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ARE TOXIC OXYGEN RADICALS INVOLVED IN THE PATHOGENESIS OF REFLEX SYMPATHETIC DYSTROPHY?

R.J.A. GORIS,† L.M.V. DONGEN and H.A.H. WINTERS

Catholic University, Nijmegen

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A crossover study was performed for patients with RSD to evaluate the therapeutic efficacy of the hydroxyl radical scavenger DMSO. All patients were given DMSO locally 5 times a day during one week, and a placebo during one week. Before and after each treatment, subjective evaluation was performed by both the patient and the examinor as to clinical activity of RSD, and measurement was performed of the range of motion (ROM) of all joints in the affected extremity.

DMSO was the most effective treatment as to improvement of ROM ($p = 0.035$) and as to overall improvement ($p = 0.001$). The efficacy of the hydroxyl radical scavenger DMSO indicates that RSD primarily involves an inflammatory process rather than a sympathetic reflex. As during the last 20 years no single report was published studying RSD in terms of inflammation, it is suggested that such studies are urgently needed to elucidate the real nature of RSD.

KEY WORDS: Reflex sympathetic dystrophy, Sudeck's atrophy, toxic oxygen radicals, hydroxyl radical scavenger, DMSO, inflammation.

INTRODUCTION

Reflex Sympathetic Dystrophy (RSD) is a poorly understood syndrome occurring in about 5% of injured patients.[1] It is a major cause of prolonged disability and pain after injury, and often results in permanent loss of function and even of employment.[2,3]

The pathogenesis has been linked with the sympathetic system but remains obscure, and hitherto no treatment has proved uniformly successful.[1] Even interference with the sympathetic system by regional guanethidine infusion, sympathetic blocks or sympathectomy is independable.[2,3] Though Mitchell[4] in his original work on causalgia pointed out an inflammatory component and Sudeck,[5,6] throughout his life defended the view that this syndrome concerned an untoward inflammatory response to injury, the inflammatory theory presently has no adherents. This is the more puzzling as most symptoms during the early stages of RSD can be summarized as rubor, calor, dolor, tumor and functio laesa, occurring also in areas remote from the primary injury, and as all these symptoms increase in severity by exercising the affected extremity.

Inflammatory responses involve the production of toxic oxygen free radicals by activated fagocytic cells.[7] This response is normally aimed at suppressing the inflam-

† Address for correspondence: Prof. Dr. R.J.A. Goris, Department of General Surgery, University Hospital St Radboud, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

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matory stimulus, but an untoward excessive production of oxygen radicals might result in destruction of healthy tissue as well.[8]

We hypothesized that RSD might be caused by an excessive untoward local inflammatory response to trauma, whereby some unknown stimulus induces the continuous production of toxic oxygen radicals, resulting in destruction of healthy tissue including skin, subcutaneous tissue, muscle, tendon sheaths, ligaments, joint capsules, bone, and peripheral nerves.

Though the role of the hydroxyl radical in pathological processes has not been clearly established hitherto, the hydroxyl radical scavengers dimethyl sulfoxide (DMSO) and Mannitol were used tentatively in a pilot study with 9 RSD patients, and seemed effective in suppressing the acute inflammatory signs.[9] This study concerns a prospective crossover study in 20 patients with RSD to evaluate the therapeutic efficacy of the hydroxyl radical scavenger DMSO. The therapeutic efficacy of this anti-inflammatory treatment could be confirmed.

MATERIALS AND METHODS

Within the period October 1984–April 1985 20 patients presenting at our outpatient department with a diagnosis of Sudeck were entered into the trial. A diagnosis of RSD may be made on the following basis.

1) Symptoms of inflammation: rubor, calor, dolor, tumor, loss of active range of motion (ROM). These symptoms of inflammation increase with exercising the affected extremity.

2) The symptoms involve areas remote from the primary injury.

3) Abnormal hair growth, abnormal nail growth, hyperhydrosis, palmar fasciitis.

4) Atrophy of skin, subcutaneous tissue, muscle, etc.

