The Use Of Remifentanil As The Primary Agent For Analgesia In Parturients

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Learning Objectives for this Self Study:

Upon completion of this study, the CRNA will be able to:

1. Discuss the significance of remifentanil use as a primary analgesic agent in parturients for whom neuraxial anesthesia is not an option.

2. Identify clients in which neuraxial anesthesia might be contraindicated.

3. Compare the efficacy of select medications in the control of pain in paturients.

4. Appraise findings in current evidence to determine to what extent remifentamil is a viable option for pain management in parturient patients.

5. Explain dosing and timing parameters that warrant consideration in the administration of remifentanil for the treatment of labor pain.

In order achieve optimal patient outcomes in anesthesia patients, it is important to consider multiple options for pain control, especially when traditional options pose a problem, or are not options. In particular, there are parturient clients for whom the use of neuraxial anesthesia (epidural and spinal blockade) is not an option. In these case an alternative option, that warrants consideration for patient centered anesthesia practice is the use of remifentanil (ultiva). Guidelines for the use of remifentanil in obstetric patients are sparse, poorly developed and are not readily available to anesthesia practitioners.

Pain Associated with Labor

There is no question about the amount and extent of pain associated with child birth. There are some common interventions used to ameliorate pain, including the use of epidural anesthesia. However, there are several reasons that an epidural may be contraindicated during labor including the presence of coagulopathies, anticoagulation therapy, prior back surgery, patient refusal, or the inability to safely place an epidural. In labor patients for whom neuraxial anesthesia is not an option, there are limited alternative choices that have been explored or considered. Once such possibility deserving of consideration is the use of the opioid remifentanil as the primary analgesic for the management of pain associated with labor.

Olufolabi et al identified "that the cyclical pattern of labor pain, as compared with continuous postoperative surgical pain, would benefit from bolus delivery of a short-acting drug that produced its analgesic effect only during contractions and was without significant maternal and fetal side effects." [1] One such drug that should be considered is remifentanil (ultiva).

The Importance of Exploring Remifentanil as an Option for Treating Labor Pain

The use of remifentanil in the parturient as the primary analgesic is significant for several reasons; the most salient of which is the basic human right to the management of pain. Pain, as defined by the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage." [2] Labor is a cause of severe pain for many women and is a problem that should be addressed and managed in accordance with the needs and wishes of the individual patient. Interventions that alleviate or eliminate pain are not merely a matter of beneficence, but also form part of the duty to prevent harm.[3]

The variations in pain perception among women in labor creates an essential component in the administration of anesthesia in the provision of patient-centered anesthesia care. One recent study identifies that the perception of labor pain was equivalent to a digit amputation without anesthesia.[4] Even though variability regarding the intensity of pain exists among women during labor, the majority of women do experience more than minimal pain during this time.[5] Negative psychological effects of pain associated with labor can occur in some women. "Psychological harm can be experienced through the provision or withholding of labor analgesia, underscoring the tremendous variability in the meaning of labor pain for different women." [5] Interventions to alleviate pain in labor have effects on much more than the physical aspects of pain, but also include the emotional and psychological factors.

Epidural analgesia is considered the standard for pain management during labor.[5] Access to pain management is a right that is fundamental and should not be withheld or denied to any patient regardless of age, ethnicity, or socioeconomic status. This right is violated if a parturient is unable to partake in standard methods used for managing the pain of labor. The significance of analgesia during labor is related to the access parturients have to care. "Equity is concerned with maximizing fairness in the distribution of healthcare services… and minimizing disparities in health."[6] By utilizing an intervention such as remifentanil, the alleviation of pain associated with labor encompasses a greater portion of this population.

A patient's perception of their analgesic regimen is also a concern. It is central for a provider to address this intervention that is rooted in reliable evidence. The use of patient-controlled analgesia (PCA) puts the patient in control when dosing of medication occurs and is considered the gold standard for acute pain management.[7] Patient satisfaction with remifentanil as a primary analgesic for labor pain is an important topic within this context. There is evidence that maternal satisfaction is influenced by factors other than age, ethnicity, socioeconomic status, pain, medical interventions, and continuity of care, when women evaluate their childbirth experiences. These overriding factors have been identified as personal expectations, the amount of support

from caregivers, quality of the caregiver-patient relationship, and maternal involvement in decision making. The results of pain, pain relief, and intrapartum medical interventions on the satisfaction of parturients are not as obvious, direct, or powerful as the influences and impact of the attitudes and behaviors of caregivers.[8\]

In order to provide optimal anesthesia care to clients, the body of knowledge on which evidence-based practice is founded must continue to evolve as new information and research comes to light.9 Certified Registered Nurse Anesthetists (CRNAs) have been recognized as influential providers in the area of pain management as the knowledge and skills possessed required to address this issue are essential to the study and understanding of acute and chronic pain.[10] Reviewing the current evidence related to the use of remifentanil as a primary agent for analgesia in parturients enables the CRNA to make a recommendation or construct a set of guidelines that may be used in clinical practice. This recommendation or guideline can provide a basis for knowledge and safety of anesthesia delivery while enhancing the provision of care to parturients.

Reflection Box 1.

> ***"Interventions that alleviate or eliminate pain are not merely a matter of beneficence, but also form part of the duty to prevent harm."*** [3]
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> 1. To what extent do you agree with above statement?
> 2. How has the belief, or lack of, influenced your CRNA practice?
> 3. Identify a situation in which you think this goal was less than optimal. Who was involved? What was done? What would you do differently, if anything, if a similar situation occurred?

Foundational Principles

Pharmacokinetics and pharmacology of remifentanil, is an essential for the CRNA to effectively and safely provide efficient anesthesia interventions. Pain associated with labor is highly personal and varies greatly among individual patients.[5, 10] There are three stages of labor that must be considered when discussing the physiologic basis for pain related to each. The first stage of labor has two phases- latent and active- and is defined as the onset of labor which progresses to the complete dilation of the cervix. The second stage of labor begins when the cervix is fully dilated (10 cm), and ends when delivery of the infant is complete. The third stage occurs with delivery of the placenta.[10] For purposes here, only the first and second stages will be considered.

Pain of Labor

Labor can be defined as progressive dilatation of the cervix in association with repetitive uterine contractions.[11] The pain of labor arises from several sources. These include contraction of the myometrium against the resistance of the cervix and perineum, progressive dilatation of the cervix and lower uterine segment, and stretching and compression of pelvic and perineal structures. Two manifestations of pain have been identified by parturients. They are a non-localized cramping which is referred to surface dermatomes on the abdomen and sharp, and localized back pain that is from referred pain to dermatomes and sclerotomes.[10] Each stage of labor has different origins and pathways.

