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ORIGINAL RESEARCH

# Cryoneurolysis versus radiofrequency ablation outcome on pain experience in chronic low back pain (COPE): a single-blinded randomised controlled trial

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## ABSTRACT

**Objective** A comparison of cryoneurolysis or radio frequency (RF) with placebo in patients with facetogenic chronic low back pain (LBP) for patient global impression of change (PGIC), pain intensity, function and quality of life, with 1-year follow-up.

**Design** Single-centre, single-blinded placebo-controlled randomised controlled trial.

**Setting** Single-centre study.

**Participants** Inclusion from March 2020 to September 2022: consenting adults over 18 years of age, LBP>3 months, average Numeric Rating Scale LBP≥4 average last 14 days and a positive response to a diagnostic medial branch block (≥50% pain reduction after 60 min).

**Interventions** 120 patients were block randomised 1:1:1 to cryoneurolysis, RF or placebo of the medial branch nerves. Physical therapy was added after 4 weeks for all groups.

**Main outcome measures** Primary outcome was PGIC 4 weeks after the intervention. Secondary outcomes included pain intensity (Numeric Rating Scale, NRS), quality of life (Short Form 36, EQ-5D-5L), disability (Oswestry Disability Index), depression (Major Depression Inventory) and catastrophising (Pain Catastrophising Scale). Outcomes were measured at 4 weeks, 3, 6 and 12 months.

**Results** There was no statistically significant difference in PGIC at 4 weeks between cryoneurolysis and placebo (risk ratio (RR) 2; 95% CI 0.75 to 5.33, p=0.17) and RF and placebo (RR 1.6; 95% CI 0.57 to 4.49, p=0.37), except PGIC for cryoneurolysis at 6-month follow-up (RR 5.1; 95% CI 1.20 to 22.03, p=0.03). No statistically significant differences were found in secondary follow-up endpoints.

**Conclusions** Denervation of the medial branch nerve by either cryoneurolysis or RF compared with placebo did not demonstrate significant improvement in PGIC, pain intensity, function and quality of life in patients with facetogenic chronic LBP at short-term or long-term follow-up.

**Trial registration number** NCT04786145.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Radio frequency denervation and cryoneurolysis for chronic low back pain are widely used in clinical practice despite lack of evidence.

⇒ No randomised controlled trials have yet been conducted in which cryoneurolysis is compared with radio frequency denervation and placebo to alleviate facet joint derived chronic low back pain.

### WHAT THIS STUDY ADDS

⇒ Neither cryoneurolysis nor radio frequency denervation showed an effect on the patient global impression of change, pain intensity, function and quality of life at short-term or long-term follow-up compared with placebo.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings do not support the use of cryoneurolysis or radio frequency denervation for facet joint derived chronic low back pain implicating a need to change clinical practice.

## INTRODUCTION

Chronic low back pain (CLBP) is defined as persistent or fluctuating LBP for more than 3 months,[1] with a wide spectrum of aetiologies.[2 3] In 15%–54% of patients, lumbar facet joints have been implicated as the cause.[4–7] The diagnosis of lumbar facet joint derived pain (facetogenic LBP) is complex and combines several factors; symptomatology, imaging, physical examination and confirmation by diagnostic block administered at the pain generator.[8]

Several treatment modalities for facetogenic CLBP are being used, but none have been shown effective for long-term pain relief.[9 10]

Radio frequency (RF) denervation has been used for decades; however, its effectiveness is disputable due to inconclusive or low-quality evidence to support long-term pain relief.[5 6 8 10] Pain relief is presumably achieved by axonotmesis (second-degree peripheral nerve injury), in which RF energy creates fractional heat to disrupt the peripheral nerve pathways.[11] Randomised controlled trials (RCTs) on the effectiveness of RF on facetogenic CLBP have shown moderate-quality evidence for short-term pain relief and function improvement when compared with placebo.[11] Only one study has compared RF to standard care (standardised exercise programme) in facetogenic CLBP.[10] This study found no clinically important improvement in CLBP between the two groups.[10] The short-term effect of RF may be beneficial in a follow-up physical therapy programme, as it could enable patients to become more active compared with patients without this add-on effect.

Another proposed method of managing CLBP is cryoneurolysis, which has gained much interest in recent years, due to its reported efficacy and low occurrence of side effects in the literature.[12] Cryoneurolysis is suggested to alleviate pain by axonotmesis at temperatures below minus 20°C, causing reversible axon degeneration with no risk of neuroma formation or marked neuritis.[13 14] No RCT has yet been conducted to support the effectiveness of cryoneurolysis on facetogenic CLBP.

Therefore, the objective of this study was to compare the short-term and long-term effect of cryoneurolysis or RF with placebo when combined with physical therapy, on patient global impression of change (PGIC), pain intensity, quality of life and functional status in patients with facetogenic CLBP.

