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General discussion
In this thesis I present the results of the analysis of the primary outcomes (satisfaction with analgesia and costs) of the RAVEL trial and of sub analyses addressing secondary outcomes regarding safety. The RAVEL trial compared the use of remifentanil PCA to epidural analgesia as analgesia during labour.

We found that women randomised to epidural analgesia were more satisfied with their pain relief than women randomised to remifentanil PCA. There was no difference in costs between both strategies. With respect to safety, remifentanil PCA increases the risk of maternal desaturation as was shown in the RAVEL cohort as well as in meta-analysis of previously published studies. Pain relief during labour with remifentanil does not appear to increase the risk of persistent postpartum pain.

In this final chapter I will first discuss our findings in relation to the results of previous studies and discuss the strengths and weaknesses of our study. I will finish with questions that remain after previous described findings and give directions for future research and focus on implications for clinical care.

**Effectiveness of remifentanil PCA and satisfaction with pain relief**

Superiority of epidural analgesia to remifentanil PCA in improving pain intensity scores was established in the first trials comparing these types of analgesia but equality in satisfaction with pain relief was suspected.¹ ² These studies, however, were powered to detect a difference in pain intensity scores not a difference in satisfaction. The RAVEL trial showed that remifentanil PCA is inferior to epidural analgesia with respect to satisfaction with pain relief. Our findings regarding pain intensity were comparable to previous published studies showing significantly lower pain intensity scores in the epidural group. Since our study was designed to prove equality in satisfaction with analgesia between both strategies there was sufficient power to reject equality.

Our subgroup analysis shows that epidural analgesia is superior to remifentanil PCA with respect to pain intensity and satisfaction in all subgroups including multiparous women. However, theoretically a group of women might benefit from having access to remifentanil PCA as an alternative to epidural analgesia. These are the women that deliver quickly after the request for analgesia, they can be multiparous women or nulliparous women in the last part of the first stage of labour. In the following paragraph I will discuss this matter.

Subgroup analysis in our study of only multiparous women showed that this subgroup is more satisfied with epidural analgesia than with remifentanil PCA. Logtenberg et al performed a randomised controlled trial of remifentanil PCA and epidural analgesia with the same study design as the RAVEL trial in women of low obstetric risk.³ Their results were the same as the RAVEL trial with respect to pain intensity scores and satisfaction. They found no significant difference in satisfaction with analgesia in their subgroup analysis of multiparous women. In their study, women were more likely not to receive any analgesia despite of their request when randomised to epidural analgesia. In the remifentanil allocated group 10% did not receive analgesia compared to 25%
in the epidural allocated group. This could be due to anaesthesiologists being reluctant to start epidural analgesia when rapid progression to the second stage of labour is expected or because these women delivered before the epidural catheter could be placed. We hypothesize that this subgroup of women (i.e. multiparous women) with a request for pain relief might benefit from having access to alternatives to epidural analgesia such as remifentanil PCA which are possibly quicker and easier to start. Further research on satisfaction with analgesia in multiparous women at all stages of labour is needed.

Women delivering within a relative short time after a request for analgesia might benefit from having access to alternative pain relief other than epidural analgesia. An RCT comparing remifentanil PCA to fentanyl and meperidine PCA showed that remifentanil PCA provide better reduction of pain intensity scores than controls but that pain scores return to baseline after four hours.4 With these data Douma et al. concluded that remifentanil PCA should be considered only when delivery is expected within this time frame. Considering these results a subgroup of women that could benefit from alternatives to epidural analgesia are parturients who request analgesia late in the first stage of labour, when a quick delivery is expected. Future studies with adequate power are needed to make a good assessment if these women that are expected to deliver within a relative short time after a request for analgesia, could benefit from alternative methods of analgesia like remifentanil. Until these studies are performed the results of our study demonstrate that epidural analgesia is superior to remifentanil PCA in terms of efficacy and satisfaction.

