

Extracorporeal Shock Wave Therapy for Injection Site Panniculitis in Multiple Sclerosis Patients

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Key Words

Injection site reaction · Panniculitis · Interferon β · Glatiramer acetate · Multiple sclerosis · Extracorporeal shock wave therapy

Abstract

Background: Painful cutaneous injection site reactions may hamper treatment with interferon β (IFN- β) and glatiramer acetate (GA) in multiple sclerosis (MS) patients. **Objective:** To maintain therapy adherence, efficient therapeutic modalities for these subcutaneous inflammatory lesions are urgently needed. We tested the application of local extracorporeal shock wave therapy (ESWT). **Methods:** We applied 5 sessions of ESWT to 8 patients suffering from MS who had developed painful panniculitis at the injection sites of either IFN- β or GA. Clinical outcomes, i.e. pain reduction and regression of induration, were assessed 3 and 6 months after completion of the ESWT using a visual analogue score. **Results:** All patients showed both significant pain reduction and reduction of the skin induration in the treated lesions, while in untreated control lesions there was no improvement. **Conclusion:** ESWT proved to be a non-invasive, safe and efficient physical treatment modality for injection-induced painful cutaneous side effects of disease-modifying drugs in MS.

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Background

Multiple sclerosis (MS) is a chronic auto-immune inflammatory disease of the central nervous system. It is the most common cause of neurological disability in young adults [1]. The therapy for the acute inflammatory phase is the use of systemic corticosteroids [2]. Interferon β_{1b} (IFN- β_{1b}), IFN- β_{1a} as well as glatiramer acetate (GA) are approved as first-line treatment for relapsing-remitting MS [3]. These disease-modifying drugs are administered by subcutaneous (Betaferon[®], Rebif[®], Copaxone[®]) or intramuscular (Avonex[®]) injections. The therapy aims to slow down the disease progression and to reduce clinical exacerbations. Although not being curative, these disease-modifying drugs can improve the patient's quality of life remarkably [4]. Frequent side effects of this therapy are injection-induced local skin reactions. Transient reddening of the skin and pain are the most common features, but severe reactions with panniculitis and lipatrophy are more common than previously assumed [5]. The therapy of these cutaneous side effects is challenging. To maintain therapy adherence and patient satisfaction, it is essential to inform the patients about these potential adverse events as well as to offer the best possible treatment in case of their occurrence.

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Extracorporeal shock waves are defined as a sequence of sonic pulses characterized by high peak pressure, fast pressure rise and short life cycle [6]. In the 1980s, extracorporeal shock wave lithotripsy was first used for the treatment of urolithiasis [7]. Orthopaedics then used extracorporeal shock wave therapy (ESWT) to treat non-union fractures, tendinopathies, chronic epicondylitis [8], myofascial pain syndrome [9], plantar fasciitis [10], musculoskeletal disorders [11] and osteonecrosis [12]. The first application of ESWT in dermatology was in recalcitrant skin ulcers [13, 14]. Recently, ESWT was also effectively used as treatment for angina pectoris [15].

Methods

From September 2010 to June 2012, we applied ESWT to 8 patients suffering from relapsing-remitting MS, who had developed painful panniculitis at the injection sites of either IFN- β or GA. Written informed consent explaining the procedure as well as the aim of the ESWT and the follow-up was obtained. Clinical presentation (localization, size, aspect, induration) of the skin lesions was recorded in a standardized case report form. Photo documentation was performed when skin changes were visible, e.g. hyperpigmentation, livedo reticularis and/or lipatrophy. No biopsies were taken. Subjective pain and clinical induration of the skin lesions were assessed using a visual analogue scale (VAS, scored 1–10). ESWT was applied once a week for a cycle of 5 sessions in an outpatient setting. All patients completed this cycle of treatment. All ESWT sessions were conducted by two operators using a Duolith[®] SD1 device (Storz Medical AG, Switzerland). We delivered 2,000 shots with an energy flux rate of 0.25 mJ/mm² and a pulse frequency of 4 Hz over an area of maximum 100 cm². The treatment area was targeted on the most painful or most indurated lesion. To improve conduction, ultrasound gel was applied. No analgesic premedication was necessary. Treatment tolerance and the occurrence of side effects were noted. The treatment lasted between 15 and 30 min. The clinical follow-up was done 3 and 6 months after completion of the 5 ESWT sessions. Statistical analysis was performed using the Wilcoxon signed-rank test. *p* values <0.05 were considered statistically significant.

