Pain following extremity injury:
Management, Predictions and Outcomes

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Contents

Chapter 1

General Introduction

PAIN; AN ACUTE PROBLEM WHICH MIGHT BECOME CHRONIC

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" by the International Association for the Study of Pain (IASP) (1). Pain can be classified as either acute or chronic. Acute pain has a biological value, it can be a sign that something dangerous is occurring in the body. Acute pain typically occurs as a consequence of injury or trauma and may be associated with symptoms of inflammation. This pain is unpleasant but necessary. Nevertheless, there are also situations when pain experiences are unnecessary. This happens when pain has lost its value as a signal of danger. This pain without any useful biological function is called chronic pain.

Acute pain

Acute pain is described as being "the normal, predicted physiological response to an adverse chemical, thermal or mechanical stimulus associated with surgery, trauma and acute illness" (2). Yet patients' attitudes, beliefs, and personalities strongly affect their immediate experience of acute pain.

Acute pain can be either nociceptive or inflammatory. Both states of acute pain are protective and adaptive, and therefore have a biological function. Nociceptive pain is pain that results from activation of high thresholds peripheral sensory neurons (nociceptors) by intense chemical, thermal of mechanical noxious stimuli. Signals from these nociceptors travel primarily along small myelinated A-delta and unmyelated C sensory afferent fibers to the dorsal horn of the spinal cord where they make synaptic contact with other neurons. The signals travel post-synaptic mainly along the spinothalamic tract of the spinal cord to the thalamus and sensory cortex (3). The signaling continues also partly to the hypothalamus and the limbic system, the loci being important in determining the emotional reactions to pain (4). The nociceptive input and transmission signaling is under the influence of both local and spinal neural activity. These can be either inhibiting or facilitating.

Inflammatory pain is pain that occurs in response to tissue damage and inflammation. This pain is protective. Not in the same way as nociceptive pain because tissue damage has already occurred, but by enabling healing and repair to occur undisturbed. The pain results from the release of sensitizing inflammatory mediators that lead to a reduction in the threshold of nociceptors that innervates the inflamed tissue. This process is called peripheral sensitization. Peripheral sensitization is augmented by important biological processes that result in central sensitization of the spinal cord and dorsal horn. As a consequence of an increase in the excitability of neurons in the central nervous system (CNS), inflammatory processes are also associated with exaggerated responses to normal sensory inputs. These phenomena, named allodynia or hyperalgesia, although evoked within a matter of minutes, can outlast the precipitating tissue damage for several hours or days. Spinal cord nociceptive neurons may become sensitized by repeated brief stimulation, which leads to prolonged

spontaneous discharge. This mechanism may hypothetically increase the level and duration of pain. This means pain can arise spontaneously in the absence of any stimulus. In inflammatory pain this hypersensitivity is however still a reaction to a defined peripheral pathology such as injury. Importantly is that in a healthy state the pain is reversible, so that pain is temporary and subsides after recovery of the tissue damage.

Chronic pain

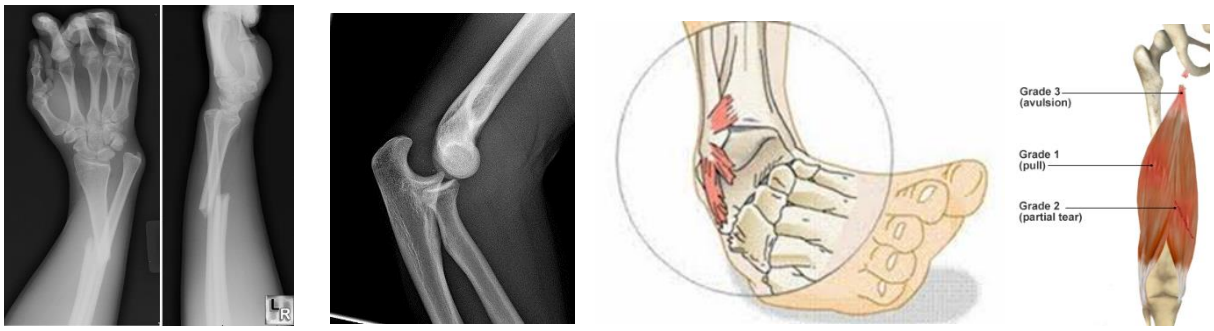
Chronic pain is defined as "pain that persists beyond normally expected healing" (5). Traditionally, the distinction between acute and chronic pain relies upon an arbitrary interval of time from onset; the two most commonly used are three months and six months since the onset of pain (6). Acute and chronic pain are also different clinical entities. Chronic pain that is not protective, but maladaptive, results from abnormal functioning of the nervous system. Complex changes occur in primary sensory neurons in response to the exposure to inflammatory mediators or as a result of peripheral injury (7). Imaging studies have shown that chronic pain patients have altered activation in higher centers of the brain such as somatosensory cortices, cingulate cortex and insula and prefrontal cortex (8).

Chemical and physiological processes in the dorsal horn may be altered by ongoing noxious stimulation from peripheral input leading to increased excitability and synaptic efficacy of neurons in central nociceptive pathways. This process of central sensitization may cause pain and chronification of pain even in the absence of noxious stimuli, inflammation or tissue damage (7). Pain in these situations arises spontaneously, can be elicited by normally innocuous stimuli, is exaggerated and prolonged in response to noxious stimuli, and spreads beyond the site of injury. In chronic pain, this hypersensitivity is not related to any peripheral pathology like in inflammatory pain, but a result of altered neural processing. The pain is no longer coupled, as in acute pain, to the presence, intensity, or duration of particular peripheral stimuli.

Musculoskeletal injury and acute pain

Musculoskeletal injury refers to damage of muscular and skeletal systems of the body. In this thesis the focus will be on musculoskeletal extremity injury due to blunt trauma. Injuries caused by penetrating trauma, such as sharp wounds, will not be discussed.

Injuries to the musculoskeletal system can be classified according to body structures that are damaged. Some injuries may involve more than one structure. Four types of musculoskeletal injuries are (i) fracture – a break of disruption in bone tissue; (ii) dislocation or also called luxation- a displacement or separation of a bone from its normal position at a joint; (iii) sprain – a partial or complete tearing or stretching of ligaments and other tissue at a joint and (iv) strain – a stretching and tearing of muscle or tendon fibers (figure 1).



Fracture Dislocation Sprain Strain

Figure 1: types of musculoskeletal injury

The annual injury rate of musculoskeletal complaints lies between 20 to 25% (9, 10). In the Netherlands, more than one-quarter of the patients with musculoskeletal injuries visits the Emergency Department (ED) (10). The most common musculoskeletal injuries are those involving the back or spine, followed by sprains, dislocations, and fractures of the extremities—the sum of which account for almost one-half of all musculoskeletal injuries.

Acute pain and musculoskeletal extremity injury are inevitably interrelated to each other since musculoskeletal injury causes nociceptive pain by activation of nociceptors by intense noxious stimuli. This pain has a useful function, defending the patient against harmful external stimuli, which may induce tissue injury and become life threatening. Also inflammatory pain occurs in response to tissue injury and inflammation and is to prevent for further damage and to achieve an undisturbed healing and repair. It hypersensitizes surrounding tissue, increasing sensitivity and encouraging the patient to leave the tissue alone and allow it to heal. Musculoskeletal injuries are usually painful (11, 12), especially bone injuries are painful because the periosteum has the lowest pain threshold of the deep somatic structures (13).

Multifactorial experience of pain

The IASP's definition of pain emphasizes that pain is not a directly observable or measurable phenomenon, but rather a subjective experience that bears a variable relationship with tissue damage (14). Pain is not only nociception which involves the stimulation of nerves that convey information about potential tissue damage to the brain. Pain is the subjective perception that results from the transduction, transmission, and modulation of sensory information. In the experience of pain include besides nociception and pain two additional dimensions in which cognitions and emotions play an important role; suffering and pain behaviour (15). So the nociceptive input may be filtered through an individual's genetic composition, prior learning history, current psychological status, and sociocultural influences.

During the past decades, there has been an explosion of research on both acute and chronic pain, with significant advances in understanding its etiology, assessment, and treatment. Various models of how pain functions have evolved: from the gate control theory of pain

(16), the conceptual model of sensory-discriminative, the cognitive-evaluative, and motivational pain experience model (17), to the body-self neuromatrix model of pain (18) and the biopsychosocial model of pain (19).

Over the years it has become clear that pain experience is determined by a multitude of factors. Although the focus has historically been directed towards sensory mechanisms, more attention is being placed to factors related to cognitive, affective, behavioral, and homeostatic factors, and even genetics. Pain is ultimately a subjective, private experience, but it is invariably described in terms of sensory and affective properties. Each individual experiences pain uniquely, and a range of psychological, contextual, cultural and socioeconomic factors can interact with physical pathology to modulate a patient's report of symptoms and subsequent disability.

Prognostic factors for the transition from acute to chronic pain

It is increasingly recognized that acute and chronic pain may represent a continuum rather than distinct entities. Chronic pain patients often relate their pain onset to acute injury such as surgery or trauma (20-24), drawing attention to the need to prevent the progression from acute to chronic pain. The importance of addressing the link between acute and chronic pain has been emphasised by many studies in the last decades (25-30).

The transition of acute to chronic pain is however still a complex and poorly understood developmental process. A range of injury-, psychosocial-, socio-environmental and patient-related factors has been associated with the persistence and chronification of pain (25, 26, 29, 30). Factors known for its prognostic validity are listed in table 1.

