Universiteit
Leiden
The Netherlands

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

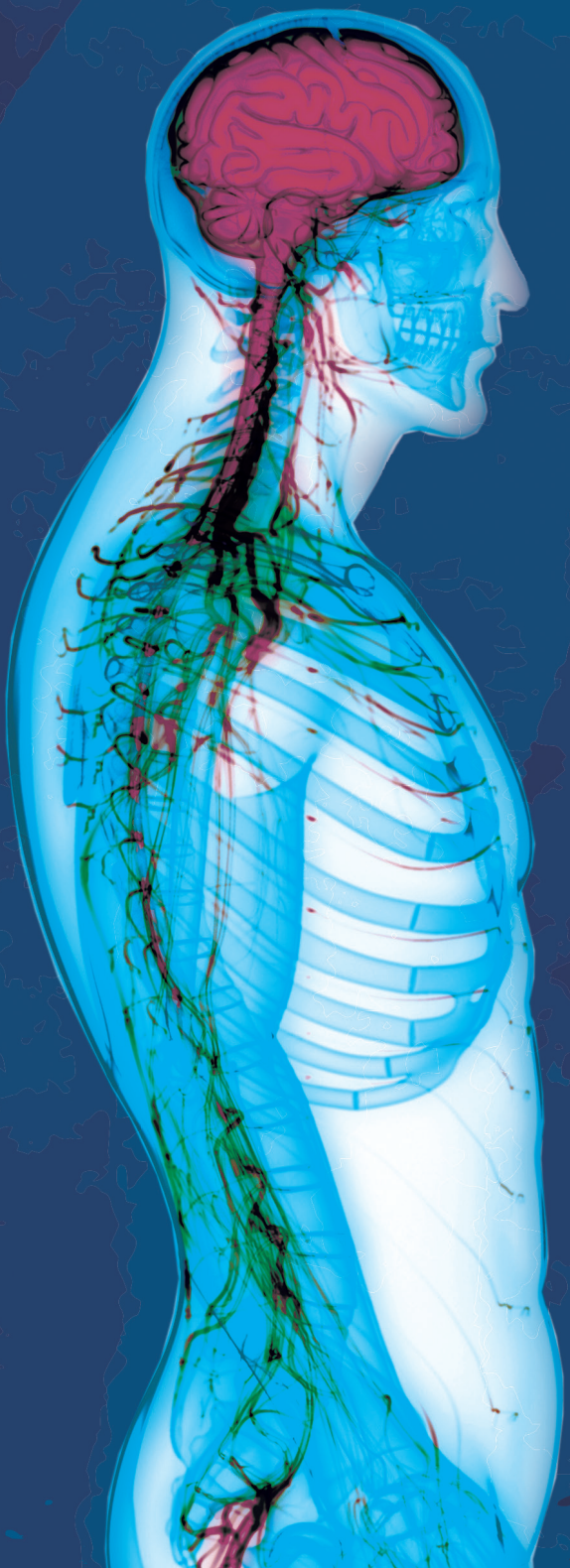
Hoogd, S. de

Citation

Hoogd, S. de. (2021, October 28). *Does it still hurt?: Perioperative opioid analgesia in different patient populations*. Retrieved from https://hdl.handle.net/1887/3221331

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3221331

Note: To cite this publication please use the final published version (if applicable).



Section I

General introduction and background

Chapter 1

Introduction

Scope and rationale of the investigations

Pain is an unpleasant and emotional experience, associated with actual or potential tissue damage according to the definition of International Association of the Study of Pain[1]. Acute, as well as chronic postoperative pain, is a multidimensional and complex problem that contains physiological and biopsychosocial aspects[2]. Pain is receiving increasing worldwide attention over the past years. Studies investigating acute postoperative pain report a reduction in incidence over the years, even though overall numbers remain quite high[3]. In the United States, more than 80% of patients that underwent surgery experience acute postoperative pain. The majority of these patients rate the severity of this pain as moderate or severe[4]. Other studies report that at least half of postoperative patients experience adequate pain relief[5]. Postoperative pain can become chronic when it lasts two to three months after surgery and is beyond the healing of injured tissue and the related inflammatory processes[6,7]. An estimated percentage of 10 to 50% of the patients undergoing all types of surgery develop chronic postoperative pain[6,8,9].

