Analgesic effectiveness of subcutaneous carbon-dioxide insufflations as an adjunct treatment in patients with non-specific neck or low back pain

A pragmatic, open, randomized controlled trial

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SUMMARY. Objectives: To evaluate the analgesic effectiveness of subcutaneous carbon-dioxide insufflations in addition to standard physical treatment in patients with non-specific neck or low back pain. Design: A pragmatic, randomized controlled trial. Setting: Rehabilitation hospital inpatients. Interventions: Patients received either subcutaneous carbon-dioxide insufflations (10 treatments) and standard physical treatment or standard physical treatment only. Outcome measures: Affective pain perception (42-point scale), sensory pain perception (30-point scale), pain intensity (100 mm visual analogue scale). Results: Between-groups differences were –2.2 [95% CI –5.2; +0.9] (affective pain perception), –1.2 [–3, 0; + 0.7] (sensory pain perception), and –6.5 [–14; +1.0] (pain intensity) respectively in favour of subcutaneous carbon-dioxide insufflations. Conclusions: Subcutaneous carbon-dioxide insufflations do not seem to be a worthwile adjunct in the given setting of inpatient rehabilitation. Trials in a monotherapeutic setting, which aim more at the efficacy of subcutaneous carbon-dioxide insufflations, might help to solve this issue.

INTRODUCTION

Subcutaneous carbon-dioxide insufflations (SCI) are used almost exclusively in Central Europe as a serial treatment modality in naturopathy.[1] Sources are gas from natural springs or medical (purified) CO_2. Unlike medical CO_2 gas, spring gas contains small amounts of other compounds (normally less than 5 vol %) like N_2, Ar, He, O_2, H_2, H_2S or CH_4.[2,3] The first insufflations are presumed to have been carried out in Royat (France) at the beginning of the 20th century.[4]

'Headache' (including migraine), various 'musculoskeletal affections' (mainly neck and back pain, osteoarthritis, and enthesopathy), and 'peripheral arterial occlusive disease' are considered conditions for which SCI may be indicated.[5]

SCIs are ascribed mainly analgesic effects.[6] The mode of action is unknown. Some authors[5,7] propose that the observed analgesia is the result

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of a local increase of subcutaneous blood flow.[8,9]

In 1960, Diji and Greenfield[10] found mean relative skin temperature rises of 1.5˚C compared to injections with laughing gas, air-or cyclopropane, if 50% (CO_2/N_2O gas mixture) or 100% CO_2 gas had been insufflated subcutaneously. The authors interpreted their findings as evidence of a specific vasodilator action of CO_2. Today, CO_2 is widely accepted as natural vasodilator with local properties like oxygen or the hydrogen ion.[11,12] The vasodilatation induced by the freely diffusible CO_2-gas is based most probably on a direct effect on the vascular tone[13] (e.g. via an alteration of the membrane calcium flux[14]).

On the basis of a recent systematic review,[15] considering English, Czech and German language papers, five randomized[6,16–19] and two non-randomized controlled trials[20,21] on the clinical effectiveness of SCI were identified. The conditions included in the studies were peripheral arterial occlusive disease, Fontaine stage II,[6,16,19,20] headache,[18,20] and stable angina pectoris.[17] Three studies evaluating SCI in addition to standard physical therapy (SPT),[6,17,19] as well as one study comparing SCI with, 'dry needling'[18] (a kind of sham needling, where needle injection is performed without substance administration) provided effects in favour of SCI. All studies comparing SCI with CO_2 gas baths[16] or combined interventions, including SCI,[20,21] showed no differences between groups. However, the methodological quality of all these trials was too low to draw valid conclusions.[15] No study achieved a score of ≥50 points on the Maastricht-List[22] (maximum: 100 points).

Referring to musculoskeletal conditions, evidence on the clinical effectiveness of SCI is only available from uncontrolled clinical trials.[7,23]

The following trial aims to evaluate the analgesic effectiveness of SCI in addition to SPT in patients with non-specific neck or low back pain.

METHOD

Pragmatic approach

The study was designed as pragmatic trial.[24,25] The rationale for choosing this approach was to evaluate, whether SCI are a worthwhile adjunct in a clinical context, in which they are often applied. We did not include a placebo control, because responses in clinical practice are based on both the specific and non-specific effects of a treatment modality.[25] In other words, we focused on the effectiveness rather than the efficacy of the intervention.

