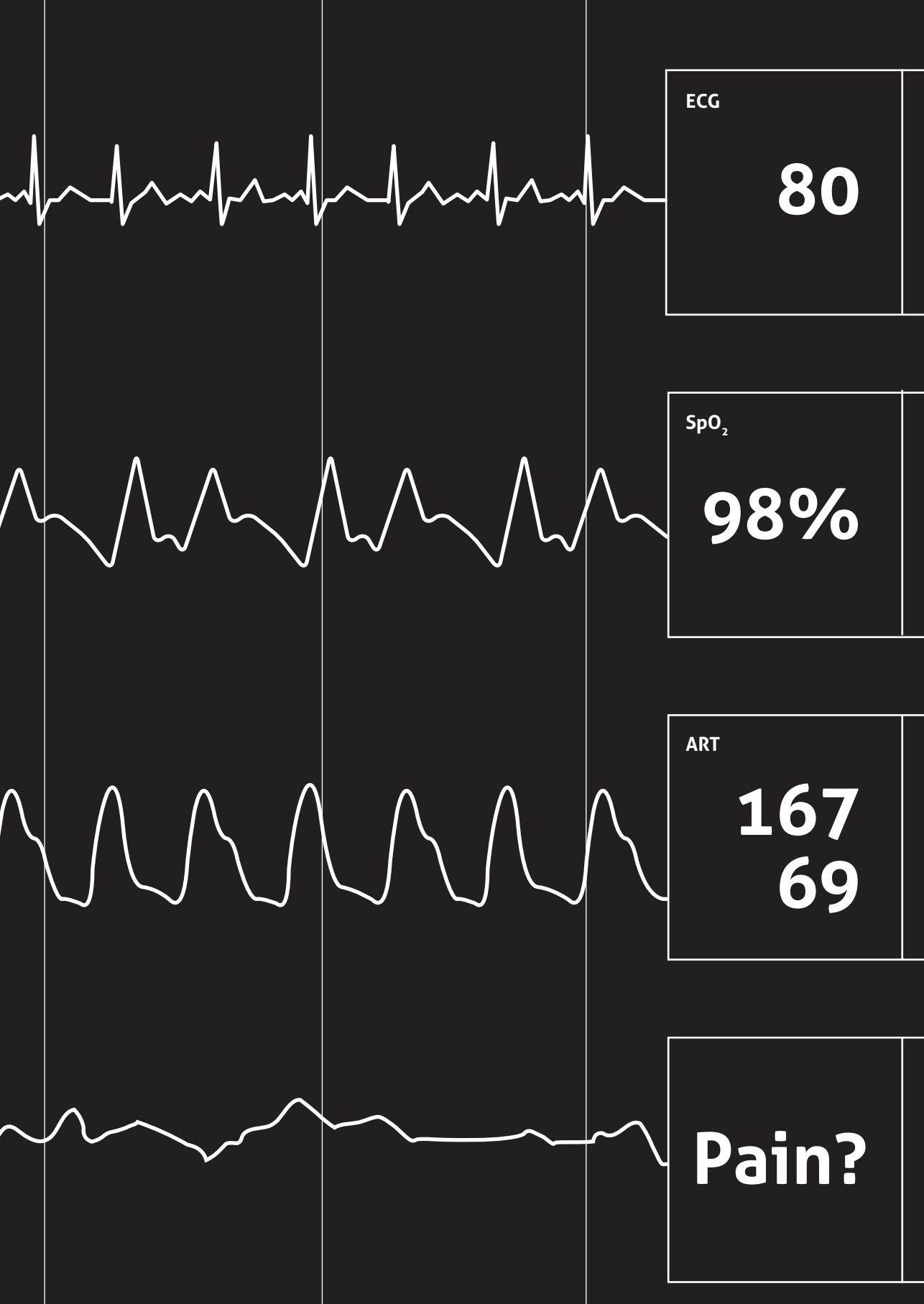
ECG
80
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Pain?

GENERAL INTRODUCTION

CH. 1 section I

Acute postoperative pain is not an unusual phenomenon. More than 77% of patients admitted to the intensive care unit (ICU) after cardiac surgery suffer from pain [1, 2]. It has been reported before that pain may lead to longer duration of mechanical ventilation and length of stay in the ICU [3]. Furthermore, acute postoperative pain may develop into *chronic pain* [4-8], which was observed in 11 to 56% of patients one year after cardiac surgery [6, 9-12].

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" [13]. Pain is always subjective and can be captured in a biopsychosocial model in which psychological factors and the social context are recognized as major determinants of actual pain of an individual [14]. In the hospital setting, however, as we cannot change a patient's previous course of life, psychological history and social context, we first of all focus on pain prevention, assess whether patients are nevertheless in pain, and if so, offer the best possible treatment. Pain assessment is performed best by a patient's self-report, but patients may (temporarily) be unable to self-report pain. One of the challenges for health care workers lies in the recognition and treatment of pain in these patients, for example patients in the ICU.

