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Amputation in patients with complex regional pain syndrome

A COMPARATIVE STUDY BETWEEN AMPUTEES AND NON-AMPUTEES WITH INTRACTABLE DISEASE

A. Midbari,
E. Suzan,
T. Adler,
E. Melamed,
D. Norman,
S. Vulfsons,
E. Eisenberg

From Rambam Health Care Campus

Aims

Amputation in intractable cases of complex regional pain syndrome (CRPS) remains controversial.

The likelihood of recurrent Complex Regional Pain Syndrome (CRPS), residual and phantom limb pain and persistent disability after amputation is poorly described in the literature. The aims of this study were to compare pain, function, depression and quality of life between patients with intractable CRPS who underwent amputation and those in whom amputation was considered but not performed.

Patients and Methods

There were 19 patients in each group, with comparable demographic details. The amputated group included 14 men and five women with a mean age of 31 years (SD 12) at the time of CRPS diagnosis. The non-amputated group consisted of 12 men and seven women and their mean age of 36.8 years (SD 8) at CRPS diagnosis. The mean time from CRPS diagnosis to (first) amputation was 5.2 years (SD 4.3) and the mean time from amputation to data collection was 6.6 years (SD 5.8).

All participants completed the following questionnaires: Short-Form (SF) 36, Short Form McGill Pain questionnaire (SF-MPQ), Pain Disability Index (PDI), the Beck Depression Inventory (BDI) and a clinical demographic questionnaire.

Results

The amputation group showed consistently better results compared to the non-amputation group in the following parameters: median pain intensity (VAS): 80 (inter-quartile range (IQR) 13 to 92) *vs* 91 (IQR 85 to 100); p = 0.007; median SF-MPQ score 28 (IQR 9 to 35) *vs* 35 (IQR 31 to 38), p = 0.025; median PDI: 42 (IQR 11 to 64) *vs* 58 (IQR 50 to 62), p = 0.031; median BDI: 19 (IQR 5 to 28) *vs* 27 (IQR 21 to 32), p = 0.061 (borderline significant) and in six of the eight SF-36 domains.

Take home message: Amputation should be considered as a form of treatment for patients with intractable CRPS.

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■ A. Midbari, MD, Pain Physician
■ E. Suzan, PHD, PHD - Pain Research Unit
■ E. Eisenberg, PROF, Professor
Institute of Pain Medicine, Pain Research Unit, Rambam Health Care Campus, P.O. Box 9602, Haifa 3109601, Israel.

■ T. Adler, B.A, Head Nurse, Pain Relief Clinic
■ S. Vulfsons, MD, Director, Pain Relief Clinic
Institute of Pain Medicine, Rambam Health Care Campus, Haifa, Israel.

■ E. Melamed, MD, Orthopaedic Surgeon
Rambam Health Care Campus, Department of Orthopedics Haifa, Israel.

■ D. Norman, MD, Orthopaedic Surgeon
Rambam Health Care Campus, Department of Orthopedics, Haifa, Israel

Correspondence should be sent to Dr A Midbari; e-mail: amidbari17@gmail.com

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Complex Regional Pain Syndrome (CRPS) can become a disabling chronic condition.[1,2] Beside the dominant severe pain, the syndrome is characterised by hyperalgesia / allodynia, sympathetic, motor and trophic changes,[3-5] uncertain pathophysiology[6,7] and prognostic factors,[8] limited efficacy of treatment[9,10] and frequently changing diagnostic criteria.[11,12]

The poor response to a large variety of treatments, persistent pain, dysfunction and severely impaired quality of life can lead to the decision to amputate the affected limb in some patients with CRPS.[13] Although some reports of the outcome of amputation in patients with CRPS have been published, this form of treatment in these patients remains controversial.[10,13,14] Questions regarding prognostic factors for 'successful' versus 'failed' amputation, the preferred timing of surgery and the optimal level of amputation, and the risks of recurrent CRPS post-operatively are still unresolved.