Over the last decades it has been suggested that little improvement has been made in postoperative pain management[4]. In the Netherlands, nationwide programs such as the guideline for postoperative pain from the Dutch Society of anesthesiology[10] have been implemented to address postoperative pain, amongst others because pain is a quality indicator in Dutch hospitals[11]. It has been recognized that pain and inadequate pain relief are a heavy burden for the patient, and may have great impact on quality of life and performance of activities of daily living[9,12]. Optimal application and implementation of (inter)national guidelines of pain management and pain relief may decrease morbidity and mortality and increase quality of life in postoperative patients.

Experimental pain studies in animals demonstrated that after surgical incision peripheral and central sensitization occur. A painful stimulus, like surgical incision, activates nociceptors which transduce this 'noxious' information into an electrical signal. This signal is transmitted from the periphery to the central nervous system along ascending peripheral C- and A□-fibers[13]. Complex mechanisms with involvement of C- and A□-fibres have been identified that contribute to acute postoperative pain[14]. C- and A□-fibres terminate in the dorsal horn of the spinal cord. Within the spinal cord, more complex interactions occur between excitatory and inhibitory interneurons and descending inhibitory tracts from higher centres exert their effect. Finally, the pain signal is entering the brain where somatosensory information is processed and pain perception occurs. Besides the ascending tracts from periphery to the brain, descending inhibitory tracts facilitate the modulation

of pain[13]. The functionality of these descending pain modulation in patients can be examined by a pain model using diffuse noxious controls (DNIC). Normally, after a noxious stimulus, peripheral sensitization of the accompanying receptors leads to short-term, transient pain sensitivity. Repetitive activation by noxious stimuli could transform to central sensitization, which amplifies, spreads and extend the periods of pain and has the potency to result in chronic postoperative pain[15]. The main triggers of central sensitization are neuronal, immune, and glial related, involving for example the N-methyl-D-aspartate (NMDA) receptors, glutamate and other neuromodulators[15].

Clinically, several risk factors have been identified for acute postoperative pain and the development of chronic postoperative pain. For acute pain, a large meta-analysis (53 362 patients) identified nine significant risk factors for poor acute pain control after all kind of surgeries[16]. The risk factors identified are younger age, female sex, history of depressive symptoms, use of preoperative analgesia, history of smoking, history of anxiety symptoms, presence of preoperative pain, use of preoperative analgesia and higher body mass index (BMI). Although the severity of acute postoperative pain is important, it appears that the rate at which acute pain resolves is also important[17]. The duration of severe pain in the initial 24 hours postoperatively predicted the chance of developing chronic postoperative pain[18]. A 10% increase in time spent in severe pain was associated with a 30% increase of chronic postoperative pain 12 months after surgery. This makes acute postoperative pain an evident risk factor for the transition of acute to chronic postoperative pain. Other relevant risk factors for chronic postoperative pain can be divided in surgery or patient specific risk factors. Younger age, the female gender, psychosocial factors such as anxiety, preceding pain and genetic susceptibility are patient specific factors that can contribute as a risk factor for chronic postoperative pain[6,7]. Surgery specific risk factors have also been investigated, for example type of surgery, duration of surgery and anaesthetic technique[7]. Because there is a high degree of inter-individual difference in pain response, genetic variation has also been investigated to explain pain variability[19].

Opioids are the cornerstone for postoperative pain management. Intraoperative and postoperative administration of opioids is essential in preventing and managing acute and chronic postoperative pain. Despite the extensive use of opioids, there are still gaps in knowledge about its use, optimal dose or its negative effects especially in different populations such as adult and paediatric patients after cardiac surgery or obese patients.

