Randomized Trial

Short-Term Treatment with Parecoxib for Complex Regional Pain Syndrome: A Randomized, Placebo-Controlled Double-Blind Trial

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Background: Complex regional pain syndrome (CRPS) is characterized by signs and symptoms of peripheral inflammation, which leads to peripheral neural sensitization associated most frequently (in about 70%) with blunt pressure hyperalgesia. Therefore, we hypothesized that treatment of CRPS patients with a selective COX-2-inhibitor would alleviate the abnormally low pressure pain threshold (PPT) and reduce pain intensity and edema.

Methods: Twenty patients with CRPS type I (n = 16) and II of the upper limb and abnormally low PPT were double-blind randomised into 2 groups of 10 patients each to receive a 2-day intravenous treatment of either 80 mg parecoxib per day (group I) or placebo (NaCl 0.9%, group II). Standardized quantitative sensory testing (QST) using the DFNS protocol was performed before and after treatment. Pain intensity (NRS 0 – 10); circumferences of the fingers II, IV, and V (mm); PPT (kPa, thenar/hypothenar); and adverse events were recorded daily. Statistics: Wilcoxon-test, Mann-Whitney-U-test, Friedman-test, Fisher-test, significance level: $P < 0.05$.

Study Design: Proof of concept trial performed in randomized, placebo-controlled, double blind style .

Setting: Pain Management Center in Germany.

Results: There were no group differences in PTT or other QST parameters. After treatment, PPT decreased insignificantly in group I (median [range]; before: 224.0 [121.0 – 52937] kPa, afterwards: 186.4 [101.4 – 526.5] kPa) and increased insignificantly in group II (before: 207.6 [170.0 – 320.5] kPa; afterwards: 235.4 [163.5 – 349.9] kPa). Pain scores and finger circumferences remained unchanged in both groups.

Limitations: Due to difficulty in recruitment the trial was closed after inclusion of 20 patients.

Conclusion: In the present proof-of-concept trial, short-term treatment with the selective COX-2-inhibitor parecoxib influenced neither PPT nor edema or pain. COX-2 might be less important than previously assumed. However, the results are limited due to the small number of patients, short-term treatment, and focus on the PPT, which could have led to false negative results of the present study and covered the expected therapeutic effect.

Key words: Parecoxib, complex regional pain syndrome, pressure pain threshold, pressure hyperalgesia, quantitative sensory testing, inflammation

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The complex regional pain syndrome (CRPS) occurs after trauma of the distal limbs (1). Its exact underlying mechanisms remain unclear (2,3) and its treatment is still a challenge (1). Analysis of the sensory profiles of patients with CRPS from the database of the German Research Network for Neuropathic Pain (DFNS) showed signs of both peripheral and central sensitization; most frequent findings were hyperalgesia to pressure (~70%) and heat (~40%) (4), both considered signs of peripheral sensitization (5,6).

Furthermore, patients with CRPS present, at least in the early stages of the disease, signs of inflammation like edema or vasodilatation (3,7). Previous studies reported pro-inflammatory cytokine profiles in cerebrospinal fluid (8), plasma (9,10), and blister fluid (11-13). This disbalance involves several cytokines, e.g. tumor necrosis factor α (TNF-α) or interleukins IL-2, IL-6, IL-8, which are differently related to the cyclooxygenase 2 (COX-2). IL-6 and TNF–α influence the regulation of MCP-1 (monocyte chemoattractant protein-1) and nerve growth factor (NGF), which in turn stimulate the COX-2 expression (14-16). COX-2 is involved in the synthesis of prostaglandin E2 (PGE-2), PGI-2, and other prostaglandins from arachadonic acid. PGE-2 can directly and indirectly activate nociceptive receptors leading to pressure and heat hyperalgesia and increases the vascular permeability leading to edema (17,18). PGI-2 also causes vasodilatation and plasma extravasation (19). This suggests that COX-2 plays a key role in these cascades and that selective COX-2-inhibition could be beneficial including a more favorable adverse effect profile contrary to the risks and side effects of anti-TNF-α or corticoids, which showed some analgesic effect in CRPS (7,20,21).