Subjects

All consecutive patients of an inpatient, orthopaedic rehabilitation hospital, referred from general practitioners or specialists, were considered possible candidates for study inclusion. Subjects had to report neck and/or low back pain to be enrolled into the study. Further inclusion criteria were pain intensity ≥40 mm on a 100 mm long visual analogue scale, duration of current pain episode ≥1 month, and written informed consent. Persons with malignant disease, radicular syndrome, inflammatory disease or surgery in the treatment area were excluded.

Registration and randomization

Every patient met the investigator (AD), who checked the eligibility criteria. After informed consent was given, the investigator called an independent, external study coordinator (TB) via a telephone hotline, who registered date of study entry, initials and date of birth of every participant. The investigator was told the running trial number, treatment assignment and name of the physician (n = 2), who performed the injections. The allocation of patients to treatment and the assignment of care providers to patients were based on pre-established lists of random permuted blocks of size 20 and 10 respectively. The randomization lists were prepared by the study coordinator.

Intervention

Persons referred to the investigational treatment group (SCI-group) received 10 SCI in addition to SPT (see below). The injections were given once a day, except for Saturday and Sunday. SCI were bilaterally administered at the site of maximum tenderness. If no tender points could be elicited, injections were given at defined locations (about 1 cm paracervical at the C6/C7 level and/or 2 cm paralumbar at the L5/S1 level). In neck pain 2 × 50 ml, in low back pain 2 × 100 ml, and in neck and low back pain 4 × 50 ml of CO_2 gas was insufflated. Each injection was documented on a list and signed by the therapist.

The treatment device (MedServ GmbH, Leipzig, Germany) consisted of a high-pressure gas cylinder with liquified CO_2 (50 bars), a standard pressure-reducing valve reducing the pressure to 1.5 bars, a tube junction, and a volume adapter for delivering a fixed gas volume of 25 ml CO_2 gas per injection. At the outlet of the volume adapter a bacterial filter and a tube attachment were installed.

Persons referred to the control group received only SPT. SPT consisted of a defined combination of physical interventions (4 × exercise therapy at the discretion of the physical therapist, 30 min per session; 4 × hot peat packs, 15 min per session; 4 × therapeutic continuous ultrasound, 800 kHz, 0.7 W/cm^2, 10 min per session; 4 × TENS, 100 Hz, intensity adjusted to suit the patient, 15 min per session; 2 × health education on pain control, 60 min per session).

The intervention period for both study arms was 12 days.

Persons were advised not to change type or dose of their existing pain medication during the trial.

In order to increase participation rate and minimize drop-outs as well as for ethical reasons, controls were offered to be treated with SCI after the end of the study period.

Outcome criteria

Affective pain perception, sensory pain perception, and pain intensity were selected as primary outcome criteria. Secondary outcome measures were not defined. Affective and sensory pain perception were measured by the so-called 'Schmerzempfindungsskala' (SES) according to Geissner,[26,27] a validated German Language pain questionnaire. Pain intensity was assessed by a 100 mm long visual analogue scale.[28,29]

The SES is a self-report dimension-specific instrument based on the McGill Pain Questionnaire.[30] The reason for its development was psychometric shortcomings of the McGill Pain Questionnaire.[31,32] The questionnaire measures affective pain perception (SES-affective) by 14 items, and sensory pain perception (SES-sensory) by 10 items. Methodological and contents-related considerations suggest a combination of the two dimensions to a total pain score not to be reasonable.[26,27,31,32] For each item, a 4-point Likert scale is used. The response options are coded by numerical values from 1 to 4 (1 = 'does not apply at all', 2 = 'applies somewhat', 3 = 'applies to a large extent', 4 = 'applies precisely'). The scores for SES-affective and SES-sensory are calculated by summing up the (marked) numerical values for each dimension. Accordingly, the range for SES-affective varies between 14 und 56, for SES-sensory between 10 und 40. Missing values are replaced by the mean of all valid answers. For SES-affective, a maximum of 2 missing values may be replaced, for SES-sensory only one. High scores correspond to high pain perception. SES-affective/SES-sensory was found to have high internal consistency (0.92/0.96) and test-retest reliability (0.81/0.95).[27] Convergent validity could be demonstrated with pain measures, pain-related disability, depression and anxiety (correlation coefficient = 0.3–0.6). Pain perception did not correlate (divergent validity) with sociodemographic and pain history data (0.0–0.2).[26]

