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SYSTEMATIC REVIEW

Health economic evaluation of different treatment strategies for peripheral entrapment mononeuropathies: a systematic review

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ABSTRACT

Introduction: In this era of cost-conscious health systems, it is of utmost importance to identify and establish the most cost-effective treatment option. However, in the case of peripheral entrapment mononeuropathies there is alack of data regarding economically effective treatment strategies. Therefore, the objective was to conduct an economic evaluation including both costs and benefits of various treatment strategies applied to peripheral entrapment mononeuropathies to estimate the relative cost-effective treatment regimens.

Areas covered: Over the 19 years, seven excellent-high quality economic evaluations of three types of peripheral entrapment mononeuropathies were identified in four countries. Our findings showed that surgery was the most cost-effective therapy followed by same cost efficacy of infiltrative therapy and conservative therapy for peripheral entrapment mononeuropathies. However, the fact that surgery was the most common comparator (n = 6) in our selected studies cannot be neglected.

Expert opinion: Due to huge methodological variability, the finding of surgery as the cost-effective treatment strategy remains tentative and the decision about the most suitable clinical and cost-effective therapy should be individualized from case to case. Moreover, the economic evaluation of all possible treatment strategies for peripheral entrapment mononeuropathies over alonger period of analysis is required in future studies.

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KEYWORDS
Peripheral entrapment mononeuropathies; health economic evaluation; surgery; infiltrative therapy; conservative therapy

1. Introduction

In all painful diseases, the prevalence of a neuropathic component is 35% as reported by some studies [1]. The etiology of neuropathic pain is either peripheral polyneuropathy or mononeuropathy [2]. Mononeuropathies may have different causes, but entrapment is the most crucial one [3].

The peripheral entrapment mononeuropathy (PEMN) is a neuropathy due to either structural abnormality like compression, displacement, traction of a nerve, or by any intrinsic pathology of the nerve, such as a nerve cell tumor [4]. This mechanical pressure induced by either structural or intrinsic causes results in highly specific and predictable neurological symptoms of pain, sensory, and motor ailments [5]. Examples of such nerve entrapment are carpal tunnel syndrome, ulnar nerve entrapment, chronic migraine headaches, and nerve entrapment associated with diabetes mellitus [5–8]. Due to the broad heterogeneity of studies, there is a lack of accurate data concerning prevalence of PEMNs. However, the estimate scatters around a wide range of 1%, 6.9%, and 10% due to lack of consensus on a definition and diagnostic procedure used for PEMNs [1].

Depending on specific anatomic location of nerve entrapment, different types of PEMN vary in prevalence and economic cost depending on territorial region. The most common one is carpal tunnel syndrome, i.e., median nerve entrapment at wrist [5]. Its prevalence in the United States (US) population is 3.72%, with income loss per 93 patients over a period of 6 years estimated at 45,000-89,000 USD [9]. Moreover, in United Kingdom (UK) the prevalence of carpal tunnel syndrome is 0.36% [10], while in the Netherlands, it is 0.6% in men and 9.2% in women [11]. In addition, the economic burden of carpal tunnel syndrome in Brazil was estimated at R$29,463,148.80 (9,065,584 USD in 2016 US dollar at a rate of R $1 = 0.31 USD) between the period of 2008–2016 [12].

The second common PEMN is ulnar nerve entrapment also known as cubital tunnel syndrome [5], a nerve compression in the arm [13]. In the US alone the estimated prevalence of ulnar nerve entrapment is 1% [14] while in UK 1.87% cases of ulnar nerve entrapment were reported in a total of 10,000 presentations in 253 primary care units in the year of 2000 [15]. Similarly, the cost of one surgical procedure of ulnar nerve entrapment in Brazil during the period of 2008–2016 ranged from R$318.88 to R$539.74 (98 to 166 USD in 2016 US dollar at a rate of R$1 = 0.31 USD) [16].

A newer theory also includes chronic migraine headaches as a symptom of entrapped nerves at specific trigger sites which effects 1% to 3% of the world population [6,7]. In the US adult population, the prevalence of chronic migraine headaches is 2% with the cost of treatment estimated at 17 billion

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Article highlights

- This is the first systematic review which critically assesses the economic implications of peripheral entrapment mononeuropathies, all of the included studies were of excellent-high quality as per Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, performed in the US, UK, Netherlands, and Spain.
- According to our findings, surgery if considered as first-line therapy for peripheral entrapment mononeuropathies demonstrates a more favorable economic perspective. However, due to huge methodological variability between selected studies we could not conclude surgery to be chosen as the first therapeutic option for peripheral entrapment mononeuropathies and we recommend selecting therapy on a case by case basis.
- Our review will help researchers and decision-makers to identify gaps in the health/economic context of peripheral entrapment mononeuropathies and inform future economic evaluations to draw a more authentic conclusion about cost-effective treatment strategies for peripheral entrapment mononeuropathies.