## METHODS

### Study design and participants

This single-centre, single-blinded RCT was registered at ClinicalTrials.gov (NCT04786145).[1–10] We refer to the published study protocol.[15] Between 2020 and 2022, 120 patients were included through referrals to the Department of Neurosurgery at Aarhus University Hospital in Denmark. Included were patients ≥18 years of age with LBP > 3 months, 14-day average pain intensity >4 on NRS and a positive diagnostic block. Excluded were patients with nerve root or spinal cord compression, signs of inflammatory or erosive processes in the spine on MRI, neurological deficits in the lower extremities, major comorbidity, chronic inflammatory disease, active malignancies, antithrombotic or antiplatelet treatment which could not be paused for a week and severe psychiatric disease.

### Diagnostic medial branch (facet joint) block

To assess whether pain was facetogenic, a blinded supra-articular injection was used as the diagnostic medial branch block (MBB), where 2 mL were administrated as an infiltration anaesthetic around the facet joint. The procedure was performed by the same physician during the first consultation, as follows: with the patient in prone position, the facet joints were marked 1.5 cm lateral and posterior to the spinous process of pain generator bilaterally, the level above and below, in total three vertebral levels. For every facet joint (six in total), a 22-gauge spinal needle was inserted directly onto the facet joint bone. A 2 mL of 1% lidocaine was injected. Advancement to the randomisation stage was allowed if patients had a reduction in NRS (0=no pain, 10=worst pain imaginable) >50% after 60 min.[16 17]

### Randomisation and blinding

The patients were block randomised with allocation ratio 1:1:1, respectively, to receive cryoneurolysis, RF or placebo. Time between the enrolment (where the MBB was administered) and intervention phase was at most 2 weeks, however, some participants had longer time between the two phases due to the COVID-19 lockdowns. The allocation code was concealed in 120 identical opaque and sealed envelopes. One surgeon (KT) did all the procedures and did not participate in the follow-up. The assigned intervention was blinded for the patients, the physical therapists, the data managers who did the follow-ups and the biostatistician who analysed the data. Unblinding occurred either at the time of drop-out or after 12 months follow-up.

### Intervention

Each patient was placed in prone position. The sterile procedure was done with local anaesthesia; 20–30 mL 1% lidocaine with epinephrine. Medial branch nerve (MBN) was identified for all groups with fluoroscopy and sensory stimulation (0.5 volts for cryoneurolysis and radio frequency ablation (RFA) with pulse time of 1 ms and frequency of 50 Hz).[1] For every facet joint, two needles were inserted directly into the site of the anatomic course of the MBN into the angle between the superior articular and the transverse process and[2] into the inferior border of the transverse process at the level of the inferior articular process.[3] For cryoneurolysis and placebo, generic branded 14 gauge introducer needles were used, and for RF, 22 gauge radiopaque RF cannula needles (105/PMF22-100-5, Avanos Medical, Alpharetta, Georgia, USA). After confirming probe placement, 1 mL lidocaine hydrochloride 10 mg/mL with 5 µg/mL epinephrine was administered through the introducer needle per location prior to allocated treatment. Cryoneurolysis was performed with a freezing time of 60 s per location at minus 80°C using a Metrum Cryoflex apparatus (Cryo-S Painless, Metrum Cryoflex, Warsaw, Poland). RF was performed at plus 80°C. Application time was 90 s per location using a Baylis Pain Management RFA Generator apparatus (PMG-230, Baylis Medical, Montreal, Canada). Identical setup was used for the placebo group; however, instead of treatment, a 60 s sound bite of the cryoneurolysis machine was played during the procedure to mimic

active cryoneurolysis treatment. All patients were blinded behind sterile draping applied for the procedure.

### Postprocedural care

All follow-ups were conducted at the outpatient clinic by scientific staff blinded to the treatment allocation. All patients had a follow-up at 4 weeks, 3, 6 and 12 months. A few follow-up sessions had to be done by telephone interview due to the COVID-19 pandemic.

All three groups received a physical therapy programme specifically designed for the study starting after 4 weeks and continued for 3 months; a pretraining consultation and six physical therapy sessions of 60 min duration over 4–6 weeks in small groups of a maximum of 10 people led by two physical therapists. Individual adjustments were made during each group sessions and all participants received education in pain management. Home training in between sessions was encouraged. Due to the COVID-19 pandemic, one-third of the patients were instructed by their physical therapists through telephone or group video calls instead of on-site physical therapy sessions. All patients were asked to refrain from cointerventions during the physical therapy period. Cointerventions were specified as surgery, manual or chiropractic therapy and other back pain-related exercise or physical therapy programmes.

### Outcomes

Primary outcome was defined using the PGIC.[18] The PGIC is a 7-point patient self-reporting scale of overall improvement after treatment ranging from (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse or (7) very much worse. A PGIC score of 1 or 2 ('very much improved' or 'much improved') at 4 weeks follow-up was considered a positive and clinically relevant outcome.