Based on Lisrel models, SES-sensory forms an important part of SES affective, while SES-affective has an additional quantity independent from SES-sensory.[26,32] It is assumed that this additional quantity refers to emotional strain and disposition factors, while SES-sensory covers mainly organic factors of illness.[26] The outcome criteria were assessed prior to treatment, after five, and after 10 injections.

Evaluation of adverse events

Study participants could contact a doctor 24 hours a day. Additionally, adverse events were regularly assessed by open questions after the 5th and 10th insufflation. Patients graded severity of adverse events on a 4-point rank scale ('mild', 'moderate', 'severe', 'very severe').

The investigator assessed the strength of the relationship between adverse events and the intervention given in four categories ('not related', 'possibly related', 'probably related', 'definitely related').

Description of the study population

The study population was described by sociodemographic characteristics (sex, age, body mass index, marital status, living together with a partner, employment status), and clinical variables (duration of the current pain episode, location of pain, analgesic consumption, concomitant diseases, overall health status).

Data Analysis

Statistical analysis was based on a one-sided hypothesis. A one-sided formulation of the study hypothesis seemed to be justified, because all controlled trials, identified in a previously performed systematic review,[15] evaluating SCI in addition to SPT (n = 3) showed effects in favour of SCI.[6,17,19] There was no evidence for SCI to be associated with any kind of relevant adverse reactions, neither clinically nor physiologically.[15] SCIs have, therefore, been considered a risk-free treatment modality with little side effects.[2,3]

The target sample size was set to at least 50 persons per group. This number yields a power of 80% to detect a moderate effect size difference (standardized response mean = 0.5) between the treatment groups when limiting one-sided α to 0.05.[33]

Primary analysis was done by two-way repeated measures ANCOVA. For each of the three outcome measures one test was performed. An adjustment for multiple testing was not defined in the study protocol, because we expected at least moderate correlations between the three pain-assessment measures. In a large pain population (description below), intercorrelations of 0.61 (SES-affective/SES-sensory), 0.54 (SES-affective/pain intensity), and 0.40 (SES-sensory/pain intensity) could be found.[26] 'Treatment' (SCI yes/no) was defined as a between-groups factor and 'change in outcome-score after the 5th and 10th insufflation' as a 2-level within-groups factor. To increase power, baseline-values of the outcome criterion tested were included as a covariate into the analysis.[34] Other covariates were not defined in the planning stage. Analysis was done on an intention-to-treat basis.[35] SPSS 8.0 for WINDOWS (SPSS Inc. Chicago) was used for statistical analysis.

For formal, unit-free description of treatment effect, standardized response means (SRM)[36] were calculated between and within groups.

Raw values of SES-affective and SES-sensory were standardized in relation to a large (n = 1048), non-specific pain population by means of a T-transformation (mean = 50, SD = 10). This was done to give an impression of the clinical relevance of the findings. The reference population formed a sample of persons with different pain locations and/or diagnoses, where both sexes as well as different age and socio-economic groups were distributed in approximately the same proportions.[26] Accordingly, it was supposed, that T-values less than 40 indicate 'below average' pain perception, T-values between 40 and 60 an 'average' pain perception and T-values greater than 60 an 'above average' pain perception.

T-values were subdivided into three categories according to the above-mentioned grading and the frequency of each category before and after treatment was presented in a 3 × 3 cross tabulation (Table 4). On this basis, a simple description of the individual course of treatment was possible. Furthermore, the 'number needed to treat' (NNT)[37] effect measure could be calculated. NNT denotes the number of patients who need to be treated to achieve an additional favourable change.[37]

Protection of subjects

The study was run according to the ethical guidelines of the Declaration of Helsinki. The trial protocol was approved by the local ethics committee (Sächsische Landesärztekammer, Dresden, Germany). Participants could leave the study, at any time, for whatever reason. The patients were informed verbally and in written form about contents, purpose and conduct of the study, and provided signed consent.

