



CHILDREN'S & WOMEN'S HEALTH CENTRE OF BRITISH COLUMBIA

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SUBJECT INFORMATION AND CONSENT FORM

Title of Study:

Ketamine and Hydromorphone PCA analgesia for Antineoplastic-Induced Pediatric Mucositis

Principal Investigator:

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1. INTRODUCTION

Your child is being invited to take part in this research study because your child is receiving pain medicine (called hydromorphone) using Patient Controlled Analgesia (PCA) (a method where the patient can control their pain relief medication) to treat the pain of oral mucositis (painful sore in the mouth often caused by cancer fighting drugs).



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2. YOUR PARTICIPATION IS VOLUNTARY

Your child's participation is entirely voluntary, so it is up to you to decide whether or not to have your child participate. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to your child during the study and the possible benefits, risks and discomforts.

If you do decide to have your child participate, you will be asked to sign this form. You are still free to withdraw at any time and without giving any reasons for your decision.

If you choose not to be involved or to withdraw your child from the study, you do not have to tell us why. The medical care that your child will be receiving will not be any different or less than the care he/she would normally receive. Please take time to read this information and ask any questions that may help you understand the study before you decide whether to be in the study or not.

3. WHO IS CONDUCTING THE STUDY?

This study is being conducted by Dr Carolyn Montgomery (principal investigator) and the pain management doctors (Drs Lauder, Purdy and Ansermino), and nurse (Ms Court) oncologists (Dr Strahlendorf) and research assistants (Ms Lim) in the Departments of Anesthesiology, Pharmacology and Therapeutics and Oncology at BC Children's Hospital. No investigator is receiving any remuneration for conducting or being involved with any part of the study and there is no possibility of benefit to the investigators from commercialization of any research findings.

4. BACKGROUND:

Pediatric oral mucositis is a challenging and severe pain problem. The use of pain medication called hydromorphone (Dilaudid) patient controlled analgesia (PCA) is standard practice at BC Children's Hospital. A recent survey of our previous 22 patients showed a median (half higher values and half lower values = the "middle" value) worst daily pain score of 7/10 (values ranged from 4-10). Undesirable drug effects in this group included nausea and vomiting (82%), altered mood (14%), sleepiness (14%) and itching (55%).

Ketamine (Ketalar) is an established intravenous (small plastic tube inserted in vein) pain medicine in common use at BC Children's Hospital in the emergency room and cancer clinic where it is used for sedation and for painful procedures like lumbar puncture and bone marrow tests in doses up to 2 milligrams/kilogram (mg/kg).

Ketamine, while an excellent pain reliever, when used in larger doses (typically greater than 2 mg/kg) has side effects that increase with the dose and include drooling (increased saliva flow), increased blood pressure, increased heart rate,



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increased brain pressure (which would be harmful in children with brain injuries), hallucinations, and rapid eye movements (which is not good for eye surgeries). We do not expect these side effects at the doses we are using.

In the last 10 years, several adult studies have looked at combining low-dose (less than 1/10) ketamine with morphine or hydromorphone (opioid medications – family of pain relieving medicines) to improve pain management and decrease the side effects of these drugs, which include constipation, nausea and vomiting, itching, sleepiness, mood changes, trouble urinating and decreased breathing. The ketamine may work to reduce the amount of opioid used by blocking pain receptors that decrease opioid medication's effectiveness.

An intravenously given mixture of morphine and low-dose ketamine is currently in common use at a Canadian Pediatric Hospital as a primary pain relief technique for pain due to mucositis and for other complicated post-operation pain management problems.

We are wondering if a combination of hydromorphone and low-dose ketamine would work better to treat mucositis pain than hydromorphone alone.

5. WHAT IS THE PURPOSE OF THE STUDY?

The main purpose of the study is to see what is the best concentration of 3 doses of ketamine (K) to combine with our standard hydromorphone (HM) [**Solution 1:** HM 0.2 and K 0.2 mg/ml (1:1) 20 mg/20mg in 100 ml, **Solution 2:** HM 0.2 and K 0.6 mg/ml (1:3) 20 mg/60 mg in 100 ml, **Solution 3:** HM 0.2 and K 1 mg/ml (1:5) 20 mg/100 mg in 100 ml]. We are trying to find the best concentration that provides adequate pain relief with minimum side effects. The results from this study may allow us to do a larger different study that will test whether the use of the ketamine-hydromorphone mixture results in less drug side effects and improved pain relief.

Neither ketamine nor hydromorphone are experimental medicines. Ketamine is often used in sedation (calming, sleepy) for children, but not officially approved for use in pain management in children. Hydromorphone is a commonly approved pain relief drug. But we believe that the combination of these two medications will improve your child's pain caused by mucositis.

Each year at BCCH, there are about 20 children who get mucositis and are able to use hydromorphone PCA. We expect that it will take about 2 years to enroll 20 children in this study. While a combination of ketamine and morphine is in common use for complicated pain problems at another Canadian Pediatric Hospital, the combination of ketamine and hydromorphone has not been studied. The best strength of the solution has also not been studied.



