Remifentanil in Labor Analgesia

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Literature Review

Introduction of the Problem

According to the CDC (2019), approximately 3,747,540 children are born every year. Though no two births are the same, labor has the potential to be the most intense and excruciating physical pain a woman experiences in her life. Various anesthetic techniques have been utilized to help control the overwhelming discomfort. Neuraxial anesthesia, which includes spinal, epidural, or a combined spinal-epidural technique, is the gold standard for pain control in laboring patients (Lee et al., 2017). Over two-thirds of laboring women receive some form of neuraxial anesthetic (Butwick et al., 2018). By directly injecting a local anesthetic into the neuraxial space, the anesthesia provider can offer quick and reliable pain relief (Osterman & Martin, 2011).

Seemingly forgotten, a subset of parturients cannot experience the benefits of neuraxial anesthesia. This barrier is due to several absolute and relative contraindications. Absolute and relative contraindications may include patient refusal, anatomic limitations, thromboprophylaxis, allergy to local anesthetics, and medical conditions, such as coagulation abnormalities, elevated intracranial pressure, or local infection at the injection site (Gupta & Partani, 2018). These women rely on options other than neuraxial anesthesia for labor pain control. Systemic opioids have been used as an alternative; however, they have been criticized due to limited evidence for efficacy. To manage labor pain, the ideal opioid should have a rapid onset and offset, rapid metabolism, and minimal side effects for both the mother and neonate. This ideal systemic opioid must also provide analgesia without inhibiting the mother's ability to participate in labor (Lee et al., 2017). Investigation for an ideal opioid that would overcome these issues has led anesthesia providers to remifentanil to manage labor pain. Remifentanil is an ultra-short-acting

synthetic opioid with fast onset and is rapidly metabolized by non-specific plasma and tissue esterases in both the parturient and fetus (Lee et al., 2017).

In Central Illinois, a Level 3 Perinatal center encounters parturients with contraindications to neuraxial anesthesia. These women's pain control options are limited to nursing-driven nitrous oxide and intravenous bolus doses of opioids. This project aims to educate obstetrical anesthesia providers, obstetricians, residents, and pharmacists on remifentanil patient-controlled analgesia (PCA) for laboring parturients as an alternative to neuraxial analgesia for this subset of parturients. Findings from the literature review will be presented via a live PowerPoint presentation to key stakeholders from the anesthesia, obstetric, and pharmacy departments by August 2022. An evidenced-based remifentanil PCA dosing regimen will be recommended. A post-education assessment will evaluate participants' knowledge and a post-assessment survey will assess buy-in following implementation. Participants will be questioned about their perceptions of remifentanil PCA for laboring parturients and its utility as an alternative to neuraxial anesthesia. The intended outcome will be measured by the achievement of established benchmark scores on the assessment.

Search Strategy

A search of scholarly journals and articles was conducted to review the literature on remifentanil patient-controlled analgesia for parturients. The following University Library databases were utilized: CINAHL Plus with Full Text, Cochrane Database of Systemic Reviews, MEDLINE Complete, PubMed, and EBSCO Host. To refine the topic of interest, a combination of key search terms were utilized: "labor" AND "remifentanil", "remifentanil" AND "patient-controlled analgesia," "parturient" AND "remifentanil", "labor analgesia" AND "remifentanil". Populations other than parturients were excluded from this review. Both vaginal and cesarean

section modes of delivery were included. The reference search parameters included articles from 1998 to present. Articles greater than five years old were included only if they contained information pertinent to the topic. Of the 124 articles discovered, 78 abstracts were reviewed, and 44 articles were included in this review. The John Hopkins Research Evidence Appraisal Tool was utilized to evaluate the level of evidence for each retained article. The totals included 17 level one articles, 10 level two articles, 7 level three articles, 2 level four articles, and 8 level five articles.

Results

The literature review outcomes are to obtain the current evidence regarding remifentanil and its use in labor analgesia for parturients with contraindications to neuraxial techniques. The literature review includes six main sections: remifentanil for labor analgesia, pharmacokinetics and pharmacodynamics, patient-controlled analgesia delivery methods, comparison of remifentanil with other analgesic modalities, adverse effects, and safety measures.

Remifentanil for Labor Analgesia

Pain relief is essential and frequently requested by parturients during labor. The use of remifentanil in the parturient as the primary analgesic is significant for several reasons; the most prominent of which is the basic right to pain management. This right is violated if a parturient is unable to partake in standard methods used for managing pain. Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Raja et al., 2020). 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 a part of the duty to prevent harm (Brennan et al., 2007).

