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ARTICLE

Neuropathic pain in spinal cord injury: topical analgesics as a possible treatment

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Abstract

Study design Review of the literature and semi-structured interviews.

Objective To explore the possible use of topical analgesics for the treatment of neuropathic pain (NP) in spinal cord injury (SCI).

Setting Institute for Neuropathic Pain, Soest, The Netherlands.

Methods A review was performed of studies on topical analgesics for SCI-related NP published up to May 2019. In addition, eight persons with SCI-related NP who were treated with topical analgesics were interviewed in a semi-structured interview on their experience with topical analgesics.

Results Seven studies (five case reports and two case series) were found that evaluated the use of topical analgesics for SCI-related NP. None of the studies used a control treatment. Topical analgesics included baclofen, ketamine, lidocaine, capsaicin, and isosorbide dinitrate. All studies reported a decrease in NP over time. Persons interviewed were 49–72 years of age and all but one had an incomplete SCI. They used topical agents containing phenytoin, amitriptyline, baclofen, ketamine or loperamide. All showed a decrease in pain of at least 3 points on the 11-point numeric rating scale during this treatment.

Discussion/conclusions Evidence on the use of topical analgesics in SCI is scarce. Case reports, case series and interviews suggest that the use of topical analgesics can be beneficial in treating SCI-related NP. Placebo-controlled studies are required to investigate the effect of topical analgesics on SCI-related NP.

Introduction

Neuropathic pain (NP) is a common condition among people with spinal cord injury (SCI). The prevalence of NP in SCI is estimated at 53% [1]. Chronic pain in SCI is known to have a negative effect on quality of life [2–4]. NP has been described as the most severe type of pain in SCI [5]. Health care professionals and people with SCI point out NP as one of the most important challenges in SCI [6, 7].

Systemic anticonvulsants (pregabalin and gabapentin) are the most evidence-based pharmacotherapies in treating SCI-related NP to date. Other common pharmacological treatment options include antidepressants, opioids, and cannabinoids [8, 9]. However, the effectiveness of pharmacological treatments is suboptimal [8, 9]. Also, their long-term use is associated with the risk of developing adverse events on the central nervous system, like somnolence, fatigue, and drowsiness [9, 10]. Therefore, many people with SCI use non-pharmacological interventions, such as physical therapy, psychological therapy, or homeopathy as main or supplementary treatment of NP.

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However, the use of non-pharmacological treatments for SCI-related NP is not supported by scientific evidence and, consequently, current guidelines on SCI-related NP rarely include such treatments [11, 12].

The use of topical analgesics has been studied in peripheral NP. A recent single-blind placebo-controlled trial showed a positive effect of phenytoin 10% cream compared to placebo in persons affected with several types of peripheral neuropathies [13]. It is hypothesized that changes in peripheral nerves influence SCI-related NP [14, 15]. Also, clinical practice does show positive results of the use of topical analgesics for SCI-related NP [16, 17]. Therefore, the aim of this study is to explore the possible use of topical analgesics as a treatment for SCI-related NP by a literature review and interviews with persons with SCI treated with topical analgesics for NP.

Methods

First, a literature search was performed in Pubmed, Embase, and Web of Science using the following keywords: "spinal cord injury", "neuropathic pain", and "topical". Titles and abstracts were screened for relevance to the subject. The participant's characteristics, location of pain and type of treatment were extracted from the included studies. As it was expected that the search would produce only few and low-quality studies, a systematic review approach with meta-analysis was considered not applicable.

In addition to the literature search, a convenience sample of people from the Institute for Neuropathic Pain in the Netherlands were invited for a telephone interview. The Institute for Neuropathic Pain is an outpatient clinic specialized in treating persons with NP, not associated to a University Medical Center. Inclusion criteria were: having SCI, suffering from NP and being treated with topical analgesics at the time of the interview or in the past. The topical analgesic containing an active pharmaceutical ingredient (API) was administered at the outpatient clinic. If the pain decreased in 30 min, the treatment was considered effective and the treatment was prescribed. A structured interview scheme was developed including questions on demographics, level and etiology of SCI, years affected, use of topical analgesics and pain score on the 11-point numeric rating scale (NRS) before and after application of topical analgesics. Ratings of pain severity before and after application were asked on the most recent time the participants used the treatment. The interview questions were asked for the most effective type of API.