Results

Eight female patients suffering from MS were included. The age ranged from 24 to 58 years (median of 42 years). Six patients were treated with IFN- β (2 Rebif[®], 4 Betaferon[®]) and 2 patients with GA (Copaxone[®]). The treatment with IFN- β and GA was continued after instruction of the optimal injection technique and rotation of injection sites.

Five patients treated with IFN- β showed painful subcutaneous nodules (0.5–2 cm in diameter) on the thighs laterally or the abdomen (fig. 1), whereas 1 patient showed indurated plaques (10 cm in diameter) on both thighs lat-



Fig. 1. Local cutaneous injection site reaction. Inflammatory plaques after subcutaneous injection of IFN- β .



Fig. 2. Local cutaneous injection site reaction. Lipatrophy after subcutaneous injection of GA

erally. Assessment after 3 and 6 months following ESWT showed full remission of the skin lesions in 4 patients and partial remission in 2. Clinically a decrease in the skin induration was palpable resulting in softer and more elastic skin in the treated areas.

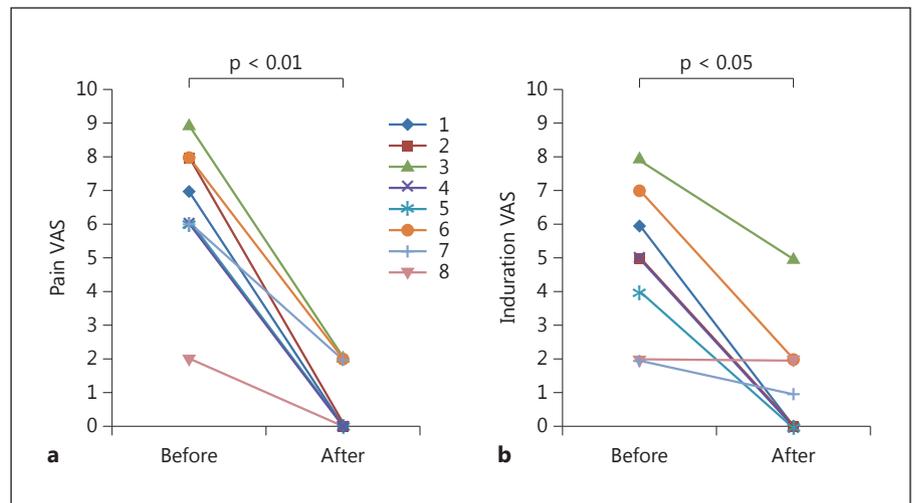


Fig. 3. a Pain VAS. **b** Induration VAS.

The 2 patients treated with GA showed lipatrophy ventrally on the thighs with deep painful indurations (fig. 2). After completion of ESWT an improved local sensory reception with decrease in pain and restored general well-being was reported. The lipatrophy, however, persisted.

Before ESWT all patients complained about lesional dysaesthesia and allodynia. In 4 of the 8 patients the first ESWT session was already followed by pain reduction. Immediately after the fifth ESWT session all patients reported a significant pain decrease. Figure 3a summarizes the significant decrease in the pain VAS score. The regression of induration was scored with a system analogous to the VAS from 1 to 10, 10 representing the most indurated finding (fig. 3b).

In comparison to the treated lesions, no clinical difference was found in the untreated lesions.

The ESWT was generally well tolerated. The only side effects during the application of the shock waves were transient electric sensations and mild pain especially in areas with little subcutaneous tissue and underlying bone. Overall patient satisfaction was considerably high and most of the patients wished to continue ESWT in further affected areas.