The literature regarding the outcome of amputation in patients with CRPS is scarce and provides information on no more than 150 patients.[13,15] An early report of lower-limb amputation in patients with CRPS (termed Reflex Sympathetic Dystrophy (RSD) at that time) showed minimal or no improvement in 'overall physical feeling' in eight of ten

amputees.[16] In another series of 28 patients, there were a total of 34 amputations. Recurrent RSD in the stump and phantom limb pain were found following 28 and 24 of the 34 amputations, respectively. RSD had been present for five months to 18 years (median 2.5 years).[17] In that series, only 17 amputations led to improved function and 11 to relief of pain. Only two patients were able to use a prosthesis. Unfavourable outcomes were reported in two other series.[18,19] In one series, 'a marked post-amputation deterioration' was noted in all 11 patients who underwent this procedure.[18]

A recent review of the literature involving 107 patients with CRPS who underwent 111 amputations found more favourable results than those reported earlier, with a lower incidence of recurrent pain in the stump and a lower rate of phantom limb pain.[13] Conclusions regarding satisfaction and quality of life could not be drawn due to the infrequent reporting of formal outcomes.

Two recent reports yielded even more favourable outcomes following amputation with an improvement in quality of life (20/21, 95%), major reduction in pain (18/21, 86%), improved mobility (17/21, 81%), higher quality of sleep (14/21, 67%) and willingness to undergo amputation again (18/21, 86%) despite a high percentage of phantom limb pain (17/21, 81%).[14] A high rate (27/35, 77%) of phantom limb pain one year following amputation for CRPS was also reported by Bodde et al,[15] but recurrent CRPS was much less common (7/26, 27%).

Thus, the evidence on the outcome of amputation in patients with CRPS comes from retrospective reports. There are no comparative studies. The aim of our study was to evaluate the effect of amputation in patients with CRPS in our institution over the past two decades, on pain, depression, functioning and quality of life comparing them to patients with CRPS who have not undergone amputation.

Patients and Methods

Patients. This study had ethical approval and was conducted at Rambam Health Care Campus between July 2013 and February 2014. A total of 20 patients with CRPS who underwent amputation between 1995 and 2013 were identified. The diagnosis was based on the original International Association for the Study of Pain (IASP) diagnostic criteria for CRPS[4] even though newer criteria for diagnosing CRPS have been suggested.[12] The medical records of all patients were obtained and reviewed. Data on symptoms, signs (and thereby diagnostic criteria), level and exact indication for the amputation and previous treatments were collected. All patients were contacted by mail or telephone and requested to participate in the study, of whom 19 agreed. Study questionnaires and consent forms were sent to them by mail. All 19 patients gave written consent to participate in the study and completed the questionnaires, as the amputation group. Whenever needed, patients were contacted by telephone or invited to visit the pain clinic to obtain missing information. Interviews were undertaken by an investigator (AM) who was not a member of the treatment team. A control group of patients with CRPS was identified based on the following criteria: a) patients who met the same diagnostic criteria (4); b) were seen for routine follow-up at the pain clinic during the study period; c) had persistent symptoms despite having received routine forms of treatment for CRPS including multimodal medication, nerve blocks, intravenous infusions (i.e. ketamine, lidocaine), neuromodulation (i.e. spinal cord stimulation, intrathecal drug delivery pumps), physical and psychological interventions, and/or rehabilitation; d) amputation was discussed either by them or by their treating physician during the past year, but had not been performed.

Outcome measures. The following questionnaires were used: Short-Form (SF)-36[20] for assessment of heath related quality of life; Short Form McGill Pain Questionnaire (SF-MPQ)[21] for the quantification of pain; the Pain Disability Index (PDI)[22] for the assessment of pain intensity and pain-related disability; a visual analogue score (VAS 0 to 100);[23] the Beck Depression Inventory (BDI)[24] for the assessment of depression. Details of the demographic details of the patients and data on all previous and current pharmacological and non-pharmacological treatments were recorded. Amputees were also requested to answer specific questions related to the current site of pain (i.e., stump, phantom), change in the intensity of pain following amputation and whether or not, based on their experience, they would recommend other patients with intractable CRPS to undergo amputation.

Statistical analysis. The Kolmogorov-Smirnov test was used to test the normal distribution of quantitative variables. Parametric and non-parametric testing using the *t*-test, Mann-Whitney U test, chi-squared test and Kruskal-Wallis test (with multiple comparisons) as appropriate were used to detect significant differences in the quantitative variables between the groups. Fisher's exact test was used for differences between categorical variables. Multivariate logistic regression was used for the detection of predictive parameters for 'successful' amputations. A p-value < 0.05 was considered statistically significant. SPSS version 21 (IBM Corp., Armonk, New York) was used for statistical analysis.

