Does it still hurt? Perioperative opioid analgesia in different patient populations

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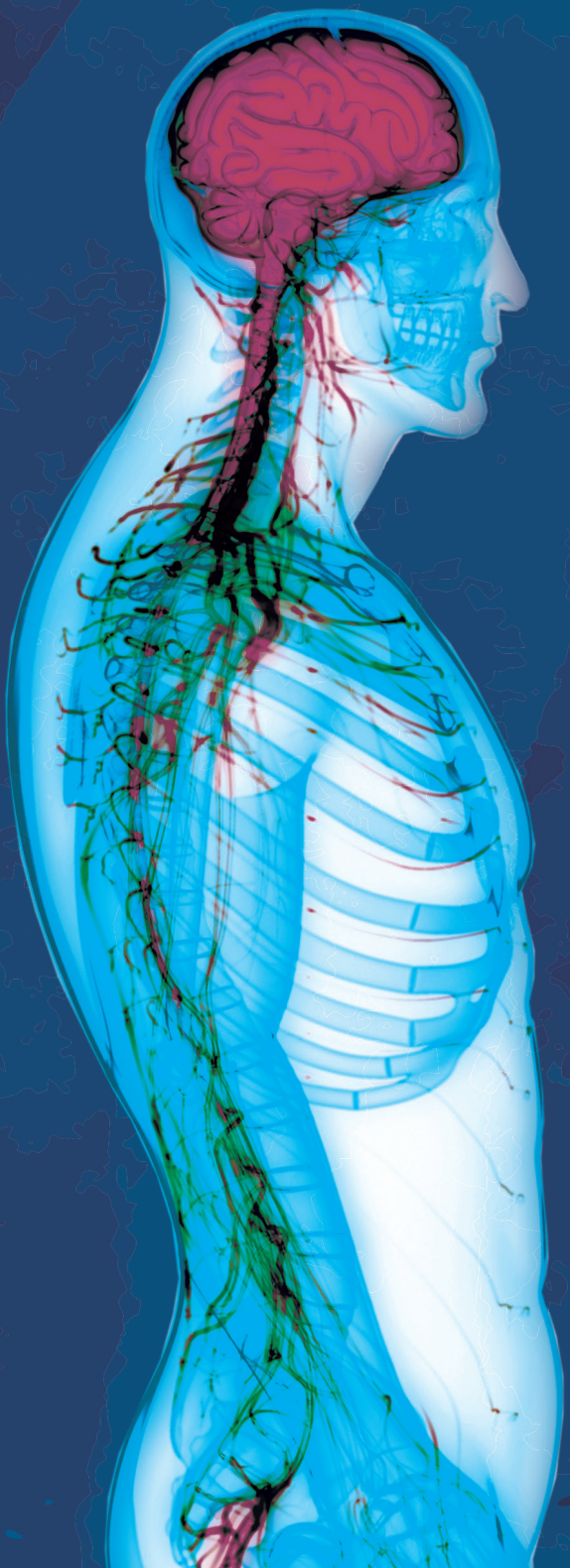

Section V

Summary, considerations and perspectives

Chapter 10

The impact of opioids on postoperative pain in different patient populations: summary, conclusions and perspectives

Summary and conclusions

The last decades it is increasingly recognized that acute as well as chronic postoperative pain is an important topic. With the increase in life expectancy and increase of the elderly population it is expected that the population of (chronic) pain patients will increase. In the Netherlands, nationwqide programs have been initiated to address postoperative pain, amongst others because pain is a quality indicator in Dutch hospitals[1]. Around 80% of patients undergoing surgery experience acute postoperative pain rated as moderate or severe[2]. Studies show that only half of postoperative patients experience adequate pain relief[3]. Multiple risk factors for the development of acute postoperative pain have been identified, for example younger age, female sex, anxiety, and use of preoperative analgesia[4]. In addition, acute postoperative pain is also a risk factor for the development of chronic postoperative pain. Chronic postoperative pain lasts 2 to 3 months after surgery and is beyond the healing of injured tissue and the related inflammatory processes[5,6]. The incidence of chronic postoperative pain varies widely, but it is estimated that 10 to 50% of the patients undergoing surgery develop chronic postoperative pain[5,7,8]. Chronic postoperative pain is variously defined and described, which probably plays a role in the wide variation in reported incidence. Type of surgery is also of importance, since especially surgical procedures where major nerves trespass the surgical field are associated with chronic pain[5]. Therefore, chronic pain is associated with a variety of surgical procedures such as amputation, breast surgery, thoracotomy, inguinal hernia repair, coronary artery bypass, and caesarean sections[5,9]. Risk factors identified for the development of chronic postoperative pain are acute postoperative pain, younger age, female gender, psychosocial factors such as anxiety, preceding pain and genetic susceptibility[5,6].

Pain and inadequate pain relief are a heavy burden for the patient and have an impact on the quality of life and performance of activities of daily living[8,10]. Moreover, this condition has also a high economic burden since in chronic pain patients unemployment rates and claims for incapacity benefit are high[11]. The optimal use and implementation of (inter)national guidelines for pain assessment and subsequent pain management and relief may decrease morbidity and mortality and increase quality of life in postoperative patients. Intraoperative and postoperative opioids play a major role in preventing and managing postoperative pain. Despite the extensive use of opioids for postoperative pain management, knowledge for optimal use in special patient populations is lacking.