USD per year [7]. In UK, 7.6% of males and 18.3% of females have reported migraine headaches [17]. Similarly, up to 33% of chronic nerve compression is also diagnosed in the diabetic population that results in diabetic neuropathy and ultimately diabetic foot ulcers [18] with incidences of 3–4% in the US population [19]. Other less prevalent types of PEMNs include the entrapment of the superficial radial nerve in the distal forearm, peroneal and lateral nerve entrapment, Morton's neuroma, and piriformis syndrome [5].

The treatment of PEMNs usually begins with conservative therapies such as patient education, drug trials, splinting and physiotherapy for at least 3 months. In case of failure of conservative therapies, the infiltrative therapy which includes the local administration of corticosteroid injection alone, anesthetic injection alone, or a combination of anesthetic with corticosteroid or OnabotulinumtoxinA is normally tried. Surgical intervention is usually considered when non-surgical therapy failed to control the ailment [5]. However, in this era of cost-conscious health systems, it is of the utmost importance to identify and establish the most cost-effective treatment option [20]. To maintain and restore productivity of a large portion of our population, a cost-effective treatment option is of paramount importance. For this purpose, the principles of health economics play an important role in selection of a cost-effective treatment strategy for PEMNs, and lowers the avoidable financial burden of PEMNs on the healthcare industry and government [21]. The field of pharmacoeconomics, a subdiscipline of health economics, applies the principles and methodology of health economics to the field of pharmaceutical policy [22]. It focuses mainly on costs and benefits of drug or drug therapies to provide a clear view of economic and health consequences of the alternatives by selecting a pharmaceutical product which has a minimum cost and maximum therapeutic efficacy [23].

Therefore, the purpose of writing this systematic review was to conduct an economic evaluation including both costs and benefits of various treatment strategies applied for PEMNs in order to estimate a cost-effective and successful treatment regimen.

2. Methods

2.1. Search strategy

A systematic electronic literature search of PubMed, Google Scholar, Cochrane Central Register of Control Trials, Science Direct and Clinical Trials Registry (ClinicalTrials.gov) was conducted between January 2000 and December 2019 as per PRISMA guidelines [24]. Recent and related journal articles, bibliographic search of the recent systematic reviews and meta-analyses were also carried out.

The PubMed database was searched by augmenting the terms of health economics with entrapment mononeurotherapy while others were inspected using three key terms only i.e., 'Pharmacoceconomics, treatment, and entrapment neuropathy'. A scan of all abstracts and titles was carried out to exclude articles that did not meet our inclusion criteria which required individually evaluated full-text articles. Reviews, editorials, letters, case reports, correspondences, methods or protocol papers, conference papers, and abstracts were also screened out. Searched keywords in PubMed were formatted as follows:

Peripheral entrapment mononeuropathy OR Nerve entrapment OR Entrapment mononeuropathy OR Compression mononeuropathy OR Trapped mononeuropathy OR Tunnel syndrome OR Tunnel neuropathy OR Carpal tunnel syndrome OR Cubital tunnel Syndrome OR Ulnar nerve entrapment OR Ulnar Neuropathy OR Guyon's canal syndrome OR Peroneal nerve entrapment OR Meralgia paresthetica OR Suprascapular nerve entrapment OR Posterior interosseous nerve syndrome OR Anterior interosseous nerve syndrome OR Piriformis syndrome OR Pudendal nerve entrapment OR Radial tunnel syndrome OR Pronator syndrome OR Morton's neuroma OR Tarsal Tunnel Syndrome OR Tibial neuropathy

AND

Treatment OR Therapy OR Pharmacotherapy OR Therapeutics OR Cure OR Medication OR Splinting OR Physical therapy OR Physiotherapy OR Surgery OR Decompression surgery

AND

Cost OR Economic cost OR Economic evaluation OR Economic analysis OR Economics OR Pharmacoeconomics OR Pharmacoeconomic's analysis OR Cost analysis OR Cost-effectiveness OR Cost-effective analysis OR CEA OR Cost-utility analysis OR Utility analysis OR CUA.

2.2. Selection of studies

Our inclusion criteria contained any randomized control trial or observational study which valued both cost and outcome of different treatment strategies irrespective of line of treatment for PEMNs and language restriction. Included subjects were diagnosed with any kind of PEMN regardless of the gender or age, diagnostic criteria used, etiology, and associated pathology.

Studies limited to the cost of illness, cost minimization analysis, partial economic assessment, and cost analysis of highly specified subjects like cancer, pregnancy, geriatrics, etc., were excluded. Articles addressing cost analysis of

subtreatment techniques such as economic comparison of endoscopic carpal tunnel release and open carpal tunnel release, screening or diagnostic strategies, and treatment of multiple nerves entrapment like thoracic outlet syndrome were also excluded out.

The selected titles and abstracts were dually screened for eligibility criteria by the reviewers. Discrepancies were resolved after discussion and rechecking the articles. Full consensus was achieved between the authors before inclusion of the articles.