Results

Literature review

Five case reports and two case series (two and five participants) describe the use of topical analgesics in SCI-related NP [16–22]. Characteristics and results of the case reports are shown in Table 1 and those of the case series are shown in Table 2. All studies reported positive effects of topical analgesics on the severity of NP. However, none of the studies compared the use of topical analgesics to placebo or alternative treatment. All but one study and one case series used lidocaine and capsaicin. One study and one case series described a novel topical analgesic with 5% baclofen cream (case report) and 10% ketamine cream (case series).

Persons interviewed

Eight persons (four men) treated at the Institute for Neuropathic Pain were interviewed on their current or past experience of topical analgesics. Their age ranged from 49 to 71 years. Characteristics and their experienced pain relief are shown in Tables 3 and 4. All but one person were suffering from incomplete SCI. Six persons were experiencing below level NP and two were experiencing at level NP. Treatment included topical analgesics with the following APIs: phenytoin (anticonvulsant), baclofen (antispastic), ketamine (anesthetic), amitriptyline (antidepressant) or loperamide (opioid). Persons were informed to apply the topical analgesic when needed with a maximum of four times a day. Different topical APIs were tested on each person at the outpatient clinic. The next topical API was used if the previous did not suffice in effect on pain. Time to effect after administration of the topical analgesic ranged from instant effect to 30 min. Topical analgesics were used two times a day on average. All but one participant (participant 2) were current users of topical analgesics. Participant 2 stopped the treatment 1 year ago at the time of the interview, due to decreasing effect. All mentioned a decrease of at least 3 points on the NRS. All mentioned they were satisfied with the treatment and would recommend it to a friend or had recommended it already. One person (participant 2) reported getting a rash from previously used topical phenytoin 10%.

Discussion

Little is known about the use of topical analgesics in SCI-related NP. Solely case reports and case series on this treatment modality could be found in the literature. Case

Table 1 Characteristics of case reports.

Article	# of persons	Patient characteristics	Pain characteristics	Intervention	Results
Hans et al. [18]	1	54-year-old male Non-traumatic T11[a] Pain at level	Spontaneous pins and needles with mechanical allodynia at T11	Lidocaine 5% patch 12 h on/off Patch applied on the T11 dermatome on the abdomen.	Decrease of pain after 4 h and almost complete disappearance after 12 h. Pain slowly increasing several hours after removal of patch.
Wasner et al. [19]	1	55-year-old male Traumatic T12 AIS D Pain below level	Ongoing burning, shooting, and stinging. Fairly symmetrical in two thighs. NRS 5	Capsaicin 0.6% Lidocaine 5% patch 12 h on/off. 7 days treatment phase and 7 days washout phase (where no patches were applied) One patch per thigh covering the painful area.	Capsaicin increased thermal pain Lidocaine: reduction of pain by about 45% in treatment phase. Analgesic effect still reported after 1 year of treatment.
Kopsky et al. [16]	1	63-year-old male Non-traumatic C5[a] Pain at and below level	burning pain in his right armpit, upper back, and neck. NRS 6.	cream consisting of: 0.075% capsaicin 3% lidocaine 0.4% isosorbide dinitrate Applied to right armpit, upper back, and neck	Decrease of pain NRS 6–3 in 1 month.
Kopsky et al. [17]	1	71-year-old female L3 AIS D Non-traumatic At and below level	Tingling, pins and needles, burning, and numbness in both legs	Baclofen 5% On every neuropathic pain area located on both legs	Complete resolution of neuropathic pain from NRS 6 after 1 month. More difficulties walking, frequently falling because of decreased pain.
Freo et al. [20]	1	67-year-old male Non-traumatic T5 incomplete[b] At level	Burning and shooting pain on the left side of the thorax with allodynia on the left side of the thorax	Lidocaine 5% patch 12–16 h per day	Decrease of mean NRS from 6 to 2 and worst NRS from 9 to 4. Effect continuing in period without patch.

AIS ASIA (American Spinal Injury Association) Impairment Scale, *NRS* Numeric Rating Scale.

[a]Completeness of injury is not mentioned in study.

[b]AIS classification is not mentioned in study.

Table 2 Characteristics of case series.