ICU patients are at risk for pain from surgery, underlying illness or injury, immobility, medical interventions and pre-existent (chronic) conditions. Pain in rest should be distinguished from procedural pain caused e.g. by mobilization, removal of chest tubes, tracheal suction, and insertion of central venous catheters. Pain *in rest* was reported in 33% of 1381 mechanically ventilated patients in the DOLOREA study in 44 ICUs in France and Luxembourg [15]. In a mixed ICU, the incidence of pain in rest was 51%, and did not differ between medical and surgical intensive care patients [3, 15]. In another study, 86-90% of patients experienced pain after cardiac surgery in the first two days in the ICU [1]. In yet another study, 77% of patients after cardiac surgery recalled to have suffered pain while in the ICU [2]. *Procedural* pain, was reported in at least 22% of almost 6000 ICU patients in 169 mixed ICUs [16]. In particular posture change and chest tube removal were experienced as painful, with mean pain intensity of 4.9 and 6.6 on a scale from 0 to 10, respectively [16, 17].

Negative effects of inadequate analgesia such as a metabolic/hormonal stress response with increased myocardial oxygen consumption and tachycardia [18-20], as well as respiratory insufficiency [21-23] may lengthen duration of mechanical ventilation and ICU length of stay [3]. Consequently, international [24] and national societies (Nederlandse Vereniging voor Intensive Care (NVIC)) recommend routine assessment and treatment of pain [25]. These recommendations are mostly based on the observed shortened duration of mechanical ventilation and length of stay in the ICU upon the introduction of sedation protocols [26-29]. Even though these sedation protocols usually include analgesics, only few studies focus on pain assessment and analgesia. In a post-hoc analysis of the above-mentioned DOLOREA study [15], systematic pain assessment was associated with shorter durations of ventilator support and ICU-stay [30]. In a smaller single-centre study, the introduction of systematic assessment of pain coincided with a decrease of pain incidence, nosocomial infections, and duration of mechanical ventilation [3].

Pain management is considered an important healthcare benchmark. The Dutch Health Care Inspectorate introduced the performance indicator "postoperative pain"

for hospitals, which indicates that hospitals are required to report the percentage of *actually performed* with respect to the *scheduled* number of postoperative pain assessments and the percentage of patients with a pain score higher than 7 on the numeric rating scale (NRS from 0 to 10) [31] any time within the first 72 hours after surgery [32].

In several studies acute pain rated with a NRS ≥4 was associated with a higher risk of the development of chronic pain [4-8]. The IASP defines chronic pain as pain without apparent biological value that has persisted beyond the normal tissue healing time of 2 months after surgery in general [13], although others suggest 3 months or more [33]. Chronic pain after cardiac surgery is reported between 11 and 56% of patients one year after surgery [6, 9-12]. Patients suffering from chronic thoracic pain report a significantly lower physical and mental health status compared with patients without chronic thoracic pain [9, 12, 34, 35]. Literature on chronic pain after cardiac surgery is scarce, although more than 2 million open-heart surgeries are performed annually [36]. The available reports show a wide range in incidence of chronic pain. This may be due to the use of different inclusion criteria, which complicates comparison.

This thesis focuses on both acute and chronic pain in patients after cardiac surgery. First, various aspects of acute pain in the direct postoperative period – when patients are admitted to the ICU – are evaluated. This includes the impact of the introduction of a pain management program, the effect of morphine on procedural pain due to an inevitable medical procedure, changes in serum stress hormones during procedural pain, and compliance to the ICU pain protocol. Next, the occurrence of chronic pain one year after cardiac surgery is studied. Here possible risk factors for chronic pain such as acute pain experienced in the ICU during the first 3 postoperative days are identified.

Acute pain in the ICU

Pain assessment

Pain is a subjective experience. International consensus states that the gold standard to ascertain the presence and intensity of pain is a patient's self-reported experience. Patients admitted to the ICU are often not capable of self report because they are too ill or heavily sedated. Then, the attending nurse involved in daily care is the best person to assess the patient's pain. A suitable instrument is the Numerical Rating Scale (NRS), which has been found valid to assess pain by proxy by the attending nurse [37]. The NRS is based on a scale from 0 to 10 in which 0 represents "no pain" and 10 represents "the worst possible pain " [31]. The NRS has a maximum acceptable pain score of 3 [19].

