diclofenac (5%). More than 10% of the sample reported having at least one MS relapse *per* year, and 48% have known relapses triggers. The other drug interventions used by participants are listed in Table III. Using of interferon was associated with higher risk of temperature elevation and anti-pyretics use ($p < 0.034$). Of common MS-related symptoms, the heat-sensitive participants reported a significantly higher occurrence of several symptoms than did those who were not heat sensitive, for example, excessive sweating, dizziness, fatigue, nausea, vomiting, weakness in legs, concentration difficulties, pain, and urination urgency (Table I).

Table I

Baseline demographics and other parameters of multiple sclerosis patients

Variables (n = 117)			
Gender	**Values (%)**	**Average age (years)**	p
Male	79 (67%)	39.50	< 0.001
Female	38 (33%)		
Frequency of comorbid conditions in the multiple sclerosis sample			< 0.001
Comorbidities	**Number**	**%age**	
Epilepsy	3	2.56	
Depression	4	3.41	
Neurogenic bladder	3	2.56	
Migraine	2	1.70	
Anxiety	2	1.70	
Anxiety - Depression	1	0.85	
No comorbidities	102	87.17	
Sensitivity to sun exposure - elevated temperature - exercise			< 0.001
41	No	35.04	
76	Yes	64.95	
Type of sensitivity			< 0.01
Elevated temperature	52	44.44	
Exercise	1	0.85	
Elevated temperature + exercise	2	1.70	
All	21	17.94	

Intervention to the above sensitivity			< 0.001
Yes	29	24.78	
No	88	75.21	
MS Symptoms associated with elevated temperature exposure			< 0.001
Excessive sweating			
Yes	38	32.47	
No	79	67.52	
Fatigue			
Yes	75	64.10	
No	42	35.90	
Dizziness			
Yes	16	13.68	
No	101	86.32	
Nausea			
Yes	2	1.71	
No	115	98.29	
Vomiting			
Yes	1	0.85	
No	116	99.15	
Dizziness + Nausea			
Yes	3	2.56	
No		97.44	
Dizziness + Nausea + Vomiting			
Yes	17	14.53	
No	100	85.47	

Table II

Pharmacological and non-pharmacological interventions

Pharmacological interventions			*p*
OTC Medication usage	***Value***	***%age***	< 0.001
No	56	47.86	
Yes	61	52.14	
Type and frequency of OTC Medications			< 0.001
Paracetamol 1000 mg monthly	5	4.27	
Paracetamol 1000 mg weekly	2	1.71	
Paracetamol 1000 mg biweekly	8	6.84	
Paracetamol 1000 mg daily	5	4.27	
Paracetamol 500 mg monthly	6	5.13	
Paracetamol 500 mg weekly	8	6.84	
Paracetamol 500 mg biweekly	4	3.42	
Paracetamol 500 mg daily	10	8.55	
Solpadiene® weekly	1	0.85	
Solpadiene® daily	1	0.85	
Ibuprofen 800 mg daily	1	0.85	
Ibuprofen 600 mg biweekly	1	0.85	
Ibuprofen 600 mg weekly	1	0.85	
Paracetamol 500 mg daily + Ibuprofen 400 mg weekly	1	0.85	
Paracetamol 500 mg weekly + Solpadiene® weekly	1	0.85	
Paracetamol 1000 mg biweekly + Ibuprofen 600 mg biweekly	1	0.85	
Paracetamol 1000 mg daily + Rofenac® biweekly	1	0.85	
Paracetamol 500 mg daily + Ibuprofen 600 mg daily	1	0.85	
Ibuprofen 400 mg daily	1	0.85	
Diclofenac monthly	2	1.71	
Non-pharmacological Intervention to the heat sensitivity			< 0.001
Shower	8	6.84	
Switch to cold temperature	18	15.38	
Triggers of relapses			< 0.001
Yes	57	48.72	
No	60	51.28	
Triggers of relapses			
Stress	40	34.19	