2.3. Data extraction and quality appraisal

All stages of the study selection, data extraction, and quality assessment were independently assessed by each author. Data were extracted via standard data form containing first author name, country/year of investigation, sample size, gender/age, study design, pathology, applied diagnostic procedure, cost perspective, currency, discount rate, cost/incremental cost-effectiveness ratio (ICER)/incremental cost utility ratio (ICUR), relevant outcome, and detail of funding received for each study. We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement to assess the quality of the economic analyses [25]. The study satisfying 100% of relevant CHEERS items was rated as of excellent quality, between 75% and 99% as high quality, 50% and 74% as medium quality, and below 50% was rated as low quality.

In addition, we converted and adjusted the converted cost values for inflation in selected studies into 2020 US dollars ($) using country-specific consumer price index data from the World Bank to facilitate comparison between studies set in different countries [26].

3. Results

3.1. Literature search

The initial records searched from databases were 2,947 while 107 articles were directly identified through searching of health economic journals and a total of 3,054 studies were included. After removing duplicates, 2,344 studies were screened out. Of these, 1,888 studies were excluded from the abstract/title screen stage. After the full text review, 253 studies were excluded for varying reasons (Figure 1). In the last stage of data extraction, 196 studies were excluded because these studies were centered only on cost of illness and cost minimization analysis or were related to cost analysis of subtreatment techniques only. In final, seven studies from four countries were identified in the period from January 2000 to December 2019 (Figure 1) [7,21,27–32]. Out of a total of seven selected studies, one study reported their results in two parts, i.e., one part for clinical outcome and the other for cost outcome respectively [27,28].

3.2. Baseline characteristics

There are three types of PEMN which were covered in our selected studies as carpal tunnel syndrome in four studies [27–31], chronic migraine headaches in two studies [7,21], and diabetic neuropathy in only one study [32]. The reported sample size in our chosen studies was 120 [27,28], 234 [29], 120 [30], 176 [31], and 1,677 [32] with a total of 2,327, except the studies of Shauly et al. and Schoenbrunner et al. that didn't have information about representative samples of patients [7,21]. Moreover, two out of seven studies reported the full demographic data of their samples with a total of 354 subjects [29,30]. The average age of included subjects in these two studies was 57.6 years; participants were 28.2% male and 71.8% female [29,30].

3.3. Quality assessment of included studies

According to the assessment criteria set by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement, we rated one study as excellent quality [32], and 6 as high quality [7,21,27–31] for decision makers as shown in Table 1.

3.4. Methodological characteristics of included studies

Out of seven studies, four were from the US [7,21,30,32], and the remaining three were from Spain, UK and the Netherlands respectively [27–29,31]. The oldest one was published in the year of 2006 [31] and the latest study was in 2020 [7].

The diagnosis of included subjects for PEMNs was made by either clinical, physical, or by electrophysiological tests as a single or combined procedure. The common cost perspective procedure applied was societal perspective in four studies [7,21,27,28,31] followed by National Health Service (UK) [33], third-party insurance [30] and Medicare (US) perspective [32]. Time horizon of analysis in our included studies varied from 6 months to 37.6 years.

The four studies were sponsored by different organizations [7,27–29,31], while three were not funded [21,30,32]. Most of the studies (n = 2) were trial based [27,28,31], three used a Markov model [7,21,32], and the remaining two studies were linear and logistic regression model, and a retrospective study respectively [29,30]. A 3% discount rate was applied in only one study [32]. The details of methodological characteristics of the included studies are shown in Table 2.

3.5. Health economic evaluation of included studies regarding the type of PEMN

To present the effectiveness of treatment under comparison, the author calculated ICER/ICUR values for all of seven studies. Direct medical cost was compared in 3/7 studies [29,30,32] while 3/7 studies used both direct and indirect cost [21,27,28,31]. One remaining study didn't provide sufficient information about included cost [7]. These cost values (both direct and indirect) were converted and inflated into 2020 US dollars ($), for the 6/7 studies shown in Table 3. The rates based on the end year of investigation of the respective study were used as: Euro (Spain) €1 = 1.181 USD [27,28], British pound £1 = 1.2302 USD [29], Euro (Netherlands) €1 = 0.923 USD [31]. The relevant data regarding the