Results

Patients. The amputation group included 14 men and five women. Their mean age at the time of the diagnosis of CRPS was 31 years (standard deviation (SD) 12). A total of 18 patients had CRPS in the leg and one in the hand. Above knee amputation was performed in 11 patients, below knee in seven and above elbow in one. Amputation was performed in all patients at a level of healthy skin, a few centimetres proximal to the affected area. The causes of CRPS were soft-tissue damage, fracture and surgery in nine, eight and two patients, respectively. In all patients, intractable pain was the main indication for amputation although the presence of infection in five and a fracture in an already CRPS-affected limb in one patient contributed to the decision to amputate. Notably, one patient underwent

Table I. Demographic and medical data in the two groups. Results presented as numbers (%) or mean values with standard deviation (SD) and medians as appropriate

Parameter	Amputation group	Non-amputation group	p-value
Male gender (%)	14 (*74*)	12 (*63*)	p = 0.73*
Mean (SD) age at diagnosis (yrs)	31 (12)	36 (8)	p = 0.19†
CRPS location in leg	18 (*95*)	17 (*90*)	p = 1.00*
Mean time (yrs, SD) between CRPS diagnosis and data collection (median)	11.7 (5.9) (11.7)	7.4 (5) (7.2)	p = 0.027†
Cause of CRPS			p = 0.62*
Soft-tissue damage	9 (*47*)	9 (*47*)	p = 1.00
Fracture	8 (*42*)	6 (*32*)	p = 0.73
Surgery	2 (*11*)	4 (*21*)	p = 0.66
Mean time (yrs, SD) between CRPS diagnosis and amputation (median)	5.2 (4.3) (3.7)	-	-
Final cause of amputation			
Intractable pain	13 (*68*)	-	-
Infection	5 (*26*)	-	-
Fracture‡	1 (*4*)	-	-
CRPS in the dominant side of the body	13 (*68*)	15 (*79*)	p = 0.48*

* Fisher's exact test
† *t*-test
‡ Fracture in limb already affected by Chronic Regional Pain Syndrome (CRPS)

Table II. Comparisons of clinical data between amputees and non-amputees

Parameter	Amputation group (n = 19)	Non-amputation group (n = 19)	p-value
Questionnaires (mean, SD, median)			
Pain intensity (VAS)	59 (38) (80)	91 (8) (91)	p = 0.007*
SF-MPQ score	24 (14) (28)	34 (6) (35)	p = 0.025*
PDI score	37 (24) (42)	55 (13) (58)	p = 0.031*
BDI score	18 (13) (19)	26 (10) (27)	p = 0.06*
SF-36 score			
Physical functioning	37 (34) (30)	13 (18) (5)	p = 0.024*
Role physical	34 (43) (0)	7 (18) (0)	p = 0.061*
Role emotional	44 (45) (33)	9 (24) (0)	p = 0.008*
Energy	45 (29) (40)	23 (15) (25)	p = 0.011*
Emotional well being	55 (29) (56)	40 (19) (36)	p = 0.24*
Social functioning	59 (31) (50)	33 (25) (25)	p = 0.011*
Pain	36 (31) (32)	8 (17) (0)	p < 0.001*
General health	52 (31) (45)	37 (17) (30)	p = 0.11*
Use of medications (n (%))			
Opioids	10 (*53*)	17 (*90*)	p = 0.029†
NSAIDs	3 (*16*)	9 (*47*)	p = 0.08†
Antidepressants	4 (21)	12(63)	p = 0.02†
Anticonvulsants	8 (42)	18 (95)	p = 0.001†

VAS, visual analogue score; SF-MPQ, Short Form McGill Pain questionnaire; PDI, Pain Disability Index; BDI, Beck Depression Inventory; SF-36, Short Form-36; NSAIDs, non steroidal anti-inflammatory drugs
* Mann-Whitney U test
† Fisher's exact test

repeated amputation in the same leg and another patient had two amputations in one leg and another amputation in the other, all for intractable pain due to recurrent CRPS. The mean time between the diagnosis of CRPS to the (first) amputation was 5.2 years (SD 4.3) and the mean time between amputation and data collection was 6.6 years (SD 5.8).

In the non-amputation group, there were 12 men and seven women. Their mean age at the time of diagnosis of CRPS was 36 years (SD 8). A total of 17 patients had CRPS in the leg and two in the hand. The causes of CRPS were soft-tissue damage, fracture and surgery in nine, six and four patients, respectively. The mean duration of CRPS was 7.4 years (SD 5). The demographic details and medical data are summarised in Table I.