Opioids in cardiac surgery patients

In adults, cardiac surgery such as coronary artery bypass grafting (CABG) and heart valve replacement are two of the most frequently performed surgeries worldwide[20]. It is known that the risk of postoperative pain in cardiac surgery is high, because of the prolonged duration of surgery and multiple other causes such as intraoperative tissue retraction and dissection, multiple intravascular cannulations, chest tubes left after surgery, and multiple invasive procedures simultaneously[21]. Patients after cardiac surgery with controllable pain, recover faster and have lower risk on cardiovascular complications, pneumonia, and hypercoagulability[22]. In addition to the high incidence of acute postoperative pain, the incidence of chronic postoperative pain is also among the highest compared to other kind of surgeries[9]. Chronic postoperative pain affects even 37% patients in the first 6 months after cardiac surgery, which declines to 17% after two years[23]. Over the last years there is a growing body of literature investigating risk factors for the development of chronic postoperative pain. Younger age, non-elective surgery and female gender have been identified as a risk factors for chronic postoperative pain after cardiac surgery but are impossible to influence[24,25]. Increased acute postoperative pain, anxiety before surgery[24,25] and the use of remifentanil[25] are risk factors that can be managed. Especially the use of remifentanil for intraoperative analgesia is interesting from a pharmacological point of view and is potentially a risk factor that can be eliminated easily. Remifentanil is an ultra-short-acting, hyper potent, μ-opioid receptor agonist[26] which is often used during surgery because of its favourable pharmacokinetic and pharmacodynamic properties[27]. Because remifentanil may affect the NMDA receptor directly or indirectly[28,29], it has been hypothesized that signalling of this NMDA receptor may lead to opioid induced hyperalgesia[30]. The clinical relevance of "remifentanil induced hyperalgesia" is still under debate and therefore more research in this field is warranted.

In children, morphine is the most commonly used drug used for postoperative pain management after cardiac surgery[31]. The pharmacokinetics of morphine has been studied extensively across the paediatric population in all different kind of settings[32], including cardiac surgery[33,34]. Studies investigating the pharmacodynamics of morphine in children are scarce, while it is known that untreated pain after major surgery in neonates and infants results in increased stress hormone levels and prolonged behavioural consequences[35]. To optimize paediatric pain management after cardiac surgery, more insight is needed in the combined pharmacokinetic/pharmacodynamic field of data.

Opioids in obese patients after surgery

Another special patient population that needs increased attention is the (morbidly) obese population. There has been a major increase in prevalence of individuals that are overweight (a BMI above 25 kg/m^2), obese (a BMI above 30 kg/m^2), severely obese (a BMI above 35 kg/m^2) or morbidly obese (a BMI above 40 mg/km^2)[36]. It has been estimated that in 2025, if this rising trend continues, the prevalence of obesity is around 18% for men and 21% for women[36]. With obesity, morbidity and mortality significantly increase[37]. Obese patients are more at risk for all kind of potentially serious health conditions such as cardiovascular disease, diabetes, cancer, osteoarthritis, liver and kidney diseases[38]. For these reasons, obese patients are presenting more frequently for surgical procedures with accompanying complications such as postoperative pain. There is little evidence that obesity itself has impact on postoperative pain[39]. On the contrary, opioids are feared in obese population because of the increased risk for respiratory depression, respiratory failure, and other opioid adverse effects[40,41]. Therefore, knowledge on the extent into which the physiological changes associated with obesity influence the pharmacokinetics of opioids is essential. Morphine is frequently used for postoperative pain management but the pharmacokinetics of morphine and its pharmacologically active metabolites in (morbidly) obese patients has not been studied in detail.

The objective of this thesis

Postoperative pain is a relevant complication and has in potential great impact on patients. The role of opioids in postoperative pain and postoperative pain management, especially in different kind of patient populations, is not thoroughly studied. Therefore, this thesis aimed to contribute to perioperative pain management in different patient populations with the focus on opioid analgesia.

In *section II,* the focus is on adult cardiac surgery patients. 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. Although studies are diverse and sample sizes are small, there are indications that intraoperative remifentanil may influence the occurrence of acute postoperative hyperalgesia and may result in chronic postoperative pain. To address this issue, a randomised controlled trial investigating the influence of remifentanil on acute and chronic postoperative pain was designed and described in **chapter 3**. In **chapter 4,** we report the outcomes of this randomised controlled trial on acute and chronic postoperative pain 3, 6 and 12 months after surgery. In addition, we investigated the short and long term effects of remifentanil

on experimental pain using the measurement of thermal detection and pain thresholds, which is described in **chapter 5**. To investigate a potential genetic component in this cohort of cardiac surgery patients, **chapter 6** describes the potential influence of two genes that are associated with postoperative pain on acute, chronic and experimental pain.