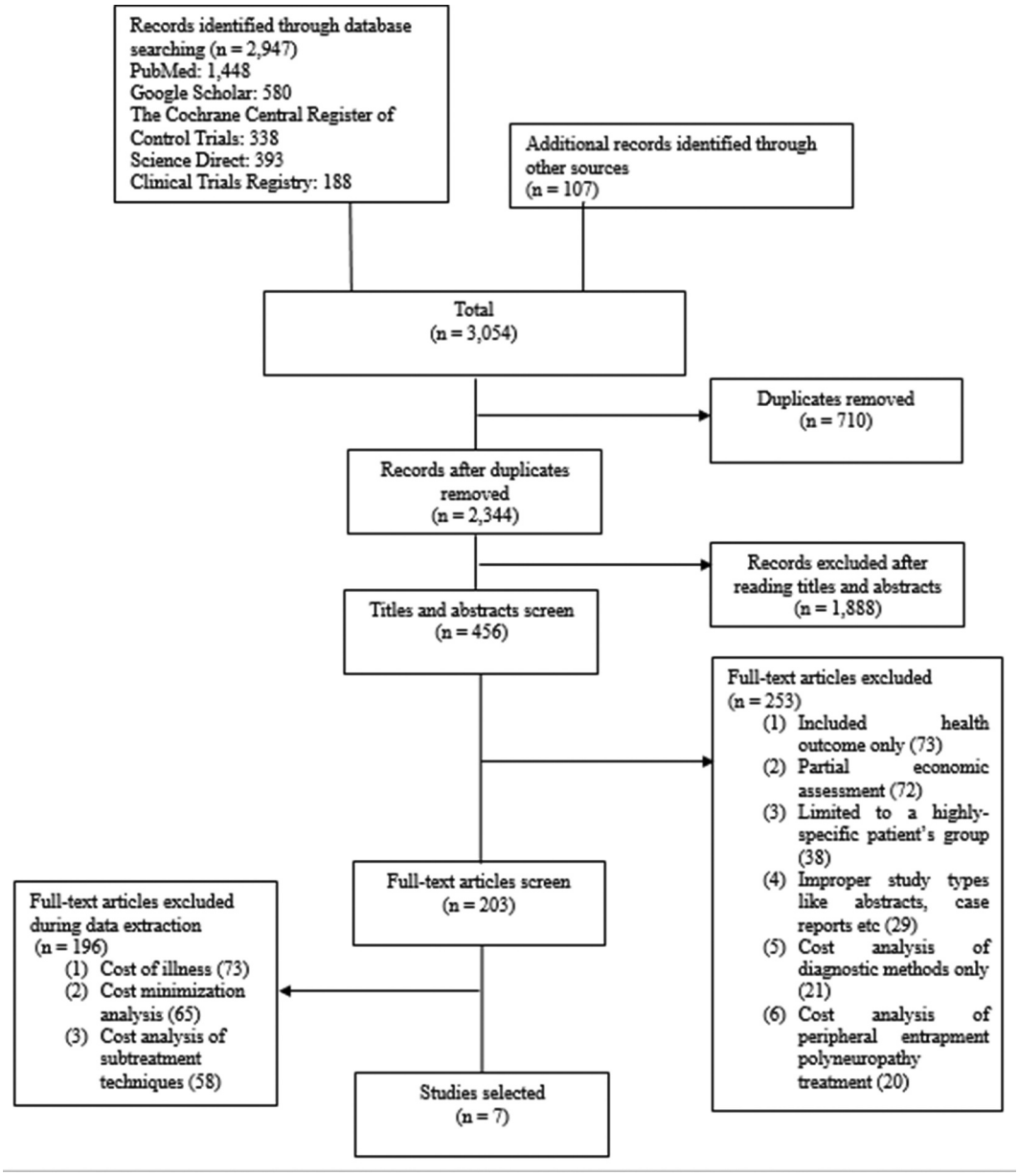

Figure 1. Flowchart of the searching and screening studies.

economic comparison of our selected studies are shown in Table 4.

Table 1. Quality of included studies against Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [25].

Study	CHEERS items satisfied	CHEERS items not satisfied	Relevant CHEERS items	Percent (%) satisfied	Quality
Fernandez-de-Las, 2019 [27,28]	20	3	23	87	High
Chesterton, 2016 [29]	21	2	23	91	High
Pomerance, 2009 [30]	18	5	23	78	High
Korthals, 2006 [31]	20	2	22	91	High
Shauly, 2019 [21]	19	4	23	83	High
Schoenbrunner, 2020 [7]	20	3	23	87	High
Sarmiento, 2018 [32]	23	0	23	100	Excellent

In our studies, the patients of three types of PEMN, i.e., carpal tunnel syndrome, chronic migraine headaches, and diabetic neuropathy were included.

3.5.1. Carpal tunnel syndrome

There were four studies which included the patients with carpal tunnel syndrome [27–31]. Pomerance et al. compared non-surgical treatment (physical therapy, splinting, and then corticosteroid) to surgical treatment with an ICUR of surgery versus non-surgery of only -$64.03/QALY (Quality Adjusted for Life Year), and supports surgery for carpal tunnel syndrome confirmed by nerve conduction test [30]. Korthals et al. also concluded surgery was cost-effective when compared to splinting, and preferred for patients with carpal tunnel syndrome in the Netherlands. The ICUR of surgery versus splinting was -€40 which means that surgery was €40 cheaper than

Table 2. Summary of methodological characteristics of health economic studies for treatment strategies of peripheral entrapment mononeuropathies.

