Subject information for participation in a medical-scientific study

The PaPa Trial

'The PaPa Trial: Paracetamol as an adjunct to intrapartum Remifentanil/PCA. An RCT of multimodal pain management during labor.'

Introduction

Dear Madam,
We ask you to participate in a medical scientific study.
Participating is voluntary. In order to participate your written consent is required. You receive this letter because soon you will go into labour to have your baby. Whether you need pain relief during your delivery, cannot be predicted at this time. If you need pain relief, usually there is the choice between epidural analgesia (EA) and Remifentanil / PCA. The PaPa Trial is only for women who use Remifentanil during their birth. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves. Read this information carefully and ask the researcher if you have any questions. You can also contact the independent expert mentioned at the end of this letter for additional information. You can also discuss it with your partner, friends or family. Further information about participating in a medical scientific study can be found in the brochure 'Medical research. General information for subjects'.

1. General information

This trial is performed by Reinier de Graaf, Mother&Child Center. The Medical Ethics Review Committee Leiden The Hague Delft (METC-LDD) has approved this study. General information about the assessment of research can be found in the brochure 'Medical research. General information for subjects'. For this study, 80 subjects are expected to participate.

2. Purpose of the study

The purpose of this study is to research if Paracetamol reduces Remifentanil use when added to Remifentanil/PCA as intrapartum pain management. The effect of Paracetamol is compared to the effect of a placebo. A placebo is an agent without an active substance, a 'fake' agent.

3. Background of the study

Paracetamol is often the first choice of treatment for acute pain. During childbirth however, Paracetamol is hardly used. In the Netherlands, labour pain is mostly treated with epidural analgesia or Remifentanil / PCA. The substances used for this are morphine-like agents, also called opiates. Complications with the use of Remifentanil are rare but serious: a sharp decline in the blood oxygen level, too slow or superficial breathing, or a too slow heartbeat. Also side effects such as nausea and vomiting can occur. Research into pain treatment after surgery shows that giving Paracetamol reduces the use of opiates. There are several studies that showed that Paracetamol during labour is as effective as, for example, Pethidine or Tramadol, with fewer side effects.

4. What participation involves

Participation in the study starts the moment you get pain relief with Remifentanil and ends after the birth of your child. If you participate, this will take a maximum of a few hours. The exact duration of participation is difficult to predict because the duration of the childbirth cannot be predicted. First we determine whether you can participate. Women older than 18 who choose pain relief with Remifentanil during their birth are eligible to participate in the PaPa Trial. You cannot participate if you have taken other medicinal pain relief four hours prior to the start of Remifentanil, when you are hypersensitive to Paracetamol (Acetaminophen), have a severe liver or kidney disease or are severely malnourished. When you participate, you will receive Remifentanil as usual. In addition, 1 gram Paracetamol (10 mg / ml, therefore 100 ml) or Placebo (100 ml NaCl 0.9% / “Saline”) is given via the drip/ infusion. You do not have to undergo any extra drip or other intervention for this. Which subjects receive Paracetamol and which placebo is randomly drawn. The study is set up double blind, this means that both you and the healthcare provider do not know whether you receive Paracetamol or Placebo.

Measurements
Remifentanil works by self-administration through a PCA pump (Patient Controlled Analgesia). This means that you can control how often you press the button for a dose of Remifentanil. There is a blockage on the infusion pump, you can press as many times as you want, but you cannot overdose yourself. When you participate in the PaPa Trial, it is recorded how often you press the button and how often the pump actually delivers a dose. This is registered every half hour up to three hours after starting the Remifentanil pump (if you have not yet given birth). It is also documented whether there was a need for oxygen administration, and if and how often you had to vomit and how long the cervical dilatation took in minutes from starting the pain treatment. Your child's Apgar score and cord blood gas (pH value) are documented. The Apgar score is a test that gives a quick impression of the overall condition of a newborn baby (neonate). This score is obtained for every newborn baby. The umbilical cord blood gas / pH value gives additional information about the condition

of the newborn baby. An umbilical cord blood gas is determined at every birth in Reinier de Graaf. A small amount from the umbilical cord blood is taken after the cord is cut, you and your baby do not notice this.

Different from usual care
As standard care, a healthcare provider is continuously present in the room in the first hour after starting Remifentanil. The documentation of the requests and administrations of Remifentanil doses is not done apart from the PaPa Trial. Compared to usual care with Remifentanil, you will not notice much of your participation in the PaPa Trial. Reading the infusion pump will not be a burden on you. The other information that is important for the PaPa Trial (oxygen administration, frequency of vomiting, duration of cervical dilatation, Apgar score and cord blood gas) are already documented as usual care.

5. What will be expected of you

When participating in the PaPa Trial you do not have to do anything other than what you would do without participation in the study. The treatment with Remifentanil and the care that you receive are the same. The only difference is that the above mentioned information will be documented on a checklist that is in available your room for this purpose. It is important that you indicate when you no longer want to participate in the study.