Comparisons between amputees and non-amputees. A summary of comparisons between the two groups is presented in Table II. Fisher's exact test and *t*-testing showed no statistically significant differences in any of the demographic data between the two groups with the exception of the time between the diagnosis of CRPS and the collection of data, which was significantly longer in the amputation

Table III. Dividing amputees into subgroups according to the degree of success of the amputation. Results presented as numbers with percentages or mean values with standard deviation (SD) and median as appropriate

Parameter	Successful (n = 8)	Intermediate (n = 3)	Unsuccessful (n = 8)	p-value
Male gender	5	2	7	p = 0.50*
Mean age (yrs) at diagnosis (SD) (median)	27.7 (11.5) (23)	19.6 (1.5) (19)	39 (9) (42)	p = 0.039†‡
CRPS in leg	7	3	8	p = 0.48*
Mean time (yrs) between CRPS diagnosis and amputation (SD) (median)	5.2 (3.4) (5)	8.6 (9.5) (3.5)	4.0 (1.6) (3.6)	p = 0.89‡
Cause of CRPS (n (%))				p = 0.71*
Soft-tissue damage	5 (*62*)	1 (*33*)	3 (*37*)	
Fracture	2 (*25*)	2 (*67*)	4 (*50*)	
Surgery	1 (*12*)	0	1 (*12*)	
Final cause of				
Intractable pain	5 (*62*)	3 (*100*)	5 (*62*)	
Infection	3 (*38*)	0 (*0*)	2 (*25*)	
Fracture	0 (*0*)	0 (*0*)	1 (*12*)	
Level of amputation (n (%))				p = 0.58*
Above knee/elbow	4 (*50*)	2 (*67*)	6 (*75*)	
Below knee	4 (*50*)	1 (*33*)	2 (*25*)	
Mean pain intensity (VAS) (SD) (median)	30.8 (34.5) (13)	53.7 (37.5) (61)	90.1 (6.7) (90.5)	p = 0.011†‡
Mean % pain relief (SD) (median)	94 (8) (96)	43 (11) (50)	2 (7) (0)	p < 0.001†‡
Mean SF-MPQ score (SD) (median)	11.5 (10.5) (8)	29.7 (4.7) (28)	34.5 (6.9) (36)	p = 0.002†‡
Mean PDI score (SD) (median)	21.6 (24.6) (15.5)	31.3 (17.6) (41)	55.5 (11.8) (59.5)	p = 0.032†‡
Mean BDI score (SD) (median)	10.3 (10.3) (9.5)	19.7 (13.7) (22)	25.8 (12.4) (26.5)	p = 0.041†‡

* chi-squared test
† statistically significant difference between unsuccessful versus successful amputations
‡ Kruskal–Wallis test
CRPS, Chronic Regional Pain Syndrome; SF-MPQ, Short Form McGill Pain Questionnaire; PDI, Pain Disability Index; BDI, Beck Depression Inventory

group than in the non-amputation group (mean 11.7, SD 5.9 *vs* 7.4, SD 5; *t*-test; p = 0.027).

The median (VAS) for pain during the week prior to completion of the questionnaires was significantly lower in the amputation group than in the non-amputation group (80 inter-quartile range (IQR) 13 to 92) *vs* 91 (IQR 85 to 100); Mann-Whitney U test, p = 0.007). Similarly, the median SF-MPQ score, PDI score, and six of the eight health-related quality of life (SF-36) domains, all had significantly more favourable scores in the amputation group than in the non-amputation group. The BDI also had a favourable score at a marginal level (p = 0.061). When looking at the severity of depression, the number of patients with moderate to extremely severe depression (BDI > 21) was eight in the amputation group and 15 in the non-amputation group. Conversely, the number of patients with normal BDI scores (< 10) in the two groups were six and two, respectively. The number of patients using opioids, antidepressants and anticonvulsants for the control of pain was also significantly lower among the amputation group.

Additional outcomes of amputation. None of the 19 amputees was totally pain-free at the time of evaluation. The most prevalent pain was phantom limb pain in 17 patients (89%) followed by pain in the stump in eight (42%) and recurrent CRPS in the amputated limb in six (32%). Most patients had more than one type of pain: five of six with recurrent CRPS in the amputated limb also had phantom pain. Seven of eight patients with pain in the stump, without recurrent CRPS, also had phantom limb pain. Six other patients had phantom pain only. Nonetheless, 12 patients (63%) reported an improvement in the pain as a result of the amputation. Improvement following the amputation was also reported in relation to the consumption of analgesics and in the quality of sleep, each by ten patients (53%), improvement in the ability to function by 11 (58%). Only two (10%), however, resumed employment. None of the patients in the control group was working at the time of the evaluation. A total of ten patients (53%) used a prosthesis. Importantly, 13 (68%) stated that they would recommend amputation for patients with advanced CRPS whereas five (26%) would not recommend it and one was uncertain with respect to such a recommendation.

