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Quantitative three-phase bone scintigraphy in the evaluation of intravenous regional blockade treatment in patients with stage-I reflex sympathetic dystrophy of upper extremity

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Objective: To investigate the role of quantitative three phase bone scintigraphy (QTPBS) in the evaluation of efficacy of intravenous regional blockade treatment in patients having reflex sympathetic dystrophy (RSD) of the upper extremity. ***Material and Methods:*** Twenty-six patients with stage-I RSD were focused on in this study. Patients were treated with physical therapy and intravenous (I.V.) regional blockade therapy consisting of dexamethasone and lidocaine. All patients were clinically evaluated before and 1 month after the completion of the therapy protocol. QTPBS was applied to patients before therapy and 1 month after the therapy. As a control group, 11 healthy subjects also underwent QTPBS. Perfusion, hyperemic and fixation indices were calculated from three-phase bone scintigraphy. ***Results:*** All patients showed statistically significant clinical improvement after the therapy ($p < 0.01$). Pre-treatment, perfusion (1.67 ± 0.63), hyperemic (1.44 ± 0.48) and fixation (1.69 ± 0.48) indices of patients were higher than those of healthy subjects (PI: 0.95 ± 0.05, HI: 0.94 ± 0.06, FI: 1.01 ± 0.2) ($p < 0.01$) and all indices significantly decreased after the treatment (PI: 1.33 ± 0.46, HI: 1.18 ± 0.23, FI: 1.42 ± 0.26) ($p < 0.01$). ***Conclusion:*** I.V. regional blockade therapy combined with corticosteroids is a simple, safe and effective method for the treatment of patients with stage-I RSD in the upper extremity. QTPBS is a valuable and objective method to evaluate the response to therapy and may be useful for staging of patients and predicting the response to therapy.

Key words: quantitative bone scintigraphy, reflex sympathetic dystrophy, blockade therapy, response evaluation

INTRODUCTION

Reflex sympathetic dystrophy (RSD) (algodystrophy, Sudeck's atrophy or complex regional pain syndrome) is a clinical syndrome, usually characterized by chronic or intermittent pain, swelling in a distal extremity, trophic skin changes and additional signs and symptoms of vasomotor and sudomotor instability.[1–3] Many diseases, precipitating events or drugs have been associated with RSD. Although trauma (especially fractures or peripheral nerve injuries) is accepted as the most common precipitant of RSD, it can also appear after myocardial infarction, or related to pancoast tumor, use of barbiturates/antituberculous drugs, or it can be idiopathic.[3–5] Three clinical stages (acute, dystrophic and atrophic) are defined for RSD. Because the atrophic stage is usually the most refractory to therapy, early diagnosis and start to treatment in the acute stages are the goal of management in RSD.[3,6]

The diagnosis of RSD is made primarily on clinical grounds. However, there is no consensus regarding an objective marker for its diagnosis. It has been shown that

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Table 1 Classification and clinical criteria for the RSD[3]

Definite
1. Pain associated with allodynia or hyperpathia
2. Tenderness
3. Vasomotor and sudomotor changes
Cool, palid extremity (vasospasm)
Warm, erythematous extremity (hyperemia)
Hyperhidrosis or hyper trichosis
4. Dystrophic skin changes
Shiny skin with loss of normal wrinkling
Atrophy
Scaling
Nail changes (color, friable)
Thickened palmar/plantar fascia
5. Swelling (pitting or nonpitting edema)
Probable
1. Pain and allodynia
2. Vasomotor or sudomotor changes
3. Swelling
Possible
1. Vasomotor or sudomotor changes
2. Swelling

Table 2 Staging of RSD14

Stage I
Duration of weeks to months. The limb has non-focal pain, swelling with associated joint stiffness and decreased range of motion. There are increased skin temperature and pain peaks at the end of this period.
Stage II
Duration of 3–6 months. Pain continues but decreases over time. Swelling involves into thickening of the dermis and fascia. The extremity becomes cooler. Early signs of atrophy and osteoporosis become evident.
Stage III
Atrophic stage. Pain persists, atrophy is exacerbated with continued decreased range of motion and increased joint stiffness. The extremity demonstrated decreased vascularity and is cooler.

three-phase bone scintigraphy (TPBS) is the most useful objective test for the diagnosis of RSD[7–10] as increased activity in all phases of TPBS suggesting RSD. On the other hand, evaluation of the response to therapy in RSD is still challenging, and the utility of TPBS for this purpose is controversial.[11–13]

The objective of this study is to determine whether quantitative three-phase bone scintigraphy (QTPBS) can be used as an objective criterion for determining the efficacy of intravenous regional blockade therapy in patients having RSD of the upper extremity.