This thesis aimed to contribute to the quality of postoperative pain management in different patient populations with the focus on opioid analgesia. In this chapter

the findings of the studies presented in this thesis are summarized and future perspectives are discussed.

Opioid analgesia in adult cardiac surgery patients

In *section II*, the focus is on adult cardiac surgery patients and on both acute and chronic postoperative pain. In adults, cardiac surgery belongs to the most frequently performed types of surgery worldwide with a known high risk on postoperative pain[12,13]. Patients after cardiac surgery with controllable pain, recover faster and have lower risk for complications[14]. Multiple studies suggest that the use of remifentanil, an ultra-short-acting and hyper potent opioid, is associated with an increase in acute and chronic postoperative pain when used during surgery[15,16]. In **chapter 2,** we present an overview of the literature on the associations of intraoperative remifentanil administration with acute postoperative pain, hyperalgesia, and chronic postoperative pain. From the studies that were identified, almost half found higher acute postoperative pain, higher postoperative analgesic requirements after intraoperative remifentanil use, or both. Coanaesthetics to some extent were found to influence this incidence, with studies using volatile agents (i.e. sevoflurane or nitrous oxide) reporting increased pain levels. Less evidence for increased postoperative pain was found when remifentanil was combined with total intravenous anaesthesia or a combination of anaesthetics. For chronic postoperative pain, only few studies were available and study design varied extensively. A potential association between the use of intraoperative use of remifentanil and chronic pain was found but no clear conclusions could be made. Further research with the primary goal to investigate the effect remifentanil infusion on acute and chronic postoperative pain was therefore needed. For this reason, a randomized controlled trial investigating the effect of remifentanil on acute and chronic postoperative pain was designed and the protocol is described in **chapter 3.** Patients received standardized anaesthesia with propofol and fentanyl boluses given at predetermined times and were randomized between remifentanil infusion and additional fentanyl boluses. In **chapter 4**, the results of this randomized controlled trial on the effect of remifentanil on acute and chronic postoperative pain 3, 6 and 12 months after surgery are reported. In this study, 126 adult patients undergoing cardiac surgery via sternotomy were included. Based on a self-report questionnaire, at 12 months after surgery there was no significant difference in incidence of chronic thoracic pain between the remifentanil and fentanyl groups (20% vs. 18%, respectively; p=0.817). At three months, however, significantly more patients in the remifentanil group reported chronic thoracic pain (51% vs. 33%; p=0.047). This effect was more pronounced in younger patients and in patients receiving a higher dose of

remifentanil (both $p<0.05$). In addition, in the first 24 and 48 hours after surgery, morphine consumption in the remifentanil group was significantly higher than in the fentanyl group (34.3 mg (interquartile range (IQR) 25.3 to 48.2) vs. 30.2 mg (IQR 19.2 to 38.1), p= 0.028; and 46.8 mg (IQR 33.8 to 59.2) vs. 39.0 mg (IQR 6.2 to 51.4), p=0.047, respectively). In conclusion, intraoperative use of remifentanil during cardiac surgery does not impact chronic postoperative pain one year after surgery. Nevertheless, remifentanil increases analgesic requirements and chronic postoperative pain until three months after surgery.

To investigate pain levels after cardiac surgery in a more objective manner, thermal detection and pain thresholds were measured in this randomized controlled trial of which the results were reported in **chapter 5**. Warm and cold detection and pain thresholds three days and 12 months after cardiac surgery were measured. The use of remifentanil, presence of postoperative chronic pain, age, opioid consumption and preoperative quality of life were tested as a predictor for altered pain sensitivity measured with thermal thresholds at 12 months after surgery. Both warm and cold detection and pain thresholds were not significantly different between the remifentanil and fentanyl groups three days as well as 12 months after surgery ($p>0.05$). No significant predictors for altered pain sensitivity were identified. We conclude that using quantative sensory testing we cannot confirm earlier reports of increased pain sensitivity one year after the use of remifentanil in this randomised study.

In this cohort of cardiac surgery patients, we also investigated potential genetic components of pain. **Chapter 6** describes the potential influence of *OPRM1* (mu-opioid receptor) and *COM*T (catechol-O-methyltransferase enzyme) polymorphisms in postoperative acute, chronic and experimental thermal pain. No association was found between COMT haplotype and other pain outcomes or OPRM1 polymorphisms and the different pain modalities. Patients in the fentanyl group with the COMT high-pain sensitivity haplotype required less postoperative morphine compared with the average-pain sensitivity haplotype (19.4 (16.5 to 23.0) vs. 34.6 (26.2 to 41.4); p=0.00768), but not to the low-pain sensitivity group (30.1 (19.1 to 37.7); p=0.13). In conclusion, COMT haplotype appears to explain a small part of the variability in acute postoperative pain in adult cardiac surgery patients.

