usually feasible for an epidural catheter to be re-inserted in an emergency. It also requires the anaesthetist to explain this additional procedure to the patient and gain informed consent in a challenging situation. This extra workload i.e., explaining, gaining informed consent, and inserting a spinal anaesthetic, may be stressful for the anaesthetist. Also, they are now required to perform a procedure in a time-pressured and high-stakes environment. Performance anxiety may also play a part if the anaesthetist is very keen to avoid a general anaesthetic, for example, if they feel the patient’s airway looks particularly difficult or the patient has pre-eclampsia and would therefore be at a higher risk of complications.

Patient perspectives should also be considered. The author has found no published literature specifically relating to patient preference regarding epidural or spinal anaesthesia for emergency Caesarean section. However, it is reasonable to think that a patient who has a working labour epidural already has confidence in the technique and as a result, may feel more reassured with epidural anaesthesia for emergency Caesarean section as compared to alternatives.

In summary, labour epidurals providing satisfactory analgesia should be considered for a top up to provide epidural anaesthesia for emergency Caesarean sections. In fact, this is one of the main benefits of siting labour epidurals in patients who are at a higher risk for Caesarean section and is a strong feature of obstetric anaesthesia practice using the principles of Planning, Preparation and Pre-emption. In addition, there are disadvantages to the alternative of removing the labour epidural and using a spinal anaesthesia. Furthermore, there are cost, environmental, anaesthesiologist, and patient considerations that may support the choice of epidural anaesthesia over spinal.

REFERENCES

SP22.1 REMIFENTANIL PCIA HAS NO PLACE IN LABOR ANALGESIA

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Introduction
Neuraxial techniques represent the gold standard for labor analgesia. They compare favorably to other proposed alternatives in terms of efficacy and safety.
Among potential alternatives, Remifentanil patient-controlled intravenous analgesia (PCIA) has been suggested to be a valuable option for labor analgesia either in case of contraindication to neuraxial techniques or even as a routine alternative.
However, before proposing and promoting Remifentanil PCIA in this indication, it is paramount to consider the real efficacy, the safety profile and the benefit-risk ratio of this drug.
Pharmacology
Remifentanil is an ultra-short acting μ-receptor agonist with a rapid onset of action and a rapid elimination. It is metabolized to an inactive metabolite by plasma and tissue esterases.
The blood-brain equilibration occurs in 1.2–1.4 min. The context sensitive half-life is 3.5 min and is independent of the duration of administration.
In theory, the rapid onset of analgesia (30–60 sec) which peaks at 2.5 min could offer advantage for labor analgesia. However, the mean duration of a uterine contraction is 70 sec and a bolus administered at the beginning of a contraction is likely to provide analgesia for the next contraction. During pregnancy, because of an increased volume of distribution and an increased clearance, Remifentanil plasma concentrations are approximately 50% of those found in non-pregnant women.
Remifentanil crosses the placenta rapidly as demonstrated by the mean umbilical vein to maternal artery concentration ratio of 0.88. However, Remifentanil is rapidly metabolized.
and redistributed in the fetus as demonstrated by the mean umbilical artery to umbilical vein concentration ratio of 0.29.1

**Conclusion:** From a pharmacologic viewpoint, Remifentanil may provide advantages in comparison with other opioids proposed for labor analgesia.

**Neuralgic efficacy for labor analgesia**

Several studies and meta-analysis have evaluated the anaglicolic efficacy of Remifentanil PCA in comparison with other techniques for labor analgesia.

**Remifentanil vs nitrous oxide**

Nitrous oxide for labor analgesia has only modest analgesic effects.2,3 Remifentanil PCA alone or in combination with nitrous oxide has been demonstrated to provide more effective analgesia than nitrous oxide alone. However, the reduction in pain scores with Remifentanil PCA is usually mild.4,5

**Remifentanil vs other parenteral opioids**

A large variety of opioids including pethidine (meperidine), morphine, fentanyl, sufentanil, alfentanil and tramadol have been used for parenteral labor analgesia despite their poor efficacy in this indication.6-9