Pain management in the ICU

Clinical practice guidelines recommend systematic evaluation of pain [24]. Few studies, however, have addressed the effects of the introduction of a pain management system and pain education program in the ICU on the occurrence of pain; more studies concerning sedation protocols are available. Table 1 provides an overview of studies on pain and sedation management in the ICU. The studies differ among others in medical diagnosis, study design, and primary and secondary aims, which demonstrates that they should be compared with caution. Seven of the 16

pain and sedation protocol studies from Table 1 did not chose "pain" or "sedation" as a primary aim, but focused on duration of mechanical ventilation and either ICU or hospital length of stay. The first part of the table shows six studies on a total of 2079 patients that compared control patients with patients treated according to a pain protocol. Significantly less pain was found in the pain protocol group in four studies [3, 27, 38, 39], for example a reduction of the incidence of pain from 63 to 42% in the study by Chanques *et al* [3] (Table 1). Of these studies, Diby *et al*. reported specifically on pain after cardiac surgery when they introduced a postoperative pain treatment program in the ICU by training, pocket guidelines, regular audits, and feedback [38]. In that study, significantly more patients were always or often pain-free after the implementation of this program (11% vs. 37%, P =0.005). Two other studies [40, 41] did not report a difference in pain scores between the control and intervention group, but reported on other advantages of the pain protocol such as reduced duration of mechanical ventilation and/or length of stay. The second part of Table 1 shows 10 studies on a total of 2419 patients that compared control patients with patients treated according to a sedation protocol. The most obvious goal of the introduction of a sedation protocol would be the depth of sedation. However, sedation scores were the primary aim in only 3 studies [42-44], whereas duration of mechanical ventilation [28, 42, 45-49], ICU [42, 44, 45] or hospital length of stay [42, 44], the incidence of ventilator associated pneumonia [42, 50], doses of analgesics/ sedatives [42], ICU and hospital outcome [42] and incidence of delirium [43] were reported in others. In fact, only 4 studies actually reported sedation scores [42-44, 47]. Six studies [28, 42-44, 46, 47] included pain treatment in their sedation protocol, although only 2 of them reported pain scores [43, 44]. The study by Quenot *et al* [50] excluded patients who received opioids. In conclusion, although the design and protocols of the studies presented in Table 1 vary considerably in content and execution, they show that the introduction of a pain and/or sedation management protocol may result in lower pain scores, more sedation scores within target range, shorter duration of mechanical ventilation and a shorter length of stay in the ICU. The best design of such a protocol for patients in the ICU after cardiac surgery and the role of the patient data monitoring system (PDMS) still need to be established.

Procedural pain

Procedure-related pain, i.e. pain caused by interventions such as mobilization, the removal of chest tubes, tracheal suction and the insertion of central venous catheters, is the most common form of healthcare-induced pain [51]. Patients recall these interventions as strong negative memories of the time in the ICU [2]. Procedural pain seems difficult to treat, and some patients will experience unacceptable pain despite treatment [6, 15]. Posture change and chest tube removal have been identified as the most painful procedures [16, 52]. International guidelines [24] recommend preemptive analgesia and/or non-pharmacologic interventions (e.g. relaxation exercises) prior to chest tube removal. Table 2 summarizes 8 studies in 560 patients randomized between different strategies to prevent pain due to chest tubes removal after cardiac surgery. The relevance of studies on pain due to chest tube removal is shown by 4 trials in which patients in the placebo groups reported pain scores between 5 and 7.2 on a scale from 0 -10 [53-56]. Two studies showed that topically applied medication resulted in significantly lower pain scores than in control groups

[56, 57]. Interpleural administration of bupivacaine did not lower pain scores compared with placebo [58]. Intravenous opioids were used with success in 3 out of 4 studies [53, 55, 57, 59]. Patients experienced more discomfort on the removal of the second chest tube in a study comparing Entonox and Isoflurane for the removal of the first and second chest tube [60]. The authors suggest that the arousal or anxiety caused by the removal of the first chest tube amplified the distress caused by the removal of the second one. The use of procedural and sensory information prior to the removal of chest tubes, was not apparent on pain scores in a study comparing intravenous morphine or ketorolac [59]. The effect of baseline analgesia and VAS scores before the intervention is not clear from these studies; in fact only the studies by Casey *et al* [53] and Akrofi *et al* [57] reported standard baseline analgesia and only half of the studies in Table 2 showed pain scores before the removal of chest tubes.

Stress hormones as biomarker for procedural pain

Changes in heart rate, blood pressure, and respiratory rate have been used as surrogate markers of pain. In ICU patients these parameters are largely influenced by disease severity and medication. An alternative method may be measurement of stress hormones, such as cortisol, adrenalin, and noradrenalin, which are thought to be released systemically in a sympathetic stress response triggered by e.g. pain [20]. If measurements of stress hormones correlate with subjective reports of patients who are able to report pain, stress hormones may become useful in research as surrogate markers for procedural pain in the ICU.