Opioids after paediatric cardiac surgery

Section III focuses on the use of morphine in children after cardiac surgery. In children, morphine is commonly used for analgesia after cardiac surgery but

little is known about its analgesic efficacy in relation to plasma concentrations. Therefore, in **chapter 7** we report on the pharmacodynamics of morphine in children after cardiac surgery using repeated Time-to-Event (RTTE) modelling. In this study, data from a previous published study on morphine pharmacokinetics and morphine requirements in 35 children aged 3 to 35 months after cardiac surgery receiving morphine as loading dose (100 μg/kg) followed by continuous infusion (40 μg/kg/hr) were analysed[17]. Events were defined as rescue morphine bolus doses and/or increases in infusion rate as guided by validated pain scores (i.e. COMFORT-B). During the postoperative period (median 38 (IQR 23 to 46) hours), 130 events (median 4 (IQR 1 to 5) per patient) occurred, with the majority in the first 24h (107/130). Median morphine concentration during an event was 29.5 ng/ml (range 7 to 180 ng/ml). A RTTE model in which the hazard of rescue morphine decreased over time (half-life 18 hours; $p<0.001$) was found to describe the hazard for rescue events well. Counterintuitively, an increase in hazard for rescue morphine was seen at higher morphine concentrations (21.9% at 29.5 ng/ml; $p<0.001$). However, the confidence interval was wide, indicating that the actual influence of increased morphine concentration on the hazard could in fact be small. Still, morphine concentrations in this study are much higher compared to the previously suggested therapeutic range of 10 to 20 ng/ml. Although the evidence supporting this therapeutic range is limited, it was unexpected that rescue dosing was still required upon these high concentrations. The fact that 24% of the rescue morphine was administered within one hour of a previous dose, suggest that morphine is maybe not the ideal opioid to be used as rescue medication. Thus, in children after cardiac surgery receiving protocolized morphine infusions and rescue doses, we observed a significant number of rescue events. Rescue morphine was required at a wide range of morphine concentrations and further increase of the morphine concentration did not lead to a decrease in hazard. Future studies should focus on a multimodal approach using other opioids or other analgesics to treat breakthrough pain in children.

Pharmacokinetics of opioids in obese patients

In *section IV,* we focus on the obese patient population. As noted, the obese population is growing over the last decades. The increasing numbers will also result in an increase in the number of obese patients that undergo surgery and require treatment for postoperative pain.

First, in **chapter 8**, we present an overview of the literature about the influence of obesity on pharmacokinetic and pharmacodynamic parameters in adults. In this review, physiological changes associated with obesity are discussed. An overview

is provided on the alterations in absorption, distribution, drug metabolism and clearance in (morbid) obesity focusing on general principles that can be extracted from pharmacokinetic studies. Future research should focus on connecting obesity-related physiological changes with changes in pharmacokinetic and/or pharmacodynamics parameters and vice versa. In addition, efforts should focus on implementation of these model-derived dosing recommendations in clinical practice.

Second, in **chapter 9**, we present the pharmacokinetics of morphine in obese patients when compared to non-obese healthy volunteers. The clinical use of morphine is characterized by a large inter-individual variability in analgesic effect, in which the role of (morbid) obesity is unclear. The aim of this study was to investigate the influence of obesity on the pharmacokinetics of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) through a combined analysis in morbidly obese patients and non-obese healthy volunteers. Data from 20 morbidly obese patients [mean body mass index 49.9 kg/m^2 (range 37.6 to 78.6 kg/m^2) and weight 151.3 kg (range 112 to 251.9 kg)) and 20 healthy volunteers (mean weight 70.6 kg (range 58 to 85 kg)) were included. Morbidly obese patients received 10 mg of intravenous morphine after gastric bypass surgery, with additional morphine intravenous doses as needed. Healthy volunteers received an intravenous bolus of morphine of 0.1 mg/kg followed by an infusion of 0.030 mg/kg/h for 1 h. In morbidly obese patients, elimination clearance of M3G and M6G was decreased substantially compared with healthy volunteers ($p<0.001$). Regarding glucuronidation, only a slight decrease in the formation of M6G and a delay in the formation of M3G was found (both $p<0.001$). Obesity was also identified as a covariate for the peripheral volume of distribution of morphine ($p<0.001$). From this study, we can conclude that metabolism of morphine is not altered in morbidly obese patients. Morphine concentrations proved similar between the morbidly obese patients and non-obese patients, indicating that no weight-based dosing adjustments are necessary. However, decreased elimination of both M3G and M6G is evident, resulting in a substantial increase in exposure to these two metabolites. The clinical consequences of this findings are uncertain and are potentially only of interest upon prolonged administration of morphine.

Perspectives

In this section the results that were obtained in this thesis are discussed from a broader perspective. First, we will evaluate the use remifentanil in cardiac surgery in light of the results of section II of this thesis. Second, lessons to be learned from studies in obese and paediatric patients are outlined. Lastly, pain measures in

clinical pain studies and clinical practice are discussed.