Article	No of cases	Patient characteristics	Pain characteristics	Intervention	Results
Trbovic et al. [21]	2	Male Non-traumatic T5 (1) and C5 (2) AIS D At level (1) and below level (2)	(1): Spontaneous sharp and burning T2–T8 with allodynia (2): Continuous burning at left hip extending to knee with allodynia	Capsaicin 8% plaster applied for 1 h, then removed as a daily treatment.	(1) Complete resolution of pain 2 weeks after application from NRS 7. hyperesthesia over the application site for 24 h. (2) Complete resolution of pain 2 weeks after application from NRS 8.
Rabi et al. [22]	5	All Male All Traumatic All below level pain All NRS before application >5 (1) T10 AIS A (2) C4 AIS B (3) T12 AIS A (4) T6 AIS A (5) C4 AIS C	Usage of pain diaries is described but no information about pain characteristics is given.	Ketamine 10% applied three times a day for a total of 2 weeks.	Pain reduction varying from 14% to 63% 1 h after application. Post-application score after 2 weeks was similar to post-application score after 1 h.

AIS ASIA (American Spinal Injury Association) Impairment Scale, *NRS* Numeric Rating Scale.

Table 3 Characteristics of persons interviewed.

ID	Sex	Age	Level	Etiology	Completeness	Localization	Current oral neuropathic pain medication	Past oral neuropathic pain medication
1	F	71	T5	Non-traumatic	Incomplete	Below level	Opioids	Anticonvulsants
2	M	63	C5	Traumatic	Incomplete	Below level	None	None
3	F	62	T12	Traumatic	Incomplete	Below level	None	Anticonvulsants Tricyclic antidepressants
4	F	59	C6	Traumatic	Incomplete	At level	None	Anticonvulsants
5	M	63	C3	Traumatic	Incomplete	Below level	Anticonvulsants	None
6	F	49	C3	Traumatic	Incomplete	Below level	Spasmolytics	Opioids
7	M	72	C3	Traumatic	Incomplete	Below level	Tricyclic antidepressants	Anticonvulsants Tricyclic antidepressants Opioids
8	M	50	T5	Traumatic	Complete	At level	None	None

F female, *M* male.

reports, case series and interviews with people with SCI treated at the Institute for Neuropathic Pain, describe a positive effect of topical analgesics on SCI-related NP.

Several theories on the mechanism of SCI-related NP exist. Its etiology is thought to be multifactorial. Altered firing of thalamic and cortical neurons, increased responsiveness to peripheral stimulation from the dorsal root and peripheral changes itself are believed to play a role in the pathophysiology of NP [14]. Current treatment of SCI-related NP is based on the central mechanism, as oral anticonvulsants and antidepressants are the most studied treatments [9]. To understand the rationale behind the use of topical analgesics, it is important to consider the changes and influence of peripheral nerves in SCI-related NP. SCI Rat models have shown the presence of peripheral sensitization in NP [15]. Sensitized nociceptors were found in the forelimbs of rats suffering from SCI. In vitro nociceptor responses of SCI rats showed a lowered mechanical and thermal threshold and increased spontaneous activity compared to naive and sham rats 35 days post injury. The increased background activity caused by this peripheral sensitization could explain the spontaneous pain in persons with SCI. Furthermore, there are reports that the degree of peripheral inflammation and neutrophil accumulation are modulated by the central nervous system [15, 23]. Low-grade peripheral inflammation is believed to be one of the causes of SCI-related NP shown in animal models [15]. The pathophysiology of this phenomenon has not been described in human studies.

The studies described in our results section suggest that peripheral influences play a role in SCI-related NP in humans. As described by Wasner, the effect of the lidocaine patch in a person with SCI was similar to the effect of a lidocaine patch in people with local peripheral NP syndromes [19]. NP in peripheral neuropathies is caused by an ectopic discharge by the damaged afferent neurons. In addition, intact afferents that share the territory innervated also show a spontaneous discharge of action potentials. These abnormalities found in intact afferents are likely to account for the fact that topical treatments are effective [24]. This phenomenon has also been observed in other types of central NP. In poststroke pain a pilot study of eight people suffering from a stroke showed a decrease in NP after a peripheral nerve block using lidocaine 2% was performed, showing that peripheral nerve blockage can influence pain in damage to the central nervous system [25].

Whether completeness of injury is related to the mechanism of NP in SCI is not studied to date. From people interviewed, all but one suffered from incomplete SCI. The pain described in the person interviewed suffering from a complete lesion was at the level of injury. Partial innervation at this level may play a role in the occurrence of NP. All but one of the case series describe the effect in persons with incomplete lesions. The case series on topical ketamine describes three out of five persons with complete SCI [22]. Pain phenotyping has been considered of importance in the treatment of NP [26, 27]. Adjusting treatment to the specific pain related symptoms can be a promising way to alter the treatment specific to the pain mechanism [28]. Completeness of injury can be an important parameter in different NP phenotypes. Further studies on the mechanism on NP and phenotypes in NP in SCI are needed to consider the role of completeness of injury in SCI-related NP.

