A Review of Scrambler Therapy for Chronic Neuropathic Pain

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Abstract

Introduction: An increase in accidental death related to prescription opioid abuse prompts the identification of novel strategies to treat chronic pain at a low risk to patients and their communities. Scrambler therapy (ST) has recently emerged as a viable treatment option for patients with neuropathic pain (NP), prompting a systematic review of the literature.

Materials and Methods: We conducted a literature search in PubMed, Embase, and other search engines with the key words scrambler therapy, Calmare®, and neuropathic pain.

Results: Fifteen studies met the inclusion criteria for the literature review. Each of these studies reported varying degrees of pain reduction when patients were treated via ST.

Discussion: ST appears to effectively treat a variety of NP syndromes; however further sham controlled studies are needed to validate this claim.

Keywords: Chronic pain; Neuropathic pain syndromes; Scrambler therapy

Introduction

The treatment of neuropathic pain (NP) has proven to be challenging, not only to primary care physicians, but also to pain specialists. Many surveys have reported that only 50% of the patients with NP experience satisfactory pain relief despite aggressive poly-pharmacy, likely due to limited efficacy and side effects that develop during dose titration [1,2]. Opioids have also been shown to alleviate NP with 50% improvement; however, recent increases in accidental death due to prescription opioid abuse and lack of evidence for long term therapeutic benefits necessitate safer and more effective strategies [3-5]. One strategy that has received significant attention is peripheral nerve stimulation. Melzak and Wall's pioneering work with the gate theory opened the field to TENS. While this treatment modality is shown to alleviate pain in a number of NP syndromes, in many cases, the effect is suboptimal requiring patients to remain on medications [6,7]. More recently, an innovative peripheral nerve stimulation approach was introduced: scrambler therapy (ST). ST focuses on the novel concept of blocking pain information by feeding the brain with non-pain information via cutaneous nerves [1]. ST is a non-invasive, non-painful, non-pharmacological intervention that can significantly reduce, and on occasion obliterate, chronic pain [8]. Although ST's mechanism of action is unclear, the current hypothesis suggests that ST substitutes "pain" information for "non-pain" information. The ST device generates 16 different types of action potentials sequentially, while using algorithms that take into account previous outputs, frequency, duration, and amplitude of modulation. This process determines the patient-specific cutaneous electro stimulation necessary to block pain signals, tailoring treatment for an individual's maximal pain relief. Though there are independent studies reporting pain relief with ST, variability in pain relief intensity and duration of effect exists in the literature. This variability makes it difficult to predict responses of individual patients with various NP syndromes. Our study aims to review the current body of literature regarding ST.

Materials and Methods

Literature search and grading of evidence

The literature search was done utilizing PubMed and Embase with the keywords ST, peripheral nerve stimulation and Calmare®. By using other combinations of words and other search engines, the yield did not increase. First, studies were classified (I–IV) according to decreasing value of evidence.

A Class I study is an adequately data-supported, prospective, randomized, placebo-controlled clinical trial with masked outcome assessment in a representative population (n>25 patients receiving active treatment). It should include (a) randomization concealment; (b) clearly defined primary outcomes; (c) clearly defined exclusion/inclusion criteria; (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences. A Class II study is a randomized, placebo-controlled trial performed with a smaller sample size n<25 or that lacks at least one of the above-listed criteria a-e. Class III studies include all other controlled trials. Class IV studies are uncontrolled studies, case series, and case reports. Recommendations were based on the level of evidence (A-C, as follows) for each of the putative therapeutic indications of a given ST

protocol. Level A (definitely effective or ineffective) requires at least 2 convincing Class I studies or one convincing Class I study and at least 2 consistent, convincing Class II studies. Level B (probably effective or ineffective) requires at least 2 convincing Class II studies or one convincing Class II study and at least 2 consistent, convincing Class III studies. Level C (possibly effective or ineffective) requires one convincing Class II study or at least 2 convincing Class III studies. No recommendations were made in the absence of at least 2 convincing Class III studies providing similar results on the same type of clinical features with similar stimulation method. For this grading, when several studies with the same indication and methodology came from a single research group, they were considered once (according to their best class). Following this analysis, we propose an overview of the level of evidence that can be currently recommended for a given therapeutic indication of ST [9].