Table 1: Prognostic factors for developing chronic pain

	Injury	Whiplash	Surgery	Acute back/neck pain
Pre-incident				
Demographic	Younger age (27) Female (27)	Increased age (31) Female (32)	Younger age (33-35) Female (36)	Increased age (37)
Physical	Poor health (27) Lower function (25, 27) Past persistent pain (26)	Neck pain (31, 32, 38) Lower function (32) Poor health (32)	Pain(33, 34); Poor health (29); Genetic predisposition (35)	Previous episodes of pain (39)
Psychological	Past depressive feelings (26); Past anxious feelings (26); Past alcohol dependence (26)		High anxiety (33-35) Depression(35) Fear of surgery (40)	Poor psychosocial status (39)
Social	Low income (27) Low education (25, 27, 41); Work status (not working) (42)	Lower education (38)		Lower education (43) Work status (43) Lower job satisfaction (43)

Table 1: Continued				
Peri-incident				
	Injury site/body region (26); High injury severity (26, 42)	High injury severity (32);Vehicle type (32)	Surgery type (33, 34) Long duration of surgery (29); Anaesthetic techniques(35)	
Post -incident				
Physical	High pain severity (25, 42); Pain intensity (current and 24-hour) (26); Pain management, opioid on day assessment (26)	High pain severity (32);Whiplash-associated disorder grade (38) Number of initial physical symptoms (31, 32, 44)	High pain severity (29, 45)	High pain severity (43); Neurological symptoms/signs(39)
Psychological	Lower self-efficacy (41); High anxiety (26) Anger (26); Low pain control (26, 42); Pain emotions; catastrophizing (26)	General distress (32) Fear avoidance (44) Lower self-efficacy (46); Helplessness(47) Somatization (48)	Lower social support (49); Low optimism (29)	Fear avoidance (39) Emotional distress (37, 43); Pain catastrophizing(50)
Care context	No fault, compensation system (25)			

Most studies were involved in identifying prognostic factors for post-surgical chronic pain or chronic whiplash-associated disorder. Studies that determine prognostic factors for chronic pain after injury are limited even though injury is a common cause of chronic pain. Moreover, the focus of most research on prognostic factors for pain and disability following acute injury has been on outcomes following major trauma, severe life threatening injuries or specific injuries (25-27, 41). There has been a relative lack of research addressing minor or moderate injuries despite the knowledge that these injuries are common and contribute significantly to the burden of injury both with respect to short term as well as lifetime morbidity. Furthermore, many studies in which prognostic factors after injury were investigated had a retrospective design, or only one follow-up assessment thereby making it difficult to determine the causality between prognostic factor and the process of chronification.

Impact of pain following injury

The health problem of musculoskeletal injury can induce severe acute pain considering associated osseous and soft-tissue involvement. Adequate pain management leads to earlier mobilization and faster rehabilitation (51).

In this regard, more than half of the injured patients reported still moderate to severe pain at hospital discharge (11, 52, 53), which becomes chronic in up to 56% of cases (25, 28, 54, 55).

Being in pain is quite uncomfortable for most people. Chronic pain can become more complex over time with further development of underlying pathologies and associated sequelae (56). Patients with chronic pain are at increased risk for emotional disorders such as anxiety, depression, and anger, maladaptive cognitions such as catastrophizing and poor coping skills, functional deficits and physical deconditioning due to decreased physical activity and fear of re-injury, as well as basic nociceptive dysregulation (57). Because of this, chronic pain often leads to complex social and psychological maladaptations affecting patients' quality of life, leads to health care overutilization, as well as many other substantial costs for example due to productivity loss (58). After acute orthopaedic injury, only 68% of the patient were able to return to work within 6 months; and of those, 56% returned to modified work as a result of ongoing injury related limitations (59).

The significant social and financial costs to the injured patient and their family as well as the costs to the employer of replacing a worker off work underscore the public health impact of these injuries in terms of lost work days as well as the costs associated with ongoing rehabilitation. Chronic pain and related disability is a substantial economic problem and remains one of the most costly conditions in modern western society (60, 61). Preventive strategies are necessary to avoid the consequences of chronic pain.

Improving pain management in emergency medicine

Even though acute pain following musculoskeletal injury serves an initial purpose, acute pain should be managed properly because it can result in various physiological changes that have important effects on the patient's clinical course.

Advances in knowledge of pain do not necessarily lead to the same degree of progress in patient care. Previous studies have shown that 78% to 91% of patients visiting the ED have a chief complaint related to pain (11, 52, 62, 63). While acute musculoskeletal pain is a frequent complaint among patients in the ED, its management is often neglected, placing patients at risk of oligoanalgesia. This term "oligoanalgesia in the ED" was already in 1989 coined by Wilson and Pendleton to describe the poor pain treatment of ED patients (64). Although the prevalence of pain is high, adequate pain treatment is still a problem. An insufficient proportion of patients receives analgesics and pain relief remains unsatisfactory. Acute pain in ED patients appears undertreated worldwide which is reflected by the high prevalence of severe pain at discharge and the low percentage of patients receiving analgesics while in pain (11, 52, 53, 65-67).

Studies revealed that acute pain management is still less than optimal and there is significant room for improvement. The disappointing results of acute pain management are not only important in terms of patient suffering. It has been suggested that unrelieved pain may also lead to adverse physiological effects such as cardiovascular side-effects and negative effects on respiratory function, coagulation and immune function (68, 69). Moreover, failure to

relieve acute pain may result in increased anxiety, inability to sleep, demoralization, a feeling of helplessness, loss of control, inability to think and interact with others (70).
In addition to the short-term effect of inadequate pain management, it is suggested it can also lead to chronic pain. Advances in the elucidation of the biologic mechanisms underlying the development of both acute and chronic pain suggest that inadequately treated acute pain can result in the sensitization of the peripheral and central nervous system, which may ultimately lead to the development of chronic pain (71, 72).
As written previously pain is complex. Various possibilities exist to diminish acute musculoskeletal pain. Opportunities to relieve pain are nearly infinite within the practice of emergency medicine; from pharmacological and injury treatment to cognitive-behavioral interventions and homeopathy.
Different strategies to enhance pain management have been developed in response to inadequate pain relief such as pain management protocols or clinical guidelines and staff educational interventions and have shown to be useful (73-79). Furthermore, it is recognized pain assessment is critical to optimal pain management. Reliable and accurate assessment of acute pain is necessary to ensure patients experience safe, effective and individualized pain management. Yet, inaccurate pain assessment is a consistent finding worldwide in various clinical settings including the ED and was identified as the most powerful predictor of poor pain management (80, 81).

THE PROTACT STUDY AND THIS THESIS

Against this background, the PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients (PROTACT)-study was designed. The PROTACT-study was initiated as a one year prospective follow-up study (figure 2) with the primary aim to determine prognostic factors involved in the transition from acute to chronic pain after extremity injury. This will give the ability to target high-risk patients in the emergency setting and to intervene on one or more of this factors thereby preventing the development of chronic pain. Secondary objectives were to describe current prevalence and pain management of acute pain in the ED and to determine the consequences of extremity injury and developing chronic pain post-injury in terms of quality of life.
During a 22 months inclusion period of the PROTACT-study, adult patients with isolated musculoskeletal extremity injury attending the ED of the level one trauma centre Medisch Spectrum Twente in Enschede, The Netherlands, were invited to participate. Participants were asked during the follow-up period to complete 4 or 5 questionnaires depending on patient's pain outcome at six months follow-up. Additionally, data from the emergency medical services (EMS), ED and hospital electronic patient registry were collected. Collected data includes potential prognostic factors, injury-related characteristics, pain, pain management and quality of life outcomes. Ethical approval for the study was obtained from

the Medical Research Ethics Committee TWENTE on Research Involving Human Subjects (CCMO no. NL368.38044.11) on august 25, 2011.

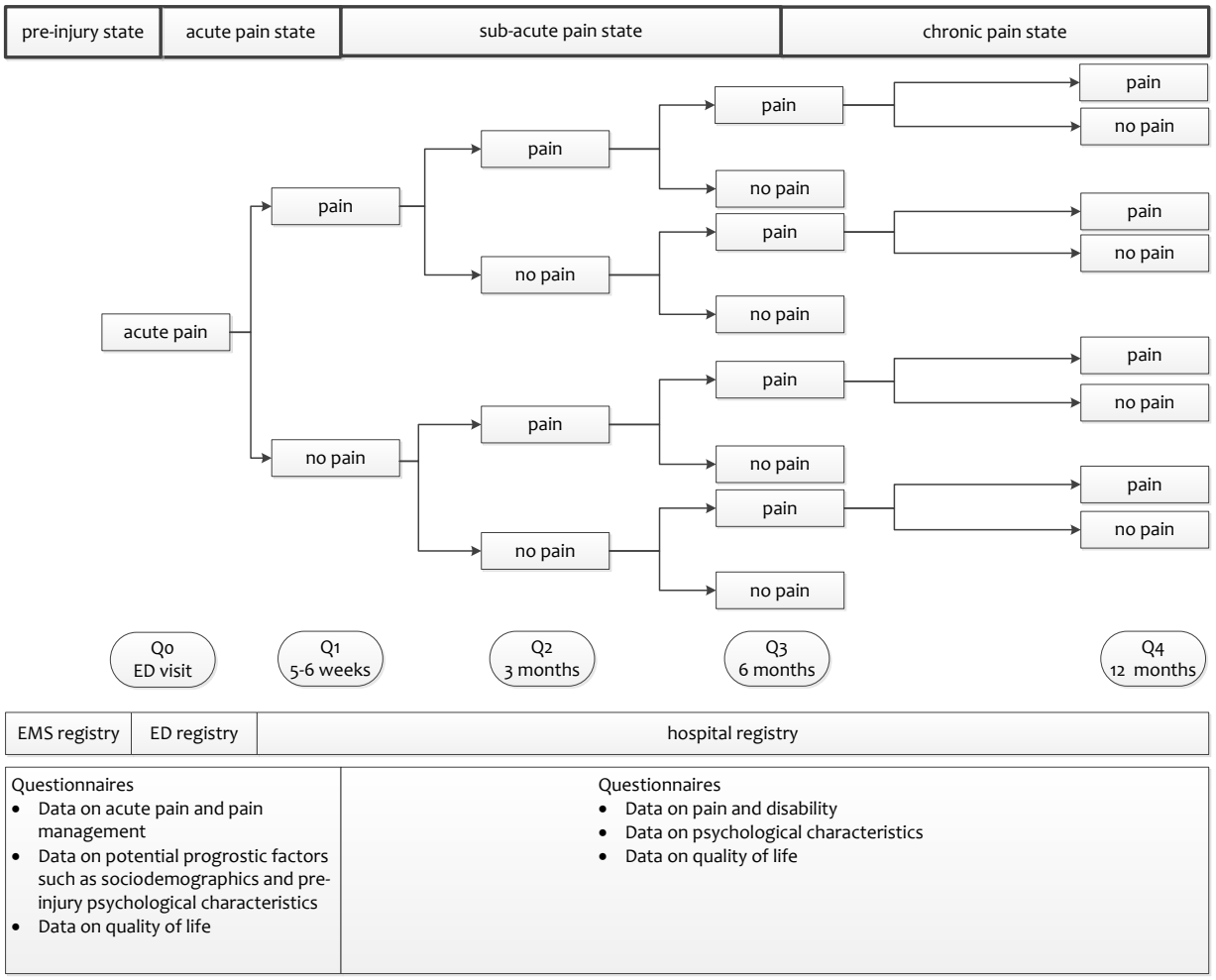


Figure 2: Study design of the PROTACT-study. A prospective study for at least 6 months follow-up. If participants experience pain in injured body part at 6 months follow-up, data was also collected at one-year follow-up.