Section III focuses on children after cardiac surgery. In children, morphine is commonly used for analgesia after cardiac surgery but not much is known about its analgesic efficacy in relation to plasma concentrations. Therefore, in **chapter 7** we report the analysis of the pharmacodynamics of morphine in children after cardiac surgery using repeated Time-to-Event (RTTE) modelling.

In *section IV*, we focus on the obese patient population. As already noted, the obese population is growing over the last decade and with this, obese patients that undergo surgery and experience 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. Second, we present in chapter 9 the analysis of the pharmacokinetics of morphine in obese patients when compared to non-obese healthy volunteers.

In *section V* - **chapter 10**, the results and conclusions of this thesis are summarized and discussed, and future perspectives are presented. In this chapter, perspectives are given concerning postoperative pain management with opioids in different patient populations. Finally, ideas are provided for further pharmacological interventions or studies regarding optimizing postoperative pain management.

Literature

1. Merskey, H. & Bogduk, N. Part III: Pain Terms: A Current List with Definitions and Notes on Usage. in *Classification of Chronic Pain, Second Edition, IASP Task Force on Taxonomy* 209–214 (1994).
2. Cheatle, M. D. Biopsychosocial Approach to Assessing and Managing Patients with Chronic Pain. *Med. Clin. North Am.* 100, 43–53 (2016).
3. Buvanendran, A. *et al.* The Incidence and Severity of Postoperative Pain following Inpatient Surgery. *Pain Med.* 16, 2277–83 (2015).
4. Gan, T. J., Habib, A. S., Miller, T. E., White, W. & Apfelbaum, J. L. Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. *Curr. Med. Res. Opin.* 30, 149–160 (2014).
5. Apfelbaum, J. L., Chen, C., Mehta, S. S. & Gan, T. J. Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. *Anesth. Analg.* 97, 534–40, table of contents (2003).
6. Kehlet, H., Jensen, T. S. & Woolf, C. J. Persistent postsurgical pain: risk factors and prevention. *Lancet* 367, 1618–1625 (2006).
7. Chapman, C. R. & Vierck, C. J. The Transition of Acute Postoperative Pain to Chronic Pain: An Integrative Overview of Research on Mechanisms. *J. Pain* 18, 359.e1-359.e38 (2017).
8. Johansen, A., Romundstad, L., Nielsen, C. S., Schirmer, H. & Stubhaug, A. Persistent postsurgical pain in a general population: Prevalence and predictors in the Tromsø study. *Pain* 153, 1390–1396 (2012).
9. Macrae, W. A. Chronic post-surgical pain: 10 Years on. *Br. J. Anaesth.* 101, 77–86 (2008).
10. Dutch Society of Anesthesiology. *Guideline: Postoperative Pain*. (2013).
11. Sommer, M. *et al.* The prevalence of postoperative pain in a sample of 1490 surgical inpatients. *Eur. J. Anaesthesiol.* 25, 267–74 (2008).
12. Mongardon, N. *et al.* Assessment of chronic pain after thoracotomy: a 1-year prevalence study. *Clin. J. Pain* 27, 677–681 (2011).
13. Steeds, C. The anatomy and physiology of pain. *Surg.* 31, 49–53 (2013).
14. Pogatzki-Zahn, E. M., Segelcke, D. & Schug, S. A. Postoperative pain—from mechanisms to treatment. *Pain Reports* 2, e588 (2017).
15. Mifflin, K. A. & Kerr, B. J. The transition from acute to chronic pain: Understanding how different biological systems interact. *Canadian Journal of Anesthesia* 61, 112–122 (2014).
16. Yang, M. M. H. *et al.* Preoperative predictors of poor acute postoperative pain control: A systematic review and meta-analysis. *BMJ Open* 9, e025091 (2019).
17. Chapman, C. R., Donaldson, G. W., Davis, J. J. & Bradshaw, D. H. Improving individual measurement of postoperative pain: The pain trajectory. *J. Pain* 12, 257–262 (2011).
18. Fletcher, D. *et al.* Chronic postsurgical pain in Europe: An observational study. *Eur. J. Anaesthesiol.* 32, 725–734 (2015).
19. Young, E. E., Lariviere, W. R. & Belfer, I. Genetic basis of pain variability: recent advances. *J. Med. Genet.* 49, 1–9 (2012).
20. Roger, V. L. *et al.* Heart disease and stroke statistics--2012 update: a report from the American Heart Association. *Circulation* 125, e2–e220 (2012).

