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Pain response to open label placebo in induced acute pain in healthy male adults

Study protocol

Study type: prospective, randomized, assessor blinded crossover study

Categorisation: Risk category B

Study registration: clinicaltrials.gov (intended)

Study identifier: None

Principal investigators:

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Investigational product/ medication:	open label placebo
Protocol version and Date:	Version 1.5 27.10.2017

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Abbreviations:

DLPC	dorsolateral prefrontal cortex
NEG	non-educated group
nPEG	non Placebo educated group
NRS	numeric rating scale
OLP	open label placebo
OMT	oral mucosal tissue
PA	placebo analgesia
PEG	placebo educated group
PR	placebo reactions
i.v.	Intravenous
sTNFaRII	soluble tumour necrosis factor alpha Receptor II

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Signature Page

This is to confirm that the study protocol and appendices contain all the information and regulations needed to conduct the study and that the study will be conducted and documented in all its parts in accordance with the study protocol.
I agree to conduct this study in accordance to the Declaration of Helsinki and its amendments, ICH Good Clinical Practice Guidelines (ICH-GCPG) and applicable regulations and laws. In particular, I will obtain approval by the Independent Ethics Committee (IEC) prior to study start and signed informed consent from all participants included in the trial. In addition, I will allow direct access to source documents and agree to audits by the sponsor and to inspections from regulatory authorities. I will ensure that the investigational product(s) supplied by the sponsor are being used only as described in this protocol.

Sponsor-Investigator:

Name	**PD Dr. med. Ruppen Wilhelm**		
Function	**Principal investigator, Chair of the Pain Relief Unit, Senior physician**		
Institution	**Department of Anaesthesia, University Hospital Basel**		
Address	**CH-4031 Basel, Switzerland**		
Date	21. 9. 17	**Signature**	

Name	**Dr. med. Tobias Schneider**		
Function	**Back-Up Principal investigator, Senior physician**		
Institution	**Department of Anaesthesia, University Hospital Basel**		
Address	**CH-4031 Basel, Switzerland**		
Date	21.09.2017	**Signature**	

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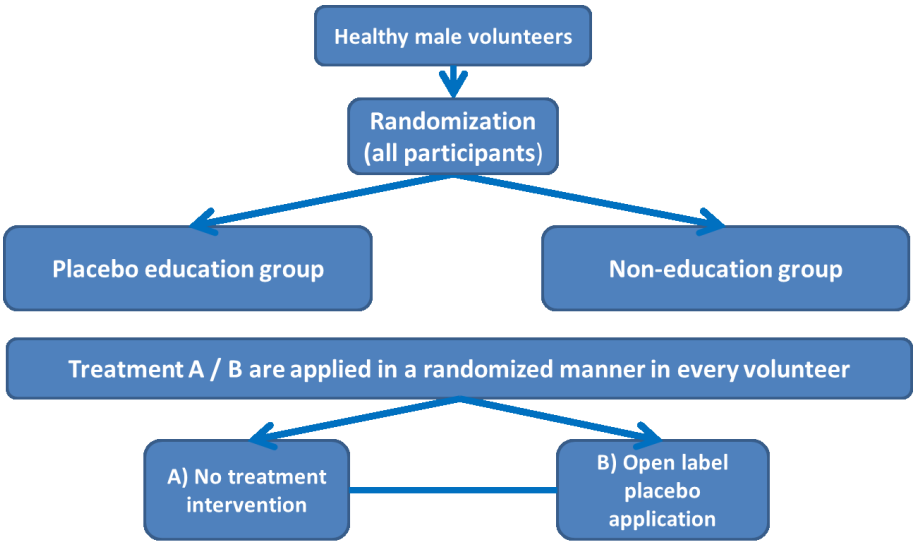
Study Synopsis:

Sponsor/ Sponsor Investigaor:	Wilhelm Ruppen, PD Head of the Pain Unit Department of Anaesthesiology/ Pain Relief Unit Spitalstrasse 22 4031 Basel CH Phone: +41613286496 E-mail: Wilhelm.ruppen@usb.ch
Study Title:	**P**ain response to **o**pen **l**abel placebo in induced **a**cute **p**ain in healthy male adults
Short Title/ Study ID:	**POLAP-Study**
Protocol Version and Date:	Version 1.4 21.09.2017
Trail registration:	Clinicaltrails.gov (intended)
Study category and Rationale:	Category B: This study involves the use of an established pain model, a placebo (NaCl), and a carrier solution (Ringer Lactate). No other drugs will be applied. However, it is our understanding that even NaCl 0.9% used within the guidelines of suggested use (1 ml injection) mandate pro forma a category B, since volunteers have no indication for NaCl 0.9%. In our study NaCl 0.9% is not the investigational product. Any other carrier solution without an analgesic potential (placebo) could have been used. We are not performing a classical medical drug trail, therefore catogory B has to be applied.
Background and Rationale:	Open label placebo treatment studies have reached great interest in research in the recent past. Current studies suggest that placebos have a clinically significant effect, even if patients and treating physicians know they are using a placebo. This is true for chronic pain states like chonic low back pain [1] and chronic disease like the irritable bowel syndrome [2]. However, data regarding the response of acute pain to open label placebo are lacking. The neuro-biologic basis of placebo analgesia (PA) has been studied for over 40 years, since Levine at al. showed that the opiate antagonist naloxone could annul placebo analgesia after wisdom tooth extraction [3]. We know today that the mediation of PA is complex and involves several pain modulation systems like the opioidergic descending pain control [4], the endogenous cannabinoid system [5], the dorsolateral prefrontal cortex [6] and takes even place at spinal cord level [7]. To activate and maximize the cascade of PA, psychologic mechanisms play the key role. Three key points can determine the placebo reaction

	(PR): 1) patient expectations [8-11] 2) physician – patient communication [12, 13] 3) conditioning [14, 15]. These interactions are mainly investigated in the context of chronic pain conditions. **Study aims:** To investigate pain response to an open label placebo application in healthy male adults in a well-established acute pain model [16]. **Importance of the study:** Until today there are no studies investigating open label placebo effects in acute pain. Additionally, a potential effect should be examined in a clinical setting (e.g. a model mimicking surgical wound pain). This is however of great clinical value because: Firstly, open label placebo administration releases the treating physician from the ethical dilemma to deceive the patient with a placebo treatment. Secondly, beside possible cost effectiveness, reduced dosages of active pain medication (as well as the possible avoidance of opioids) due to placebo application could result in a better safety profile especially in older patients or patients otherwise at high risk of side-effects. The dose extending potential of placebos has been shown in clinical studies, but was never proved in an open-label placebo intervention in an acute pain model.
Objective(s):	Primary: To investigate the effect of open label placebo application on acute pain in an experimental model of acute pain. Secondary: • To investigate the effect of education prior to an open label placebo application. • To investigate the effect of open label placebo application on biomarkers of stress (saliva cortisol)
Outcome(s):	**<u>Primary outcome:</u>** Pain response measured by the Area under the Pain Curve (AUPC) using the numeric rating scale (NRS) from minute 30 to 100 after inducing definded pain in an experimental setting. Main comparison: The effect of open label placebo v.s. no treatment intervention. **<u>Secondary outcomes:</u>** 1. The pain response measured by the AUPC (NRS every 10 minutes during electrical stimulation) will be used for further comparison of the two different treatment interventions every participant recieves during the study.

<table>
<tr><td></td><td>
2. Hyperalgesia and allodynia will be measured analogously to the NRS as above.

3. Saliva concentration of cortisol, measured at baseline, 30, 60 and 100 minutes after pain induction.
</td></tr>
<tr><td>Study design:</td><td>
A prospective randomized, assessor-blinded trial. In order to address our aims, participants will receive each of the two treatments listed below. Patients will furthermore be randomized to receive an open-label placebo education denoted with a 1 in the treatment set (A, B_1) or to receive no open-label placebo education denoted with a 2 in the treatment set (A, B_2).