Epidural Analgesia (EA) is considered the most effective treatment to relieve labor pain (Lin et al., 2014). Due to concern for contraindications and limited availability of epidural analgesia, systemic opioids have been used as an alternative with widespread and increasing use; however, their use has been criticized due to limited efficacy (Volmanen et al., 2011). In addition, with the rise in parturients with severe morbidity such as deep vein thrombosis, pulmonary embolus, mechanical heart valve, or arrhythmia, discontinuation of thromboprophylaxis may not be possible to enable the timely provision of neuraxial analgesia (Karol & Weiniger, 2021). Alternative strategies for pain relief may also be necessary for patients where administration of epidural analgesia may be technically challenging due to obesity or spinal abnormalities (Soens et al., 2008). By utilizing an intervention such as remifentanil PCA, anesthesia providers can alleviate pain associated with labor in women with contraindications to neuraxial anesthesia.

The first study of the use of remifentanil in labor analgesia was published in 2000 and included only four women (Olufolabi, 2000). The study was terminated due to significant side effects in the absence of adequate pain control (Olufolabi, 2000). Changes to the mode and amount of remifentanil administered have led to more effective pain control, with few observed adverse side effects (Olufolabi, 2000). More recently, a study showed that 82% of women reported they were either satisfied or very satisfied with their labor analgesia with the use of remifentanil patient-controlled analgesia (Melber et al., 2019).

To achieve optimal patient outcomes and satisfaction in the obstetric population, providers should consider multiple options for pain control, especially when neuraxial anesthesia is contraindicated. In the United States, parenteral opioids commonly used include meperidine, morphine, fentanyl, butorphanol, and nalbuphine. In the United Kingdom and Norway, pethidine

administered intramuscularly is the most used opioid during labor (Devabhakthuni, 2013). Also, in the United Kingdom, 49% of obstetric wards use patient-controlled analgesia with remifentanil as the most common agent (Devabhakthuni, 2013).

Pharmacokinetics and Pharmacodynamics

Remifentanil, brand name Ultiva, is a synthetic opioid with a strong affinity for the mu-opioid receptor and less affinity for the delta- and kappa-opioid receptors. The opioid is 92% protein-bound, lipid-soluble, and competitively antagonized by naloxone (Glass et al., 1999). Remifentanil has a chemical structure similar to other piperidine derivatives, but an ester linkage allows metabolism by non-specific esterases in blood and other tissues (Glass et al., 1999). Remifentanil has a rapid onset, small volume of distribution, rapid redistribution, and clearance (Glass et al., 1999). The context-sensitive half-life is three to five minutes and independent of infusion duration, making the drug an excellent option for patient-controlled analgesia (Glass et al., 1999). One study compared a three-hour infusion of remifentanil to equipotent concentrations of alfentanil (Kapila et al., 1995). Complete recovery of the respiratory drive occurred within 15 minutes of remifentanil infusion discontinuation, compared with greater than 45 minutes for alfentanil (Kapila et al., 1995).

After a similar intravenous dose in pregnant and nonpregnant women, the plasma concentration of the pregnant women was half that of nonpregnant women (Glass et al., 1999). This pharmacokinetic difference is due to physiologic changes during pregnancy, including increased volume of distribution, lower concentration of plasma proteins, and increased non-specific esterase activity (Glass et al., 1999). This is relevant because larger and more frequent bolus doses may be required in a parturient to achieve an effective plasma concentration. Like other opioids of the piperidine class, remifentanil is highly lipophilic and readily crosses the

placenta. However, unlike other opioids, the fetus rapidly metabolizes remifentanil, as demonstrated by the analysis of the remifentanil concentration in the umbilical cord, uterine artery, and umbilical vein (Kan, 1998). Another study by Welzing et al. (2011) demonstrated that preterm infants, 24 – 36 weeks' gestation, exhibited a high non-specific esterase activity in the umbilical cord blood comparable to that of term infants. These findings suggest that remifentanil may be safer option than other systemic opioids for the fetus (Welzing et al., 2011; Kan et al., 1998). Remifentanil has similar pharmacodynamic properties to other potent mu-opioid receptor agonists, including dose-dependent analgesia, respiratory depression, and sedation. Details about the adverse effects of remifentanil are discussed further in the *Adverse Events* section.

Patient Controlled Analgesia Delivery Methods

Remifentanil's unique pharmacokinetic properties are appropriate for patient-controlled analgesia (PCA) during labor (Kan et al., 1998). Research has been conducted to determine the optimal dose and mode of remifentanil administration in managing labor pain. Remifentanil can be administered as an intermittent PCA bolus with a lockout interval, and a background infusion can be added if desired. Many of the studies investigating remifentanil used different and unique dosing schedules. Most studies reported a wide variation in bolus dosing to achieve patient relief, indicating that a fixed-dose regimen may underestimate or overestimate patient requirements (Balki et al., 2007; Shen et al., 2013; Jost et al., 2013; Balcioglu et al., 2007; D'Onofrio et al., 2009).