Pain during the first stage of labor is mostly visceral pain resulting from uterine contractions and cervical dilatation.12 This pain is mediated by T10-L1 sympathetic nerve fibers, and the nerves at this level are responsible for transmitting pain sensation related to cervical dilation.[10] In the first stage of labor, pain is initially confined to the T11–T12 dermatomes during the latent phase, but eventually involves the T10–L1 dermatomes as the labor enters the active phase. Parturients describe this pain as dull in nature and often poorly localized.[11] The visceral afferent fibers responsible for labor pain travel with sympathetic nerve fibers, first to the uterine and cervical plexuses, then through the hypogastric and aortic plexuses before entering the spinal cord with the T10–L1 nerve roots.[12]

The second stage of labor is entered as cervical dilation becomes complete and fetal descent begins. During this stage, pain is transmitted by the same afferent nerves activated during the first stage of labor (T10-L1) with the addition of nerves at the S1-S4 levels. These nerves of the sacral plexus innervate the cervix, vagina, and perineum.[5, 10] Compression and stretching of muscles and ligaments in the pelvic region produce pain that is mediated by the sacral plexus.[10] This stretching and compression of perineal structures may intensify pain.[12]

Pharmacology of Remifentanil

In addition to an understanding the physiology of pain in labor, the pharmacology of the drug in question- remifentanil- must also be considered. Remifentanil is a selective mu (μ) agonist similar in potency to fentanyl. Its ester linkage makes remifentanil structurally unique and renders the drug susceptible to hydrolysis by nonspecific plasma and tissue esterases to metabolites that are inactive. The onset and duration of action for remifentanil are very short making it rapidly titratable. Effect-site (blood/brain) equilibration time is 1.1 minutes and elimination half-time is 6 minutes. An estimated 99.8% of remifentanil is eliminated during the distribution (0.9 minute) and elimination (6 minutes) half-time.[12] This short duration of action and minimal accumulation with repeated doses or infusion, make remifentanil particularly well suited for procedures that are briefly painful but for which little postoperative analgesia is required.[14]

The pharmacokinetics of remifentanil are characterized by a small volume of distribution (30 liters), rapid clearance, and low interindividual variability as compared to other drugs. Rapid effect-site equilibration equates to a quickly achieved steady state plasma and effect-site concentration. Additionally, the plasma concentration is nearly independent of infusion duration due to the short context-sensitive half-time. Changes in infusion rates of remifentanil are paralleled by prompt changes in drug effect. These attributes make the pharmacokinetics similar in obese and lean patients. Due to the low interindividual variability, it is recommended that clinical dosing regimens be based upon ideal body mass and not total body weight.[13]

Metabolism by nonspecific plasma and tissue esterases to inactive metabolites make remifentanil unique. The principal metabolite is remifentanil acid which is 300-4,600 times less potent than the parent drug. Excretion is primarily via renal pathways and it is unlikely that the pharmacokinetics are changed in the presence of renal or hepatic failure as esterase metabolism is usually preserved in these states.[13] Esterase metabolism has little variability between individuals and contributes greatly to the predictability of drug effect. Minimal changes are related to extremes of age, renal dysfunction, or hepatic dysfunction enabling easy titration and rapid dissipation, even after prolonged infusion.[15]

Adverse effects resulting from the administration of remifentanil are similar to those of any other potent opioids.[16] These include, but are not limited to lightheadedness, dyspnea, blurred vision, chest pain, muscle stiffness or

tightness. With remifentanil use, profound analgesia may be achieved with minimal effect on cognitive function, and low doses of remifentanil can be used to maintain anesthesia in spontaneously breathing patients.[15, 17]

Remifentanil is licensed for induction and maintenance of general anesthesia; however, it is currently an 'off-label' use in obstetrics.[17] Even though remifentanil is not licensed for use in obstetric patients, administration of drugs outside their product license is a common occurrence in obstetric anesthesia.[18]

Conditions in Which Standard Neuraxial Anesthesia Is a Non-option

Several factors must be considered when discussing the use of neuraxial anesthesia for labor analgesia. These include generally recognized absolute and relative contraindications for neuraxial anesthesia such as bleeding or clotting disorders (coagulopathies), severe hypovolemia, elevated intracranial pressure, valvular heart disease, infection at injection site, or patient refusal.[10] Additional factors include anticoagulation therapy, prior back surgery, or the inability to perform a neuraxial anesthetic. This discussion is not intended to be all-inclusive, but rather to highlight several clinically relevant factors regarding the subject of neuraxial anesthesia being a non-option for some parturients.

The existence of coagulopathies in a patient may be pre-existing or therapeutic in nature. Frank coagulopathies represent an absolute contraindication to the administration of neuraxial anesthesia. Concern with performing neuraxial anesthesia in parturients with coagulopathy is due to an increased risk of epidural hematoma formation.[5] The incidence of occurrence is rare but the resultant neurological damage may be permanent.[10]

Thrombocytopenia is an intrinsic coagulopathy that is defined as a platelet count of less than 100,000/mm^3. The use of neuraxial anesthesia is generally not recommended for parturients with platelet counts below 100,000/mm^3 however, some practitioners may have a lower cutoff.[10] One disorder involving thrombocytopenia that may be encountered in the parturient is autoimmune thrombocytopenic purpura (ATP). In ATP, antibodies directed against platelet antigens are produced primarily in the spleen, where phagocytosis by macrophages occurs.[5] This destruction of platelets leads to decreased platelet counts and an increased risk for bleeding. The anesthesia provider should consider clinical evidence of bleeding, recent platelet count, a recent change in platelet count, quality of platelets, adequacy of other coagulation factors, and the risks versus the benefits of performing neuraxial anesthesia. It is important to note "clinical judgment represents the most important means of assessing the risk for epidural hematoma in an individual patient." [5]

It is important to consider the impact of anticoagulation therapy in the parturient as this poses a contraction to traditional neuraxial anesthesia. The use of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) may be encountered in the parturient being treated for coagulopathic states such as thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). The American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines are specific regarding neuraxial anesthesia in the presence of anticoagulant use.[18] For the parturient receiving IV heparin, there should be at least a one-hour delay between needle placement and heparin administration.[19] The safety of neuraxial blockade in patients receiving doses greater than 10,000 units of UFH daily, or more than twice daily dosing of UFH, has not been established. Protamine reversal of heparin therapy to allow administration of neuraxial anesthesia is not recommended.[5] For parturients who are receiving treatment with the LMWH enoxaparin, neuraxial anesthesia should be performed at least 12 hours after the last prophylactic dose or 24 hours after higher doses (1 mg/kg every 12 hours).[19] Parturients receiving anticoagulation therapy may be excluded from the benefits of neuraxial anesthesia.

Skeletal deformities such as scoliosis, arthritis, osteoporosis, and fusion or scarring of the vertebrae are relative contraindications to neuraxial anesthesia. Needle placement may be difficult and the spread of medications in the epidural space may be limited by these anatomic alterations.[10] Guidelines for epidural anesthesia after spinal surgery are not clearly defined.[20] Posterior approach surgical techniques often obliterate or distort the epidural space from fibrous scar tissue formation, blood clot organization, or metalwork crossing the midline.[20] Combined with the fact that anatomical landmarks for neuraxial anesthesia may be difficult to assess, regardless of the parturients history of corrective surgery, this approach to pain management is one that requires careful scrutiny. The disadvantages of neuraxial anesthesia include technical difficulties in identifying the epidural space, patchy or poor analgesia, unintentional subdural or intrathecal catheter placement, and postdural puncture headache.[21] Both parturients and anesthesia providers may be willing to attempt neuraxial anesthesia in these situations, however, the risks versus the benefit must be understood and accepted by all parties.