<table>
<tr><th>TREATMENT</th><th>General (visible)</th><th>Open drug application</th></tr>
<tr><td>A→ No treatment intervention</td><td>Infusion RL
Infusion rate: 100ml/h</td><td>No</td></tr>
<tr><td>$B_{1,2}$ →Open-label Placebo alone</td><td>Infusion RL
Infusion rate: 100ml/h</td><td>OLP</td></tr>
</table>

Each patient will receive exactly one of the two treatments sets (e.g. A, B_1 or A, B_2) in a randomized oder.
</td></tr>
<tr><td>Inclusion/
Esxclusion criteria:</td><td>
<u>Inclusion criteria:</u>
• Healthy male volunteers (American Society of Anaesthesiologist's Class I or II)
• Body mass index between 18 and 25kg/m^2
• Able to understand the study and the NRS scale
• Able to give informed consent

<u>Exclusion criteria:</u>
• Recreational drug abuse
</td></tr>
</table>

	• Regularly taking medication potentially interfere with pain sensitation (analgesics, antihistamines and calcium and potassium channel blockers) • Neuropathy • Chronic pain • Neuromuscular or psychiatric disease • Known or suspected kidney or liver disease
Measurements and procedures:	Healthy male adults are recruted via an advertisment on the homepage of the University of Basel. After informed consent, but before any intervention, the participiants are randomized to a placebo educated and a non-educated group. The education group will receive an education about placebos and their effects prior to study intervention during the placebo will be applied. Every participiant will pass trough two interventions with electrical induced pain, defined at a NRS of six for 100 minutes each. Between the sessions a minimal two weeks washout period will be hold. During the two interventions participiants receive the following treatments delineated above in a randomized manner.
Study medication/ Study product:	Intravenous application of: open label placebo (2ml saline 0.9%).
Control intervention	During one intervention (A) we do not apply any treatment at all during the intervention time. This to control for habitation effects during current application and create a comparison.
Number of Participants with Rationale:	Based on our sample size calculation, we will require 22 participants. Recent estimates state that some 20-30% of patients are placebo-non-responders. Consequently, we will include 29 patients. However, with an estimated drop-out of 10% we plan to recruit 32 paitents. Patients dropping out will be replaced.
Study duration:	The duration of the study from the first participant in to the last participant out is 14 weeks. Duration of an individual participant: minimum 2 weeks (time from primary assessment with 1st intervention until 2nd intervention).
Study Schedule:	First inclusion: December 2017 Last intervention in April 2018.
Investigator(s):	Tobias Schneider, MD Senior Physician Department of Anaesthesiology University of Basel (USB) Spitalstrasse 22 4031 Basel CH Tel.: +41613285165 Fax: +41612655720 E-mail: tobias.schneider@usb.ch

	Eckhard Mauermann, MD, MSc Research Fellow, Department of Anaesthesiology University of Basel (USB) Spitalstrasse 22 4031 Basel CH Tel.: +41787200189 Fax: +41612655720 E-mail: eckhard.mauermann@usb.ch Oliver Bandschapp, PD Senior Physician Department of Anaesthesiology University of Basel (USB) Spitalstrasse 22 4031 Basel CH Tel.: +41613286513 Fax: +41612655720 E-mail: oliver.bandschapp@usb.ch Julian Lüthi Scientific assistant, doctoral candidate Department of Anaesthesiology University of Basel (USB) Spitalstrasse 22 4031 Basel CH Tel.: +41613285165 Fax: +41612655720 E-mail: julian.luethi@stud.unibas.ch Wolfgang Koppert, Prof. Carl-Neuberg-Straße 1 30625 Hannover Tel: +49 511532 2489 Fax: +495115323642 E-mail: koppert.wolfgang@mh-hannover.de Wilhelm Ruppen, PD Head of the Pain Unit Department of Anaesthesiology University of Basel (USB) Spitalstrasse 22 4031 Basel CH Tel.: +41613286496 Fax: +41612655720 E-mail: wilhelm.ruppen@usb.ch
Study Center(s):	Monocentric study: Basel University Hospital
Statistical Considerations:	We will conduct a number of analyses as delineated in the statistics section. Briefly put, for each of the hypotheses a simpler, generally paired nonparametric test will be conducted. Additionally, a mixed-effects model will be employed to attain further information and account for the order of treatments, and the effect of time.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-G, as well as all

	national legal und regulatory requirements.

Study summary in local language:

In der jüngeren Vergangenheit haben unverblindete Placebo Behandlungen bei der Behandlung von Schmerzen das Interesse der Wissenschaft auf sich gezogen. Aktuelle Studien geben Hinweise darauf, dass eine Placebo Behandlung effektiv sein kann, obwohl Patient und behandelnder Arzt wissen, dass mit einem Placebo behandelt wird. Dies konnte bisher vor allem für chronische Schmerzen und das Reizdarmsyndrom und bei chron. Rückenschmerzen gezeigt werden. Daten über die mögliche Effektivität einer offenen Placebo Behandlung bei akuten Schmerzen fehlen bis zum heutigen Tag.

Studienziele:
Wir wollen das Ansprechen von Schmerzen auf eine offene Placebo-Applikation bei 32 gesunden männlichen Probenden anhand eines gut etablierten Akut-Schmerzmodels (Koppert et al.) untersuchen. Dies um einen Beitrag zur Fragestellung zu leisten, ob eine offene Placebo Behandlung bei akuten Schmerzen sinnvoll und unterstützend eingesetzt werden kann.

Relevanz der Studie:
Zum heutigen Zeitpunkt gibt es in der Literatur keine Studien, welche die Anwendung von offener Placebo-Applikation bei akuten Schmerzen untersuchen.

Aus Autorensicht ist dies jedoch von grossem klinischem Interesse, da:

A) Die offene Placebo Applikation befreit den Behandler vom ethischen Dilemma, den Patienten mit einer Placebo Behandlung zu täuschen.
B) Neben einer möglichen Kosten-Ersparnis durch die Placebo Applikation können durch Dosisreduktionen der üblichen Schmerzmedikamente gerade Hochrisiko Patienten für mögliche Medikamenten Nebenwirkungen von einer offenen Placebo Applikation profitieren.
   Dieser Dosis reduzierende Effekt konnte bei Studien bezüglich chronischer Schmerzen bereits gezeigt werden, wurde aber nicht für akute Schmerzen untersucht.

Primärziele:
Untersuchung der Effekte einer offenen Placebo-Applikation auf akute Schmerzen induziert in gesunden Probanden in einem experimentellen Akutschmerzmodel.

Sekundärziele:
- Untersuchung des Einflusses von Probanen-Edukation bezüglich Placebo-Analgesie vor einer Placebo Applikation.
- Untersuchung des Effektes der offenen Placebo Applikation auf Stress assoziierter Biomarker (Speichel Kortisol)

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Study schedule:

We plan to include the first patient in December 2017 and to finish with the last intervention in April 2018.

The duration of the study from the first participant in to the last participant out is 5 months. Duration of an individual participant from T0-T2 (cp. figure 1) will be approximately 2-3 weeks weeks (time from primary assessment with 1st intervention until 2nd intervention).

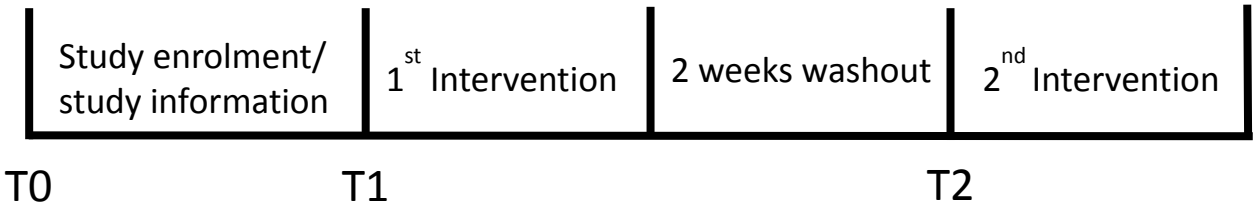

Figure 1: Study time course for a participant. T= time point

Visit	Description	Involved stuff	Duration
Inclusion/ Randomization/ Education	• Check of inclusion/ exclusion criteria • Discussion of open questions prior to study inclusion • Obtain written consent • Randomization to PEG or nPEG • Placebo education depending on randomization	• Study nurse • Investigator not involved in treatment interventions	Administrative tasks: 30min Placebo education 10-15min
1st intervention	• Treatment A-B depending on randomization • Application of open label placebo in treatment B (study nurse; investigator not present) • Assessment of outcomes (investigator)	• Study nurse • Investigator	Preparation time: 30 min Intervention time: 100 min
2nd intervention	• Second treatment (i.e. treatment B if treatment A applied in 1st intervention). • Application of open label placebo in treatment B (study nurse; investigator not present) • Assessment of outcomes (investigator)	• Study nurse • Investigator	Preparation time: 30 min Intervention time: 100 min

Table1: Overview of interventions, involved study stuff and time course

1. Administrative structure:

1.1 Sponsor:

Department of Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy of the University Hospital Basel

1.2 Sponsor investigators:

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1.4 Statistician (Biostatistician)

When required, assistance will be obtained by the Clinical Trails Unit of the University of Basel.