'Successful' *versus* 'unsuccessful' amputations. Based on the reduced level of pain following amputation, patients were divided into three sub-groups. Those with > 50% pain relief (eight) were regarded as successful amputations, those with 30% to 50% pain relief (three) were considered as intermediate success and when those with < 30% pain relief (eight), were considered to have had an unsuccessful amputation. Due to the small number in the intermediate group (three), a statistical comparison was only possible between the successful and unsuccessful groups (Table III). The Kruskal–Wallis test revealed no statistically significant differences in any of the demographic data between these groups (gender, age at the time of diagnosis, affected limb, time between CRPS diagnosis and amputation, cause of CRPS or level of amputation). In contrast, the intensity of pain (VAS) and magnitude of pain relief were significantly better in the successful group. Similarly, the SF-MPQ score, PDI, and the BDI score were all significantly better in the successful subgroup compared with the unsuccessful subgroup.

Prediction of successful amputation. Table IV shows the results of the multivariate logistic regression aimed to

Table IV. Multivariate logistic regression for prediction of 'successful' amputation

			95% CI for odds ratio	
	p-value	Odds ratio	Lower	upper
Age at diagnosis	0.067	1.163	0.990	1.366
Dominance side of amputation	0.198	0.081	0.002	3.727
Time from CRPS diagnosis and amputation	0.462	1.313	0.636	2.712
Constant	0.147	0.008		

CI, confidence interval; CRPS, Complex Regional Pain Syndrome

identify variables capable of predicting the outcome of amputation. Three independent variables - age, the dominance of the affected limb and time between diagnosis and amputation were included in the regression model (gender was excluded due to the small number of women). Only age at the time of diagnosis showed a trend (p = 0.067) to predict a better outcome: younger age tended to increase the likelihood of having a successful amputation.

Discussion

Chronic CRPS can be a severely disabling condition, intractable and resistant to a large variety of treatments.[2,9,10] Nonetheless, physicians usually refrain from considering amputation as a form of treatment, even in the most severe cases. This view is based on the fact that little evidence is available to support amputation in CPRS.[10,15] Only a few case reports and a few small case series have been reported.[15-19,25]

The present study is the first to include a control group of patients with intractable CRPS, in whom amputation has been considered but not performed. The results show, that although not all patients benefit from amputation, all outcome measures in the amputation group were better that those in the non-amputation group.

Pain and allodynia are major components of suffering and low quality of life in patients with CRPS. These elements have therefore been a dominant outcome measure in most studies related to the treatment of this condition. Although 12 patients reported improvement in the original pain as a result of the amputation, the overall improvement in the pain score, with a median change in the VAS of 11 points in the entire group, was not substantial. This change, it seems, is not clinically significant. However, improvement following the amputation was also reported in relation to the consumption of analgesics, the quality of sleep and the ability to function. All these elements bear clinical significance.

Following amputation, three main types of pain have been reported: recurrent CRPS with pain in the stump, pain in the stump without recurrent CRPS and phantom limb pain.

Recurrent CRPS. Recurrent CRPS in the stump was reported by six patients, all belonging to the unsuccessful group of amputees. This figure is based on patients' reports only (symptoms) and has not been supported by physical examinations (signs). Nonetheless, a similar rate of recurrent CRPS was reported recently (7 of 26 amputees, 27%) although the follow-up duration has not been reported.[15] In contrast, an exceptionally high rate of recurrent CRPS in the stump was also reported by Dielissen et al in 1995.[17] The discrepancies in the rate of recurrent CRPS recurrences in different studies may arise from inconsistencies in the diagnostic criteria for CRPS used by different authors. Previous criteria described by Veldman et al[26] in 1993 were broader than the somewhat stricter IASP[4] criteria which have been used in more recent studies and those described by Bruehl et al.[27]