As compared to pethidine, Remifentanil PCA is associated with a greater decrease in VAS scores after 1 hour but this difference disappears after 1 hour.10

The RESPITE trial, a multi-center, randomized controlled study reported that Remifentanil PCA instead of I.M. pethidine was associated with a significant lower proportion of women requesting epidural analgesia (19% vs 41%). Nevertheless, even if the mean VAS pain score in the Remifentanil PCA group was significantly lower than in the I.M. pethidine (50 vs 65), the reduction in VAS pain scores was similar in both groups (-25) and was corresponding to a mild analgesic effect in line with previous studies.12

Compared with fentanyl, Remifentanil PCA provides either no analgesic benefit or only a transient benefit limited to the first hour of administration.10,11

**Remifentanil vs neuraxial analgesia**

Several randomized controlled trials and two meta-analysis have compared the analgesic efficacy of Remifentanil PCA with epidural analgesia for pain relief during labour.

All these studies clearly demonstrate the superiority of epidural labour analgesia in terms of pain scores and reduction in pain scores compared to Remifentanil PCA. In addition, these studies underline the limited duration of the analgesic effect of remifentanil as opposed to the sustained and superior analgesic effect of epidural analgesia.14-18

**Conclusion**

Remifentanil PCA provides better analgesia than nitrous oxide and pethidine but epidural analgesia provides significantly better analgesia than Remifentanil PCA.

In addition, the mild analgesic efficacy of Remifentanil PCA is fading with the progression of labour and the duration of administration.

**Neonatal safety**

**Remifentanil vs neuraxial analgesia**

In a 2014 meta-analysis of 5 RCTs including 886 patients and comparing Remifentanil PCA with epidural analgesia, Apgar scores were similar between both groups. Intriguingly, Remifentanil was associated with a slightly higher UA pH value.17

Another meta-analysis of 11 RCTs and 3039 patients published in 2021 did not identify significant difference in the incidence of Apgar Score < 7 at 1 and 5 minutes between groups.18

**Remifentanil vs pethidine**

In a 2011 systematic review, the results of 7 studies on 349 patients comparing Remifentanil versus meperidine (pethidine) for labor analgesia were analyzed.

Six of these 7 studies reported no difference in Apgar scores. One was terminated early because of significant lower Apgar scores in the meperidine group.

No difference was reported in the 3 studies reporting on cord pH.11

Neurological and adaptive capacity score (NACS) was reported in 2 studies. One study reported significant lower NACS at 30 min but not at 120 min with meperidine.11

In the largest study comparing Remifentanil PCA with IM pethidine, the RESPITE trial, there was a higher incidence of non-reassuring fetal heart rate (NRFHR) requiring interventional delivery with IM pethidine versus Remifentanil PCA (26% vs 14%). However, Apgar scores, incidence of fetal acidosis, need for neonatal resuscitation and NICU admission were similar.12

**Remifentanil vs Fentanyl**

In a 2010 prospective, randomized, double-blind study comparing PCA with Remifentanil meperidine or fentanyl, no difference was found in Apgar scores, cord pH and BE, NACS and CTG reactivity.10

In a 2012 retrospective cohort study comparing Remifentanil vs Fentanyl PCA, Fentanyl was found to be associated with a higher need for neonatal resuscitation.13

**Conclusion**

In terms of neonatal safety, compared to pethidine, Remifentanil is associated with better neonatal outcomes evaluated by NACS and incidence of NRFHR. Compared to fentanyl, Remifentanil is associated with better Apgar scores and lower need for neonatal ventilation.

Compared to neuraxial analgesia, there is no difference in Apgar scores.

Of note, in many studies, Remifentanil was discontinued during the seconds stage of labor for fear of neonatal depression and expert authors advise the availability of oxygen, naloxone and pediatrician when Remifentanil PCA is used for labor analgesia.19

**Maternal safety**

In the first study reporting the use IV remifentanil for labor analgesia published in 2000, only 4 women were included and this study was terminated early because of the incidence of maternal side effects (sedation, desaturation and airway obstruction).20

More than 20 years later, accumulating evidence from numerous studies and case reports have reinforced this concern.