Previous studies have suggested a relationship between treatment effects in neuropathic pain and the sensory phenotype, which is supposed to reflect the underlying mechanism (22,23). Therefore, using this approach may improve the understanding of the underlying pain mechanisms and contribute to a mechanism-based treatment (24). As the sensory and cytokine profiles of CRPS patients suggest an important role of inflammation, at least in the early stages (3), we hypothesized that COX-2 inhibition leads to a reduction of the peripheral sensitization and correspondingly to normalization of the decreased pressure pain threshold (PPT) and subsequently to pain relief.

Methods

Patients

Patients with CRPS were recruited in a department of pain medicine between July 2009 and October 2011, after approval of the local ethics committee (Ref. Nr.: 3394-09) and the Federal Institute for Drugs and Medical Devices of Germany (EudraCT-Nr.: 2009-009433-14, ClinicalTrials.gov Identifier: NCT01523379). All patients were informed about the study procedure, study drug, the possibility of receiving a placebo, and any side effects. They were all able to understand the study modalities and agreed in written form to participate in the study, knowing they could resign from the study at any time.

We included in-patients with confirmed diagnosis of CRPS of the upper limp according to the Budapest criteria (25), supported by characteristic enhanced bone metabolism in the late phase of a 99-m technetium-3-phase bone scintigraphy in the first 8 months (exception: n = 2, with scintigraphy performed > 9 month after disease onset) (26-28). Included were patients with CRPS type I (n = 16) and type II (n = 4; affected nerve: median nerve n = 2, ulnar nerve n = 1, brachial plexus n = 1), aged >18 years with abnormally low PPT (according to (29): n = 14; abnormal side-to-side difference according to (30): n = 6).

Exclusion criteria were any contraindications for treatment with parecoxib (history of severe cardiovascular disease, cardiac insufficiency [NYHA II-IV] coronary heart disease, peripheral artery occlusive disease, or severe hypertension with values constantly > 140/90 mmHg; acute kidney disease; acute coagulation disorder; gastric or duodenal ulcer or positive history of gastrointestinal bleeding in the last 5 years; chronic inflammatory bowel disease; severe liver dysfunction; hypersensitivity to parecoxib or sulphonamides; allergy to acetylsalicylic acid, nonsteroidal anti-inflammatory drugs or other cyclooxygenase-inhibitors; pregnancy and lactation; as well as cerebral diseases [e.g. stroke] and neurological systemic diseases [except for incipient distal polyneuropathy with normal PPT on the contralateral control side]), which could influence the interpretation of the results of the quantitative sensory testing (QST). Patients taking one of the following medications (currently or for the last 3 days) were also excluded: ketoconazole, rifampicin, phenytoin, carbamazepine, dexamethasone or other systemic corticoids, nonsteroidal anti-inflammatory drugs, immunosuppressives, or TNF-α-inhibitors.

Study Drug

The study drug was parecoxib, a prodrug that is rapidly and almost completely converted to its active metabolite valdecoxib by carboxylesterases. Valdecoxib is a highly selective COX-2-inhibitor (IC50 = 0.005μM in vitro, ED50 = 0.24mg/kg in vivo), while inhibiting COX-1 in a competitive way at higher concentrations (IC50 = 150μM in vitro, ED50 > 200mg/kg) (31). Due to the only moderate COX-1 inhibition, the effects on the gastrointestinal tract and blood platelets are low; therefore, the function of blood platelets is unchanged and the frequency of upper gastrointestinal bleeding is low (32). The analgesic efficacy of valdecoxib was demonstrated in inflammatory rat models and several clinical trials, proving efficacy in postsurgical pain management after arthroscopic knee surgery, hip arthroplasty, endsoscopic retrograde cholangiopancreatography or cesarian delivery (33-35), and in acute osteoarthritis pain or renal colic (36-38).