6. Possible side effects Paracetamol

Very rare (affects less than 1 in 100 people):
Hypersensitivity to Paracetamol. You will notice this from skin rashes, hives and feeling wheezy. Consult your healthcare provider for these symptoms (obstetric nurse). She will report this to the clinical obstetrician and / or midwife and gynaecologist. Tell your pharmacy that you are hypersensitive to acetaminophen. The pharmacy team can then ensure that you do not receive Paracetamol or other medication containing Acetaminophen in the future.

7. Possible advantages and disadvantages

It is important that you carefully consider the possible pros and cons before you decide to participate. Paracetamol can reduce the use of Remifentanil (opiate), but that is not certain. When you participate in the PaPa Trial you get pain relief with Remifentanil as usual, combined with Paracetamol or Placebo (Saline/ NaCl 0.9%). Saline is already given as an infusion fluid for connecting Remifentanil. A disadvantage of participating in the study may be that you are hypersensitive for Paracetamol while you didn't know this yet. However, this chance is small (less than 1: 100) All of these things are described below under point 4, 5 and 6.

8. If you do not want to participate, or would like to stop participating in the study

You decide whether you want to participate in the study. Participation is voluntary. If you do not want to participate, you will be treated in the usual way when you need pain relief during delivery. If you do participate, you can always change your mind and still stop, even during the investigation. You will then be treated in the usual way. You don't have to say why you stop. You must, however, immediately report this to your healthcare provider. The data collected until the moment you stop will be included in the study. If after starting the PaPa Trial important, new information comes up, you will be informed about this and you will be asked again if you want to participate. If there is any new information about the study, that is important for you, the investigator will inform you of this. You will then be asked if you wish to continue your participation.

9. End of the study

Your participation in the study stops as

- you choose to stop
- you get unexpected physical reactions that may be related to the combination of Remifentanil and Paracetamol.
- The Reinier de Graaf, the government or the evaluating medical ethics review committee, decides to stop the investigation.

The entire investigation is complete when all participants are ready.
When you wish, after processing all data, the researcher will inform you about the most important results of the study. This happens about a year after your participation. The researcher can also tell you which group you were in (Paracetamol or placebo) If you do not want this, you can tell the researcher. She may not tell you then.

10. Use and storage of your data

Your personal data is stored for this study. This concerns data such as your name, address, date of birth and information about your health. Collecting, using and storing your data is necessary to answer the questions posed in this study and to be able to publish the results. We ask your permission for the use of your data.

Confidentiality of your data

To protect your privacy, your data is given a code. Your name and other data that can directly identify you will be omitted. Only with the key of the code, data can be traced back to you. The key to the code remains stored securely in the local research institution. The data that is used for analysis only contains the code, but not your name or other information that can identify you. Also in reports and publications about the research, the data is not traceable to you.

Access to your data for review

Some people can get access to all your data at the research location. Also to the data without code. This is necessary to be able to check if the investigation is performed properly and reliably. Persons who get access to your data for review are: the committee that monitors the safety of the investigation, a monitor of Reinier de Graaf and national supervisory authorities, for example the Health and Youthcare Inspectorate (IGJ). They keep your information secret. We ask you to give permission for this inspection.

Retention period of data

Your data is stored on the study location according to the standard 15-year term. You can indicate on the consent form whether you agree with this. If you do not agree with the saving of your data, you can still participate in the PaPa Trial. Your data will be deleted after processing.

Storage and use of data for other studies
Your data may still be of interest after the end of this study for other clinical research in the area of treatment of labour pain. For this your data will be stored for 15 years. You can indicate on the consent form if you do or do not agree with this. If you do not consent to this, you can still participate in the current study.

Information about unexpected findings

During this research, by chance, something can be found that is not relevant to the study, however relevant to you. If this is important for your health, then you will be informed by your obstetric care provider. You can then go to your doctor or specialist and discuss what needs to be done. We also ask permission for this.

Withdrawal of consent

You can always withdraw your consent for the use of your personal data. This applies to this study and also for the storage and use for the future research. The study data that has been collected until the time you withdraw your consent will still be used in the study.

More information about your rights concerning the processing of data

For general information about your rights concerning the processing of your personal data, please consult the website of the Dutch Data Protection Authority.
If you have any questions about your rights, please contact the person responsible for the processing of your personal data. For this study it is: Reinier de Graaf. See Appendix A for contact information, and website.
If you have any questions or complaints regarding the processing of your personal information, we recommend that you contact the study site. You can also contact the Data Protection Officer of Reinier de Graaf or the Dutch Data Protection Authority.

Registration of the study

Information about this study is also included in a summary of medical research, namely www.trialregister.nl. No data that can be traced back to you is included. After the study, the website contains a summary of the results of this study. You can find this study under Trial NL7863.

11. Insurance for subjects

Everyone who participates in this study has an insurance policy. The insurance covers damage from the investigation. Not all damage is covered. You can find more in Appendix B. It also states to whom you can do damage report.

12. Informing general practitioner and midwife

A letter is sent to your general practitioner and midwife after delivery. This letter contains a summary of the course of your birth. Your participation in the PaPa Trial will be added to this letter. This is for your own safety. If you do not consent to this, you cannot participate in this study.

13. No compensation for participation

You will not be paid for participating in this study. The study medication and registration of data for the research cost you nothing.