Temperature	4	3.42	
Stress + temperature	12	10.26	
postpartum	1	0.85	
Elevated temperature scale (1 - 5) answered by the patients			< 0.001
1	24	20.51	
2	15	12.82	
3	28	23.93	
4	26	22.22	
5	24	20.51	

Table III

Data for medication use

Prescribed RRMS Medications	***Value***	***%age***	***p***
Fingolimod, 0.5 mg, Oral, Daily	29	24.79	0.034
Rituximab	2	1.71	
Interferon beta-1b, 250 mcg, SubQ	1	0.85	
Interferon beta-1b, 8 MU, SubQ, Every other day	5	4.27	
Interferon Beta-1a (Avonex®) 30 mcg PLS, weekly	10	8.55	
Interferon beta-1b, 0.25 mg, SubQ, Every other day	3	2.56	
Interferon Beta-1a (Avonex®) 44 mcg PLS, weekly	32	27.35	
Interferon Beta-1a (Rebif®) 22 mcg PLS	3	2.56	
Dimethyl fumarate	1	0.85	
Natalizumab	14	11.97	
No MS Medication	14	11.97	
Teriflunomide, 14 mg, Oral, Daily	3	2.56	

There are many factors that contribute to a patient's quality of life that are not directly related to their health [24]. An individual's level of independence, social context, and psychological state are all considered while determining these characteristics [25]. Quality of life measurement is becoming more and more significant in MS research [26, 27]. MS sufferers' quality of life was found to be significantly lower than that of the general population in a number of studies [28]. Other chronic conditions such diabetes, congestive heart failure, myocardial infarction and hypertension were found to be related with a lower quality of life than MS [29]. The incidence and severity of quality of life (QOL) issues in MS patients treated with antipyretics such paracetamol and ibuprofen increased over time in this study. Previous studies that looked at these antipyretics independently found the same results [30, 31]. This study examined the impact on quality of life (QOL) of MS patients' usage of antipyretics and heat sensitivity, sun exposure, rising temperatures, and exercise-induced body temperature increase were all associated with antipyretic use, which reduced the risk of overheating in individuals who had previously used antipyretics.

Activation potentials can be fully blocked in demyelinated axons (*e.g.* by exercise) with just minor temperature rises (*e.g.* triggered by exercise) [32]. MS fatigue may be caused by an obstruction due to high temperatures [33]. Despite the fact that previous MS exercise research supports cooling treatments, such as cold bath pre-cooling and vacuum hand cooling chambers, the evaluated procedures were obtrusive or non-standardizable [34, 35]. It's easier and less expensive to use an antipyretic effect instead. Antipyretic mechanisms need to be studied in greater detail in the future. To be sure that the current findings are supported by additional research in larger samples, due to the limited sample size, caution must be used when interpreting the results. Further research should use self-reported exercise heat sensitivity as an important inclusion criterion.

Multiple sclerosis affects young adults aged 20 to 40. In addition to vitamin D levels and environmental factors like Epstein Barr Virus infection, which has been researched extensively, several genetic factors contribute to the development of MS [14, 36]. According to one study, 264 MS patients were hospitalized in Beijing Tiantan Hospital, China, from January 2002 to December 2012, and all clinical data were collected. A higher rate of recurrence was found in the high latitude group (123/179 *vs.* 51/81, p = 0.001), but there was no difference in age, gender, disease duration or onset between the two groups. Exogenous variables are associated with the development of multiple sclerosis, as shown in present study and many others [37]. MS can affect any part of the central nervous system, some patients have symptoms that are different from others, but some common symptoms include continence symptoms, altered sensation, muscular changes, sexual disabilities, constipation, pain, cognitive impairment, and visual changes. QOL impairments in MS patients are also induced by another crucial element, which is the temperature or Uhthoff's phenomenon [38]. Temperature sensitivity or Uhthoff's phenomenon occurs in 60 - 80% of MS patients, and is caused by exposure to warm environments, exercise, or hot baths, and lasts until the temperature returns to normal [39].