Study Design

The trial was designed as a proof-of-concept trial examining the effects of intravenous application of COX-2-inhibitor on pressure hyperalgesia. Therefore, an intravenous 2-day treatment with parecoxib was chosen, to achieve quick results, according to a previous study (39). The trial was not designed to examine the therapeutic efficacy of COX-2-inhibitors in general in the treatment of CRPS.

The primary outcome parameter was the PPT; secondary outcome parameters were HPT, pain, edema, and HADS-scores. For a one-sided t-test with a type I error of $\alpha = 0.05$ and a power of 80%, we expected to include about 28 patients to find a reduction of PPT of one z-score in the parecoxib group and 0.5 z-score in the placebo group. A similar group size (n = 10) was used in another study on CRPS comparing systemic and regional paracoxib application, where significant pain was reported (39).

Due to difficulties in recruitment, the trial was closed after inclusion of 20 patients. They were randomized and double-blinded into 2 groups (n = 10) to receive intravenous parecoxib or placebo by one of the authors (CM) using a computer software. The unblinding list was only amenable to the hospital pharmacist, who prepared the infusions. For emergency, unblinding envelopes containing the patient ID and group allocation were available.

On 2 consecutive days patients in the parecoxib group were treated with 40 mg parecoxib twice a day, while the placebo group received NaCl 0.9%. The infusions looked identical and had a standardized label containing the date of treatment, the initials, and the patient ID. Participants, care providers (one exception, see below.), and those examining the outcome parameters and analyzing the data were blinded.

A QST using the DFNS protocol (30) was performed at baseline one day prior to treatment and was repeated one day after the 2-day treatment period. Additionally, PPT according the QST using the DFNS protocol was assessed additionally daily: on day one after the first application, on day 2 after the third application. Edema of the second, fourth, and fifth finger were recorded daily using rings assessing the circumference of the fingers (mm). Pain intensity was recorded daily using the 11-point numerical rating scale (NRS 0 – 10).

Tilidine/naloxone (up to 600 mg/day) and sublingual buprenorphine (up to 2.4 mg/day) were set as escape medication.

Quantitative Sensory Testing

QST was assessed according to the standardized DFNS protocol (29,30), which includes 13 parameters by testing thermal detection thresholds for cold (CDT: cold detection threshold) and warmth (WDT: warm detection threshold), paradoxical heat sensation (PHS) during the procedure of alternating warm and cold stimuli (TSL: thermal sensory limen), thermal pain thresholds for cold (CPT: cold pain threshold) and heat (HPT: heat pain threshold), mechanical detection thresholds for touch (MDT) and vibration (VDT: vibration detection threshold), mechanical pain thresholds for pinprick (MPT: mechanical pain threshold) and blunt pressure (PPT: pressure pain threshold), a stimulus–response–function for pinprick sensitivity (MPS: mechanical pain sensitivity), dynamic mechanical allodynia (DMA: dynamic mechanical allodynia), and the temporal and special pain summation to repetitive pinprick stimuli (WUR: wind-up ratio). For all parameters negative (loss of function) as well as positive (gain of function) phenomena were assessed.

All QST subtests except for the PPT were accomplished on the affected side at the dorsum of the hand and contralateral. The PPT was measured on the thenar (n = 19) or hypothenar (n = 1) (depending on the most painful area) of the affected side and contralateral using a pressure gauge device (FDN 200, Wagner Instruments, Greenwich, CT, USA; probe area 1 cm^2, pressure up to 2000 kPa, ramp 50 kPa/s). The final threshold was the arithmetic mean of 3 series.

Questionnaires

Pain intensity (maximal, minimal, and average pain) was assessed daily using the 11-point numerical rating scale (0 = no pain, 10 = maximal imaginable pain). Average pain intensity during the last 4 weeks was recorded on day 0. The German version of the Hospital Anxiety and Depression Scale was used on day 0 and 3 to assess symptoms of anxiety and depression (HADS-A and HADS-D) (40).