1.5 Pharmacy:

Not required. Placebo (NaCl 0.9%) given as a market-batch.

1.6 Monitoring Institution:

The monitoring of our study will be performed by

Esther Seeberger
Study Manager/ Study nurse
Dep. of clinical research/ Dep. of Anaesthesiology University Hospital Basel
Spitalsstrasse 22
4031 Basel
Tel: +41613287424
Fax: +41612655720
E-mail: esther.seeberger@usb.ch

For further information c.p. separate monitoring plan.

1.7. Data Safety Monitoring committee:

c.p. 1.6

1.8 Any other relevant Committee, Person, Organization, Institution:

n/a

2. Ethical and Regulatory aspects:

2.1 Study registration:

This study will be registered with www.clinicaltrails.gov upon approval.

2.2 Categorization of the study:

Category B: This study involves the use of an established pain model, a placebo (NaCl), and a carrier solution (Ringer Lactate). No other drugs will be applied. However, it is our understanding that even NaCl 0.9% used within the guidelines of suggested use (1 ml injection) mandate pro forma a category B, since volunteers have no indication for NaCl 0.9%. In our study NaCl 0.9% is not the investigational product. Any other carrier solution without an analgesic potential (placebo) could have been used. We are not performing a classical medical drug trail, therefore catogory B has to be applied.

2.3 Competent Ethics Committee (CEC):
The responsible investigator will ensure that approval from an appropriately constituted CEC is sought for the clinical study, in this case the EKNZ.

Reporting duties will be conducted within standard times. No relevant changes will be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study will be reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported like explained in the corresponding chapter. No secondary analyses are planned at this point. In the event that these should be desired at some point, permission will be sought from the CEC**.**

2.4 Competent Authorities (CA)
n/a

2.5 Ethical Conduct of the Study
The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, in case of medical device: the European Directive on medical devices 93/42/EEC and the ISO Norm 14155, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports if required and be informed about study stop/end in agreement with local requirements.

2.6 Declaration of interest
No conflict of interest.

2.7 Patient Information and Informed Consent
The investigator team (physician or study nurse) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort participation may entail. Each participant will be informed that the participation in the study is voluntary and that he may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. Participants will confirm that adequate time for reaching a decision was allocated.

The participant information sheet and the consent form will be submitted to the CEC/EKNZ to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant will read and consider the statement before signing and dating the informed consent form, and will be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or designee) and it will be retained as part of the study records.

2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilizing subject identification code numbers.

For data verification purposes, authorized representatives of the Sponsor (-Investigator) or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2.9 Early termination of the study

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns
- insufficient participant recruitment
- when the safety of the participants is doubtful or at risk
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise

As a study with no active medication the only risk for the participants is infection or allergic local skin reaction by the insertion/ material of the microdialysis membrane. We don't expect any infection during the study period. But if there occurs more than one we stop using membranes from the same charge. If another infection manifests the study is terminated. Participants are monitored for skin infections during the second study date and are told to contact the study team in case of suspected infection. (24 hours contact hotline is listed in the participant information)

For study reasons vital signs of participants are recorded during every intervention. We don't expect safety issues during the investigation, but in case of development of health threat during an intervention, the experiment is directly stopped. If this occurs more than once study is stopped until a clear reason is identified and terminated if it cannot be eliminated.

2.10 Protocol amendments

The PI or persons delegated by the PI may make amendments to the protocol. The submission of amendments as well as their approval will be communicated internally as needed.

Substantial amendments are only implemented after approval of the CEC/EKNZ.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor, the CEC, and Swiss medic. Such deviations shall be documented and reported to the sponsor, the CEC, and Swiss medic as soon as possible.

All non-substantial amendments are communicated to the CEC and Swiss medic within the Annual Safety Report (ASR).

3. Background and rationale

Open label placebo treatment studies have reached great interest in research in the recent past. Current studies suggest that placebos have a clinical significant effect, even if patients and treating physicians know they are using a placebo [1, 2]. This is true for chronic pain states and chronic disease like the irritable bowel syndrome.

Placebo reactions (PR) describe positive physiologic and psychologic changes after the administration of pharmacologic effect-free substances, shine operations or interventions, or after therapeutic symbols or rituals.

PR are based on multiple psycho-social components influencing the treatment context [17] as well as through activation of different neuro-psychopharmacologic systems. It has been shown that there are different kinds of placebo reactions depending on the involved physiologic system, the diseases or specific therapy [17, 18].

PR have been proven to be effective in numerous clinical and experimental studies in adults [19] and children [20]. These reactions have been identified as complex psycho-neuro-biologic reactions.

The neuro-biologic basis of placebo analgesia (PA) has been studied for over 40 years, since Levine at al. showed that the opiate antagonist naloxone could annul placebo analgesia after wisdom tooth extraction [3].

Petrovic et al. detected common mechanisms in opioid analgesia and PA, with similar activation of the opioidergic descending pain control system through placebo application [4]. The dorsolateral prefrontal cortex (DLPC) plays a central role as neuronal context mediator in this system. Trans-cranial magnet stimulation over the DLPC [6] or application of naloxone [4] can stop the processing of expectation-induced PA completely. Functional imaging indicates that inhibition of nociceptive afferents takes place even at spinal cord level in PA [7]. Beside endogenous opioids other neuropharmacologic mediators are involved in processing and transmitting PA. Benedetti at al. could detect the neuropeptide Cholecystokinine as an antagonist of PA [21]. Furthermore the dopaminergic system [22] and in the non-opioid mediated PA the endogenous cannabinoid system [5] play an important role. An intensifying effect of PA is also known for the neuropeptide oxytocin for both sexes [23] and for vasopressin in women [24].

To activate and maximise the cascade of PA, psychologic mechanisms play the key role. Three key points can determine the PR: 1) patient expectations 2) physician – patient communication 3) conditioning.

Ad 1): PA can be induced through suggestion, associative learning and social observing learning. So enchant self-efficacy expectations and positive expectations of treatment can reduce anxiety and stress [8, 9]. For example, promoting positive expectations before application of an opioid or a NSAID analgesic is about 30% to 100% more effective than a blinded application [10, 11].

Ad 2): A resent published meta-analysis showed that trust in the treating health care professional is associated with subjective improvement of symptoms, satisfaction and life quality of patients [12]. Egbert et al showed that an instructive and encouraging preoperative

informative conservation has significant impact on postoperative morphine consumption and hospital stay [13].

Ad 3) Due to conditioning processes during verum treatment it is possible transfer the verum treatment effects to a placebo treatment [14]. Benedetti at al. showed that for morphine imitation. This conditioning works for days and weeks [15]. As mentioned before, after conditioning, placebos have been used successfully as dose extenders [25] with the potential to reduce side effects, addiction potential and last but not least have the potential to be cost effective.

Study aims:

We want to investigate pain response to an open-label placebo application in healthy male adults in a well-established pain model first described by Koppert et al. [16]. This as a contribution to the ongoing discussion, if the use of open label placebo in acute pain management can be useful and supportive.

3.1 Importance of the study

Until today there are no studies investigating open label placebo effects in acute pain. This is however of great clinical value because:

Firstly, open label placebo administration releases the treating physician from the ethical dilemma to deceive the patient with a placebo treatment.

Secondly, beside possible cost effectiveness, reduced dosages of active pain killers due to placebo application could result in a better safety profile especially in older patients or patients otherwise at high risk of side-effects. The dose extending potential of placebos has been shown in clinical studies [25], but was never proved in an open label placebo intervention in an acute pain model.

4. Study objectives

4.1 Primary objective

To investigate the effect of open label placebo application on acute pain in an experimental model of acute pain (simulating wound pain).

4.2 Secondary objectives

- To investigate the effect of education prior to an open label placebo application.
- To investigate the effect of open label placebo application on biomarkers of stress (saliva cortisol, OMT sTNFII-R)

5. Study outcomes

5.1 Primary outcome

Pain response measured by the Area under the Pain Curve (AUPC) using the numeric rating scale (NRS) from minute 40 to100 after inducing definded pain in an experimental setting. Main comparison: The effect of open label placebo v.s. no treatment intervention.