RESULTS

Progress through various trial stages

One hundred and forty-nine subjects were recruited within a time span of 4 months (17 March 1999 to 7 July 1999); 140 met the eligibility criteria and could be randomized (Fig. 1). One person referred to the SCI-group refused both study participation and follow-up assessment immediately after randomization. Six controls were contaminated by SCI during the 2nd half of the study period. Apart from the one withdrawal, all subjects in the SCI-group received 10 treatments.

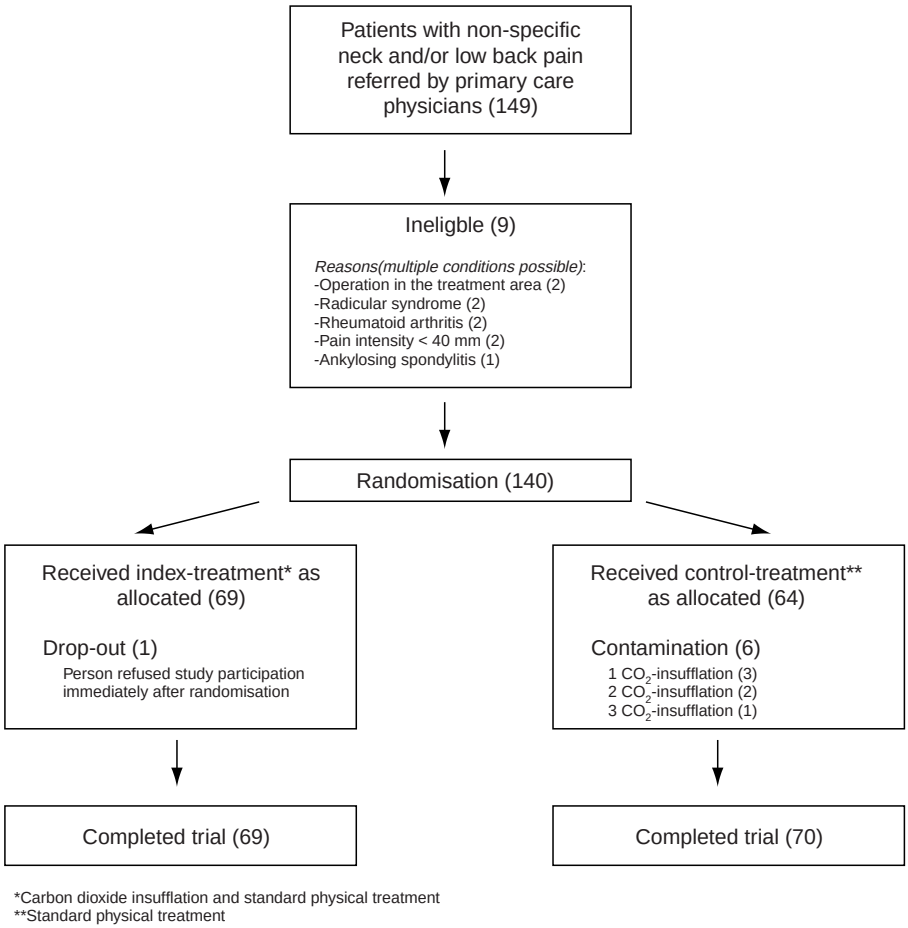

Fig. 1 Trial stages

Description of the study population, baseline comparability

The study covered an older, mainly female, mostly retired population with an 'average' pain perception and a high portion of musculoskeletal comorbidity (Table 1).

Slight imbalances between groups were found for 'analgesic consumption', 'overall health' and 'employment status'.

Primary analysis

Between-groups differences for SES-affective, SES-sensory, and pain intensity were –2.2 [95% Cl –5.2; +0.9], –1.2 [–3,0; +0.7], and –6.5 [–14; +1.0]), respectively, in favour of SCI (negative values indicate a decrease in pain perception).

In ANCOVA, between-groups comparisons showed a tendency ($P < 0.1$) towards superiority of the SCI-group for all outcome criteria (Table 2), but no statistical significance was obtained (one-sided P between 0.05 and 0.07). Within-groups effects were highly statistically significant ($P < 0.001$). Missing follow-up values of the only drop-out were replaced by summing up the mean pre/post changes in the SCI-group to the baseline values of the outcome measures.

