ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>MAGnesium-oral supplementation to reduce PAin in patients with severe PERipheral arterial occlusive disease. The MAG-PAPER randomized clinical trial protocol.</th>
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<tr>
<td>AUTHORS</td>
<td>Venturini, Monica; Zappa, Sergio; Minelli, Cosetta; Bonardelli, Stefano; Lamberti, Laura; Bisighini, Luca; Marta, Zangrandi; Turin, Maddalena; Rizzo, Francesco; Rizzolo, Andrea; LATRONICO, NICOLA</td>
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GENERAL COMMENTS

General remarks:
The protocol describes a study in which pain in patients with peripheral arterial occlusive disease is treated with oral magnesium compared with placebo.
Although date and version identifier is not noted one must assume that the protocol in its present form is the final protocol. As such, the protocol adheres to the SPIRIT standards (http://www.spirit-statement.org/)
The title is self-explanatory.
The trial has been registered in clinical trials and is not yet recruiting. The protocol describes roles and responsibilities of the researchers participating in the study.
Background and rationale is well described. The authors clearly identify the inconsistent findings on the efficacy of magnesium on pain reduction in clinical studies.
Objectives are clearly described.
The study is a single-center randomized double-blind clinical trial.
Test drug will be 300 mg Magnesium Oxide compared with fructose 10 gram. However, as placebo is fructose, one must question whether true blinding exists. Will the patients be able to spot the placebo based on taste alone? The researchers should take this question into account.
Participants: This is well described. However, the protocol does not take any pre-existing Magnesium intake into consideration. Patients already taking magnesium in any form should probably be excluded from the study.
Outcome measure:
The primary outcome is the oxycodone dosage needed to achieve satisfactory analgesia defined as NRS ≤4 after 14 days of therapy. How will the authors deal with patients not reaching NRS ≤4?
The secondary outcomes are: level of pain relief on day 2 measured...
using PRS; time needed to achieve satisfactory analgesia (NRS≤4); time needed to achieve a reduction of pain of 50% (PRS = 50%). How will the authors deal with patients not reaching these objectives?

Data management, or a data analysis plan, is only described in very loose terms. This section should probably be expanded somewhat.

Ethical approval has been obtained.

Some minor typographic errors and several errors in citing references (including references nos. 6, 10, 13, 14, 15, reference no. 16 that has been retracted!, 18, 19, 20, 26, 36, 47) detract from the overall impression of the protocol.

**REVIEWER**
Prof Gisèle PICKERING
Laboratory of Fundamental and Clinical Pharmacology of Pain, Neurodol Inserm1107, Faculty of Médecine
Clinical Investigation Center, CIC Inserm 1405, University Hospital Clermont-Ferrand

**REVIEW RETURNED**
30-Jul-2015

**GENERAL COMMENTS**
This is overall a very interesting protocol.

Point 4:
Magnesium accurate chemical composition (SO4?, ionic composition?) and pharmaceutical form (apart from the glass tube container) should be exhaustively described (size, shape, colour, placebo form etc)
Is the main Hospital Pharmacy involved in the preparation? Who will prepare the treatments? who will verify the blinding procedure?These points are vague in the protocol

Statistics:
The authors refer to their own data in 90 patients. Please give literature data and compare your own data (20-25 mg) to the literature
The authors consider a diminution of 30% between Mg and placebo:
This point is the most important in the protocol. How did they choose this expected difference? Own data? Literature?

Ethics and dissemination
For how long and where will be kept the records during and after completion of the study?

**VERSION 1 – AUTHOR RESPONSE**
Reviewer 1
Dr. Søren Mikkelsen

1. Will the patients be able to spot the placebo based on taste alone?
   The patient expects to take something sweet, and magnesium (as Mag Orosolubile®) has a sweet slightly fruity taste. The fructose (the placebo) has also sweet taste. The taste is not the same but similar and each patient will assume either Magnesium or Fructose.

2. The protocol does not take any pre-existing magnesium intake into consideration.
- We thank the reviewer for this observation. We have updated the exclusion criteria, so that patients that were already taking magnesium in any form will be excluded. (See pag 4, paragraph ‘Participants’).