5.2 Secondary outcomes

1. The pain response measured by the AUPC (NRS every 10 minutes during electrical stimulation) will be used for further comparison of the two different treatment interventions every participant recieves during the study. We compare the participants received a education about placebo to the non prior educated participants.
2. Hyperalgesia and allodynia will be measured analogously to the NRS as above.
3. Saliva concentration of cortisol, measured at baseline, 30, 60 and 100 minutes after pain induction.

5.3 Safety outcomes

General patient well-being will be assessed by a consultant anaesthesiologist.

5.4 Safety and Tolerability Assessment

The participant will be under constant supervision during the course of stay by anaesthetist staff.

6. Investigational medical product

Placebo:

The placebo will be applied via a 5ml syringe containing 5ml of saline 0.9%. Application is done via a venous access inserted at the beginning of the experiment.

7. Study design

7. 1 Subjects and Study Center:

Type and number of study participants: 32 healthy male volunteers.

Number and location of participating centers: monocenter study, University Hospital Basel, Switzerland

7.2 General study design and justification of design

An assessor-blinded, randomized crossover study design will be applied. Each patient will undergo each of the two treatments (A-B) listed below. Furthermore, patients will be randomized to either receive placebo education or to not receive placebo education (e.g. B_1 = placebo education; B_2= no placebo education). In other words, each patient will receive one of the two following treatment sets: either (A, B_1) or (A, B_2); the individual components of these sets will be randomized.

TREATMENT	General (visible)	Open drug application
A→ No treatment intervention	Infusion RL Infusion rate: 100ml/h	No

$B_{1,2}$ →Open-label Placebo alone	Infusion RL Infusion rate: 100ml/h	OLP

Table 1: Overview study interventions

In each treatment the patient will receive a standard infusion containing only Ringer lactate (RL) infused at a rate of 100ml/h. The purpose of this infusion is simply to keep venous access.

To avoid any systematic bias the assignment of the study groups will be performed in a balanced randomized manner. To control for excitement and habituation effects we operate the interventions in a randomized order in every participant.

The participants are recruited by an advertisement on the University of Basel homepage and eligible volunteers will be included on a “first come, first served” basis.

Study participants are orally and written informed about study aims and interventions before the first assessment.

7.3 General participant information

Every participant is informed that he will receive an open label placebo during one of the two interventions and no treatment in the other intervention. In addition, every participant receives the explanation that a placebo is an inactive substance therefore contains no active ingredient. A general explanation of the term “placebo effect” is also given to every volunteer.

7.4 Participant education in in the placebo education group

The participants randomized to the PEG will receive additionally an education about placebos prior to the first intervention with following content (adopted from prior open label placebo studies [1, 2] and adapted to the current study design):

A) Showing data about the possible strength of a placebo effect. Abstracts of prior placebo investigations are presented [1, 2].
B) The possible automatically response of the body to placebo application is discussed. Pavlov dogs experiments and effects of prior studies are presented to the volunteer.
C) Education that a positive attitude towards placebos can be helpful but is not necessary for the placebo effect [8-10].
D) A television news report of an open label placebo education is shown to the participant at the end of the education session. (excerpted from: http:// www.nbcnews.com/video/nightly-news/40787382#40787382). To ensure proper understanding we add a German subtitle to the original report (English).

The education is done via a slide show, performed exactly the same in every volunteer. The duration of the presentation is about 10 minutes. (Slides are attached at the appendix of this protocol.) The investigator of the treatment interventions is not involved in placebo education prior to intervention.

7.5 Experimental design

Acute pain will be induced through electrical stimulation in an established model first described by Koppert et al.[16]. (For detailed experimental setup cp. Chapter 7.6-7.7)

Before the first intervention participants will be randomized to:

1) A placebo education group

2) A non-placebo education group

Participants in both groups will undergo the pain model two times. Every participant will receive treatment as follows in a sequential cross-over design (cp fig. 1).

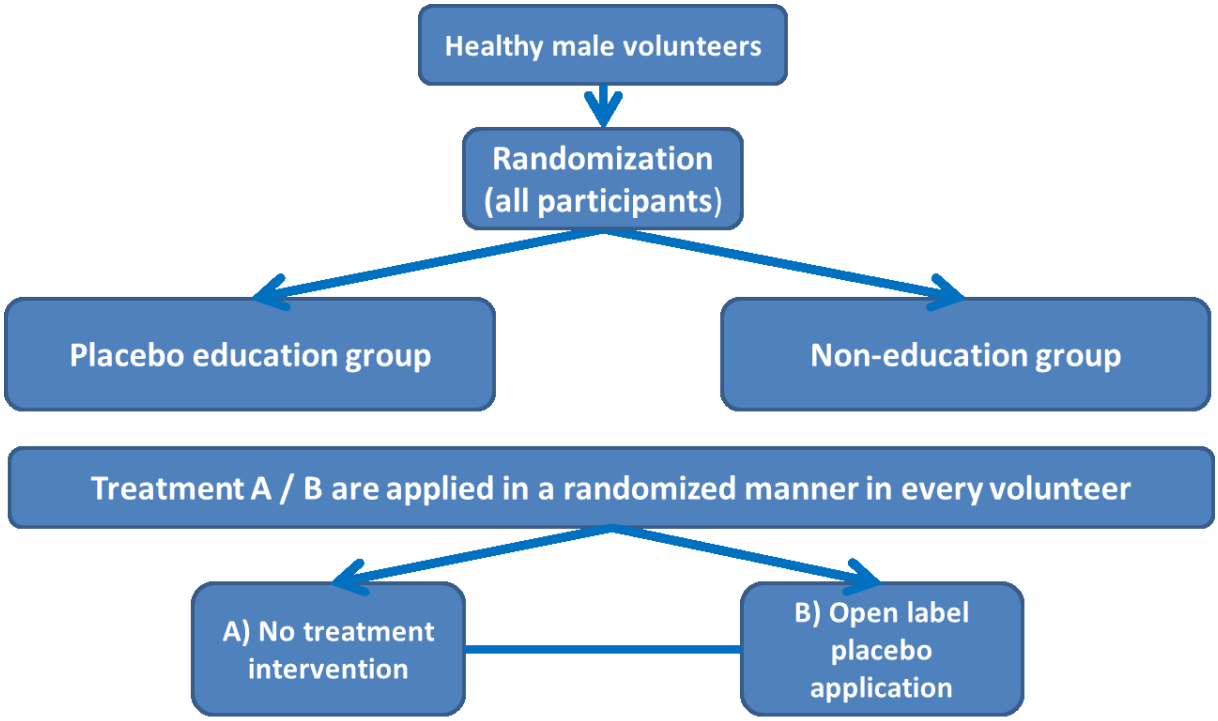


Figure 1: Experimental design

During every experiment levels of saliva cortisol levels are collected at baseline, 30min, 60min and 100min after pain induction (cp. Fig. 4).

A washout period of two weeks well be instituted to prevent contamination (cp. Fig 1).

Randomization as well as preparation and application of the hidden and not hidden study medication will be executed by study stuff not involved in assessments during the intervention. During the individual experiment pain scores, hyperalgesia and allodynia will be assessed and documented by an investigator blinded to the treatment group.

7.6 Experimental setup

Every participant will be intensive familiarized with the pain scale, the intradermal electrical stimulation model evoking pain, hyperalgesia and allodynia examination. A training session would be rather invasive and includes the risk of habituation and is therefore not applied. Previous studies conducted by our research group using this model have also shown that this is not required.

The model we use in this study was first described by Koppert at al.[16]. It has been used in numerous studies investigating pain, pain medications, hyperalgesia and allodynia [26-31]. Our utilized pain model has been shown to provoke stable areas of secondary hyperalgesia

to pinprick and touch caused by an activation of mechanoinsensitive C-nociceptors [32] (a class of nociceptors shown to be activated electrically, preferentially at high current densities, as used in this model [33, 34]).

7.7 General setup of intradermal electrical stimulation (cp. Figure 3)

Two microdialysis catheters with internal stainless steel wires are inserted in parallel into the intradermal, volar surface of the contralateral forearm for a length of approximately 10mm and are separated 5mm from each other. The catheters are filled with 0.9% saline and a continuous flow of 0.2µl/min ensured by a syringe pump (Perfusor®) to facilitate conduction. The stainless steel wires are attached to a constant current stimulator (manufactured by Koppert et al.) and monophasic, rectangular electrical pulses of 0.5ms duration are applied with alternating polarity at 2 Hz. The current will be increased to target a pain rating of 6 of 10 on a numeric rating scale (NRS) (0= no pain and 10 maximum tolerable pain). Three further increases in current will be made every 5 min for the next 15min to compensate for habituation. This final current will be kept constant until the end of the particular experiment (100min cp. figure 4). After calibration to NRS 6 there is no further increase of the current.