Parturients with severe, uncorrected hypovolemia are considered to have relative contraindication to neuraxial anesthesia.[10] Severe hypovolemia can precipitate a vagal response that results in profound bradycardia, or possibly transient cardiac arrest patients who are healthy. Bradycardia is mediated by left ventricular mechanoreceptors which are activated by a decrease in venous return and the resulting reduction of end-systolic volume.[22] It is recommended that epidural blockade be used with great care or even avoided in patients with hypovolemia in whom venous return is impaired.[22]

The use of neuraxial techniques always presents a risk of dural puncture with an epidural needle. Puncture of the dura may create a hole in the dural tissue and subsequent cerebrospinal fluid leak. Patients with elevated intracranial pressure have an increased risk for brain herniation. Epidural catheter placement and addition of large volumes of local anesthetic may cause an increase in already elevated intracranial pressures.[10]

The presence of valvular heart disease, such as idiopathic hypertrophic subaortic stenosis (IHSS) or other fixed-volume cardiac states, are a relative contraindication to neuraxial anesthesia when considered clinically mild to moderate in severity. Neuraxial techniques are contraindicated in patients with severe cardiac disease.[12] Physiologic changes such as bradycardia, decreased systemic vascular resistance, and decreased venous return are all changes that can be encountered with neuraxial anesthesia. These physiologic changes are not tolerated and may cause hypotension that results in severe coronary hypoperfusion and cardiac arrest.[10, 12] Each patient requires evaluation, and the risks versus the benefit must be understood and accepted by all parties if the implementation of a neuraxial technique is considered.

Infection at the site of needle placement for neuraxial anesthesia is a concern due to the risk of disrupting the body's physiologic protection mechanisms. The epidural needle may deposit infectious or noxious agents beyond the skin into the underlying tissue, peridural space, and past the blood-brain barrier into the subarachnoid space.[10] The use of neuraxial anesthesia in the presence of sepsis or bacteremia may dispose a parturient to the spread of the infectious agents into the epidural or subarachnoid space and increase the risk for meningitis or the formation of an epidural abscess.[10, 12] These risks make neuraxial anesthesia an absolute contraindication in the presence of infection at the needle site.

The most compelling contradiction for not using neuraxial anesthesia is patient refusal. Parturients may have concerns related to neuraxial anesthesia

including potential for short or long-term complications, fear of pain with implementation, fear of numbness or altered sensation, lack of control over the anesthetic, or the inability to obtain adequate anesthesia. Proper preparation, education, and collaboration are keys to successful interaction with patients.[10] In cases where a parturient declines the use of neuraxial anesthesia techniques, the provider must be prepared to offer an alternative for managing the pain associated with labor. Alternatives provide access to pain management, and uphold the fundamental right that pain management should not be withheld or denied to any patient.[3]

Reflection Box 3. Neuraxial anesthesia techniques vs. alternative anesthesia methods

1. Consider cases in which you used Neuraxial anesthesia techniques.
2. Have there been cases in which would have considered alternatives to neuraxial anesthesia?
3. What were the factors that prompted a desire for an alternative technique?

Remifentanil in Clinical Practice

The literature that compiled and reviewed in the most current studies (meta-analysis, systematic review, reviews of literature, and focused review) revealed that the use of remifentanil as a primary analgesic for the management of labor pain is an accepted practice. When implemented appropriately (regardless of methodology), it is more effective than IV meperidine but less effective than an epidural.[23-26] A 2010 Cochrane Review investigated different parenteral opioids for maternal pain relief during labor and concluded that there is insufficient evidence to identify the best opioid for pain relief.[27] (Insert Table 1 here)

An Overview of Remifentanil (Ultiva)

Classification and Metabolism	Intravenous opioid with rapid onset and brief duration. Regulated as a schedule II substance	The brief duration results from rapid metabolism by plasma and tissue esterases, and not from hepatic metabolism or renal excretion.
Potency	100 times more potent than morphine.	Fentanyl is also 100 times more potent than morphine.
Administration and Duration	Administered via continuous intravenous infusion	Effects begin in minutes and end 5 to 10 minutes once stopped.
Common Dose	*For Surgical Anesthesia*: 0.05 to 2 mcg/kg/min (Current evidence varies)	*For Post-Operative Anesthesia*: 0.025 to 0.2 mcg/kg/min (Current evidence varies)
Adverse Effects	*During Infusion*: respiratory depression, hypotension, bradycardia, and muscle rigidity sufficient to compromise breathing	*Post infusion*: nausea (44%), vomiting (22%), and headache (18%).

Adapted From: Lehner RA. (2013) Pharmacology for nursing care (8th Ed.). Elsevier: St. Louis

In a 2012 meta-analysis by Schnabel et al evaluating the efficacy of remifentanil PCA compared with other techniques for labor analgesia, 12 randomized controlled trials with a total of 593 participants, 269 of which received remifentanil, were included. Of the 12 trials in the meta-analysis, healthy term parturients (ASA classification I and II) without a history of opioid use, drug abuse, allergy to remifentanil or abnormal hepatic or renal function were included. Four different active comparators were investigated– meperidine, fentanyl, nitrous oxide, and epidural analgesia. Due to limited data, the authors were only able to pool data for the comparison between remifentanil and either meperidine or epidural analgesia.[23]

Eight trials compared remifentanil with meperidine in this meta-analysis; 208 parturients received a remifentanil PCA and 209 received meperidine either via PCA, as a continuous infusion, or as an intramuscular injection. In all 8 of the trials, patients receiving remifentanil had a lower mean pain score after 1 hour compared with patients receiving meperidine (mean difference -2.17cm, 95% CI -2.7 to -1.64, P<0.001). Five trials found that women had significantly higher satisfaction scores if they received remifentanil but because all trials used different scores for maternal satisfaction, these results could not be pooled and were reported only qualitatively.[23]

Three trials investigated the efficacy of a remifentanil PCA in comparison with an epidural; 51 parturients received remifentanil and 51 received an epidural. In all of the included trials, women in the remifentanil group had a higher mean pain relief score after 1 hour compared to the epidural group (mean difference 1.89cm, 95% CI 0.63 to 3.15, P=0.003). Satisfaction scores with the analgesic regimens were comparable.[23]

The conclusions supported in this meta-analysis indicated that remifentanil provided better analgesia than intravenous or intramuscular meperidine and that epidural analgesia provided better pain relief than remifentanil during labor. It was recommended that large, randomized controlled trials with a focus on safety and patient satisfaction using consistent administration methods be conducted.[23] In this meta-analysis the authors failed to find sufficient evidence for dosing regimens and no clinical recommendations regarding dosing or implementation were presented.

A 2011 systematic review by Leong et al comparing remifentanil and meperidine for labor analgesia included 7 studies with a total of 349 patients; however, only 3 studies were suitable for quantitative synthesis in a meta-analysis (233 total patients). The review was performed using a previously specified protocol outlining the aim, search strategy, eligibility criteria, data extraction strategy, and statistical analysis methods to be used. The authors assessed for adequacy of sequence generation, allocation sequence concealment, blinding, and the completeness of follow-up. For studies that were judged to be at higher risk of bias, a sensitivity analysis was performed to assess whether the inclusion of these studies significantly biased the result. The primary outcome was pain scores assessed using the 0-100mm Visual Analog Scale (VAS).[24]

All seven studies measured the pain scores using the 0-100mm VAS scale; however, only three studies were included in the meta-analysis. Three studies were excluded because the VAS data were presented graphically and a fourth study was excluded because pain scores were presented using median and interquartile ranges. The authors noted that all four excluded studies found a significant reduction in VAS scores with remifentanil compared with meperidine (P<0.05, which establishes statistical significance). The results of the three studies that reported using the means and standard deviations of VAS scores were quantitatively combined and it was shown that there was a reduction of mean VAS score at 1 hour of 25mm for remifentanil compared with meperidine

(P<0.001, 95% CI 19 to 31mm). When all seven studies were included in the meta-analysis, remifentanil reduced the mean VAS scores at 1 hour by 25mm compared with meperidine (95% CI 20 to 29mm). Compared with the sensitivity analysis of all 7 studies, the summary estimate of the 3-study analysis was unchanged, although the precision was reduced, as reflected by a wider confidence interval.[24]

These showed that remifentanil reduced the mean VAS score more than meperidine. It is important to note that there is substantial clinical heterogeneity demonstrated in these studies with the drug regimens varying greatly.[24] Even though this systematic review included all studies involving laboring parturients, most studies excluded high-risk patients with obstetric complications, multiple gestation, and preterm labor. As a result, it is difficult to generalize the results to these populations. In order to better quantify the side-effect profile and determine optimal dose regimens, large, well-conducted, randomized controlled trials that compare remifentanil with meperidine or other labor analgesics are recommended. The authors concluded that the optimal drug-delivery doses and regimens remain to be determined.[24] No recommendations regarding dosing or implementation were provided.