Costs of remifentanil PCA and epidural analgesia

One previous trial and one review report on the costs of epidural analgesia versus intravenous analgesia.5,6 In general costs of labour analgesia consists of two components, first baseline costs for labour which are equal in both groups and second incremental costs associated with complications and involvement of anaesthesiological nursing and staff. In both the study of Macario and our study cost effectiveness analysis was not performed because direct or indirect benefits for society are largely intangible. The incremental costs for analgesia of epidural analgesia were estimated by Macario et al. at $338, largely because of the increase in costs due to involvement of an anaesthesiologist.

Our trial was, to our knowledge, the first trial addressing costs of remifentanil PCA and epidural analgesia. From an economic perspective, there is no preferential pain treatment in labouring women. Though not statistically significant, remifentanil PCA would appear to be less expensive than epidural analgesia. The difference in total costs from the start of labour until ten days postpartum is -282 euro, the difference in costs of analgesia only is -2 euro. The main difference is due to a difference in costs for neonatal admission and since there is no difference in the percentage of neonates admitted or the reasons for admission between groups we have to assume this difference is based on chance. When developing the study protocol and calculating a possible difference in costs we thought that remifentanil PCA would be administered without the intervention of an anaesthesiologist, thus making it the less expensive alternative due to lower personnel costs. Our
economic evaluation proved otherwise, there is no significant difference in costs between both strategies.

Safety of remifentanil PCA as labour analgesic

The major concern with remifentanil are respiratory complications which could be life threatening to both mother and fetus. Previous studies show lower saturation scores and more episodes of desaturation in women using remifentanil PCA compared to epidural analgesia. Our meta-analysis (chapter 7) confirms the findings on maternal respiratory complications reported previously. We included 14 RCTs and 2 observational studies. Compared to other opioids there was no significant difference in maternal desaturation (SpO2 <95%) in women treated with remifentanil PCA. However, five studies did report a higher incidence of desaturation, so a distinct trend towards more desaturation was observed. Compared to epidural analgesia women using remifentanil PCA had significantly more desaturation (SpO2 <90% and <95%). The incidence of low respiratory rate (<8) was poorly reported but no significant difference was found.

Five case-reports have been published on serious complications in women using remifentanil during labour, three describe a respiratory arrest and two a cardio-respiratory arrest. Of the cases of respiratory depression one occurred in a woman treated with only continuous infusion (rate 0.1 µg-kg-min), one in a woman that had previously had epidural analgesia so an opioid overdose was suspected and one in a woman treated with 40 µg boluses with a lockout of 2 minutes. Of the cases of cardio-respiratory arrest one woman received a bolus dose of 400 µg due to a mistake in the preparation of the medication and the other received remifentanil after also receiving codeine and diamorphine so in this case an opioid overdose was also suspected. All authors judge that maternal monitoring, especially monitoring saturation and one-to-one nursing is vital and that this one-to-one nursing entails that a nurse trained in basic life support and mask ventilation should be present in the labour room at all times.

Safety of women using remifentanil PCA as labour analgesia is only guaranteed with strict monitoring and safety measures. As desaturation is a late sign of respiratory depression one-to-one nursing or capnography are the only methods to detect respiratory depression when it occurs. Because it was unclear how labouring women on remifentanil in Dutch hospitals were monitored, the Dutch Health Inspectorate (Inspectie voor de Gezondheidszorg: IGZ) ordered the Societies of Gynaecologists (NVOG), Anaesthesiologists (NVA), Midwives (KNOV) and clinical Pharmacologists (NVZA) in 2013 to develop a guideline for the use of remifentanil PCA on the labour ward after learning that remifentanil was used outside of clinical trials in numerous Dutch hospitals. It is important that women are monitored by a health care professional that is trained in basic life support as the most important side effect of a potent opioid like remifentanil is respiratory depression. An anaesthesiologist, obstetrician or clinical midwife should be present in the labour room during the first 30 minutes after the start of remifentanil and after every increase in bolus dose. A nurse should be present for the minimum of the first hour but continuous one-to-one nursing is advised. Because our study (chapter 6) showed that oxygen saturation is significantly lower at all times we argue that one-to-one nursing should be mandatory when using remifentanil for labour analgesia.
It is unclear at this moment to what extend these recommendations are implemented in Dutch hospitals. Only hospitals that comply with these recommendations will have a safe infrastructure for the administration of remifentanil on the labour ward. In future perspectives we will propose ways to evaluate compliance with guidelines and registration of side-effects and adverse events.