Secondary outcomes were as follows:

- Change in PGIC at day 1, 3, 6 and 12 months follow-up.[18]
- Change in pain intensity from baseline to day 1, 4 weeks, 3, 6 and 12 months follow-up in the pain NRS scale 0–10[17] and the Pain Catastrophising Scale (PCS; scale 0–52).[19 20] Pain at baseline was collected on the day of selection, however, before the diagnostic block was administered and before the intervention.
- Change from baseline to 6 and 12 months follow-up in the Oswestry Disability Index (ODI; scale 0–100)[21] and the EQ-5D-5L.[22]
- Change from baseline to 12 months follow-up for change in Major Depression Inventory (MDI; scale 0–30)[23] and the Short Form 36 (SF-36) (scale 0–100).[22]

100 of the 120 original baseline data for the secondary outcomes (PCS, ODI, EQ-5D-5L, MDI and SF-36) were lost due to an office renovation in which the paper forms that were stored in a locked cabinet were moved and destroyed before the data was entered in a dedicated REDCap database under the auspice of Aarhus University. Therefore, no baseline data on the secondary outcomes other than NRS (separate form, different cabinet) were available, and the analysis plan deviated accordingly from the protocol. All follow-up data were available.

### Sample size

A score of 1 or 2 on the PGIC at 4 weeks follow-up was considered a significant improvement of change. We postulated that 50% of the participants who receive an active treatment (cryoneurolysis or RF) and 5% of the placebo group would report a significant improvement after the intervention, and used this difference for the sample size calculation.[24] With a power of 0.8, a two-sided $\alpha$ of 0.025, and a correlation of 0.5 for repeated measurements, 30 patients per group were needed. However, anticipating potential study withdrawal, 120 patients were included.

### Patient and public involvement

Patients were not involved in the design, data collection or analysis of the study.

### Statistical analysis

All statistical analyses were conducted using Stata V.17 software (StataCorp) by an external biostatistician blinded to the treatment allocation.[25]

Baseline characteristics were expressed as mean with SD for continuous variables and treatment groups were compared using analysis of variance. The categorical variables were expressed as percentages or counts and groups were compared using Pearson's $\chi^2$ test. Baseline results showed imbalance or uneven distribution of gender and alcohol consumption among the three groups. Therefore, all analyses were adjusted for gender and alcohol consumption.

Primary outcome was analysed using a generalised linear model with log-link function. Treatments were compared by calculating the risk ratio (RR) with 95% CI. Statistical significance was confirmed if p values were less than 2.5% according to protocol.

The secondary outcomes were dichotomised and analysed, adjusting the SEs for the repeated measurements per patient. Continuous outcomes were analysed using a linear regression model or linear mixed models in the presence of repeated measurements. The groups were compared by calculating the differences and their 95% CIs. If necessary, the log-transformed outcome was analysed.

## RESULTS

### Baseline characteristics of the patients

A total of 120 patients were included from March 2020 to September 2022. No drop-out or loss to follow-up occurred at 4 weeks (primary outcome). Four patients dropped out and two were lost to 12-month follow-up (see figure 1). Most demographics and baseline characteristics of the three groups were similar (see table 1). The mean age was 46.5±15.2, 47.5% were men with a slightly uneven distribution among the three groups with 62.5% women

