PEER REVIEW HISTORY

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ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Study protocol for a randomised, double-blinded, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)</th>
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<td>AUTHORS</td>
<td>Juel, Jacob; Olesen, Søren; Olesen, Anne; Poulsen, Jakob; Dahan, Albert; Wilder-Smith, Oliver; Madzak, Adnan; Frøkjær, Jens; Drewes, Asbjørn</td>
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VERSION 1 - REVIEW

| REVIEWER             | Prof A Weinbroum  
The Tel Aviv Sourasky Medical Center  
The Sackler Faculty of Medicine, Tel Aviv University  
Tel Aviv, Israel |
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<td>REVIEW RETURNED</td>
<td>15-Dec-2014</td>
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GENERAL COMMENTS

The MS I have received is actually the study protocol, written in a future tense, containing no results and no discussion. As such it is unpublishable.

| REVIEWER             | Philip Finch  
Perth Pain Management Centre, Australia |
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<td>REVIEW RETURNED</td>
<td>10-Dec-2014</td>
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GENERAL COMMENTS

The authors of this protocol intend to study the effects of s-ketamine on the pain of chronic pancreatitis (CP). They postulate that s-ketamine, by blocking NMDA receptors, will reduce "central sensitisation" thereby reducing pain. Ketamine has widespread receptor effects and its action on the NMDA receptor is only one.1,2 This reviewer has several issues with this paper:  
As a protocol it might be suitable for the introduction and methods sections of a definitive paper describing the results of the trial. In its present form, it does not advance knowledge on the subject of pain causation and treatment in CP.  
There are some minor grammatical errors, see:  
• Abstract page 5, lines 20 and 46.  
• Article summary page 8, line 4.  
Many of references are quite dated and some recent studies on the pharmacological treatment of CP have not been included.  
The doses of oral ketamine are quite low for providing meaningful analgesia (in this reviewer’s personal experience) and the need for a period of intravenous administration at the start is unclear; especially in light of a previous study by one of the authors of this submitted protocol which found that the effect of s-ketamine iv infusion did not outlast the infusion.3 There would be considerable additional monitoring and costs. Sublingual ketamine is well absorbed. Why
not omit the intravenous infusion of s-ketamine?
Lastly, the need for 3 MRI studies seems excessive and the purpose of these studies is unclear.


REVIEWER
Güralp O. Ceyhan, MD
Professor of Surgery
Vice-chairman
Department of Surgery,
Klinikum rechts der Isar,
Technical University of Munich

REVIEW RETURNED
04-Jan-2015

GENERAL COMMENTS
In their submitted study protocol " Study protocol for a randomized, double-blind, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)" Juel et al. introduce a very well designed study protocol which focuses on the pain treatment of chronic pancreatitis patients. For this, the authors designed a clinical trial in which S-ketamine is infused in patients with chronic pancreatitis and followed by an oral administration of increasing S-ketamine. After administration of S-ketamine patient visits will be performed to document the analgesic effect of S-Ketamine.

The group of Drewes and colleges are well-known and even opinion leaders in the field of pancreatic pain and chronic pancreatitis. In the past, the group has contributed with well-designed studies to this very special field in pancreatology and published milestone papers in this field. However, although the author provided a well-constructed and clear structured randomized, double-blind and placebo-controlled study a few minor points have to be raised.

The main hypothesis of this submitted study protocol is that NMDA-Receptors will be antagonized by S-ketamine and with this nociception in chronic pancreatitis patients. Unfortunately, the authors miss to provide a clear link between the NDMA-Receptors and the pathogenesis of chronic pancreatitis or current knowledge of NMDA receptors in chronic pancreatitis. Please provide more information in the introduction part about the importance of NMDA-receptors in chronic pancreatitis to better understand the aim of the proposal.

One further important question concerns the exclusion criteria. The authors want to mask iv ketamine-related side effects by iv midazolam administration. However, the authors do not state how to react on potential side effects during the further oral treatment of S-Ketamine and how to guarantee the blinded fashion of the study here. In this aspect, the authors also might consider to exclude patients with clear ongoing side effects of ketamine.

The authors described that blood sampling is intended for further
biochemical screening but missed to provide any detailed information about the parameters to be analyzed. This becomes even more important, when considering that “any clinically significant laboratory abnormalities” might lead to patient exclusion. Therefore, the authors are encouraged to list the aimed serological parameters to give a better insight especially in terms of exclusion.

Although power calculation seems to present the total number of intended patients seems to be a few. Can the authors comment on this once again in detail.