None of the studies described compare the effect of the topical analgesics to placebo treatment. Placebo-effect can play an important role in topical analgesic treatment. A systematic review on knee-osteoarthritis pain shows an increased effect of topical placebo compared to oral placebo (Standardized Mean

Table 4 Type of pain, patient-reported effects on pain and topical analgesics of persons interviewed.

ID	Location of NP	Type of NP	Pain (NRS) before application	Pain (NRS) after application	Time to effect (min)	Applications per day	Current topical analgesic	Past topical analgesic(s)
1	Shin/feet	Ongoing burning	8	4	20	3	Phenytoin 10%	Amitriptyline 10%
2	Upper back Feet	Upper back: ongoing burning Feet: ongoing tingling	8	5	10–15	3	None	Baclofen 5% Amitriptyline 10% Phenytoin 10%
3	Lower legs/feet	Ongoing burning Evoked pins and needles in cold temperature	7	4	10–15	2	Phenytoin 5%	Amitriptyline 5% Baclofen 5%
4	Hands	Burning evoked by touch	8	4	15–30	2–3	Phenytoin 10%	Amitriptyline 10%
5	Entire body from head down	Ongoing burning Intermitting tingling/pins and needles	5	2	30	2–3 (per week)	Baclofen 5%	Ketamine 10%
6	Right arm Left leg	Ongoing burning/tingling/pins and needles Increased by cold temperature	9	5	30	2	Amitriptyline 10%	Baclofen 5%
7	Both legs	Cold/hot not specifically evoked	5	2	30	2	Loperamide 5%	None
8	Chest	Ongoing pain: strap around chest	8	3	0	1–2	Baclofen 5%	None

NRS Numeric Rating Scale.

Difference: 0.20, 95% credible interval: 0.02–0.38) [29]. In addition, topical treatment with placebo can remain to have an analgesic effect, even after it has been revealed to the participant that it has no chemical compound [30]. The act of treating the skin, even without the chemical compound, seems to have a significant effect on pain in osteoarthritic pain. In contrast to this, another meta-analysis found that individuals with SCI and NP have no significant placebo response in clinical trials testing pharmacologic interventions lasting 4 weeks or longer [31]. Because no placebo-controlled studies on topical treatment in SCI exist, this meta-analysis did not include studies using topical treatments.

Using topical analgesics to treat NP has a definite advantage compared to systemic treatments when considering side effects [8, 10]. As shown in studies on peripheral NP, use of local treatments show little or no side effects, where systemic treatments with anticonvulsants and antidepressants cause considerably more [32]. This is also confirmed by reported side effects in the persons interviewed. Only one person reported a local side effect.

As described in the interviews and shown in the study on peripheral neuropathies, topical analgesics based on anticonvulsants, antidepressants, and antispastics might influence NP [13]. The effect of the topical analgesics compared to placebo can be evaluated in a double-blind placebo-controlled cross-over trial. In such a trial the participants will use both the cream containing an API and the placebo cream sequentially. Decrease in NP will be described during these treatments. This N-of-1 response test has been used in clinical practice to establish a personalized treatment [33, 34].

Limitations of this study include a low number of people interviewed and that the effect of topical analgesics to NP was asked as part of the interview and not longitudinally during treatment. Therefore, the NRS before and after applying the topical analgesic rely on a person's memory of the NP. This might have given another result if the person was asked longitudinally during their treatment. In addition, someone could be more driven to consent to an interview, if the treatment was effective. A misrepresentation of the treatment effect should therefore be taken into account.

Conclusion

The body of evidence on topical analgesics on SCI-related NP is scarce. Case reports in the literature and interviews with persons suggest a beneficial effect of topical analgesics in SCI-related NP. Placebo-controlled studies on topical analgesics in SCI-related NP are required to confirm its pain reducing effect.

Data availability

The data can be provided by the authors on request.

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Compliance with ethical standards

Conflict of interest DJK is holder of two patent applications: Topical phenytoin for use in the treatment of peripheral neuropathic pain (WO2018106107); and Topical pharmaceutical composition containing phenytoin and a (co-)analgesic for the treatment of chronic pain (WO2018106108).

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