



Clinical trial results:

A multicentre double-blind randomised controlled trial to assess the clinical- and cost-effectiveness of facet-joint injections in selected patients with non-specific low back pain: a feasibility study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-003187-20 |
| Trial protocol | GB |
| Global end of trial date | 31 March 2017 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 29 March 2019 |
| First version publication date | 29 March 2019 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 008021 BLT |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN12191542 |
| ClinicalTrials.gov id (NCT number) | NCT03339362 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Barts Health NHS Trust |
| Sponsor organisation address | 3rd Floor, 1 St. Martin's Le- Grand, London, United Kingdom, EC1A 4NP |
| Public contact | Dr Vivek Mehta, Barts Health NHS Trust, 44 07740950868, vivek.mehta@bartshealth.nhs.uk |
| Scientific contact | Dr Vivek Mehta, Barts Health NHS Trust, 44 07740950868, vivek.mehta@bartshealth.nhs.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 March 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 March 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 March 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the feasibility of conducting a definitive study to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

The definitive trial will be deemed feasible if we are successful in standardisation of the method of injection and the test-run of the sham procedure, and if we are able to recruit and retain patients to the proposed trial design.

Protection of trial subjects:

Potential participants will initially be given a copy of the participant information sheet and given a verbal explanation of its contents. This will include details on the nature of the study, the implications and constraints of the study protocol, and any known side effects and risks involved in taking part in the study. Participants will be told that they are free to withdraw from the study at any time for any reason, without prejudice to future care or obligation to give the reason for withdrawal. They will be given as much time as they wish to consider the information, and to ask questions.

A medically qualified and experienced investigator (Principal Investigator or a medically qualified person within the research team with authority given by the site Principal Investigator, documented on the site delegation log) will obtain written informed consent. Participants will be expected to sign and date the form to indicate their consent. The original signed form will be retained at the study site, and a copy given to the participant and a copy in the site medical records.

Prior to any study-specific procedures being carried out, participants will sign and date the latest approved version of the informed consent form.

Background therapy:

This study seeks to examine the feasibility of undertaking a fully powered double-blind randomised controlled trial ('definitive trial') to evaluate the clinical- and cost-effectiveness of facet-joint injections compared to a sham procedure, in patients with non-specific low back pain of more than three months' duration.

The definitive trial will be deemed feasible if we can demonstrate successful standardisation of the method of injection and the test-run of the sham procedure that the proposed study design is deemed acceptable by patients and clinicians, and we are able to recruit and retain sufficient patients.

Evidence for comparator:

Diagnostic tests: Medial branch nerve blocks were carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

Patients who received a 50% pain reduction after diagnostic tests were then enrolled on the study. These patients were randomised to receive either active arm or sham arm. A spinal needle was placed within the facet-joint under X-ray guidance, and 0.5ml 0.5% bupivacaine with 20mg methylprednisolone (active) or 0.5ml normal saline (placebo) was injected per joint. Four facet-joints were injected, at two bilateral lumbar levels.

Following interventions, both groups (active vs sham) completed a 12 weeks of combined physical and

psychological programme with trained specialist physiotherapists as recommended by NICE guidelines.

As this was a feasibility study, we do not propose to formally inferentially test differences in outcomes or costs between or within the groups. Recruitment and attrition rates were calculated with 95% confidence intervals. The mean and standard deviations for primary and secondary outcomes were reported for the two groups at baseline and all follow-up visits.

Treatment Groups:

Active: Bupivacaine and Methylprednisolone

Placebo: Normal Saline

All three drugs are licensed for use by the MHRA and were used as licensed. Patients were randomized to one treatment group following positive response of diagnostic test.

| | |
|---|--------------|
| Actual start date of recruitment | 01 July 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 16 |
| Worldwide total number of subjects | 16 |
| EEA total number of subjects | 16 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 16 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The following patients were recruited from one investigator site from Jan 2016- Dec 2016. Actual number of patients recruited:

- 16 patient consented, 4 withdrawn
- 12 patients passed diagnostic tests, 2 failed diagnostic tests
- 9 patients randomised
- 8 patients completed trial, 1 loss to follow up.

