Remifentanil and its Applications in the Management of Parturient labor pain

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Abstract

The purpose of this research study project is to educate student nurse anesthetists and anesthesia providers about the many benefits of using Remifentanil in the obstetric population. Treating labor pain has always been a difficult task to achieve for anesthesia providers throughout the century. Once continuous laboring epidurals (CLE) were founded, it was quickly entitled the “gold standard” for managing labor pain. However, there are several obstetrical patient populations that are unable to receive an epidural. As more obstetric disorders are encountered that prohibit placement of an epidural, student registered nurse anesthetists need to be educated and informed on alternative labor pain analgesics.

A literature review of Remifentanil and its management of labor pain was conducted in preparation for this study. After the literature review was completed, a PowerPoint presentation was assembled and presented to 26 SRNAs during their class that focused on the obstetric population and anesthesia management. Pre-tests were administered prior to the PowerPoint presentation to evaluate the SRNAs baseline knowledge on Remifentanil. After completion of the lecture, each student filled out post-tests in order to assess the effectiveness of the lecture. Data were then analyzed using the paired sample t test, which yielded statistical significance with a P value <0.05. In conclusion, the improvement of the posttests when compared to the pre-tests suggested that the SRNAs developed a better understanding of Remifentanil as a drug as well as its administration for controlling labor pain among the parturient.

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Problem

Since the 1990s, Remifentanil had been used as an adjunct for pain relief in the surgical setting. Recently, several studies had investigated the role of Remifentanil in the setting of managing obstetrical labor pain. Currently, continuous epidural analgesia is the "gold standard" for managing labor pain, however there has not been an effective pain relief agent for those patients who cannot receive an epidural. Due to the pharmacokinetics of Remifentanil, it has the potential to help decrease labor pain in patients unable to receive epidurals.

The purpose of this project was to educate other student nurse anesthetists and anesthesia providers about the benefits of Remifentanil in the obstetric population. Remifentanil patient controlled analgesia (PCA) is a viable alternative in the management of labor pain in specific parturient patient populations. Frequently, there are patients where an epidural may not be possible, such as: increased risks for thrombosis, those with former congenital heart correction surgeries, infections, bleeding disorders, spinal abnormalities, or patient refusal (Devabhakthuni, 2013). In these cases, Remifentanil PCA's would be an effective option in controlling their labor pain.

With a Remifentanil PCA, the parturient would bolus herself upon the beginning of the uterine contraction so that the peak of the drug is associated with the intensity of the contraction. Theoretically, this would help the laboring woman be able to actively participate in the laboring process, all the while herself controlling the amount of medication needed to alleviate the labor pain. This psychological component can also help to make the labor experience more tolerable.

Up until this point, parturients who were unable to receive epidural analgesia could only be treated with IV medications that would ineffectively control labor pain and were associated with increased maternal and fetal complications (Hill & McMackin, 2012). Overall, the

pharmacokinetics of Remifentanil are ideal in helping to treat labor pain. If the side effects of Remifentanil could be appropriately monitored and prevented, Remifentanil PCA could be a front-runner in controlling labor pain in the absence of an epidural.

Review of Literature

Dating back since the beginning of mankind, spontaneous vaginal delivery has been considered one of the most painful experiences in a woman's life. According to Celewicz (2015), since the mid 1980s the implementation of epidurals has been considered the gold standard for controlling labor pain. However, not every woman is able to receive the benefits of an epidural; therefore, an alternative pain management therapy is needed. After a thorough review of literature was completed, Remifentanil proves to be beneficial in providing labor pain relief in parturients who are unable to receive epidurals.

This study collected data using the search engines EBSCO host, ProQuest, PubMed and Science Direct. Key words searched included "Remifentanil", "labor pain", "labour pain", "parturient" and "patient controlled analgesia." These key terms were used separately and in conjunction with others in order to provide an exhausted literature review. All articles were peer reviewed and were published within the last five years. After collecting the data, the researchers were able to develop an extensive literature review that analyzed labor pain, mechanism of Remifentanil, and potential risks and benefits of using Remifentanil for controlling labor pain.

To understand why Remifentanil would be beneficial in the obstetric population, it is important to first define characteristics of an ideal anesthetic agent. Per Hill and McMackin (2012), they identify nine properties for the ideal anesthetic:

> The properties of an ideal anaesthetic agent for labour analgesia are as follows:
>
> 1. Maternal and fetal safety
> 2. Ease of administration

3. Consistent, predictable and rapid onset
4. Maternal composure and control during the first and second states of labour
5. Analgesia through all stages of labour
6. Devoid of motor blockade, enabling ambulation and various birthing positions
7. Preserve the stimulus for expulsive efforts during the 2nd stage of labour
8. Facilitate the delivery of supplemental analgesia without the need for additional invasive procedures
9. Facilitate the delivery of anaesthesia for surgery to avoid the need for general anaesthesia (p. 16).

Now that guidelines have been established, the health care providers can evaluate the effectiveness and efficacy of Remifentanil PCA for managing labor pain.

In recent years, there have been several studies involving Remifentanil and its effects on labor pain. Remifentanil is not meant to replace the epidural as "the gold standard" of managing labor pain, however it does have a place in certain patient populations. According to Liu et al. (2014), since neuraxial analgesia may be contraindicated in some obstetric patients, Remifentanil PCA is an attractive option for managing labor pain due to its pharmacokinetics.