Adherence to protocols

Hospital departments in general, and intensive care units in particular, are struggling with non-adherence to guidelines in general [61, 62] and more specifically to pain management protocols [15, 63]. Even in the context of observational studies in which caregivers knew they were being monitored, pain assessment was not performed according to acceptable standards [64]. Likewise, Watt-Watson *et al* demonstrated that patients after coronary artery bypass grafting actually received only 33–47% of the prescribed dose of analgesics despite the fact that they experienced considerable pain [65]. Non-compliance to pain management protocols in pediatric ICUs was previously shown to be a thorny issue [63, 66, 67]. It may well be that health professionals are not aware of the existence of protocols, or do not agree with the protocols, or do not expect beneficial outcomes [68]. Even if a pain management program seems successful in reducing pain in patients in the ICU after cardiac surgery, evaluation of adherence to the protocol may identify items that can be improved and therefore continuous surveillance over time is essential.

Chronic pain

The incidence of chronic thoracic pain after cardiac surgery via sternotomy varies from 11 to 56% [6, 9-12], depending on both the definition and the population studied [69]. Patients who suffer from chronic thoracic pain experience a significantly lower physical and mental health status compared with patients without chronic thoracic pain [9, 12, 34, 35]. In a cross-sectional study by Taillefer *et al*, chronic pain interfered with various aspects of patients' daily living, including general activity (39%), sleep

(37%), walking ability (33%), mood (30%), enjoyment of life (28), and relations with others (21%) [34].

The exact pathophysiology of the development of chronic pain after surgery has not been clarified yet. Multiple factors are held responsible for the development of chronic pain, but are of varying importance. One such factors is the severity of acute postoperative pain, but research on the relation between acute postoperative and chronic pain after cardiac surgery is sparse [4-8, 70]. In a study by Steegers *et al*. [71], patients with chronic pain after coronary artery bypass grafting recalled significantly more intense wound pain in the first week after the operation than did the group without chronic pain (87% versus 68% at least moderate pain, P=0.0002).

In addition, a positive relation between chronic pain after cardiac surgery and the consumption of opioids on the surgical ward and ICU has been described in a retrospective study [34], while another publication reported a relation with consumption of opioids on the second and third postoperative days [10]. The only prospective study on the relation between acute postoperative pain after cardiac surgery on the incidence of chronic pain showed a possible association between the presence of moderate to severe acute postoperative pain on the fourth day after surgery and chronic post-sternotomy pain at rest one year after cardiac surgery [6]. Other previously reported risk factors for the development of chronic pain after cardiac surgery are young age [10, 12, 35, 71] and large body mass index (BMI) [35], as shown in Table 3. Table 3 includes 8 studies reporting on a total of 3820 patients with incidences of chronic pain varying between 11 and 30% at 1 to 3 years after surgery. Inclusion criteria vary between the articles; most studies included elective surgery patients, some excluded patients older than a certain age, one article included women only [72]. Five studies are retrospective studies and only two prospective articles evaluated acute postoperative pain in addition to chronic pain. Information on acute pain while in the ICU and perioperative analgesia in relation to chronic pain is warranted, as this may provide possibilities for preventing the development of chronic pain.

Table 1 Literature overview of the impact of the introduction of a pain/sedation protocol in the ICU [3, 27, 28, 38-50]