Few trials have specifically addressed the delivery of remifentanil when used as the primary analgesic for managing labor pain. The methods investigated included PCA with background infusion, PCA without background infusion, and a continuous remifentanil infusion without any patient control. Balki et al. conducted a randomized controlled trial in 2007 to

compare the efficacy of two remifentanil regimens for PCA in labor analgesia. Remifentanil was administered as a 50 mcg/mL solution. All patients initially received a standard regimen of a continuous infusion of 0.025 mcg/kg/min and a PCA bolus of 0.25 mcg/kg with a two-minute lockout and four-hour limit of 3mg. As labor progressed and additional pain relief was needed, parturients received higher doses of either the continuous infusion or the PCA boluses, depending on which group they had been randomly assigned. The variable continuous infusion group had a stepwise increase in their infusion rate from 0.025 mcg/kg/min to 0.05 mcg/kg/min, 0.075 mcg/kg/min, and 0.1 mcg/kg/min, while the bolus remained unchanged at 0.25mcg/kg (Balki et al., 2007). In the variable bolus group, the bolus dose was increased stepwise from 0.25mcg/kg to 0.5 mcg/kg, 0.75mcg/kg, and 1 mcg/kg, while the infusion remained constant at 0.025mcg/kg/min (Balki et al., 2007). Each step was maintained for 15 minutes before progressing to the subsequent step (Balki et al., 2007). Mean patient satisfaction and pain scores were similar between the two groups and the overall difference in pain scores was not statistically significant (Balki et al., 2007). However, the authors recommended delivery of remifentanil as a bolus of 0.25mcg/kg with a 2-minute lockout with a continuous background infusion of 0.025 – 0.1mcg/kg/min due to fewer side effects compared to the variable bolus group (Balki et al., 2007).

An observational study by D'Onofrio and colleagues (2013) evaluated the efficacy and safety of continuous remifentanil infusion in 205 parturients. The initial infusion of 0.025 mcg/kg/min was increased in a stepwise manner to a maximum dose of 0.15 mcg/kg/min. The mean visual analog score (VAS) before the infusion was 9.4 and decreased to 5.1 after 5 minutes and 3.6 after 30 minutes (D'Onofrio et al., 2013). Maternal arterial blood pressure and heart rate were maintained within 20% of baseline values in all women (D'Onofrio et al., 2013). None of

the patients required oxygen supplementation or the administration of naloxone and 87% of parturients were satisfied with their analgesia (D'Onofrio et al., 2013).

Another prospective, randomized, double-blinded RCT conducted by Shen et al. (2013) aimed to compare the effects of remifentanil for labor analgesia given by either PCA or continuous infusion. The PCA group was administered remifentanil using increasing stepwise boluses from 0.1 - 0.4 mcg/kg in 0.1mcg/kg increments with a 2-minute lockout (Shein et al., 2013). The continuous infusion group used rates from 0.05 - 0.2 mcg/kg/min with incremental increases of 0.05 mcg/kg/min on request (Shen et al., 2013). The two groups were similar regarding patient characteristics, but pain scores were significantly lower, and pain relief scores were significantly higher in the PCA group compared to the infusion group (Shen et al., 2013). The authors concluded that remifentanil administered with an incremental PCA bolus was the superior analgesic compared to continuous infusion without a bolus (Shen et al., 2013). Similar maternal side effects and placental transfer were present in both groups (Shen et al., 2013).

The speed of the patient-controlled bolus is also important. Jost et al. compared a modified remifentanil PCA technique where an initial 60 mcg bolus infused quickly and then tapered off or stopped if the patient stopped pressing the PCA button to a conventional group where a 20-mcg bolus infused slower and increased up to 55 mcg based on the patient's analgesic response and side effects. The modified remifentanil PCA method utilized a computer-controlled roller infusion pump tested and developed by external university engineers (Jost et al., 2013). The modified method of administration resulted in fewer analgesic requests and lower pain scores (Jost et al., 2013). Additionally, there were fewer settings changes than in the conventional group (Jost et al., 2013).