Remifentanil in cardiac surgery

In *section II* of this thesis we have focused on the use of remifentanil during cardiac surgery. Toward the end of the 20th century, the number of cardiac surgery patients increased and surgery became more complicated with increasing age and comorbidities of these patients. The end of the "high-dose opioid anaesthesia" era started with the development of intravenous anaesthetic agents with rapid on- and offset, and was complete with the introduction of an ultra-short-acting opioid. Remifentanil is nowadays often used during cardiac surgery because of its favourable pharmacokinetic and pharmacodynamic properties[18]. Remifentanil is a short-acting, hyperpotent μ-opioid receptor agonist of which the clearance is independent of renal of hepatic function[19]. A systematic review on general anaesthesia and analgesia showed that, when compared with other intraoperative opioids, remifentanil was associated with clinical signs of deeper analgesia and anaesthesia, faster recovery (shorter extubation time), fewer respiratory events requiring naloxone and more frequent postoperative analgesic requirements[20]. In studies that evaluate fast-track cardiac anaesthesia with remifentanil, however, no superiority of remifentanil compared to sufentanil[21] or low-dose fentanyl[22] was found with regards to the time of recovery. Despite the vital use of opioids during surgery for preventing and treating peri- and postoperative pain, opioids are also associated with opioid induced hyperalgesia (OIH)[23,24]. Although OIH was first thought to be associated with all opioids, the strongest association was found with remifentanil[15]. OIH is demonstrated in animal models and human volunteers, but the clinical impact in patients is difficult to estimate since studies are diverse and sample sizes are small, as discussed in chapter 2[25]. Nevertheless, a systematic review showed a small but significant increase in acute postoperative pain and opioid consumption after (high) doses of remifentanil[15]. After four hours, a mean difference of 7.1 cm on a 100 cm scale (95% confidence interval (CI): 2.8 to 11.3) was found. More recently, an analysis of a large medical record database found similar outcomes with evidence of increased postoperative pain and opioid consumption in patients that underwent abdominal surgery and received remifentanil during surgery[26]. The pain score at arrival in the recovery area (NRS1) and the maximum pain score (NRSmax) during stay in the recovery area were both higher in the remifentanil group compared to the control group (mean NRS1 1.52 vs. 1.28; $p<0.001$; mean NRSmax 2.47 vs. 2.17; $p<0.001$). These results correspond with the findings presented in chapter 4; cardiac surgery patients that received remifentanil during surgery needed more morphine in the first 48 hours after

surgery to maintain acceptable pain scores (46.8 mg (IQR 33.8 to 59.2) vs. 39.0 mg (IQR 6.2 to 51.4), p=0.047). In conclusion, data show that remifentanil has a negative impact on acute postoperative pain, but absolute differences are small and potentially not of great clinical impact.

The number of studies that investigated the impact of the use of remifentanil on chronic postoperative pain are limited. In our hospital, an observational follow up study on 90 cardiac patients found that remifentanil was a risk factor for the development of chronic pain at 12 months in a dose related manner[27]. As reviewed in chapter 2, only three other studies evaluated long-term effects of remifentanil on pain outcome parameters, but they varied with regards to the type of surgery, the sample size, and the study design (Table 3, page 30). Recently, a secondary analysis of pain outcomes from a prospective, randomized, open-label trial that compared remifentanil and fentanyl on perioperative hyperglycemic response in cardiac surgery was published[28]. This is one of the few studies with prolonged follow up data available but has some important differences with our study in chapter 4. First, the recent study was not powered on postoperative pain but on hyperglycemic response. Second, patients in the remifentanil group received very high doses of remifentanil (median total cumulative dose of 11 mg of remifentanil; >80 μg/kg) whereas the fentanyl group received no remifentanil. In chapter 4, patients in the remifentanil group received a mean dose of 2.1 mg (25 μg/kg) remifentanil and also fentanyl (21 μg/kg). Similar to what we found in our study, patients in this recent study in the remifentanil group received more opioids directly after surgery. In contrast to the study results of chapter 4, postoperative chronic pain three months after surgery was not significantly different between the groups while after 6 and 12 months there were no differences on the incidence of chronic postoperative pain between the groups, which is in line with our results. Overall, the incidence of chronic postoperative pain in both groups during follow up (3, 6 and 12 months) was (much) higher compared to our study, which could be an explanation for the differences in results found in both studies after three months. For example, chronic postoperative pain after 3 months was present in 61% of patients in the fentanyl group versus 58% of patients in the remifentanil group (p=0.79), which is high compared to the results of chapter 4 in which 31% versus 51% of patients presented with chronic postoperative pain after three months, respectively (p=0.047).

Based on these results, it seems that there are no long term negative consequences of the use of remifentanil during cardiac surgery. On the other hand, our results in chapter 4 show that remifentanil has a negative impact on acute postoperative pain and potentially this effect can persist up to three months after surgery. The

question therefore is, is there an advantage of remifentanil that outweigh these (small) disadvantages on acute and chronic postoperative pain? The main advantage of remifentanil could be shorter time to extubation which could result in faster recovery and length in hospital stay[29]. Others state that the use of remifentanil results in increased hemodynamic stability during surgery[30] or in a decrease in the use of hypnotics and sedatives[31]. On the other hand, studies investigating fast-track cardiac surgery with remifentanil lack evidence for a superiority of remifentanil on these parameters[21,22]. A systematic review concludes that remifentanil does not seem to offer an advantage for lengthy, major interventions, but may be useful for selected situations[20].

We conclude that even if the use of remifentanil results in remifentanil induced hyperalgesia and has impact on postoperative pain, the clinical impact of this hyperalgesia is low and diminishes over time when given for cardiac surgery in the dosages described in chapter 4. Generally, the impact of remifentanil on postoperative pain after cardiac surgery is therefore low. At the same time, one of the post-hoc analyses of our study showed that patients with a high dose of remifentanil (≥ 1875 µg) and below the age of 65 year had a higher risk of postoperative pain at three months after surgery. This could be an argument to avoid high-dose remifentanil in younger patients.