The pilot study showed that hair growth, nail growth, hyperhydrosis, and palmar fasciitis are not uniformly present. The presence of atrophy is only typical for the late stage of RSD. We did not utilize these symptoms for selection. We selected only patients with at least four out of six symptoms of inflammation, and with involvement of areas remote from the primary injury.

Excluded from the trial were all patients needing treatment for a condition obviously related to the genesis of RSD such as a delayed union, presence of trigger point, etc. Also excluded were patients with open wounds, skin ulcers, or infection in the affected area, because DMSO might interfere with their healing. After gaining informed consent, the patients were randomized as to starting with the placebo or DMSO.

Treatment consisted of locally painting the affected extremity 5 times a day with a solution provided by the hospital pharmacy in identical bottles marked treatment A or treatment B. The bottles contained either DMSO 50% in water or plain water. As dimethyl sulfoxide has an onion-like smell well-known to the researchers, the study could not be performed double-blinded. The patients were not informed about the content of the bottles.

DMSO and placebo were given for one week each, so the trial period concerned fourteen days. During this period all other treatments were stopped, including physiotherapy. The patient was instructed to exercise actively, within the limits of pain, twice an hour during a few minutes.

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On days, 0, 7 and 14 all patients were examined according to a standard protocol including subjective assessment of all six symptoms of inflammation and measurement of total active range of motion (ROM) in all individual joints of the affected extremity. Color slides with standard exposure in 8 standard positions were made, and ninhydrin tests performed each time.

After finishing both treatments, patient and researcher were requested to indicate the preferred treatment, based on clinical symptoms of inflammation. Objective evaluation was possible due to the systematic measurement of ROM.

Statistical methods

The percentage of preferences for one of both treatments amongst the patients was tested against 50%, utilizing the sign test. If the resulting p-value was below 0.05, the difference in both preference percentages is called significant.

RESULTS

21 patients were entered into the trial, as one had to be replaced because the patient failed to comply to the protocol. Of the 20 patients, 5 were male and 15 female. The average age was 45 (22–84 years). Seven patients were referred to our clinic because of RSD not responding to classical treatment. The duration of RSD was 1 month in 2 patients, 1–2 months in 10 patients, 3–6 months in 5 patients, and 1.5–, 2.5–, and 6 years in 1 patient each. RSD was present in the hand in 15 patients, in the foot in 3 patients and was limited to 1 finger in 2 patients. The primary injury was a Colles fracture in 5 patients, stenosing tendovaginitis in 3, a panaritium tendineum in 1, finger fracture in 3, a contusion or distortion in 3, a tennis elbow operation in 1, osteosynthesis because of an ankle fracture in 1, a mallet finger in 1, an extensor tendon lesion in 1, and an arthrodesis of the metacarpophalangeal joint I in 1 patient. There was no relation whatsoever between the severity of the primary injury or the

TABLE I

Symptoms in 20 patients with RSD at time of first examination

1. Symptoms of inflammation	
rubor	19
calor	18
dolor	16
tumor	19
functio laesa	17
increasing with exercise	20
2. nail growth	8
hair growth	10
hyperhydrosis	14
palmar fasciitis	5
3. atrophy	4*

* = duration of RSD: 8 weeks, 9 weeks, 5 months, 6 years

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TABLE II

Results of subjective and objective evaluation

	placebo better	DMSO better	no difference
– subjective (patient)	1	13	6
– subjective (researchers)	1	16	3
– increase in R.O.M.	3	12*	2 (3***)
CONCLUSION	1	15**	4

* sign test: $p = 0.035$
** sign test: $p = 0.001$
*** 3 patients had a normal R.O.M. throughout the study period

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accuracy of primary treatment and the severity of RSD. The symptoms found by us at the primary examination are given in Table I.