Pre-assignment

Screening details:

A total of 693 patients were screened during Jan 2016-Dec 2016. 16 recruited. Inclusion:

- 1.18 to 70 years
- 2.Low back pain of three months or greater duration.
- 3.Average pain score 4/10 or more 7 days before recruitment
4. Dominantly paraspinal tenderness
5. Completed at least 2 conservative treatments

Period 1

| | |
|------------------------------|----------------|
| Period 1 title | Enrolment |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

Patients must meet the inclusion criteria and pass the diagnostic test to proceed in the trial.

Arms

| | |
|-----------|-----------------|
| Arm title | Diagnostic Test |
|-----------|-----------------|

Arm description:

Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised.

| | |
|--|----------------|
| Arm type | screening test |
| Investigational medicinal product name | Lidocaine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Perineural use |

Dosage and administration details:

Diagnostic medial branch nerve blocks will be carried out at each painful level with X-ray guidance, using a spinal needle to inject 0.5ml 1% lidocaine per level. A positive response is defined as a 50% or greater pain reduction (measured using a pain intensity numerical rating scale) assessed in the standing position, lasting for over 30 minutes (i.e. the duration of action of lidocaine).

| Number of subjects in period 1 | Diagnostic Test |
|--------------------------------|-----------------|
| Started | 16 |
| Completed | 11 |
| Not completed | 5 |
| Physician decision | 5 |

Period 2

| | |
|------------------------------|-------------------------------------|
| Period 2 title | Randomisation |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Data analyst |

Blinding implementation details:

Eligible and consented participants will be individually randomised in a 1:1 ratio to receive either the facet-joint injection (intervention group) or a sham (placebo injection) procedure (control group).

Arms

| | |
|------------------------------|------|
| Are arms mutually exclusive? | No |
| Arm title | Sham |

Arm description:

Sodium chloride 0.9% intravenous infusion BP ('normal saline')

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Sodium chloride 0.9% intravenous infusion BP ('normal saline') |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Periarticular use |

Dosage and administration details:

The sham group will receive normal saline 0.9% 0.5ml.

| | |
|------------------|--------------|
| Arm title | Intervention |
|------------------|--------------|

Arm description:

The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone.

The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Methylprednisolone acetate BP 40mg/ml, |
| Investigational medicinal product code | |
| Other name | Depo-Medrone 40mg/ml |
| Pharmaceutical forms | Solution for solution for injection |
| Routes of administration | Intraarticular use |

Dosage and administration details:

The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Bupivacaine hydrochloride BP 0.5% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for suspension for injection |
| Routes of administration | Intraarticular use |

Dosage and administration details:

The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine.

| Number of subjects in period 2 | Sham | Intervention |
|---------------------------------------|------|--------------|
| Started | 4 | 5 |
| Completed | 4 | 4 |
| Not completed | 0 | 1 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------|
| Reporting group title | Diagnostic Test |
|-----------------------|-----------------|

Reporting group description:

Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised.

| Reporting group values | Diagnostic Test | Total | |
|---|-----------------|-------|--|
| Number of subjects | 16 | 16 | |
| Age categorical | | | |
| Patients aged 18 to 70 years attending pain clinics identified during routine clinical assessment of non-specific low back pain | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 16 | 16 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| 18-70 years | 0 | 0 | |
| Age range | 0 | 0 | |
| Age continuous | | | |
| age 18- 70 years | | | |
| Units: years | | | |
| median | 39 | | |
| full range (min-max) | 18 to 70 | - | |
| Gender categorical | | | |
| Patients are suitable for the facet-joint injections and with negative pregnancy test | | | |
| Units: Subjects | | | |
| Female | 9 | 9 | |
| Male | 7 | 7 | |

