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Quality of life after amputation in patients with advanced complex regional pain syndrome: a systematic review

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- The majority of included studies (8 out of 11, *n* = 54) supported the concept of considering amputation for selected, unresponsive cases of complex regional pain syndrome (CRPS) as a justifiable alternative to an unsuccessful multimodality nonoperative option.
- Of patients who underwent amputation, 66% experienced improvement in quality of life (QOL) and 37% were able to use a prosthesis, 16% had an obvious decline in QOL and for 12% of patients, no clear details were given, although it was suggested by authors that these patients also encountered deterioration after amputation.
- Complications of phantom limb pain, recurrence of CRPS and stump pain were predominant risks and were noticed in 65%, 45% and 30% of cases after amputation, respectively and two-thirds of patients were satisfied.
- Amputation can be considered by clinicians and patients as an option to improve QOL and to relieve agonizing, excruciating pain of severe, resistant CRPS at a specialized centre after multidisclipinary involvement but it must be acknowledged that evidence is limited, and the there are risks of aggravating or recurrence of CRPS, phantom pain and unpredictable consequences of rehabilitation.
- Amputation, if considered for resistant CRPS, should be carried out at specialist centres and after MDT involvement before and after surgery. It should only be considered if requested by patients with poor quality of life who have failed to improve after multiple treatment modalities.
- Further high quality and comprehensive research is needed to understand the severe form of CRPS which behaves differently form less severe stages.

Keywords: amputation; complications; criteria; CRPS; pain; phantom pain; quality of life

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Introduction

Complex regional pain syndrome (CRPS) is a chronic, painful, infuriating, inflammatory disorder that usually affects limbs and can lead to long-term physical and psychological disability. Various modes of intervention have been tried to relieve pain and disability with inconsistent success rates.[1–3] Life-changing, aggressive interventions such as amputation of affected limbs become the inescapable choice and are often demanded by patients to relieve their constant intractable pain and suffering.[3]

Veldman et al proposed the first ever comprehensive criteria,[4] followed by the International Association for the Study of Pain (IASP) criteria and the Budapest or Bruehl criteria.[5,6] Multiple theories have been proposed in the literature to explain possible underlying mechanisms of clinical manifestations seen in patients with CRPS.[7] The peripheral and central sensitization model by Rockett[8] proposed that afferent neurons transmitting pain stimuli to the dorsal horn of the spinal cord and central nervous system (CNS) develop enhanced sensitivity because of a persistent initial noxious stimulus. Baron et al[9] proposed that release of substance P, calcitonin, and similar neuropeptides led to neurogenic inflammation. The exact pathway and mechanisms are not known but Janig and Koltzenburg[10] suggested 'coupling' of sympathetic and somatic afferent neurons.

Mos et al[11] reported that the incidence of CRPS in the general population is up to 26.2 cases of CRPS per 100,000 individuals. His results were based on a Netherlands

Table 1. Review question

Population	Intervention	Comparator if available	Outcome
Adult patients with advanced, resistant CRPS (both types of CRPS i.e. type 1 and 2)	Amputation due to CRPS or its complications	Patients with advanced CRPS but did not have amputation	Quality of life (QOL) after amputation

Note. CRPS, complex regional pain syndrome.

Table 2. Eligibility criteria

Inclusion criteria	Exclusion criteria
Adults (> 18 years of age) with advanced, resistant CRPS which has failed to respond to conservative measures	Children (i.e. < 18 years old) Less severe CRPS or conservative measures not used
Strictly follow one of the standard diagnostic criteria of CRPS	No clear diagnostic criteria followed Ambiguous to distinguish clinical picture from CRPS or other pathology
Amputation due to CRPS or severe complications of resistant CRPS	All other conservative interventions or amputations due to other reasons
All relevant studies (all designs) before October 2017	
Outcome: Quality of life assessed (either by standard tool or descriptive analysis)	No assessment of quality of life after amputation
Studies in English language or studies in languages other than English but translation accessible	Full-text article translation in English not available

Note. CRPS, complex regional pain syndrome.

population and followed internationally accepted criteria. Sandroni et al[12] suggested that the incidence can be as high as 5.46 per 100,000 persons in the USA.