In a 2014 randomized controlled trial comparing Remifentanil with epidural analgesia, Stocki et al. demonstrated a significant reduction in respiratory rate and Spo2 with remifentanil.

Hypoxemia alarm was triggered in 68% of patients in the remifentanil group despite continuous supplementary O2 administration vs 16% in the epidural group.

26% of patients in the remifentanil group exhibited apnea events vs 0% in the epidural group.15

A secondary analysis of data collected in this previous study was published in 2017 by Weiniger C et al. Apnea...
episodes lasting more than 30 sec were detected in 52% of patients receiving remifentanil. Interestingly, pulse oximetry, the most frequently used monitor to detect respiratory depression during labor, detected less than 15% of apneas.21

Two meta-analyses have addressed the issue of maternal hypoxemia as secondary endpoints. In 2020, Lu et al. reported a significantly higher risk of respiratory depression with Remifentanil PCIA as compared to epidural analgesia (RR: 2.86 (1.65–4.96), p= 0.0002). (22) In 2021, Zhang et al. reported also an increased risk of maternal oxygen desaturation with Remifentanil PCIA as compared to epidural analgesia (RR= 3.23, 95% CI 1.98–5.30).18

In addition, several case reports have described respiratory arrest and cardiac arrest in patients using Remifentanil PCIA for labor analgesia.23 24

As a consequence, several editorials and review articles have been published to raise awareness of this risk of maternal respiratory depression and to challenge the validity of Remifentanil PCIA for labor analgesia.25–28

By contrast, several cohort studies aimed to be reassuring.

In a 2019 retrospective analysis, Melber AA et al. reported the results of a 6 years audit (2010–2015) of the outcome data of the RemiPCA SAFE network. Among 5740 data sets, no need for maternal ventilation or cardiopulmonary resuscitation was reported.

Of note, during this period, despite the remifentanil bolus dose was progressively reduced to a mean dose of 18 µg, the incidence of maternal hypoxia remained as high as 24%.

The authors themselves also acknowledged that underreporting of severe events could not be excluded.29

In another 2019 retrospective single-center study, Murray H et al. reported outcomes on 8100 women receiving Remifentanil PCIA for labor analgesia between 2005 and 2014.

Up to 53% of patients required supplementary oxygen administration for maternal desaturation but no additional severe incident was reported.

Nevertheless, the authors themselves acknowledge the low-quality evidence provided by these data on maternal safety outcome and emphasize the need for a constant presence of a midwife for uninterrupted monitoring and management of respiratory depression.30

A nationwide survey in 61 maternity units in the Netherlands aiming to collect data on serious adverse events related to the use of Remifentanil for labor analgesia was published in 2019 by Logtenberg S et al. Over a period of more than 10 years they identified 17 cases of single maternal desaturation and 10 maternal cases of apnea, bradycardia and/or cardiac arrest. All cases were resolved without irreversible damage. Despite underreporting of serious adverse events was likely, the conclusion was that the risk of potentially life-threatening adverse events seems to be low.11

When Remifentanil PCIA was compared to pethidine, maternal desaturation was 3 times more frequent with Remifentanil in the RESPITE trial.12

This result is in line with the results of another randomized trial demonstrating a significantly higher incidence of maternal desaturation with Remifentanil than with fentanyl and meperidine.10

Conclusion

Maternal respiratory depression is more common with Remifentanil than with other opioids or epidural analgesia.

Remifentanil Dosing regimen.

Among all the studies published since 2000, bolus size ranges from 0.1 to 1.0 µg/kg. Lockout interval ranges from 1 to 5 minutes and a minority of studies have used a background infusion ranging from 0 to 0.2 µg/kg/min.9

These large variations in the proposed Remifentanil PCIA regimen underline the challenge of matching analgesic efficacy with maternal safety and the narrow therapeutic index of this drug for labor analgesia.