Table 1 Baseline Characteristics*§§

	Index group *n* = 70	Control group *n* = 70	Total *n* = 140
Female/male ratio (no.)	53/17	55/15	108/32
Age (years)	65.6 ± 5.5	64.2 ± 8.7	64.9 ± 7.3
Body mass index (kg/m^2)	28.2 ± 3.6	28.3 ± 4.7	28.3 ± 4.2
Duration of current pain episode (no.) 1–3 months	2	1	3
3–6 months	66	67	133
> 6 months	2	2	4
Location of pain (no.)			
neck pain	31	35	66
low back pain	21	13	34
neck and low back pain	18	22	40
Analgesic consumption (no.)			
1. non-opioid analgesic#	31	23	54
a. NSAID**	26	17	43
b. other nonopioid analgesic§	5	4	9
c. combination of a and b		2	2
2. opioid analgesic#	3		3
3. combination of 1 and 2		3	3
Comorbidity (no.)†			
Osteoarthritis‡	43	39	82
Osteoporosis	12	17	29
Cardiovascular diseases##	36	29	65
Overall health status (no.)			
'good'	33	38	71
'moderate'	31	21	52
'poor'	6	11	17
Marital status (no.)			
single	5	8	13
married	49	43	92
divorced	6	6	12
widowed	10	13	23
Live context (no.)			
living together with a partner yes/no	19/51	25/45	44/96
Employment status (no.)			
employed	2	6	8
unemployed	2	3	5
disability pension	6	7	13
old age pension	60	53	113
housewife		1	1
Pain intensity (mm)	62.2 ± 13.2	63.9 ± 15.2	63.1 ± 14.2
Affective pain perception (range: 14–56)	28.6 ± 9.9	29.8 ± 11.1	29.2 ± 10.5
	(46.0 ± 9.0)	(47.1 ± 10.1)	(46.6 ± 9.6)
Sensory pain perception (range: 10–40)	18.2 ± 6.5	18.7 ± 6.7	18.5 ± 6.6
	(49.6 ± 10.1)	(50.3 ± 10.2)	(50.0 ± 10.1)

*Plus-minus values are means ± SD
§§Values in paranthesis denote standardized values in relation to a non-specific pain reference sample[26]
**Diclofenac, indomethacin, ibuprofen or meloxicam
§Paracetamol, propyhenazone, acetysalicylic acid, flupirtine or ergotamine
#Tilidine or tramadol
†according to the referring primary care physician
‡Osteoarthritis of the hip, knee, shoulder or hand
##Coronary heart disease, arrhythmia, heart failure or hypertension
NSAID: non-steroidal antiinflammatory drug

Table 2 Effects of Subcutaneous Carbon Dioxide Insufflations on Pain Perception*

	Baseline-Score	Mean change in score after five injections	Mean change in score after 10 injections	P**,+
Affective pain perception				
SCI-group (*n* = 70)	28.6 ± 9.9	–5.3 ± 9.0	–8.5 ± 8.0	0.067
control-group (*n* = 70)	29.8 ± 11.1	–4.1 ± 9.2	–6.4 ± 10.2	
Sensory pain perception				
SCI-group (*n* = 70)	18.2 ± 6.6	–2.4 ± 5.8	–3.9 ± 5.4	0.049
control-group (*n* = 70)	18.7 ± 6.7	–1.1 ± 5.1	–2.8 ± 5.7	
Pain intensity				
SCI-group (*n* = 70)	62.2 ± 13.2	–15.0 ± 17.5	–26.1 ± 23.3	0.058
control-group (*n* = 70)	63.9 ± 15.2	–11.6 ± 18.5	–19.7 ± 21.7	

*Plus-minus values are means ± SD
**Main effect of the between-groups factor 'treatment' in the Repeated Measures ANCOVA, covariate: baseline-values of the outcome measure tested
+*P*-value for a one-sided test

Secondary analysis

Effect size differences

Standardized response means between groups varied between 0.1 and 0.2 after five insufflations and increased between 0.2 and 0.3 after 10 injections (Table 3). Standardized response means in the SCI-group were about one-third higher than SRM in the control-group. The most pronounced longitudinal effects were found for pain intensity, the smallest for sensory pain perception.