End points

End points reporting groups

| | |
|---|-----------------|
| Reporting group title | Diagnostic Test |
| Reporting group description: Patients were screened for eligibility to enter the study. Patients who passed the diagnostic test were then randomised. | |
| Reporting group title | Sham |
| Reporting group description: Sodium chloride 0.9% intravenous infusion BP ('normal saline') | |
| Reporting group title | Intervention |
| Reporting group description: The active group will receive methylprednisolone acetate (Depo-Medrone) 20mg per joint. A maximum of four joints will be injected i.e. a maximum total dose of 80mg Depo-Medrone. The active group will additionally receive 0.5ml 0.5% bupivacaine per joint. A maximum of four joints will be injected i.e. a maximum of 2ml 0.5% bupivacaine. | |

Primary: Numerical rating pain score

| | |
|---|-----------------------------|
| End point title | Numerical rating pain score |
| End point description: | |
| End point type | Primary |
| End point timeframe: Baseline and 6 months follow up | |

| End point values | Sham | Intervention | | |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: pain scores | | | | |
| arithmetic mean (standard deviation) | | | | |
| baseline | 9.5 (\pm 1.0) | 8.4 (\pm 1.5) | | |
| follow up | 7.5 (\pm 1.9) | 7.0 (\pm 1.6) | | |

Statistical analyses

| | |
|---|---------------------|
| Statistical analysis title | Analysis |
| Statistical analysis description: As this is a feasibility study, we do not propose to formally inferentially test differences in outcomes or costs between or within the groups. We shall report mean and standard deviations for primary and secondary outcomes for the two groups at baseline and all follow-up visits. | |
| Comparison groups | Sham v Intervention |

| | |
|---|----------------------|
| Number of subjects included in analysis | 9 |
| Analysis specification | Post-hoc |
| Analysis type | other ^[1] |
| P-value | < 0.05 |
| Method | mean and SD |
| Parameter estimate | not reported |
| Point estimate | 5 |
| Confidence interval | |
| level | 95 % |
| sides | 1-sided |
| lower limit | 2 |
| Variability estimate | Standard deviation |
| Dispersion value | 0 |

Notes:

[1] - Mean and standard deviations.

Secondary: Brief Pain Inventory

| | |
|--|----------------------|
| End point title | Brief Pain Inventory |
| End point description: | |
| Pain intensity and characteristics: Brief Pain Inventory (BPI) (Short Form) Modified, with its 11-point NRS Short Form McGill Pain Questionnaire. As movement could potentially influence the intervention (lumbar facet-joint injections or sham), all numerical rating scores were assessed in the standing position | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and 6 months follow up | |

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: scores | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline average pain | 7.5 (± 1.9) | 7.0 (± 1.0) | | |
| Follow up Average pain | 5.3 (± 4.5) | 5.6 (± 2.6) | | |
| baseline least pain | 6.0 (± 2.7) | 6.0 (± 3.5) | | |
| follow up least pain | 5.3 (± 2.2) | 5.0 (± 2.8) | | |
| baseline worst pain | 9.3 (± 1.5) | 7.2 (± 2.2) | | |
| follow up worst pain | 6.3 (± 4.7) | 6.0 (± 3.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Oswestry Disability Index, mean

| | |
|-----------------|---------------------------------|
| End point title | Oswestry Disability Index, mean |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 6 months follow up

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mean points | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 48.8 (± 19.9) | 43.0 (± 15.0) | | |
| follow up | 42.6 (± 34.0) | 39.9 (± 26.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: McGill Pain Questionnaire, mean

| | |
|-----------------|---------------------------------|
| End point title | McGill Pain Questionnaire, mean |
|-----------------|---------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 6 months follow up

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mean scores | | | | |
| arithmetic mean (standard deviation) | | | | |
| baseline | 3.3 (± 2.0) | 4.5 (± 2.0) | | |
| Follow up | 3.5 (± 2.9) | 3.4 (± 2.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Pain Self Efficacy Questionnaire

| | |
|-----------------|----------------------------------|
| End point title | Pain Self Efficacy Questionnaire |
|-----------------|----------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 6 months follow up