A study showed more than 58% of 256 MS patients in an eastern region of Sweden with a disability score (EDSS) of 0 reported heat sensitivity, and the regression analysis shows that heat sensitivity is a significant factor in a number of other common MS symptoms, including fatigue, concentration difficulties, pain, and urination urgency ($p < 0.001$), so temperature sensitivities should be considered when assessing the health of MS patients [40]. To diagnose MS, hot baths were often utilized in the past. The particular mechanism of temperature-dependent conduction slowing/ blocking in demyelinated axons in MS is unknown. There are just a few pharmacological intervention studies that focus on showing any form of medicine with an impact on enhancing temperature sensitivity in MS patients and their quality of life [39]. The current study further corroborates the previous findings that heat sensitivity in patients with multiple sclerosis highly impacts the QOL.

A MS relapse occurs when new symptoms appear or old symptoms worsen. The relapse and symptoms vary. A relapse can be an incident of ocular neuritis, excessive exhaustion, or balance issues. A patient with one symptom relapses, indicating a solitary CNS inflammation, while CNS inflammation in multiple areas causes two or more symptoms at the same time [39]. High body temperature occurs when prostaglandin concentrations increase in certain brain regions, altering the activation level of nerves that control internal body temperature in the hypothalamus. This elevation is considered as a cause of several issues and treated with antipyretic medications. NSAID, aspirin, and acetaminophen are common antipyretic medications used to treat high body temperature [22]. The current study also found disparities in the prevalence of issues among MS types. There was a very small proportion of patients with number relapses. In a double-blind randomized controlled pilot trial, 12 patients were given either 650 mg aspirin or a placebo, and then put on a lower body cycle ergometer. In heat-sensitive patients, aspirin or acetylsalicylic acid (ASA) reduced body temperature after exercise by 56% [41]. In a randomized open label research, two groups of 30 patients having side effects after 6 months of therapy were randomized for 5 weeks to acetaminophen, naproxen, or ibuprofen. They wanted to see if non-prescription drugs could help reduce IFN beta-1a treatment-related side effects. Most patients in both groups reported side effects with all pain medications. After 5 weeks, 50% of patients had no fever, chills, injection site soreness, or headache. The cognitive subset improved with all three drugs ($p = 0.05$), but the physical subset improved with naproxen ($p = 0.05$) and ibuprofen ($p = 0.03$). While acetaminophen improved the cognitive, but not the physical side effects of IFN beta-1a, naproxen and ibuprofen improved the physical side effects more than acetaminophen. MS relapses induce pain, with patients reporting paroxysmal dystonia and neuropathic pain. Pain reduces quality of life in MS patients, and around 12% report it as their worst symptom [42]. In our study patients' pain levels ranged from mild to severe, which is similar to other research. Taking disease-modifying medications has been shown to impair quality of life [43]. The outcomes may vary depending to the availability of drugs with varying side effects [43]. Self-injections with adverse effects include injection site reactions and flu-like symptoms may reduce quality of life. Another key aspect to convey is that patients may not see the benefits of these medications, which may lead to low adherence and relapses, lowering quality of life [44]. In our analysis, there was no statistically significant difference between those on disease-modifying treatment and those not on it. The reasons why people refuse to take prescriptions are unknown. Newer treatments with less frequent injections and oral drugs may improve quality of life. In our study, quality of life tended to lag behind mean findings. This was probably due to increased disability and other comorbidities that come with ageing. Ones with progressive and long-term diseases rate their quality of life worse than younger patients. In other words, disability and disease duration affect quality of life. Our sample was young, and future studies may compare data from an older population.

Conclusions

MS is a condition that has a significant impact on the patient's quality of life. It is still difficult to handle medically and socially. We stress the need of assessing MS patients' quality of life. Our findings revealed some links between patient characteristics and QOL. Patients' quality of life can be improved if healthcare providers are aware of it. To offer holistic care for MS patients, clinicians should routinely examine quality of life along with symptomatic assessments, laboratory tests, and neuroimaging. As a result of this study, more specialized MS clinics, multidisciplinary MS care teams, and support groups will be established.

Conflict of interest

The authors declare no conflict of interest.

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