The last visit will take place 13 weeks after primary infusion. This follow-up period seems to be to short since not all chronic pancreatitis patients might develop an acute phase of their pancreatitis during this time period. Is it not feasible to have the last visit at least after 6 months?

What about patients with an acute phase of chronic pancreatitis? Will they also be included into the study? And according to this last remark, is there any time-limit of disease duration after initial diagnosis for inclusion or can also patients with first-time diagnosis of chronic pancreatitis be included into the study?

VERSIOIN 1 – AUTHOR RESPONSE

Reviewer Weinbroum's review can be disregarded

Our reply: Noted.

Reviewer Name Prof A Weinbroum
Institution and Country The Tel Aviv Sourasky Medical Center
The Sackler Faculty of Medicine, Tel Aviv University Tel Aviv, Israel
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The MS I have received is actually the study protocol, written in a future tense, containing no results and no discussion. As such it is unpublishable.

Our reply: The above comment is disregarded, as stated in the above by the editor.

Reviewer Name Philip Finch
Institution and Country Perth Pain Management Centre, Australia
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors of this protocol intend to study the effects of s-ketamine on the pain of chronic pancreatitis (CP). They postulate that s-ketamine, by blocking NMDA receptors, will reduce “central sensitisation” thereby reducing pain. Ketamine has widespread receptor effects and its action on the NMDA receptor is only one.1,2
Our reply: We thank the reviewer for this comment. We are aware of the extra NMDA receptor effects of ketamine, however we have decided to focus on the NMDA receptor, as we believe it is key in central sensitisation.

Embedded in the paragraph, S-ketamine and central sensitisation, is already the following acknowledging the great point of the reviewer:

It is classified as a non-competitive NMDA receptor antagonist, but acts on multiple receptors including opioid-receptors.

We have added to following sentence after the above:
Hence, analgesia induced by S-ketamine may be partly mediated by actions on opioid receptors, however the main analgesia is induced by the NMDA receptor antagonism.

This reviewer has several issues with this paper:
As a protocol it might be suitable for the introduction and methods sections of a definitive paper describing the results of the trial. In its present form, it does not advance knowledge on the subject of pain causation and treatment in CP.

Our reply:
We agree with the reviewer, and hence the introduction has been revised accordingly. It now reads:

Chronic pancreatitis (CP) remains a major source of morbidity in Northern Europe with an annual incidence of approximately 10 per 100,000 inhabitants. A typical cause is long-term excessive use of alcohol, although genetic, environmental and autoimmune factors have also been associated with CP. It is a disease characterized by progressive destruction of the pancreatic gland and as it evolves, significant impairment of exocrine as well as endocrine functions. Within 5 years of diagnosis endocrine and exocrine insufficiencies develop in approximately 50 % and 80 % of patients with CP, respectively. These conditions are usually managed sufficiently with anti-diabetic treatment and pancreatic enzymes to optimize metabolic and nutritional status, whereas the treatment of pain in CP is more intricate. This progressive destruction also leads to pain, which is the most common symptom in CP, and up to 90 % of patients have chronic abdominal pain, often worsened by acute pain exacerbations typically requiring hospitalisation. Hence, pain is a major burden for most CP patients and it has been associated with impaired psychosocial functioning, physical disability and decreased life quality. It is recognized that chronic pain may alter central pain processing e.g. central sensitization, as the continuous damage of the pancreatic nerves may in time lead to central sensitisation of the pain system. The key component in this process is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor. The initial analgesic medication in painful chronic pancreatitis will often involve opioids in the absence of pathology suitable for endoscopic or surgical interventions. However, opioid-based analgesia often only shows limited effectiveness in these patients and it is frequently accompanied by undesirable side-effects. However, a NMDA receptor antagonist, e.g. S-ketamine, could potentially be able to reverse this central sensitization by its action on the NMDA receptor. Thus providing long-term pain relief in sufferers of chronic pain.

The reviewer wrote:
There are some minor grammatical errors, see:
• Abstract page 5, lines 20 and 46.
• Article summary page 8, line 4.

Our reply: We thank the reviewer for noticing these errors. Article summary has been deleted as the editor asked for, and the abstract corrected.
The reviewer wrote:
Many of references are quire dated and some recent studies on the pharmacological treatment of CP have not been included.

Our reply: It is much appreciated. We have followed the point of the author and added a recent publication on the pharmacological treatment of CP, hence a novel review has been added. We agree with the reviewer that some papers are a little dated, however some are considered key papers in the field.