Incidence of favourable findings

Thirty-two persons in the SCI-group (46%) compared to 27 controls (39%) reported favourable changes in SES-affective (Table 4). Comparable effects could be detected for SES-sensory. For both outcome criteria, the benefit increase was 7 percentage points, which yields a NNT of 14.

Incidence of pain aggravation

Three controls reported an aggravation of affective pain symptoms, while sensory symptoms exacerbated in four subjects in the SCI-group and five controls (Table 4).

Incidence of adverse events

Possible SCI-related adverse events occurred in two female controls. The first case was a low back pain sufferer, who was erroneously contaminated by SCI during the study-period. Ten minutes after insufflation, the affected person reported malaise, hypersalivation, metallic taste and dizziness. This reaction lasted for 15 min. The second case was a neck pain sufferer, who received SCI after the completion of the study. Six hours after the third insufflation, the affected woman complained of headache, nausea and vomiting. The symptoms lasted for about 2 h. In both cases adverse events led to discontinuation of the treatment at the request of the subject.

Severity of adverse events were graded in levels from 'moderate' to 'very severe' in both cases.

The investigator stated a 'probable' relationship with SCI in the first, and a 'possible' association in the second case. Persons receiving only SPT reported no adverse events.

Influence of pain location on treatment effect

In an exploratory three-way repeated measures ANCOVA with 'treatment' and 'pain location' as

Table 3 Description of the treatment effects by standardized response mean+

	After five injections	After 10 injections
Between-groups*		
affective pain perception	0.13	0.23
sensory pain perception	0.24	0.20
pain intensity	0.19	0.29
Within-groups (SCI-group)		
affective pain perception	0.54	1.0
sensory pain perception	0.37	0.68
pain intensity	0.94	1.47
Within-groups (control)		
affective pain perception	0.35	0.60
sensory pain perception	0.18	0.44
pain intensity	0.61	1.01

+Values between > 0.2 and 0.5 indicate small, between > 0.5 and 0.8 moderate and > 0.8 good effects.[33]
*all effects in favour of subcutaneous carbon dioxide insufflations

Table 4 Description of individual course

	At the completion of the study			
	Below average	**Average**	**Above average**	
SES-affective, SCI-group				
At baseline				
below average	19	0	0	
average	26	19	0	improved: 32
above average	1	5	0	impaired: 0
SES-affective, control-group				
At baseline				
below average	20	1	1	
average	19	19	1	improved: 27
above average	1	7	1	impaired: 3
$ABI = SR_I - SR_C = 32/70 - 27/70 = 0.07$; $NNT = 1/ABI = 1/0.07 = 14$				
SES-sensory, SCI-group				
At baseline				
below average	8	3	0	
average	17	29	1	improved: 28
above average	2	9	1	impaired: 4
SES-sensory, control-group				
At baseline				
below average	4	3	0	
average	14	34	2	improved: 23
above average	1	8	4	impaired: 5
$ABI = SR_I - SR_C = 28/70 - 23/70 = 0.07$; $NNT = 1/ABI = 1/0.07 = 14$				

SR_I: success rate in the investigational-group
SR_C: success rate in the control-group
ABI: absolute benefit increase
NNT: number needed to treat

between-groups factors, 'change in outcome-score after the 5th and 10th insufflation' as within-groups factor, and many potential prognostic factors as covariates (e.g. age, sex, analgesic consumption, musculoskeletal comorbidity, overall health status, etc.), no evidence was found for the assumption that pain location would influence treatment effects. The *P*-value for SES-affective was 0.7, for SES-sensory 0.4 (main effect of the between-groups factor 'pain location').

DISCUSSION

This study indicates a statistical tendency towards superiority of SCI as an adjunct treatment to SPT in patients with non-specific neck or low back pain, but no statistically significant was observed. Based on a formal grading proposed by Cohen,[33] the observed differences between the two treatment groups (between-groups SRM) are small and seem to be of little clinical relevance. From the results of this trial one can conclude that SCI may play only a minor role, if any at all, in addition to SPT in elderly persons with non-specific neck or low back pain in an inpatient rehabilitative setting.

In pragmatic trials there are various factors ('imperfections') that can mask a true benefit between treatment and control. In this trial, five factors might have been responsible for effect masking: control treatment, study condition, inclusion of patients, characteristics of the study sample and treatment regimen.