Lastly, a randomized study by Balcioglu et al. conducted in 2007 sought to assess and compare the efficiency and safety of remifentanil PCA combined with two different supplementary background infusions. Both groups received the same fixed loading and demand remifentanil doses of 20 mcg and 15 mcg, respectively, with a 5-min lockout between boluses (Balcioglu et al., 2007). One group received a background infusion of 0.1 mcg/kg/min, and the other received a background infusion of 0.15 mcg/kg/min (Balcioglu et al., 2007). The VAS of the group receiving the 0.15 mcg/kg/min background infusion was significantly lower than the other group (Balcioglu et al., 2007). Hemodynamic parameters and fetal heart rates between the two groups were not different (Balcioglu et al., 2007). The 0.1 mcg/kg/min background infusion group also required more demand dosing, although there were no differences between the total amount of remifentanil administered between both groups (Balcioglu et al., 2007). It was determined that a remifentanil PCA with a 15-mcg demand dose and 0.15 mcg/kg/min continuous supplementary infusion is an effective choice for parturients in labor (Balcioglu et al., 2007).

The RemiPCA SAFE network was developed in Switzerland in 2009 with the aim of becoming a quality assurance network for the safe application of remifentanil PCA for labor (Melber et al., 2018b). Through this process, the safety profile of remifentanil has improved over time. For example, the initial bolus dosing recommendation was 20 to 40 mcg with a 2-min lockout. Based on submitted data, including the incidence of maternal hypoxia, neonatal hypoxia, oxygen supplementation, and bag-mask ventilation, the bolus dose was then reduced to 10 to 30 mcg. Following the bolus dose reduction, the mean bolus dose was subsequently reduced from approximately 27 to 18 mcg. Pain reduction decreased with this bolus dose change, yet maternal satisfaction remained steady (Melber et al., 2018b). Current literature indicates that

maternal adverse events are associated with remifentanil bolus doses of 40 mcg and above or with the concomitant use of long-acting opioids (Melber et al., 2018b).

Comparison of Remifentanil with Other Analgesic Modalities

IM Meperidine. IM meperidine, also known as pethidine or Demerol, is the most used opioid during labor in Europe (Devabhakthuni et al., 2013). The RESPITE trial in the UK was an open-label, multicenter, randomized controlled trial in 14 UK maternity centers, including 400 women, between 2014 and 2016 (Wilson et al., 2018). The study compared remifentanil PCA to intramuscular meperidine. The conversion to epidural was halved in women who received remifentanil PCA compared with meperidine (Wilson et al., 2018). Remifentanil PCA's conversion rate was 19% compared to the meperidine's conversion rate of 41%, suggesting that more women required better pain relief using meperidine than remifentanil PCA (Wilson et al., 2018). A study by Duoma et al. (2010), including 159 parturients, confirmed that the rate of conversion to epidural anesthesia was higher for the meperidine group than for the remifentanil group.

A secondary outcome, looking at the mode of delivery, revealed that a higher proportion of women in the remifentanil group had a spontaneous vaginal delivery and required fewer instrumental vaginal deliveries (Wilson et al., 2018). The cesarean delivery rate between remifentanil PCA and meperidine was the same (Wilson et al., 2018). In addition, remifentanil was associated with a decrease in mean VAS and overall higher satisfaction scores compared to meperidine (Duoma et al., 2010; Leong et al., 2011). This evidence suggests remifentanil is superior to IM meperidine due to a more significant reduction in pain scores, increased maternal satisfaction score, fewer conversions to epidural analgesia, increased spontaneous vaginal

delivery, fewer required instrumental delivery, and similar safety profile (Wilson et al., 2018; Duoma et al., 2010; Leong et al., 2011)

Fentanyl. Marwah and colleagues (2012) conducted a five-year retrospective cohort study where patients either received a remifentanil PCA with an initial continuous background infusion rate of 0.025 mcg/kg/min, titrated to 0.05 mcg/kg/min if inadequate analgesia was experienced, and a bolus of 0.25 mcg/kg with a lockout interval of 2 min or fentanyl PCA. The mean pain scores were similar between the two groups, showing moderate decreases in pain (Marwah et al., 2012). This study also showed that more women from the fentanyl PCA group switched to epidural analgesia compared to the remifentanil group (Marwah et al., 2012). However, the remifentanil group had greater maternal desaturations (Marwah et al., 2012), Comparing neonatal safety profiles, the fentanyl group has lower neonatal Apgar scores and a higher need for neonatal resuscitation compared to the remifentanil group (Marwah et al., 2012).

Another study by Douma and colleagues (2010) revealed that remifentanil PCA reduced VAS scores to a greater extent after one hour compared with fentanyl PCA; however, there was no difference in VAS scores thereafter. Again, the remifentanil PCA group had a higher prevalence of oxygen desaturation compared to fentanyl PCA (Douma et al., 2010). Overall, the evidence suggests that women in the remifentanil PCA group, compared to the fentanyl PCA group, had similar pain scores, decreased conversion to epidural analgesia, and decreased neonatal adverse effects (Douma et al., 2010; Marwah et al., 2012). However, remifentanil PCA parturients had an increased prevalence of maternal oxygen desaturation (Douma et al., 2010; Marwah et al., 2012).