This dissertation is divided into seven chapters and is structured as follows. Chapter 2 describes the results of a study on the current state of pain management following extremity injury. The study aims to investigate how often pain management is provided in the prehospital phase and ED, how this effects pain relief and to identify prognostic factors for clinically relevant pain relief in the ED.

Chapter 3 represents the outcome of the primary aim of the PROTACT-study. In this chapter the incidence and prognostic factors for the development of chronic pain are described.

The purpose of the study in chapter 4 is to detect changes in patient's health-related quality of life (HRQoL) over time- from pre-injury state to full recovery or to chronic pain and related disabilities to determine the impact of extremity injury and chronic pain on health.

The pre-post intervention study in chapter 5 aims to evaluate the effect of an intervention focusing on one of the prognostic factors of chronic pain. To intervene the transition from

acute to chronic pain, a nurse-initiated acute pain management protocol based on a Dutch evidence-based guideline was implemented to further optimize pain management and reduce the severity of pain immediately after injury.

In chapter 6 the discrepancies in pain assessment between patients and nurses are analysed. Furthermore, risk factors for underassessment of patients' pain by nurses are identified that might reduce pain rating discrepancies and optimize pain management. Finally, in chapter 7 the findings of the PROTACT- study are put in the perspective of current knowledge, and further elaborate on conceptual and methodological issues concerning pain management in emergency care and predictions and patient outcomes in terms of persistence of pain and quality of life. Finally, recommendations for further research are formulated, the implications for clinical practice and education are described and main conclusions are drawn.

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Chapter 2

Pain management in the emergency chain: The use and effectiveness of pain management in patients with acute musculoskeletal pain

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ABSTRACT

OBJECTIVE: While acute musculoskeletal pain is a frequent complaint in emergency care, its management is often neglected, placing patients at risk for insufficient pain relief. Our aim is to investigate how often pain management is provided in the prehospital phase and emergency department (ED) and how this affects pain relief. A secondary goal is to identify prognostic factors for clinically relevant pain relief.

DESIGN: This prospective study (PROTACT) includes 697 patients admitted to the ED with musculoskeletal extremity injury. Data regarding pain, injury and pain management were collected using questionnaires and registries.

RESULTS: Although 39.9% of the patients used analgesics in the prehospital phase, most patients arrived at the ED with severe pain. Despite the high pain prevalence in the ED, only 35.7% of the patients received analgesics and 12.5% received adequate analgesic pain management. More than two-third of the patients still had moderate to severe pain at discharge. Clinically relevant pain relief was achieved in only 19.7% of the patients. Pain relief in the ED was higher in patients who received analgesics compared to those who did not. Besides analgesics, the type of injury and pain intensity on admission were associated with pain relief.

CONCLUSIONS: There is still room for improvement of musculoskeletal pain management in the chain of emergency care. A high percentage of patients was discharged with unacceptable pain levels. The use of multimodal pain management or the implementation of a pain management protocol might be useful methods to optimize pain relief. Additional research in these areas is needed.

BACKGROUND

Acute pain is a frequent complaint of patients requiring emergency medical care. In many patients, pain is the primary motive for visiting the Emergency Department (ED). Previous studies have shown that 61% to 91% of patients visiting the ED have a chief complaint related to pain (1-6).

Although pain is acknowledged as a major public health issue, the gap between the increasing knowledge of pain, treatment and the effective application of it is large (7). The term "oligoanalgesia", introduced in 1989, has been used to describe the phenomenon of poor pain management in the ED through the underuse of analgesics (8). Acute pain in EDs appears undertreated worldwide which is reflected by the high prevalence of severe pain at discharge and the low percentage of patients receiving analgesics while in pain (1-3, 5, 6, 8-15). Previous studies have found that the proportion of adults receiving analgesics for painful conditions, such as musculoskeletal injury ranged between 11% and 64% (1, 8-11, 13, 14). Moreover, the percentage of patients discharged with severe pain ranged from 11% to 29% (1, 5, 6). Despite substantial advances in pain research over the last decades acute pain management is still often neglected, placing patients at risk for oligoanalgesia (1, 13, 15).

In the Netherlands, musculoskeletal injury has a high incidence of approximately 20% each year, and more than one-quarter of these patients visits the ED (16). Patients presenting with acute musculoskeletal pain to the ED are usually triaged to a low triage category which typically results in an extended waiting time for pain relief or oligoanalgesia (17). A review shows that patient's pain experience is often underestimated (18); for examplenurses underestimate the pain intensity of musculoskeletal pain in 95% of the patients (19). As a result insufficient pain relief occurs frequently (1, 8), especially in patients with fractures (1, 9, 10, 20).

Early and effective pain treatment is important to reduce both short-term and long-term consequences of acute pain. Patients become increasingly more sensitive to painful stimuli if the pain is uncontrolled for a longer period of time (21). Therefore, treatment of moderate to severe pain should be a priority when a patient came to the ED. Moreover, adequate pain management leads to earlier mobilization, faster rehabilitation and possibly earlier discharge from the hospital (22). Inadequate pain management is likely to result in decreased productivity and diminished patients' quality of life (22). In addition, oligoanalgesia is a risk factor for the development of chronic pain (23, 24).

Although the importance of timely pain management is acknowledged, it is also recognized that there are barriers to effective pain relief in emergency patients (25). The right type of analgesic at an adequate dose at the right moment is necessary to successfully reduce pain. In addition, it is relevant to know if any and which type of pain management was provided in the prehospital phase in order to provide sufficient pain management in the ED and to optimize pain management in the chain of emergency care.

The aims of this study are to investigate how often and which type of pain management is used in patients with musculoskeletal extremity injury presented in emergency care including the prehospital phase and ED. The second objective is to explore the effectiveness and adequacy of pain management in the ED with an emphasis on a clinically relevant reduction in pain. Finally, prognostic factors for clinically relevant pain relief will be identified. Knowledge of these prognostic factors may help physicians explore ways to overcome barriers to properly provide analgesia in patients with musculoskeletal extremity injury.

PATIENTS AND METHODS

Study design and setting

This study is part of a one-year prospective follow-up study; the "PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients" (PROTACT). Adult patients with musculoskeletal extremity injury attending the ED of the level one trauma centre Medisch Spectrum Twente in Enschede, The Netherlands, were invited to participate. The ED of Medisch Spectrum Twente is a 24 hours a day, 7 days a week ED (24/7 ED). The catchment area for ED is about 264,000 individuals and the ED service treats approximately 27,000 patients annually. Ethical approval for this study was obtained from the regional Medical Research Ethics Committee on Research Involving Human Subjects (CCMO no. NL368.38044.11). All participants provided written informed consent.

Study population

Eligible patients were consecutively recruited for the study when admitted to the ED during a 22 month period from September 2011 until July 2013. Inclusion criteria for participation were: (i) patients who had musculoskeletal extremity injury caused by blunt trauma; (ii) patients who had sufficient communication skills and a basic knowledge of the Dutch language; and (iii) patients aged between 18 and 70 years. Exclusion criteria were: (i) patients with life or limb threatening conditions; (ii) patients with multiple trauma; (iii) patients with documented cognitive disability; (iv) patients suffering from hallucinations, delusions or suicidal ideation; (v) patients with alcohol or drugs intoxication and (vi) patients who were living outside the 'catchment area' served by the hospital. For the purpose of this study, we excluded patients who did not provide pain scores both on admission and at discharge.

Procedures and data sources

Patients admitted to the ED who met the study criteria were informed by a (triage) nurse about the purpose of the study. Those who agreed to participate were asked to provide informed consent and to complete a questionnaire. The questionnaire and informed consent sheet were returned to either a mailbox in the waiting room or sent by ordinary mail. Eligible

patients who were not invited by the nurse to participate received an invitation and questionnaire by mail within one week of the ED visit.

The questionnaire included a validated tool to measure pain intensity and questions about sociodemographic data, pain management, and time between injury and ED admission. In addition to the data obtained from the questionnaire, data from the ED electronic patient registration system were used. The registry is a fully electronic emergency medical record registry where each entry, order, or activity is automatically time-stamped for pre–specified ED events. The registry includes patient demographics (date of birth, sex), referrer, triage urgency level, triage pain score, type of analgesics, medical diagnoses (e.g. injury type and location), type of non-pharmacological pain management, time of providing pain management and refusal to use analgesics.

If patients arrived by ambulance, additional data regarding the use and type of analgesics in the ambulance were retrieved from the registry of the regional Emergency Medical Services (EMS).