3. How will the authors deal with patients not reaching NRS ≤4?
- We will titrate therapy every two days, so it is virtually impossible that patients do not reach the target after an observation/intervention period of 14 days. If the pain intensity remains exceedingly high despite medical treatment, the reason can be an acute limb ischemia or wound infection with or without osteomyelitis requiring invasive treatments (surgery/interventional radiology via angiography). These cases are rare and will be analyzed in the assigned arm, according to the intention to treat analysis.

About patients with residual pain on day 14th, they will remain in charge to the acute pain service.

4. Data management and data analysis should probably be expanded somewhat.
- We have modified the text according to the reviewer suggestion, Data management plan: see pag 5-6, paragraph ‘Data collection’.

5. Errors in citing references.
- We apologize for errors in reporting the references. We have now revised accurately all references according to the Journal’s style.

Concerning the Reference n°16, we rechecked the journal website, and found no evidence of paper retraction; in fact, the paper is freely available for download.

Reviewer 2
Prof Gisèle Pickering

1. Magnesium accurate composition and pharmaceutical form should be exhaustively described. Is the main Hospital Pharmacy involved in the preparations? Who will prepare the treatments? Who will verify the blinding procedure?
- We thank the reviewer for these questions that helped us to improve the description of the protocol. We will use MAG OROSOLUBLE®-Sanofi Aventis, a orosoluble magnesium; one dose contains magnesium oxide 300 mg, citric acid, monosodium citrate, sorbitol, aspartame, sodium cyclamate and lemon flavoring. We modified the text reporting the specific composition of the drug used (see pag 4, paragraph ‘Intervention, Procedure and Standard Care’). We also reported that magnesium and placebo are in the form of white powder, indistinguishable from each other to the eye and touch, and specified who and how will prepare the drug and placebo. Finally, we specified that the two members of the Acute Pain Service in charge for preparing the drugs will not take part in data recording, including the assessment of the outcome measures. (see pag 5, paragraph ‘Randomization and Blinding’).

2. Please give literature data and compare your own data (20.25 mg) to the literature.
- In literature few studies have evaluated the treatment of chronic pain in patients with severe peripheral arterial occlusive disease. Samolsky Dekel BG and colleagues used slow-release oxycodone (daily dose 27.8 ± 12 mg) for non-surgical patients and in ambulatory patients. (Samolsky Dekel BG et al. Pain management in peripheral arterial obstructive disease: oral slow-release oxycodone versus epidural L-bupivacaine. Eur J Endovasc Surg 2010;39:774-8).


In chronic non-cancer pain, opioid should be kept at the lowest possible dose to reduce the risk of side-effects, especially in the elderly vasculopatic frailty patients (Pergolizzi J et al. Opioids and the management of chronic severe pain in the elderly: consensus statement of an International Expert Panel with focus on the six clinically most often used World Health Organization Step III opioids (buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone). Pain Pract 2008 Jul-Aug;8(4):287-313).


We have reviewed the data of our 270 ambulatory patients treated for severe peripheral arterial occlusive disease from January 2012 to December 2014 and found an average oxycodone dose of 20.25 mg (SD 10 mg) as the dose to effectively treat pain.

3. The authors consider a diminution of 30% between Mg and placebo. How did they choose this expected difference?

- A 30% reduction in opioid consumption is reported in several clinical studies in various settings. Morphine consumption was 30% lower in patients receiving magnesium compared to the control group in the Seyhan's study (Seyhan TO et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. Br J Anaesth 2006;96:247-52). The cumulative mean morphine doses in postoperative period (48 h) were 91 mg in the control group and 65 mg (a 30% difference) in the magnesium group in the Tramer's study (Tramer MR et al. Role of magnesium sulfate in postoperative analgesia. Anesthesiology 1996;84:340-7).

The best scheme of treatment of vascular pain, referring to our experience, would be a lower oxycodone dose (5 mg) in the morning, when the pain is less intense and the cognitive impairment is not tolerate, and a greater dose (10 mg) in the evening, when the pain is more intense and the side effects more tolerate.