21. Mueller, X. M. *et al.* Pain location, distribution, and intensity after cardiac surgery. *Chest* 118, 391–6 (2000).
22. Liu, S. S. & Wu, C. L. Effect of postoperative analgesia on major postoperative complications: a systematic update of the evidence. *Anesth. Analg.* 104, 689–702 (2007).
23. Guimarães-Pereira, L., Reis, P., Abelha, F., Azevedo, L. F. & Castro-Lopes, J. M. Persistent postoperative pain after cardiac surgery: a systematic review with meta-analysis regarding incidence and pain intensity. *Pain* 158, 1869–1885 (2017).
24. Choinière, M. *et al.* Prevalence of and risk factors for persistent postoperative nonanginal pain after cardiac surgery: a 2-year prospective multicentre study. *CMAJ* 186, E213-23 (2014).
25. van Gulik, L. *et al.* Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *Eur. J. Cardiothorac. Surg.* 40, 1309–1313 (2011).
26. Westmoreland, C. L., Hoke, J. F., Sebel, P. S., Hug Jr, C. C. & Muir, K. T. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79, 893–903 (1993).
27. Thompson, J. P. & Rowbotham, D. J. Remifentanil--an opioid for the 21st century. *Br. J. Anaesth.* 76, 341–343 (1996).
28. Fletcher, D. & Martinez, V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. *Br. J. Anaesth.* 112, 991–1004 (2014).
29. Kim, S. H., Stoicea, N., Soghomonyan, S. & Bergese, S. D. Intraoperative use of remifentanil and opioid induced hyperalgesia/acute opioid tolerance: systematic review. *Front. Pharmacol.* 5, 108 (2014).
30. Guntz, E. *et al.* Effects of remifentanil on N-methyl-D-aspartate receptor: an electrophysiologic study in rat spinal cord. *Anesthesiology* 102, 1235–1241 (2005).
31. Zeilmaker-Roest, G. A. *et al.* An international survey of management of pain and sedation after paediatric cardiac surgery. *BMJ Paediatr. open* 1, e000046-2017–000046. eCollection 2017 (2017).
32. Krekels, E. H., Tibboel, D., Danhof, M. & Knibbe, C. A. Prediction of morphine clearance in the paediatric population : how accurate are the available pharmacokinetic models? *Clin. Pharmacokinet.* 51, 695–709 (2012).
33. Elkomy, M. H. *et al.* Pharmacokinetics of Morphine and Its Metabolites in Infants and Young Children After Congenital Heart Surgery. *AAPS J.* 18, 124–133 (2016).
34. Valkenburg, A. J. *et al.* Pharmacodynamics and Pharmacokinetics of Morphine After Cardiac Surgery in Children With and Without Down Syndrome. *Pediatr. Crit. Care Med.* 17, 930–938 (2016).
35. Anand, K. J. & Aynsley-Green, A. Measuring the severity of surgical stress in newborn infants. *J. Pediatr. Surg.* 23, 297–305 (1988).
36. NCD Risk Factor Collaboration (NCD-RisC). Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants. *Lancet (London, England)* 387, 1377–1396 (2016).
37. Global BMI Mortality Collaboration *et al.* Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. *Lancet (London, England)* 388, 776–86 (2016).
38. Pi-Sunyer, X. The Medical Risks of Obesity. *Postgrad. Med.* 121, 21–33 (2009).

39. Budiansky, A. S., Margarson, M. P. & Eipe, N. Acute pain management in morbid obesity - an evidence based clinical update. *Surg. Obes. Relat. Dis.* 13, 523–532 (2017).

40. Lloret Linares, C. *et al.* Pharmacology of morphine in obese patients: clinical implications. *Clin. Pharmacokinet.* 48, 635–51 (2009).

41. Rose, D. K., Cohen, M. M., Wigglesworth, D. F. & DeBoer, D. P. Critical respiratory events in the postanesthesia care unit. Patient, surgical, and anesthetic factors. *Anesthesiology* 81, 410–418 (1994).