Measures and definitions

Pain intensity

Pain intensity was measured in the questionnaire using the Numerical Rating Scale (NRS). The NRS of acute pain was validated for use in the ED (26-29) and retrospective one-week recall of pain intensity was reliable and valid (30, 31). Patients were asked to fill in a number from 0 to 10 to represent their pain severity, where 0 is "no pain" and 10 "the worst pain imaginable" in response to the questions: "How severe was your pain on ED admission?" and "How severe was your pain at ED discharge?". NRS scores were converted to the categorical groups of (i) no pain (NRS 0); (ii) minimal pain (NRS 1-2); (iii) mild pain (NRS 3-4); (iv) moderate pain (NRS 5-6); (v) severe pain (NRS 7-8); and (vi) very severe pain (NRS 9-10).

Analgesics administered or self-initiated intake in prehospital phase

Data regarding the use and type of analgesics in prehospital phase were collected by questionnaires and retrieved from the registry of the regional EMS. In the questionnaire the patient could indicate if any type of analgesics was taken on his or her own initiative or was given by a health professional such as a General Practitioner (GP), before attending the ED.

Analgesics administered in the ED

The type of analgesic administered in the ED was obtained directly from the ED patient registry. Analgesics administered (if any) were categorized as follows: (i) no analgesics; (ii) nonopioids such as paracetamol (acetaminophen) or non-steriodal anti-inflammatory drug (NSAID); (iii) mild opioids such as codeine and tramadol; and (iv) major opioids such as morphine and fentanyl.

Adequate analgesic pain management in ED

The Pain Management Index (PMI) combines an analgesics score and a pain intensity score to determine adequacy of pain management. The PMI is based on the WHO guidelines and orginally designed for cancer pain management and has since been used in other pain studies, including acute pain in patients visiting the ED (15, 32-34). The PMI is considered a valid and reliable measure for pain management (35). The analgesics score was calculated based on the analgesics provided in the ED. No pain medication was scored as '0', nonopioids as '1', mild opioids as '2', and major opioids as '3'. For patients who received more than one type of analgesic, the most potent analgesic as per PMI definition was used. The pain intensity score for PMI was calculated using NRS on ED admission as reported by the patient. A pain intensity score of '0' was defined as no pain (NRS 0), '1' minimal and mild pain (NRS 1-4), '2' moderate pain (NRS 5 -6) and '3' severe and very severe pain (NRS 7-10). The PMI was calculated by substracting the pain intensity score from the analgesic score. Possible scores ranged from -3 to +3. Patients with negative PMI scores were classified as receiving inadequate analgesics management.

Duration of ED stay

The duration patients were in the ED was obtained from the ED patient registry. Time in the ED represents the time recorded from ED admission to ED discharge and was reported in minutes.

Non-pharmacological treatment in ED

Data regarding type of non-pharmacological treatment were obtained from the ED patient registry and were categorized as follows: (i) no pain treatment; (ii) immobilization; (iii) reposition; (iv) compression; (v) coldpack; and (vi) others.

Clinically relevant pain relief

Clinically relevant pain relief for acute pain was defined as 33% or more decrease in pain intensity (36). The relation between demographic factors (sex and age), pain characteristics (pain intensity on admission), pain management characteristics (analgesics or non-pharmacological pain management in the ED, analgesic use in prehospital phase and the duration of ED stay) and injury related characteristics (type of injury, urgency level), were investigated to identify their association with clinically relevant pain relief.

Data analysis

Descriptive data are presented as means with standard deviations (SD) or 95% confidence intervals (CIs) for differences in continuous variables as medians with interquartile ranges (IQR, 25^{th} -75^{th} percentile) for time variables and as frequencies for categorical variables. Pain

intensity differences were calculated by subtracting the pain score at discharge from the pain score on admission. In addition, to determine the percentage of reduction this pain intensity difference was divided by the pain score on admission. Pain intensity differences between the different approaches to pain management were analysed using two-tailed Student's *t* test and mean differences with corresponding 95% CIs were calculated. A p-value <0.05 is considered statistically significant. Boxplots were used to give a graphical representation of the association between the type of pain management and the type of analgesics, and the pain intensity difference between admission and discharge.

Univariate and multivariate analyses were performed to identify prognostic factors for the dichotomous outcome variable clinically relevant pain relief. Associations between categorical variables and the outcome variable were investigated using chi-squared tests. Odds ratios (ORs) and corresponding 95% CIs were calculated and interpreted as the relative risk of the presence of a potential risk factor for clinical relevant pain relief compared to the absence of risk factor (reference group). Because pre-selection of prognostic factors based on p-values estimated from univariate analyses may result in unstable prediction models (37), all candidate prognostic factorswere considered in the multivariate analysis. Backward stepwise selection of all candidate variables was applied using the likelihood ratio test with a p-value of 0.157 according to Akaike's Information Criterion. Adjusted Odds Ratios (ORadj) and corresponding 95% CIs were calculated. All data were analysed using SPSS version 21.0 (IBM Corporation, Armonk, NY).

RESULTS

Patient characteristics and pain intensity

Overall, 1994 adult patients with musculoskeletal extremity injury caused by blunt trauma met the inclusion criteria. Written informed consent and questionnaires were obtained from 803 patients of whom 697 patients filled in both pain scores on admission and at discharge. Distribution of age and sex among the nonresponders was not significantly different from the participating patients.

Median age of the 697 patients was 47.2 years (IQR 30.7-58.1) and 56.1% were women (table 1). A fracture was the most common reason for admission (70.2%). Patients reported a high frequency of pain, both on admission (98.9%) and at discharge (97.7%). Overall, the mean self-reported pain intensity score changed from 6.50 on admission to 5.64 at discharge (difference 0.86; 95% CI 0.71-0.99). Figure 1 shows the percentage of patients with pain levels at discharge within pain intensity categories on admission. Overall, 560 out of 697 (80.3%) patients had moderate to severe pain on admission and, more than two-third of the patients (67.6%) had moderate to severe pain at discharge.

Table 1: Characteristics of 697 patients with acute musculoskeletal trauma	
Age, median (IQR)	47.2 (30.7-58.1)
Gender, women, N (%)	391 (56.1%)
Time in ED, median (IQR)	100 min (72-143)
Pain on admission, N (%)	689 (98.9%)
Pain intensity score on admission, mean (SD)	6.5 (2.4)
Pain at discharge, N (%)	682 (97.7%)
Pain intensity score at discharge, mean (SD)	5.6 (2.5)
Documented pain intensity score at triage, mean (SD)	4.0 (1.4)*
Injury type, N (%)	
Fracture	489 (70.2%)
Dislocation	33 (4.7%)
Sprains & strains	89 (12.8%)
Contusion	69 (9.9%)
Muscle rupture	17 (2.4%)

*= 9 missings

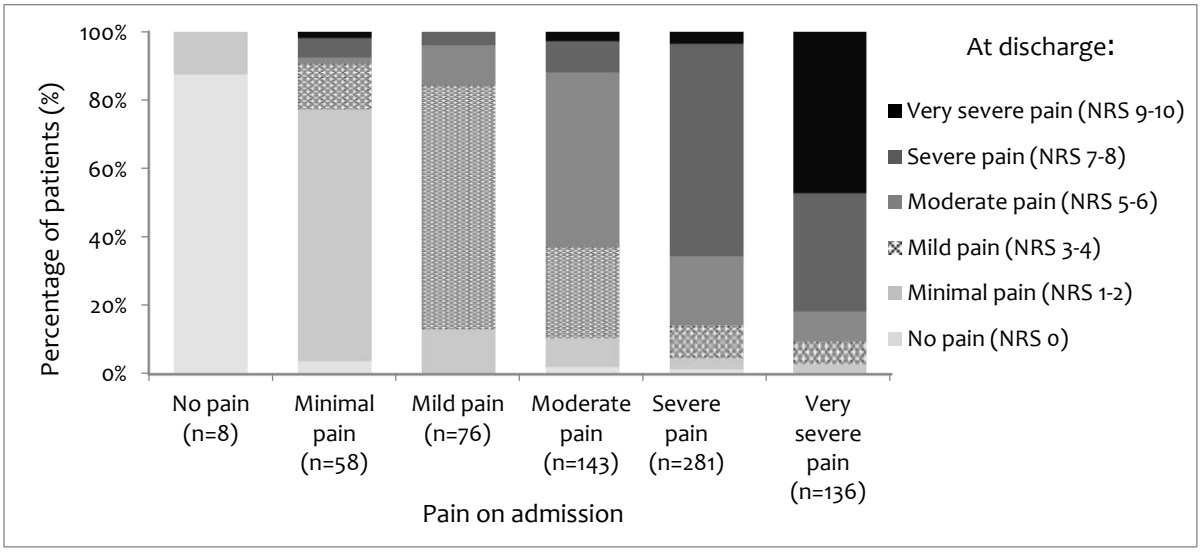

Figure 1: The percentages of patients with reported pain levels at discharge by pain intensity on admission

Type of pain management in ED

Overall, 609 out of the 697 patients (87.4%) received pain management in ED. Most patients (n=360) received non-pharmacological treatment only, 59 patients received analgesics only, and 190 patients a combination of both non-pharmacological treatment and analgesics. Figure 2 shows the percentage and type of pain management that was provided to patients in the ED according to their pain intensity on admission. The percentage of patients who received analgesics, with or without non-pharmacological treatment, increased when pain was more severe from 0% (no pain) to 72% (very severe pain).