In a 2008 review by Hill, the use of remifentanil as an alternative to neuraxial anesthesia for labor is explored due to "A growing number of women [who] either do not want or cannot have an epidural for labor." [18] A total of eight case reports and studies were included in this review. Evaluation of individual studies and statistical methods for comparing results are not included in this review.

Primary findings in this review related to the specific topic of interest indicate that remifentanil has been shown to provide effective analgesia, especially during the first stage of labor. The author states that remifentanil is currently the most suitable systemic opioid for obstetric use and even though it has a rapid onset and offset, the timing cannot be matched to that of a single uterine contraction. Recommendations regarding dosing assert that the appropriate PCA dosing regimen is a 40mcg remifentanil bolus with a 2-minute lockout period. In the author's institution, remifentanil PCA is offered for routine use as a labor analgesic with dosing as stated above. It is further recommended that parturients receiving PCA remifentanil should have one-to-one nursing care, availability of oxygen saturation monitoring, and oxygen supplementation if required.[18]

Van De Velde (2005) concluded that "…the analgesic efficiency of remifentanil for labor pain has been demonstrated and that it seems superior to other parenteral opioid alternatives." Van De Velde also states, "We cannot at the moment recommend remifentanil for routine use in labor analgesia. However, with careful monitoring and skilled personnel present at all times in the labor and delivery ward, remifentanil is an option to treat certain patients in which more conventional options are contraindicated, as has been demonstrated by several other recent case reports." The recommendation indicates that a bolus between 0.2 and 0.5mcg/kg with a lockout period of 2 to 3 minutes and no background infusion seems to be a reasonable option.[25] Additional trials are recommended to establish maternal and neonatal safety of remifentanil use in this population.

A focused review of nine studies, which sought to summarize the efficacy of remifentanil as a labor analgesic, was compiled and published in 2009 by Hinova and Fernando. They concluded that the analgesic effects and suitability of remifentanil for first-stage labor is well supported. It was noted that the timing of dosing could not currently be matched to the cyclic nature of labor pain. The analysis of the studies included demonstrated that remifentanil produces clinically effective, but not complete, analgesia, with conversion rates to neuraxial analgesia <10%.[26]

The investigators recommend an appropriate PCA dose regimen is a 40mcg remifentanil bolus with a 2-minute lockout. They strongly suggest that clinical guidelines be in place to ensure routine oxygen saturation monitoring, treatment of maternal desaturation with oxygen supplementation if needed, and one-to-one care using trained personnel.[26] Statistical evaluation of the individual studies and the methods used for comparing results are not included in this review. The authors state that more work is needed to establish the optimal drug administration regimen for remifentanil use in this population.

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Remifentanil Compared to other Parenteral Opioids

Three randomized controlled trials (RCTs) evaluated the efficacy of remifentanil compared to other narcotics administered parenterally for labor analgesia. In all three trials, remifentanil was compared to meperidine.[28-30] In addition to a comparison of remifentanil and meperidine, one trial also compared the efficacy of remifentanil and fentanyl.[29] Remifentanil was a more effective overall in all three studies.

A 2005 double-blind RCT was conducted by Blair et al with the purpose of comparing the analgesic efficacy and safety of remifentanil with meperidine when both were administered using a PCA device. Forty parturients were randomly selected to receive either remifentanil 40mcg with a lockout of 2 minutes or meperidine 15mg with a lockout of 10 minutes. An averaged dose (40mcg) rather than a calculated weight-based dose of remifentanil was chosen.

VAS scores for pain during the study and for overall pain were similar for both groups with a mean score of 6.4cm ± 1.5cm for remifentanil and 6.9 ±1.7cm for meperidine. Overall satisfaction with analgesia in labor was higher for remifentanil and more women chose to continue using remifentanil up to and during delivery than chose to continue with meperidine.[28] No recommendations were made by the authors regarding dosing or implementation in clinical practice.

A randomized, double-blind study by Douma et al was conducted to compare the analgesic efficacy of remifentanil to meperidine and fentanyl via PCA delivery. One hundred and eighty parturients enrolled, of which 159 completed the study. Fifty-two received remifentanil, 53 received meperidine, and 54 received fentanyl. The characteristics of the parturients did not differ statistically. Women allocated to the remifentanil group received a 40mcg loading dose, 40mcg boluses with a lockout of 2 minutes, and a maximum dose limit of 1200mcg/hr. Those in the meperidine group received a 49.5mg loading dose, 5mg boluses with a 10-minute lockout, and maximum overall dose limit of 200mg. Those in the fentanyl group received a 50mcg loading dose, boluses of 20mcg with a 5-minute lockout, and a maximum dose limit of 240mcg/hr. A P-value of <0.05 was considered statistically significant.[29]

There was no difference in baseline pain scores between the groups and in all groups, pain scores decreased significantly from baseline 1 hour after the start of treatment. Intergroup comparison showed that the decrease in pain scores after 1 hour was greater in the remifentanil group compared with the fentanyl and meperidine groups. After hours 2 and 3, the decrease in pain scores did not differ significantly between the three groups. In all groups, pain scores returned to pre-treatment values within 3 hours after the initiation of treatment.[29]

The efficacy of meperidine, fentanyl, and remifentanil PCA for labor analgesia varied from mild to moderate in this study. Remifentanil PCA provided better analgesia than meperidine and fentanyl PCA during the first hour of treatment. The authors recommend the use of remifentanil only in the last phase of cervical dilation and with continuous monitoring. Further studies were recommended to determine the safety of remifentanil especially with relation to its respiratory effects.[29]

Another double-blind RCT evaluated was conducted by Evron et al in 2005. Eighty-eight healthy term parturients were enrolled in the study and were randomly assigned to receive either increasing doses of PCA remifentanil or an IV infusion of meperidine. For the 43 parturients randomized to receive remifentanil, each received a bolus of 20mcg as a starting dose, regardless of weight, with a 3-minute lockout interval. The dose was increased every 15 to 20 minutes by 5mcg increments, on patient request, to a maximum dose limit of 1500mcg/hr. The 45 parturients who were randomized to the meperidine group received 75mg of meperidine in 100mL of normal saline over 30 minutes and in case of insufficient analgesia, another dose of 75mg, followed by 50mg when necessary, was administered, to a maximum dose of 200mg of meperidine. [30]

The authors concluded that PCA remifentanil use during labor and delivery was associated with improved VAS scores, higher patient satisfaction, and less need to cross over to epidural analgesia compared to IV meperidine. The use of remifentanil appeared to provide better analgesia than meperidine throughout labor and delivery and has minimal maternal or neonatal side effects. It was further stated that the findings in this study may justify the use of remifentanil as a systemic opioid in labor and delivery whenever there is a contraindication to neuraxial analgesia however, a large study is still necessary to investigate the maternal and fetal side effects. Continuous monitoring of the oxygen saturation of the parturient is recommended to decrease the likelihood of maternal and neonatal hypoxemia.[30]

Although more and larger studies are justified, the evidence that currently exists supports the use of remifentanil. The efficacy of using remifentanil in managing parturient pain is clear, and should be considered as a mainstream medication of choice. Maternal and neonatal hypoxia are a risk for the use of any opioid analgesia.

