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Summary
This thesis describes the results of the RAVEL (remifentanil patient controlled analgesia versus epidural analgesia in labour) trial. The RAVEL trial was a randomised controlled equivalence trial (N=1358) comparing remifentanil patient controlled analgesia (PCA) and epidural analgesia as pain relief during labour. Because previous studies showed that, although epidural analgesia is superior to remifentanil PCA in terms of reduction of pain intensity scores, satisfaction with analgesia seemed to be comparable, we designed this trial as an equivalence trial to demonstrate equivalence in satisfaction with pain relief. 

Chapter 1 is a general introduction where the most relevant literature and background information that form the basis of this thesis are provided.

Before start of the RAVEL trial we aimed to assess the use of remifentanil PCA and epidural analgesia in the Netherlands and to investigate beliefs of obstetricians and anaesthesiologists on analgesia through an online questionnaire. The Dutch guideline “Medicamenteuze pijnbestrijding tijdens de baring” advises to use remifentanil PCA only in clinical trials and to have epidural analgesia available for all women 24/7. As the use of remifentanil PCA is not recorded in the LVR (Landelijke Verloskundige Registratie) and it was not clear if epidural analgesia was available in all Dutch hospitals 24/7 a questionnaire seemed the right way to investigate these questions. The results of this questionnaire are presented in chapter 2. According to official LVR data 26.6% of women received some kind of medical pain relief during labour in 2010 (15% epidural analgesia, 11.6% opioids). 81% of respondents to the questionnaire stated that epidural analgesia was available to all women 24/7 on their request with 92% availability during all hours if there is a medical reason. Remifentanil PCA was used in 44% of teaching hospitals and 55% of district hospitals. The mean use of remifentanil PCA in hospitals that offered it was 23%. Comparing results of hospitals only offering epidural analgesia to hospitals offering both epidural analgesia and remifentanil PCA shows that in hospitals where only epidural analgesia was available the use of analgesia was 20% (8-43%) while in hospitals where both epidural analgesia and remifentanil PCA were available the use of analgesia was 38% (26-63%) (p<0.001).

Chapter 3 outlines the study protocol for the RAVEL trial as it was published before the start of the trial.

Chapter 4 describes the results of the primary research question on equivalence of patient satisfaction with remifentanil PCA compared to epidural analgesia. Satisfaction with pain was measured using a Visual Analogue Scale (VAS) throughout labour in all women and with these serial measurements an Area Under the Curve (AUC) was calculated. The AUC for pain appreciation during labour for all randomised women was lower in the remifentanil PCA group (difference -2.8, 95% CI -6.9 to 1.3). This does not exclude a potential clinically relevant difference; therefore we could not conclude that the treatments are equivalent. Furthermore, in the subgroup of women who did actually receive analgesia, the AUC for pain appreciation after start of pain relief was significantly lower in women with a request for pain relief randomised to remifentanil PCA (difference -10.4, 95% CI -13.9 to -7.0).
The same results were seen in the AUC for pain intensity scores; these were significantly higher in women randomised to remifentanil PCA. Women randomised to remifentanil PCA requested pain relief more often than women randomised to epidural analgesia (RR 1.3, 95% CI 1.2-1.5). Maternal and neonatal outcome we not significantly different in both groups. Some side effects were more often reported in women who did receive analgesia. Temperature was significantly higher and hypotension more frequent in the epidural analgesia group. Oxygen saturation was significantly lower with remifentanil PCA. There were four respiratory depressions reported of <8 breaths per minute in the remifentanil PCA group and none in the epidural group. Nausea was reported more frequent in the group randomised to remifentanil PCA, but vomiting and itching were not.

As our hypothesis was that remifentanil PCA would be equivalent to epidural analgesia with respect to patient satisfaction we planned to perform a cost effectiveness analysis. Because equivalence was not proven we performed a cost evaluation. Chapter 5 presents these results. Mean costs for women randomised to remifentanil PCA were €2900 versus €3183 for women randomised to epidural analgesia (mean difference -€282 (95% CI -€611 to €47)). The largest part of this difference can be attributed to the higher costs of neonatal admission in the epidural group. This non-significant difference in costs for neonatal admission was -196 (95%CI -465 to 73). After the trial was finished a Standard Operating Procedure (SOP) for the use of remifentanil PCA on the labour ward was developed by the Dutch Heath Care Inspectorate (IGZ). So additionally we added scenario analysis post hoc to address the influence of the presence of an anaesthesiologist at the start of remifentanil PCA and to address the influence of continuous one to one nursing during administration of remifentanil. Taking only the costs of analgesia into account, the costs of remifentanil PCA increase when an anaesthesiologist is present at the start of analgesia and increase even more with continuous one to one nursing. Only when no anaesthesiologist is involved in the administration of remifentanil PCA and there is one to one nursing for only the first hour there is a significant difference in costs of analgesia in favour of remifentanil PCA.

In chapter 6 we evaluate respiratory complications and temperature in women using remifentanil. In concurrence with other published data we showed that women experience more episodes of desaturation and have an overall lower mean SpO2 when using remifentanil. Epidural analgesia is associated with a greater incidence of fever and significantly higher temperature overall. Remifentanil PCA has an effect on maternal SpO2 with significantly lower mean SpO2 during the labour period. The effect on time course of saturation differs between remifentanil and epidural analgesia. We also saw more desaturation episodes <92% in the remifentanil group. This shows that respiratory complications are a serious problem associated with remifentanil and that continuous monitoring by trained personnel is advised.

After the publication of the RAVEL trial and the STER (Saturation and Temperature in Epidural analgesia and Remifentanil PCA) a meta-analysis of maternal parameters incorporating all published randomised controlled trials and observational studies that compared efficacy and side effects of
remifentanil with any other labour analgesic was performed. The results of this meta-analysis are presented in chapter 7. Overall, although results are not significant, a distinct trend towards more desaturation was seen during administration of remifentanil PCA compared to other opioids. There were significantly more episodes of desaturation (SpO2 <95%) during administration of remifentanil PCA compared to epidural analgesia. Furthermore, there was more sedation in remifentanil PCA compared to epidural analgesia, more pruritus in remifentanil compared to other opioids. There seemed to be no difference in low respiratory rate (<8) or hypotension, however these incidents are rare and were poorly reported. There was no difference in CTG tracings, neonatal scores and mode of delivery between groups. Close observation of parturients receiving remifentanil, particularly continuous oxygen saturation monitoring and the availability of oxygen is strongly recommended.

We retrospectively surveyed women on the prevalence of persistent pain following childbirth that began during delivery. The aim of this study was to examine the prevalence of persistent postpartum pain (PPP) in a Dutch cohort and to evaluate a possible causal role for specific risk factors and the use of analgesia on the development of chronic pain after childbirth. The results of this study are presented in chapter 8. We observed that in 495 women, at a mean time of 2.3 postpartum years, 6.1% complained of significant pain related to delivery. A protective effect was observed following CS, while none of the other risk factors influenced the prevalence of PPP. Importantly, treatment of labour pain with either EA or RPCA had no effect on the occurrence of pain. One possible explanation for the lower incidence of PPP after caesarean section could be that postoperative treatment after caesarean section with epidural analgesia or opioids and thus effective analgesia protects from developing PPP. Our results further show important implications of PPP on the physical and mental health of the women in pain.