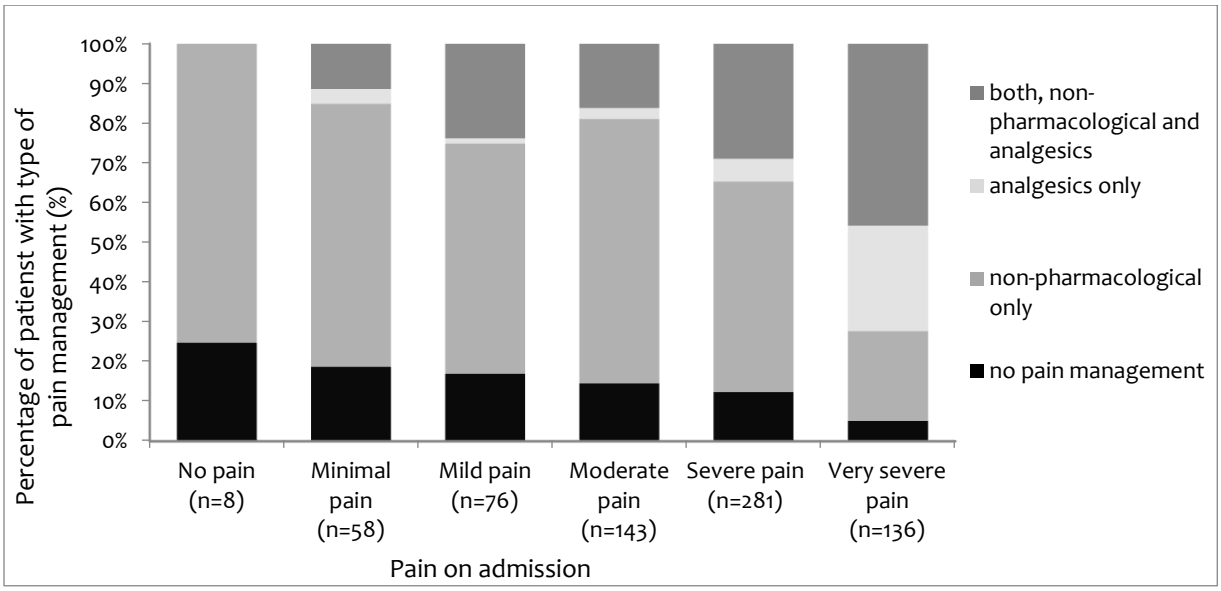

Figure 2: Percentage of patients with type of pain management provided in the ED by pain intensity on admission

Analgesics use in the chain of emergency care

Figure 3 gives an overview of the analgesic use in the chain of emergency care. Patients came to the ED by four different routes. Overall, 278 out of the 697 patients (39.9%) used one or more analgesics in the prehospital phase. A high percentage of patients (41.6%) was self-referred and 20.7% of these self-referrals did use analgesics before attending the ED. This percentage is somewhat lower than the overall of 25.1% of patients who self-initiated the intake of analgesics, mostly the nonopioid paracetamol. Of the 337 patients who visited a GP or other health professional before attending the ED, 58 patients (17.2%) received analgesics, mostly the nonopioid paracetamol. Out of the 279 patients who did not receive analgesics, 102 patients (32.6%) had already taken analgesics themselves. For 50 out of the 337 patients (14.8%) the GP was the first link in the chain where they received analgesics. In the ambulance, 48 out of the 77 patients (62.3%) received analgesics, mostly the short-acting major opioid Fentanyl. For 45 out of the 77 patients (58.4%) the ambulance was the first link in the chain where they received analgesics. Yet, the patients who used analgesics in prehospital phase (n=278) had a higher mean pain score of 7.00 on admission compared to 6.17 for those patients not taking analgesics (difference of 0.82; 95%CI 0.47-1.18).

In the ED, 249 out of the 697 (35.7%) patients received analgesics. Most common analgesics provided in the ED were the nonopioid paracetamol and major opioid morphine. Of all the patients, 100 patients (14.3%) were offered analgesics but refused to use any. Of those who refused, 21 patients already received analgesics before hospital admission. Yet, half of the patients in pain (n=348) did not get analgesics offered.

In total, 420 out of the 697 patients (60.3%) used analgesics somewhere in the chain of emergency care. The ED was for 147 out of the 420 patients who used analgesics (35.0%) the first link in the chain where they received these analgesics. Most patients (65.4%) who

received analgesics at more than one link in the chain received different types of analgesics. For example, most patients with mild or major opioid also received paracetamol or NSAID somewhere in the chain of emergency care (Appendix A). A specific overview of generic names of provided analgesics is given in Appendix B.

	Self-initiated (n=697)	GP or other health professional (n=337)	Ambulance (n=77)	ED (n=697)
No analgesics	522 (74.9%)	279 (82.8%)	29 (37.7%)	448 (64.3%)
Analgesics	175 (25.1%)	58 (17.2%)	48 (62.3%)	249 (35.7%)
Nonopioid paracetamol	124 (70.9%)	38 (65.5%)	4 (8.3%)	149 (59.8%)
Nonopioid NSAID	37 (21.1%)	14 (24.1%)	-	17 (6.8%)
Nonopioids paracetamol + NSAID	12 (6.9%)	4 (6.9%)	-	23 (9.2%)
Mild opioid	-	-	-	-
Major opioid	1 (0.6%)	1 (1.7%)	22 (45.8%)	41 (16.5%)
Paracetamol + mild opioid	1 (0.6%)	-	-	4 (1.6%)
Paracetamol + major opioid	-	-	3 (6.3%)	11 (4.4%)
Paracetamol + NSAID + mild opioid	-	-	-	1 (0.4%)
Paracetamol + NSAID + major opioid	-	-	-	3 (1.2%)
Other (e.g. ketamine)	-	1 (1.7%)	12 (25.0%)	-
Other + major opioid	-	-	7 (14.6%)	-

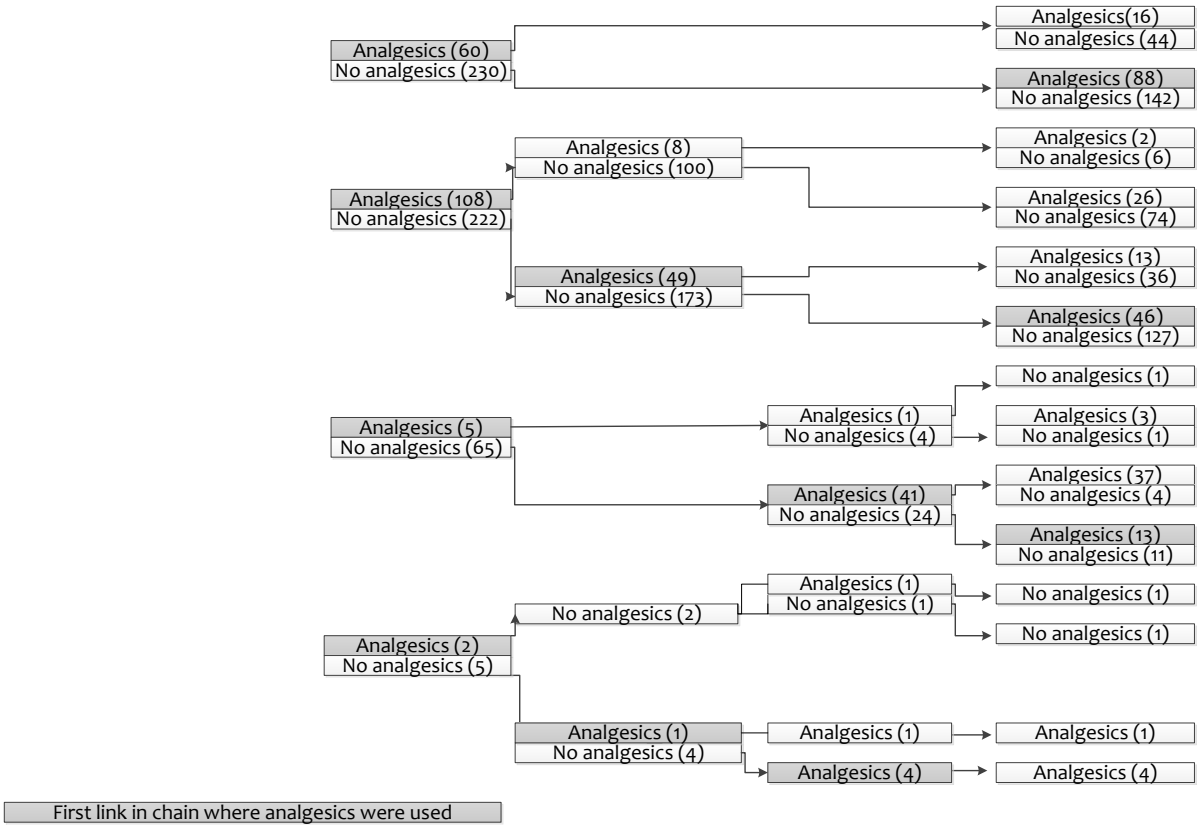

Figure 3: Analgesic use in the chain of emergency care

Adequate analgesic management in ED

The PMI score, which was used to calculate the adequacy of pain management, showed that only 87 (12.5 %) out of 697 patients received adequate pain management (Table 2). Of the remaining 610 patients, 440 (72.1%) received no analgesics and 170 (27.9%) were given inappropriate analgesics according to the PMI. Out of the 560 patients who had moderate to very severe pain on admission, 52 patients (9.3%) received adequate analgesic pain management. While 87.5% of the patients received inadequate pain management, only 35 patients (5.0%) were not satisfied with their treatment at the ED.

Table 2: Pain management Index Score of analgesic use in the ED (n=697)

	Intensity of pain on admission			
Analgesic type	None (0)	Minimal and mild (1)	Moderate (2)	Severe and very severe (3)
No analgesic (0)	0 (n=8)	1 (n=102)	-2 (n=116)	-3 (n=222)
Nonopioid (1)	1 (n=0)	0 (n=23)	-1 (n=24)	-2 (n=142)
Mild opioid (2)	2 (n=0)	1 (n=0)	0 (n=1)	-1 (n=4)
Major opioid (3)	3 (n=0)	2 (n=4)	1 (n=2)	0 (n=49)

*87 out of 697 patients (12.5%) received adequate pain management during ED visit (zero's or positive scores); 440 out of 610 patients (72.1%) who received inadequate treatment (negative scores) received no analgesics; 70 out of 610 patients (27.9%)) who received inadequate treatment were given inappropriate analgesics according to their pain intensity.