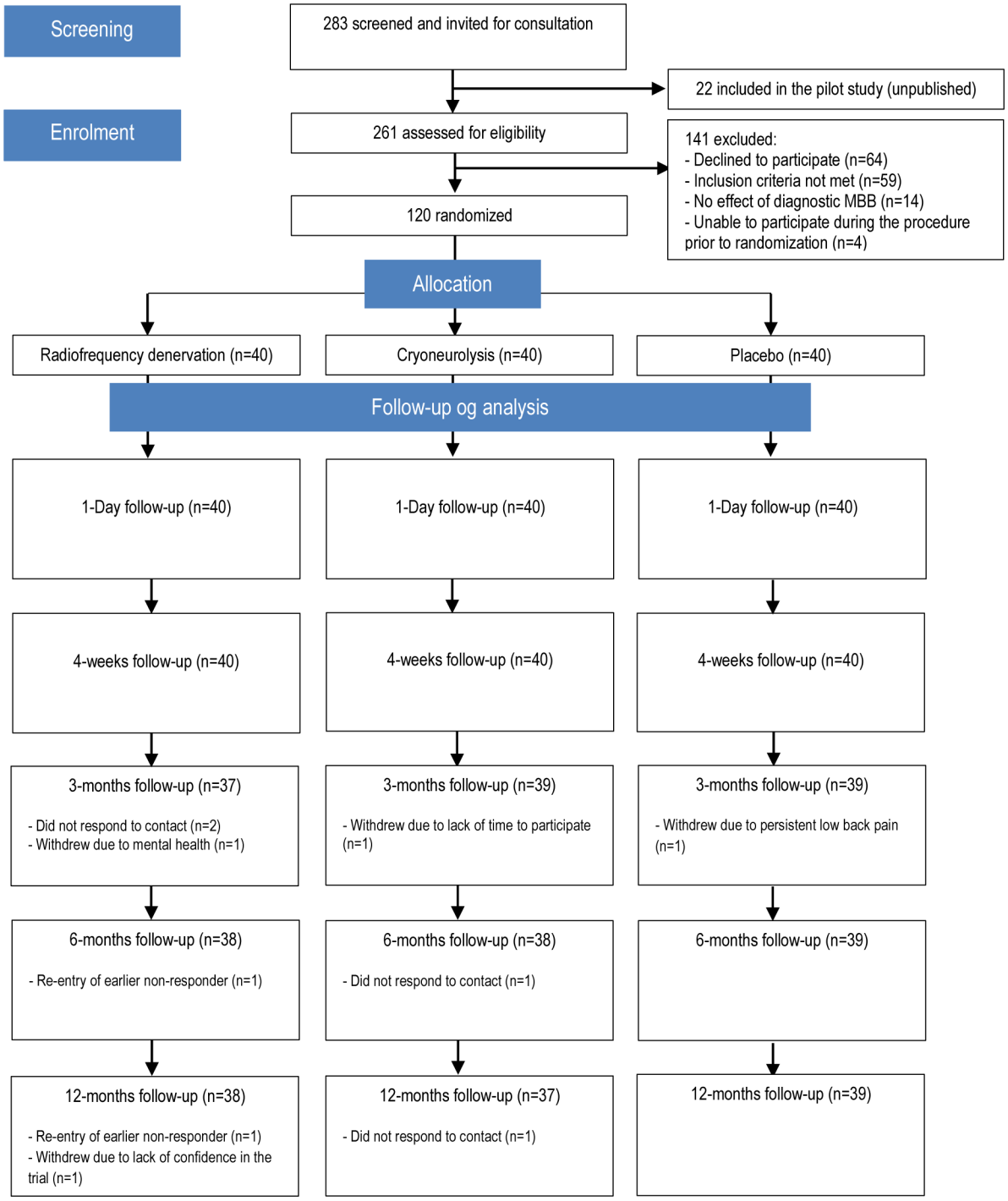


**Figure 1** CONSORT flow diagram. Randomisation, follow-up and data collection. CONSORT, Consolidated Standards of Reporting Trials.

in the RF group. Patients with CLBP>24 months were 82.5% and 78.3% had no prior spinal surgeries. Mean NRS (and SD) at baseline were for RF, cryoneurolysis and the placebo group 5 (1.7), 5.3 (1.8) and 5.2 (1.8), respectively. An uneven distribution of smokers and alcohol intake among the three groups was observed with more non-smokers in the RF group (82.5%) and fewer alcohol drinkers (32.5%) in the placebo group were observed (see table 1).

## Primary and secondary outcomes

Analysis of the primary outcome, PGIC 1 or 2, for cryoneurolysis and RF denervation compared with placebo at 4 weeks follow-up, yielded an RR of 2 (95% CI 0.75 to 5.33) for cryoneurolysis and 1.6 (95% CI 0.57 to 4.49) for RF denervation (see table 2). These findings suggested that the risk or chance of scoring PGIC of 'very much improved' or 'much improved' was twice as high for cryoneurolysis and 60% higher for RF denervation than