Remifentanil has a strong affinity to mu opioid receptors and a weaker affinity to delta and kappa opioid receptors. One of the unique characteristics of Remifentanil is that it has a rapid onset of action of 1 minute, low volume of distribution, peak effect of 2 minutes, duration of action of 20 minutes, and a high clearance rate, which makes it easier to titrate (Celewicz et al., 2015). Remifentanil is rapidly metabolized by tissue and plasma esterases into carboxyl acid, which is 46,000 times less potent than the original form of the drug. Remifentanil has a

metabolite but it does not have any analgesic qualities that can cause late respiratory depression in the mother or neonate (Celewicz et al., 2015).

Like any administered opioid, there are concerns about respiratory depression in the neonate upon delivery. While Remifentanil crosses the placental barrier, it does not accumulate in the fetus like other opioids would. According to Tveit et al. (2013), while the Remifentanil dose in the fetus is 50% of the maternal concentration, there is still concerns for neonatal safety, especially due to respiratory depression. This study suggested that more studies with larger patient populations were needed for a definite conclusion.

Remifentanil has multiple attractive characteristics for treatment of labor pain, however it is not without risk. Potential complications include respiratory depression and oxygen desaturation. In the study conducted by Hill and McMackin (2012), episodes of respiratory depression were transient and were resolved with administration of oxygen via nasal cannula and reduction in the infusion dose of Remifentanil. This study concluded that only four out of 21 women experienced an oxygen saturation of less than 90% for 15 seconds with the lowest respiratory rate being 8 breaths per minute. In the study by Stocki et al. (2014), oxygen saturation levels were closely monitored during all apnea events. Oxygen saturation levels remained above 94% throughout Remifentanil PCA infusions with 59.3% of the 27 apnea events recorded and only 22.2% of apnea events resulted in oxygen saturation levels less than 94% (Stocki et al., 2014).

Another study conducted by Messmer (2015) researched maternal oxygen desaturation during Remifentanil patient controlled analgesia in sixty-one parturients. The study defined a desaturation episode as an oxygen saturation level less than ninety percent. All the women who experienced oxygen desaturation levels during Remifentanil PCA infusion recovered

spontaneously without the need of any intervention such as naloxone or ventilatory support. Messmer (2015) found that while maternal desaturation occurred frequently, the results were comparable to maternal oxygen desaturation levels when nitrous oxide and pethidine were used alone in laboring patients.

Due to these potential significant complications, it is imperative that parturients on Remifentanil PCA's be closely hemodynamically monitored, have additional oxygen available, one-to-one nursing care, and Remifentanil educated staff (Liu et al., 2014). Although not as significant, other side effects of Remifentanil as well as with any other opioids, a risk for nausea, vomiting, and pruritus exists. The literature review did not reveal any significant occurrence of these side effects. Tviet et al. (2014) stated, "No statistical difference between remifentanil PCIA and epidural analgesia were detected in the incidence of nausea, vomiting, or pruritus" (p. 24).

According to the literature review, the two major frontrunners for controlling labor pain intravenously were Remifentanil and Pethidine (Meperidine). Midwives first used Pethidine in the 1950s by single shot intramuscular dose. Other preparations of Pethidine are PCA dosing intramuscularly and intravenously. Pethidine is a weak base synthetic opioid that can easily travel across the fetal membrane barrier and become trapped in the new acidotic environment (Hill & McMackin, 2012). Because of ion trapping and its active metabolite, norpethidine, the effects of respiratory depression are more pronounced in the neonate than in the maternal circulation. Due to the extremely long half-life of norpethidine of 62 hours, it has been linked with prolonged sedation and respiratory depression in the neonate, not to mention its limited efficacy (Hill & McMackin, 2012). Fentanyl can also be used intravenously for labor pain but is used less frequently due to being associated with lower Apgar scores in the neonates, slower onset of action, and inadequate pain relief during the first stage of labor (Devabhakthuni, 2013).

Per Liu et al. (2014), epidurals still remain the most effective method for controlling labor pain, but Remifentanil may play a vital role in controlling labor pain when epidurals are contraindicated in a parturient. All of the articles from the literature review conclude that epidurals are superior to Remifentanil PCA infusions, but Kranke et al. (2013) explained that many women during studies opted to have a Remifentanil PCA infusion because it was more readily available and did not always require the presence of an anesthesia provider. One concern with the use of Remifentanil PCA infusions is that since it is more cost effective than epidurals, hospitals may push for its use without implementing close monitoring by obstetric staff or anesthetists (Kranke et al., 2013). Remifentanil PCA infusions may not replace the use of epidurals for controlling labor pain, but it may be a desirable option for women who wish for less invasive analgesia and may want to have a sense of control during the laboring process.

One qualitative study conducted by Fair and Morrison (2011) revealed that women's level of control during their delivery process directly related to their overall satisfaction. The importance of being in control and being part of decision making helped to improve the overall labor experience. Fair and Morrison (2011) found that "high levels of control during labor and delivery significantly increases birth satisfaction and may aid in decreasing the incidence of traumatic perceptions of birth and postpartum depression" (p. 21). Another study by Devabhakthuni (2013) found that Remifentanil was safe and lead to a high maternal satisfaction rate among parturients. The study reported that 62 to 88% of post partum mothers demonstrated high levels of satisfaction even though their pain was not completely eliminated with the Remifentanil PCA delivery system (Devabhakthuni 2013). After reviewing literature, Remifentanil PCA could increase maternal control over pain relief while providing enough analgesia per the mother's preference.