Non-pharmacological treatment

In total, 550 out of the 697 patients (78.9%) received non-pharmacological treatment in the ED. Of these, 446 patients (81.1%) underwent immobilization only or in combination with reposition, compression or cold pack (Appendix C). Compression was used in 22.7% of the patients.

The effects of pain treatment in the ED

Clinically relevant pain relief, a pain reduction of 33% or more during ED visit, was achieved in 137 out of the 697 patients (19.7%). The effects of analgesics and non-pharmacological treatment on change in pain intensity during the ED visit are depicted in Figure 4A.

Most patients who did not receive any pain management did not experience pain relief, and 12.5% achieved clinically relevant pain relief. Patients who received only non-pharmacological treatment had a mean pain reduction of 0.68, and 17.5% achieved clinically relevant pain relief. Most patients who received only analgesics had a mean pain reduction of 1.54, and 22.0% achieved clinically relevant pain relief. Patients who received both analgesics and non-pharmacological treatment had a mean pain reduction of 1.34, and 26.3% achieved clinically relevant pain relief. Patients who were administered analgesics had a higher mean pain reduction, 1.39 compared to 0.56 of those who received no analgesic (difference of 0.83; 95%CI 0.53-1.11) and achieved also more clinically relevant pain relief, 25.3% vs. 16.5%

(difference of 8.8%; 95%CI 2.6-14.9). Similar results were found in a subgroup of patients with moderate to severe pain on admission. Patients who were administered analgesics had significantly higher mean pain reduction, 1.53 compared to 0.89 of those who received no analgesic (difference 0.64; 95%CI 0.34-0.95). Also clinical relevant pain relief was higher in patients who received analgesics, 25.7% vs. 18.9% (difference of 6.7; 95%CI -0.2-13.7).

The effects of the type of analgesics administered in the ED on change in pain intensity of patients during the ED visit are graphed in Figure 4B. The 189 patients who received a nonopioid had a mean pain reduction of 1.37, and the 55 patients who received a major opioid had the highest pain reduction: 1.59.

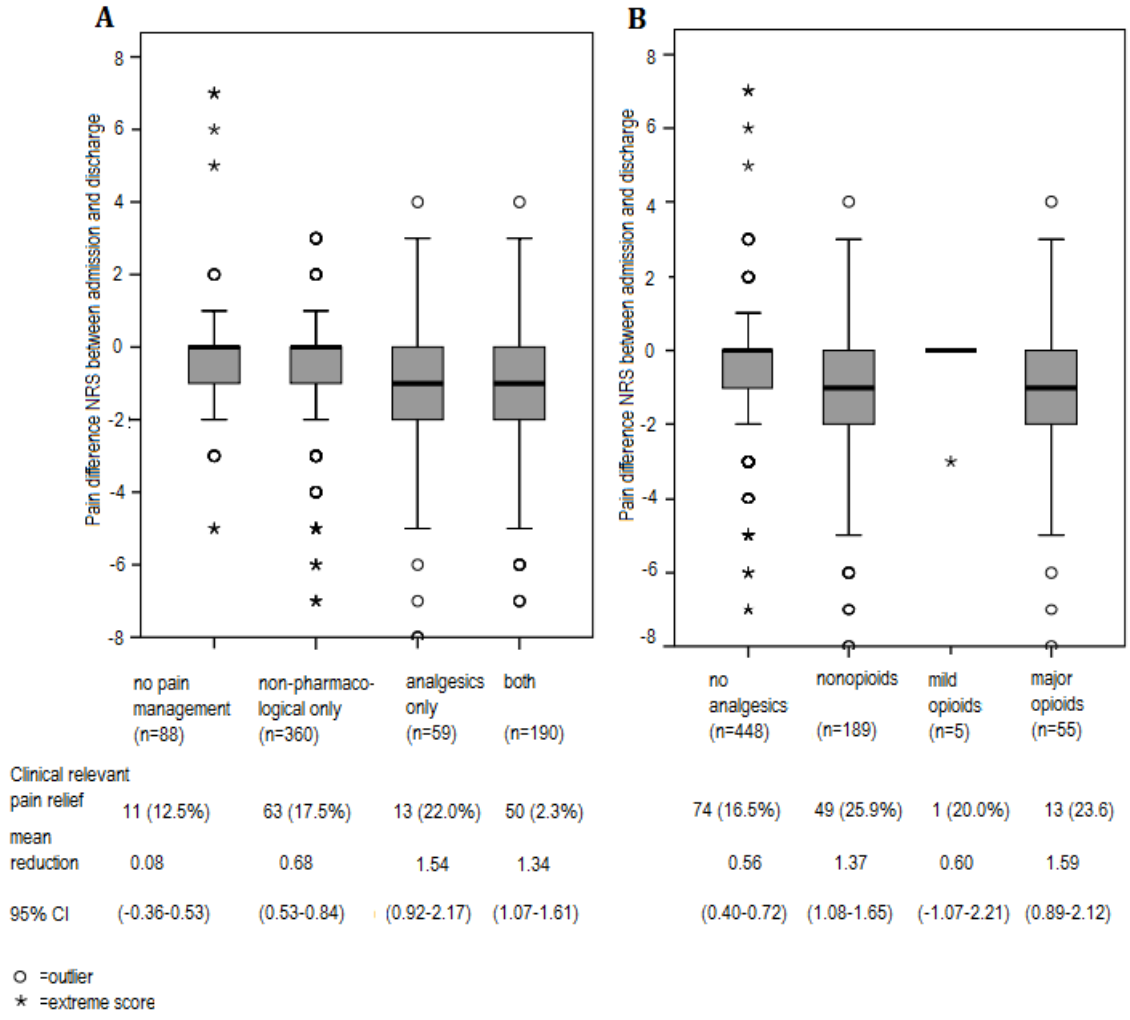

Figure 4 A: A boxplot with the effects of the type of pain management on the pain intensity of patients between admission and discharge. Mean pain reduction is given with corresponding 95% CIs. **B** A boxplot with the effects of (if any) type of analgesics on pain intensity of patients between admission and discharge. Mean pain reduction with corresponding 95% CIs are given

Patients who received *adequate* analgesic pain management according to PMI had a mean pain reduction of 1.03 and patients with *inadequate* treatment a mean pain reduction of 0.83 (difference of 0.20; 95% CI -0.21-0.62). Clinically relevant pain relief was similar in both groups, around 20%. Of the patients who had moderate to very severe pain on admission, mean pain reduction was significantly higher in those who received adequate pain management (1.65)

compared to those who received inadequate treatment (1.09) (difference of 0.56; 95% CI 0.04-1.08). Clinically relevant pain relief was achieved in 23.1% of moderate to severe pain patients who received adequate pain management compared to 21.5% of those who received inadequate treatment (difference of 1.6%; 95% CI -10.2% -13.4%).

Of the patients who were not satisfied with their treatment (n=35), 14.3% achieved clinically relevant pain relief compared to 21.3% who were satisfied with treatment (difference of 7.1%; 95% CI -6.0- 21.9) Patients who were satisfied with their treatment had more pain relief during ED visit (difference of 0.53; 95% CI -0.11-1.17).

Table 3: Association between different factors with clinically relevant pain relief

		Mean pain reduction (SD)	Clinical relevant pain relief No (n)	Yes (n)	OR (95% CI)	ORadj (95% CI)
Sex	Men	0.63 (1.84)	253	53	1.00 (referent)	-
	Women	1.03 (1.87)	307	84	1.31 (0.89-1.91)	
Age	18-29 years	0.69 (1.89)	139	29	1.00 (referent)	-
	30-39 years	0.35 (1.45)	72	10	0.67 (0.31-1.44)	
	40-49 years	0.75 (1.69)	113	25	1.06 (0.59-1.91)	
	50-59 years	0.97 (1.92)	128	32	1.20 (0.68-2.09)	
	60-69 years	1.30 (2.04)	108	41	1.82 (1.06-3.11)	
Injury type	Fracture	0.98 (1.77)	385	104	1.00 (referent)	1.00 (referent)
	Dislocation	1.78 (2.99)	20	13	2.41 (1.16-5.00)	2.67 (1.23-5.76)
	Sprains & strains	0.41 (1.57)	78	11	0.52 (0.27-1.02)	0.56 (0.28-1.11)
	Contusion	1.01 (1.74)	64	5	0.29 (0.11-0.74)	0.30 (0.12-0.78)
	Muscle rupture	0.94 (2.36)	13	4	1.14 (0.36-3.57)	1.31 (0.41-4.23)
Urgency Level	Standard	0.65 (1.74)	408	83	1.00 (referent)	-
	Urgent	1.29 (1.88)	136	46	1.66 (1.10-2.50)	
	Very Urgent	1.75 (3.15)	16	8	2.46 (1.02-5.93)	
Time in ED	<60 min	0.74 (1.73)	94	19	1.00 (referent)	-
	60- <120 min	0.78 (1.79)	269	61	1.12 (0.64-1.98)	
	120-≤ 180 min	0.98 (2.03)	147	42	1.41 (0.78-2.58)	
	>180 min	1.08 (1.96)	50	15	1.48 (0.70-3.17)	
Pain intensity	No and minimal pain	+0.61 (1.86)	55	6	1.00 (referent)	1.00 (referent)
on ED admission	Mild pain	+0.09(1.22)	66	10	1.39 (0.48-4.06)	1.56 (0.52-4.67)
	Moderate pain	0.70(1.71)	103	40	3.56 (1.42-8.92)	3.98 (1.57-10.13)
	Severe pain	1.15 (1.78)	225	56	2.28 (0.94-5.57)	2.44 (0.98-6.11)
	Very severe pain	1.60 (1.92)	111	25	2.07 (0.80-5.33)	1.50 (0.55-4.09)
Analgesics in ED	No analgesic	0.56 (1.71)	374	74	1.00 (referent)	1.00 (referent)
	Analgesics	1.39 (2.02)	186	63	1.71 (1.17-2.50)	1.72 (1.12-2.65)
	Nonopioid	1.37 (1.95)	140	49	1.79 (1.17-2.67)	1.75 (1.16-2.74)
	Mild opioid	0.60 (1.34)	4	1	1.26 (0.14-11.27)	1.60 (0.16-16.11)
	Major opioid	1.51 (2.27)	42	13	1.56 (0.80-3.06)	1.60 (0.74-3.44)
Non-pharmacological pain management in ED	No	0.67 (2.31)	123	24	1.00 (referent)	
	Yes	0.91 (1.73)	437	113	1.33 (0.82-2.15)	
Analgesic in prehospital phase	No	0.75 (1.89)	338	81	1.00 (referent)	
	Yes	1.02 (1.82)	222	56	1.05 (0.72-1.54)	