As was stated at the beginning of this section, in the context of cardiac surgery, an opioid-based anaesthesia has been the cornerstone of perioperative management for decades. Due to global opioid concerns and an increased emphasis on enhanced recovery following cardiac surgery the concept of an opioid-free cardiac surgery is currently being explored using a multimodal analgesic management[32]. The wide range of availability of nonopioid analgesics (nonsteroidal anti-inflammatory drugs, acetaminophen, N-methyl-D-aspartate antagonists, alpha-2 agonists, local anaesthetics, gabapentinoids, and others) in combination with innovative regional analgesic techniques contributes to the feasibility of opioid-free or opioid-sparing (cardiac) surgery[33]. A meta-analysis of non-cardiac surgery studies has reported benefits with opioid-free anaesthesia, but the included studies were small and heterogenous[34]. A recent randomized study in 364 patients that underwent major or intermediate non-cardiac surgery showed that opioid-free surgery is not without consequences. The study was terminated early since patients in the opioid-free balanced anaesthesia with dexmedetomidine group had more postoperative hypoxemia, delayed extubation, prolonged PACU stay, and intraoperative bradycardia[35]. This study showed that opioid-free anaesthesia is not that easy to achieve. The data related to multimodal nonopioid interventions in cardiac surgical patients are limited. Grant et al. 2020 performed a study to assess the

association between nonopioid interventions employed as part of an enhanced recovery program for cardiac surgery and intraoperative opioid administration[36]. Patients undergoing cardiac surgery received 5 nonopioid interventions, including preoperative gabapentin and acetaminophen, intraoperative dexmedetomidine and ketamine infusions, and regional analgesia via serratus anterior plane block. These nonopioid interventions were associated with a reduction of intraoperative opioid administration but, low and ultralow intraoperative opioid use was not associated with significant differences in postoperative outcomes[36].

Summarizing, the field of opioid-free analgesia during surgery is growing due to increased focus on enhanced recovery programs and increasing rates of opioid prescriptions and opioid-related deaths worldwide[37]. The current incidence of postoperative pain remains high and multimodal analgesia could be beneficial for patients. Data of opioid-free analgesia in cardiac surgery patients is limited and future prospective studies are necessary to establish the role and advantages of opioid-sparing or opioid-free strategies in the setting of cardiac surgery.

Opiates in special patients populations; lessons learned.

Paediatric patients

In chapter 7 we focus on children as a special population that are treated with opiates. Regulatory and ethical guidelines for research in children are fairly restrictive which makes it more challenging to conduct clinical trials in this population[38]. In addition, the numbers of patients are smaller, age and weight varies widely and consent has to be obtained from parents. This makes pain research in children challenging and the progression in healthcare slow. Pain has an emotional load for both parents and children and possibly even for clinicians. Together with the task to minimize risk and/or harm in research, it is plausible that the traditional treatment strategy of postoperative pain in children is generally conservative and “step down”, i.e. start with high doses of analgesics and step down to lower doses or other less potent analgesics. From a pharmacological point of view, it is known that a higher dose does not always have an additional benefit on efficacy. This is underlined in chapter 7, where we found that at high morphine concentrations, there was no effect of additional rescue doses of morphine on the hazard for rescue events after paediatric cardiac surgery. Other studies show that it is also possible to use non-opioids as primary analgesic after surgery. The study of Ceelie et al. showed in a randomized controlled trial that infants who receive intravenous paracetamol as primary analgesic after major non-cardiac surgery that was ended with a single morphine loading dose at the end of surgery,

require the same amount of additional rescue morphine than those who receive a continuous morphine infusion[39]. This study shows that a "step up", i.e. primary analgesic of paracetamol with additional morphine, strategy for analgesics after surgery is also feasible in children. In this respect, it is important to highlight that in this study all infants received intravenous opioids during surgery, with a loading dose of morphine at the end of surgery. A recent study investigating the reduction, or replacement, of morphine by IV paracetamol in children (0 to 36 months old) after cardiac surgery will give more important information on this topic after cardiac surgery[40]. This study finished recently including 208 patients in four paediatric cardiac surgery centres and data are expected soon.

The results of the study described in chapter 7 also showed that need for rescue analgesia was required at a wide range of morphine concentrations (7 to 180 ng/ml). During an event, the median morphine concentration was 29.5 ng/ml and the majority of events (n = 111 (85%)) occurred above 20 ng/ml. This finding can have multiple explanations. First, the concentration-effect relation of morphine in the acute postoperative setting is possibly not strong which is reflected by the finding that patients with the highest concentrations do not experience the highest effect. Second, this could be also an effect of the difficulty for nurses to distinguish between pain and agitation. Over the last years, efforts are made to improve pain and sedation management with the implementation of standardized protocols resulting in more adequately sedated children[41]. Still, there is potential for improvement since under- and oversedation occur in 10 and 30% of the assessments in critically ill children admitted to the intensive care unit[42]. Recently, a study reporting on the same cohort of patients in chapter 7, found that of the patients that received midazolam as part of the analgesia and sedation protocol, only a marginal effect of midazolam concentrations on the COMFORT-B scores were found[43]. If this is a result of the combination of morphine and midazolam or the low midazolam dosages is uncertain. Still, both chapter 7 and this recent study, confirm that the optimal analgesic and sedation protocol for children after cardiac surgery has not yet been found. The recently finished study in children where rescue morphine is investigated next to IV paracetamol[40] could bring us a step closer to this goal by analysing rescue doses in this setting using the same methods as chapter 7 in which RTTE modelling was applied. In this study, where it is expected that some patients have only morphine rescue without a continuous infusion of morphine as they were randomized to the paracetamol group, data will be available of patients with low or absent morphine concentrations at time of an event. These data were not available for our analysis and would be of added value in the RTTE model.