Adverse Events

To record adverse events, 19 items (nausea, emesis, absence of appetite, obstipation, thirst, xerostomia, fatigue, distress, vertigo, sweating, anxiety, agitation, adynamia, difficulties in concentration, insomnia, pruritus, headache, back pain, and sore throat) were recorded daily using an 11-point numerical rating scale (0 = no complaints, 10 = maximal severe complaints). An increase of ≥ 2 points was considered a drug-induced adverse event. A sum score, including the intensity (NRS) of all adverse events was calculated (reaching from 0 to 11*19 = 190) and the difference between the sum score on day 3 and day 0 was compared between both groups.

Additionally, the patients were examined daily and blood (blood count, liver enzymes, and creatinine) was controlled on day one, 2, 3, and 2 days after the end of the treatment.

Statistical Analysis

According to the DFNS protocol, all QST data except for PHS, CPT, HPT, and VDT were transformed logarithmically before statistical analysis (30). QST data were transformed into z-scores and referred to the DFNS reference database considering age, gender, and testing area (29,30). A z-value is considered abnormal if it is < -1.96 or > 1.96. It is calculated using the following formula:

$$\text{Z-value} = (\text{Mean}_{\text{single patient}} - \text{Mean}_{\text{reference data base}}) / \text{SD}_{\text{reference data base}}$$

The statistical package for social science (SPSS; version 19) was used for data analysis. Mann-Whitney-U-test was used to analyze differences between both groups for PPT (including analysis of the subgroup of patients with duration of disease ≤ 6 month), HPT, pain, circumferences of the fingers, and HADS. Differences of the data within the groups at baseline and after treatment were analyzed by Wilcoxon-Test. Friedman-Test was used to analyze PPT changes between baseline, day one, day 2, and after treatment. Due to the small number of cases, the exact Fisher-test was used to analyze the frequency of adverse events. For analysis of the statistical power the program G*Power (version 3.1) was used. Significance level was set at $P < 0.05$. Results are presented as median (range).

Results

Patients

No patient requested escape medication or resigned from the study. All 20 patients were included in the analysis. There were no significant group differences in age, duration of disease, and pain (Table 1).

Quantitative Sensory Testing

Sensory Profiles

According to the inclusion criteria, the median PPT before treatment was outside the normal range (Fig. 1). Both groups presented similar sensory loss for the mechanical thresholds at baseline (Fig. 1), with more pronounced sensory loss for cold detection in the placebo group (median z-score: -1.4 vs. 0.2 in the parecoxib group, n.s.; Fig. 1). The median z-scores of the thermal pain thresholds were slightly increased in both groups, but only in the parecoxib-group out of range (median z-score CPT: 2.5, HPT: 2.9; Fig. 1). The profiles did not change significantly after treatment in any group.

Pressure Pain Threshold

PPT differed between the groups neither at baseline ($P = 0.6$, power = 19.3%) nor after treatment ($P = 0.28$, power = 8%). In the parecoxib group no significant difference occurred on any day during the treatment ($P = 0.58$). PPT remained unchanged in the parecoxib group after treatment ($P = 0.8$; power = 18.6%). In contrast, PPT values in the placebo group increased significantly from baseline to day 2 ($P = 0.04$) but not compared to the assessment after treatment ($P = 0.07$; power = 71.1%, Table 2).

In the subgroup of patients with disease duration ≤ 6 months the results showed a similar insignificant trend. Values in the parecoxib-group decreased slightly from (median [range]) 284.49 (134.1… 529.7) kPa before treatment to 232.2 (143.9… 526.5) kPa afterwards ($P = 0.75$, power = 31.6%). In the placebo-group they increased slightly from 181.49 (170… 320.5) kg to 240.4 (173.0… 349.9) kPa ($P = 0.27$, power = 89%). After treatment the subgroups did not differ.

Table 1. Clinical data.