**Table 1** Baseline characteristics

| | All randomised (n=120) | Cryoneurolysis group (n=40) | Radio frequency denervation group (n=40) | Placebo group (n=40) | P value |
|---|---|---|---|---|---|
| Age, mean (SD), year | 46.48 (15.24) | 49.33 (15.86) | 42.90 (15.74) | 47.23 (13.68) | 0.16* |
| Gender (n=120) | | | | | 0.20† |
| Male, n (%) | 57 (47.5) | 19 (47.5) | 15 (37.5) | 23 (57.5) | |
| Female, n (%) | 63 (52.5) | 21 (52.5) | 25 (62.5) | 17 (42.5) | |
| Height in cm, mean (SD) (n=115) | 174.7 (8.6) | 173.9 (8.7) | 173.9 (8.6) | 176.7 (7.5) | 0.361* |
| Weight in kg, mean (SD) (n=115) | 84.4 (19.4) | 81.6 (20.3) | 84.9 (20.5) | 86 (17.2) | 0.478* |
| Smoker (n=104) | | | | | 0.411† |
| Yes, n (%) | 12 (11.5) | 4 (12.1) | 4 (10.8) | 4 (11.8) | |
| No, n (%) | 92 (88.5) | 29 (87.9) | 33 (89.2) | 30 (88.2) | |
| Never smoked n (%) | 61 (66.3) | 15 (51.7) | 23 (69.7) | 23 (76.7) | |
| Ex- smoker, n (%) | 31 (33.7) | 14 (48.3) | 10 (30.3) | 7 (23.3) | |
| Alcohol intake per week (n=105) | | | | | 0.091† |
| Yes, n (%) | 58 (55.2) | 22 (64.7) | 23 (60.5) | 13 (39.4) | |
| 1–14 units/week | 55 (94.8) | 21 (95.5) | 21 (91.3) | 13 (100) | 0.290† |
| >14 units/week | 3 (5.2) | 1 (4.5) | 2 (8.7) | 0 (0) | |
| No, n (%) | 47 (44.8) | 12 (35.3) | 15 (39.5) | 20 (60.6) | |
| Current NRS at baseline, mean (SD) (n=120) | 5.1 (1.8) | 5 (1.7) | 5.3 (1.8) | 5.2 (1.8) | 0.812* |
| Duration LBP symptoms (n=120), n (%) | | | | | 0.344† |
| >3 to <12 months | 5 (4.2) | 2 (5) | 3 (7.5) | 0 (0) | |
| >12 to <24 months | 16 (13.3) | 6 (15) | 3 (7.5) | 7 (17.5) | |
| >24 months | 99 (82.5) | 32 (80) | 34 (85) | 33 (82.5) | |
| Vertebral body treated (n=120), n (%) | | | | | 0.351† |
| TH12–L2 | 2 (1.7) | 0 (0) | 2 (5) | 0 (0) | |
| L2–L4 | 3 (2.5) | 2 (5) | 0 | 1 (2.5) | |
| L3–L5 | 9 (7.5) | 2 (5) | 3 (7.5) | 4 (10) | |
| L4–S1 | 106 (88.3) | 36 (90) | 35 (87.5) | 35 (87.5) | |
| Past lower back surgeries (n=119), n (%) | | | | | 0.219† |
| Yes, n (%) | 25 (21) | 12 (30) | 5 (12.5) | 8 (20.5) | 0.186† |
| 1 surgery | 15 (60) | 8 (66.7) | 2 (40%) | 5 (62.5) | |
| 2 surgeries | 5 (20) | 3 (25) | 0 (0) | 2 (25) | |
| >3 surgeries | 5 (20) | 1 (8.3) | 3 (60) | 1 (12.5) | |
| No, n (%) | 94 (79) | 28 (70) | 35 (87.5) | 31 (79.5) | |
| Physiotherapy usage (n=111), n (%) | | | | | 0.929† |
| Yes, n (%) | 100 (90.1) | 33 (91.7) | 33 (89.2) | 34 (89.5) | |
| No, n (%) | 11 (9.9) | 3 (8.3) | 4 (10.8) | 4 (10.5) | |
| Chiropractor usage (n=103) | | | | | 0.399† |
| Yes, n (%) | 72 (69.9) | 19 (57.6) | 27 (77.1) | 26 (74.3) | |
| No, n (%) | 31 (30.1) | 14 (42.4) | 8 (22.9) | 9 (25.7) | |
| Medication daily usage (n=120), n (%) | | | | | |
| Opioids | 32 (26.7) | 11 (27.5) | 10 (25) | 11 (27.5) | 0.707† |
| Job status (n=117), n (%) | | | | | |
| Working/student | 77 (64.2) | 20 (28.6) | 29 (37.7) | 28 (36.4) | 0.199† |
| Transfer income | 40 (33.3) | 19 (47.5) | 9 (22.5) | 12 (30) | 0.097† |
| Due to CLBP | 20 (50) | 9 (45) | 5 (25) | 6 (30) | 0.194† |

Continued

**Table 1** Continued

| | All randomised (n=120) | Cryoneurolysis group (n=40) | Radio frequency denervation group (n=40) | Placebo group (n=40) | P value |
|---|---|---|---|---|---|
| Diagnostic block (MBB) (n=120) | | | | | |
| NRS pre-MBB, mean (SD) | 5.2 (1.8) | 5.1 (1.7) | 5.3 (1.9) | 5.2 (1.7) | 0.906* |
| NRS post-MBB, mean (SD) | 1.4 (1.1) | 1.2 (1.1) | 1.4 (1.1) | 1.6 (1.2) | 0.539* |
| Duration of MBB pain relieving effect (n=120), n (%) | | | | | |
| 1–3 hours | 45 (37.5) | 15 (37.5) | 12 (30) | 18 (45) | 0.276† |
| <24 hours | 38 (31.7) | 13 (32.5) | 14 (35) | 11 (27.5) | |
| <1 week | 21 (17.5) | 10 (25) | 7 (17.5) | 4 (10) | |
| >1 week | 16 (13.3) | 2 (5) | 7 (17.5) | 7 (17.5) | |

*P value from two-way ANOVA test.
†P value from Pearson's $\chi^2$ test.
ANOVA, analysis of variance; CLBP, chronic LBP; LBP, low back pain; MBB, medial branch block; NRS, Numeric Rating Scale.

for placebo at 4 weeks follow-up prior to physical therapy. However, the findings were not statistically significant. No difference was found when adjusting for gender and alcohol consumption. The same was true for PGIC 1–2 at all follow-up times. There was only a statistically significant difference at 6 months follow-up between cryoneurolysis and placebo (RR 5.1; 95% CI 1.20 to 22.03).

The secondary outcomes showed similar results. No statistically significant differences between the groups were found in pain intensity, quality of life, functional status, pain catastrophising and depression at any follow-up time (see tables 3 and 4). Only pain catastrophising at 3 months follow-up was lower in the RF denervation group compared with placebo (12.5±10.6) and higher in the cryoneurolysis group compared with placebo (19.1±13.8) (see table 4).