In conclusion, worldwide there is a large variation in morphine dosing after cardiac surgery in children. Chapter 7 shows that morphine rescue on top of high-dose continuous infusion morphine does not lead to an additional effect on the hazard for rescue events after cardiac surgery. Future studies are planned to optimize the use of analgesics and sedatives in children after cardiac surgery.

Obese patients

In recent years, there has been a major increase in prevalence of overweight and obese patients[44]. With obesity, patients are more likely to undergo surgery since morbidity and mortality significantly increases[45]. Postoperative pain management in obese patients is challenging since patients have increased risk for opioid side effects[46,47] and PKPD parameters for drugs in obese patients could be altered as described in chapter 8. For example, acetaminophen (paracetamol) is a frequently used analgesic in the postoperative setting for postoperative pain management. The study of van Rongen et al. showed that both acetaminophen peak concentrations and area under the plasma concentration-time curves (AUCs) were substantially lower in morbidly obese patients[48]. Lower exposure results probably in lower effectiveness, but an increase in dose in these patients remains under debate since the role of earlier and greater formation of CYP2E1-mediated metabolites may contribute to acetaminophen hepatotoxicity in case higher dosages are given[49]. Based on these results, there is still room for optimizing the dose and possibly the efficacy of acetaminophen in obese patients.

In this thesis, we focused on morphine which is another frequently used analgesic after surgery. For morphine, there was limited information about the impact of morbid obesity on PK parameters. Therefore, in chapter 9, we studied morphine in morbidly obese patients that underwent bariatric surgery and compared the data to healthy volunteers. We found that the pharmacokinetics of morphine in obese patients versus healthy volunteers was not different which means, based on the PK of morphine, that an obese patient of 150 kg should receive a similar dose compared to a patient of 70 kg. We report also that a decreased elimination of both morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) in obese patients is evident, resulting in a substantial increase in exposure to these two metabolites. Regarding the relevance of this finding, it has been suggested that M3G is responsible for side-effects and pain enhancement[50], while M6G has a potent analgesic action[51]. However, these effects have been debated as the effects were not established in clinical studies. M3G has much lower affinity for the opioid receptor compared to morphine or M6G with M6G concentrations being typically very low compared to M3G and morphine concentrations[52]. Both morphine

metabolites have a hydrophilic character which result in a lower penetration rate of the blood-brain barrier compared to morphine[53]. PK and PD studies after the administration of M6G itself show that M6G has potential analgesic activity, but lower compared to morphine[54,55]. Effect site concentrations 12 to 22 times greater than those of morphine are needed to obtain a similar analgesic effect for M6G[55]. For M3G, rat studies indicate that prolonged exposure to M3G may contribute to the side effects of morphine such as morphine-induced tolerance and opioid-induced hyperalgesia[56]. Therefore, the clinical impact of decreased clearance of morphine metabolites in morbidly obese patients that receive short term morphine for postoperative analgesia is not clear and is potentially only of interest when morphine is continuously administered over a prolonged period of time.

Besides the clinical impact of increased morphine metabolites in obese patients, the physiological changes underlying these increased metabolites could potentially be important for other drugs. The physiological explanation of decreased elimination of morphine glucuronides is found in the alterations in multidrug resistance proteins MRP2 and MRP3 as a result from (prolonged) obesity or non-alcoholic steatohepatitis (NASH)[57,58]. These transporters are responsible for the in- and efflux of molecules from hepatocytes to the bile and vice versa. Due to the challenges of both diagnosing the stage of NASH and quantifying alterations in liver transporters in patients, clinical studies to evaluate the precise impact of these transporters are difficult since liver biopsy is the gold standard but expensive and invasive[59]. Recently, a physiologically-based pharmacokinetic (PBPK) model was developed to predict morphine and morphine-3-glucuronide exposure in NASH by incorporating NASH-related changes in hepatic transporters[60]. Based on the assumptions in this PBPK model, this study shows that of the NASH-related physiological changes, NASH-mediated transporter alterations had the highest effect on M3G exposure with an increased area under the curve of 43%, while morphine exposure was not substantially altered[60]. These findings highlight the importance of NASH related transporter changes and are in line with the results of chapter 9. From these results regarding the impact of obesity on hepatic transporters, we anticipate that the PK of other drugs may be influenced. For example, mice studies suggest that MRP transporters are involved in the metabolism of anticancer agents such as methotrexate[61]. For this, more studies evaluating the influence of hepatic transporters and bile acid homeostasis on the PK of drugs in morbidly obese patients and after bariatric surgery are needed, which will ultimately also result in increased understanding of the pathophysiological changes associated with obesity. Regarding morphine, we conclude that there is no need to give a higher

dose of morphine or dose morphine per kilogram body weight in obese patients. In obese patients plasma concentrations of morphine glucuronides will be higher compared to non-obese weight patients but particularly upon short term use there is no evidence for clinical (side) effects of these concentrations.

Pain measures in clinical pain studies and clinical practice

Pain has been defined as an "unpleasant sensory and emotional experience associated with actual or potential tissue damage" by the International association for the Study of Pain[62]. The experience of pain is a complex interaction among biological, psychological, behavioural and social-cultural factors[63]. Patients' self-reporting of their pain is regarded as the gold standard of pain assessment measurement. Despite increasing attention for pain over the years, there are still a lot of opportunities for improvements in postoperative pain management[2]. Pain research has a broad spectrum of outcome measures, many of which we have used in this thesis. The proper use and knowledge of these outcome measures is important to improve postoperative pain management, and therefore we here discuss the outcome measures used in this thesis.