Throughout the literature review, information was obtained that was pertinent to Remifentanil relieving labor pain, pharmacokinetics, indications, and different side effects of Remifentanil. The literature reviews also helped to narrow down the specific benefits of using Remifentanil during labor to help ease pain and the different monitoring techniques necessary when using this medication on an obstetric ward.

Project Description

To ensure this study is within ethical bounds, the project was submitted to the IRB and Scientific Review Committee at ADU. In order to effectively educate student registered nurse anesthetists (SRNA) and other anesthesia providers about this different application of Remifentanil, a power-point presentation was provided. The audience consisted of 26 student registered nurse anesthetists who studied at Adventist University of Health Sciences (ADU) Nurse Anesthesia Program. The power-point presentation explained how Remifentanil works, its application to the obstetric population, side effects, and compared Remifentanil to other treatments for labor pain. After informed consent was obtained from the student population, a pre-test was administered. The pre-test measured the students' baseline knowledge of Remifentanil and its uses in the obstetric population. After the pre-test was administered and collected, the power-point presentation was conducted.

Once the Remifentanil presentation was concluded, a post-test was administered in the same fashion to evaluate the student's retention of the presentation. The results of the pre-test and post-test was analyzed and organized into a chart. The chart was displayed along with the rest of the Remifentanil Capstone Project during the Graduate Poster Presentation at Adventist University of Health Sciences. Both staff and students alike had the opportunity ask questions about the research project.

Evaluation Plan

In order to evaluate the success of this quantitative study on Remifentanil PCA in labor pain, a sample of 26 junior SRNAs at ADU took a pre and post-test after hearing a PowerPoint presentation on the role of Remifentanil PCA's in the parturient population in the Spring semester of 2017. The pre and post-tests were administered to evaluate the retention of knowledge and learning that has occurred in the convenience sample of 26 SRNAs at ADU.

Both the pre and post-tests included the same questions so that a statistical growth could be shown in this study. Prior to the start of the presentation, each student received a packet, which comprised of the consent form, the pre-test and a post-test with the post-test folded within an envelope. Both the pre and post-test was numbered so that each student could be compared anonymously. As expected, the average percentage between the pre and post scores showed statistical significance. Earlier in the project, the researchers expected a 40% increase in test scores on the post-tests when compared to the pre-tests. After implementing the capstone presentation, the increase in test score between the pre and post-test was 38.99%. Such a high score indicated that the students were able to learn from the PowerPoint presentation and could answer questions in relation to that subject.

The higher post-test scores indicated that the students were able to identify the mechanism of action, indications, benefits, and pharmacokinetics of Remifentanil and its use with labor pain. After the pre-test was graded, it was obvious that the students had limited knowledge in regards to Remifentanil PCA's and how they could be implemented for managing labor pain. Because of the dramatic increase in scores, it suggested that the PowerPoint presentation was effective in teaching the SRNAs about Remifentanil and its management in labor pain. After the pre and post-tests were collected, a statistician at the Adventist University

of Health Sciences Research office used SPSS to analyze the data in order to measure the outcomes of this research study.

Results and Conclusions

The results of the pre-test scores showed that teaching was needed in regards to the purpose of Remifentanil PCA's in the parturient population. Even though the pre-test average score was 52.93%, there was still need for much knowledge-based improvement over this subject. The results of the pre-test showed a standard deviation of 0.18978 as well as a standard error mean of 0.03722. As shown by the standard deviation and standard error mean, students taking the pre-test scored around the same.

After the PowerPoint presentation was completed, the anesthesia students were instructed to complete the post-test that was given to them in an envelope. The post-tests were administered in envelopes to prevent students from filling them out during the presentation and therefore causing a skewing of results. Once the students completed the post-tests, the tests were collected and the students were free to leave. The post-test results showed that there was an increase in average in regards to pre and post-test scores. Whereas in the pre-test, the students had an average score of 52.93%, the post-test showed an average of 91.92%.

This dramatic increase concluded that the students retained knowledge from the presentation and was able to answer questions regarding Remifentanil whereas prior to the PowerPoint presentation, there was a knowledge deficit. The post-test standard deviation was 0.09389 along with a standard error mean of 0.01841. The standard deviation from the post-test showed that once again, students scored similarly when taking the test. The standard error mean also correlated with the standard deviation and appropriately showed a smaller number, which concluded that there was less variety in test scores throughout the post-test.

The obtained t value of -9.551 was associated with a p value of less than the conventional .05 level of confidence. Therefore, it can be concluded that the average scores increased significantly between pre-test and post-test administrations. The statistical analysis of this data was completed by Dr. Roy Lukman at Adventist University of Health Sciences in the research office.

Capstone Data Analysis:

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post-Test	-.40000	.21354	.04188	-.48625	-.31375	-9.551	25	.000

Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	.5192	26	.18978	.03722
	Post-Test	.9192	26	.09389	.01841

The pre-set goals of this project was met once the test scores were collected. After reviewing the post-presentation data, it was clearly obvious that there was an increase in understanding of how Remifentanil PCA's work in the parturient population. It was clearly evident that the PowerPoint presentation was successful and students were able to retain

pertinent knowledge and successfully answer post-test questions. The increase in average test scores from 52.93% to 91.92% showed the anticipated outcome of improving the understanding of how Remifentanil PCA's could function as an alternative to epidurals in labor pain.