Pain protocol						
Article	**ICU patients**	**Primary endpoint**	**Study design**	**Results on pain/agitation/delirium**	**Other outcome**	**Remarks**
Mansouri et al 2013 [40]	N=201 Medical/ surgical	*Pain (NRS, BPS) *Agitation (RASS) *Delirium (CAM-ICU)	Randomization between control group (pain and agitation assessed when ordered, medication prescribed by doctors) and protocol group (hourly assessment of pain, agitation and delirium)	*In protocol group patients had NRS<4 or BPS<6 during 95% of the time in the ICU *Patients were within target RASS 72% of time in the ICU *Delirium occurred in 8.5% of patients *No assessments for the control group	*Significantly shorter mechanical ventilation (19 vs. 40 hours) *Significantly shorter ICU LOS (97 vs. 170 hours) *Significantly lower mortality (13 vs. 23%)	Randomized study, staff was not blinded. As patients were on the same ICU, a crossover effect between groups cannot be excluded.
Skrobrik et al 2010 [39]	N=1214 Medical/ surgical	*Medication use *Medication induced coma *Delirium (ICDSC)	Before and after implementation of systematic evaluation of pain (NRS, BPS), delirium and agitation (RASS) levels, education and treatment algorithm	*Significantly less pain (mean NRS 1.2 vs. 1.6) *No difference in sedation levels *No difference in delirium incidence *Significantly less subsyndromal delirium (25 vs. 33%) *Significantly more patients with ICDSC=0 (41 vs. 33%)	*Significantly less opioid equivalents, lorazepam *Significantly more often patients without sedation *Significantly less medication-induced coma (7 vs. 18%) *Significantly shorter ICU LOS (5 vs. 6 days) *Significantly shorter hospital LOS (27 vs. 55 days) *Significantly shorter mechanical ventilation (6 vs. 8 days) *Significantly lower 30day mortality (23 vs. 29%)	Retrospective comparison with database for control group
Diby et al 2008 [38]	N=133 Cardiac surgery	Pain (VAS)	Before and after implementation of systematic evaluation of pain levels, education and treatment algorithm	*Significant lower VAS at rest (2.7 vs. 2.2) *Significant lower recalled VAS (3.8 vs. 2.6) *Significantly more patients often or always pain free (37 vs. 11%)	Significantly less patients with sleep disturbances (35 vs. 68%)	
Robinson et al 2008 [41]	N=143 Trauma	*Duration of mechanical ventilation *Hospital and ICU LOS *Opioids and propofol use	Before and after implementation of systematic evaluation of pain, delirium and agitation levels, education and treatment algorithm	No registration in control group, no scores of intervention group reported	*Significantly shorter mechanical ventilation (1.2 vs. 3.2 days) *Significantly shorter hospital LOS (12 vs. 18 days) *Significantly less use of opioids and propofol *No significant difference in ICU LOS	Retrospective comparison between groups in database
Chanques et al 2006 [3]	N=230 Medical/ surgical	*Pain (NRS, BPS) *Agitation (RASS)	Before and after implementation of systematic evaluation of pain and agitation levels, education and treatment algorithm	*Significantly lower incidence of pain (42 vs. 63%) *Significantly lower incidence of agitation (12 vs. 29%)	*Significantly shorter duration of mechanical ventilation (65 vs120 hours) *Significantly less nosocomial infections (8 vs. 17%) *Significantly more escalations and de-escalations of analgesic and psychoactive drugs *No significant difference in ICU LOS *No significant difference in ICU mortality	
MacLaren et al 2000 [27]	N=158 Medical/ surgical/ neurologic	*Pharmacologic costs *Duration of mechanical ventilation *ICU LOS *Sedation (modified Ramsay score) *Analgesia (modified VAS)	Before and after protocol implementation	*Significantly more often sedation and pain assessment (77 vs. 63%) *Tendency towards longer sedation (123 vs. 88 hours, NS) *Significantly less discomfort (11 vs. 22%) *Significantly less pain (6 vs. 10%)	*Significantly lower hourly cost of sedation *Significantly lower mean hourly dose of propofol *Significantly higher mean hourly dose of lorazepam	Patients who received analgesics only were excluded

Sedation protocol						
	ICU patients	Primary aim	Study design	Results on pain/agitation/delirium	Other outcome	Remarks
Porhomayon et al 2013 [44]	N=200 Surgical	*Sedation (RASS) *Duration of mechanical ventilation *ICU and hospital LOS	Before and after sedation protocol implementation (pain (NRS) treated first)	*Significantly less continuous and more intermittent analgesia and sedation *Significantly less fentanyl and midazolam use *Significantly more sedation scores within sedation goals (87% vs. 74%) *Significantly lower pain scores NRS<5 (73 vs. 80%)	*Significantly shorter duration of mechanical ventilation (4 vs. 6 days) *No significant difference in number of tracheotomies	More NRS>5 after implementation
Hager et al 2013 [43]	N=202 Medical with ALI	*Sedation (RASS) *Delirium (CAM-ICU)	*Sedation (RASS) *Delirium (CAM-ICU)	The average daily pain score per patient in the protocol group was 0.5 (0.0, 1.3) (pain in the control group was not assessed)	*Significantly less ICU days per patient with narcotic and benzodiazepine infusions (33% vs. 74% and 22% vs. 70%) *Significantly more RASS scores per patient indicating greater wakefulness (−1.5 vs. −4.0) *Significantly more days per patient without sedation (50% vs. 20%) *Significantly less coma (RASS −4 or −5) (23% vs. 65%) *Significantly more patients were often awake and not delirious (19% vs. 0%) *Significantly more delirium (38% vs. 20%)	Data of the control group were retrospectively retrieved from the database No report of duration of mechanical ventilation, ICU or hospital LOS
Hahn et al 2013 [49]	N=42	Duration of mechanical ventilation	Before and after sedation protocol implementation Retrospective study	No scores reported	No significant difference in duration of mechanical ventilation	Underpowered due to less included patients than needed Protocol was not included
Bucknall et al 2008 [46]	N=312 Medical/ surgical/ trauma	Time from start of mechanical ventilation until successful weaning from mechanical ventilation	RCT: Control group: sedatives prescribed by physician Intervention group: implementation of sedation (SAS) protocol Pain (no scale) treated first	No scores reported	*No significant difference in weaning time *No significant difference In hospital mortality *No significant difference in ICU and hospital LOS *No significant difference in hospital mortality *No significant difference in incidence of self-extubation *No significant difference in % receiving a tracheotomy	>80% of patients in both groups received propofol and no benzodiazepines Open study A crossover effect between groups cannot be excluded as the study was performed in one unit
Arabi et al 2007 [42]	N=210 Medical/ surgical/ trauma	N=210 Medical/ surgical/ trauma	Prospective, 4 study arms comparing protocolized versus non-protocolized and before versus after staff education Pain treated first Pain (VAS) and sedation (SAS) score every 4 hours	*Significant reductions in administered midazolam, fentanyl and propofol, especially in protocolized group after education *Significant more patients in targeted sedation range (calm) and significantly less patients deeply sedation in groups after education *No pain scores reported	*Two groups after education had significant lower incidence of VAP (11% vs. 28%), a trend towards shorter duration of mechanical ventilation (8-10 days vs. 11-12 days P=0.055) and shorter hospital LOS (40/41 days vs. 50/55 days P=0.08) *No significant difference in ICU LOS, ICU or hospital outcome	The authors suggests that education improved sedation management better than the use of a protocol alone.