There are two types of CRPS based on aetiology: CRPS 1 in the absence of nerve damage and CRPS 2 (causalgia)[13] when associated with nerve damage. Veldman et al[4] and Hooshmand and Phillips[14] classified CRPS into various stages based on severity.

Objectives

This systemic review is secondary research that is based on the principle of systematic collection and presentation of data from primary research.[15] Currently, there is very limited information and guidelines for treatment of the advanced, severe form of CRPS.[7] The focus of this study is to systematically review the research conducted on advanced, chronic, non-responding, irreversible, dysfunctional stages of CRPS which require sacrifice of the limb by surgical amputation and the effect of this on quality of life. Since this study was a systematic review, ethical approval was not required.

Literature review, materials and methods

Methodology was planned on the basis of guidelines set by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and York University systematic review recommendations to improve the quality of study. This systematic review protocol was approved and formally registered with the Health Department of the University before the study began. Inclusion criteria were drafted on the PICO model (Table 1). Strict inclusion and exclusion criteria were involved in the study (Table 2). Also, studies which could not be translated into English were excluded.

No language limit was applied initially in the search exercise to avoid language bias, although surprisingly some publications point out that even excluding non-English literature has generally little or no effect on outcome in a systematic review.[16] An extensive literature search was carried out and included following databases: Embase, MEDLINE, PsycINFO, Database of Abstracts of Reviews of Effects (DARE), The National Institute for Health and Care Excellence, Cochrane Library (including Cochrane Central Register of Controlled Trials – CENTRAL), Scottish Intercollegiate Guidelines Network (SIGN), EPPI-Centre, PubMed, European Medicine Agency (EMA).

The search terms utilized were CRPS, ('complex regional pain syndrome'), RSD ('reflex sympathetic dystrophy'), 'sudeck's atrophy', 'amputation', 'amputee', 'amputat*'. No time limit was applied for searches.

Randomized controlled trials (RCTs) are considered to be the ideal choice of selection for systematic reviews as they provide a higher level of evidence and reliable treatment of effect as stressed by research and also by Cochrane guidelines for systematic reviews.[17] Although RCTs give the best evidence, in rare diseases, where it is ethically difficult or impossible to randomize, for instance amputation cannot be randomized and the incidence of advanced stages of CRPS are rare and difficult to predict, RCTs are not possible. As a result, using studies at relatively lower levels of hierarchy of evidence as compared with an RCT was the inevitable choice and justified. For this study, two researchers independently searched the clinical evidence available to reduce selection bias. No time limit was applied for searches, and databases were searched from