The research project was successful in increasing the knowledge of Remifentanil in the student nurse anesthetists at ADU. However, there was a limitation in the small participant sample size. For this research project to be more credible, a much larger subject sample size should be obtained. It would also be interesting to see if the subject population was broadened to include all anesthesia providers, which way this would influence the pre and post scores.

This PowerPoint presentation not only helped the students become familiar with Remifentanil pharmacodynamics but helped them better understand the parturient labor pain and different options that could be used to control labor pain. In the future, this PowerPoint presentation can be used as a tool by other educators who are interested in incorporating the use of Remifentanil PCA's during labor into their own clinical practice, thereby increasing the knowledge of other practioners they may encounter as well.

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Appendix A

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

Our names are **Abigail Evans** & **Tessa Fajardo** and we are MSNA students in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). We are doing a Capstone Project called ***Remifentanil Analgesia and its applications in the Management of Parturient Labor Pain*.** This project is being supervised by Dr. Manuel Tolosa. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to increase understanding among Student Registered Nurse Anesthetists regarding the pharmacokinetics, risk factors and benefits for using Remifentanil PCA's as a treatment in managing labor pain.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will address your understanding of Remifentanil and its applications in the obstetric population. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 1 hour.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain additional understanding about the benefits and risks of using Remifentanil as a treatment for labor pain.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. You

will be given a pre-numbered pre-assessment that will be matched to a post-assessment with the same number as a tool to evaluate the presentation outcome. You are not required to write your name or any identification information on either assessment. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 1 hour of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, please feel free to contact Abigail Evans at abigail.vinton@my.adu.edu or Tessa Fajardo at tessa.schultz@my.adu.edu. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

_____ _____

Participant Signature **Date**

_____

Participant Name (PRINTED LEGIBLY)

Appendix B

Pre-Post Test

1. Remifentanil is metabolized by:
    a) Kidneys
    b) Hoffman elimination
    c) Plasma & Tissue esterases
    d) Hepatic metabolism
2. The context-sensitive half-life of Remifentanil is:
    a) 3 minutes
    b) 7 minutes
    c) 15 minutes
    d) 20 minutes
3. During Remifentanil administration, the fetal bloodstream concentration is ___% of the maternal bloodstream concentration?
    a) 75%
    b) 100%
    c) 50%
    d) 25%
4. The preferred administration route of Remifentanil is:
    a) Intrathecal
    b) Intravenous
    c) Sublingual
    d) Intramuscular
5. Select the answer that is TRUE about how Remifentanil works:
    a. It is a synthetic drug that has a high affinity to the mu opioid receptor and weak affinity to delta and kappa receptors
    b. It is a synthetic drug that has a high affinity to the delta opioid receptor and weak affinity to mu and kappa receptors
    c. It is a synthetic drug that has a high affinity to the kappa opioid receptor and weak affinity to delta and mu receptors
    d. It is a synthetic drug that only works of the kappa receptors.

6. What is the “gold standard” for managing labor pain?
    a. Remifentanil PCA infusion
    b. Meperidine (Pethidine)
    c. Continuous epidural
    d. Both a & c
7. Which of the following are contraindications for epidural placement?
    a. Local infection
    b. Thrombocytopenia
    c. Patient refusal
    d. Spinal abnormalities
    e. All of the above
8. Remifentanil has a very short onset of action and duration of action.
    a. True
    b. False
9. Remifentanil has an active metabolite that is _____ times less potent than its original form
    a. 46
    b. 220
    c. 10,000
    d. 46,000
10. Which of the following are potential side effects of Remifentanil PCA infusions (select 2)?
    a. Nausea/vomiting
    b. Fetal tachycardia
    c. Oxygen desaturation
    d. Diarrhea

Appendix C

Case Study

- 32 year old parturient G2 P1 is admitted onto the labor and delivery floor at 3:00am. She is 3cm, 50% effaced and pain 7/10. She is requesting an epidural for pain control.
- The SRNA goes into perform the preoperative assessment. The patient's history includes no previous medical problems and an uneventful pregnancy. The parturient had an epidural placed for the last pregnancy and had a successful vaginal delivery. The previous epidural was placed easily.
- Five minutes later the nurse enters the room reporting a platelet level of 50.
- What are your options?

History of Remifentanil

- FDA approved drug on July 12, 1996.
- Patented by Glaxo Welcome incorporate
- Introduced into clinical practice in Germany (1996).
- Since then, it has sparked interest in adapting use of Remifentanil into PCAs for managing labor pain.
- Other uses of Remifentanil include neurological surgeries and other surgeries such as thyroidectomies that require no use of muscle relaxants.