Table 1 Literature overview of the impact of the introduction of a pain/sedation protocol in the ICU [3, 27, 28, 38-50]

continued

Sedation protocol						
	ICU patients	**Primary aim**	**Study design**	**Results on pain/agitation/delirium**	**Other outcome**	**Remarks**
Quenot et al 2007 [50]	N=423 Medical mechanically ventilated patients	VAP	Before and after protocol implementation Control group: sedation adjusted according to physician prescriptions Protocol: adjustment of sedatives by nurse every 3 hours	*Significantly lower daily doses of sedatives *No pain scores reported	*Significant lower incidence of VAP (6 vs. 15%) *Significant shorter duration of mechanical ventilation (4 vs. 8 days)) *Significant less extubation failure (6 vs. 13%) *No significant difference in hospital mortality	Patients who received analgesics were excluded
Elliot et al 2006 [47]	N=423 Medical mechanically ventilated patients	Duration of mechanical ventilation	Before and after protocol implementation Control group: sedation and analgesia according to physician Protocol: adjustments of analgesics and sedatives according to pain and target sedation score (Ramsay)	*Significantly more sedation scores in target (50 vs. 13%) *No pain scores reported	*No difference in duration of mechanical ventilation (6 vs. 5 days (P=0.99) *Significantly longer ICU LOS (8 vs. 7 days) *No difference in incidences of tracheotomies, reintubations and self-extubations	
De Jonghe et al 2005 [48]	N=102 Mechanically ventilated patients without acute brain injury	Duration of mechanical ventilation	Before and after protocol implementation Control group: sedation adjusted according to physician prescriptions Protocol: 3 hourly adjustments according to Adaptation to Intensive Care Environment instrument	No scores reported	*Significantly shorter duration of mechanical ventilation (4 vs. 10 days) *Significantly shorter time to arousal after initiation of mechanical ventilation (2 vs. 4 days) *Significantly fewer patients with pressure sores (19 vs. 37%)	
Brattebø et al 2004 [45]	N=285 Surgical	*Duration of mechanical ventilation *ICU LOS	Before and after protocol implementation Control group: no systematic sedation assessment Protocol: nurse guided adjustment of sedatives according to sedation assessments	No scores reported	*Mean ventilator time decreased by 2.1 days (95% CI 0.7 to 3.6 days) from 7.4 days before intervention to 5.3 days after intervention. *Mean ICU LOS decreased by 1.0 day (95% CI –0.9 to 2.9 days) from 9.3 days to 8.3 days.	Protocol not shown
Brook et al 1999 [28]	N=321 Medical	Duration of mechanical ventilation	RCT between traditional non- protocolized physician prescribed medication or nurse implemented sedation protocol (pain treated first)	*Significantly more patients received intermittent fentanyl (29 vs. 11%) *In both groups 41% of patients received continuous sedation, but the duration of sedation was significantly shorter (4 vs. 6 days) * No pain scores reported	*Significantly shorter duration of mechanical ventilation (89 vs. 124 hours) * Significantly shorter ICU LOS (6 vs. 8 days) *Hospital LOS significantly shorter (14 vs. 20 days) *No significant difference in hospital mortality, the development of organ system derangements or reintubation *Significant less often tracheotomy (6 vs. 13%)	

ALI acute lung injury, BPS behavioral pain scale, CAM-ICU Confusion Assessment Method, ICDSC Intensive Care Delirium Screening Checklist, ICU intensive care unit, LOS length of stay, NRS numeric rating scale, NS not significant, OPAS objective pain assessment scale, RASS Richmond Agitation-Sedation Scale, RCT randomized controlled trial, SAS Sedation-Agitation Scale, VAP Ventilator associated pneumonia, VAS visual analogue scale.