MATERIALS AND METHODS

Subjects

Twenty-six patients (mean age: 29.7, 20 male, 6 female) having definitive clinical criteria (Table 1)[3] and 11 healthy subjects (mean age: 24, 11 male) were focused on in this study. All patients had stage I RSD with symptoms persisting for less than three months[14] (Table 2). The clinical features of the patients are given in Table 3. The patients were randomly selected and treated with intravenous regional blockade consisting of dexamethasone (4 mg) and Lidocaine (5 m*l*). Three to five regional blockades were performed in each patient at one-week intervals.[15] All these patients also underwent standard physical therapy (5 days per week, total 20 sessions, consisting of contrast bath, exercise, ultrasonic therapy on stellate ganglion). All patients were clinically evaluated before and 1 month after the completion of the therapy protocol. QTPBS was applied to patients before therapy and 1 month after the therapy. As a control group, 11 healthy subjects also underwent QTPBS.

Clinical Evaluation

All patients were evaluated clinically according to the following criteria:

1. Spontaneous and exertional pain: Present pain intensity and pain resulting from effort were evaluated using a visual analog scale method with 101 units and scored (0 no pain, 100 most severe pain).
2. Local temperature differences between hands were measured with an electronic thermometer in °C.
3. Finger to palm distance was measured with a ruler in cm.
4. Functional capacity: Functional capacity was scored during handwriting, paper holding and key turning (0: no function, 1: function not completed due to pain, 2: function completed with pain, 3: full function).

Quantitative Three Phase Bone Scintigraphy

740 MBq (20 mCi) Tc 99m Methylene diphosphonate (MDP) was injected from the unaffected antecubital vein. The injection was delayed at least 1 minute after tourniquet release to prevent reactive hyperemia.[16] Forty dynamic frames (2 sec/frame, 64 × 64 matrix) were acquired with the patient's palms facing down on the surface of a GE 400 ACT gamma camera system equipped with a general purpose collimator. Five-min static images (256 × 256 matrix) were obtained at 3–5 min (blood pool image) and 3 hours (delayed image) after injection of MDP.

Processing of images: Frames of dynamic images were reframed. Simultaneous symmetric, rectangular regions of interest (ROIs) were placed on both affected and healthy wrist-hand complexes on reframed images and dynamic images. Separate time-activity curves of these ROIs were generated and the area under these curves

Table 3 Clinical features of patients

n	Age	Sex		Precipitating factors					
		M	F	Fracture	Trauma	SI*	Infection	SGI**	Idiopathic
26	29.7	20	6	16	6	1	1	1	1

*SI: surgical intervention, **SGI: shot gun injury

Table 4 Comparison of clinical results of patients

Parameter	Pre-Rx*	Post-Rx**	p-value
Spontaneous pain	36.20 ± 5.22	12.4 ± 4.16	< 0.01
Exertional pain	55.2 ± 5.16	17.60 ± 3.2	< 0.01
Temperature	0.44 ± 0.05	0.14 ± 0.03	< 0.01
Finger-palm distance	3.56 ± 0.41	0.43 ± 0.16	< 0.01
Hand writing	1.56 ± 0.16	2.95 ± 0.15	< 0.01
Paper holding	1.81 ± 0.16	2.14 ± 0.09	< 0.01
Key turning	1.42 ± 0.15	2.98 ± 0.08	< 0.01

*Pre-Rx: pre therapy, **Post-Rx: post therapy

Table 5 Perfusion, hyperemic and fixation indices in patients with RSD before and after therapy and control subjects

	PI^{+}	HI^{++}	FI^{+++}
Control subjects* (11 subjects)	0.95 ± 0.05	0.94 ± 0.06	1.01 ± 0.2
RSD patients**			
Before therapy	1.67 ± 0.63	1.44 ± 0.48	1.69 ± 0.48
After therapy (1 mo)	1.33 ± 0.46	1.18 ± 0.23	1.42 ± 0.26

$^{+}$PI: perfusion index, $^{++}$HI: hyperemic index, $^{+++}$FI: fixation index

* Differences were statistically significant for RSD patients and normal group (Mann Whitney U test, $p < 0.01$)