Discussion

Injection of IFN- β or GA can cause cutaneous adverse events. Transient painful local erythema after subcutaneous injection of IFN- β or GA is the most common cutaneous side effect, which occurs in up to 60% of the patients. Local pain and inflammation at the injection sites

are also described. The symptoms may occur after a few weeks or up to several years following initiation of the therapy [16]. Women show a greater risk to develop such skin reactions, with an 8.1:1 ratio [17]. The local skin reaction is influenced by the technique and depth of the injection [18]. It was observed that injection sites on arms and thighs develop skin reactions more frequently than areas with a higher proportion of subcutaneous fat tissue [19]. Severe local skin reactions such as panniculitis and lipatrophy are probably more frequent than assumed, with an occurrence of up to 40% [5]. The pathophysiology is not fully understood. It is assumed that the high immunogenicity of IFN- β and GA causes a local cytokine imbalance. The release of pro-inflammatory cytokines and chemokines leads to a recruitment of T cells and macrophages, resulting in a local inflammatory reaction [20]. Furthermore, the drugs themselves can induce a local inflammatory response through both a direct toxic effect on the adipocytes and a hypersensitivity reaction. In this process vasospasms and thrombogenesis can follow, which may lead to necrosis and even ulceration. Subsequent postinflammatory septal fibrosis and fat lobule atrophy cause residual lipatrophy [21]. Histological findings mostly show a lobular panniculitis with perivascular lymphocyte infiltrates similar to panniculitis induced by insulin injection or to lupus panniculitis [5, 22].

These adverse events of the immunomodulating MS drugs can impair the patient's quality of life to such an extent that not infrequently they request cessation of the therapy despite a proper clinical response to the medication [23]. To maintain quality of life and to ensure the

patient's compliance and adherence to the therapy, it is essential on one hand to inform the patient about these potential adverse events of the treatment, but on the other hand to deal with them promptly and efficiently. However, the treatment of these cutaneous side effects is difficult. Instruction of proper handling of the injection is essential. It is recommended to let the medication warm up to room temperature prior to injection. One should avoid droplets on the cannula and inject perpendicularly to the skin [24]. It is reported that auto-injectors can reduce local reactions in about 60% [25, 26]. A switch from subcutaneous to intramuscular application can be considered, since fewer inflammatory reactions were observed with intramuscular injection [27, 28]. Zecca et al. [29] reported about minimizing skin reactions by halving the volume of the IFN-1 β _{1b} diluent (0.54% sodium chloride solution). Superficial redness of the skin occurring directly after injection can be treated with the use of cold packs and application of topical corticosteroid ointment, preferably under occlusion. Treatment of panniculitis is rather difficult and challenging. Topical corticosteroid ointments are of limited value. The only approach mentioned in the literature for severe cutaneous side effects is the use of endermology to treat injection-induced lipatrophy [30].

In this observational proof of concept study without blinded assessment we were able to demonstrate the efficacy of ESWT for painful injection site panniculitis in 8 MS patients. Operation of the ESWT device is easy due to its hand piece resembling an ultrasound scanner. The applicator used had a diameter of 6 cm. Its flexibility enables the use in a wide range of cutaneous localizations. The treatment itself is usually well tolerated with no severe side effects occurring during and following ESWT. A significant reduction of pain was observed immediately after completion of the therapy with a lasting effect in the follow-up visits. After 6 months the pain VAS and induration VAS decreased significantly. Off course, at the present time the small number of patients limits the validity and significance of the data.

Several studies over the last 10 years have shown that ESWT promotes angiogenesis, increases perfusion in ischaemic tissues, decreases inflammation, enhances cell differentiation and accelerates wound healing [31–33]. The hypothesis behind these biological reactions is that shockwaves trigger a response in body cells, which is called biomechanical transduction [34]. Kuo et al. [35] demonstrated an increased tissue perfusion with neo-angiogenesis through higher expression of vascular endothelial growth factor and endothelial nitric mono-oxide

synthetase. Furthermore, suppression of local inflammatory reactions as well as upregulation of cell proliferation, especially in fibroblasts and keratinocytes, have been observed. These effects are related to membrane hyperpolarization, activation of rat sarcoma protein [31] and upregulation of growth hormones, mainly transforming growth factor- β ₁ and vascular endothelial growth factor [32, 33]. The mechanism of the analgesic effect of ESWT is not yet clear. Rompe et al. [36] supposed an analgesic effect by overstimulation and changes in permeability of nerve cell membranes [37]. Furthermore Hausner et al. [38] provided evidence of improved axonal regeneration of peripheral nerves in the rat.