Nitrous Oxide. Nitrous oxide is an inhaled anesthetic used for labor pain relief. It is administered in a mixture of 50% nitrous oxide and 50% oxygen (Markley & Rollins, 2017).

One randomized controlled trial compared the use of remifentanil PCA with inhaled nitrous oxide. In this small study, 15 patients were randomized to receive an intravenous remifentanil PCA bolus of 0.4 mcg/kg with a 1 min lockout or intermittent inhaled 50% nitrous oxide (Volmanen et al., 2005). Pain was assessed using a verbal 11-point pain score (Volmanen et al., 2005). Pain intensity and relief scores were better with remifentanil compared with nitrous oxide (Volmanen et al., 2005). Most parturients preferred remifentanil to nitrous oxide (Volmanen et al., 2005). Varposhti et al. (2013) compared nitrous oxide to nitrous oxide with a remifentanil infusion. They concluded that the addition of remifentanil to nitrous oxide produced better analgesia than nitrous oxide alone (Varposhti et al., 2013). The addition of remifentanil did not cause an increase in maternal or neonatal side effects (Varposhti et al., 2013).

Neuraxial Analgesia. According to the guidelines of the American Society of Anesthesiologists (ASA) and American College of Obstetricians and Gynecologists (ACOG), epidural analgesia is recommended as the most flexible and effective analgesic modality in obstetrics with the fewest sedative effects (Jelting et al., 2017). In a systematic review of randomized control trials, 20 studies concluded that women using remifentanil PCA were more satisfied with pain relief than women receiving parental opioids but were less satisfied than women receiving epidural analgesia (Jelting et al., 2017). More recently, a meta-analysis of randomized trials (RCTs) was conducted to compare the effect and safety of remifentanil PCA to epidural analgesia in labor (Zhang et al., 2021). 11 RCTs were included and compared in terms of analgesic effect, delivery mode, and maternal, as well as neonatal safety (Zhang et al., 2021). They concluded that average VAS were higher with remifentanil PCA, yet there was no significant difference in maternal satisfaction scores for pain relief (Zhang et al., 2021). This indicates that mother's receiving remifentanil PCA or epidural analgesia were satisfied with the

anesthetic methods used during labor. The neonatal safety profile and rate of spontaneous vaginal delivery were comparable, but remifentanil PCA encountered more oxygen desaturations (Zhang et al., 2021).

Another study by Sugur and colleagues (2020) divided 37 pregnant women into two groups, a remifentanil PCA with a background infusion or an epidural PCA with a background infusion. Maternal-fetal heart rate, VAS, blood pressure, oxygen saturation, nausea, vomiting, and sedation were recorded (Sugur et al., 2020). Both methods provided adequate analgesia; however, VAS scores were higher in the remifentanil group (Sugur et al., 2020). Newborn Apgar scores and maternal satisfaction were similar in both groups, but maternal oxygen desaturation was not reported (Sugur et al., 2020). A similar study comparing remifentanil PCA, patient-controlled epidural analgesia (PCEA), and spontaneous labor concluded that remifentanil PCA and PCEA have similar VAS scores at 30 minutes and 1 hour after analgesia (Jia, 2020). However, VAS scores in the remifentanil PCA group were significantly higher at the full opening of the uterine orifice and at fetal delivery (Jia, 2020). There were no significant differences in delivery mode, neonatal asphyxia rate, or maternal oxygen saturation between the three groups (Jia, 2020).

In other studies, remifentanil had a higher spontaneous vaginal delivery rate with decreased instrumentation use when compared to epidural analgesia (Pillay, 2019; Melber et al., 2019; Murray et al., 2019; Zhang et al., 2021). No statistically significant difference was noted between the total duration of labor, the duration of latent and active phases of the first stage of labor, the duration of the second stage of labor, average VAS pain scores, and overall satisfaction scores when comparing epidural analgesia and remifentanil PCA (Ismail & Hassanin, 2012). Studies comparing epidural analgesia to remifentanil PCA have concluded no difference in

neonatal outcomes (Douma et al., 2011; Ismail & Hassanin, 2012; Stourac et al., 2014; Tveit et al., 2012; Evron et al., 2005; Zhang et al., 2021). The evidence from this review suggests epidural analgesia provides superior pain relief with minimal side effects compared to remifentanil PCA. These findings are in alignment with current ASA and ACOG recommendations (Jelting et al., 2017). Remifentanil may offer parturients an option for safe labor analgesia when epidural is contraindicated.