Study	Country/Year of investigation	Pathology	Diagnostic criteria	Perspective	Currency	Time frame	Model	Funding received
Fernandez-de-Las, 2019 [27,28]	Spain/2018	CTS with symptoms of 12 months	Clinical, physical tests and by electrodiagnosis	Societal	Euro (€)	1 year	RCT	Yes
Chesterton, 2018 [29]	United Kingdom/ 2014-16	Mild or moderate CTS for longer than 6 weeks	Clinical and by physical tests	NHS (UK)	British pound (£)	6 months	Linear and logistic regression model	Yes
Pomerance, 2009 [30]	United States/2002-07	Mild to severe CTS	Clinical, physical tests and by electrodiagnosis	3rd party insurance	United States dollar ($)	1 year	Retrospective study	No
Korthals, 2006 [31]	Netherlands/ 1998-2000	CTS	Clinical and by electrodiagnosis	Societal	Euro (€)	1 year	RCT	Yes
Shauly, 2019 [21]	United States/ 2017	Chronic migraine headaches	Patient not involved directly	Societal	United States dollar ($)	-	Decision-analytical Markov model	No
Schoenbrunner, 2020 [7]	United States/ 2019	Chronic migraine headaches	Patient not involved directly	Societal	United States dollar ($)	37.6 years	Decision-analytical Markov model	Yes
Sarmiento, 2018 [32]	United States/ 2017	Diabetic neuropathy	International consensus on diabetic foot [33,34]	Medicare (USA)	United States dollar ($)	5 years	Markov model	No

CTS: Carpal Tunnel Syndrome; NHS (UK): National Health Service (United Kingdom); RCT: Randomized Control Trial

splinting in a single treatment and caused less waking up at night than splinting [31].

Fernandez-de-Las et al. compared surgery and manual physical therapy in the setting of Spain. The incremental 374 QALYs showed greater benefit in favor of manual physical therapy, and concluded manual physical therapy as both clinically and cost-effective [27,28]. Chesterton et al. considered treatment of carpal tunnel syndrome in primary care settings with single corticosteroid injection versus night-resting splints. The corticosteroid injection was concluded to be cost-effective over 6 months when compared to night-resting splints in mild or moderate carpal tunnel syndrome [29].

3.5.2. Chronic migraine headaches

Two studies conducted in the US applied Markov model to compare two different treatment strategies of chronic migraine headaches. The comparator of decompression surgery was common in both studies versus corticosteroid

Table 3. Extracted mean costs in 2020 US dollars ($) and resulted outcome for treatment strategies of entrapment mononeuropathies from each included study [26].

Disease	Treatment strategy	United States	United Kingdom	Netherlands	Spain
Carpal tunnel syndrome	Splinting		$395.87*, 0.396 QALYs [29]	$2,920.11**, 72% success rate [31]	
	Manual physical therapy				$14,733.22**, 50.15 QALYs [27,28]
	Palpation guided corticosteroid injection		$438.26*, 0.404 QALYs [29]		
	Non-Surgical Treatment (Splint/physical therapy/ corticosteroid)	$4,149.34* [30]			
	Surgical treatment (Open carpal tunnel release/Endoscopic Carpal tunnel release)	$3,817.15* [30]		$2,940.85**, 92% success rate [31]	$202,729.45**, 44.3 QALYs [27,28]
Chronic migraine headaches	Corticosteroid injection therapy	$37,962.11**, 6.34 QALYs [21]			
	Migraine decompression surgery	$10,843.16**, 7.06 QALYs [21]			
Diabetic neuropathy	Patient education program	$23,944.06*, 5.9 QALYs [32]			
	Surgical treatment of tibial neurolysis	$37,385.96*, 6.3 QALYs [32]			

QALYs: Quality Adjusted for Life Years
*Direct cost only, **Both direct and indirect cost

Table 4. Summary of health economic evaluation by included studies for treatment strategies of peripheral entrapment mononeuropathies.