Stump and phantom limb pain. Nearly three-quarters of our patients reported stump limb. However, it was attributed to recurrent CRPS in less than half of them. Similar results were reported recently by Bodde et al[15] where recurrent CRPS was noted in 27% (7/26). Thus, in most patients with CRPS who have undergone amputation, residual limb pain is not caused by other reasons such as a neuroma. Residual limb pain commonly complicates amputations which are undertaken for indications other than CRPS.[28]

The mean prevalence of phantom limb pain in patients who undergo amputation for all indications is about 80%,[29] equally high following traumatic amputations and amputations due to peripheral vascular disease.[30] These results are in line with our findings and with those reported in three studies on phantom pain in patients with CRPS who have undergone amputation, which range from 77% to 89%.[14,15,17] Two points are noteworthy. First, in spite of the high prevalence of stump and phantom pain, nearly two thirds of the patients reported improvement in the pain, and half were able to reduce their analgesic usage following amputation. Secondly, pain in the stump was reported by three of the eight patients who had a successful amputation, and phantom limb pain by all eight patients in that category. Hence, it seems that the recurrent CRPS in the stump, rather than non-CRPS related pain or phantom limb pain is a reason for patients to regard their amputation as being unsuccessful.

Functioning. All eight amputees in the successful group and three in the other two groups reported functional improvement following amputation. The fact that ten patients were able to use a prosthesis can be regarded as an important achievement. Nonetheless, a much lower success rate was reported with regards to resumed employment

following amputation, since only two amputees returned to work. Higher rates of employment among CRPS amputees have been reported by others.[13,14] These discrepancies can possibly be attributed to differences in the availability of suitable re-training programmes, to social or cultural factors or to the relatively early time of assessment after amputation in four of our patients (< one year).

Many parameters including PDI, six of eight domains of health-related quality of life and depression, scored higher in the amputation group. These results, and those of others on the quality of life and functioning of patients with CRPS who have undergone an amputation, support the conclusion that these variables tend to improve following amputation.[14,16,17] Indeed, nearly 70% of our patients stated that they would recommend to others with similar severity of CRPS to theirs, to undergo amputation. Interestingly, three patients in the unsuccessful group made the same recommendation despite having recurrent CRPS in the stump. Thus, it seems that even if the improvement in the intensity of the pain is minimal or unnoticeable, patients would still recommend amputation as a reasonable form of treatment. There is not a clear explanation for this, although it might be easier for the patients to avoid an exacerbation of pain due to the accidental touching of their stump than might occur if the affected leg remained in place. An additional explanation is that the outcome is better when: a) the patients themselves request an amputation and b) if the outcome matches their pre-amputation expectations.[15]

This study has limitations. First, the small number of patients limited the ability to correlate the factors that predict the outcome statistically. Secondly, the study population consisted of two different groups of patients, a fact that raises two limitations: we do not have baseline preoperative data for the amputees, therefore comparison of baseline data between the two groups has not been possible and the length of time between the diagnosis of CRPS and the collection of data differed considerably between the two groups. The fact that the two groups consisted of the same number of patients is accidental. Thirdly, co-morbidity was present in the affected limb in six patients in the amputation group, infection in five and fracture in one. Although the outcome does not seem to have been influenced by these factors, a potential contribution of these factors to the decision to undergo amputation cannot be ruled out. Fourth, our demographic data, which consists mostly of young men, whose lower limbs were predominately affected in both groups, is different the typical cohorts of patients which have been previously reported.[1,31] It may be that our patients were those with the most intractable CRPS and therefore might represent a unique subgroup of patients with this condition, possibly with atypical epidemiological characteristics. This assumption is supported by other publications on amputation in patients with CRPS, where relatively young age and lower-limb predominance were also reported.[13,15] Lastly, we have chosen to use the relatively old IASP diagnostic criteira[4] and not the more recent suggested criteria,[12] for being congruent with the criteria that were available to the treating physicians at the time they diagnosed many of the amputees.

This study provides comparative data suggesting that amputation could be considered as a form of treatment for patients with 'end stage', otherwise intractable CRPS. Nonetheless, patients with this condition in whom amputation is considered should be informed about the risks of recurrent CRPS as well as of residual limb and phantom pain post-operatively.

Author contributions:
A. Midbari: Data collection, data analysis, writing the paper.
E. Suzan: Data collection, writing the paper.
D. Norman: Performed surgeries.
E. Melamed: Performed surgeries, data collection.
T. Adler: Data collection.
S. Vulfsons: Writing the paper.
E. Eisenberg: Data collection, data analysis, performed surgeries, writing the paper.

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