## Complications and adverse events

Three patients reported complications and adverse events: one in the cryoneurolysis group and two in the RF

**Table 2** Patient Global Impression of Change (PGIC) scale among groups*

| | RR Unadjusted | 95% CI Unadjusted | P value Unadjusted* | RR Adjusted† | 95% CI Adjusted† | P value Adjusted† |
|---|---|---|---|---|---|---|
| 1 day PGIC<2 (n=120) | | | | | | |
| Cryoneurolysis denervation | 0.9 | 0.35 to 2.19 | 0.776 | 0.8 | 0.32 to 2.15 | 0.696 |
| Radio frequency denervation | 1 | 0.41 to 2.41 | 1.000 | 0.9 | 0.35 to 2.22 | 0.786 |
| 4 weeks PGIC<2 (n=120) | | | | | | |
| Cryoneurolysis denervation | 2 | 0.75 to 5.35 | 0.167 | 1.6 | 0.63 to 4.20 | 0.313 |
| Radio frequency denervation | 1.6 | 0.57 to 4.49 | 0.372 | 1.2 | 0.43 to 3.27 | 0.752 |
| 3 months PGIC<2 (n=115) | | | | | | |
| Cryoneurolysis denervation | 1.5 | 0.69 to 3.27 | 0.308 | 1.4 | 0.663 to 2.88 | 0.439 |
| Radio frequency denervation | 1.2 | 0.51 to 2.75 | 0.692 | 0.9 | 0.40 to 2.17 | 0.873 |
| 6 months PGIC<2 (n=115) | | | | | | |
| Cryoneurolysis denervation | **5.1** | **1.20 to 22.03** | **0.028** | **4.4** | **1.04 to 18.72** | **0.045** |
| Radio frequency denervation | 3.6 | 0.79 to 16.31 | *0.098* | 2.6 | 0.56 to 12.14 | 0.225 |
| 12 months PGIC<2 (n=114) | | | | | | |
| Cryoneurolysis denervation | 2.5 | 0.68 to 8.85 | 0.168 | 1.7 | 0.46 to 6.06 | 0.432 |
| Radio frequency denervation | 3.1 | 0.90 to 10.57 | 0.074 | 2.2 | 0.66 to 7.58 | 0.197 |

RR for PGIC<2 active treatment compared with placebo at 4 weeks, 3, 6 and 12 months follow-up.
Highlighted in bold, a statistical significant risk ratio of 5.1 (unadjusted) and 4.4 (adjusted) was found in the cryoneurolysis group for PGIC < 2 compared with the placebo group at 6-month follow up.
*Pairwise comparison of cryoneurolysis and radio frequency denervation with reference to placebo.
†Adjusted for gender and alcohol consumption for n=105.
RR, risk ratio.

**Table 3** Pain intensity, Numeric Rating Scale (NRS) among groups

| | All randomised (n=120) | Cryoneurolysis group (n=40) | Radio frequency denervation group (n=40) | Placebo group (n=40) | P value* |
|---|---|---|---|---|---|
| Baseline | | | | | |
| Current NRS, mean (SD) | 5.1 (1.8) | 5 (1.7) | 5.3 (1.8) | 5.2 (1.8) | 0.812 |
| 14-day highest NRS, mean (SD) | 8.3 (1.3) | 8 (1.4) | 8.5 (1.3) | 8.4 (1.1) | 0.273 |
| 14-day average NRS, mean (SD) | 5.7 (1.3) | 5.5 (1.3) | 6 (1.5) | 5.6 (1.2) | 0.189 |
| Preprocedural | | | | | |
| NRS, mean (SD) (n=120) | 5.2 (1.8) | 5.3 (2.2) | 4.95 (1.9) | 5.5 (1.8) | 0.451 |
| Immediately postprocedural | | | | | |
| NRS, mean (SD) (n=120) | **2 (2)** | **1.4 (1.4)** | **2.1 (2.1)** | **2.5 (2.1)** | **0.034** |
| 1-day NRS | | | | | |
| NRS, mean (SD) (n=120) | 4.2 (2.3) | 4.3 (2.4) | 3.8 (2.1) | 4.6 (2.6) | 0.158 |
| 4 weeks NRS | | | | | |
| Current NRS, mean (SD) (n=118) | 4 (2.2) | 3.95 (2.2) | 4 (2.2) | 3.98 (2.2) | 0.995 |
| Highest NRS, mean (SD) (n=104) | 6.3 (2.5) | 6.1 (2.5) | 6.4 (2.6) | 6.3 (2.4) | 0.855 |
| Average NRS, mean (SD) (n=113) | 4.2 (2) | 4.1 (2) | 4.1 (2) | 4.4 (2) | 0.728 |
| 3 months NRS | | | | | |
| Current NRS, mean (SD) (n=115) | 4.1 (2.2) | 4.2 (2.5) | 3.6 (2) | 4.5 (1.9) | 0.205 |
| Highest NRS, mean (SD) (n=97) | 6.4 (2.2) | 6 (2.5) | 6.2 (2.5) | 7.1 (1.5) | 0.127 |
| Average NRS, mean (SD) (n=110) | 4.4 (2) | 4.3 (2.1) | 4 (2) | 4.8 (1.7) | 0.194 |
| 6 months NRS | | | | | |
| Current NRS, mean (SD) (n=115) | 4.7 (2.4) | 4.5 (2.4) | 4.7 (2.8) | 4.7 (2.1) | 0.916 |
| Highest NRS, mean (SD) (n=93) | 7 (2.5) | 6.4 (2.8) | 7.1 (2.5) | 7.5 (1.9) | 0.186 |
| Average NRS, mean (SD) (n=109) | 4.8 (2.3) | 4.6 (2.4) | 4.8 (2.5) | 5.1 (1.9) | 0.639 |
| 12 months NRS | | | | | |
| Current NRS, mean (SD) (n=114) | 4.6 (2.5) | 4.6 (2.8) | 4.4 (2.9) | 4.8 (2.2) | 0.821 |
| Highest NRS, mean (SD) (n=114) | 6.8 (2.5) | 6.8 (2.6) | 6.6 (2.9) | 7.1 (2) | 0.674 |
| Average NRS, mean (SD) (n=114) | 5.1 (2.5) | 5.0 (2.7) | 4.9 (2.7) | 5.3 (2.2) | 0.796 |