Adverse Events

Maternal adverse events due to remifentanil include maternal apnea, hypoxia, respiratory depression, bradycardia, pruritis, nausea and vomiting, and cardiac arrest (Logtenberg et al., 2019). Desaturation, oxygen saturation under 94%, is the main adverse effect affecting 25 - 75% of parturients (Stocki et al., 2014; Tveit et al., 2012; Melber et al., 2018b; Duoma et al., 2015). Risk factors for maternal desaturation while using remifentanil PCA included breathing room air and PCA use during the second stage of labor (Messmer et al., 2016). However, the finding of more frequent desaturation during the second stage is expected and has been reported in women who have not received opioids (Messmer et al., 2016). Maternal desaturation in the second stage is due to physiologic changes during pregnancy and the periods of apnea resulting from bearing down against a closed glottis to push the fetus through the fully dilated birth canal (LoMauro & Aliverti, 2015). Pregnant women have a decreased tolerance to apnea due to the cephalad shift of the diaphragm decreasing functional residual capacity (LoMauro & Aliverti, 2015). Body mass index, age, parity, oxytocin, and remifentanil bolus size were not independent risk factors for maternal desaturation (Messmer et al., 2016). Authors also noted little difference in the prevalence of maternal desaturation episodes during the second stage of labor in earlier studies of nitrous oxide and meperidine use during labor (Messmer et al., 2016).

A descriptive study by Logtenberg and authors (2019) looked at maternal and neonatal adverse events attributed to remifentanil PCA during labor and investigated the clinical circumstances and management of these cases. From the 61 hospitals surveyed in the Netherlands between January to March 2018, 27 cases of serious maternal adverse events were reported (Logtenberg et al., 2019). Of the 23 cases involving oxygen desaturation, 17 were single events and were treated by encouraging breathing and/or discontinuation of remifentanil PCA and/or supplemental oxygen (Logtenberg et al., 2019). Five cases of desaturation occurred in combination with apnea (Logtenberg et al., 2019). These five cases were associated with background infusion of remifentanil with simultaneous PCA boluses (Logtenberg et al., 2019). Only one case required bag-mask ventilation and naloxone administration intravenously (Logtenberg et al., 2019). All severe adverse events were resolved without serious morbidity or mortality (Logtenberg et al., 2019). Melber and authors (2018b) analyzed data collected between 2010 and 2015 and reported an incidence of hypoxemia, defined as oxygen saturation <94%, in 26% of parturients receiving remifentanil PCA. However, there was no need for maternal ventilation or cardiopulmonary resuscitation despite desaturation (Melber et al., 2018b).

Aaronson et al. (2017) surveyed academic medical centers in the United States using remifentanil for labor analgesia. Thirty medical centers were included in the study and reported nine cases of maternal respiratory depression, with two resulting in cardiac arrest (Aaronson et al., 2017). No complications occurred in medical centers where remifentanil was utilized more than ten times in the previous year (Aaronson et al., 2017). Several obstetrical units in the UK have also demonstrated that the routine use of remifentanil PCA strengthens provider skills and reduces the risk for severe maternal adverse events (Melber et al., 2019).

Some other adverse effects of remifentanil may be mild, including nausea or pruritis, requiring little to no intervention. Compared with neuraxial analgesia, no differences were found in the rate of minor adverse events, including pruritis, nausea, or vomiting (Liu et al., 2014). Neuraxial opioids with local anesthetics are often used in epidural infusions, which can cause side effects similar to systemic opioids in some parturients.

Neonatal. When neonatal Apgar scores at 1 min and 5 min were compared, no difference was found between maternal remifentanil and epidural analgesia (Liu et al., 2014; Tveit et al., 2012; Zhang et al., 2021; Jelting et al., 2017; Karadjova et al., 2019). No statistically significant differences were found in neonatal Apgar scores at 1 min and 5 min between IV remifentanil and IM meperidine (Liu et al., 2014). In addition, Konefal et al. (2013) found no significant differences in neonatal oxygen saturation, heart rate, and blood pressure for the first 24 hours between full-term newborns of mothers with and without remifentanil PCA. Safety measures must always be in place, including the availability of oxygen, pediatric advanced life support (PALS) training, intravenous naloxone, and a pediatrician.