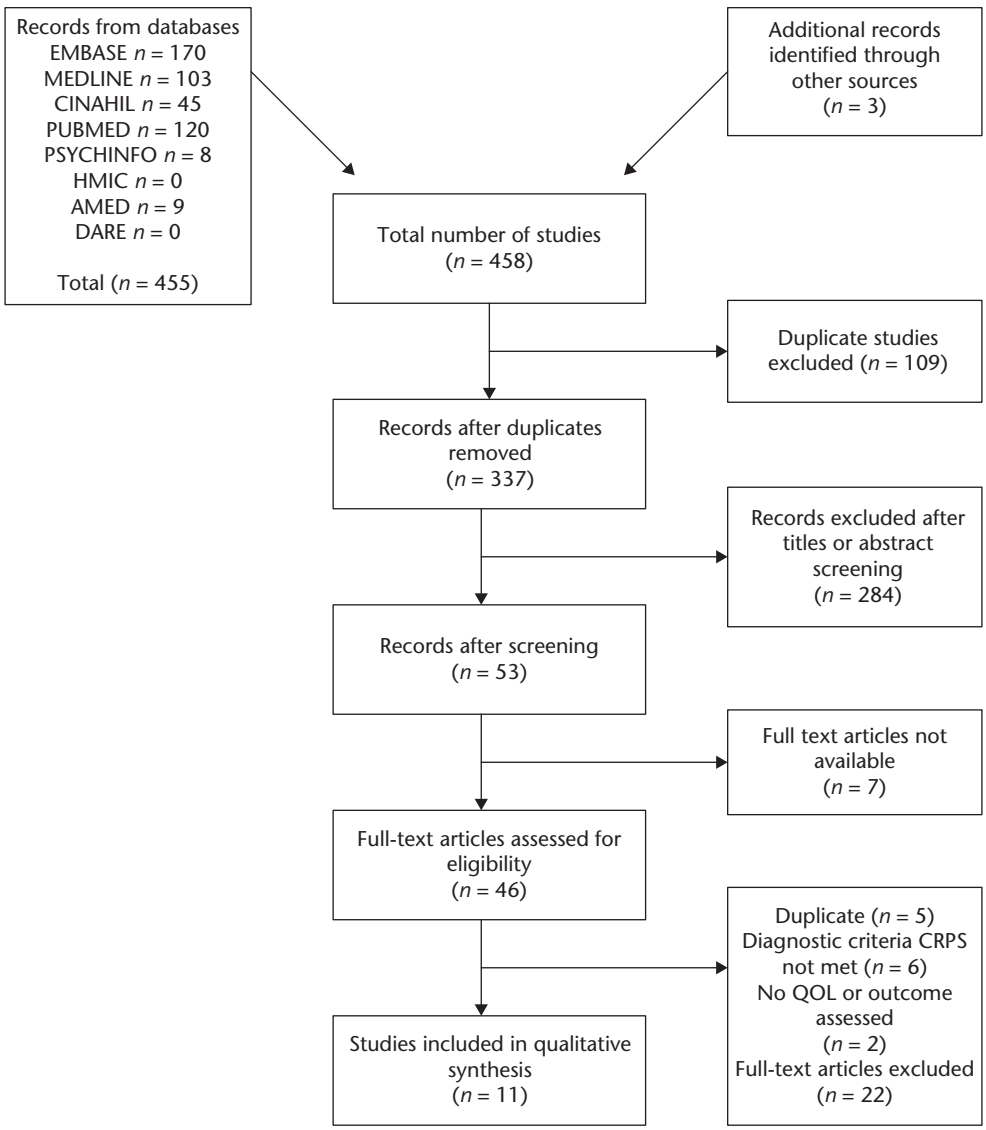

Fig. 1 PRISMA flowchart for study selection.

their beginning to date of search to include as much related evidence as available.

A total of 455 studies were highlighted after a search of databases. Two studies were added after screening of references of relevant articles. Eleven studies met the inclusion criteria (Fig. 1).

To minimize selection bias, agreed criteria for diagnosis of CRPS were strictly followed. However, as it is complex disease and some of the studies were quite old, even before the international guidelines were set, importance of such research was not ignored and therefore grouped separately so that the results can be dissected individually highlighting strengths, weaknesses, quality of study and outcomes (see Table 3 for examples).

It was noted that some of the authors published the different aspects of research and details in more than one paper.[18,19] In such cases, missing information was added from other articles after making sure it was representative of the same population as given in the main article.

Data items

Various models for data extraction tools have been suggested in the literature which range from qualitative to quantitative data.[20] The variables in data extraction included title, source, year, country, eligibility criteria, diagnostic criteria, duration of CRPS, type of study, population, demographics, intervention, control, outcomes, quality of life (QOL), complications, prosthesis type, satisfaction, study aims, key findings, summary, ethics, data collection method, data analysis method and recommendations. Sanderson, Tatt and Higgins[21] identified 86 tools for the purpose of quality assessment and supported their usefulness.