7.8 Procedures/ Recordings/ Interventions before and during electrical stimulation

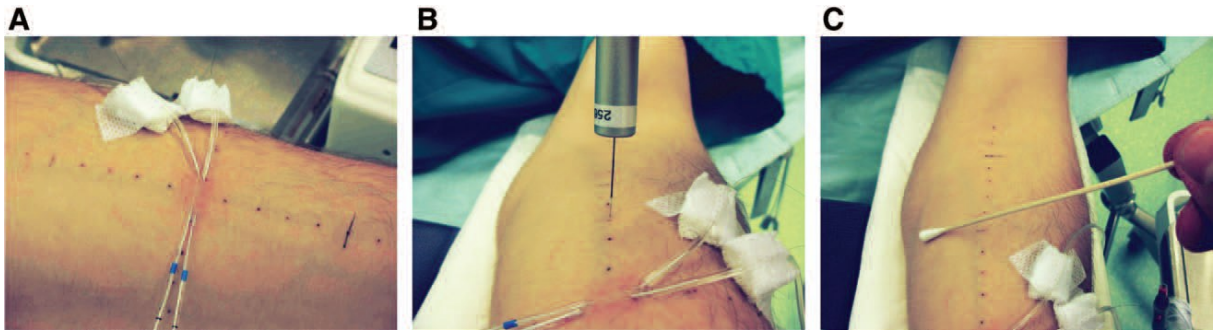
Measurement of pain:

After adjusting for habituation as delineated above, pain, hyperalgesia, and allodynia will be assessed every ten minutes after time-point for possible OLP-application, using the NRS until the end of the individual session after 100 minutes (cp.Figure 4).

Measurement of hyperalgesia and allodynia:

Immediately after every pain rating the area of pinprick hyperalgesia is determined using a 256 mN von Frey filament and allodynia is determined using a dry cotton swab. Measurements are conducted from a more distant to a more central site along four orthogonal lines (distal, proximal, lateral, and medial) that will be drawn onto the skin with tick marks indicating each centimetre (cp. picture 1). Distal and proximal measurements will begin 12cm from the site of electronical stimulation; whereas the lateral and medial measurements were begin 6cm from this site. In both cases the used filament will be moved towards the site of stimulation in 0.5 cm increments until the subject reports either increased pain sensations from the von Frey filament (hyperalgesia) or an unpleasant “rougher” sensation from the cotton swab (allodynia). To create an area from these linear measurements, the assumption is made, that this field has the shape of an ellipse. The area is calculated using the formula $1/4\pi D \cdot d$.

Pain, hyperalgesia and allodynia measurement are exactly the same in both experimental interventions.



Picture 1: A: microdialys catheter inserted intra-cutaneous at the forearm; B: testing hyperalgesiawith 256 mN von Frey filament; C: testing allodynia with a cotton swap.; adopted with permission from Mauermann et al., Anesthesiology, 2016. 124(2): p. 453-63.

7.9 Application of study medication

As mentioned before a venous access is installed at the forearm not used for experimental measurements.

There are two different treatment options every volunteer receives during the two experimental interventions.

A) No medical or open label placebo (OLP) treatment during the intervention.
B) Application of OLP 30 min after calibration for NRS 6.

7.10 Open label placebo application

Open-label placebo is given during Treatment B. A pain expert of the study stuff (the same person for one participant during the two interventions) applies placebo in treatment B. For an open-label placebo application the volunteer is orally informed that he will receive an intravenous placebo ("medical" not active substance) now. To strengthen positive expectations the study nurse assures the patient that placebos can have a strong effect on pain before application of the syringe content. The placebo is then injected intravenous while the investigator ensures that the volunteer watches the injection. The oral information text is standardized is exactly the same in every participant. (For the orginal text in german language cp. appendix)

7.11 Achievement of blinded medication application

A venous access is placed before every intervention session starts. An infusion of Ringer lactate with an infusion speed of 100ml/h (controlled via infusion pump) will be attached. The investigator performing the testing during the intervention leaves the test-room before possible placebo application. He is blinded if treatment A or B is applied. This, to ensure objective data collection.

The randomisation code is kept in a locked up folder in the office of the principle investigator Tobias Schneider with restricted access only to the in intervention planning involved study personal, namely: Monika Kirsch and Tobias Schneider

Unblinding is done after the last last experimental intervention. The Randomization is than open to the study stuff taking part in the analysis of obtained data.

7.12 Collection and processing of biomarkers

Saliva collection and processing

Oral fluids are collected to measure cortisol levels in response to induced pain. To control for diurnal variations of neuroendocrine parameters all experiments will be carried out between 4pm and 7pm.

Consistent with the procedures incorporated be Dickerson et al. [35] we decided to obtain the biological parameters in this study from oral fluids. Saliva levels of cortisol [36] are reliable and highly correlated with plasma levels. Therefore it is a less reactive, less invasive but reliable method to measure neuroendocrine immune activity.

To ensure a non-contaminated measurement participants are asked:

- Not to use non-prescription medications or alcohol within 24 hours before measurement
- To refrain from exercise and caffeine at least 2 hours to testing session
- Not to eat foods that may cause bleeding of the gums (e.g. potato chips) or brush their teeth for at least 2 hours prior to testing session.

Collection of saliva for cortisol determinations

A collection device (Salivette®) is placed into the mouth on the top of the tongue for 2.5min per sampling time point. Cortisol in saliva is in its unbound biologically active form and its concentration is independent of saliva flow rate [37].

Time points of measurements

Basic value:

After arrival of the participant for the intervention a 15 min rest must be hold before the first collection. The first collection during the first experimental intervention is to make the participant familiar with the procedure and will not be used for later analyses. A second collection will be performed directly after the test collection.

Further collections:

Saliva will be further collected as follows during the experimental intervention (cp. figure 4):

1. 30 min after constant electrical stimulation before application of study medication
2. 30 min after completed application of the study medication
3. 60 min after completed application of the study medication

After collection the oral fluids samples are immediately refrigerated before being transferred and will be stored at -80°C until further analysis, if analysis cannot be performed within 6 hours after collection.

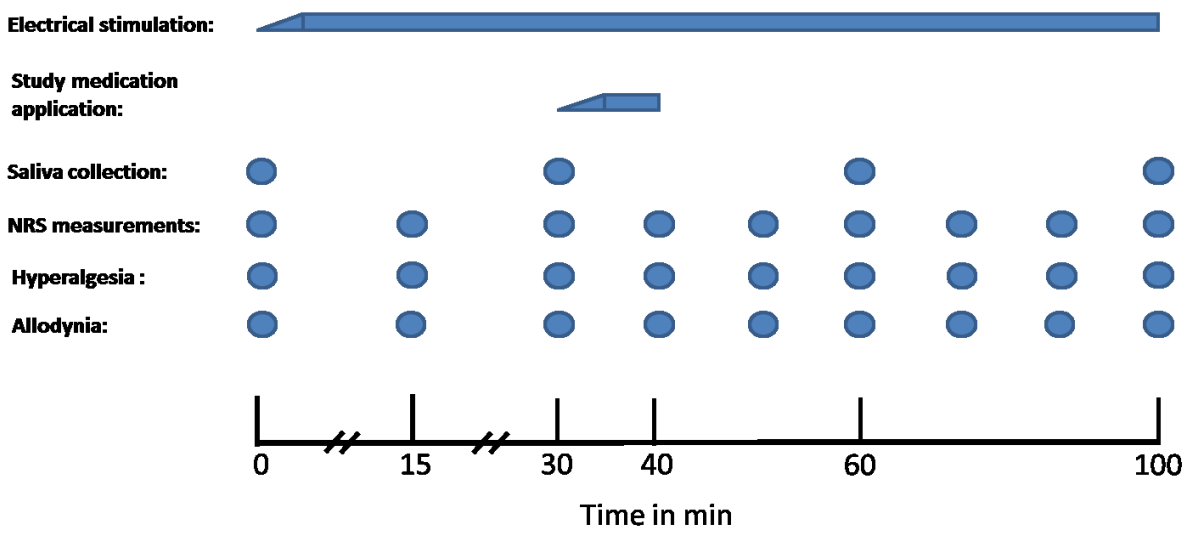


Figure 4: Schedule for measurement of pain, hyperalgesia, allodynia, biomarker collection and application of study medication during an individual study intervention session.