*in additional article by Awissi

Articles up to 2014 were found through PubMed with search terms “implementation sedation/ pain protocol ICU”, “systematic pain evaluation ICU”, “sedation/pain protocol ICU/ critically ill”, “sedation algorithm ICU” and “implementation pain program cardiac surgery”. References from the articles found through this search were crosschecked for more literature on the subject. Only articles describing the effects of the implementation of a pain/sedation protocol were presented in the table.

Table 2 Literature overview of pain levels during and analgesia for chest tube removal in patients in the ICU after cardiac surgery [53-60]

Article	N	Time after surgery (hrs)	Intervention	VAS during CTR	Conclusion	Remarks
Casey et al 2010 [53]	60	20-60	RCT 1) 0.5 µg/kg remifentanil 2) 1.0 µg/kg remifentanil 3) placebo	VAS (0-10 cm) 1) 1 [0,2] 2) 0 [0,2] 3) 5 [3,6]	There was significantly less pain in the remifentanil group compared to placebo; without a difference between 1) and 2)	Group 1 and 2 experienced significantly lower blood pressure Group 2 experienced significantly more respiratory depression
Demir et al 2010 [54]	90	<24	RCT: packs on insertion site* 1) cold (4°C) 2) placebo (18-22°C) 3) no pack	VAS (0-10 cm) 1) 6.8 (±2.3) 2) 7.1 (±2.2) 3) 7.2 (±2.1)	After CTR group 1) had a significantly lower pain intensity and a prolonged length of time until analgesics were needed. There was no difference in anxiety levels	Assessment after removal of all (2-3) drains VAS 15 min after CTR: 1) 2.0 (±1.1) 2) 2.7 (±1.9) 3) 2.7 (±1.7)
Joshi et al 2007 [55]	141	?	RCT: 10 minutes before CTR iv 1) fentanyl 2 µg/kg 2) sufentanil 0. 2 µg/kg 3) placebo	VAS (0-100 mm) 5 minutes after CTR 1) 20.1 (±6.9) 2) 13.6 (±6.6) 3) 28.0 (±8.4)	Pain scores in the sufentanil group were significantly lower compared with the fentanyl and placebo group	Pain assessments took place 5 minutes after CTR; there were no pain scores from during CTR. Pain scores after CTR were significantly lower than 10 minutes before CTR in the fentanyl and sufentanil groups. Pain scores after CTR were significantly higher than before CTR in the placebo group
Akrofi et al 2005 [57]	66	<24	RCT 1) 0.1 mg/kg IV morphine* 2) 20 mL 0.5% bupivacaine sc* 3) inhaled 50% Entonox	VAS (0-100 mm) 1) 15.0 mm [7,27] 2) 9.5 mm [3,18] 3) 37.0 mm [13,56]	Pain scores were significantly higher in the Entonox group compared with the bupivacaine group and the morphine group.	Two sizes of chest tubes were used randomly (this had not been taken into account for the study procedure) Patients who had chest tubes size 19F(silicone) had significantly less pain on CTR than those with rigid plastic tubes 28F.
Singh et al 2005 [56]	53	24-72	RCT: topical** 1) 50 mg valdecoxib in 5 g gel 2) 5 g liquid paraffin All patients had 2 chest tubes and received at random valdecoxib on one tube site and paraffin on the other	VAS (0-10 cm) 1) 2 [2,4] 2) 5 [4,6]	Pain scores were significantly lower in the valdecoxib group No adverse effects were encountered.	Not completely blinded : 1) blue gel 2) colourless liquid The right chest tube and was removed first. VAS before and after CTR was also lower in group 1 than in 2 1) 1 [0, 2] 2) 2 [0, 3.5] (P=0.034) VAS after CTR: 1) 2 [0.5, 2.5] 2) 4 [2, 5] (P=0.0002)

Table 2 Literature overview of pain levels during and analgesia for chest tube removal in patients in the ICU after cardiac surgery [53-60]
continued