** Differences were statistically significant between before and after therapy values (Paired samples t-test, $p < 0.01$)

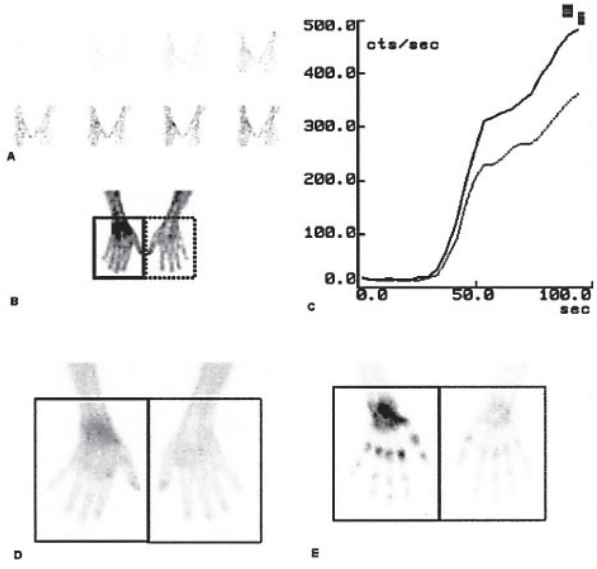

Fig. 1 Processing of three-phase bone scintigraphy in a patient before therapy. A: Perfusion phase, B: ROI placement on the perfusion image, C: Time-activity curve, D: Blood-pool image and ROI placement, E: Delayed image and ROI placement. Dynamic scintigraphy reveals increased perfusion in the right upper extremity. The right extremity shows persisted lateralization in blood pool phase and increased periarticular uptake in delayed image (PI: 1.59, HI: 1.57, FI: 1.90).

(AUC) was computed. Perfusion index (PI) was calculated by dividing the AUC of the affected side by that of the healthy side. Symmetric, rectangular ROIs were placed on both affected and healthy wrist-hand complexes on blood-pool and delayed images. In each of the ROIs, the average number of counts was recorded. Uptake ratios were calculated by dividing the average counts of the affected hand by those of the corresponding mirror region in the healthy hand. Uptake ratios of blood pool images were defined as hyperemic index (HI) and ratios of delayed images were defined as fixation index (FI) (Fig. 1).

Statistical analysis

All results are expressed as mean ± SD. Quantitative indices were normally distributed as ascertained by the Kolmogorov-Smirnof test. Statistical analysis was performed using the Mann-Whitney U test and paired samples t-test as appropriate. A p value <0.01 was considered statistically significant. All analysis were performed with Systat statistical package (SPSS, Chicago, IL).

RESULTS

Clinical Evaluation

All patients well tolerated the I.V. blockade therapy without any side effects. They showed statistically significant clinical improvement in both pain and functional capacity after therapy ($p < 0.01$, Table 4).

Scintigraphic Evaluation

Pre-treatment, perfusion (1.67 ± 0.63), hyperemic (1.44 ± 0.48) and fixation (1.69 ± 0.48) indices of RSD patients were significantly higher than those of healthy subjects (PI: 0.95 ± 0.05, HI: 0.94 ± 0.06, FI: 1.01 ± 0.2) ($p < 0.01$). All indices significantly decreased after treatment (PI: 1.33 ± 0.46, HI: 1.18 ± 0.23, FI: 1.42 ± 0.26) ($p < 0.01$, Table 5, Figs. 2, 3, 4, 5).