Pain scales

In section II as well as in section III of this thesis, pain scales like numerical rating scale (NRS) and comfort behavioural (COMFORT-B) scale were used in a standardized pain protocol. In adults, it is common to use the NRS for pain intensity, which showed its validity in studies with pain provoking procedures and after analgesic treatment[64]. The COMFORT-B scale is a multifactorial pain scale that is validated for the use for postoperative pain in neonates and infants[65]. Still, certain aspects of these pain scales have to be taken into account when used in clinical studies.

First, if self-reported, patients must understand the basics of a 0 to 10 scale where the lowest score means "no pain" and the highest score the "worst pain imaginable" pain. It is acknowledged that better communication and patient assessment skills will help improve and tailor pain management[66]. A study in chronic low back pain patients illustrated that poor communication between physician and patients resulted in worse pain management. Over- and underestimation of pain related impairment by the physician resulted in lower treatment responses (resp. 71.7% and 24.3%)[67]. For daily clinical practice in hospitals, this underlines the need for pretreatment patient training by experienced health care providers about pain scales such as the NRS.

Second, how the NRS for measuring pain intensity in pain research is used may vary widely which could complicate the comparison of outcomes between studies or interventions. For example, pain assessment of acute pain after surgery can be executed at rest (static pain) or during mobilization (dynamic pain), but this is not always specified in study protocols and reports. Effective relief of dynamic pain facilitates patients' mobilization and therefore may have a positive effect on long-term outcome after surgery. Future studies therefore need to take both pain at rest vs. pain during mobilization into account[68]. In hindsight, in chapter 4 we should have assessed the NRS both in rest and during mobilization to be able to further optimize pain management in cardiothoracic surgery patients.

Another aspect of the NRS score as outcome measure is that multiple scores are needed to measure pain relief. Pain scales, like the NRS, are best used to measure pain at the moment of assessment, as memory of pain is usually not accurate and often coloured by changing context[69]. This makes timing of assessment of pain relief using NRS scores also important, but time consuming because every administration of analgesics needs evaluation. Therefore, the implementation of a standardized pain protocol with repetitive NRS scores is important since studies show that this improves postoperative outcomes[70,71]. In addition, education for nurses regarding pain and its treatment should receive continuous attention[71].

Finally, in order to relief the workload and administrative burden for nurses that record pain scores, self-assessment and recording of pain by patients could be further developed and studied. A study in oncology patients showed that a self-reporting bedside pain assessment tool provides a reliable and effective way of assessing pain[72]. Recently, a proof-of-concept study in the Netherlands showed that the majority of postoperative patients (90%) were able to correctly self-record their acute postoperative pain with a smartphone application and were positive (60%) about the ease of the recording[73]. This shows that this is a promising technical development which could save time for nurses while pain reporting and evaluation of effects of pain medication is facilitated. This field of self-reporting pain using electronic devices is also emerging in patients with chronic pain conditions[74].

Consumption of analgesics

In chapter 4, we used cumulative consumption of analgesics as pain outcome measurement after cardiothoracic surgery which was facilitated by the earlier implementation of a pain titration protocol several years ago[75]. In this study, the cumulative consumption of opioids could be used as measure for the effectiveness of the postoperative pain management because the NRS scores reported were similar between groups. In this setting, patients receiving intraoperative remifentanil

received significantly more morphine 48 hours after surgery compared to patients receiving intraoperative fentanyl, which implies that patients in the remifentanil group requested were in need of pain relief. Evaluation of the NRS values showing similar NRS values in both groups confirmed that the pain titration protocol was well implemented. The consumption of analgesics is of interest as clinical pain outcome measure because the administration of more analgesics not only reflects ineffectiveness of the current treatment for the individual of interest but could also result in more side effects as result of the increased dose. We emphasize that a prerequisite for the use of this measure is that a standardized pain protocol and adherence to this protocol is guaranteed.

Quantative Sensory Testing

Quantative sensory testing (QST) collectively refers to a group of procedures that assess the perceptual responses to systematically applied and quantifiable sensory stimuli[76]. QST is used as a tool for objective pain assessment in basic mechanistic studies, clinical studies for diagnostic and monitoring purposes and pharmacological studies to evaluate the efficacy of analgesics[77]. In chapter 5, we report thermal detection and pain thresholds in patients receiving remifentanil or fentanyl both three days and one year after cardiac surgery. No differences in detection and pain thresholds between remifentanil and fentanyl were found three days or one year after surgery and no prognostic factor for chronic postoperative pain QST was found. Despite the use of QST in experimental and clinical studies, its use in clinical practice for (predicting) acute postoperative pain seems limited. The main reason is that evidence for the use of QST in this area is conflicting[78]. This also applies for chronic postoperative pain as reviewed recently[79]. The most promising results are found in studies that evaluate the dynamic pain processing system using QST[79]. For example, measurement of diffuse inhibitory noxious control (DNIC) was of predictive value for chronic postoperative pain. DNIC occurs when the response from a painful stimulus is inhibited by another noxious stimulus. It gives a dynamic view of the pain processing system and reflects the "pain-inhibits-pain" paradigm[77,80]. Patients with preoperative impaired conditioned pain modulation or DNIC were found to have a greater likelihood of developing chronic postoperative pain[81,82]. Still, large replication studies are not available. Other reasons that QST has not made it to clinical practice are related to the fact that the standardized QST protocol is labour intensive, requires expensive equipment and highly trained operators to complete the tests and interpret the data[76]. It seems that QST protocols needs to become shorter and simpler to operate and to interpret to be more clinically useful in the future.