Gold Standard for Labor pain

- Since the mid 1980s the implementation of **epidurals have been considered the "gold standard" for controlling labor pain.**
- Contraindications to an epidural:
  - Increased risks for thrombosis
  - Those with former congenital heart correction surgeries
  - **Local infection**
  - **Thrombocytopenia**
  - **Spinal abnormalities**
  - **Patient refusal**

Ideal Intravenous Anesthetic

- According to Hill and McMackin (2012), they identify nine properties for the ideal anesthetic.
- The properties of an ideal anaesthetic agent for labour analgesia are as follows:
  - Maternal and fetal safety
  - Ease of administration
  - Consistent, predictable and rapid onset
  - Maternal composure and control during the first and second stages of labour
  - Analgesia through all stages of labour
  - Devoid of motor blockade, enabling ambulation and various birthing positions
  - Preserve the stimulus for expulsive efforts during the 2nd stage of labour
  - Facilitate the delivery of supplemental analgesia without the need for additional invasive procedures
  - Facilitate the delivery of anaesthesia for surgery to avoid the need for general anaesthesia (Hill & McMackin, 2012, p. 16.)

Characteristics of Remifentanil

- Potent, ultra short-acting synthetic opioid analgesic
- Belongs to the anilidopiperidine class of synthetic opioid.
- Trade Name: Ultiva
- Drug Class: Opioid, General Anesthetic Adjunct
- Scheduled II controlled substance
- Pregnancy Risk: Category C (Risk cannot be ruled out)
- International Union of Pure and Applied Chemistry (IUPAC) name: Methyl 1-(3-methoxy-3-oxopropyl)-4-(*N*phenylpropanamide)piperidine-4-carboxylate

Characteristics of Remifentanil

- Used for light sedation → General anesthesia. Also used for Electroconvulsive (ECT) therapy
- **Preferred route of administration: Intravenous**
- Highly lipid soluble
- 100-125 stronger than Morphine
- Relatively same potency as Fentanyl

Pharmacokinetics

- **Strong affinity to mu-1 opioid receptors and a weaker affinity to delta and kappa opioid receptors.**
- Low volume of distribution
- Peak effect: 2 minutes
- Duration of Action: 20 minutes
- High Clearance rate: approx. 40ml/kg/min (easier to titrate)

Pharmacokinetics, cont'd

- **Context Sensitive Halftime: 3 minutes** (after a 4 hr. infusion)
- Rapid blood-brain equilibration half-time of 1 minute
- Rapid recovery (5-10 minutes) of patient independent of duration of drug administration.
- Terminal elimination half-life: 10-20 minutes
- Does not cause histamine release

Metabolism

- Unlike other opioids, Remifentanil has a propanoic acid-methyl *ester* linkage → undergoes rapid hydrolysis by non-specific **plasma/tissue esterases**.
- Normal drug action in patients with atypical cholinesterase.
- DOES NOT ACCUMULATE
- 70% bound to plasma proteins, with 2/3 binding to alpha-1-acid-glycoprotein
- Metabolized to Carboxyl acid → **46,000x less potent** than the original form
- Excretion depends on renal clearance, but metabolites are mostly inactive → so not influenced by hepatic or renal failure.

Contraindications to Remifentanil PCA

ABSOLUTE CONTRAINDICATIONS

- Allergic to Fentanyl analogs
- Other parenteral opioid administration within preceding 4 hours.

RELATIVE CONTRAINDICATIONS (per several order sets)

- Pre-eclampsia
- Multiple Pregnancy

*Because of glycine formulation, Remifentanil is contraindicated for epidural or intrathecal administration.

Pricing

- 1mg vial: $30.19
- 3mg vial: $57.20
- 5mg vial: $118.15

Potential complications

Adverse effects that are characteristic of mu-opioids:

- **Respiratory depression**
- *Oxygen desaturation*
- Bradycardia
- Hypotension
- Skeletal muscle rigidity
- *Nausea and vomiting*
- Respiratory depression in the neonate (needs further study)

Respiratory Depression

Hill, D., & McMackin, P. (2013). Review of opioid pca for labour analgesia. *Fetal and Maternal Medicine Review, 23*(1), 15-31. http://dx.doi.org/10.1017/S0965853952000010

- According to Hill & McMackin, the greatest concern with the use of Remifentanil PCA systems is maternal respiratory depression.
- One study found 4 out of 21 laboring women experienced an oxygen saturation less than 90% for 15 seconds and the lowest recorded respiratory rate was 8 bpm.
- Blair et al. in one study found that occurrence of respiratory depression from Remifentanil was similar when compared to pethidine.
- The authors suggested one to one nursing care with close oxygen saturation monitoring and having oxygen via nasal cannula readily available.

Messmer, A., Potts, J., & Orlikowski, C. (2016). A prospective observational study of maternal oxygenation during remifentanil patient-controlled analgesia use in labour. *Anaesthesia, 71*, 171–176. doi:10.1111/anae.13329

- Prospective, observational study of maternal oxygen desaturation during Remifentanil PCA.
- Pulse oximetry values recorded every 8 seconds
- Desaturation was defined as O2 sat < 90%.
- Sample size: 61 parturients. From 148 hrs of data, 176 desaturation episodes occurred.
- Lowest saturation during each episode 87%.
- All desaturation episodes recovered spontaneously w/o the need of any interventions such as Narcan or ventilator support.
- "Although these findings suggest desaturation occurs more frequently during remifentanil patient-controlled analgesia, the results are comparable with earlier oximetry studies of women who received nitrous oxide and pethidine during labour" (Messmer, Potts & Orlikowski, 2016).