8. Medical products and Medications used during the study

8.1 Medication used:

Carrier solution: Ringer Lactat Fresenius 1000ml Infusion solution. License number: 42692 (Swissmedic); license holders: Fresenius Kabi (Schweiz) AG, Oberdorf NW

NaCl 0.9%: NACL Bichsel Inj. Lös 0.9% 10ml ampulle; license number: 29800 (Swissmedic); license holder: Dr. Bichsel AG, Interlaken

All medication will exclusively be used as an unaltered medical batch.

8.2 Medical products used for the pain model:

Current stimulator: Digitimer S7; Digitimer, Hertfordshire, United Kingdom

Microdialysis catheter: self-manufactured at the laboratory of Koppert et al. University Hopsital Hannover

8.3 Medical products used for the infusion application/ patient monitoring:

Controlled Infusion application: Injectomat Agilia, Producer: Fresenius Kabi; PZN: 4377569

Infusion application: Original B. Braun Perfusor® Syringe 50 ml PZN: 00570097; Original B. Braun Perfusor® Line IV Standard, Luer Lock PZN: 06100642;

Venous catheterization: B. Braun Vasofix® Safety 20G or 18G, CE-number: 0123 Producer of all products: B. Braun Melsungen AG

Storage conditions:

Study medications are stored with the medications for regular pain treatment in the chronic pain unit, according to the manufactures specification at room temperature and protected from light.

9.Study population

9.1 Recruitment of volunteers

Volunteer recruitment will occur by an advertisement on the University Basel homepage, an occlusion will occur on a “first come, first served” basis.

9.2 Inclusion criteria

- Healthy male volunteers (American Society of Anaesthesiologist’s Class I or II)
- Body mass index between 18 and 25kg/m^2
- Able to understand the study and the NRS scale
- Able to give informed consent

9.3 Exclusion criteria

- Recreational drug abuse
- Regularly taking medication potentially interfere with pain sensitation (analgesics, antihistamines and calcium and potassium channel blockers)
- Neuropathy
- Chronic pain
- Neuromuscular or psychiatric disease

Inclusion and exclusion criteria will be checked prior to inclusion into the study.

Informed written consent is obtained from every participant after detailed oral and written information by the study stuff.

9.4 Subject Withdrawal

Subjects may withdraw from the study at any time and for any reason (stating reason is not required). If patients elect to do so, data will be anonymized and no further analyses conducted. To replace this study drop-out, an additional patient will be recruited. Drop outs will be reported in the final publication.

The following reasons result in withdrawal:

- AE challenging the health of the subject if continuing the study
- Severe protocol violations
- Administrative troubles

9.5 Expense allowance for participants

Participants will receive a financial compensation for their expenditure of time and possible travel expenses. This compensation is standardized and will be graded with respect to attended interventions.

A one-time financial compensation will be awarded to patients completing the study (250 CHF). The compensation is graduated. Compensation for the first interverntion is 100 CHF, for the second 150 CHF. In the event of early termination (before/ during first intervention), patients will be compensated with 20 CHF/h.

10. SAFETY

10.1 Drug studies

During the entire duration of the study, all adverse events (AE) and all serious adverse events (SAEs) are collected, fully investigated and documented in source documents and case report forms (CRF).
Study duration encompassed the time from when the participant signs the informed consent until the last protocol-specific procedure has been completed, including a safety follow-up period.

10.2 Definition and assessment of (serious) adverse events and other safety related events

An AE is any untoward medical occurrence in a patient or a clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study procedure. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
[From ICH E2A and E6, “investigational” term only in E6]

A Serious Adverse Event (SAE) is classified as any untoward medical occurrence that:

- results in death
- is life-threatening,
- requires in-patient hospitalization or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

In addition, important medical events that may not be immediately life-threatening or result in death, or require hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above should also usually be considered serious. [ICH E2A]
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.
SAEs should be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination (including safety visit) will be further followed up until recovery or until stabilisation of the disease after termination.

10.3 Assessment of Causality

Both Investigator and Sponsor-investigator make a causality assessment of the event to the study drug, based on the criteria listed in the ICH E2A guidelines:

Relationship	Description
Definitely	Temporal relationship Improvement after dechallange* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship

	Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

10.4 Unexpected Adverse Drug Reaction

An "unexpected" adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. [ICH E2A]

10.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)

The Sponsor-Investigator evaluates any SAE that has been reported regarding seriousness, causality and expectedness. If the event is related to the investigational product and is both serious and unexpected, it is classified as a SUSAR.

10.6 Assessment of Severity

The Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 of the National Cancer Institute (published may 2009) are used to classify severity of possible adverse events.

10.7 Reporting of serious adverse events (SAE) and other safety related events

All SAEs will be reported immediately and within a maximum of 24 hours to the Sponsor-Investigator of the study. The Sponsor-Investigator will re-evaluate the SAE and return the form to the site. SAEs resulting in death are reported to the local Ethics Committee (via local Investigator) within 7 days.

10.8 Reporting of SUSARs:

A SUSAR will to be reported to the local Ethics Committee (local event via local Investigator) within 7 days, if the event is fatal, or within 15 days (all other events).

10.9 Reporting of Safety Signals:

All suspected new risks and relevant new aspects of known adverse reactions that require safety related measures, i.e. so called safety signals, must be reported to the Sponsor-Investigator within 24 hours. The Sponsor-Investigator must report the safety signals within 7 days to the local Ethics committee.

10.10 Follow up of (Serious) Adverse Events:

The participant will be told which test substance he had taken to avoid future complications. In case of an acute allergic reaction, the participant is referred to our emergency department

and the study is discontinued. The participant is informed about the applied test substance and will eventually be referred to an allergologist to verify allergic reaction in order to avoid future exposure.

11. Statistical Methods

11.1 Hypothesis

Main hypotheses

We first hypothesize that open label placebo administration leads to a significant reduction in the area under the pain curve (AUPC) from minute 40 to minute100 compared to no open-label placebo in induced acute pain in healthy male adults (i.e. $B_{1/2}$ vs. A)

Secondary Hypotheses

Secondly, we hypothesize that education and conditioning further reduce the AUPC in the same period of time compared to those patients receiving open-label placebo without education in induced acute pain in healthy male adults (i.e. B_2 vs. B_1).

Finally, we hypothesize that the observed differences in the AUPC will be reflected in both hyperalgesia and allodynia as well as by biomarkers.

11.2 Determination of sample size

Sample size has been determined by a Wilcoxon signed-rank test for the AUPC for Treatments A and B. The AUPC is the product of the NRS x Time. 7 measurements of NRS will be made in total, one every ten minutes. We expect the area under the curve to be 50 NRSxminutes based on a general difference of 1 NRS point and some time for the effect to fully develop. We expect the standard deviations in both groups to be 1 NRS or 60 NRS*min. Using a t-test with a 20% mark-up for non-parametric data we have arrived at a required number of patients of 22. However since 20-30% of participants can be expected to be non-responders to placebo [38] and expecting 10% drop out we have arrived at a total number of patients to be recruited of 32.

11.3 Statistical criteria of termination of the trail:

Upon completion. With such a small sample size, no interim analysis will be conducted.

11.4 Planned Analyses, Datasets, and Analysis Populations:

For the first hypothesis (AUPC for $B_{1/2}$ vs. A) we will conduct a Wilcoxon signed-rank test. Additionally, we conduct a mixed effects model using the AUPC as the dependent outcome and the treatment, the session order (e.g. Treatment B before Treatment A) time during electrical stimulation (in minutes), and finally the individual. This will allow for a more differentiated analysis accounting for temporal and sessional habituation in explaining the treatment effect.

For the effect of education, we will compare the AUPC of: Treatment B_1 vs Treatment B_2, again by a Wilcoxon signed-rank test.

The outcomes hyperalgesia and allodynia, as well as biomarkers will be examined analogously to the respective comparisons with the AUPC.

11.8 Interim analysis:
Given the small sample size and limited time, no interim analysis will be conducted.

11.9 Safety analysis:
None. However, patients will be under the continuous surveillance of anesthesiology staff.

11.10 Deviation(s) from the original statistical plan:
The statistical plan will be published prior to commencement on clinicaltrials.gov. Any deviations from the statistical plan will be reported and justified in the final report.