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Remifentanil Compare to Neuraxial Anesthesia

The discussion thus far has identified contraindications neuraxial anesthesia, and a comparative analysis of medications used in parturient pain. The efficacy of remifentanil is clearly supported. Now the focus is toward looking at the evidence that compares the use of remifentanil to neuraxial anesthesia.

There are three salient studies that looked at the use of remifentanil compared to neuraxial techniques, specifically epidural analgesia, which is considered the gold standard for management of labor pain.[5] In all three studies, neuraxial techniques were superior to remifentanil for the management of labor pain.

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Tveit et al conducted an RCT the stated objective of which was to compare the analgesic efficacy and side effects of remifentanil PCA with epidural analgesia during labor. Thirty-nine parturients were randomized to receive either remifentanil PCA or epidural anesthesia. The epidural contained ropivacaine 1mg/ml and fentanyl 2mcg/ml; an initial bolus dose of 10ml, followed by a 5ml top-up after 5 minutes (total 15ml) was given before the start of infusion at 10ml/hr. Thereafter, the midwife was allowed to adjust the infusion dose (5-15ml/hr) and give rescue doses of 5ml if needed. Starting bolus of remifentanil was 0.15mcg/kg, increases of 0.15mcg/kg were allowed every 15 minutes with no maximum limit. The PCA lockout time was 2 minutes, bolus infusion speed 2ml/min (100mcg min) and no background infusion. Due to a technical problem with the infusion pumps after inclusion of 39 patients, the study was closed early, leaving the number of participants close to the estimation from the power calculation.[31]

The mean baseline VAS pain scores were somewhat higher in the remifentanil group at 82mm ±13.3 vs 70mm ±16.2 for the epidural group, but the pain scores were reduced in both groups during the first hour of analgesia with the remifentanil group VAS of 38mm ±17.3 and the epidural group VAS 23mm ±30.2 (P=0.066). Overall, there were no significant differences in pain reduction between parturients receiving remifentanil and epidural at the time points registered between 15-240 minutes. After 2 hours, pain scores in the remifentanil group tended to return towards baseline, thus remifentanil seemed to produce less analgesia than epidural anesthesia in this phase of labor. The authors note that at the end of first and second stage, pain reduction was comparable between the groups, as was the maximal reduction in average pain score. The mean dose of ropivacaine was 33mg (range 5-84mg) and fentanyl dose of 67mcg (range 10-168mcg). Five patients received an extra bolus dose of 5ml (rescue medication) because of unsatisfactory analgesia. A remifentanil mean dose of 0.40mcg/kg (range 0.15-0.60mcg) was reached after 1 hour. Maximum bolus dose during the study period was 0.70mcg/kg (range 0.30-1.05mcg). The mean doses at end of first and second stage were 0.65 and 0.38mcg/kg (ranges 0.3-1.05mcg and 0.15-0.9mcg), respectively.[31]

The authors concluded that both treatments provided good analgesia, but that there were higher pain scores in the remifentanil group. Pain reduction at the end of first and during second stage and maximum pain reduction were similar. Based upon current knowledge, the authors recommend the maximum remifentanil dose should not exceed 0.7mcg/kg and that remifentanil PCA be used as a stepwise bolus dose regimen, with dose steps of 0.15mcg/kg and a 2-minute lockout time. Large-scale, randomized controlled trials are recommended to assess dosing regimens, analgesic efficacy, and side-effects.[31]

A 2011 study by Ismail and Hassanin sought to determine the difference in duration of labor, the mode of delivery, average VAS pain scores, maternal overall satisfaction with analgesia, side effects and neonatal outcomes in nulliparous women who received early labor analgesia with either epidural, PCA with remifentanil or combined spinal-epidural (CSE) techniques. The study included 1,140 healthy parturients who were randomized to receive either epidural analgesia (380), PCA remifentanil (380), or CSE analgesia (380). It is important to note that the primary outcome measured was the rate of cesarean delivery. In the epidural group, an 8ml dose of 0.125 % levobupivacaine with 2mcg/ml

fentanyl was administered through the epidural catheter and a continuous infusion of 8ml/hr of 0.125 % levobupivacaine and 2mcg/ml fentanyl was initiated. Further boluses of 5-10ml of 0.125 % levobupivacaine were given upon request. In the CSE group, a needle-through-needle technique was performed with 2mg levobupivacaine and 15mcg fentanyl (total volume of 2mL) injected intrathecally with the epidural catheter inserted and connected to the same continuous infusion used in the epidural group. In the remifentanil group, the PCA device was set to deliver 0.1mcg/kg of remifentanil diluted with saline and given as a solution of 25mcg/mL as a bolus infused during a period of 1 minute, with a lockout time of 1 minute. During the study, the PCA bolus was increased following a dose escalation scheme (0.1–0.2–0.3–0.5–0.7–0.9mcg/kg) after every second contraction until the parturient answered 'no' to the question whether she would like to get more efficient pain relief or until a maximum dose of 0.9mcg/kg was achieved. [32]

No statistically significant differences were observed among the three groups with regard to average VAS score at analgesia request (epidural group 64.5mm ±12.84, remifentanil group 66.4mm ±11.50, CSE group 65.8mm ±12.10, P=0.089). CSE group showed a score of 22.56mm ±7.57 versus 34.3mm ±9.8 for remifentanil and 35.6mm ±10.2 for epidural (P=0.000). The authors concluded in terms of labor duration, average VAS pain scores, and maternal overall satisfaction score with analgesia, CSE analgesia is superior to that provided by epidural analgesia or PCA with remifentanil for pain relief. There were no differences in the mode of delivery, side effects or neonatal outcomes between the three techniques.[32] Other than the method used within the study, no further recommendations regarding remifentanil PCA dosing or implementation were provided.

A randomized clinical trial that compared remifentanil and neuraxial techniques was published by Stocki et al in 2014.[33] The primary objective was to demonstrate noninferiority of remifentanil labor analgesia compared with epidural analgesia in laboring women. Thirty-nine parturients participated with random allocation of 19 in the remifentanil group and 20 in the epidural group. Remifentanil was given as a bolus dose and titrated to effect from 20mcg up to a maximum of 60mcg as required with an initial lockout interval of 2 minutes and no background infusion. The PCA bolus/lockout interval was titrated to an end point of either patient comfort, or a maximal bolus dose of 60mcg/minimal lockout interval of 1 minute. For the epidural group an incremental initial loading dose of 15ml of 0.1% bupivacaine with 50mcg fentanyl was administered followed by patient-controlled epidural analgesia infusion of 0.1% bupivacaine with fentanyl 2mcg/ml. A basal infusion of 5ml/hr, with patient-controlled bolus of 10ml and 20-minute lockout was initiated. Additional epidural bolus doses (either 0.1% bupivacaine 10ml during the first stage of labor or 1% lidocaine 8ml during the second stage of labor) were administered to treat breakthrough pain. [33]