14. Do you have any questions?

For questions, please contact the principal investigator, Ms. M.A.A. Lansbergen-Mensink. For independent advice on participating in this study, you can contact the independent expert, gynaecologist, Dr. N. van Gemund. She knows a lot about the PaPa Trial, but has nothing to

do with this study. If you have complaints about the investigation, you can discuss with the investigator or your treating physician. If you prefer not to do this, then you can contact the complaints officer of the Reinier de Graaf. All information can be found in appendix A: Contact details.

15. Signing of informed consent form

In expectation of your birth, you can think about participating in the PaPa Trial. If you need pain relief during labour, and the choice is Remifentanil, you are asked to decide on participation in this study. If you give permission, we will ask you to sign the accompanying consent form. Your written permission indicates that you have understood the information and agree with participation in the study. Both you and the researcher will receive a signed version of this consent statement.

Thank you for your attention.

16. Appendices with this information

A. Contact details Reinier de Graaf
B. Information about the insurance
C. Consent form(s)
D. Brochure “Medical Scientific Research General information for the subject” (February 2019 version)

Appendix A: contact details for Reinier de Graaf

Investigator:
Ms. Marjolein (M.A.A.) Lansbergen-Mensink
Reinier de Graafweg 5, 2625AD Delft
Department 2C: Mother&Child center
Marjolein1.Lansbergen@rdgg.nl
015-2604085
015-2603769

Research nurse:
Mw. A. van der Ster
A.vanderSter@rdgg.nl
015-2603979

Independent expert:
Dr. N.van Gemund, gynaecoloog
n.vangemund@franciscus.nl
010 - 461 6202

Complaints:
Reinier de Graaf Department for Handling of Claims
Functionary of complaints
Mevrouw G. Kloppers-Hozee
Antwoordnummer 10263
2600WB Delft
015-2604441

Data Protection Office of the institution
For more information about your rights: :
Functionary for Data Protection of Reinier de Graaf:
Mw. A. Hulshof-Buurman
06-28792929
fg@rdgg.nl

Appendix B: information about the insurance

Reinier de Graaf has taken out insurance for everyone participating in this study. The insurance covers damage resulting from participation in the study. This applies to damage incurred during the study or within four years after the end of your participation in the study. You must have reported damage to the insurer within these four years.

The insurance does not cover all damage. The bottom of this text explains briefly what damage is not covered.
These provisions are in the Medical Research Involving Human Subjects Act. This decree is on www.ccmo.nl, the website of the Central Committee on Research Involving Human Subjects (see 'Library' and then 'Laws and regulations').

In case of damage, you can contact the insurance company [or claims representative] directly.

The insurer of the study is:	
Name:	Centramed
Address:	Maria Montessorilaan 9, 2719 DB Zoetermeer
Telephone number:	070-3017070
E-mail	info@centramed.nl
Policy number:	624.529.703

The insurance offers a coverage of € 650.000 per subject and € 5.000.000 for the entire study and copy the amount of the policy, this must be at least € 7.500.000 per year for all the studies of the same sponsor.

The insurance will **not** cover the following damage:

- damage due to a risk about which you were informed in the written information. This does not apply if the risk is more serious than anticipated or if the risk was very unlikely;
- damage to your health that would also have occurred if you had not taken part in the study;
- damage due to not (completely) following directions or instructions;
- damage to your offspring, due to a negative effect of the study on you or your offspring;
- damage due to an existing treatment method when studying existing treatment methods.

Appendix C: Consent form

'The PaPa Trial: Paracetamol as an adjunct to intrapartum Remifentanil/PCA. An RCT of multimodal pain management during labor. '

I have read the information letter. I was also able to ask questions. My questions have been answered sufficiently. I have had enough time to decide whether or not to participate.

I understand that participation is voluntary. I also know that I may decide at any time to not participate or to stop participating in the study. Without having to provide any reason.

I give consent for my general practitioner and midwife treating me to be informed of my participation in this study. I know that for study monitoring purposes some individuals could have access to all my data. Those people are listed in this information letter. I consent to that access by these persons.

I give consent for my general practitioner and/or treating specialist to be informed of unexpected findings which are (may be) of interest for my health.

I □ **give**

□ **do not give**
consent for the further storage of my personal data and retention for future research into the area of [my disorder and/or the method of treatment].

I □ **give**

□ **do not give**
consent to being contacted again after this study for a follow-up study.

I □ **would like**

□ **would not like**
to be informed about the treatment I have had/in which group I was.

I want to participate in this study.

Name of subject: ……..

Signature: Date : __ / __ / __

I certify that I have fully informed this subject about the said study.

If information becomes known during the study that could influence the consent of the subject, I will inform him/her of this on time.

Name of investigator (or his/her representative):……

Signature: Date: __ / __ / __

<if applicable>
Additional information was provided by:
Name:……
Function:……..

Signature: Date: __ / __ / __

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* Delete that which is not applicable.

The subject will receive a complete information letter, together with a signed version of the informed consent form.

Appendix D: Medical Research. General information for subjects.

https://www.government.nl/documents/leaflets/2016/03/31/medical-research