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mean scores | | | | |
| arithmetic mean (standard deviation) | | | | |
| baseline | 27.0 (± 7.7) | 22.6 (± 12.2) | | |
| follow up | 28.3 (± 21.7) | 33.2 (± 19.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: SF-12

| | |
|-----------------|-------|
| End point title | SF-12 |
|-----------------|-------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and follow up (6, 12 and 24 weeks)

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mean scores | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline MCS | 43.4 (± 10.0) | 30.4 (± 4.6) | | |
| Baseline PCS | 32.7 (± 6.0) | 33.1 (± 6.7) | | |
| Follow up MCS | 47.2 (± 22.1) | 38.1 (± 13.5) | | |
| Follow up PCS | 34.4 (± 12.5) | 39.5 (± 13.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital Anxiety and Depression Score, mean

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|-----------------|---|
| End point title | Hospital Anxiety and Depression Score, mean |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 6 months follow ups

| End point values | Sham | Intervention | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 4 | 5 | | |
| Units: mean | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline Anxiety | 7.5 (± 3.4) | 12.0 (± 1.2) | | |
| Baseline Depression | 6.8 (± 3.9) | 10.4 (± 3.4) | | |
| Follow up Anxiety | 6.7 (± 5.7) | 10.0 (± 3.9) | | |
| Follow up Depression | 7.7 (± 8.1) | 8.7 (± 7.1) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Patients will be asked if they experience any adverse events at every visit after signing the consent form (visits: diagnostic test, randomisation, 4, 6, 12 and 24 weeks post intervention).

Adverse event reporting additional description:

Patients will be asked if they experience any Adverse events (AE) at every visit after consent. Any study related serious adverse events (SAEs) will be recorded in the subjects' notes, the CRF, the Sponsor SAE form and reported to the sponsor within 24 hours of the PI or co-investigators becoming aware of the event.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|--------------------|-----------|
| Dictionary name | SNOMED CT |
| Dictionary version | 1 |

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | randomisation |
|-----------------------|---------------|

Reporting group description:

patients experienced adverse event after randomised injections.

| Serious adverse events | randomisation | | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Swelling at injection site | Additional description: Patient experienced swelling at site of injection after diagnostic injections | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| urinary incontinence | Additional description: Urine incontinence. Patient visited Clinical Department in emergency dept. regarding urine incontinence | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 2 %

| | | | |
|---|---|--|--|
| Non-serious adverse events | randomisation | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 9 (44.44%) | | |
| Psychiatric disorders | | | |
| Depression postoperative | Additional description: Patient experienced severe depression as a result of his back pain and medication. He visited his GP to have his medication changed. He has reported it has helped. | | |
| subjects affected / exposed | 1 / 9 (11.11%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Flare up | Additional description: Patient experienced flare up following injections | | |
| subjects affected / exposed | 4 / 9 (44.44%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 January 2016 | Information updated for patient safety section: "what happens if something happens?" (REC approval required only for NHS permission) -minor amendment for protocol: TSC and DMC details updated (REC approval required to include minor amendment re:16 Sep 2015) |
| 17 June 2016 | -Patients can be recruited from spinal, pain and orthopaedic clinics. -CPP information made clearer. -Lidocaine removed as IMP and now a non-IMP -Storage of IMP -Change of CI and PI at coordinating centre. |
| 12 December 2016 | End of recruitment. 1/3 sites opened for recruitment only. Now single centre |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---|--------------|
| 12 December 2016 | End of recruitment for all three centres. The study was designed to be a multi-centre study but became a single centre study. We were unable to receive NHS permission to recruit and perform the study at the other two sites. Thus limiting our population type and unable to reach our target population size for the study. | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

- population type- many patients had previous injections or back surgery
- unable to recruit from other sites
- delays receiving approvals to start the study

Notes: