# A Prospective Clinical Series followed by A Multicenter Double-blind Randomised Placebo-Controlled Clinical Trial

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Primary Objective: To prove the hypothesis that Intradiscal Methylene blue is capable of longer pain reduction and better global perceived effect in patients suffering from chronic axial low back pain from discogenic origin then a placebo treatment...

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON46869

**Source**
ToetsingOnline

**Brief title**
Intradiscal Methylene Blue for discogenic low back pain

### Condition

- Other condition
- Tendon, ligament and cartilage disorders

**Synonym**
Low Back Pain; discogenic pijn

**Health condition**

discogene lage rugklachten

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Medisch Universitair Ziekenhuis Maastricht
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** discogenic pain, Methylene Blue, treatment

## Outcome measures

### Primary outcome

Main study parameter is pain at 6 months measured by the NRS according to Jensen (Jensen and McFarland 1993)(mean pain NRS; measured three times a day for 4 days,) and the Patients Global Perceived Effect (PGIC) measured by the 7 point Likert Scale (Farrar, Young et al. 2001)

These parameters are registered at baseline and at the standard follow-up moments (6 weeks, 3, 6, 12, 24 months).

Main study parameter of the CS and RCT is also complications and side effects.(Dworkin, Turk et al. 2005) Number of adverse and serious adverse events.

### Secondary outcome

Secondary study parameters/endpoints

-Disability measured by the Oswestry Disability Index(Baker, Pynsent et al. 1989)

-Quality of life measured by the Rand-36(Ware and Sherbourne 1992; Dworkin, Turk et al. 2005)

-Cost effectiveness.

-Used analgesics

-MPQ-DLV (McGill Pain Questionnaire- Dutch Language Version).(Melzack 1987)

Other study parameters

After informed consent baseline values of possible confounders are registered:

-Demographics, length, weight, BMI

-Neurological status

-MPI-DLV (pain related psychosocial and behavioral aspects)(Dworkin, Turk et

al. 2005)

-MRI

Tertiary parameters:

- MRI classification (Pfirrmann grading scale, Modic Changes, High Intensity

Zone).

# Study description

**Background summary**

Rationale and Objectives: To prove the hypothesis that Intradiscal Methylene blue is capable of longer pain reduction than the best available treatment (conservative treatment) in patients suffering from axial low back pain of discogenic origin. Secondary objective will be to assess cost-effectiveness, improvement in physical function, and quality of life. Tertiary objective is to assess disc Magnetic Resonance imaging (MRI) and provocative discography in patients with low back pain of discogenic origin.

Study design: Multicenter prospective Clinical Case series followed by a randomized clinical trial . In this RCT intradiscal Methylene blue injection will be compared to a sham treatment. The treatment group as well as the control group will receive best treatment available.

Study population: Patients (age >18 and < 65 years) suffering from axial low

back pain from discogenic origin. This study will be done in the Pain Management Centres of Arnhem; Rijnstate, Leiderdorp, Eindhoven, and Maastricht.

Main study parameters/endpoints: Main study parameter are pain, Global Perceived Effect and disability at 6 months measured by a Numeric Rating Scale weighted according to Jensen. Secondary outcome includes cost effectiveness, the Oswestry Disability Index , the McGill Pain Questionnaire- Dutch Language Version, and a Quality of Life questionnaire. Tertiary objectives are to assess early disc degeneration between groups by MR imaging and to develop a prediction model for success of intervention.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: After intake and treatment the patients will be followed-up at 6 weeks and at 3, 6,12, and 24 months after the initial intervention (6 site visits). During the intake visit a physical examination is done. Before each visit questionnaires have to be filled in by the patient. The treatment itself is performed under local analgesia and is generally well tolerated without side effects or complications.
The treatment group has the opportunity to benefit from the possible positive effects from the intradiscal methylene blue treatment, i.e. longer pain relieve and better functional status,. Patients in the control group have the possibility to benefit in the same way after 6 months.

## Study objective

Primary Objective:
To prove the hypothesis that Intradiscal Methylene blue is capable of longer pain reduction and better global perceived effect in patients suffering from chronic axial low back pain from discogenic origin then a placebo treatment. To prove that MB treatment is safe and causes little side effects

Secondary Objective(s):
To establish the effect of MB treatment on disability, cost effectiveness, and quality of life.

Tertiary Objective:
To compare MRI images before and after discography and objectify the presence of anatomical disc alterations and signs of early disc degeneration.
To compare Magnetic Resonance imaging (MRI) and provocative discography in patients with low back pain of discogenic origin.

## Study design

3. STUDY DESIGN

This study starts with a prospective clinical case series(CS) to validate the

following randomized Clinical Trial (RCT) After proper inclusion in the CT a group of 15 patients with one or two level discogenic low back pain will be treated at the symptomatic level with MB. Assessments occur at 6 weeks, 3,6,12 and 24 months. Positive result of the prospective CS, defined as a decrease of 2 points in the NRS scores and GPE( global perceived effect) "much improved" and "very much improved" will be used as determinants of a clinically important difference (Farrar, Young et al. 2001) in at least two out of five patients , without complications or side effects, will be followed by a randomized placebo-controlled clinical trial RCT . Results of the CS and RCT will be published.
The RCT is designed as a multicentre randomised placebo-controlled clinical trial with comparison of an Intradiscal Methylene Blue injection with an intradiscal Placebo injection. Patients will be randomly selected for treatment with MB or Placebo injection. Follow-up assessment will be at 6 weeks and at 3 months, 6,12, and 24 months after the initial intervention. After six months, patients in the control group are allowed to have the MB injection. Finally, patients are asked by their treating physician to undergo a second lumbar MRI scan to assess anatomical alterations or degeneration of the intervertebral disc.

**Intervention**

MB treatment group
All patients with discogenic LBP follow a standardized treatment schedule.The conservative treatment consists of medication according the scheme of the World health organisation ( WHO). Step 1 ( Paracetamol and eventually NSAID*s), and step 2: non-opioid medication: Tramadol .
When there is no treatment effect patients receive provocative discography. When a discography is positive the patient is included and randomised into the MB or the placebo group. A discography is considered positive when the patient's pain can be reproduced, with a minimal NRS score of 7 (or 70% of max pain) according International Standards (ISIS) guidelines. At least one adjacent disc should perform as a negative control disc. A maximum of two positive discs are accepted in this study.
After proper patient selection and informed consent patients are scheduled for this methylene blue (MB) study.
1: MB groep: intradiscale injectie van 1 ml methylene Blauw ( 10mg/ml) met 1ml 2% Lidocaine hydrochloride en 0.5 ml iohexol 300(contrast)
2: ( RCT) placebogroep: intradiscale injectie van 1ml isotoon zout met 1ml 2% lidocaine hydrochloride en 0.5 ml iohexol 300(contrast)

Both patient and Anaesthesiologist are blinded to the injected material. Because MB is blue the Anaesthesiologist who performs the discography will not

participate in the follow-up of the patients.
The procedure is performed in day-care. Patients are discharged 2 hours post procedure.

Use of co-intervention
Up to six months, new medication is restricted to Paracetamol, NSAIDs or Tramadol. Except for physiotherapy, no interventional therapies are allowed in this period. After six months, the MB treatment is available for patients from the control group and prescription of new medication is free.

**Study burden and risks**

Adverse and serious adverse events
All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

All SAEs will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.

Theoretically there is a possibility that nerve damage (thermal or mechanical) or discitis can occur after an intradiscal therapy. If so the best standard of care for their specific complication will be provided to the subject.

Follow-up of adverse events
All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

Axial low back pain of presumed discogenic origin of at least 6 months duration and non responsive to treatment of at least 6 months conservative medical management.;History consistent with discogenic low back pain ( e.g. predominant axial pain produced on lumbar motion, significant functional limitation in sitting duration and tolerance) A neurological exam without marked motor deficit. Age between18 and 65 years and painintensity should be NRS 5 or higher. In provocative discography Modified Dallas classification grade 1 to 4 and a provoked pain of at least NRS 7 or >=70% of worst pain.

## Exclusion criteria

Severe disc degeneration at the affected level as evidenced by >50% disc height loss on plain anteroposterior and lateral lumbar radiographs or CT/MRI.;- Extruded or sequestered herniated nucleus pulposus at the affected level(s).;- Body Mass Index BMI of >= 35;- Mean pain with NRS below 5;- Previous lumbar back surgery ( e.g. Laminectomy, discectomy or fusion);- Invasive intradiscal procedure previously performed at the same level.;- Moderate to severe spinal stenosis due to osteophyte and/or ligamentous overgrowth as evidenced by MRI or CT, provided stenosis is the cause of pain.;- Moderate to severe endplate degenerative changes at the affected levels;- Grate 1-2 spondylolisthesis;- Pregnancy;- Coagulopathy or oral anti-coagulant therapy;- Infection;- Patients incapable of following verbal or written instructions or with psychiatric problems potentially interfering with cooperation in the study;- Discography: ;That shows a posterior annular disruption to extend into the outer annulus or beyond the confines of the outer annulus.;-;Discography without pain reproduction at the affected level( s), or with discordant pain at adjacent unaffected levels at up to 50 Psi above opening pressure.;-;Pain provocation in disc at pressures >50 Psi above opening pressure;-;In provocative discography Modified Dallas classification grade 0 and 5.

# Study design

## Design

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| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 15-04-2011 |
| Enrollment: | 80 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | methylthionine chloride |
| Generic name: | methylene blue |

# Ethics review

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|---|---|
| Approved WMO Date: | 16-08-2010 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 21-02-2011 |
| Application type: | First submission |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

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|---|---|
| Approved WMO Date: | 11-03-2011 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 21-12-2012 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 21-01-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 24-03-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 14-04-2014 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |
| Approved WMO Date: | 26-04-2018 |
| Application type: | Amendment |
| Review commission: | METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2010-022025-15-NL |
| CCMO | NL32511.068.10 |

# Study results

Date completed: 26-02-2019

Actual enrolment: 84