	Parecoxib (n = 10)	Placebo (n = 10)
Age (years), median (range)	46.5 (40… 57)	51 (22… 69)
Height (m), median (range)	1.73 (1.53… 1.88)	1.77 (1.54… 1.97)
Weight (kg), median (range)	80 (45… 119)	74.5 (50… 158)
BMI (kg/m²), median (range)	26.1 (19.22… 34.2)	24.4 (21.8… 46.17)
Gender (female)	5	5
Affected side		
Right	6	9
Duration of disease (months), median (range)	5.5 (4… 36)	8 (1… 17)
Duration of disease ≤ 6months	6	4
Average pain (NRS) in the last 4 weeks, median (range)	5 (*0… 9)	5 (1… 8)
Maximal pain (NRS) in the last 4 weeks, median (range)	6.5 (3…10)	7.5 (1… 9)
Precipitating event		
fracture	4	5
crush injury	1	3
cast-immobilisation	1	-
surgery	3	-
others	1	1
unknown	-	1
Patients with positive symptom categories		
sensory symptoms	10	10
vasomotor symptoms	9	9
sudomotor/edema symptoms	10	9
motor/trophic symptoms	10	10
Patients with positive sign categories		
sensory signs	8	9
vasomotor signs	10	8
sudomotorik/edema signs	7	5
motor/trophic signs	10	10
Patients with 4 symptoms	9	8
Patients with 4 signs	5	2
Medication		
anticonvulsives	6	5
antidepressants	4	4
moderate acting opioids (WHO step II)	1	3
strong acting opioids (WHO step III)	1	1
no medication	-	1

CRPS = Complex regional pain syndrome; NRS = Numeric rating scale; *one patient rated pain with "0."

Heat Pain Threshold

HPT was similar in both groups at baseline (Fig. 1, Table 2). Both groups showed a discrete but insignificant decrease of HPT after treatment (Table 2).

Changes of Pain and Clinical Signs

Pain

In both groups maximal pain intensities were similar before treatment and decreased insignificantly after

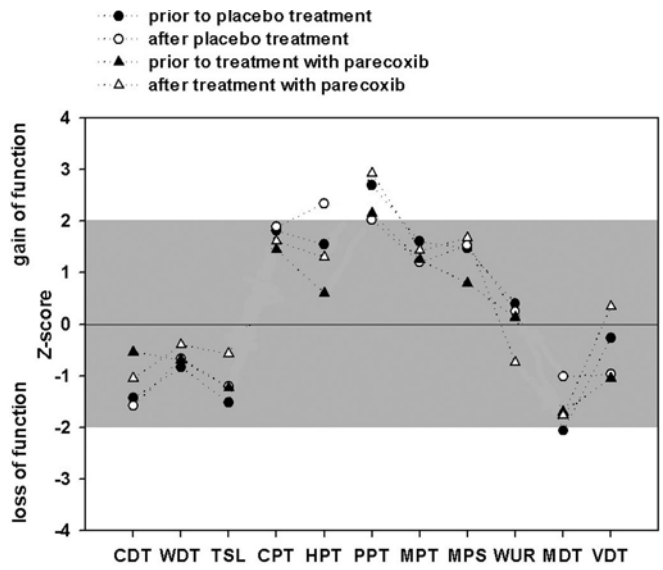

Fig. 1. *Sensory profiles before and after treatment with placebo and parecoxib, respectively. Data are presented as median values. Normal range of z-scores from -1.96 to 1.96 is highlighted in gray. CDT: cold detection threshold; WDT: warm detection threshold; TSL: thermal sensory limen; CPT: cold pain threshold; HPT: heat pain threshold; PPT: pressure pain threshold; MPT: mechanical pain threshold; MPS: mechanical pain sensitivity; WUR: wind-up ratio; MDT: mechanical detection thresholds; VDT: vibration detection threshold.*

treatment (Table 2). In the parecoxib group, 3 patients achieved a pain relief ≥ 50%, in the placebo group one had a pain relief > 30% and another 2 ≥ 50%.

Edema

The finger circumferences showed no significant difference between the groups at baseline and no significant change after treatment in both groups (Table 2).

Mood Changes

At baseline both HADS-A and HADS-D were slightly higher in the parecoxib group, without reaching statistical significance (Table 2). Both scores slightly increased in the parecoxib group, while a decrease was observed for both of them in the placebo group (all n.s.).