Statistical significant finding is hightlighted in bold.
*P value from two-way ANOVA test.
ANOVA, analysis of variance.

group. One cryoneurolysis patient had hyperesthesia and allodynia in the left lower extremity immediately after the intervention and onwards. The patient continued in the trial but was referred to spinal cord stimulation treatment after 3 months. The RF patients experienced pain in other parts of the lower back outside the treated area; one reported local discomfort and paresthesia around the hip and inguinal region 4 weeks after treatment but the pain resolved within 3 months after a short-term, low-dosage treatment with gabapentin.

## DISCUSSION

In this RCT, no statistically significant difference was found in primary and secondary outcomes when comparing cryoneurolysis, and RF with placebo at any time of follow-up. Only at 6 months follow-up, a statistically significant difference between cryoneurolysis and placebo was found on PGIC. However, the wide 95% CI indicates a great degree of imprecision of the estimate of true effect of the interventions and this finding is likely to be by chance due to multiple testing.

Major strengths of this study were the high-quality setup of the trial, few dropouts and minimal loss to follow-up, and a long-term follow-up period. The use of patient-reported outcome measures (PROM) was in accordance with the recommended outcomes for pain research.[16 17]

CLBP is defined by its symptoms and not a diagnosis. MBB was performed to assess whether the pain was facetogenic. Precise diagnostic measures for facetogenic LPB do not currently exist. The accuracy and validity of MBB as a screening tool are based on conflicting evidence. Some studies have shown 75%–80% accuracy identifying patients with facetogenic CLBP[26 27] while other studies have reported a high incidence of false-positives of up

Table 4 Quality of life and functional status among groups follow-up results

| | All randomised (n=120) | Cryoneurolysis (n=40) | Radio frequency denervation group (n=40) | Placebo (n=40) | P value* |
|---|---|---|---|---|---|
| SF-36 (MCS) | | | | | |
| 12 months SF-36 MCS, mean (SD) (n=110) | 49.9 (10.98) | 49 (12.1) | 50.2 (10.5) | 50.3 (10.6) | 0.621 |
| SF-36 (PCS) | | | | | |
| 12 months SF-36 PCS, mean (SD) (n=110) | 37.4 (9.84) | 36.4 (10.2) | 39.1 (10.2) | 36.4 (9.1) | 0.961 |
| EuroQual Group 5 Dimension 5-Level Quality of Life (EQ-5D-5L) | | | | | |
| 6 months EQ-5D-5L, mean (SD) (n=115) | 0.69 (0.23) | 0.68 (0.28) | 0.68 (0.23) | 0.72 (0.16) | 0.153 |
| 12 months EQ-5D-5L mean (SD) (n=114) | 0.66 (0.24) | 0.63 (0.23) | 0.67 (0.27) | 0.67 (0.22) | 0.125 |
| Owestry Disability Index (ODI) | | | | | |
| 6 months ODI, mean (SD) (n=115) | 14.3 (8.5) | 14.5 (9.5) | 14 (8.8) | 14.6 (7.4) | 0.955 |
| 12 months ODI, mean (SD) (n=114) | 14.2 (8.8) | 15.1 (10.2) | 13.1 (8.8) | 14.4 (7.1) | 0.600 |
| Other outcome scores among groups follow-up results | | | | | |
| Pain Catastrophising Scale (PCS) | | | | | |
| 4 weeks PCS, mean (SD) (n=120) | 16.4 (10.4) | 17.6 (11.1) | 17 (10.9) | 14.6 (9.2) | 0.389† |
| 3 months PCS, mean (SD) (n=115) | *15.6 (11.7)* | ***19.1 (13.8)*** | ***12.5 (10.6)*** | ***15.3 (9.7)*** | ***0.036***† |
| 6 months PCS, mean (SD) (n=115) | 15.9 (11) | 15.8 (13.1) | 15.6 (10.5) | 16.3 (9.5) | 0.956† |
| 12 months PCS, mean (SD) (n=114) | 14.6 (12.7) | 15.9 (11.6) | 13.1 (11.6) | 14.8 (10.9) | 0.619† |
| Major Depression Inventory (MDI) | | | | | |
| 12 months MDI, mean (SD) (n=112) | 11.4 (9.5) | 12.8 (10.1) | 10.2 (9.4) | 11.4 (9) | 0.336† |