Factors associated with clinically relevant pain relief

Overall, 19.7% of the patients had clinically relevant pain relief during ED visit. Table 3 shows the association between candidate prognostic factors for clinically relevant pain relief, sex, age, pain intensity on admission, analgesic use in the ED, non-pharmacological pain

management in the ED, analgesic use in prehospital phase, duration of ED stay, type of injury and urgency level, and clinically relevant pain relief. All candidate prognostic factorswere to some extent associated with the prediction of relevant pain relief except for the duration of ED stay. Of all nine candidateprognostic factors, only three prognostic factorsindependently contributed to the prediction of the outcome relevant pain relief. The final model (Table 3; ORadj) included three prognostic factors for clinically relevant pain relief, namely type of injury, pain intensity on admission and analgesic use in the ED were highly significant.

Patients who: a) received analgesics in the ED (ORadj1.72; 95% CI (1.12-2.65)); b) had a dislocation (ORadj 2.67; 95% CI (1.23-5.76)); and c) had moderate (ORadj 3.98; 95% CI (1.57-10.13)) to severe pain (ORadj 2.44.; 95% CI (0.98-6.11)) on admission were more likely to achieve relevant pain relief. Patients with a sprain &strain (ORadj 0.56; 95% CI (0.28-1.11)) or contusion (ORadj 0.30; 95% CI (0.12-0.78)) were less likely to achieve relevant pain relief during ED visit.

DISCUSSION

This part of the PROTACT study confirms oligoanalgesia to be a serious problem in patients with musculoskeletal extremity injury. Even though sixty percent of the patients used analgesics somewhere in the chain of emergency care, more than two-third of the patients still suffered moderate to very severe pain at discharge from the ED.

In the prehospital phase, almost forty percent of the patients used one or more analgesics. They reported a mean pain score of 7.0 on ED admission suggesting that most of these patients suffer from severe pain. Despite the fact that pain prevalence and pain intensity on ED admission were both high, only few patients actually received analgesics during their stay at the ED even when pain intensity was moderate to very severe. Moreover, only one in eight patients had adequate analgesic treatment. Patients did not receive analgesics at all or did receive an inappropriate type of analgesics for their pain intensity at admission. However, the low number of patients receiving (adequate) analgesic pain management is partly explained by almost 15% patients refusing any analgesics. In contrast to the rather low percentage of patients that received analgesics, non-pharmacological treatment was provided to most patients in the ED.

A second objective of this study was to identify patients with clinically relevant pain relief at discharge. Because statistically significant difference in pain change is mostly a matter of sample size, it is more important to know whether this difference is clinically relevant. This clinically relevant pain relief was achieved in only one out of five patients. The administration of analgesics during ED visit, the type of injury and pain intensity on admission were associated with relevant pain relief.

The present study is the first attempt to provide more knowledge about pain management throughout the chain of emergency care. The study is to our knowledge the first study where analgesic use in patients with musculoskeletal injury is described in both prehospital phase and ED. Although a high percentage of patients used analgesics somewhere in the chain of emergency care, more than one-third of these patients received their first analgesic in the ED. As pain is a primary motive of patients to present themselves to the ED (1-6), pain relief should be one of the primary foci of emergency care provision. Adequate and effective pain management is important; it leads to early mobilization and recovery and may prevent long-term consequences like chronic pain (23). The delayed provision of analgesics in the chain together with the high levels of severe pain reported on ED admission by patients who received analgesics in prehospital phase, shows that there is still room for improvement in pain management in the prehospital phase.

Pain management in the ED has been reported to be a serious problem in previous studies (1-3, 5, 6, 8-15). For instance, in a study in two Dutch EDs, 86% of a heterogeneous group of trauma patients still suffered pain at discharge, of which two-thirds reported moderate to severe pain (1). In the present PROTACT study, almost every patient suffered pain at discharge and more than two-third of the patients had moderate to very severe pain although almost 9 out of 10 patients received some kind of pain management. This shows that there is room for improvement in pain management in the ED.

These findings pose the intriguing question of how pain management can be improved. To improve pain management in the ED, a pain management protocol might increase the percentage of patients receiving analgesics. Studies have reported that a nurse-initiated protocol for pain management improves the amount of patient receiving analgesics and shortens the time to analgesic provision (38, 39). The importance of analgesic use is reflected by the significant and clinically relevant higher reduction of pain. Although the practice of prescribing analgesics, in particular opioids, has been improved in recent years (40), only a low percentage (12.7%) of the patients with severe pain in the present study received an opioid Opioid-induced side effects and fear for addiction are clinical concerns that may prevent proper prescribing Yet, the reluctance of clinicians to use opioids could be partly explained by our study population, patients with musculoskeletal injury, who often will be discharged home. The use of more potent analgesics could result in longer ED stay and the inability to be discharged home safely. Another reason may be that clinicians are too focused on 'anatomical' injury treatment and do not always follow expert recommendations regarding the use of self-reported pain intensity (41). Moreover, patients do not always desire opioids while in pain (42).

Extra attention could be paid to patients who suffered a sprain, strain or contusion. The PROTACT study showed that patients with a contusion, sprain or a strain are less likely to achieve clinically relevant pain relief than patients with fractures, while patients with a

dislocation are more likely to achieve clinically relevant pain relief. This confirms earlier findings (1). When a dislocated joint is successfully repositioned into its normal anatomical position, clinically relevant pain relief will be achieved relatively easy. Painful diagnostic procedures performed in the ED to patients with contusions, sprains or strains could be an explanation for the lower pain relief in these patients (1). Furthermore, patients with non-fracture injury may be more liable to treatment disparities than patients with fractures (41). When treating patients with musculoskeletal injury, one should pay extra attention to patients' pain, especially in patients who suffered a sprain, strain or contusion. This might improve pain relief in these patients

In addition to a pain management protocol, multimodal therapy to improve pain management is worth considering. Given the high complexity of pain (43), it is clear that no single analgesic will provide optimal pain relief. Paracetamol, NSAIDs and opioids all have different mechanisms of actions. Studies examining the use of multiple analgesics with different mechanisms of action suggest that multimodal therapies may offer an improved efficacy/tolerability balance over the use of a single analgesic (25). Fortunately, in more than half of the patients, analgesics were already given with a multimodal approach. Still there are patients who received only opioids and especially in patients with musculoskeletal extremity injury, who often have considerable tissue damage, the use of only opioids is not optimal. Pain management is expected to improve if different types of analgesics are combined to capitalize on their complementary mechanism of action (44).

The strength of the present study is the use of patients' self-reporting pain intensity instead of the documented pain scores assessed by clinicians such as physicians or nurses. Many studies are retrospective and therefore use available registry data. Because there is no objective measurement for the experience of pain, the measurement of pain relies primarily on patients' self-report. In the PROTACT study, mean pain scores documented during triage by clinicians were significantly lower than those self-reported by patients. This underestimation of pain is a common phenomenon in patients with musculoskeletal pain (18, 19, 45). While patients self-reports were used for pain intensity, registry data were used for the provision of analgesics in the ambulance and the ED. Although patients were asked to write down the name of the analgesic they used, most patients did not know which analgesic they received. Therefore, we used registry data if available. Unfortunately, registry data from GP were not available in this study. Furthermore, the effectiveness of pain management in the prehospital phase could not be assessed due to a lack of prehospital initial pain scores which unfortunately were not documented in the registries. Additionally, data on non-pharmacological pain management in the prehospital phase were poorly documented and except for cooling not asked for in the questionnaire. In order to investigate the effect of analgesic treatment in the ED, analgesics were divided in classes according to WHO guidelines, even though the name, dose and frequency for the administered analgesics were

collected. Most clinicians will start with an initial low dose according to body weight and carefully adjust the dose upwards to adequate levels (titration to effect) to reduce side effects.

Altogether, the addition of initial pain scores, availability of pain management registry from GPs, and non-pharmacological pain management in the prehospital phase in the questionnaire would have made the study even more complete.

The limitations of PMI as an index of adequate analgesic management must be acknowledged. The PMI reflects a relatively simple approach to assess the adequacy of analgesic pain management and does not address many of the complexities inherent in pain management such as side effects, contraindications to specific analgesics and does not take into account that some patients tolerate more pain than others. The PMI combines only the class of analgesics administered and the pain intensity at admission. Therefore PMI only gives an indication of the adequacy of analgesic provision, not of the effect of treatment or adequate pain relief. Furthermore, most patients received in addition to analgesic treatment, also non-pharmacological treatment

Moreover, the percentage of patients who used analgesics in the ED might be underestimated and found effects of analgesic use might be higher because of misclassification of patients. Even though medical staff was instructed to list all medications, including over-the-counter drugs, some may have neglected this, especially if the over-the-counter drugs (nonopioids like paracetamol) which were routinely administered by nurses during triage. These patients were classified as "received no analgesic". As the PROTACT study revealed that more than two-third of the patients discharged with severe pain, it is also required to monitor patients after discharge regarding analgesic use. Furthermore, to investigate whether the study participants were a selected group of patients, a substudy was performed in which several characteristics of the participants (type of injury, urgency level, documented triage pain score, pain management) were compared to a random group of hundred non-responders. Characteristics were similar, indicating that the included participants were not a selected group of patients.