Adverse Events

There were no severe adverse events. In one case within the parecoxib group the unblinding was necessary due to elevated liver enzymes (GOT max. 451 U/l [reference < 32U/l], GPT max. 136 U/l [reference < 35 U/l]), which decreased after termination of the study treatment. Only the attending physician was unblinded, the study examiner remained blinded.

The number of all adverse events did not differ between the groups ($P = 0.07$). In the parecoxib group 2 patients reported no adverse events (placebo group: n = 7), 6 patients - 1 adverse event (placebo group: n = 2), no patient - 2 adverse events (placebo group: n = 1), and 2 patients - 3 adverse events (placebo group: n = 0). None of the assessed side effects appeared significantly more often than the rest of them. Vertigo and sweating were reported most often, whereas none of them was reported more than twice in each group.

None of the patients described symptoms of gastritis or reflux during or after the infusion.

While the parecoxib group showed an increase between day 0 and day 3, the placebo group showed a decrease of the sum scores (both n.s., median [range]; parecoxib: increase from 9 [0… 40] to 12.5 [3… 36] [$P = 0.34$]; placebo-group: decrease from 25.0 [0… 62] to 19.5 [0… 59], [$P = 0.14$]). However, the calculated difference of the sum scores of the 19 items between day 3 and day 0 differed significantly between both groups ($P = 0.03$).

Discussion

In the present proof-of-concept study in patients with CRPS, both spontaneous pain and pressure hyperalgesia, as hypothesized signs of peripheral sensitization, showed no improvement after a 2-day treatment with either parecoxib or placebo. Heat hyperalgesia and edema also remained unchanged. Except for the number of adverse events, the placebo group achieved more advantageous results compared to the parecoxib

Table 2. *Changes in primary and secondary outcome parameters after treatment with parecoxib or placebo.*

Parameter	Group	Baseline = day 0 median [range]	Day 1 median [range]	Day 2 median [range]	Day 3 median [range]	Δ (day 3 – day 0) median [range]	*P*-value between the groups, day 0	*P*-value within the groups, day 0 vs. day 3
PPT	Parecoxib	224.0kPa [121.0… 529.7]	223.4kPa [101.0… 608.0]	222.5kPa [98.0… 588.6]	186.4kPa [101.4… 526.5]	-14.7 [-107.9… 85.0]	0.6	0.8
	Placebo	207.6kPa [170.0… 320.5]	211.0kPa [98.0… 372.8]	257.5kPa [173.0… 372.8]	235.4kPa [163.5… 349.9]	26.5 [-16.4… 101.4]		0.07
HPT	Parecoxib	38.2°C [33.4… 50.0]	-	-	39.8°C [34.7… 48.0]	1.6°C [-7.9… 2.3]	0.29	0.45
	Placebo	40.8°C [34.7… 48.9]	-	-	40.2°C [35.4… 48.4]	0.7°C [-8.8… 3.9]		0.72
Pain (NRS)	Parecoxib	6.5 [1… 10]	6 [0… 10]	6 [1… 10]	5.5 [1… 9]	-0.6 [-3… 1]	0.32	0.16
	Placebo	6 [1… 8]	5.5 [0… 7]	5.5 [0… 8]	5 [0… 7]	-0.7 [-3… 2]		0.17
Edema								
Digitus II	Parecoxib	61.5mm [47… 86]	61mm [47… 88]	63mm [48… 88]	62mm [48… 90]	0.5 [-2… 4]	0.44	0.40
	Placebo	66mm [58… 82]	66mm [53… 92]	66mm [59… 88]	66mm [57… 82]	-0.5 [-3… 3]		0.29
Digitus IV	Parecoxib	60mm [41… 80]	61mm [47…82]	60mm [48… 84]	57mm [48… 85]	0.9 [-2… 7]	0.53	0.49
	Placebo	63mm [55… 78]	62mm [54… 80]	61mm [55… 81]	61mm [54… 80]	0.3 [-2… 4]		0.73
Digitus V	Parecoxib	52mm [38… 74]	52mm [37… 76]	53mm [38… 74]	52mm [38… 75]	0.5 [0… 2]	0.63	0.06
	Placebo	54.5mm [48… 70]	54mm [46… 69]	53.5mm [47… 71]	54mm [46… 73]	-0.1 [-2… 3]		0.83
HADS								
A	Parecoxib	5 [0… 18]	-	-	6 [0… 15]	-0.6 [-5… 2]	0.91	0.42
	Placebo	7 [4…17]	-	-	6 [1… 13]	-1.8 [-4… 1]		0.06
D	Parecoxib	4 [0… 18]	-	-	6.5 [0… 15]	0.2 [-3… 5]	0.74	0.80
	Placebo	9 [2… 14]	-	-	5 [1… 11]	-2.1 [-9… 3]		0.12