Study	Comparators	Sample size	Outcome measure	Result/ICER/ICUR	Cost-effective treatment
Fernandez-de-Las, 2019 [27,28]	Surgery Manual physical therapy	60 58	QALYs	Manual physical therapy/Surgery = -€154,996/QALY	Manual physical therapy
Chesterton, 2016 [29]	Single injection of 20 mg methylprednisolone Acetate	116	Levine questionnaire CTS assessment [35]	Corticosteroid injection/ Night splint = £4,193/QALY	Single injection of methylprednisolone acetate
	Night splint for 6 weeks	118			
Pomerance, 2009 [30]	Surgical treatment	60	QALYs	Surgical treatment/Non 8-surgical treatment = -64.03 USD/QALY	Surgical treatment
	Non-surgical treatment (physical therapy, splinting and then corticosteroid)	60			
Korthals, 2006 [31]	Surgical treatment Splinting	87 89	General improvement in symptoms and quality of life expressed as utility (0–1)	Surgical treatment/ Splinting = -€40/one time less waking up at night than splinting	Surgical treatment
Shauly, 2019 [21]	Migraine decompression surgery Injection therapy of corticosteroid with anesthetic		QALYs	Surgical decompression/ Injection therapy = 178,163.27 USD/ QALY	Migraine decompression surgery beyond 8.25 years
Schoenbrunner, 2020 [7]	Migraine decompression surgery Long-term, targeted botulinum toxin type A (BoNTA)		QALYs		Migraine decompression surgery beyond 6.75 years
Sarmiento, 2018 [32]	Surgical treatment of tibial neurolysis Patient education program	1677	Long-term trends of development of ulcers and amputations QALYs and net monetary benefits	Tibial neurolysis/Patient education program = 31,330.78 USD/QALY	Surgical treatment of tibial neurolysis

ICER: Incremental Cost-Effectiveness Ratio; ICUR: Incremental Cost-Utility Ratio; QALYs: Quality Adjusted for Life Years; CTS: Carpal Tunnel Syndrome

injection in Shauly et al. and OnabotulinumtoxinA in Schoenbrunner et al. [7,21]. The ICUR of surgical decompression versus corticosteroid injection therapy was 178,163.27 USD/QALY [21]. The other study concluded that the mean cost per patient undergoing peripheral trigger site deactivation surgery was 10,303 USD with an effectiveness of 7.06 while the mean cost per patient undergoing long term targeted OnabotulinumtoxinA injection was 36,071 USD with an effectiveness of 6.34 yielding an incremental effectiveness of −0.72 QALYs. It should be noted that higher score of effectiveness indicates better outcome [7].

Both studies concluded surgery was a cost-effective therapy after a specific period of time during treatment. For instance, if patients require treatment in the form of corticosteroid injection for less than 8.25 years, they should not be offered surgery [21]. Similarly, another study concluded that surgery was a more cost-effective treatment than OnabotulinumtoxinA injection for refractory migraine headaches requiring treatment for greater than 6.75 years [7].

3.5.3. Diabetic neuropathy

There was only one study which included the patients of diabetic neuropathy and compared the interventions of patient education program with surgical procedure of tibial neurolysis [32]. The direct cost in US dollars ($) 2020 of patient education program was 23,944.06 USD (5.9 QALYs) while surgical procedure of tibial neurolysis was 37,385.96 USD (6.3

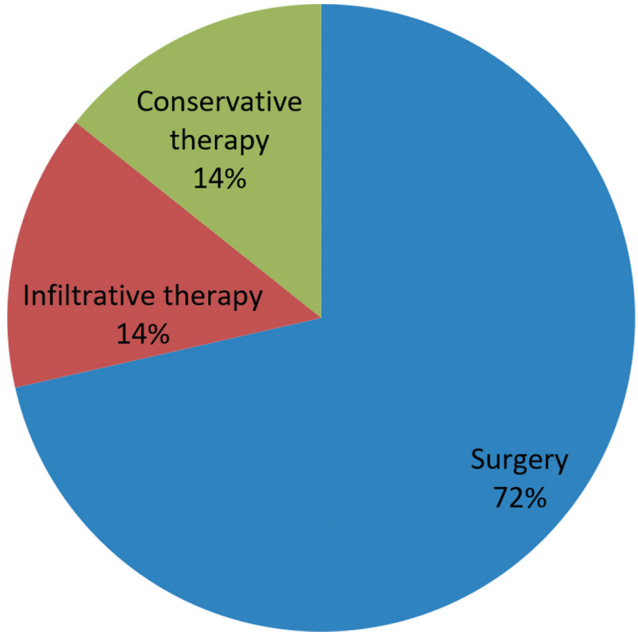

Figure 2. Comparison of different treatment strategies for peripheral entrapment mononeuroapthies in terms of cost-effectiveness. Surgery was compared in six studies, conservative therapy in five studies, while infiltrative therapy was chosen as a comparator in six studies only.

QALYs) with an ICER of tibial neurolysis versus patient education program was 31,330.78 USD/QALY. Although it was summarized that surgical intervention of tibial neurolysis was a cost-effective treatment, this was given with a recommendation that patients should be involved in making the decision about the treatment strategy chosen as a final option [32].

3.6. Health economic evaluation of included studies regarding the type of treatment strategy

Upon combining the data of the included studies, there are three types of treatment strategies for PEMN which were compared in our review as conservative, infiltrative, and surgical therapy. From the results of these studies it may be concluded that surgery was the most cost-effective therapy for PEMNs. However, the fact that surgery was also the most common comparator (6 out of 7) in our selected studies cannot be neglected (Figure 2). The details of concluding findings of our chosen studies regarding the type of treatment strategy are

1. Conservative therapy. Only one study recommended conservative physical therapy rather than surgery as a cost-effective therapeutic intervention. The manual physical therapy group received three treatment sessions including desensitization maneuvers of the central nervous system for 30-minute durations once a week over a time span of one year [27,28].