Table 3. Eligible studies fulfilling inclusion criteria

	Title	Author, Year, Country
1	Amputation in Patients with Complex Regional Pain Syndrome	Midbari et al, 2016[23] Israel
2	Resilience in Patients with Amputation because of Complex Regional Pain Syndrome Type I	Bodde et al, 2013[19] Netherlands
3	Expression of Endothelial Nitric Oxide Synthase and Endothelin-1 in Skin Tissue from Amputated Limbs of Patients with Complex Regional Pain Syndrome	Groeneweg et al, 2008[26] Netherlands
4	Amputation for Reflex Sympathetic Dystrophy	Dielissen et al, 1995[28] Netherlands
5	Pathologic Alterations of Cutaneous Innervation and Vasculature in Affected Limbs from Patients with Complex Regional Pain Syndrome	Albrecht et al, 200632 Israel
6	Complex Regional Pain Syndrome Leading to Bilateral Upper Limb Amputation: A Case Report	Pagoti et al, 200827 UK
7	Complex Regional Pain Syndrome (CRPS, RSDS) Diagnosis and Therapy. A Review of 824 Patients	Hooshmand and Hashmi, 1999[18] USA
8	Case Report, Functional Status after Trans-Femoral Amputation in Three Patients with Complex Regional Pain Syndrome	De Boer et al, 2007[25] Netherlands
9	Fluctuating Residual Limb Volume Accommodated with an Adjustable, Modular Socket Design: A Novel Case Report	Mitton et al, 2017[29] UK
10	Amputation as an Unusual Treatment for Therapy-Resistant Complex Regional Pain Syndrome, Type 1	Kashy et al, 2015[30] USA
11	Trans-tibial Amputation for Reflex Sympathetic Dystrophy: Postoperative Management	Emmelot et al, 2000[31] Netherlands

Two approaches were used in this study for quality assessment:

- Methodological Index for Non-Randomized Studies (MINORS) tool[22]
- Critical Appraisal Skills Programme (CASP) checklist (casp-uk.net/casp-tools-checklists)

Results

Results of study selection

Eleven studies were found eligible to meet the inclusion criteria. The total number of patients was 96 and the number of surgical procedures (amputations) was 107 as few of these patients underwent amputation of more than one limb. These studies were heterogeneous with diverse designs and quality. In total, 79 cases with good quality evidence were reported (Table 4).

Care was taken while synthesizing the results to keep in view the quality of these studies in order to minimize bias and to assess true effect, size and direction of treatment. Studies by Midbari et al[23] and Bodde et al[24] were designed scientifically considering the restraints of complexity and rarity of CRPS. These successfully managed to recruit and compare control groups, and enabled analysis of demographics and consideration of confounders (see Table 3 for examples of excluded study).

Cumulative results

Participants

A total of 96 adult patients with advanced resistant CRPS underwent 107 amputations due to disease or its complications. The mean age of 84 patients was 41 years. It was not possible to trace demographic details of 12 patients.[18] Males comprised 30% of the cases as compared to 70% females.

CRPS characteristics

It was clear from extracted data that three studies comprising 41 cases (41%) followed the Veldman et al diagnostic criteria as shown in the 'study characteristics' section. Twenty-six patients were able to fulfil criteria set by the IASP for CRPS and three patients were diagnosed using Budapest diagnostic guidelines. Twenty-six patients met both IASP and Budapest criteria.

The mean duration of CRPS from diagnosis to the time of amputation was four years and six months for 84 patients and no information was accessible for the remaining 12 patients.

All the patients who underwent amputation had CRPS, with advanced resistant stage that failed to resolve after multi-modality conservative measures including physiotherapy, occupational therapy, medications, analgesia, anaesthetic blocks, spinal cord stimulation and sympathectomy. Eventually patients were left with no further options and requested amputation to relieve intractable pain, improve disability, or to get rid of complications such as severe, persistent infections, which were unresponsive to treatment.