11.11 Handling of missing data and drop outs:
All available data will be used, as far as possible considering the paired nature most of the tests. As long as the participant completes both treatments and data is complete for the primary analysis, the data will count as sufficiently complete. Participants electing to drop-out of the study will be replaced by another participant. However, whatever data is available at the time of drop-out will be analysed. Data completeness will be reported in the final publication and a consort diagram will be made. If a participant withdraws his agreement from the study all obtained data will be immediately deleted. Only anonymized data will be used for publication. Obtained cortisol probes will be destroyed after analyzation and will not be used for further research.

12. Quality Assurance and Control

12.1 Data handling and record keeping / archiving:
Personal data is kept in a computer database, and all CRFs and informed consents are kept in a folder and archived for a minimum of 10 years.

12.2 Case Report Forms (CRF)
Study data is recorded with paper CRFs. For each enrolled study participant CRFs are maintained.
Participants are not identified in the CRF by name or initials and birth date; instead the participant number is used. The nursing personnel and the PIs are authorized for all CRF. As paper CRFs are used, the data is entered into an electronic database for analysis during the trial (by the study nurse and/or PhD student).

12.3 Specification of source documents
Demographic data, visit dates, participation in study and Informed Consent Forms, randomisation number, SAEs, AEs and concomitant medication, results of relevant examinations and all CRFs are considered the source documents in the study. Source documents are archived in folders at the study site with restricted access (Pain Relief Unit USB).

12.4 Record keeping / archiving
All study data will be archived for a minimum of 10 years after study termination or premature

termination of the clinical trial. All data is archived in folders at the study site with restricted access (Pain unit USB).

13. Data management:

13.1 Data Management System

The data collection is based on paper source. This data will then be transferred from paper source documentation to a secure database. This database is based on Microsoft Access and will be operated with individual user log in, time stamp, and logging of changes. For security purposes, remote log in will not be allowed. The database will be backed up periodically on the Department for Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy's server.

13.2 Analysis and archiving

Upon conclusion, the database is secured and cannot be changed anymore

13.3 Electronic and central data validation

All data will be validated when entering them into the database and a quality check will be conducted before analyses.

13.4 Monitoring

The aim of monitoring is to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to ensure that all protocol requirements, applicable local authority regulations and investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records. Regular monitoring visits at the investigator's site prior to the start and during the course of the study will be performed by independent monitors not included in the research group. The monitoring is performed by Esther Seeberger c.p. 1.6 and separate monitoring plan. The source data/documents are accessible to monitors and questions are answered during monitoring.

13.5 Audits and Inspections

Audits by the sponsor or inspections by regulatory authorities (IEC) during study or after study closure may be performed to ensure proper study conduct and data handling procedures according to ICHGCP guidelines and regulatory requirements. Audits and inspections may include verification of all source documents, check of CRFs and site files and a visual inspection of the study site. All involved parties must keep the participant data strictly confidential.

13.6 Confidentiality, Data Protection

Participant's confidentiality will be maintained at all times. The investigator affirms and upholds the principle of the participant's right to privacy and those they shall comply with applicable privacy laws.
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files. Personnel from the sponsor, the Pain Unit USB and members of IEC are obliged to respect medical secrecy and to refrain from divulging the participant's identity or any other personal information they might fortuitously be aware of.

Direct access to source documents will be permitted for purposes of monitoring, audits and inspections. All study personnel involved in this trial (Tobias Schneider, Wilhelm Ruppen, Eckhard Mauermann, Oliver Bandschapp, Julian Lüthi, Wolfgang Koppert, Silvia Wuchner, Manuela Semeraro and Monika Kirsch) will have access to protocol, dataset during and after the study (publication, dissemination).
Demographic data and personal data will be kept in the electronic database. Subjects will receive a study number upon inclusion, and in the data base only the study number will appear. Only the principal investigators will have the key. Data generation, transmission, storage and analysis of health related personal data and the storage of biological samples within this project will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5. Health related personal data captured during this project and biological samples from participants are strictly confidential and disclosure to third parties is prohibited; coding will safeguard participants' confidentiality. Project data will be handled with uttermost discretion and only be accessible to authorised personnel.

13.7 Storage of biological material and related health data:

NaCl 0.9% and Ringer's Lactate will be stored according to the manufacture specification at room temperature and protected from light. The infusion is prepared max. 1 hour before application. Saliva samples will be processed into different aliquots and kept frozen at -80°C until analysis, if analysis within 6 hours after probe drawing is not possible.

14. Publication and Dissemination Policy

We plan to publish the results in a peer-reviewed scientific journal. Upon request, we will provide the full study protocol and data (as required by some journals). The trial results might be presented at scientific congresses. The main publication will be created by Tobias Schneider, Eckhard Mauermann, OliverBandschapp, Wolfgang Koppert, Julian Lüthi and Wilhelm Ruppen. Subsequent publications of subgroups can follow thereafter and will have to be approved by the PI's. No unpublished data may be transmitted to a third party without prior written approval by sponsors and PI's. No publication or communication involving the results of the study is authorized without prior written consent from the PIs. In view of patent and confidentiality issues, however, the PIs must accept requirements on the timing of early publication.
No use of professional writers is intended. The PIs will have ultimate authority over any of the activities.

15. Funding and Support

15.1 Funding:

The study is funded by the Dep. of Anaesthesiology of the USB. There is no conflict of interest and the financing party has no influence on the protocol, analysis or publication.

15.2 Other Support:

No other financial support is expected.

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Appendix:

Text of the assessor direct before placebo application

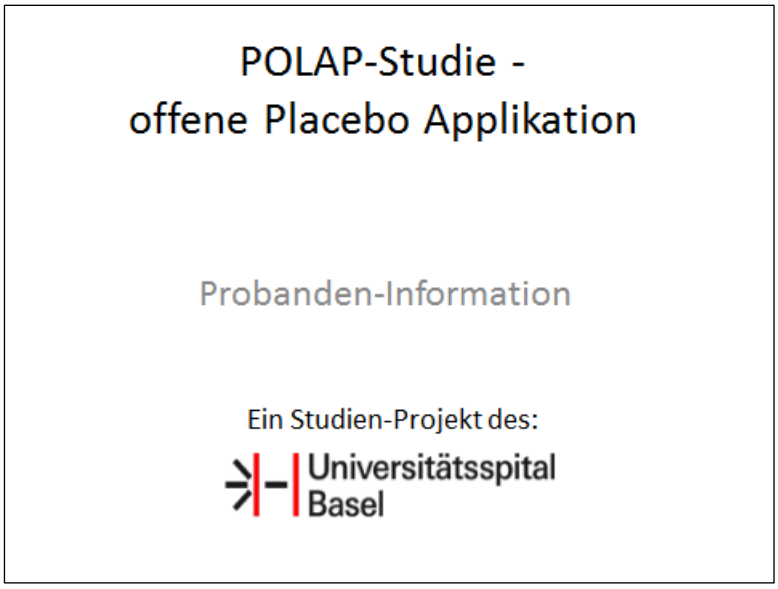
The text will be recited and is exactly the same in every participant (German language):

“ Ich werde ihnen nun ein Placebo in die Vene verabreichen. Wie sie bereits aus den Studieninformationen wissen, enthält ein Placebo keine medizinisch aktive Wirksubstanz. Wir wissen aus der aktuellen wissenschaftlichen Forschung, dass die Gabe eines Placebos einen starken positiven Effekt auf Schmerzen hat. Ich bin daher sehr zuversichtlich, dass dies auch bei ihnen zu einer deutlichen Reduktion der Schmerzen führen wird.“

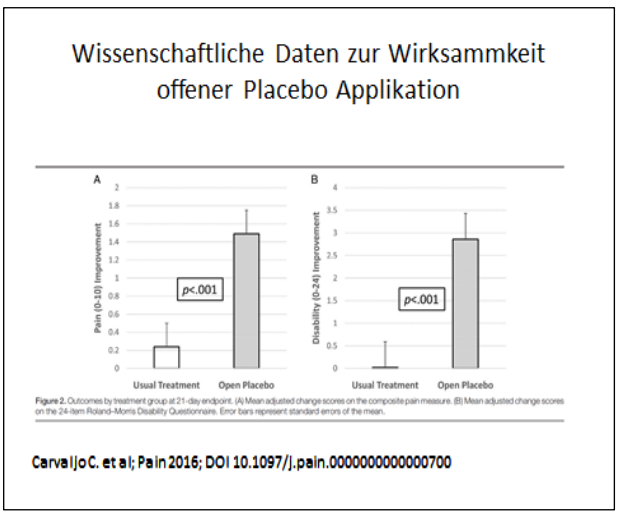
During this announcement the assessor is facing the participant and speaks with a calm, friendly voice. It is always the same person, who makes this speech.