Puntillo et al 2004 [59]	74	Mean 26	RCT 1) 4 mg morphine iv + procedural information 2) 30 mg ketorolac iv+ procedural information 3) 4 mg morphine iv + procedural and sensory information 4) 30 mg ketorolac iv + procedural and sensory information	NRS (0-10) 1) 3.0 (±2.4) 2) 3.5 (±2.9) 3) 4.5 (±3.5) 4) 2.0 (±2.8)	Pain intensity, pain distress, and sedation levels did not differ significantly among groups	The study was stopped after half of the intended 148 patients were included, as an interim analysis showed small effect sizes in pain intensity, pain distress and sedation scores with negligible clinically significance for most patients.
Bryden et al 1997 [60]	35	Second day?	RCT 2 chest tubes 1) 1st drain Entonox, 2nd Entonox + 0,25% isoflurane 2) 1st Entonox + 0,25% isoflurane, 2nd Entonox	VAS (0-100 mm) 1) 15 and 15 2) 15 and 40 (estimated from graph)	Group 2 experienced significantly more pain at 2nd CTR	Possibly, the 2nd CTR was more painful in group 2, due to less sedation to antagonize anxiety caused by 1st chest tube. Nurses chose which chest tube was removed first. Both groups reported more discomfort on second CTR.
Puntillo et al 1996 [58]	41	Mean 48	RCT 1) interpleural bupivacaine (through the chest tube) 2) interpleural saline (through the chest tube)	NRS (0-10) Overall: 4.7 (±3.4)	There was no difference in pain intensity between group 1 and 2	Patients who received ketorolac im before the procedure (not randomized) had significantly less pain (NRS 2.8±2.9) than those who did not (NRS 5.4; SD=3.9).

CTR chest tube removal, Entonox nitrous oxide in oxygen, ICU intensive care unit, NRS numeric rating scale, im intramuscular, RCT randomized controlled trial, Sc subcutaneously, VAS Visual Analogue Scale, *20 minutes before chest tube removal, **45 [IQR 40-60] minutes before chest tube removal, VAS: some articles used a scale from 0-10, others from 0-100 mm, Interquartile range [IQR], ± standard deviation

Articles up to 2014 were found through PubMed with search terms “randomized chest drain removal cardiac surgery”. References from the articles found through this search were checked for more literature on the subject.

Table 3 Literature overview on risk factors for chronic pain after cardiac surgery via sternotomy [6, 10-12, 34, 35, 71, 72]

Study	Risk factors for chronic pain	N	Incidence (%)	Study design	nclusion criteria	Information on per-operative anesthesia	Information on postoperative analgesia	Female (%)	Age (years)	BMI	Information on acute pain	Time after surgery
Gjeilo et al 2010 [12]	Younger age	465	11	P	Cardiac surgery	+	+	22	69 (24-87)	29 ±4	-	Before, 6 and 12 months
King et al 2008 [72]	1) Pain at 3 months, not at 5 days 2) Larger chest circumference 3) Use of bilateral IMA 4) Use of LIMA	326	18	P	First CABG and/or HVR Included in previous WREST study	-	-	100	66 ±11	29±6	+ POD5	3,12 months
Steegers et al 2007 [71]	1) Younger age 2) Acute pain 3) Postoperative AP	256	27	R	CABG Elective	+	+	18	65 (32-86)	-	+ recalled	16 months
Lahtinen et al 2006 [6]	Acute pain on POD4	186	17	P	CABG <70 years Elective	+	+	17	58 ±4	29±4	+ POD4	4 days 1,3,6,12 months
Taillefer et al 2006 [34]	1) Higher opioid consumption in the ward, not in the ICU 2) Shorter follow up time after surgery	564	23	R	First CABG and/or HVR Elective	-	±	26	63 (29-88)	28±5	Opioid consumption	30 ±10 months
Bruce et al 2003 [35]	1) Younger age 2) Higher BMI 3) AP before surgery	1080	30	R	CABG and/or HVR	-	-	27	66 (21-89)	28±4	-	28±15 months
Meyerson et al 2001 [11]	No association with use of the ITA	318	28	P	CABG and/or HVR <86jaar	-	-	20	65 (21-85)	-	-	1 year
Kalso et al 2001 [10]	1) Younger age 2) Higher NYHA class 3) Higher opioid consumption on POD2+3	625	28	R	CABG	-	-	23	62 (35-80)	-	Opioid consumption	24-36 months

Table 3 Literature overview on risk factors for chronic pain after cardiac surgery via sternotomy [6, 10-12, 34, 35, 71, 72]

AP angina pectoris, POD postoperative day, ICU intensive care unit, BMI body mass index, IMA internal mammary artery, ITA internal thoracic artery, LIMA left internal mammary artery, NYHA New York Heart Association, P prospective R retrospective, CABG coronary artery bypass graft, HVR heart valve replacement,

Articles up to 2014 were found through PubMed with search terms “chronic (chest) or long-term pain after cardiac surgery”. References from the articles found through this search were crosschecked for more literature on the subject.