Stocki, D., Matot, I., Einav, S., Eventov-Friedman, S., Ginosar, Y., & Weiniger, C. (2014). A randomized controlled trial of the efficacy and respiratory effects of patient-controlled intravenous remifentanil analgesia and patient-controlled epidural analgesia in laboring women. *Anesthesia and Analgesia, 118*(3), 589-597. http:dx.doi.org/10.1213/ANE.0b013e3182a7cd1b

- Compared epidural analgesia and Remifentanil PCA infusions
- Among the 40 women involved in the study, 9 women experienced apnea events for a total of 27 apnea events.
- 14 of the events occurred within the first 2 hours of Remifentanil administration
- Researchers did not find any correlation in the dose per kilogram and the number of apnea events.
- For 16 of the 27 events, the oxygen saturation stayed above 94% throughout the apnea event.
- Results: Remifentanil does provide a satisfactory level of labor analgesia.
- Final recommendations: supplemental oxygen and close oxygen saturation monitoring be performed.

Do you need special monitoring for Remifentanil PCA's?

YES!!

Special Monitoring

- One-to-one nursing care during labor
- Supplemental oxygen
- Multiple studies suggest the use of NC with ETCO2 monitoring capabilities
- Close hemodynamic monitoring
- Staff education regarding pharmacokinetics, side effects and interventions.
- Nurse anesthetist available

Liu, Z., Chen, X., Li, H., Qiu, M., & Duan, T. (2014). A comparison of remifentanil parturient-controlled intravenous analgesia with epidural analgesia: A meta-analysis of randomized controlled trials. *Anesthesia and Analgesia, 118*(3), 598-603. http://dx.doi.org/10.1213/ANE.0000000000000077

- Meta-analysis comparing the efficacy and safety of Remifentanil PCA's and epidurals for labor pain.
- Remifentanil PCA's require "careful monitoring, one-to-one nursing care throughout labor, and supplemental oxygen in some parturients" (Liu et al., 2014).
- Although parturients with an epidural had more consistent pain control, pain perception is individual and impacted by parturient's progression of labor, personal tolerance and human influences.
- The study concluded that considering the advantages of Remifentanil (less-invasive treatment, easier performance, and possible lower costs) Remifentanil PCA may be an attractive alternative to epidural analgesia.

What about Nausea and Vomiting?

Tveit, T., Halvorsen, A., Seiler, S., & Rosland, J. (2013). Efficacy and side effects of intravenous remifentanil patient-controlled analgesia used in a stepwise approach for labour: An observational study. *International Journal of Obstetric Anesthesia, 22*(1), 19-25. http://dx.doi.org/10.1016/j.ijoa.2012.09.003

- All opioids carry side effects such as pruritus, nausea and vomiting.
- Although Remifentanil is an opioid, multiple studies do not show any significant occurrence of any of these effects
- "No statistical difference between remifentanil PCIA and epidural analgesia were detected in the incidence of nausea, vomiting or pruritus" (Tviet et al., 2013, p.24).

How is the Neonate effected?

Fair, C., & Morrison, T. (2011). "I felt part of the decision-making process": A qualitative study on techniques used to enhance maternal control during labor and delivery. *International Journal of Childbirth Education, 26*(3), 21-25. Retrieved from http://resource.adu.edu/login?url=http://searc h.proquest.c om/docview/895978802?accountid=35793

- Qualitative study on techniques to help enhance maternal control during labor and delivery.'
- 31 primiparae women 26-40 weeks were interviewed 6 weeks after delivery.
- Open-ended questions were asked to gain the mothers' perspectives on experiences of control.
- Fair and Morrison (2011) found that "high levels of control during labor and delivery significantly increases birth satisfaction and may aid in decreasing the incidence of traumatic perceptions of birth and postpartum depression" (p. 21).
- "Though childbirth satisfaction is complex in nature and has multiple influencing factors, having a satisfying birth experience is crucial to a woman's perception of her birth and motherhood in general" (Fair & Morrison, 2011).

Hill, D., & McMackin, P. (2012). Review of opioid pca for labour analgesia. *Fetal and Maternal Medicine Review, 23*(1), 15-31.m http://dx.doi.org/10.10 17/S0965539612000010

- Review of Literature on options for Intravenous Opioid analgesics for labor pain.
- "No one would dispute that epidural analgesia, when sited correctly and working well gives the most complete analgesia, however a satisfactory experience **does not** require complete pain relief" (Hill & McMackin, 2012).
- Hill & McMackin (2012) argued that many times women verbalize that having control over labor pain is more important than the effectiveness of the analgesic.
- They presented the idea that a PCA delivery system might offer a better laboring experience for parturients.

Devabhakthuni, S. (2013). Efficacy and safety of remifentanil as an alternative labor analgesic. *Clinical Medicine Insights: Women's Health, 6*, 37-49. http://dx.doi.org/10.4137/CMWH.S8015

- Studied the efficacy and safety of Remifentanil in labor in 4 different studies.
- Pain scales recorded every 1 hour.
- Visual Analogue Scale (VAS) was used to gauge pain (range from 0-100mm).
- Sedation was assessed using a 5-point scale:
  - 1 = awake and alert
  - 2 = awake but drowsy
  - 3 = drowsy but arousable
  - 4 = rousable to touch
  - 5 = unarousable
- The studies concluded that remifentanil is safe and can lead to a significant reduction in pain scores from baseline despite being an incomplete analgesia.
- Many of the studies demonstrated that majority of mothers (62%-88%) had HIGH satisfaction scores after using Remifentanil.