Description of interventions (amputation)

One hundred and seven amputations were performed but only a few of the studies described the details of the procedures. De Boer et al[25] mentioned trans-femoral level of amputation in three patients but did not explain whether

Table 4. Relevant but excluded studies and justification

Author and year	Reason for exclusion
Van Der Laan et al, 1998[36]	No outcomes reported No QOL assessment ($n = 5$)
Szeinberg-Arazi et al, 1993[37]	No diagnostic criteria for CRPS/RSD. Full article not accessible ($n = 10$)
Veldman et al, 1993[4]	No outcomes for QOL after amputation ($n = 13$)
Edwards et al, 2011[38]	No specific diagnostic criteria for CRPS Overlapping co-morbidities High risk of bias, poor quality ($n = 3$)
Bovaira et al, 2016[39]	No diagnostic criteria ($n = 2$) (Searched from conference proceedings)
Krans-Schreuder et al, 2012[40]	Duplication as its updated version was later published which is included ($n = 22$)
Erdmann and Wynn-Jones,1992[41]	No diagnostic criteria for CRPS ($n = 2$)
Geertzen and Eisma,1994[42]	No diagnostic criteria ($n = 1$)

Note. CRPS, complex regional pain syndrome; QOL, quality of life; RSD, reflex sympathetic dystrophy.

it was through healthy skin margins or CRPS site. Bodde et al[19] reported 20 amputations of lower limbs and six of upper limbs, with 81% of amputations through healthy skin and the rest either at or below the level of allodynia. They proposed that level of amputation did not affect the recurrence in contrast to previous reports. In one of the studies, 18 amputations were for lower limbs while one patient had an upper limb amputation, all of which were performed above the allodynia level through healthy skin.[23] In a study by Groeneweg et al,[26] two legs and one arm were amputated. Pagoti, Lawrence and Hambidge[27] reported two upper limb amputations. Both of the studies did not specify the level of allodynia. Dielissen et al[28] conducted a review describing 15 amputations in the upper and 19 in the lower limbs at various levels. In 85% of these cases, symptoms of CRPS were present at the level of amputation. He suggested, after gathering results, that if allodynia is present at the level of amputation it can lead to recurrence. On the other hand, results from Bodde et al[19] and Midbari et al[23] did not support this idea. Mitton et al[29] and Kashy et al[30] each reported one case with amputation of a leg followed by significant improvement in quality of life and rehabilitation.

Primary outcome

Different tools were utilized by authors in selected studies for evaluation of quality of life (QOL). The selection varied from validated tools to subjective descriptions. Tools included, Short Form 36 (SF-36), WHOQOL-Bref, VAS QOL.

Isolated results of QOL

SF-36 was used by Midbari et al[23] and all the scores in the amputee group were statistically significantly better than in the non-amputee group ($p < 0.05$). Bodde et al[19] used WHOQOL-Bref for QOL measurement suggesting that the majority of amputation patients (62%) had good QOL, 23% had poor QOL and 15% had neither good or bad QOL after amputation. The three patients recruited by De Boer et al,[25] had significant improvement in QOL. The VAS tool for quality of life rating was used which showed a mean score of 3.3 before amputation and remarkable improvement to mean score of 9.3 out of 10 after amputation. Hooshmand and Hashmi[18] had narratively described outcomes among 12 cases of amputation in a review of 824 CRPS patients treated with different modalities. There was no description of QOL assessment process or other tools. However, they proposed that 11 patients had significant deterioration and experienced complications, recommending amputation should be avoided. Out of 28 patients in a series by Dielissen et al,[28] 60% had improvement of function and 40% had some degree of pain relief. Interestingly, despite persistence of pain, poor function and failure to achieve improvement in QOL in some patients, 85% of amputees were satisfied.