2. Infiltrative therapy. Only one study designated infiltrative therapy as economically effective treatment. The study was performed on mild or moderate carpal tunnel syndrome presenting in primary care. It was concluded that single corticosteroid injection was clinically effective at 6 weeks and was cost-effective over 6 months compared with night resting splints [29].

3. Surgery. Two studies concluded surgery was the most cost-effective therapy in comparison with non-surgical interventions (physical therapy, splinting and then corticosteroid) without any assumptions [30,31]. The remaining three studies reported surgery was a cost-effective therapy, but with some presumptions. For instance, patients with chronic migraine headaches that are reluctant to accept medical intervention of surgery should be offered corticosteroid injection. Secondly, the patients should be considered for surgery within three years of the initiation of injections. Moreover, if patients require treatment in the form of injections for less than 8.25 years, then they should not be offered surgery. In addition, those patients that expect their migraine disorder to resolve within the next decade should consider infiltrative therapy as a cost-effective one [21]. Similarly, another study on chronic migraine headaches concluded that peripheral trigger site deactivation surgery was more effective and less costly than injection of OnabotulinumtoxinA for treatment span of greater than 6.75 years only [7]. The third study of Sarminto et al. concluded surgical procedure of tibial neurolysis for peripheral diabetic neuropathy was cost-effective therapy, but it was also recommended that the patients of peripheral diabetic neuropathy should make an informed decision about the treatment strategy chosen as a final option [32].

4. Discussion

According to our findings, surgery was the cost-effective therapy among different treatment strategies of PEMNs. However, 85% of our selected studies choose only one intervention for surgery as a comparator that makes our results uncertain.

In an insufficient resource environment, health professionals should promote cost-effective care to achieve better health outcomes and a quality of life from available resources. Ideally decision makers would have their eyes on long-term costs and health outcomes achieved via different configurations of health services to invest accordingly. However, due to lack of evidence of cost-effectiveness, decision makers can never perform confidently [36]. Our study is one of the first systematic reviews which critically assess the cost-effectiveness of PEMNs treatment modalities. As per CHEERS statement, all of our included studies were of excellent-high quality [7,21,27–32] (Table 1). We applied both cost value and clinical outcome as per health economics principles to suggest the most successful treatment for PEMNs from seven economic evaluations. Although, we did not perform statistical meta-analysis due to clinically diversified selected studies, our descriptive analysis allows an overview of a variety of treatment interventions.

On the other hand, the selected studies showed huge methodological variability. The studies differed in type of PEMN examined, type of intervention compared, cost perspective, time frame of analysis, model applied, and outcome measure. Many studies either didn't report complications of therapy under study, or only reported minor and insignificant adverse effects [27,28]. Similarly, in our review, the number of studies evaluating surgical interventions [7,21,27,28,30,32] were greater than conservative [27–32] and infiltrative interventions [7,21,29,30]. These variations contributed significantly to the diverging results of our review.

The findings of systematic reviews that compared treatment strategies of PEMNs on clinical basis are incompatible with our results. These clinical systematic reviews either concluded therapies other than surgery were clinically effective or have insufficient data to support surgery as the first therapeutic option for PEMNs. For instance, Jimenez et al. selected seven relevant articles on different treatment strategies of carpal tunnel syndrome. The results proved non-surgical therapy including manual, traditional, and noninvasive therapies were superior to surgical treatment [37]. Similarly, Caliandro et al. considered nine randomized control trials with 587 participants of ulnar nerve entrapment and concluded that available evidence was insufficient to identify the best treatment [38]. Similarly, the results of 1,825 patients of diabetic peripheral neuropathy from 12 pieces of literature (eight prospective and four retrospective) found surgical decompression procedures to be a clinically effective therapy, but also specified the need for high-quality randomized control trials in future [39]. The same conclusion was reached by one other review which included eight studies of diabetic peripheral neuropathy [40]. In the

case of Morton's neuroma, operative treatment was suggested followed by infiltrative treatment with a recommendation that future studies with high levels of evidence are required [41]. The factors attributed to differences in conclusion of our health economic evaluation and clinical systematic reviews are differences in duration of therapy and follow-up period, dissimilarities in selection of clinical end points, number of studies selected and patient-related factors.

In addition, in determining the total cost of a particular therapy, recurrence rates, and its respective costs play an important role. We didn't find any comprehensive clinical studies in our review which included the recurrences rates with respective costs for PEMNs therapies. The study found included the recurrence rates after surgical treatment only. For instance, recurrence rate of 0.02% to 5.24% after endoscopic release was reported when the patients were followed for 736 days [42].