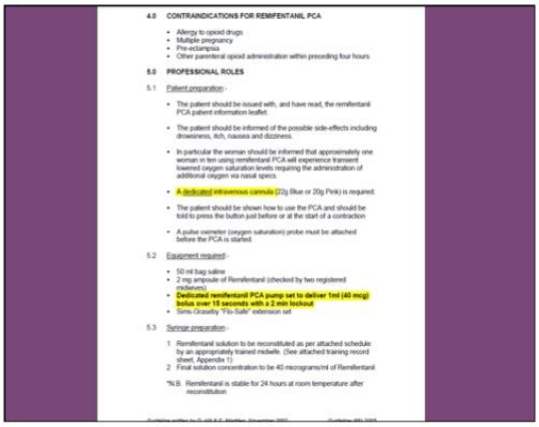
Kranke, P., Girard, T., Lavand'homme, P., Melber, A., Jokinen, J., Muellenbach, R., . . . Hönig, A. (2013). Must we press on until a young mother dies? Remifentanil patient controlled analgesia in labour may not be suited as a "poor man's epidural". . *BMC Pregnancy and Childbirth, 13*, 139. http://dx.doi.org/10.1186/1471-2393-13-139

- Studied different options for labor pain such as epidurals, Pethidine, inhaled Nitrous Oxide and Remifentanil.
- Found that Remifentanil is a good option in the "cardiovascular compromised obstetric patient e.g. aortic or valvular disease or patients presenting with a cardiomyopathy" (Kranke et al., 2013).
- Though extensively documented that Remifentanil does not provide as effective pain relief such as an epidural, many women during the studies opted to have a Remifentanil PCA since it was more readily available and allowed them to have more of a sense of control during the laboring process.

Cost of Managing Labor Pain: Epidural vs Remifentanil

- This is a controversial topic due to many factors involved in an analgesic delivery system:
  - length of labor
  - brand of epidural kit
  - ease of epidural placement
  - experience of anesthesia provider in placing epidural
  - type of local anesthetic used in epidurals
- One concern with the use of Remifentanil PCA infusions is that since it is more cost effective than epidurals, hospitals may push for its use without implementing close monitoring by obstetric staff or anesthetists (Kranke et al., 2013).

PCA ORDER SET



4.0 CONTRAINDICATIONS FOR REMIFENTANIL PCA

- Allergy to opioid drugs
- Multiple pregnancy
- Pre-eclampsia
- Other parenteral opioid administration within preceding four hours

5.0 PROFESSIONAL ROLES

5.1 Patient preparation:-

- The patient should be issued with, and have read, the remifentanil PCA patient information leaflet.
- The patient should be informed of the possible side-effects including drowsiness, itch, nausea and dizziness.
- In particular the woman should be informed that approximately one woman in ten using remifentanil PCA will experience transient lowered oxygen saturation levels requiring the administration of additional oxygen via nasal specs.
- A dedicated intravenous cannula (22g Blue or 20g Pink) is required.
- The patient should be shown how to use the PCA and should be told to press the button just before or at the start of a contraction
- A pulse oximeter (oxygen saturation) probe must be attached before the PCA is started.

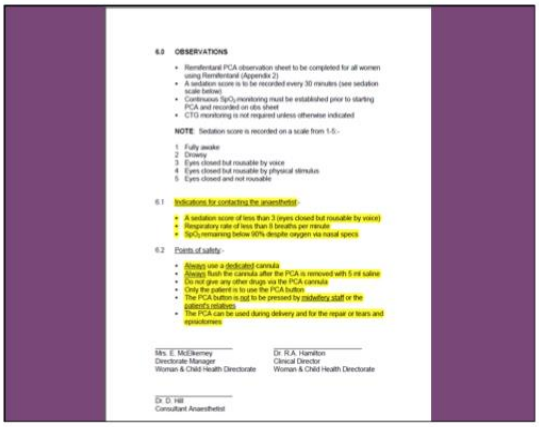
5.2 Equipment required:-

- 50 ml bag saline
- 2 mg ampoule of Remifentanil (checked by two registered midwives)
- **Dedicated remifentanil PCA pump set to deliver 1ml (40 mcg) bolus over 15 seconds with a 2 min lockout**
- Sims-Graseby "Flo-Safe" extension set

5.3 Syringe preparation:-

1. Remifentanil solution to be reconstituted as per attached schedule by an appropriately trained midwife. (See attached training record sheet, Appendix 1)
2. Final solution concentration to be 40 micrograms/ml of Remifentanil

*N.B. Remifentanil is stable for 24 hours at room temperature after reconstitution



6.0 OBSERVATIONS

- Remifentanil PCA observation sheet to be completed for all women using Remifentanil (Appendix 2)
- A sedation score is to be recorded every 30 minutes (see sedation scale below)
- Continuous SpO_2 monitoring must be established prior to starting PCA and recorded on obs sheet
- CTG monitoring is not required unless otherwise indicated

NOTE Sedation score is recorded on a scale from 1-5:-

1 Fully awake
2 Drowsy
3 Eyes closed but rousable by voice
4 Eyes closed but rousable by physical stimulus
5 Eyes closed and not rousable