Groeneweg et al[26] provided only minimal descriptive information on the outcomes without using tools of formal assessment and reported that one patient had 'dramatic' pain relief while a second patient continued to experience pain and complications. Pagoti, Lawrence and Hambidge,[27] Emmelot et al,[31] Kashy et al[30] and Mitton et al[29] also used narrative description of outcomes and discovered that four patients achieved satisfactory pain relief and use of prosthesis, improving quality of life after amputations. Analysis of two cases revealed poor outcomes in study by Albrecht et al.[32]

Combined results of QOL

Sixty-eight per cent ($n = 66$) of total cases had improvement in quality of life in terms of functional ability or general health. It was noted that less than one-third of patients experienced some degree of deterioration in QOL despite amputation. However, when analysed in sub-groups divided on the basis of quality of data, better outcomes were seen in good quality trials, which were conducted more systematically. The majority ($n = 64$) showed better quality of life while only 13 had decline in good quality studies. In contrast, the poor quality studies showed that

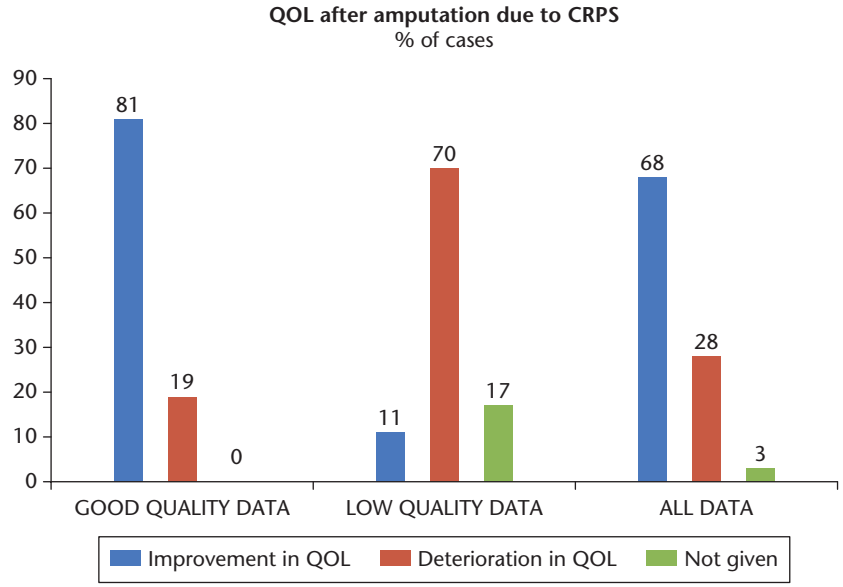

Fig. 2 Quality of life (QOL) after amputation due to complex regional pain syndrome (CRPS). Comparison of good quality studies, low quality studies and combined results of all studies.

12 out of 17 cases had worsening of QOL after amputation. Hooshmand and Hashmi[18] postulated that there was significant deterioration in overall outcomes after amputation. There were no details of methodology, follow-up duration or tools for measuring quality of life, and high risks of bias were evident (Fig. 2).

More recent and higher quality data which formed the major pool of cases and compared with controls have shown more positive consistency and direction of effect towards better quality of life after amputation.[25,26] Although they still reported complications and unsuccessful cases, the overall trend showed improvement which was statistically significant and reliable ($p < 0.05$, CI = 95%). Moreover, tools used by these studies were the most recent, reliable, valid and reproducible and are supported by enormous evidence in the literature e.g. SF-36, WHOQOL-Bref. In both comparative studies QOL showed statistically significant improvement in the amputation group in comparison with the control group (CI = 95%, $p = 0.05$). Statistical analysis in these studies was also thoroughly performed and appropriate parametric and non-parametric tests applied.

During the course of this study, an interesting finding was noted. Those studies which mentioned that a multidisciplinary approach was followed, and discussed pre-amputation expectations as well as psychological aspects of the personalities of patients, produced significantly better outcomes in post-amputation QOL. A multidisciplinary approach involved specialists from various fields such as psychiatrists, surgeons, the rehabilitation team, the pain team, physiotherapists and general physicians.