In this study, maternal pain was assessed using an 11-point verbal numerical rating scale (NRS) of 0 to 10, where 0 = no pain and 10 = the worst pain imaginable. There was no significant difference found between baseline NRS pain scores in the two groups. Both remifentanil and epidural analgesia resulted in a significant decrease from baseline NRS scores over time. It was observed that scores were significantly lower at 30 minutes in both groups with change for remifentanil of -4.7 ±0.6 and -7.2 ±0.6 for epidural (P<0.0001). Although both are effective at reducing NRS pain scores, remifentanil is inferior to epidural with regard to the magnitude of the pain score reduction at all time points. Pain scores were higher at all time points than an expected -1.5-unit difference in NRS scores. The authors state, "…a 'safe' dose or duration of administration of remifentanil cannot be recommended based on the results presented in this study." They concluded that remifentanil administration for labor requires appropriate monitoring to detect and alert for maternal apnea and although remifentanil analgesia is inferior to epidural analgesia, it may provide a satisfactory alternative when epidural analgesia is not desired or permitted. It is further stated that future studies should consider remifentanil use in the obstetric population with particular focus on respiratory monitoring and manpower requirements for implementation.[33]

In the randomized clinical trial, it was found that although remifentanil analgesia is inferior to epidural analgesia, it may provide a satisfactory alternative when epidural analgesia is not desired or permitted.

Methods of Delivery an Important Consideration

Three trials specifically address the delivery of remifentanil when used as the primary analgesic for the management of labor pain. The methods investigated are PCA with a background infusion, PCA without a background infusion, and a continuous remifentanil infusion without any patient control.

Balki et al conducted a prospective RCT in 2007 to compare the efficacy of two regimens of remifentanil PCA implemented for labor analgesia in order to determine an optimal dosing regimen.[34] Twenty parturients were randomized into two groups. Remifentanil was administered as a 50mcg/ml solution with all patients initially receiving a standard regimen of an infusion of 0.025mcg/kg/min and a PCA bolus of 0.25mcg/kg with a 2-minute lockout and four-hour limit of 3mg. As labor progressed and the patients required additional analgesia, they received higher doses of either the infusion or the PCA boluses depending upon the group to which they had been randomly assigned.

In the variable infusion, fixed bolus group, the infusion rate was increased stepwise from 0.025mcg/kg/min to 0.05mcg/kg/min, 0.075mcg/kg/min, and 0.1mcg/kg/min, while the bolus of 0.25mcg/kg remained unchanged. In the variable bolus, fixed infusion group, the bolus dose was increased stepwise from 0.25mcg/kg to 0.5mcg/kg, 0.75mcg/kg, and 1mcg/kg, while the infusion rate of 0.025mcg/kg/min was kept constant. Each step was maintained for at least 15 minutes before progressing to the subsequent one.

Mean pain and patient satisfaction scores, and cumulative doses of remifentanil were similar in the two groups. The overall difference in pain scores between the groups were not statistically significant. The variable infusion, fixed bolus group had a mean pain score of 6.09 ±0.49 and the variable bolus, fixed infusion group had a score of 5.51 ±0.46 (P=0.40) According to the authors, this pilot study suggests that remifentanil PCA is efficacious for labor analgesia. They recommend delivery of remifentanil as a bolus of 0.25mcg/kg with a 2-minute lockout and continuous background infusion of 0.025–0.1mcg/kg/min. Close monitoring of respiratory status and vitals was mandated and further trials were recommended.[34]

A 2013 prospective, randomized, double blinded RCT conducted by Shen et al aimed to compare the effects of remifentanil for labor analgesia given by either PCA or continuous infusion. Sixty parturients were randomized to be in either the PCA group, to whom remifentanil was administered using increasing stepwise boluses from 0.1-0.4mcg/kg in 0.1mcg/kg increments with a 2-minute lockout, or in the continuous infusion group, which used rates from 0.05-0.2mcg/kg/min with incremental increases of 0.05mcg/kg/min given on request.

The demographic variables, patient characteristics, remifentanil concentrations, and umbilical cord blood gases analysis were compared. The

maternal and neonatal adverse reactions and FHR tracings were analyzed.[35] The two groups were similar regarding patient characteristics. Pain scores were significantly lower at 30, 60, and 90 minutes in the PCA group and the pain relief scores were significantly higher at 60, 90, 120 minutes compared with those in the infusion group. Women reported lowest pain scores of 3 (range 2-5) for PCA and 4 (range 3-7) for continuous infusion at 60 min after the beginning of analgesia. The total remifentanil consumption during PCA administration was lower than continuous infusion with PCA group consumption of 1.34mg (range 0.89-1.69) vs 1.49mg (range 1.12-1.70) for the continuous infusion group (P=0.011). According to the authors, the results suggest that remifentanil administered with an incremental PCA bolus is a preferable alternative to continuous infusion as it provides better pain relief, but with similar maternal side effects and placental transfer. They further state that continuous monitoring of SpO2 and oxygen supplementation during intravenous remifentanil analgesia is essential.[35]

A randomized study by Balcioglu et al conducted in 2007 sought to assess and compare the efficiency and safety of the PCA use of remifentanil combined with two different supplementary background infusions. Sixty subjects were divided into two groups. Both groups received the same fixed loading and demand remifentanil doses of 20mcg and 15mcg respectively with a 5-minute lockout between bolus doses. One group then received a background infusion of 0.1mcg/kg/min and the other a background infusion of at 0.15mcg/kg/min. Meperidine was available in addition to the remifentanil if pain was not controlled. All the data were collected by the same anesthesiologist and expressed as mean ± SD, or median (range). The differences in hemodynamic parameters, VAS pain scores and sedation scores were statistically compared. [36]

Demographic data and labor characteristics of the two groups were statistically comparable and mean VAS values of the groups were similar at baseline. After PCA administration of remifentanil, the mean pain score significantly decreased at the 5-minute measurement and remained at low levels (VAS < 2) in both groups (P< 0.05). The mean pain score of the group receiving the 0.15mcg/kg/min infusion was significantly lower than that of the group receiving 0.1mcg/kg/min throughout labor and delivery (P< 0.05). No additional drug was needed for pain relief. There were no differences between the total remifentanil consumption levels of the groups with 2.4mg ±0.7 for the 0.1mcg/kg/min group vs 2.6mg ±0.4 for the 0.15mcg/kg/min group. Parturients in the group with the lower background infusion asked for more bolus than the other group. The authors concluded that for effective analgesia, PCA of remifentanil with a 15mcg demand dose and 0.15mcg/kg/min background infusion is a better choice than a 0.10mcg/kg/min infusion. They recommend that implementation occur with careful maternal and fetal monitoring.[36]

Dosing and Timing

Two studies address the subjects of the dosing and timing of remifentanil for labor analgesia. Neither study produced any particular significant recommendations related to either the timing or dosing regimen and are therefore only briefly addressed and not fully detailed.

One study addressing this topic was a prospective, randomized, single blind, crossover conducted by Jost et al to investigate differences in the analgesic efficiency, safety, and drug consumption between a modified bolus delivery regimen the authors developed and a 'classical' regimen. Both regimens included continuous background infusion with the rate of around 0.010mcg/kg/min and PCA boluses upon request. The classical regimen was 20mcg bolus increased upon the request of a parturient up to 30mcg after 20 minutes, 35mcg after 1 hour, and 45mcg after 2 hours, and 55mcg after 3 hours with a bolus infusion rate of 1.2mcg/sec. The modified regimen was based upon the length of time the patient depressed the delivery button on the PCA. The regimen had a starting bolus infusion rate of 3mcg/sec with a stepwise decrease of 20% of the initial rate every 6 seconds and terminating bolus delivery by either releasing the PCA button or reaching the maximum bolus dose of 60mcg.[37]

No serious side effects or complications were observed in the study. There were no differences in observed parameters except for slightly lower blood pressure with the modified regimen. Pain estimates were lower in women starting with the modified regimen with average estimated VAS scores of 54mm for the classical regimen and 45mm for the modified regimen (P=0.005). There were fewer requests for analgesia within the lockout period (31 vs 69, P=0.041) and fewer bolus adjustments (0 vs 25, P< 0.001) with the modified regimen. The authors note several limitations within this study and state they believe that the benefits of the modified regimen outlined herein were not fully demonstrated in this study.[37] No practical dosing or timing information was presented.