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6. WHO CAN PARTICIPATE IN THE STUDY?

Your child is eligible for this study if there is oral mucositis resulting from chemotherapy (cancer treatment) and they are currently appropriately using PCA hydromorphone pain relief. The main pain must be from mucositis. Your child will have received a previous 12 hour average of greater than or equal to 4 micrograms/kilogram/hour (mcg/kg/hour) of PCA administered hydromorphone (HM) and have self-report numerical rating scale (NRS) pain scores of greater than 5/10 with swallowing. The researchers would determine this. Your child must not have severe obesity, have an Oxygen Saturation (SpO₂) of greater than 90% on Room Air, have a normal level of consciousness (arousal score of 5), and ability to understand the self-report symptom evaluation questionnaire. The investigators will determine your child's eligibility.

7. WHO SHOULD NOT PARTICIPATE IN THE STUDY?

Your child must not already be receiving simultaneous pain medicine or sedatives such as acetaminophen, gabapentin, lorazepam, nabilone or clonidine. Your child must not have previously participated in the trial. Your child must not have a mood or behavioural problem, high blood pressure or known allergy or previous adverse reaction to ketamine.

8. WHAT DOES THE STUDY INVOLVE?

This study will take place on the cancer treatment ward of BC Children's Hospital. We plan to evaluate the use of a combination of medicines (ketamine-hydromorphone) in 20 subjects all from this hospital. You, your child, the staff and researchers will know which medicine is being used. The ketamine-hydromorphone combination will be tried for 24 hours.

Your child will already be receiving hydromorphone PCA for mucositis. Information concerning your child's age, weight, diagnosis, chemotherapy and pain management will be collected. Your child's mouth will be examined before and at 24 hours after starting treatment. Your child will answer questions about the amount of pain and other side-effects that they are experiencing due to the pain, the mucositis itself and the pain medicine being used at the start of the study, at 24 hours of therapy after starting the ketamine-hydromorphone combination and again at 24 hours after returning to regular therapy.

Because we do not know the best combination of ketamine and hydromorphone to use there will be a system *to increase or decrease* the amount of ketamine combined with the hydromorphone. The starting solution will be hydromorphone 0.2 milligrams/milliliter (mg/ml) combined with ketamine 0.6 mg/ml. This is the same concentration of hydromorphone that is routinely used in this hospital. The amount of ketamine that we are trying was determined by looking at adult studies that examined the use of ketamine in this way for postoperative pain. The setting on the PCA pump will remain the same as what your child was on before the study starts.



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The safety of your child will be ensured by doing all the routine monitoring that is done when any child is on PCA. This includes monitoring with continuous blood oxygen levels monitoring, and hourly sleepiness and breathing rate and depth checks. It is routine that an Acute Pain Service (APS) physician is immediately available 24-hours a day if there is a problem. During the study period, routine medicines for nausea and itching will be given as needed.

Increasing the Amount of Pain Medicine:

Your child will be checked at 3 and 6 hours after the start of the study solution. Your child will be asked: "When you push the button do you feel like you are receiving the right amount of medicine (pain is relieved), too much (you feel woozy or drowsy) or too little (you feel no effect)."

When more than 3 demand/received doses per hour for more than 3 hours are received (inadequate pain relief), the ketamine in the solution will be increased to 1 mg/ml. The effectiveness of this will be checked at 12 hours and 24 hours. We do not want to wake your child unnecessarily in the night so unless there are specific issues that need to be looked at there will be no assessment at 18 hours. The PCA dose delivered may be increased by 50% if necessary to improve pain management. If adequate pain management is not successful after these two increments, your child will be withdrawn from the study and returned to conventional pain relief techniques.

Decreasing the Amount of Pain Medicine:

If there are no PCA requests for more than 3 consecutive hours in the first 6 hours of treatment (adequate pain management), and/or there are medication side effects of sleepiness or mood changes, the ketamine in the solution will be decreased to 0.2 mg/ml. This will be reassessed at 12 hours and 24 hours.

Changing the Starting Dose:

If 5 consecutive subjects require the *increase* in the concentration of ketamine, all the next subjects will receive the higher concentration initially.

If 5 consecutive subjects require a *decrease* in the concentration of ketamine, all the next subjects will receive this lower concentration initially. Further evaluations, will change the dose but not concentration of the solution for 24 hours.

If your child has any complaint that is unacceptable to them or you, the symptom will be recorded and the study solution removed and replaced by the standard hydromorphone only solution.

For compassionate care reasons, if your child refuses to accept a return to conventional treatment due to perceived benefit of the experimental treatment, the study treatment will be continued with routine APS monitoring.



9. WHAT ARE MY RESPONSIBILITIES

There are no additional responsibilities or requirements necessary for you or your child in participating with this study except for co-operating with the mouth examinations, side-effect questions and the routine PCA monitoring including questions of whether the pain medicine is working.

10. WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECTS OF PARTICIPATING?

With higher doses of ketamine, side effects that may occur include: Increased flow of saliva, altered mood, (good mood and bad mood), hallucinations, vivid dreaming (pleasant and unpleasant), increased heart rate and increased blood pressure. Your child will be monitored for any of these side effects. In the adult study of postoperative pain, where a dose of ketamine 1 mg/mL was used in combination with morphine, the incidence of side effects was nausea and vomiting 24%, "vivid dreams" 6%, sleepiness 21%, and itchiness 10%. Inadequate breathing is a rare but serious side-effect anytime hydromorphone or any other opioid is used and the risk of this is typically less than 1%.

11. WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

There are no direct benefits to your child from participation in this study. The information we get from the study will be used to advise anesthesiologists and other pain researchers on the effect of different concentrations of ketamine combined with hydromorphone on pain due to mucositis and which concentration may be the best one to investigate further.

12. WHAT ARE THE ALTERNATIVES TO STUDY TREATMENT?

If you not wish to participate in the study the routine pain medicine which is hydromorphone PCA will be continued.

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If an alternate better pain relieving method becomes routine during the conduct of this study (a 2 year period) this will be offered to your child.

14. WHAT HAPPENS IF I DECIDE TO WITHDRAW MY CONSENT TO PARTICIPATE?

Your child's participation in this research is entirely voluntary. You may withdraw your child from this study at any time. If you decide to enter your child in the study and withdraw at any time in the future, there will be no penalty or loss of benefits to which you and your child are otherwise entitled, and your child's future medical care will not be affected.



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If you choose to enter the study and then decide to withdraw at a later time, all data collected about your child during his/her enrolment in the study will be retained for analysis. By law, this data cannot be destroyed.

15. WHAT HAPPENS IF SOMETHING GOES WRONG?

Signing this consent form in no way limits your legal rights against the sponsor, investigators or anyone else.

16. CAN MY CHILD BE ASKED TO LEAVE THE STUDY?

The study doctor(s)/investigators may decide to discontinue the study at any time, or withdraw your child from the study at any time, if they feel that it is in your child's best interests.

For example if the mucositis pain is unmanageable within the study or there is a change in your child's condition such that a non-mucositis pain source becomes clinically important or there is a serious event such as fever with low blood pressure or breathing problems due to new heart or lung disease. Appropriate routine pain medicine will be provided for any subject who is withdrawn from the study.

17. AFTER THE STUDY IS FINISHED

The results of this study will be shared with other doctors by presentations at meetings or by publication in scientific journals to allow them to decide whether to do further study of this combination or to use it in their patients.

18. WHAT WILL THE STUDY COST ME?

There will be no additional cost to you for your child's participation in the study. You will not be charged for any research procedure. You or your child will not receive any remuneration/reimbursement for participation.

19. WILL MY CHILD'S PARTICIPATION IN THIS STUDY BE KEPT CONFIDENTIAL?

Your child's confidentiality will be respected. No information that discloses your child's identity will be released or published without your specific consent to the disclosure.

Research records and medical records identifying your child may be inspected, in the presence of an Investigator or his or her designate, by representatives of the UBC Research Ethics Board, for the purpose of monitoring the research. However, records which identify your child by name or initials will be kept in a locked cabinet and will not be allowed to leave the Investigators' offices. Copies of relevant data, which identify your child only by code number, may be required by regulatory agencies. However, your child will not be identified by name, initials, or date of birth as part of this study data.



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20. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY CHILD'S PARTICIPATION?

If you have any questions or desire further information about this study before or during your child's participation, you can contact Dr. Montgomery at 604-875-2711.

21. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY CHILD'S RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns about your child's treatment rights as a research subject, please contact the Research Subject Information Line at the University of British Columbia Office of Research Services at 604-822-8598.



22. CONSENT TO PARTICIPATE

I have read or have had read to me all of the above. I have had enough time to consider entry to the study. All of my questions have been answered to my satisfaction. I understand that my child's participation is entirely voluntary and that he/she may refuse to participate, or I may withdraw my child from the study at any time.

The parent(s)/guardian(s) and the investigator are satisfied that the information contained in this consent form was explained to the child to the extent that he/she is able to understand it, that all questions have been answered, and that the child assents to participating in the research.

I acknowledge having received a signed and dated copy of this consent form for my own records.

Name of Subject: _____

Printed name of subject's parent / Legally acceptable representative	Signature	Date
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Printed name of subject	Signature	Date
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Printed name of witness	Signature	Date
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Printed name of principal investigator/ Designated representative	Signature	Date
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23. SUBJECT'S ASSENT TO PARTICIPATE IN RESEARCH

I have had the opportunity to read this consent form, to ask questions about my participation in this research, and to discuss my participation with my parents/guardians. All my questions have been answered. I understand that I may withdraw from this research at any time, and that this will not interfere with the availability to me of other health care. I have received a copy of this consent form. I assent to participate in this study.

Printed name of subject

Signature

Date