Results

The literature search was performed using the key words: scrambler therapy, pain, NP, chemotherapy induced peripheral neuropathy (CIPN), Calmare, Calmare®, peripheral nerve stimulation.

We identified 15 publications that met the selection criteria for inclusion in this review: 1 double-blind randomized sham-controlled study, 1 randomized open label, 8 prospective open label, 2 retrospective, and 3 case reports. Due to the level of evidence of the publications a meta-analysis could not be performed (Table 1).

Reference	Study Type	Evidence Level	N	Diagnoses	Treatment	Treatment Duration (min.)	Pain reduction	Other Outcomes	Duration of Effect
Starkweather et al. [18]	Ran[a]	II	Placebo=15, ST=15	LBP	10	30	Control, ST 47% with >50% reduction	Genetic markers for pain	3weeks
Marineo et al. [1]	Ran[b]	III	52(drug treatment n=26, ST n=26)	PS, PHN, SCS	10	45	Control 28% ST 91%	Allodynia (improved)	3 months
Notaro et al. [14]	Pros	IV	25	CP (bone)	10	30-40	66%	Sleep hours (increased)	7.7± 5.3
Pachman et al. [22]	Pros	IV	37	CIPN	10 (max.)	30	53%	Tingling (improved), numbness (improved)	10 weeks
Sabato et al. [20]	Pros	IV	226	FBSS, SP, LP, PHN, TN, PS, BP, PuN, LBP	10	30	80.1% with >50% reduction	N/A	3 months
Coyne et al. [12]	Pros	IV	39	CP (CIPN, PMP< PHN< RP)	10	45	32%	N/A	3 months
Ricci et al. [19]	Pros	IV	73	CP, non-CP	10	45	81% (pooled data)	N/A	2 weeks
Sparadeo etal. [8]	Pros	IV	91	SSSP, NP. CRPS< MSP	10	45	59%	N/A	3-6 months
Smith etal. [13]	Pros	IV	16	CIPN	10	60	59%	N/A	1-2 months
Marines, et al. [10]	Pros	IV	11	CP			95%	N/A	24 hours
Compagnone et al. [17]	Retro	IV	147	NP, NocP, mixed	10 (mean)	45	79%	Medication use (reduced), sleep quality (improved), Influence on work (improved)	3 months
Moon et al. [21]	Retro	IV	147	NP<NocP, mixed	3 (on consecutive days) or 5 (overall)	40-60	38.1% with >50% reduction	N/A	N/A
Smith and Marineo [13]	CS	IV	10	PHN	10	30	95% (VAS)	N/A	3 months
Ko et al. [16]	CR	IV	3	PHN	10	50	58%, 67%, 50%	N/A	2 weeks
Park et al. [15]	CR	IV	3	CP	10	40	57%, 100%, 67%	area of pain (reduced size)	2 months

Rand=randomized Pros=prospective, Retro=retrospective, CS=Case Series, CR=Case Report, LBP=lower back pain, PS=post-surgical pain, neuropathic NP=pain, post-herpetic neuralgia=PHN, SCS=spinal canal stenosis, CP=cancer pain, TN=trigeminal neuralgia, BP=brachial plexopathy, FBSS=failed back surgery syndrome, SP=sciatic pain, LP=lumbar pain, PuN=pudendal neuropathy, PMP=post-mastectomy pain, RP=radiation related pain, SSSP=single-site spine pain, MSP=multi-site pain, CRPS=complex regional pain syndrome, PN=peripheral neuropathy, PolyN=polyneuropathy, NocP=nociceptive pain.

a=sham-controlled; b=stratified

Table 1: Description of randomized, prospective, retrospective, and case studies reporting on pain reduction with ST treatment.