Analysis of maternal parameters from the RAVEL trial showed that maternal temperature was significantly higher in women in the epidural analgesia group, with a higher incidence of fever (temperature >38 °C), and that this persisted throughout labour. Also, more women were treated with antibiotics for suspicion of intrauterine infection. Our findings are in agreement with the results of previous studies. Our meta-analysis did not find a difference in rates of caesarean section nor vaginal instrumental delivery. This in contrast to the results of an earlier meta-analysis which showed an increased risk of vaginal instrumental delivery in women using epidural analgesia.

Concerns have been raised about long term consequences on intrapartum use of opioids and neurodevelopmental issues in childhood and a higher risk of substance abuse in adulthood. No long term follow up studies on opioids during labour have been performed to our knowledge. However, there are a few studies that address the effects of opioid use during labour in human and animal studies and follow up of children that received opioids in the NICU. Neonatal depression after opioids exposure in utero can last up to three days. Animal studies suggest that the use of opioids in infants might have an increased risk of hypersensitivity, impaired learning and neurobehavioral deficits in childhood. Follow up of neonates treated with morphine when admitted at a NICU at five and nine years of age shows no negative consequences in terms of intelligence, visual motor integration and behaviour.

The reported prevalence of persistent postpartum pain (PPP) in women who gave birth either vaginally or by CS in previous studies varies from less than 1% to almost 20%. Apart from the differences in study samples and methods to report pain, this large range might be explained by the fact that most studies did not discriminate between pre-existing and new onset pain from delivery and did not specify the location of this chronic pain. In contrast, Eisenach et al defined the primary outcome measure as pain which began during delivery at a location which could be attributed to the delivery (e.g., pelvis, perineum, and abdomen). In their study, PPP after childbirth was relatively rare, with a prevalence of 1.8% at 6 months and 0.3% at 12 months. Their study and definition of PPP is similar to the one we used for our study. In our cohort 7.3% of women reported any pain and 6.1% reported significant pain related to the delivery. Compared to spontaneous delivery, caesarean delivery provided protection against persistent pain (odds ratio, 0.12; 95% CI, 0.01–0.63, P<0.05). It is plausible that the protective effect of caesarean section is related to the postoperative treatment of pain with opioid and/or epidural analgesia. This reasoning is in agreement with the theory that severe postpartum pain is associated with a high probability of development of PPP, and suggests that effective relief of severe pain after vaginal delivery would reduce the prevalence of PPP.
Future perspectives/Implications for future research

It is still unclear which women could potentially benefit from having access to remifentanil PCA as analgesia during labour. In my opinion, only women with a contra-indication for epidural analgesia or women where placement of the epidural catheter failed should be eligible to receive remifentanil PCA at this moment.

However, as described previously, there might be women that could benefit from remifentanil PCA. First, women that are expected to deliver quickly after their request for analgesia. Future research in multiparous women and women in the final stages of labour might define more indications for the use of remifentanil as pain relief during labour.

Second, as feeling in control and informed consent are important aspects of satisfaction with childbirth one could argue that women who are counselled appropriately on effectiveness (i.e. inferior to epidural analgesia), satisfaction and side-effects, should be able to have access to remifentanil PCA, provided that appropriate measures are taken to ensure safety of both mother and fetus.

Remifentanil is a potent opioid with a serious risk of causing respiratory problems. With the right monitoring and precautions remifentanil is a viable option for labour analgesia but at this moment it is unclear whether monitoring is performed according to the recommendations in the SOP. This has to be evaluated in the near future. It is important to know which hospitals use remifentanil as analgesia during labour, which women are eligible to receive remifentanil and how they are monitored. At the time of the writing of this discussion the IGZ is evaluating the use of remifentanil and monitoring by visiting random hospitals and inspecting their infrastructure and training. We have to develop an infrastructure for continuous registration and evaluation in the future. There should be a central organ to report adverse events, respiratory depression requiring ventilation and cardiac arrest. This can be one of the Colleges (e.g. working party on maternal morbidity (INOSS/NethOSS)) or the IGZ. The IGZ describes a calamity as an unexpected or unintended event that has a possible relation to quality of care and has serious consequences for the patient or results in permanent injury or death. Since this is already the way of reporting calamities it might be sensible to use this infrastructure for the monitoring of adverse events with remifentanil.