An initial setting consisting in a 20–50 µg bolus and a 1–3 min lockout without background infusion has been proposed.9

Many recent studies promoting the use of Remifentanil PCIA used a 40 µg bolus and a 2 min lockout.10 12 14 16 30 32

The RemiPCA SAFE network decreased progressively the recommended bolus size from initially 20–40 µg (mean= 27±9µg) to actually 10–30 µg (mean= 18 ±2µg). This reduction in the bolus size was driven by safety concerns and led to a reduction in the analgesic efficacy.29

Monitoring and surveillance

The majority of authors agree that during use of Remifentanil PCIA for labor analgesia, a continuous one to one midwife care is required to detect respiratory depression and sedation. In addition, monitors to detect inadequacy of maternal ventilation (capnography and apnea monitors) or oxygenation (spO2 monitor) are recommended.

Routine supplementary oxygen administration is controversial as it might delay the detection of maternal hypoxemia.9 19

Obstetrical outcomes

Mode of delivery

A 2021 meta-analysis of randomized controlled trials compared Remifentanil PCIA versus epidural analgesia for labor analgesia. The rate of spontaneous delivery was reported in 9 studies involving 2860 patients and women receiving Remifentanil PCIA had a comparable rate of spontaneous delivery to those receiving epidural analgesia.18

Epidural Fever

Labour epidural analgesia has been reported to be associated with an increased incidence of intrapartum maternal fever. Studies comparing Remifentanil PCIA versus epidural analgesia for labor analgesia have produced conflicting results regarding the influence of the analgesic technique on maternal temperature.

In a 2015 randomized controlled trial, Douma et al. reported a significant higher incidence of maternal fever associated with epidural (37%) compared with remifentanil PCIA (10%).32

In another 2017 randomized trial, Logtenberg et al. did not find any difference in the incidence of maternal fever between Remifentanil PCIA (10%) and epidural analgesia (8%).33

In a 2020 meta-analysis including 6 randomized controlled trial and 3341 patients, Lu et al concluded that there is no solid evidence to illustrate that intrapartum maternal fever is lower with Remifentanil PCIA than with epidural analgesia.22

Risks of decreasing epidural rate

An increased use of alternative analgesia such as Remifentanil PCIA might carry the risk of an increased use of general anesthesia for intrapartum cesarean section or other obstetrical indications. This is particularly true for high-risk parturients.
such as patients undergoing a trial of labor after C-Section, obese patients and pre eclamptic patients for whom epidural analgesia is strongly recommended.

Cost-effectiveness profile

A multicenter randomized controlled trial in 15 hospital in the Netherlands (RAVEL trial) compared the costs of Remifentanil PCIA versus epidural analgesia for pain relief during labor. Cost of Remifentanil PCIA was influenced by the one to one nursing requirement and the cost of the medication whereas cost of epidural analgesia was influenced by the cost of equipment and material. Mean cost did not differ significantly between both groups.14

Conclusion

Remifentanil compares favorably to other systemic opioids for labor analgesia in terms of analgesic efficacy and neonatal depression.

Analgesic efficacy of Remifentanil is also superior to that of nitrous oxide in this indication.

However, the analgesic effect of Remifentanil remains usually modest, short-lasting and inferior to neuraxial analgesia. This modest analgesic effect is sometimes confused with the relatively high level of maternal satisfaction associated with any type of analgesic strategy.

From the maternal safety point of view, the use of Remifentanil for labor analgesia is associated with an increased risk of maternal respiratory depression and apnea. Case reports of cardiorespiratory arrests have been published.

The risk of maternal respiratory depression has led to significant reductions in the Remifentanil bolus doses proposed for labor analgesia in such an extent than one can doubt that such low doses are really effective despite the reported maternal satisfaction.

This risk of maternal respiratory depression has also led to several recommendations related to monitoring and surveillance such as a continuous one to one midwifery care and a continuous respiratory monitoring including capnography.

These safety-related requirements are most likely impossible to be met in the vast majority of maternity units.

Regarding some obstetrical endpoints such as mode of delivery and maternal hyperthermia, no benefit has been associated with the use of Remifentanil as compared to epidural analgesia.

From an economic point of view, Remifentanil does not confer any benefit.

Given all these benefits vs risks considerations, Remifentanil cannot be considered as a routine alternative to neuraxial techniques for labor analgesia.

REFERENCES