On the basis of these facts and figures, we are not able to conclude that surgery should be chosen as the first therapeutic option for PEMNs. Though, in case of chronic migraine headaches, the surgical intervention has clear evidences as a cost-effective therapy compared to infiltrative therapy. But on the other hand, the authors of both the selected studies of chronic migraine headaches concluded surgical intervention as cost-efficient specifically for those patients who require treatment for greater than 7.5 years meaning that it cannot be chosen as a starting treatment for newly diagnosed patients [7,21].

The decision about the most appropriate therapy for PEMNs should be individualized from patient to patient. For this reason, it is important to evaluate clinical outcome, patient economic status, and the risk/benefit ratio for all possible therapies on an individual basis to select the final treatment strategy. Similarly, patients should be involved in making the choice between different treatment strategies and physicians should explain clearly the risk/benefit ratio for every treatment plan to the patient.

4.1. Limitations

All of our selected studies were from the US, the UK, Spain, and the Netherlands. As the economic system of every country differs, therefore our results cannot be generalized to other countries with different economic aspects. Similarly, the conservative medication therapy like opioids which is usually a first choice for the clinicians in treatment of PEMNs was not compared in any study. Moreover, we did not find any study which economically evaluated all the possible treatments of PEMNs in one report.

The selected studies covered types of PEMN, the prevalence of which are high in the general community [5]. However, there are some types like Morton's neuroma, piriformis syndrome, posterior, and anterior interosseous nerve syndrome, etc., which also effect the community, but with low prevalence [5]. We did not find any research study which studied economic analysis of these less prevalent types of PEMN. In addition, most of the studies (6 of 7) followed patients for a short term of less than 1 year, and no study reported the recurrence cost for any type of PEMN therapy.

4.2. Expert opinion

The goal of health economics is to select a therapy with low cost and high efficacy, as health care system is increasingly under pressure to do more with less.

The prevalence of 6.9%-10% of PEMN [1], has a high impact on the corresponding treatment expenditure. According to our findings, surgery if considered as first-line therapy demonstrates a more favorable economic perspective as opposed, if it is used as second-line or third-line therapy. The surgery is a one-time cost with rapid improvement as compared to non-surgical therapies. Secondly, the longtime duration and loss of production cost due to delay in return to work for employed class, results in higher total cost of non-surgical therapies as compared to surgical treatment. Due to these reasons, the advanced surgical procedures like endoscopic technique with low rate of complications and cost is getting more importance especially in economically developed countries.

However, on the other hand the reviews which focus only on clinical outcome of different therapies have contradictory results to our findings. Similarly, to draw a real total cost it is necessary to include both primary and recurrence cost. But in case of our selected reports, the prevalence of recurrence and its respective cost were not studied.

In the end, therefore, we recommend selecting the therapy for PEMN on a case-to-case basis. For selection of the final therapy it is necessary to give importance to the patient-related factors like economic status and patient informed consent.

Our review has an impact to set a treatment guideline for disabling disorder of PEMN. The data is pertinent to clinicians especially hand surgeons working in primary, secondary, and tertiary care, administrative staff of health units in both government and private sectors, health insurance companies, and policy makers at both lower and higher levels. In addition, the protocol we applied in our review could be used to select a cost-effective therapy out of different treatment strategies for other highly prevalent and chronic diseases.

The limitations raised in our review can be minimized in future evaluations through randomized controlled trials with uniform and clear international methodological recommendations for economic analysis in healthcare. Similarly, the conclusion about the cost-effective therapy for a specific kind of PEMN in one economic setting for a longer time of analysis is more reliable than to focus on different PEMN types in one study. Though it is difficult to write a systematic review on a specific PEMN type in one economic setting due to unavailability of sufficient data. But on the other hand, primary research on types of less studied PEMN could be done in an effective way.

4.3. Conclusion

From the results of selected studies it can be concluded that surgery was the most cost-effective therapy followed by same cost and effect of infiltrative and conservative therapy. However, these findings remain tentative because surgery was the most common comparator studied by the authors in our selected

studies. Similarly, the methodological variability between our studies also contributed significantly to the diverging results of our review. Moreover, the clinical systematic reviews either concluded therapies other than surgery as clinically effective or have insufficient data to support surgery as the first therapeutic option for PEMNs. Therefore, the decision about the most appropriate therapy for PEMNs should be individualized from patient to patient on the basis of clinical outcome, patient economic status, and the risk/benefit ratio of all possible therapies. Patients should be involved in making the choice between different treatment strategies and physicians should explain the risk/benefit ratio for every treatment.

Our review has highlighted certain areas that could be studied in future economic analyses to draw a more detailed and authentic conclusion about cost-effective treatment strategy of PEMNs. The succeeding studies should focus on the health economics of PEMNs therapies in low-income countries. In addition, research articles on infiltrative therapy, conservative therapy, and on less prevalent PEMN types for a longer time of analysis (more than 1 year) to report the recurrence cost is a need to be studied in future research.

Reviewers disclosure

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Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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