Other outcomes

Patient satisfaction

Despite complications and recurrence of CRPS, the majority of patients interestingly showed a high satisfaction rate For instance, all 28 patients in the Dielissen et al. study[28] had recurrence and the majority had phantom pain but 24 out of 28 patients were still satisfied. Similarly, in another trial, even the unsuccessful group of patients with poor QOL scores felt more satisfied and improved after amputation.[23] Eight of the included studies have given details of satisfaction after amputation stating 64 patients (66%) were satisfied with amputation and seven (7%) would not recommend amputation but no information could be traced for rest of the patients regarding satisfaction.

Prosthesis use

Only 37% of patients after amputation were able to use a prosthesis. It was not possible for 42 patients to use a prosthesis either because of stump pain, recurrence or other reasons. Details were not provided for 18 patients.

Complications

Analysis of results highlighted that three complications are commonly seen in patients undergoing amputations due to CRPS which were mainly phantom pain, stump pain and recurrence of CRPS. These results were consistent with findings from previous literature.[3]

Phantom pain

Phantom pain or phantom limb pain (PLP) is the pain perceived in part of body which has been amputated.[33] Incidence can be very high and up to 85% of post-amputation

Table 5. Cumulative results

Total number of cases	*n* = 96
Mean age	41 years (84 patients)
CRPS duration	4.6 years (84 patients)
QOL	68% improved 28% deteriorated 4% not given

Note. CRPS, complex regional pain syndrome; QOL, quality of life.

cases experienced some degree of phantom pain in one study.[34] Sixty-three patients in six of the studies experienced variable levels of phantom pain. This ranged from mere phantom sensations to severe pain, but most of these patients had minor symptoms and continued to show overall improvement despite this pain, as the severity was not disabling.

Stump pain

Stump pain or persistence of non-CRPS burning pain was reported in 31 patients (32%).

Recurrence of CRPS

Forty-four out of 96 patients undergoing amputation (46%) had signs of recurrence of CRPS. It should be noted that the exact proportion of recurrence is actually debatable because stringent criteria of CRPS were not used for 28 patients.[28] Details were missing in some studies, e.g. Hooshmand and Hashmi[18] only explained recurrence of CRPS in one out of 12 patients and did not mention whether the remaining 11 had recurrence or not.

Discussion

After critically appraising and comparing heterogeneous sets of data reported over the last three decades, evidence is pointing towards a transition from deterioration to improvement in quality of life after amputation in limbs affected by resistant severe CRPS, although complications are encountered and the majority of patients never totally get rid of pain. Studies conducted earlier than 2000 advocated avoiding amputation, while trials carried out more recently supported the justification of amputation.[18,35]

It is still uncertain whether the cause of this transition is attributable to improved peri-operative care, stringent diagnostic criteria, psychological support, re-setting expectations or the selection process. Much more research is needed to discover these unknown factors in the pathology of CRPS, the mechanism of pain, the response to non-surgical and surgical interventions and the psychological and behavioural aspects of patients with this terrifying condition.

This review addressed a focussed issue and represents an attempt to add more knowledge in order to understand the impact of amputation on quality of life. It is the only review on this subject which follows strict adherence to diagnostic standards of CRPS, reducing bias, enhancing specificity and sensitivity and determining the true effect of treatment. No randomized control trials (RCT) were included in the review as no RCTs had ever been carried out due to ethical issues and the complex nature of CRPS.

There were only two high quality comparative trials while the remainder were non-comparative, observational, heterogeneous studies. Most of the studies relied on retrospective methodology for data collection thus incorporating risks of recall bias.

No exact details are available for many patients about their pre-amputation quality of life for comparison and to assess true impact of intervention over time apart from in one study by De Boer et al.[25]

Conclusions

Amputation can be considered by clinicians and patients as an option to improve QOL(Table 5) and to relieve agonizing, excruciating pain of severe, resistant CRPS but it must be acknowledged that evidence is limited, and the there are risks of aggravating or recurrence of CRPS, phantom pain and unpredictable consequences of rehabilitation.

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