The extensive control treatment seems to be the most likely factor, that no marked independent analgesic effect of SCI could be observed.

For pragmatic reasons (e.g. to mirror the clinical situation) we included patients with neck or low back pain and did not stratify by pain location before randomization. Although secondary analysis showed no influence of pain location on outcome, pain location might have affected outcome in a stratified randomization.

The presentation of any local, physical findings was not defined as inclusion criterion. Possibly, if we had focused on patients with tender points, we might have observed a more pronounced effect.

The study sample covered an older and mainly female population. Therefore, we do not know how a younger population or males would respond to SCI.

The treatment regimen used in this study was based on statements given in an uncontrolled clinical trial.[7] Perhaps less than optimal dosage, application frequency, or length of treatment period have been chosen. It is a typical feature for many existing (traditional) treatments that there is a wealth of empirical evidence, and that studies in the sense of Phase II trials aiming at the determination of appropriate dose ranges/regimens in order to provide an optimal background for clinical trials[38] are lacking.

Furthermore, non-specific components of the treatment modality (e.g. needle insertion or the therapists themselves) could have led to an effect masking, although this point does not seem very likely. It

seems more probable that the non-specific treatment components of SCI did benefit rather than harm.

To give an impression of the minor extent of pain alleviation achieved in this study in favour of the investigational therapy, we calculated the between-groups SRM in two balneotherapeutic, placebo-controlled add-on studies with a comparable rehabilitative setting (inpatients of a rehabilitation hospital).[39,40] In these studies the between-groups SRM were about two to three times higher (SRM for pain intensity were 0.6[39] and 0.8[40] respectively). However, the SPT in these trials was less extensive (exercise therapy and massage only) and the population was about 15 years younger on average.

A slight underestimation of the treatment effect can be assumed as a result of the six controls contaminated with SCI.

It takes for about 1 min to treat a person with SCI. The costs for the gas can be neglected. On this background, even a NNT of 14 still may be worth the effort.

Blinding is considered an important predictor of internal validity.[41] It is essential to separate specific from non-specific effects ('efficacy'), but may be inappropriate in studies that aim at quantifying the overall effect. In pragmatic trials physician and patient biases are not considered as detrimental, but accepted as part of physicians' and patients' overall responses to treatment.[25] In this study, blinding was explicitely not intended on the basis of the study rationale.

The study was designed as simple and pragmatic as possible. Therefore, we did not define a follow-up assessment after the end of the treatment or an outcome measure other than pain.

In the planning phase we decided to perform one-sided tests. The decision was based on the results of a systematic review on SCI.[15] Readers objecting to this rationale can double the *P*-values and make their own conclusions.

Administration of SCI causes minimal costs and SCI represent a nearly risk-free treatment modality low on side effects.[2,3] In this context the evaluation of specific effects, i.e. pharmacological effects of the CO_2 gas, seemed to be of minor relevance for patients, caregivers or insurance carriers. An explanatory trial on specific effects of SCI would be of academic interest in the first place.

Furthermore, specific efficacy of SCI cannot be tested against an undistinguishable sham treatment in a convincing manner. Nitrous oxide (N_2O) admittedly has comparable diffusibility and solubility to CO_2,[42] but it also has known analgesic effects[43,44] even in doses of 50 ml.[44]

CONCLUSION

This study indicates a statistical tendency towards superiority of SCI as an adjunctive treatment in patients with non-specific neck or low back pain in a rehabilitative setting, but no statistical significance was obtained and the effects were only of marginal clinical relevance. Most probably, the extensive control treatment could have masked a greater benefit of SCI. Other potential factors might be study condition, age, or treatment regimen.

Analgesic effectiveness of SCI in musculoskeletal conditions would be best re-evaluated as a sole therapy, within a sample of a younger population, and in a better defined pain condition. It seems worthwhile to run small-scale dose finding studies first in order to find the optimal dose range, correct frequency of dosing, and treatment period.

Since SCI are considered risk-free and low on side-effects, and represent a very low-cost treatment option, explanatory trials on specific effects seem to be mainly of academic interest and have little relevance for patients, care providers, or insurance carriers. They should be run only after overall effectiveness has been convincingly shown.

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