Another study focused on the dosing and timing of remifentanil for labor analgesia and was conducted by Volmanen et al in 2011. In this study, it was hypothesized that timing of the bolus in the contraction cycle could have importance and administering a remifentanil bolus during contraction pause would improve analgesia in early labor. Fifty parturients participated in this double-blind crossover study. Remifentanil dose of 0.4mcg/kg with a 1 minute infusion time was used during two study periods lasting 6-8 contractions. Remifentanil and saline syringes were attached to two PCA devices, one of which administered the bolus immediately after a trigger and the other targeted to start 140 seconds before the next contraction. Group 1 (n=25) received a bolus immediately after the PCA signal during the first period and after a delay during the latter period, while Group 2 (n=25) received the dosing regimens in reverse order. A lockout period of 1 minute was used.[38]

Statistical analysis showed that there was no difference in the duration of the study periods or the average contraction interval between the two dosing regimens. When the study periods were separately analyzed by comparing the groups as in parallel studies, there was no difference in the pain scores or the variables related to the analgesic effect. When the two groups were analyzed together, the mean of the pain scores during contractions was 3.3 during the first study period and 5.3 during the second (P<0.001). Remifentanil consumed during the first period was 0.067mcg/kg/min and 0.077mcg/kg/min during the second (P<0.007). Interestingly, the first study period (immediate dosing) was preferred by both groups. The authors state that the main finding of this study was that the timing of the administration of a remifentanil bolus during the uterine contraction cycle has no significance related to the timing in which a 1-minute PCA bolus is given. No further recommendations regarding timing or implementation were made.[38]

Putting This All Together

Each of the studies above were analyzed for the remifentanil dosing regimen and implementation method used. The doses, implementation methods, and recommendations found in each study are presented in Table 2. If a recommended dose or method of implementation was not specifically given, the dose and method used in conduction of the study was used as the recommended dose.

Table 2.

Author	Implementation Method	Remifentanil Dose Used	Recommendation
Schnabel et al	N/A	N/A	No recommendation
Leong et al	N/A	N/A	No recommendation
Hill	N/A	N/A	40 mcg remifentanil bolus, 2 min lockout
Van De Velde	N/A	N/A	0.2-0.5 mcg/kg bolus, 2-3 min lockout, no background infusion
Hinova & Fernando	N/A	N/A	40mcg bolus, 2 min lockout
Blair et al	Fixed PCA bolus	40mcg bolus, 2 min lockout	40mcg bolus, 2 min lockout
Douma et al	Fixed PCA bolus + loading dose	40mcg loading dose, 40mcg per bolus, 2 min lockout	40mcg loading dose, 40mcg per bolus, 2 min lockout
Evron et al	Stepwise ↑ PCA bolus	20mcg starting dose, 3 min lockout, ↑ in 5mcg increments every 15-20 min on request	20mcg starting dose, 3 min lockout, ↑ 5mcg increments every 15-20 min on request
Tveit et al	Stepwise ↑ PCA bolus	Starting bolus 0.15mcg/kg, 0.15mcg/kg ↑ every 15 min on request	PCA as a stepwise bolus dose regimen, dose steps of 0.15mcg/kg, 2 min lockout, maximum dose 0.7mcg/kg
Ismail & Hassanin	Stepwise ↑ PCA bolus	0.1mcg/kg bolus infused over 1 min, 1 min lockout, bolus ↑ 0.1mcg/kg after every 2nd contraction until satisfaction stated with current dose or max dose of 0.9mcg/kg	0.1mcg/kg bolus, 1 min lockout, bolus ↑ 0.1mcg/kg until satisfied or max dose of 0.9mcg/kg
Stocki et al	Stepwise ↑ PCA bolus	20mcg bolus ↑ to 60mcg max as required, 2 min initial lockout, no background infusion. Bolus dose & lockout interval titrated to patient comfort or a max bolus 60mcg & 1 min lockout	20mcg bolus ↑ as required, 2 min initial lockout. Bolus dose & lockout interval titrated to patient comfort or a max bolus 60mcg & 1 min lockout. No background infusion.
Balki et al	Stepwise ↑ PCA bolus or infusion rate	Infusion ↑ from 0.025mcg/kg/min in .025mcg increments up to 0.1 mcg/kg/min, bolus of 0.25mcg/kg unchanged. Bolus ↑ from 0.25mcg/kg in 0.25mcg increments up to 1mcg/kg, infusion rate of 0.025mcg/kg/min unchanged	0.25mcg/kg bolus, 2 min lockout, background infusion 0.025-0.1mcg/kg/min
Shen et al	Stepwise ↑ PCA bolus or infusion rate	0.1mcg/kg bolus, 2 min lockout, ↑ in 0.1mcg/kg increments to 0.4mcg/kg max. Continuous infusion 0.05mcg/kg/min, ↑ by 0.05mcg/kg/min increments on request, max 0.2mcg/kg/min	0.1mcg/kg bolus, 2 min lockout, ↑ in 0.1mcg/kg increments to 0.4mcg/kg max. No background infusion
Balcioglu et al	Fixed PCA bolus + loading dose + background infusion	20mcg loading dose, 15mcg bolus, 5 min lockout. Background infusion of either 0.1mcg/kg/min or 0.15mcg/kg/min.	15mcg bolus, 5 min lockout, 0.15mcg/kg/min background infusion
Jost	Stepwise ↑ PCA bolus + continuous infusion	Classic= infusion 0.010mcg/kg/min + 20mcg boluses upon request, ↑ to 30mcg after 20 min, 35mcg after 1hr, 45mcg after 2 hrs., and 55mcg after 3 hrs. Modified based on time button pressed. Starting rate 3mcg/sec with a stepwise ↓ 20% of initial rate every 6 sec, terminate at button release or 60mcg max dose	
Volmanen et al	Fixed PCA bolus	0.4mcg/kg bolus, 1 min infusion time, 1 min lockout. Traditional: bolus immediately. Other: bolus 140 sec before next contraction	0.4mcg/kg bolus, 1 min infusion time, 1 min lockout.

The overall number of studies specifically investigating the use of remifentanil in parturients are few and most look at only a small fraction of the overall parturient population. Among the specific population of interest- parturients for whom neuraxial anesthesia is not an option- the body of literature contained only a few case studies and these lacked the scientific rigor required to be included in evaluation of this topic. The literature included in this review demonstrated clinical heterogeneity; different study protocols with respect to implementation methods, dosing, timing, rate of administration, lockout intervals, and comparative drugs make it difficult to conduct comparison. Participants in included studies were quite homogeneous in nature with most being healthy ASA 1 or 2 patients who met relatively strict inclusion criteria. This is a very specific body of literature related to the efficacious and safe use of remifentanil as a labor analgesic.