Safety Measures

Given the concerns of maternal respiratory depression, standardized protocols for administration and monitoring should be implemented at a facility using remifentanil PCA for labor analgesia. These include one-to-one nursing care with an ACLS credentialed labor and delivery registered nurse (RN), continuous pulse oximetry, vital signs every 15 minutes, and continuous end-tidal capnography, as well as the immediate availability of anesthesiology personnel (Ven de Velde & Carvalho, 2016; Lin et al., 2014). Respiratory monitoring, including capnography, cannot be viewed as an alternative to the presence of a trained clinician (Marwah et al., 2012). Supplementary oxygen via nasal cannula reduced the frequency but not the severity

or duration of desaturation episodes (Marwah et al., 2012). This supports the recommendation to administer supplementary oxygen to all parturients using remifentanil PCA and reinforces the need for a high-quality protocol and nursing education to implement a remifentanil PCA program (Messmer et al., 2016). Measures should also be taken to prevent errors, especially if infrequently used at a facility, as healthcare providers' relative lack of familiarity with remifentanil in the obstetric unit can compound safety concerns (Aaronson et al., 2017). Recommendations for improving patient safety include the following:

- The anesthesia provider must be present for the first 15-20 minutes during the initiation of remifentanil infusion and until the patient's analgesia has been established (United Regional, 2018). In addition, the provider should be present when changes are made to infusion parameters (United Regional, 2018).
- The labor and delivery RN should provide one-on-one care and always remain in the room except for brief absences, not to exceed 5 minutes, while the patient is receiving a remifentanil infusion (Van de Velde & Carvalho, 2016; United Regional, 2018). The RN should be ACLS and PALS certified and educated on the side effects of remifentanil (Messmer et al., 2016; United Regional, 2018). The RN should notify the provider if they observe any signs of complications of remifentanil infusion, including excessive sedation, oxygen saturation <94%, hypotension, nausea/vomiting, pruritis, and shivering (United Regional, 2018).
- Baseline blood pressure, heart rate, oxygen saturation, respiratory rate, sedation level, and pain score should be documented before starting a remifentanil infusion (Aaronson et al., 2017; United Regional, 2018). Vital signs should be taken every 5 minutes after the initiation of infusion or after any change in dose until

analgesia has been established (Aaronson et al., 2017; United Regional, 2018). After analgesia is established, vital signs can be taken every 15 minutes (United Regional, 2018).

- Continuous oxygen saturation via pulse oximetry and end-tidal CO2 monitoring must occur during the infusion and continue 15 minutes after the infusion is discontinued (Stocki et al., 2014; Marwah et al., 2012; United Regional, 2018). Supplemental oxygen should be administered via CO2 monitoring nasal cannula (Stocki et al., 2014; Marwah et al, 2012; United Regional, 2018).
- Ensure remifentanil infusion has dedicated IV line. No other medications are to be administered in the same line, nor should the line be flushed (United Regional, 2018).
- Naloxone (Narcan) should always be at the bedside (United Regional, 2018). Orders of 0.4 mg intravenous push every two minutes as needed should be available (United Regional, 2018). Administration parameters should include if the parturient respiratory rate is less than 10, obtunded, or unarousable (United Regional, 2018).
- Nursing orders should be written to stop the infusion and contact anesthesia if the nurse observes excessive sedation, oxygen saturations <94%, bradycardia, respiratory rate <10, or shivering (Ohashi et al., 2016; United Regional, 2018).

Discussion

Obstetrical patients should have multiple options for pain control, especially when neuraxial analgesia is contraindicated. Access to adequate pain management is a fundamental right that should not be withheld or denied to any patient regardless of age, ethnicity, or

socioeconomic status. The literature supports remifentanil PCA as an acceptable alternative when neuraxial anesthesia is contraindicated. Remifentanil's rapid onset and a short time to peak analgesic effect provide optimal pharmacokinetics for women undergoing painful labor contractions (Ansari et al., 2016). In addition, remifentanil's context-sensitive half-life is time-independent, and full recovery of respiratory drive occurs within 15 minutes after prolonged infusions (Dershwitz et al., 1995). Remifentanil, which is highly lipophilic, readily crosses the placenta but is rapidly metabolized by the fetal plasma esterases (Welzing et al., 2011; Kan et al., 1998).