Cancer-related pain

Early ST researched aimed to evaluate the therapy's ability to treat CIPN in patients with cancer. Despite these efforts, there have been no double-blind sham-controlled trials, resulting in a weak level of evidence. Marineo et al. [10] conducted an initial study, involving 11 patients with terminal cancer and medication-resistant NP. Treatment of these patients included 10 to 45 minute sessions. Reduction of pain medication was achieved for 18.2% of patients, with 81.8% totally discontinuing pain medication. As a result of this early study, a follow-up open label clinical trial examined a large population of 33 subjects. These patients were also diagnosed with medication-resistant chronic NP and treatment with similar ST parameters [11]. Findings showed a decrease in Visual Analog Scale (VAS) scores for all patients. Additionally, 28% significantly reduced pain medications, with 72% of patients discontinuing pain medication entirely.

Coyne et al. [12] independently found similar results in a cohort of patients with peripheral neuropathy with a variety of etiologies. These included CIPN, post-mastectomy pain; post-surgical pain; post-herpetic neuropathy, post-radiation pain, or others such as vertebral compression fracture. The overall pain score decrease was significant and this significance was maintained when the subjects with a diagnosis of CIPN were compared to the rest of the cohort (results not shown). Thirty-nine subjects with a mean age of 56.5 were included in this study.

Twenty-three subjects were women and all subjects were treated over a period of 18 month for an average of 9.3 treatments each. The "now" pain score decreased from 6.6 before treatment to 4.5 at 14 days, and 4.6, 4.8, 4.6 at 1, 2 and 3 months respectively (p<0.001). The study also reported clinically important and statistically significant improvements in average pain, least pain, worst pain, and life interference. In addition, in an open label pilot study, Smith et al. [13] reported improvement in pain outcomes in a cohort of 16 patients with CIPN.

The effect of ST on cancer-related pain syndromes other than CIPN has also been addressed. In an open label prospective study, Notaro et al. [14] studied 25 consecutive patients with metastatic disease and reporting a decrease in pain scores from 8.4 at baseline to 2.9 after treatment (89% pain reduction), sleep hours improved from 4.4 ± 1.2 to 7.5 ± 1.1, and duration of pain relief was 7.7 ± 5.3 weeks in the absence of adverse events. These results are also consistent with case reports by Marineo in pancreatic cancer and Park et al. [15] in metastatic bone cancer [10,15].

General neuropathic pain

More recently studies address and define effect of ST in NP syndromes of non-oncologic origin. There are differences in study design among trials, mostly due to the variety of diagnoses included in studies. The diagnoses include post-herpetic neuralgia alone, a combination of NP syndromes of non-oncologic origin, and a combination of CIPN and non-cancer related pain [12,14,16,17]. A study by Starkweather et al. [18] is the only randomized, sham-controlled study. This study examines patients with low back pain (LBP) and has the main outcomes of pain and gene expression. Thirty subjects were included in this trial that reported significant reduction in "worse pain" and interference scores at 13 weeks of treatment.

There were also significant differences in pain sensitivity and differential mRNA expression of 17 pain genes, suggesting that ST can be effective in reducing pain intensity and interference in individuals with persistent LBP by altering the mechanisms of enhanced pain sensitivity. Sparadeo et al. [8] conducted a prospective open label study similar to the controlled study presented above (10 weekday treatment sessions of ST 45 min each). The authors reported pain relief across 173 patients with a variety of chronic NP diagnoses: complex regional pain syndrome (CRPS), single-site spine-based pain (e.g. spinal stenosis or LBP) and neuralgia (peripheral neuropathy, post-herpetic neuropathy, chemotherapy-induced peripheral neuropathy). All diagnosis groups experienced a mean VAS rating that was decreased by more than 50%, within all 10 daily sessions.

Another prospective open label clinical trial by Ricci and colleagues examined the effect of ST on a mixed patient population, including diagnoses of cancer-related and non-cancer pain. Like other studies of this nature, treatment occurred over 10 sessions of 45 minute durations each, in addition to a follow-up two weeks after the end of treatment [19]. Forty patients with cancer-related pain and 33 with non-cancer pain were studied for the primary outcome of change in VAS scores prior to treatment, after 10- treatments, and at 2 weeks post-treatment. Mean VAS scores were 6.2, 1.6, and 2.9 for the time checkpoints listed above, respectively. Consistent with prior studies, these results suggest ST's efficacy for NP relief and support the therapy as a potential standard of care.