Up to now no severe adverse events of ESWT have been reported.

Conclusion

ESWT is a non-invasive, practical, safe and efficient physical treatment modality for deep-seated cutaneous inflammatory injection-site reactions such as painful panniculitis in MS patients. The use of ESWT for panniculitis originating from other aetiologies remains to be studied.

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Disclosure Statement

All authors declare no conflict of interest.

References

- 1 National Collaborating Centre for Chronic Conditions: Multiple Sclerosis: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London, Royal College of Physicians, 2004.
- 2 Myhr KM, Mellgren SI: Corticosteroids in the treatment of multiple sclerosis. *Acta Neurol Scand Suppl* 2009;189:73–80.
- 3 Panitch H, et al: Randomized, comparative study of interferon beta-1a treatment regimens in MS: the EVIDENCE trial. *Neurology* 2002;59:1496–1506.
- 4 Berger JR: Functional improvement and symptom management in multiple sclerosis: clinical efficacy of current therapies. *Am J Manag Care* 2011;17(suppl 5):S146–S153.

- 5 Weise G, et al: Lobular panniculitis and lipoatrophy of the thighs with interferon- β 1a for intramuscular injection in a patient with multiple sclerosis. *J Clin Neurosci* 2012;19:1312–1313.
- 6 Mayer C, Dorfmueller C, Lachat M: Die extrakorporale Stosswellentherapie als neue Methode zur Stimulation der Heilung komplexer Wunden: eine Übersicht. *Z Wundh* 2009;1:232–237.
- 7 Chaussy C, et al: First clinical experience with extracorporeally induced destruction of kidney stones by shock waves. *J Urol* 1982;127:417–420.
- 8 Lee SS, et al: Effectiveness of initial extracorporeal shock wave therapy on the newly diagnosed lateral or medial epicondylitis. *Ann Rehabil Med* 2012;36:681–687.
- 9 Ji HM, Kim HJ, Han SJ: Extracorporeal shock wave therapy in myofascial pain syndrome of upper trapezius. *Ann Rehabil Med* 2012;36:675–680.
- 10 Radwan YA, Mansour AM, Badawy WS: Resistant plantar fasciopathy: shock wave versus endoscopic plantar fascial release. *Int Orthop* 2012;36:2147–2156.
- 11 Wang CJ: Extracorporeal shockwave therapy in musculoskeletal disorders. *J Orthop Surg Res* 2012;7:11.
- 12 Valchanou VD, Michailov P: High energy shock waves in the treatment of delayed and nonunion of fractures. *Int Orthop* 1991;15:181–184.
- 13 Schaden W, et al: Shock wave therapy for acute and chronic soft tissue wounds: a feasibility study. *J Surg Res* 2007;143:1–12.
- 14 Mittermayr R, et al: Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. *Wound Repair Regen* 2012;20:456–465.
- 15 Schmid JP, et al: Cardiac shock wave therapy for chronic refractory angina pectoris. A prospective placebo-controlled randomised trial. *Cardiovasc Ther* 2013;31:1–6.
- 16 Bayas A, Gold R: Lessons from 10 years of interferon beta-1b (Betaferon/Betaseron) treatment. *J Neurol* 2003;250(suppl 4):IV3–IV8.
- 17 Gaines AR, Varricchio F: Interferon beta-1b injection site reactions and necroses. *Mult Scler* 1998;4:70–73.
- 18 Inafuku H, et al: Cutaneous ulcerations following subcutaneous interferon beta injection to a patient with multiple sclerosis. *J Dermatol* 2004;31:671–677.
- 19 Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and the University of British Columbia MS/MRI Analysis Group. *Neurology* 1995;45:1277–1285.
- 20 Buttman M, et al: Subcutaneous interferon-beta injections in patients with multiple sclerosis initiate inflammatory skin reactions by local chemokine induction. *J Neuroimmunol* 2005;168:175–182.