6.1 Indications for contacting the anaesthetist:-

- A sedation score of less than 3 (eyes closed but rousable by voice)
- Respiratory rate of less than 8 breaths per minute
- SpO_2 remaining below 90% despite oxygen via nasal specs

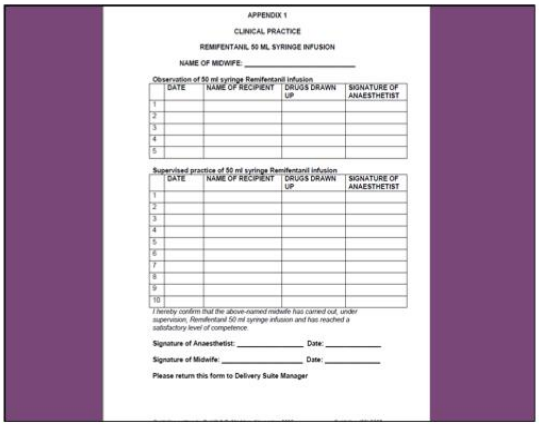
6.2 Points of safety:-

- Always use a dedicated cannula
- Always flush the cannula after the PCA is removed with 5 ml saline
- Do not give any other drugs via the PCA cannula
- Only the patient is to use the PCA button
- The PCA button is not to be pressed by midwifery staff or the patient's relatives
- The PCA can be used during delivery and for the repair or tears and episiotomies

Mrs. E. McElkerney
Directorate Manager
Woman & Child Health Directorate

Dr. R.A. Hamilton
Clinical Director
Woman & Child Health Directorate

Dr. D. Hill
Consultant Anaesthetist



APPENDIX 1

CLINICAL PRACTICE

REMIFENTANIL 50 ML SYRINGE INFUSION

NAME OF MIDWIFE: _____

Observation of 50 ml syringe Remifentanil infusion

	DATE	NAME OF RECIPIENT	DRUGS DRAWN UP	SIGNATURE OF ANAESTHETIST
1				
2				
3				
4				
5				

Supervised practice of 50 ml syringe Remifentanil infusion

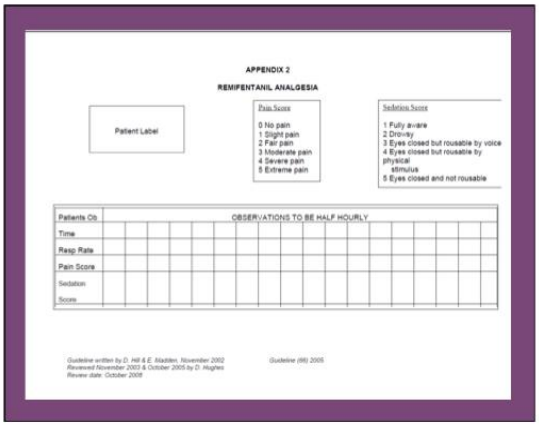
	DATE	NAME OF RECIPIENT	DRUGS DRAWN UP	SIGNATURE OF ANAESTHETIST
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				

I hereby confirm that the above-named midwife has carried out, under supervision, Remifentanil 50 ml syringe infusion and has reached a satisfactory level of competence.

Signature of Anaesthetist: _____ **Date:** _____

Signature of Midwife: _____ **Date:** _____

Please return this form to Delivery Suite Manager



APPENDIX 2

REMIFENTANIL ANALGESIA

Patient Label

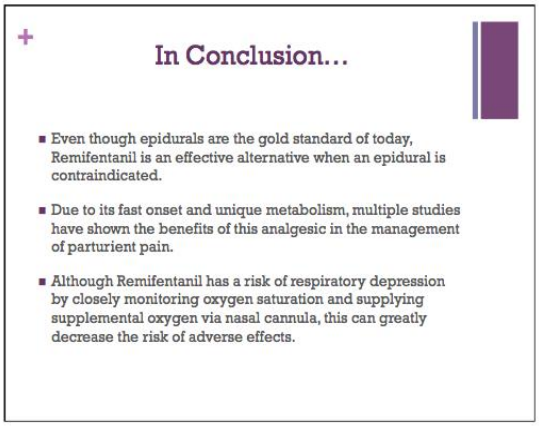
Pain Score
0 No pain
1 Slight pain
2 Fair pain
3 Moderate pain
4 Severe pain
5 Extreme pain

Sedation Score
1 Fully aware
2 Drowsy
3 Eyes closed but rousable by voice
4 Eyes closed but rousable by physical stimulus
5 Eyes closed and not rousable

Patients Ob	OBSERVATIONS TO BE HALF HOURLY
Time	
Resp Rate	
Pain Score	
Sedation Score	

Guideline written by D. Hill & E. Madden. November 2002
Reviewed November 2003 & October 2005 by D. Hughes
Review date: October 2008

Guideline (66) 2005



In Conclusion…

- Even though epidurals are the gold standard of today, Remifentanil is an effective alternative when an epidural is contraindicated.
- Due to its fast onset and unique metabolism, multiple studies have shown the benefits of this analgesic in the management of parturient pain.
- Although Remifentanil has a risk of respiratory depression by closely monitoring oxygen saturation and supplying supplemental oxygen via nasal cannula, this can greatly decrease the risk of adverse effects.

GO FORTH

AND

USE REMI!

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