The results of the treatment are given in Table II. As the range of motion was normal in 3 patients at the outset of the trial, no judgement was possible in this respect. The best treatment was DMSO in 15 cases, the placebo in 1 case, and no difference was found in 4 cases. The patient who responded better to the placebo was continued on DMSO after finishing the trial and healed completely. In the 4 patients in whom no difference was found, three healed completely on DMSO after finishing the trial. The fourth patient showed intensive fibrosis due to injury. In the 17 patients with limited ROM, 8 improved on placebo while 5 showed no change and 4 deteriorated. The average gain in ROM was 41°. On DMSO, the ROM improved in 15 patients, showed no change in 2, and deteriorated in none. The average gain in ROM was 100° (Table III).

In the placebo group 515° out of the total 798° improvement in ROM occurred in 2 patients, respectively 280° and 235°. Both patients started with the placebo treatment and in both painful passive physiotherapy was stopped according to the protocol at the start of the trial.

The patients were continued on DMSO after the end of the 2 week period of the trial, and followed up until it was established that no relapse occurred after fading out and stopping the treatment. Complete cure was obtained in 15 patients. In 3 patients a limited ROM was present due to fibrosis, once in 1 finger due to injury, once in a PIP-joint of a patient with a RSD of 5 months duration and once in 3 fingers in a patient with a RSD of 6 years duration. Persistent pain was present in 2 patients, once due to a neurinoma in the palm of the hand, and once due to RSD in the patient with RSD of 6 years duration. After the acute symptoms of RSD had disappeared, 7 patients needed additoinal treatment: 3 patients to infiltrate a painful trigger point, which only became evident after the RSD resolved, 1 patient to remove a neurinoma, and 3 patients for flexor or extensor tendon release because of sequelae of the primary injury.

In these patients needing secondary surgery, the operation was performed without bloodless field and under the protection of a continuous infusion of Mannitol. In 1 patient the RSD recurred after stopping the Mannitol, but promptly resolved after resuming this treatment.

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TABLE III

Results as to change in R.O.M. (17 patients)

	improved	deteriorated	no change	average gain in R.O.M. in 1 week
placebo	8	4	5	41
DMSO	15	–	2	100

DISCUSSION

Performing a study on RSD is difficult because most symptoms are subjective for the patient as well as for the examiner. Also the symptoms change from day to day and even from hour to hour. This was most manifest in analysing the ninhydrin tests, which show tremendous variations from one day to the other. The most reliable parameters were increase of symptoms with exercising the extremity, and measurement of ROM in all joints of the affected extremity. It also was important to relate the symptoms to the activities of the patient. Because the complaints decreased, quite a number of patients performed more activities resulting in the same amount of complaints but at a higher functional level. The efficacy of hydroxyl radical scavengers in the treatment of RSD confirms the view of Sudeck that RSD in fact is an untoward inflammatory response. The lack of consistent success in 1 patient with RSD of long standing suggests that in late cases permanent nerve damage may be present. In fact this patient's pain responded positively but only during short periods to stellate ganglion blockade.

Lastly it should be stated that treating RSD with hydroxyl radical scavengers is not a panacea. It is the more effective as the diagnosis is established earlier. In late cases, fibrosis will not resolve and even the pain may persist. Also all possible causes related to RSD should be carefully looked for and treated, such as trigger points, undiagnosed or unhealed fractures, stenosing tendovaginitis, carpal tunnel syndrome etc. Passive physiotherapy should be immediately stopped and the patient should be instructed to exercise actively within the limits of pain. Also the activities of the patient should be carefully regulated according to the symptoms of inflammation. Every increase in the inflammatory signs indicates that the patient has been doing too much. Even with the help of DMSO and Mannitol, the patient should be told that the rehabilitation period will be long and can not be forced without detrimental results. Our findings indicate that RSD in first instance is not a disease of the sympathetic nervous system, and should be studied in terms of inflammation.

CONCLUSIONS:

The therapeutic efficacy of the hydroxyl radical scavenger DMSO in the early phase of RSD, indicates that an untoward inflammatory reaction is involved, rather than (only) a sympathetic reflex.

Sudeck unsuccessfully defended this inflammatory theory throughout 42 years.

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