The reviewer wrote:
The doses of oral ketamine are quite low for providing meaningful analgesia (in this reviewer’s personal experience) and the need for a period of intravenous administration at the start is unclear; especially in light of a previous study by one of the authors of this submitted protocol which found that the effect of s-ketamine iv infusion did not outlast the infusion.3 There would be considerable additional monitoring and costs. Sublingual ketamine is well absorbed. Why not omit the intravenous infusion of s-ketamine?

Our reply: We appreciate the comments by reviewer, and for his excellent point. The dosage has been decided after discussions between the authors and may have it flaws. We decided to have an IV phase initially to give the participants a large dose of S-ketamine initially, as we think this dose may provide a relevant basis for pain relief, if followed by an oral dose. It may however prove insufficient. As of now the protocol is set in stone, as we are not able to make any changes in this protocol in terms of medicine as the study is on going and the North Denmark Region Committee on Health Research Ethics and the Danish health and medicines authority have approved it. However, we agree that sublingual S-ketamine has a great potential, and we will consider this for future studies.

The reviewer wrote:
Lastly, the need for 3 MRI studies seems excessive and the purpose of these studies is unclear.

Our reply: We acknowledge that the purpose of the MRI studies may be unclear. The MRI studies of the cerebrum have been included in the protocol, as an investigation at baseline, during ketamine dosage and at the end of the study to assess any potential changes in the cerebrum, hence a paragraph accordingly have been added to the manuscript reading:

MRI studies
The MRI studies of the cerebrum have been included in the protocol, as an investigation at baseline, during ketamine or placebo treatment, and at the end of the study to assess any potential changes in the cerebrum.


Reviewer Name Güralp O. Ceyhan, MD
Institution and Country Professor of Surgery
In their submitted study protocol “Study protocol for a randomized, double-blind, placebo-controlled, clinical trial of S-ketamine for pain treatment in patients with chronic pancreatitis (RESET trial)” Juel et al. introduce a very well designed study protocol which focuses on the pain treatment of chronic pancreatitis patients. For this, the authors designed a clinical trial in which S-ketamine is infused in patients with chronic pancreatitis and followed by an oral administration of increasing S-ketamine. After administration of S-ketamine patient visits will be performed to document the analgesic effect of S-Ketamine.

The group of Drewes and colleges are well-known and even opinion leaders in the field of pancreatic pain and chronic pancreatitis. In the past, the group has contributed with well designed studies to this very special field in pancreatology and published milestone papers in this field. However, although the author provided a well-constructed and clear structured randomized, double-blind and placebo-controlled study a few minor points have to be raised.

Our reply:
We thank the reviewer for his kind comments on our research group.

The reviewer wrote:
The main hypothesis of this submitted study protocol is that NMDA-Receptors will be antagonized by S-ketamine and with this nociception in chronic pancreatitis patients. Unfortunately, the authors miss to provide a clear link between the NMDA-Receptors and the pathogenesis of chronic pancreatitis or current knowledge of NMDA receptors in chronic pancreatitis. Please provide more information in the introduction part about the importance of NMDA-receptors in chronic pancreatitis to better understand the aim of the proposal.

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Chronic pancreatitis (CP) remains a major source of morbidity in Northern Europe with an annual incidence of approximately 10 per 100,000 inhabitants.1 A typical cause is long-term excessive use of alcohol, although genetic, environmental and autoimmune factors have also been associated with CP. It is a disease characterized by progressive destruction of the pancreatic gland and as it evolves, significant impairment of exocrine as well as endocrine functions. Within 5 years of diagnosis endocrine and exocrine insufficiencies develop in approximately 50 % and 80 % of patients with CP, respectively. These conditions are usually managed sufficiently with anti-diabetic treatment and pancreatic enzymes to optimize metabolic and nutritional status, whereas the treatment of pain in CP is more intricate. This progressive destruction also leads to pain, which is the most common symptom in CP, and up to 90 % of patients have chronic abdominal pain, often worsened by acute pain exacerbations typically requiring hospitalisation.2 Hence, pain is a major burden for most CP patients and it has been associated with impaired psychosocial functioning, physical disability and decreased life quality.3, 4 It is recognized that chronic pain may alter central pain processing e.g. central sensitization, as the continuous damage of the pancreatic nerves may in time lead to central sensitisation of the pain system. The key component in this process is aberrant activation of the N-methyl-D-aspartate (NMDA) receptor. The initial analgesic medication in painful chronic pancreatitis
will often involve opioids in the absence of pathology suitable for endoscopic or surgical interventions. However, opioid-based analgesia often only shows limited effectiveness in these patients and it is frequently accompanied by undesirable side-effects.5 However, a NMDA receptor antagonist, e.g. S-ketamine, could potentially be able to reverse this central sensitization by its action on the NMDA receptor. Thus providing long-term pain relief in sufferers of chronic pain.