The Importance of Safety

An issue that was presented in a majority of the studies is that of safety related to remifentanil use in this application. Frequently, assessed parameters that were often a secondary focus of the studies included maternal blood pressure, SPO_2, $ETCO_2$, respiratory rate, and level of sedation. In addition, fetal/neonatal assessment often included Fetal Heart Rate (FHR), umbilical cord pH, and 1 and 5-minute Apgar scores as a measure of assessing adverse response to remifentanil use for labor analgesia. On the maternal side of the safety discussion, most literature suggested that close monitoring of SPO_2, respiratory rate, and level of sedation be undertaken with the use of remifentanil.

In addition to monitoring, the use of supplemental oxygen was also frequently recommended and was implemented in many of the studies. Another frequent recommendation that many authors made was the necessity of having individual nursing care when remifentanil is used in the parturient.[18, 26, 29-31] It is also important to note that many studies investigating the feasibility of remifentanil reported a low number of adverse maternal and fetal events. This low number of adverse events may therefore cause an overestimation of the safety of remifentanil use in labor.[23]

Ethical Considerations

The ethical issues surrounding the use of remifentanil for labor analgesia require consideration prior to utilization in clinical practice. The evidence supports the use of remifentanil in the parturient as an acceptable practice. The evidence also supports that the use of this regimen can potentially expand access to pain relief during labor for those who may otherwise be excluded. The relief of pain is a basic human right and as such should not be denied.[3] Remifentanil use meets this need for the relief of pain during labor. The expansion of access and the relief of pain are certainly positive attributes of the use of remifentanil in the parturient.

There are, however, other aspects of ethical concern that each practitioner who accepts the responsibility of providing for a patient requiring or desiring remifentanil as a labor analgesic must take into consideration. It is important to emphasize that every clinical situation in which the use of remifentanil may be utilized requires a thorough evaluation by the practitioner of not only applicable clinical data, but also of the patient and their individual needs during the birthing process.

Not only must the patient be considered in this discussion, but also the unborn child who is wholly dependent upon the physiologic homeostasis provided by the mother. The use of remifentanil as a labor analgesic has proven to be both safe and effective when implemented properly. Several studies have examined the side effects of remifentanil use during the first and second stages of labor and the occurrence of serious adverse events or poor neonatal outcomes is rare.[18, 28-36] This is not to say that the use of remifentanil is totally without risk. Maternal adverse events, such as apnea and hypoxia, do occur and there are case reports of more serious events, such as cardiac arrest, that have occurred with the use of remifentanil as a labor analgesic.[39, 40]

Another major consideration when contemplating the use of remifentanil in this application is that of the risks versus the benefits. The risks and benefits of remifentanil use have been discussed above. The risk for an adverse event is increased by several factors including unfamiliarity with the remifentanil protocol, inadequate staff education, inability to provide individual nursing care, and unrealistic expectations by patients and staff.

Benefits of implementation may be either physical or nonphysical in nature. For example, a patient with thrombocytopenia due to preeclampsia and may be physically unable to tolerate any further increases in blood pressure caused by the pain of labor without becoming eclamptic; in this situation, the use of remifentanil has the potential keep the pain manageable and blood pressure out of the eclamptic range. A benefit that is nonphysical in nature may be that of a sense of self-control over the analgesia being administered.[25] By giving the parturient the control offered by a PCA, she is able to determine the level of analgesia that is appropriate based on her needs and desires. Again, this assessment of risks and benefits requires that the clinician thoroughly evaluate clinically relevant information as well as the individual needs and desires of the patient and then tailor the anesthetic plan accordingly.

A final thought regarding the ethical considerations of remifentanil use in the parturient is centered on the costs associated with not only the drug but also with implementation. This potent, short-acting narcotic is more expensive when compared to less efficacious narcotics or local anesthetics traditionally used in the management of labor pain.[41,42] In addition to the cost of the drug, safe implementation requires additional equipment such as $ETCO_2$ monitoring and additional staff to provide individual nursing care. The costs will vary by locale but there may be a substantial increase in costs to the facility with the implementation of this regimen. These increases in the cost of caring for one patient may deplete resources available for other patients and in turn, negatively affect the care that they receive due to financial constraints. Cost savings may be realized by reducing vital precautions but in so doing, may lead to catastrophic outcomes.[43]

One must consider if the risks of remifentanil use are commensurate to the benefits and if so, do the benefits then justify the cost. The value of the alleviating pain whether it is physical, mental, indicates that each provider must answer these questions that arise regarding the use of remifentanil by using his or her own clinical knowledge, personal and professional beliefs, and the individual needs and desires of patients before coming to a decision based upon that information.

Reflection

1. Based on the evidence presented, what are your thoughts about using remifentanil for labor pain in which neuraxial interventions are contraindicated?
2. What would you consider the next steps should be to have remifentanil formally approved for use in labor?
3. To what extent should a CRNA be involved in creating and designing new techniques, or exploring the efficacy of potential techniques?

Evidence-Based Recommendation

Based upon a thorough review of literature on the subject of remifentanil use in the parturient for whom neuraxial anesthesia is not an option, the use of remifentanil as a labor analgesic is an acceptable practice. The use of remifentanil is considered 'off-label' for obstetric use and there is currently no consensus on the optimal dosing regimen.[17, 18] Large-scale studies with rigorous guidelines and protocols need to be conducted to procure further evidence regarding the optimal use of remifentanil in the parturient. These recommendations would ideally include implementation information and order guidelines for the anesthetist, implementation and usage guidelines for nursing staff, and educational information for patients.

Table 3 displays the recommendations for anesthesia providers that desire to use remifentanil for labor analgesia in the parturient. A PCA bolus of 40mcg with a 2-minute lockout and no background infusion is recommended. Supplemental oxygen should be used in conjunction with continuous monitoring of SPO_2, $ETCO_2$, and cardiotocograph readings. Vital signs (BP, HR, RR, SPO_2, $ETCO_2$, Level of Consciousness (LOC), and Pain) should be documented on a Remifentanil PCA flow sheet every 5 minutes for the first 30 minutes after initiating PCA and then every 15 minutes for the duration of remifentanil use. Individual nursing care should be provided and the nurse should have Advanced Cardiovascular Life Support (ACLS) certification.

Table 3. Putting it all together

Mixture	• Remifentanil 2mg diluted in 50ml Normal saline (40mcg/ml)
Delivery Method	• PCA
Dosing	• 40mcg Bolus • 2 minute lockout
Implementation	• Dedicated IV site for Remifentanil with carrier fluid running at 100ml/hr • O2 via Nasal cannula @ 2-3L/min
Monitoring / Documentation	• Continuous SPO2 monitoring with audible alarm for ≤ 93% • Continuous ETCO2 monitoring with audible alarms for ≥ 55mmHg • Continuous cardiotocograph monitoring • Vitals (BP, HR, RR, SPO2, ETCO2, LOC, Pain) - every 5 minutes for the first 30 minutes after initiating PCA - then every 15 minutes for the duration of remifentanil use • All times and vitals documented on Remifentanil flow sheet • Reconciliation per facility protocol of Remifentanil use and waste
Staffing	• 1:1 nursing care with ACLS trained provider • Supervising Anesthetist in-house and immediately available
Other	• Concomitant use of other opioid analgesics is not recommended

It is further recommended that the Supervising Anesthetist be in-house and immediately available for the entire duration of remifentanil use. Concomitant use of other opioid analgesics is not recommended. These recommendations are an amalgamation of evidence gleaned from the studies analyzed and should not be considered absolute. CRNAs must take into account their own clinical knowledge as well as individual patient needs and desires prior to implementing remifentanil in the parturient.

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