In a retrospective review of 201 charts of patients treated with ST, Compagnone and coworkers also reported decrease in pain outcomes in a mixed cohort of patients with NP [17]. Patients reported an NRS of 7.41 (SD 2.06) before treatment and 1.60 (SD 2.22) post-treatment with a statistical significant of p<0.0001. Main diagnoses were post-herpetic neuralgia 18.40%, chronic LBP, 37.31%, polyneuropathy 10.94%, and peripheral neuropathy 14.42% with chronic pain due to other causes in the remaining 18.93%.

The difference in NRS between pre- and post-treatment was 7.41 (SD 2.06). The mean number of sessions per patient was 10, with 39 using fewer sessions due to resolution of pain. Seven patients stopped treatment due to lack of results and 2 dropped out for non-related treatment reasons.

Specific neuropathic pain syndromes

Some studies attempt to determine which NP syndromes best will respond to or benefit from ST treatment. Sabato et al. [20] treated 276 patients with ST. These patients carried a variety of NP diagnoses,

including failed back surgery syndrome, sciatic and lumbar pain, post-herpetic neuralgia, trigeminal neuralgia, post-surgical, brachial plexopathy, pudendal neuropathy and LBP. The study found significant pain reduction when all patients were pooled together and also significant reduction for each individual diagnosis. In an open label prospective trial by Ko et al. [16], 10 patients with PHN underwent 10 to 50 minute session of scrambler therapy. The authors ultimately found 95% "right now" pain reduction [16]. For three cases of elderly adults, this study looked at allodynia, in addition to pain. Longer lasting relief and diminished allodynia by the 2nd, 3rd and 5th treatments were experienced by all patients. Constant aching pain decreased by 50% in all three patients upon completion of the 10th treatment. Further, tactile allodynia was completely resolved in all three patients.

Predictors of efficacy

Efforts have been made to identify predictors of efficacy for ST treatment; however, no controlled studies currently exist. The prospective study by Moon et al. [21] is open label and evaluated 147 patients that received 3-5 treatments in 3 different centers. A successful outcome was defined as pain score improvement >50%. Overall, the success rate was 38.1%. Variables found to be associated with a positive outcome in multivariate logistic regression included the presence of neuropathic (P=0.006) or mixed (P=0.042) pain. Positive outcomes were also associated with treatment at either Walter Reed (OR=6.87; 95% CI, 1.60-29.51; P=0.010) or Seoul National University (0.012). Factors that correlated with treatment failure were disease (P=0.02) or traumatic/surgical etiologies (p=0.05; 95% CI, 0.005-0.56; P=0.015) and antidepressant use (P=0.05).

Discussion

Open label and controlled studies suggest that ST may be effective in alleviating chronic pain; however, the reported rate of pain reduction is variable [1,17,21,22]. Speculation considers the variability in the results of ST treatment as a result of heterogeneity in pain syndromes, patient selection criteria, pain diagnosis, pain locations, and range of pain intensity [23-25]. Hence, more strict inclusion criteria will be needed in future studies to determine which pain syndromes yield the best response to ST treatment.

Collectively, the data on ST for cancer-related and non-cancer pain suggests a strong analgesic effect in neuropathies that may outlast the treatment sessions [1,5,8,11,15-18, 20,21]. In addition, open label studies suggest an improvement in allodynia, tingling, and numbness. However, the level of evidence for ST treatments in NP syndromes is weak. Based on the methodology that we used to classify the level of evidence, to date there are not enough studies with adequate evidence to support any level of treatment recommendation [12].

There is one placebo-controlled randomized study that was graded as level II and a randomized trial graded as level III; however, at least two convincing class III studies are necessary to make the lowest level of recommendation (level "C", possibly effective or ineffective).

Conclusion

Although no recommendations have been made, the 15 studies identified suggest that ST is effective for the treatment of oncologic and non-oncologic types of NP.

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