- 21 Soares Almeida LM, et al: Localized panniculitis secondary to subcutaneous glatiramer acetate injections for the treatment of multiple sclerosis: a clinicopathologic and immunohistochemical study. *J Am Acad Dermatol* 2006;55:968–974.
- 22 Ball NJ, et al: Lobular panniculitis at the site of glatiramer acetate injections for the treatment of relapsing-remitting multiple sclerosis. A report of two cases. *J Cutan Pathol* 2008;35:407–410.
- 23 O'Rourke KE, Hutchinson M: Stopping beta-interferon therapy in multiple sclerosis: an analysis of stopping patterns. *Mult Scler* 2005;11:46–50.
- 24 Girouard N, Theoret G: Management strategies for improving the tolerability of interferons in the treatment of multiple sclerosis. *Can J Neurosci Nurs* 2008;30:18–25.
- 25 Brochet B, Lemaire G, Beddiaf A: Reduction of injection site reactions in multiple sclerosis (MS) patients newly started on interferon beta 1b therapy with two different devices (in French). *Rev Neurol (Paris)* 2006;162:735–740.
- 26 Lugaesi A, et al: Safety and tolerability in relapsing-remitting multiple sclerosis patients treated with high-dose subcutaneous interferon-beta by Rebiject autoinjection over a 1-year period: the CoSa study. *Clin Neuropharmacol* 2008;31:167–172.
- 27 Milanese C, et al: A post-marketing study on interferon beta 1b and 1a treatment in relapsing-remitting multiple sclerosis: different response in drop-outs and treated patients. *J Neurol Neurosurg Psychiatry* 2003;74:1689–1692.
- 28 Beer K, et al: The prevalence of injection-site reactions with disease-modifying therapies and their effect on adherence in patients with multiple sclerosis: an observational study. *BMC Neurol* 2011;11:144.
- 29 Zecca C, Yawalkar N, Gobbi C: Improvement of interferon-beta related skin reactions after diluent halving: first experience of five patients. *Patient Prefer Adherence* 2012;6:565–567.
- 30 Lebrun C, et al: Endermology: a treatment for injection-induced lipoatrophy in multiple sclerosis patients treated with subcutaneous glatiramer acetate. *Clin Neurol Neurosurg* 2011;113:721–724.
- 31 Wang FS, et al: Physical shock wave mediates membrane hyperpolarization and Ras activation for osteogenesis in human bone marrow stromal cells. *Biochem Biophys Res Commun* 2001;287:648–655.
- 32 Huemer GM, et al: Comparison of the effectiveness of gene therapy with transforming growth factor-beta or extracorporeal shock wave therapy to reduce ischemic necrosis in an epigastric skin flap model in rats. *Wound Repair Regen* 2005;13:262–268.
- 33 Meirer R, et al: Comparison of the effectiveness of gene therapy with vascular endothelial growth factor or shock wave therapy to reduce ischaemic necrosis in an epigastric skin flap model in rats. *J Plast Reconstr Aesthet Surg* 2007;60:266–271.
- 34 Yan X, et al: Improvement of blood flow, expression of nitric oxide, and vascular endothelial growth factor by low-energy shock-wave therapy in random-pattern skin flap model. *Ann Plast Surg* 2008;61:646–653.
- 35 Kuo YR, et al: Extracorporeal shock-wave therapy enhanced wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes. *Wound Repair Regen* 2009;17:522–530.
- 36 Rompe JD, et al: Analgesic effect of extracorporeal shock-wave therapy on chronic tennis elbow. *J Bone Joint Surg Br* 1996;78:233–237.
- 37 Maier M, et al: Dose-related effects of extracorporeal shock waves on rabbit quadriceps tendon integrity. *Arch Orthop Trauma Surg* 2002;122:436–441.
- 38 Hausner T, et al: Improved rate of peripheral nerve regeneration induced by extracorporeal shock wave treatment in the rat. *Exp Neurol* 2012;236:363–370.