After ensuring safe monitoring of women that are treated with remifentanil we could evaluate if this has any effect on the incidence of serious adverse events with the side note that that incidence is currently unknown. Prospective case series are the best way to assess the incidence of side effects, but because serious adverse events (respiratory arrest, cardiac arrest) are rare very large numbers are required. In absence of large enough prospective trials more large case series are needed reporting on safety to make a more accurate risk-to-benefit analysis.

Several dose finding studies have been done, most using a flexible weight-dependent dose with or without the use of background infusion. Hill et al recommend to use a dose of 40 µg with a lockout time of 2 minutes after reviewing all available data and weighing safety against efficacy. Because of an increase of respiratory complications they advise against the use of a background infusion. There are no studies comparing this dose to different doses and no studies on optimal lockout time. This might be a subject for future research. An RCT comparing 30 to 40 µg or 30 to a
weight dependent dose and after the optimal dose is established comparing a lockout time of two minutes to three minutes might answer remaining questions.

This thesis focusses on remifentanil versus epidural analgesia and shows that remifentanil is inferior to epidural analgesia with respect to efficacy and satisfaction. The study performed by Douma et al concluded that remifentanil PCA gives better analgesia than fentanyl or meperidine PCA. From this one might conclude that remifentanil might have a place between meperidine and epidural analgesia. Nitrous oxide is also used as labour analgesia, mostly by women in the final part of the first stage of labour. This is also the stage of labour where women might benefit most from remifentanil. To our knowledge one trial has been performed on efficacy of remifentanil and nitrous oxide. This was a double blind crossover trial in which remifentanil PCA and nitrous oxide were administered for 20 minutes each. Remifentanil provided better improvement of pain intensity scores and higher satisfaction. However, this was a small trial and possibly underpowered for satisfaction and both treatments were only given for twenty minutes. An RCT on satisfaction of remifentanil PCA and nitrous oxide in the last phase of the first stage of labour could establish the position of remifentanil PCA and nitrous oxide as analgesia during labour.

Long term follow up until adulthood could assess the risk of addiction or substance abuse later in life in children of mothers who were treated with opioids during labour. No such follow up studies have been performed before. However, it is unclear whether such a study is feasible because of logistical problems with very long term follow up. Follow up for even shorter periods has been proven difficult because of relocation of patients and funding difficulties. The answers to these questions might come from the follow up of large cohorts, like the Generation R study or similar future prospective cohort studies. This could help with the very large numbers needed for a not very common outcome.

In our study regarding chronic post-partum pain (PPP) we found a higher incidence of PPP than expected. This prompted the question of the prevalence of PPP in the Netherlands. We would like to study the prevalence of PPP in the Netherlands and possibly perform a prospective RCT on prophylactic analgesia in vaginal birth versus no prophylactic analgesia to test our hypothesis that the use of prophylactic analgesia explains the difference in chronic postpartum pain between women who underwent caesarean section and those who delivered vaginally.

Conclusion

Epidural analgesia provides superior analgesia to remifentanil PCA. Women randomised to epidural analgesia with a request for pain relief are more satisfied with their analgesia than women randomised to remifentanil PCA.

Costs of epidural analgesia and remifentanil PCA are not significantly different. From an economic perspective, there is no preferential pain treatment in labouring women.

Epidural analgesia is associated with a greater incidence of fever and significantly higher temperature. Remifentanil PCA has an effect on maternal SpO2 with significantly lower mean
SpO2 during the labour period. This shows that respiratory complications are a serious problem associated with remifentanil and that continuous monitoring by trained personnel is obligatory. Persistent postpartum pain affects many women. Of surveyed women, 6.1% complained of significant pain related to delivery. Since this was a retrospective follow up study this results might be explained by the study design and these findings have to be evaluated by further research.
References


3. Logtenberg 2015. Satisfaction with labor pain with remifentanil versus epidural analgesia; a randomized trial. Submitted for publication.