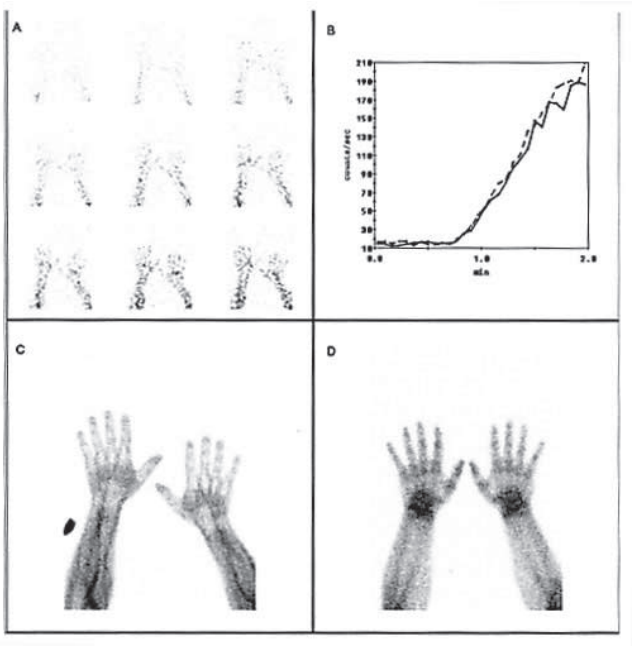

Fig. 2 Post therapy three-phase bone scintigraphy of patient in Figure 1. A: Perfusion phase, B: Time-activity curves of hands, C: Blood-pool image, D: Delayed image. Perfusion, blood pool and delayed images show normal appearance (PI: 1.08, HI: 0.99, FI: 1.04).

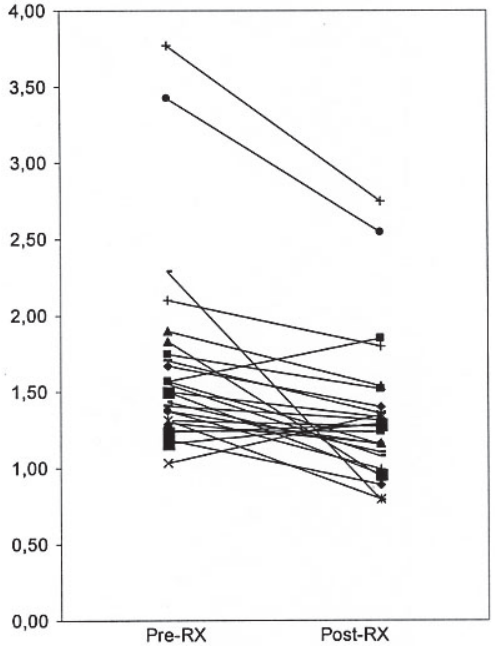

Fig. 3 Pre and post-treatment values of perfusion indices of patients.

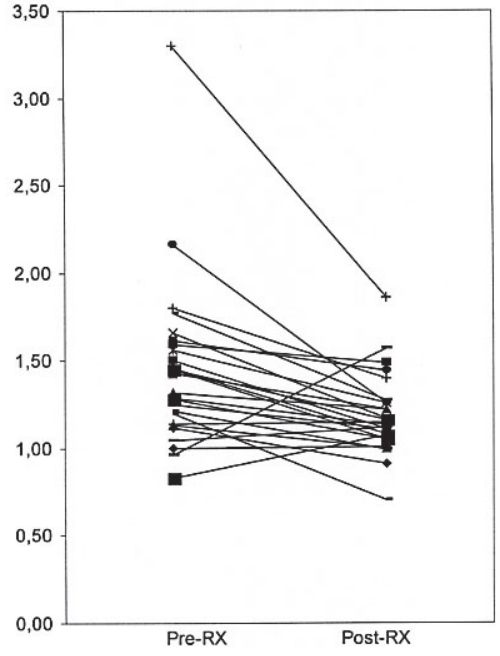

Fig. 4 Pre and post-treatment values of hyperemic indices of patients.

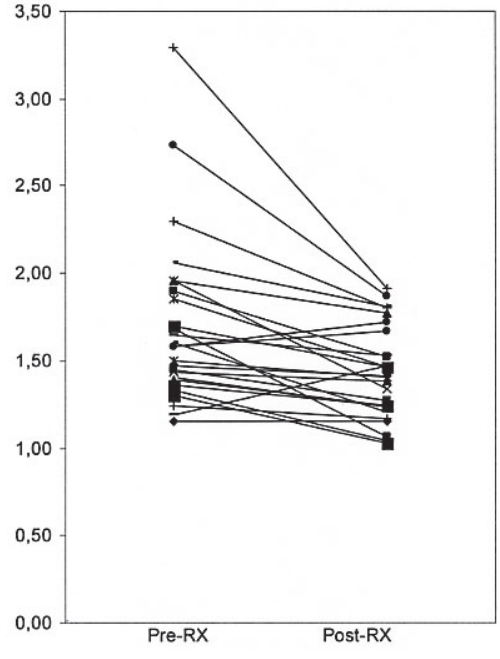

Fig. 5 Pre and post-treatment values of fixation indices of patients.