Due to these unique pharmacokinetic properties and the quick redistribution and elimination in both the parturient and the fetus, PCA is an appropriate method for administration (Kan et al., 1998). Numerous remifentanil administration regimens and settings for labor analgesia have been published, including PCA bolus with lockout, continuous infusion, and combined strategies. 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 included in these studies were homogeneous in nature with most being healthy ASA I or II patients who met relatively strict inclusion criteria. (Balki et al., 2007; Shen et al., 2013; Jost et al., 2013; Balcioglu et al., 2007; D'Onofrio et al., 2009; Tveit et al., 2013). Shen et al. (2013) conducted a double-blinded, randomized control trial comparing maternal and neonatal effects of remifentanil PCA versus remifentanil continuous infusion. The results suggest remifentanil PCA provides better pain relief with similar maternal side-effects and placental transfer (Shen et al., 2013). Their PCA regimen included a stepwise increase in PCA bolus starting at 0.1mcg/kg bolus, with increase in increments of 0.1mcg/kg to 0.4mcg/kg max (Shen et

al., 2013). Observational studies conducted by Balki et al. (2007) and Balcioglu et al. (2007) included a background infusion with their PCA bolus, both recommending different regimens. More studies are needed to determine the safest and most effective dosing regimen for remifentanil PCA infusion.

Compared to other analgesic modalities, there is evidence that remifentanil is superior to IM meperidine, IV fentanyl, and inhaled nitrous oxide. Remifentanil is superior to IM meperidine due to a greater reduction in pain scores, increased maternal satisfaction scores, fewer conversions to epidural analgesia, increased spontaneous vaginal delivery, and fewer required instrumental deliveries while maintaining similar safety profiles (Duoma et al., 2010; Leong et al., 2011; Wilson et al., 2018). Systemic IV fentanyl and remifentanil shared similar mean pain scores, but women given fentanyl were more likely to convert to epidural analgesia (Marwah et al., 2012). Remifentanil administration in parturients has led to oxygen desaturations, especially during the second stage of labor (Duoma et al., 2010; Marwah et al., 2012). When remifentanil PCA was compared to inhaled nitrous oxide, remifentanil was found to have superior analgesic effects (Volmanen et al., 2005).

Neuraxial anesthesia, including epidural analgesia, remains the gold standard for labor analgesia (Lee et al., 2017). American Society of Anesthesiologists and the American College of Obstetricians and Gynecologists also state that epidural analgesia is the most flexible and effective analgesic modality in obstetrics with the fewest sedative effects (Jelting et al., 2017). Studies included in this review elucidated that parturients using remifentanil PCA were more satisfied with pain relief than those receiving parental opioids but were less satisfied than those receiving epidural analgesia (Jelting et al., 2017; Sugur et al., 2020; Jia et al., 2020). Epidural

analgesia may provide superior pain relief, but remifentanil may be an acceptable alternative when epidural is contraindicated without increasing either maternal or neonatal side effects.

Adverse events associated with remifentanil include maternal apnea, hypoxia, respiratory depression, bradycardia, pruritis, nausea and vomiting, and cardiac arrest (Logtenberg et al., 2019). In general, when compared to other agents used for labor analgesia, remifentanil is well tolerated and safe. The primary concern is the potential for maternal oxygen desaturation. However, this is usually transient and easily corrected by a dose reduction or administration of nasal oxygen. Given maternal respiratory depression and apnea concerns, facilities must implement standardized protocols and monitoring for remifentanil PCA administration. Patients should have one-to-one nursing care and hemodynamic monitoring. Continuous maternal oxygen saturation and apnea monitoring via end-tidal capnography are the standard of care (Ven de Velde & Carvalho, 2016; Lin et al., 2014). Remifentanil PCA has been associated with increased maternal adverse events compared to epidural analgesia but an equal degree of risk as IM meperidine (Logtenberg, 2019; Wilson et al., 2018). Neonatal adverse effects, which would be associated with a low Apgar score, have rarely been associated with remifentanil. There was no significant difference between epidural and remifentanil neonatal outcomes (Liu et al., 2014). Compared to IV fentanyl and IM meperidine, remifentanil PCA had lower neonatal adverse effects (Liu et al., 2014; Tveit et al., 2012; Zhang et al., 2021). Facilities that reported using remifentanil more than ten times in the previous year had no maternal or neonatal complications from remifentanil PCA (Aaronson et al., 2017).

Conclusion

Remifentanil PCA appears to provide the most effective non-neuraxial labor analgesia, with high levels of maternal satisfaction and favorable delivery and neonatal outcomes.

However, safety measures should be implemented because of the incidence of maternal respiratory depression, maternal hypoxia, respiratory arrest, and cardiac arrest reported with remifentanil. Recommendations to improve maternal safety include one-on-one care with an ACLS trained labor nurse, an anesthesia provider in-house and immediately available, continuous pulse oximetry, continuous capnography, vital signs every 15 min, and supplemental oxygen. Every labor nurse should be capable of identifying and managing maternal apnea, educated on remifentanil, the PCA pump, and dosing for labor analgesia. Such issues currently limit the widespread adoption of remifentanil PCA protocols for routine use for labor analgesia in the United States when neuraxial anesthesia is contraindicated.

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