*P value from two-way ANOVA test.
†P value from Pearson's $\chi^2$ test.
ANOVA, analysis of variance; MCS, mental component summary; PCS, physical component summary.

to 41%.[28 29] A single MBB might have allowed for false-positive response patients to be included. On the other hand, performing multiple MBBs might increase the number of false-negatives. Multiple MBBs are reported as not being cost-effective.[10] Furthermore, the cut-off threshold of 50% to define if an MBB is positive or negative is disputable. Most studies and clinical practices use this cut-off threshold[10 30 31]; however, some studies suggested a higher cut-off threshold of 80%.[8 29 32] In this study, the diagnostic block was performed as a supra-articular infiltration anaesthetic around the facet joint in which the MBNs were blocked, correlating to the location of our target for RF and cryoneurolysis. Among the benefits of these methods are a minimised amount of X-ray and hospital visits for the participants. However, this may have affected the patient selection.

For RF, different temperatures and application times can be applied. Previous studies predominately used the setting chosen in this trial.[11] For cryoneurolysis, no prior studies have been conducted.[33] Therefore, the setting was used in accordance with the recommendations from the manufacturer.[34]

Physical therapy as an add-on for all three group may have increased the probability of no difference. However, all participants received an identical physical therapy programme, and the physical therapists were blinded to the randomisation, therefore, the absence of difference in the placebo group is less likely.

The main limitation of this study was the missing baseline data for the secondary outcomes except NRS. Fortunately, data for the primary outcome were complete.

Most studies on LBP use NRS or VAS to assess pain intensity as primary outcome; however, PGIC is a simple validated PROM to assess the overall clinically relevant change after treatment.[16 18 35 36] Clinical relevance for any surgical intervention must provide an effect that outweighs any potential complication or adverse effect. Therefore, PGIC was chosen clinically relevant at 1 or 2 (very much or much improved).[18 36] Positive or negative expectations, mental state and severity of baseline pain with or without pain-related consequences may influence the patients' assessment of PGIC.[18 37 38] The primary outcome was chosen to assess the sole effect of either cryoneurolysis or RF compared with placebo prior to physical therapy. Evaluation at 4 weeks postprocedure was chosen based on a systematic review indicating moderate-quality evidence that RF is effective in short-term pain relief in facetogenic CLBP patients.[11] Similarly, previous non-randomised studies suggest that cryoneurolysis is

effective in both the short-term and intermediate-term (6 months) assessment.[33]

ODI was reasonably low at 6 and 12 months follow-up. All three groups had similar low ODI and with no baseline for comparisons, we cannot conclude that the low mean ODI at 6 and 12 months are significant. An effect of physiotherapy cannot be excluded.

A recent systematic review on RF denervation on facetogenic CLBP found moderate-quality evidence in support of RF compared with placebo for short-term pain relief and low-quality evidence for improved function.[11] Other systematic reviews had similar findings. Al-Najjim *et al*[39] found evidence for short-term pain relief. Janapala *et al*[40] concluded that moderate evidence could support RF over placebo and other treatment modalities for both short-term and long-term improvement. The Minimal INvasive Treatment (MINT) study, a large pragmatic open-label RCT, found no added effect of RF denervation compared with standard treatment, similar to the findings in this study. Regarding cryoneurolysis, retrospective and case studies have shown effect in pain relief.[7 14 33 41 42] This RCT found RR of 2 after 4 weeks and 5.1 after 6 months for cryoneurolysis compared with placebo in managing facetogenic CLBP. CIs were wide, and this difference was not statistically significant, which could be due to the relatively small sample size of the groups. We cannot exclude a clinically relevant effect to be revealed in a larger trial; however, surgical procedural effect must always be balanced against complication risks. The number needed to treat would be higher than acceptable for a surgical procedure. Combined with no significant effect in each treatment arm and no long-term effect in our study, careful considerations must be made for further clinical trials.

The findings do not support the use of cryoneurolysis or RF alone or in combination with physical therapy for patients with facetogenic CLBP in clinical practice. A short-term effect at 4 weeks and 6 months cannot be excluded. Considering the lack of significant effect in the presented patient volume combined with complication risks, the Cryoneurolysis' Outcome on Pain Experience (COPE) study group cannot recommend cryoneurolysis or RF as treatments for facetogenic CLBP.

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