PPT = Pressure pain threshold; HPT = Heat pain threshold; NRS = Numeric rating scale; HADS = Hospital anxiety and depression scale: A = Anxiety-value, D = Depression-value.

group, though without reaching statistical significance. This was quite unexpected because parecoxib has been commonly used for CRPS treatment in our pain clinic for several years, often showing analgesic effects.

The unfavorable ratio between pro- and anti-inflammatory cytokine in CRPS patients (7-11,12,40-44) is assumed to lead to peripheral sensitization. Therefore, an inhibition of the COX-2 was expected to induce a recovery of the signs of peripheral sensitization, in particular normalization of PPT and HPT. We also hypothesized that the COX-2 inhibition, leading to reduced synthesis of PGE-2 and PGI-2, should also lead to reduction of pain and edema.

The analgesic effect of parecoxib has been mainly tested in postsurgical pain states, where it showed analgesia compared to morphine or ketorolac with an

opioid-sparing effect, reduction of rescue medication, and higher patient satisfaction (34,35,36,38). To our knowledge only one study examined the effects of COX-2-inhibitors in CRPS (39), comparing systemic and regional i.v. parecoxib and showing a pain reduction > 4 on the NRS (0 – 10) after application.

On the other hand, the analgesic effect of steroids in CRPS patients has been already demonstrated (7,16,20,21). However, corticoids not only influence COX-2, but also affect COX-1 due to inhibition of phospholipase A2 resulting in a decreased release of arachadonic acid from cell membranes. The insufficient effect of COX-2 inhibitors in the present trial indicates that the reported positive effects of corticoids in CRPS patients are due to other effects than the COX-2-inhibition. For example, it has been reported that humoral immune mechanisms with evidence of autoantibodies against nervous system structures may be also involved in the development of CRPS (45,46). Thus, mechanisms other than COX-2-effects could be more important for the generation of the typical CRPS symptoms than previously expected.

Several studies have shown that pressure and heat hyperalgesia are signs of inflammatory induced peripheral sensitization (5,47). Correspondingly, patients with CRPS show stronger pressure hyperalgesia than patients with peripheral nerve injury (PNI) (4). Furthermore, the elevated cytokines in blister fluids on the extremity affected by CRPS demonstrate a higher level of inflammation (11,12,41). The enhanced osteoblast activity found in the late phase of triple-phase bone scintigraphy in CRPS patients has also been interpreted as a result of neurogenic inflammation (27). Thus, it seemed plausible to hypothesize that the COX-2 inhibition, as one of the main regulator enzymes in inflammatory cascades, would positively affect the pressure hyperalgesia in patients with CRPS.

However, additional central mechanisms for the generation of pressure hyperalgesia have been also discussed (48). Different studies have suggested that centrally synthesized PGE-2 by increased COX-2-expression might lead to pain generation, thus explaining the analgesic effect of COX-2-inhibitors (49-51). Therefore, the analgesic effect of parecoxib may not be solely based on the reduction of peripheral sensitization but also on central modulations.