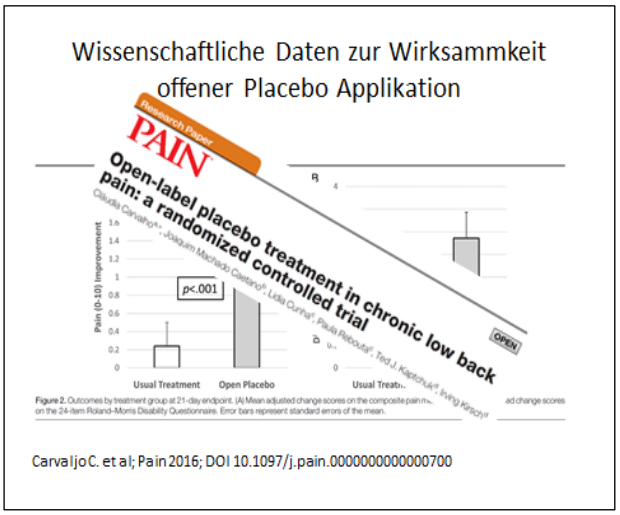
The subsequent application is good visible for the participant and the saline is injected slow over at least 30 seconds via two ml syringe, clearly recognisable for the participant.

Slides of the Presentation for the "Placebo education group" with oral given information in text form:

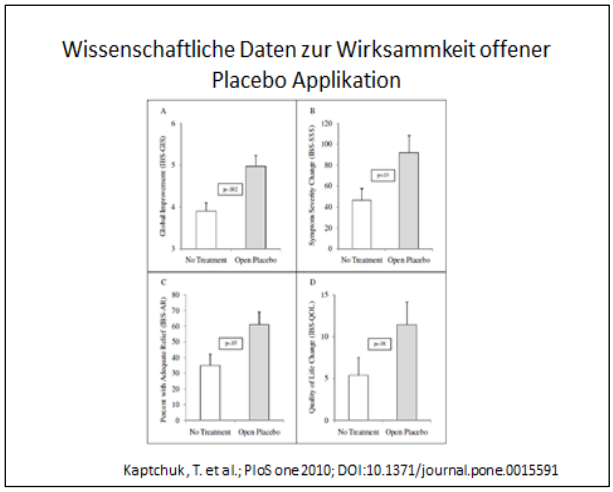


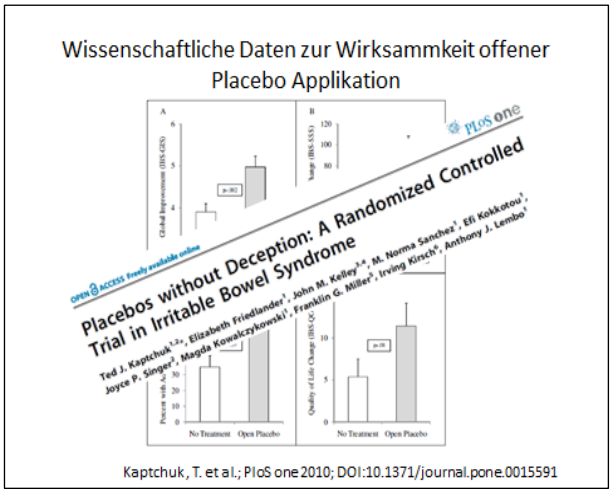
Starting slide



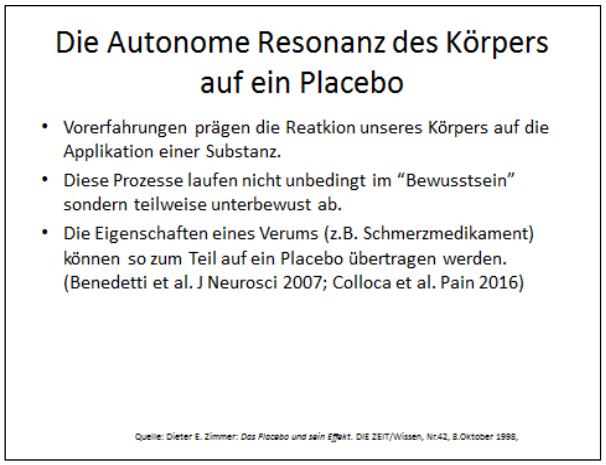


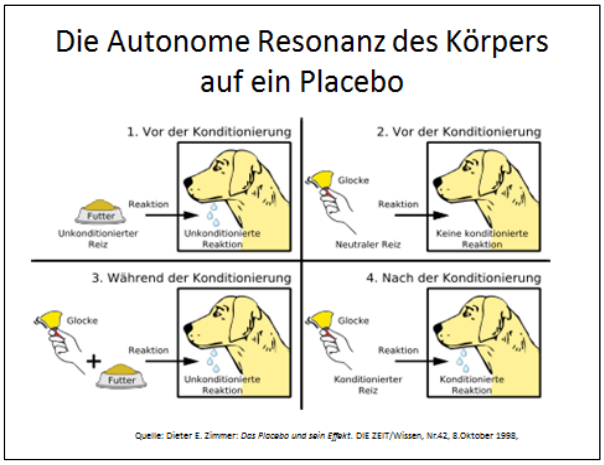
Oral information: 83 patients with chronic low back pain were enrolled in this study. The first group received a treatment as usual (consisting of physical therapy and NSAID) and the second received an open label placebo in addition to the treatment concept in group one. The result was a statistical and clinical relevant better pain relief and disability improvement in the placebo group compared to the treatment as usual group.





Oral information: 80 patients with IBS diagnosed by Rome III criteria were randomized to either open label placebo or no treatment control. The primary was the global improvement score. Secondary outcomes were symptom severity score, percent of adequate pain relief, and improvement of quality of life. For all outcomes significant better results in the open placebo group were obtained.

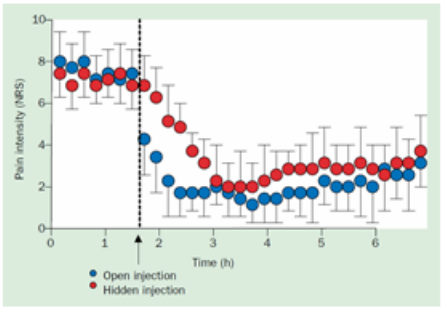




Oral information: Learning processes of our brain and body run off partially subconscious. For clarification of this processes Pawlows dogs experiment is explained to the participant. Like in Pawlows dog learning processes activate body`s own analgesic systems in response to a conditioned impulse (injection of a fluid into a vein). Benedetti et al. showed that it is possible to transfer analgesic effects of an opioid treatment to a following treatment with placebo in parts.

Einstellung/ Attitüde und Analgesie

- Eine positive Einstellung gegenüber einem Medikament und gegenüber einem Placebo verstärkt den therapeutischen Effekt.
- Sie ist aber nicht Bedingung für die Wirksamkeit

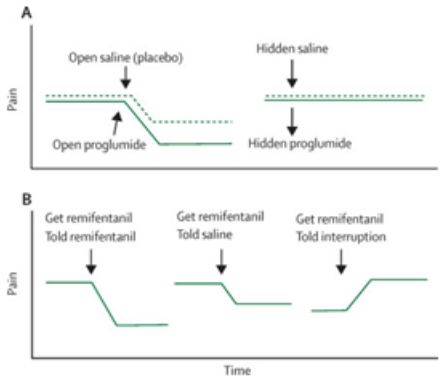


Quelle: Colloca et al.; The Lancet Neurology, 2004

Oral information: To clarify that a positive attitude towards a given medication can be helpful, but is not mandatory, data from Colloca et al are shown. Hidden application of an opioid (shown in the graph on the slide) is also effective in pain treatment. But an open application works faster and even stronger.

Verum v.s. Placebo

- Warum es Medikamente schwer haben…



Quelle: Benedetti F. et al. The Lancet Neurology 2016; doi.org/10.1016/S1474-4422(16)00066-1

Oral information: The slide from Benedetti et al. shows the strong placebo and nocebo effects. Exemplary shown for proglumide and remifentanil. New drugs have to show a significant superiority compared to placebo. Especially for pain medication this can be hard to achieve because of the strong placebo effect.

Oral information: For closure and as a summary of the presentation this 2min 19sec news report is presented to the participant.