Measures to quantify chronic postoperative pain

Chronic postoperative pain is defined as pain that develops or increases in intensity after a tissue trauma (surgical or accidental) and persists beyond three months[83]. Severe chronic postoperative pain that has a negative impact on the patient's quality of life is has a prevalence of 2% to 15%, dependent on surgical procedure and definition of chronic pain[84]. In contrast to acute postoperative pain, which is often assessed by a one-dimensional pain scale such as the NRS, there are several assessment tools for chronic pain that are multidimensional. The assessment tools that are mostly used are the Brief pain Inventory and (short form) McGill Pain Questionnaire[69], on which the questionnaire used in chapter 4 of this thesis is also based. Still, there is a large variability in outcome measures used in clinical trials for chronic pain, which hinders the evaluation of the incidence of chronic pain its impact on quality of life and the efficacy of therapeutic interventions. Studies show that chronic pain after surgery remains common and is still unrecognized and underdiagnosed[83]. Internationally, an effort has been made to provide recommendations for interpreting clinical importance of treatment outcomes in clinical trials of the efficacy and effectiveness of chronic pain treatments[85]. There was a consensus that chronic pain clinical trials should assess outcomes representing six core domains: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events, (6) participant disposition (e.g. adherence to the treatment regimen and reasons for premature withdrawal from the trial). It is recommended that two or more methods are to be used to evaluate the clinical importance of improvement or worsening for chronic pain clinical trial outcome measures[86]. In chapter 4 we used pain intensity, assessed by a 0 to 10 numerical rating scale and physical functioning, assessed by the (adapted) Brief Pain Inventory scale. In addition, a separate quality of life (short-form 12) questionnaire was used. Despite all these efforts internationally, the number of pharmacological intervention studies with prolonged follow up to evaluate impact on chronic postoperative pain is still low and mostly not conform the provided recommendations. In our opinion, decent measurements of quality of life before and after surgery is essential to measure clinical impact. The results of chapter 4 are an example why definition of chronic postoperative pain is of importance. Our results after three months showed that the intervention arm with remifentanil had more persistent postoperative pain compared to the fentanyl arm. Since we had also measurements after 6 and 12 months, we were able to report that this effect between groups disappeared over time. This emphasizes the importance of prolonged follow-up in chronic postoperative pain research to better estimate the clinical impact of new findings in the future.

To summarize, pain is an unpleasant and emotional experience, associated with actual or potential tissue damage[62]. It is a challenge to treat and prevent postoperative pain, especially in special patient populations where the optimal use of opioids is not thoroughly investigated. In this thesis we have extended the knowledge of opioids in three different populations: adult cardiac surgery patients, paediatric cardiac surgery patients and finally obese patients.

With the work presented in this thesis in adult cardiac surgery patients we show that remifentanil has impact on opioid consumption directly after surgery and on postoperative pain three months after surgery, while this effect diminishes over time and thus seems of low clinical impact. Detection and pain thresholds were not influenced by remifentanil nor by chronic pain in this population. Still, it could be argued that the use of remifentanil in some patients needs consideration since its advantages over other opioids are not that well established in the literature and according to our data, when used in younger patients and in a higher dose, remifentanil could give a potential additional risk on chronic postoperative pain.

In children that undergo cardiac surgery, morphine is the most frequently used opioid during and after surgery albeit at an enormous variation in dosing schemes between institutions[87]. This implicates that there is no consensus about an ideal dosing regime in this population and therefore we focused on morphine administered as continuous infusion with additional rescue morphine boluses as was standard of care. We found that rescue morphine was required at a wide range of morphine concentrations and that the hazard for rescue morphine was not decreasing with increasing morphine concentrations. This study does not show a strong relation between morphine concentration and efficacy in this setting where the number of rescue doses that was given was high. This questions a “step-down” analgesic approach that is often used in children after surgery, i.e. start with high doses of analgesics and step down to lower doses or other less potent analgesics. Future studies have to focus on a multimodal approach using other opioids or other analgesics to treat and prevent breakthrough pain in children.

In obese patients, we showed that there is no need for a dose increase of morphine based on its pharmacokinetics. The plasma clearance of morphine glucuronides in obese patients is decreased, which means that glucuronide concentrations could accumulated in obese patients upon prolonged administration of morphine but the clinical impact of this is probably low. What is of interest are the physiological changes in transporters that are causing this decrease in excretion clearance. Future studies evaluating the influence of hepatic transporters and bile acid homeostasis in morbidly obese patients and after bariatric surgery are needed to evaluate these changes and the impact on other drugs.

Concluding, pain is a complex puzzle among biological, psychological, behavioural and social-cultural factors. The high inter-individual variation in all these factors results in postoperative pain still being a major issue while the ultimate goal is to stay without pain after a surgical procedure. Therefore, the answer to the question: "Does it still hurt?" is: YES unfortunately. This thesis adds pieces to this complex puzzle by focusing on the use of opioids in three different patient populations.

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