On the other hand, pressure hyperalgesia was present in ~50% of the patients with PNI (4). However, inflammation seems to play only a minor role in PNI (52). The pressure hyperalgesia over the distal limb muscles in PNI could result from the recently reported abnormal activity in injured muscle afferents leading to mechanosensitivity (53).This might implicate that the pressure hyperalgesia over muscles is not a solitary consequence of inflammatory processes including elevated COX-2-levels and it has to be questioned if the chosen patients indeed presented increased expression of COX-2. In CRPS joint pain is more common than muscle pain; therefore, the pressure hyperalgesia over joints might be a better target for further studies on the effects of anti-inflammatory drugs in CRPS. Interestingly, the subgroup of patients with duration of disease ≤ 6 month showed the same trends, though high levels of inflammatory cytokines have been reported in the early stages of CRPS (3,10).

There are several possible explanations for the unexpected results of the present study. A 2-day treatment was set to achieve quick results for a proof-of-concept, while our clinical experience is based on a regular parecoxib treatment of in-patients usually lasting for one to 2 weeks also including medical treatment, occupational therapy, physiotherapy, and psychological treatment to form an optimally personalized therapy. This treatment combination is difficult to interrupt for a longer study period for ethical reasons. The progress of disease in patients with CRPS can also strongly vary in a short period (54), thus explaining the better effects of placebo as accidental results. Further on, the assessment time of PPT could have not matched the time of greatest effect of parecoxib.

Treatment on its own is also suggested to reduce the pain expectation and, as a direct consequence, pain itself also in neuropathic pain states, which could explain the slightly better effects in the placebo group (55-57), e.g. significant decrease of PPT on day 2 compared to baseline, what could be rated as a short-lasting placebo effect. However, a real placebo-effect, which could be expected in this kind of study with intravenous drug application (58), was missing. In the parecoxib treatment there were no effects on any of the treatment days compared to baseline. The symptom score of side effects showed a significant increase after treatment, which suggests that parecoxib has induced some pharmacological effects.

Indeed, the previous clinical impression of successful treatment of CRPS with parecoxib in our clinical practice could also be based on the previously reported anxiolytic effect of the drug itself (59), as patients with CRPS often show symptoms of anxiety and depressive mood and parecoxib could have

improved these symptoms, thus improving also the general impression.

Conclusion

The results of this trial are limited by the small number of included patients resulting in the low power and the possible indication bias in an in-patient population of a tertiary pain clinic, thus potentially underestimating any treatment effects of parecoxib.

To sum up, short-term treatment with this selective COX-2-inhibitor decreased neither pressure hyperalgesia nor pain intensity or edema in the selected patient group. Further clinical conclusions are currently not appropriate due to the above mentioned limitations.

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Conflicts of iInterest

There were no financial relationships that might have led to a conflict of interest. CM und TM are members of the IMI Europain project, including following industry members AstraZeneca, Pfizer, Esteve, UCB-Pharma, Sanofi Aventis, Grünenthal, Eli Lilly, and Boehringer Ingelheim. As a member of the German Research Network on Neuropathic Pain, CM has received research grants from the German Federal Ministry of Education and Research (BMBF, grants 01EM0107 & 01EM0502). CM has also received research grants from Pfizer, MSD, Mundipharma, Grünenthal, Astellas, and Lilly as well as consultant and/or speaker fees from Astellas, Sanofi Aventis, Wyeth, Pfizer, Mundipharma, and Eli Lilly. EK has been a member of the IMI Europain, she was also supported by intramural fundings of the Ruhr University Bochum (FoRUM: grant number K046-10) and has received a travel grant from Mundipharma as well as speaker fees from Grunenthal.

Authors' Contributions

AJB was involved in data acquisition, analysis and interpretation, and wrote the first draft of the paper. TM was involved in data interpretation and revised the manuscript for intellectual content. NH was involved in data analysis and revised the manuscript for intellectual content. CM was involved in the conceptualization of the study, data interpretation, and revised the manuscript for intellectual content. EKK was involved in the conceptualization of the study, data acquisition, analysis and interpretation, and revised the manuscript for intellectual content. All authors discussed the results and commented on the manuscript.

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