DISCUSSION

Bone scintigraphy is of major importance for the diagnosis of RSD. Some quantitative indices have been also used to obtain higher sensitivity and specificity.[9,17,18] TPBS is reported to be a sensitive test showing increased activity in all phases, Mackinon[8] and Werner[19] found that TPBS is not crucial in the diagnosis of RSD since delayed images are more sensitive than blood flow and blood pool images. On the other hand, there is strong evidence that

TPBS is affected by the stage of RSD. Patients with clinical stage-I RSD demonstrate increased blood flow and blood pool whereas those in clinical stage-II and III demonstrate normal, even reduced blood flow and blood pool activity.[9,20]

In this study, perfusion, hyperemic and fixation indices of RSD patients were higher than those of healthy patients. These indices are quantitative representations of increased blood flow, blood pool and metabolic activity and proof of clinical stage-I (acute phase) of RSD in our patient population.

RSD usually occurs secondary to trauma, and increased uptake may be related to the trauma rather than RSD. Atkins et al. tried to determine the nature of the increased uptake in patients with RSD of the hand precipitated by upper limb fracture and reported that increased uptake on delayed bone scintigraphy is due to RSD rather than the precipitating trauma.[10] It has been shown that quantification provides useful information regarding the natural history of the disorder and its response to therapeutic interventions.[9,10,17]

The mechanism of the increased uptake of bone seeking agents on the delayed images in RSD is unclear. Both animal studies and clinical findings support the concept of increased vascular flow as the cause of increased periarticular uptake.[21–23]

Because the incidence of poor response to treatment was significantly higher in patients with long duration of RSD (>12 months), in other words in those with the second and third stages of disease,[6] it is thought that the earlier therapy is initiated, the better will be the outcome in patients with RSD. Although prevention of the disorder is the main goal in the treatment of patients with RSD, there is no well-accepted therapeutic regimen or patient selection criteria for these patients. It seems that PI, HI and FI can be helpful in the management of patients with RSD in terms of both staging the disease and predicting the response to therapy. However, comparative studies with a sufficient number of patients and different stages have to be performed to confirm this observation.

The response to therapy seems unrelated to the initiating event or severity of trauma. Although sympathetic blockade and surgical sympathectomy are effective in pain relief in RSD patients, the application of these procedures is not easy. Therapy with systemic and local corticosteroids or calcitonin has been reported as alternative modalities.[3,18]

Poplawski et al.[15] described I.V. regional blockade therapy along with standard physical therapy in 1983. In the present study, substantial reductions in both exertion and spontaneous pain decrease in temperature and improvement in functional capacity of the affected hand were obtained with I.V. regional blockade therapy as also reported previously.[15,24,25] All patients possibly responded well to this therapy regimen, since they presented with stage-I disease and received early therapy in the acute phase. After blockade, our patients were able to perform exercise programs without any pain. Articular motion that is restricted due to hyperalgia improved and positive patient compliance observed in physical therapy and exercise programs.

Currently, the exact action of corticosteroids is unknown. It seems likely that they exert their beneficial effect by inhibiting release of inflammatory mediators, such as prostaglandins or kinins.[3]

Quantitative TPBS has confirmed the clinical response obtained with intravenous regional blockade therapy, and indices of all phases decreased significantly after treatment. Our findings are identical with the results of others where decreasing high pretreatment uptake was found after successful treatment of RSD.[9,13,18] The results of Demangeat[9] and Fialka[13] et al. showed that increased uptake in the late images during the control scintigraphy is a proof of the 'latent' form of the disease. Marked hyperfixation of the tracer at the initial scintigraphy indicates a good prognosis for the treatment outcome, while slightly increased fixation suggests a less good prognosis.[10] Kozin et al. also confirmed this observation.[7]

Our findings are not in line with the results of Zyluk and Birkenfeld where 49 treated and 16 untreated patients showed decreased uptake after treatment. They concluded that treatment had no significant effect on the decrease in uptake during the course of RSD, and TPBS had no value in monitoring the course of treatment of RSD.[11]

This study has several limitations. First, our patient population was not sufficiently large to make a more definitive conclusion. Additionally there is a strong bias in patient selection since all patients had stage-I disease. Our results need further evaluation in a larger patient population with different stages.

Conclusion: I.V. regional blockade therapy combined with corticosteroids is a simple, safe and effective method for the treatment of patients with stage-I RSD in the upper extremity. QTPBS is a valuable and objective method in the evaluation of response to therapy and may be useful for staging of patients and predicting the response to therapy.

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