The reviewer wrote:
One further important question concerns the exclusion criteria. The authors want to mask iv ketamine-related side effects by iv midazolam administration. However, the authors do not state how to react on potential side effects during the further oral treatment of S-Ketamine and how to guarantee the blinded fashion of the study here. In this aspect, the authors also might consider to exclude patients with clear ongoing side effects of ketamine.

Our reply:
The reviewer has a good point about the blinding of the oral phase. As hinted in the above, the blinding is rather intricate. We have decided not to have an active placebo, hence only participants receiving active, S-ketamine, treatment will get medication. The placebo is matched on taste, color, and viscosity, however the effect of S-ketamine hardly will be blinded. The reason for this was that we would not like to give the participants and active drug (e.g. benzodiazepine) for 4 weeks in addition to their regular and often vast current medication, only for the sake of blinding. The well being of the participants is of great important to us, hence if needed any patient who experience intolerable side effects may drop out of the study on their own discretion. To emphasize this, the following have been added to the paragraph:

If side effects are intolerable on the minimum dose during the oral phase, participants have the options to drop out of the study, an option always available to participant at any stage of the study.

The reviewer wrote:
The authors described that blood sampling is intended for further biochemical screening but missed to provide any detailed information about the parameters to be analyzed. This becomes even more important, when considering that “any clinically significant laboratory abnormalities” might lead to patient exclusion. Therefore, the authors are encouraged to list the aimed serological parameters to give a better insight especially in terms of exclusion.

Our reply:
We apologies for this inconsistence, and happily provide details of the biochemical screening. The following values will be evaluated:

Alanine transaminase
Aspartate transaminase
Albumin
Alkaline phosphatase
Bilirubins
Gamma glutamyl transpeptidase
C-reactive protein
Urea
Creatinine
Hemoglobin
Potassium
International normalisation ratio
Lactate dehydrogenase
Sodium
The following paragraph has been added to the manuscript:

**Blood samples**
The following biochemical parameters will monitored during the study:
- Alanine transaminase
- Aspartate transaminase
- Albumin
- Alkaline phosphatase
- Bilirubins
- Gamma glutamyl transpeptidase
- C-reactive protein
- Urea
- Creatinine
- Hemoglobin
- Potassium
- International normalisation ratio
- Lactate dehydrogenase
- Sodium
- White blood cell count
- Thrombocytes

The reviewer wrote:
Although power calculation seems to present the total number of intended patients seems to be a few. Can the authors comment on this once again in detail.

**Our reply:**
We have provided all details on, how we made the power calculation. It is a little unclear for us, which further information the reviewer wants. We apologize for this, and if the reviewer needs any further information please specify.

The reviewer wrote:
The last visit will take place 13 weeks after primary infusion. This follow-up period seems to be to short since not all chronic pancreatitis patients might develop an acute phase of their pancreatitis during this time period. Is it not feasible to have the last visit at least after 6 months?

**Our reply:** We thank the review for this point. As the reviewer correctly states if an acute phase of acute in chronic was need the period may be too short, however, we are including patients with painful chronic pancreatitis, hence chronic pain, there is no need for acute in chronic. The primary endpoint is pain relief during the treatment period. All patients are followed as outpatients in our clinics at the University Hospital of Aalborg any changes out side the frames of the study will be handled accordingly.

The reviewer wrote:
What about patients with an acute phase of chronic pancreatitis? Will they also be included into the study? And according to this last remark, is there any time-limit of disease duration after initial diagnosis for inclusion or can also patients with first-time diagnosis of chronic pancreatitis be included into the study?
Our reply: Patients needs to be on stable treatment, hence patients with acute in chronic will not be eligible for participation in our study. The patients must suffer from chronic abdominal pain characteristic for CP, meet the criteria for chronic pain (pain ≥ 3 days per week in at least 3 months) and must consider their pain as insufficiently treated with their usual analgesic treatment. This is a serious concern and we share the view of the reviewer. Any patient with the diagnosis of chronic pancreatitis may be included. We are using the Mayo Clinic diagnostic criteria.