Finally, the PROTACT study was conducted in a single center ED and may not represent the practices of other emergency departments and ambulance services. However, problems of pain management in emergency care extend far beyond a single ED; the high pain prevalence and low percentage of analgesic administration are comparable to other emergency departments (1, 9). In summary, pain management in both the prehospital phase and in the ED is clearly not optimal. A high percentage of patients was discharged with unacceptable levels of pain. The use of multimodal pain management or the implementation of a pain management protocol might be useful methods to optimize pain relief. Additional research regarding the best methods to manage pain in the chain of emergency care is necessary.

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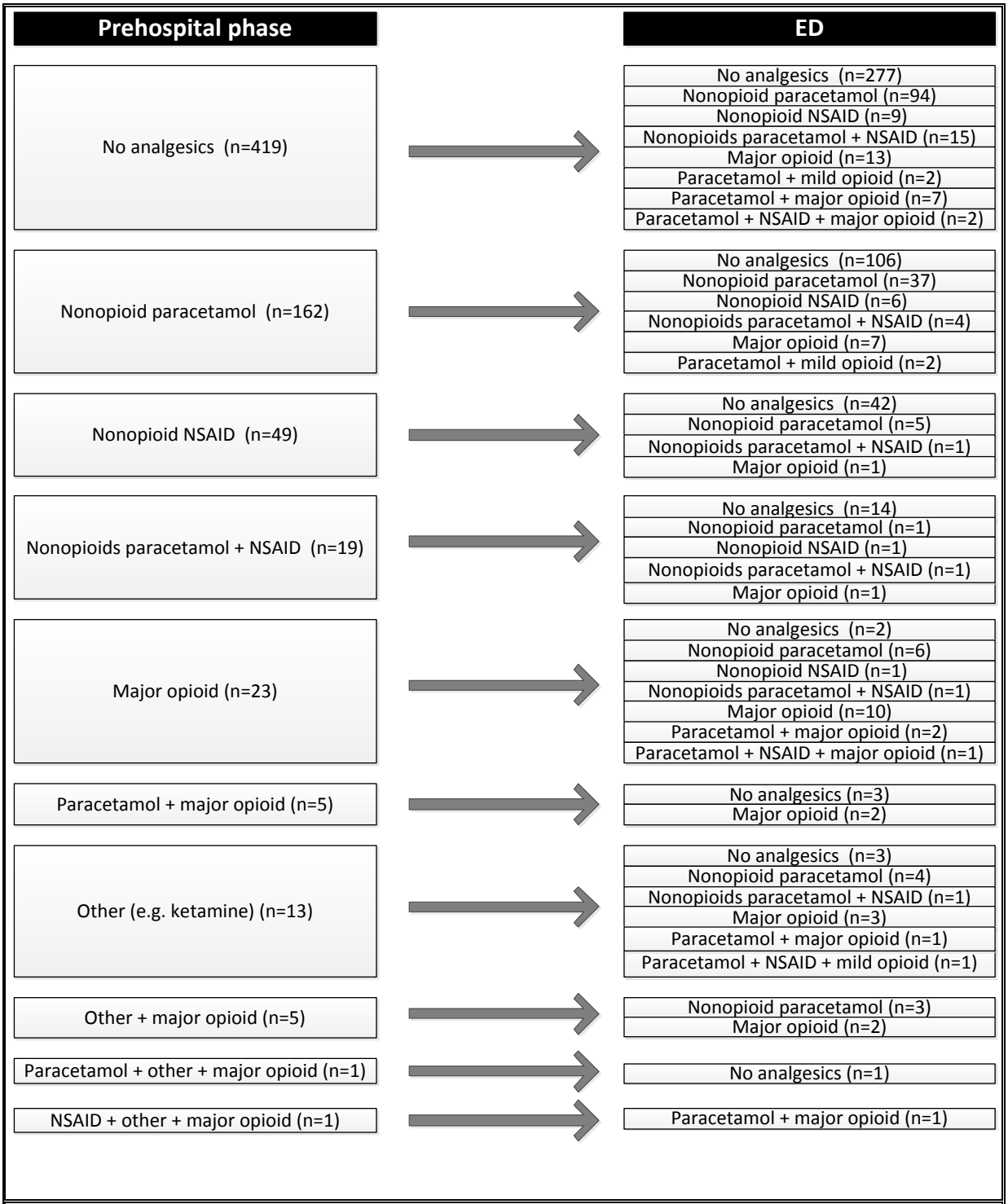
APPENDIX



Appendix A: Follow-up treatment of pain in the ED. Combination of analgesics used in the chain of emergency care.

Appendix B: Type and generic name of analgesics administered in prehospital phase and the ED

Ambulance medical emergency services (n=77)			N (%)
	No analgesics 29 (37.7%)		
	Analgesics 48 (62.3%)		
		Nonopioids	4 (8.3%)
		Paracetamol IV	4
		Mild opioids	0 (0.0%)
		Major opioids	32 (66.7%)
		Fentanyl	22
		Fentanyl +paracetamol	2
		Morphine+paracetamol	1
		Fentanyl +esketamine	4
		Fentanyl + 50% N2/ 50% O2	3
		Other	12 (25%)
		Esketamine	11
		50% N2/ 50% O2	1
Self-initiated (n=697)			N (%)
	No analgesics 522 (74.9%)		
	Analgesics 175 (25.1%)		
		Nonopioids	173 (98.9%)
		Paracetamol	124
		Paracetamol+ibuprofen	9
		Paracetamol+diclofenac	3
		Ibuprofen	27
		Diclofenac	5
		Aspirin	3
		Meloxicam	1
		Mild opioids	1(0.6%)
		Zaldiar	1
		Major opioids	1(0.6%)
		Oxycodone	
General practitioner or other health professional (n=337)			N (%)
	No analgesics 279 (82.8%)		
	Analgesics 58 (17.2%)		
		Nonopioids	56 (96.6%)
		Paracetamol	38
		Paracetamol+ibuprofen	1
		Paracetamol+diclofenac	3
		Ibuprofen	9
		Ibuprofen +diclofenac	1
		Diclofenac	3
		Naproxen	1
		Major opioids	1 (1.7%)
		Morphine	1
		Other	1 (1.7%)
ED			N (%)
	No analgesics 448 (64.3%)		
	Analgesics 249 (35.7%)		
		Nonopioids	189 (75.9%)
		Paracetamol	149
		Paracetamol+ibuprofen	1
		Paracetamol+diclofenac	22
		Diclofenac	17
		Mild opioids	5 (2.0%)
		Tramadol+paracetamol	4
		Tramadol+paracetamol+di	1
		Major opioids	55 (22.1%)
		Morphine	40
		Morphine+paracetamol	11
		Morphine+	3
		Piritramide	1

Appendix C: Non-pharmacoloAppendix C: Non-Pharmacological pain management in ED			
Non-pharmacological pain management in ED			N (%)
No non-pharmacological	147 (21.1%)		
Non-pharmacological	550 (78.9%)		
		Immobilization	381 (69.3%)
		Immobilization+reposition	27 (4.9%)
		Immobilization+compression	28 (5.1%)
		Immobilization+cold pack	10 (1.8%)
		Reposition	1 (0.2%)
		Compression	95 (17.3%)
		Compression+cold pack	2 (0.4%)
		Coldpack	1 (0.2%)
		Others	5 (0.9%)

Chapter 3

Incidence and prognostic factors of chronic pain after isolated musculoskeletal extremity injury

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ABSTRACT

BACKGROUND: Chronic pain in patients is usually related to an episode of pain following acute injury, emphasizing the need to prevent progression from acute to chronic pain. Multiple factors in the acute phase might be responsible for perpetuating the pain. The presentation of patients at the emergency department (ED) presents a prime opportunity to identify patients at high-risk for chronic pain and to start appropriate treatment.

METHODS: The PROTACT-study is a prospective follow-up study aiming to estimate the incidence and prognostic factors responsible for the development of chronic pain after musculoskeletal injury. Data including sociodemographic, pain, clinical, injury- or treatment related, and psychological factors of 435 patients were collected from registries and questionnaires at ED-visit, 6 weeks, 3- and 6 months follow-up.

RESULTS: At six months post-injury, 43.9% of the patients had some degree of pain (Numeric Rating Scale (NRS) ≥1) and 10.1% had chronic pain (NRS≥4). Patients aged over 40 years, in poor physical health, with pre-injury chronic pain, pain catastrophizing, high urgency level and severe pain at discharge were found to be at high-risk for chronic pain.

CONCLUSIONS: Two prognostic factors, severe pain at discharge and pain catastrophizing, are potentially modifiable. The implementation of a pain protocol in the ED and the use of cognitive–behavioural techniques involving reducing catastrophizing might be useful.

BACKGROUND

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (1). Pain can be classified as acute or chronic. Acute pain is unpleasant but necessary; it can be a sign that something dangerous, like injury, is occurring in the body. Nevertheless, there are situations when pain experiences are unnecessary. This happens when pain persists and loses its value as warning signal. This pain is called chronic pain.

Chronic pain is a major health problem. In a recent review, the prevalence of chronic pain was estimated to be 22% (2). Moreover, chronic pain often leads to psychosocial problems, work disability and health care overutilization (3). Therefore chronic pain is a substantial economic burden and remains one of the most costly conditions in western society (4).

The link between acute and chronic pain has been subject of investigation in many studies (5, 6). Chronic pain patients often relate their pain onset to acute injury such as surgery or trauma (7, 8). However, the transition of acute to chronic pain is a complex and poorly understood developmental process. A range of injury-, psychosocial-, socio-environmental and patient-related factors has been associated with the chronification of pain (5, 6).

Most studies identified prognostic factors for post-surgical chronic pain or chronic whiplash-associated disorder (9, 10). Studies that determine prognostic factors for chronic pain post-injury are limited even though chronic pain is a frequent adverse outcome of injury. The incidence of moderate to severe chronic pain after musculoskeletal injury ranges from 11 to 56%, and depends on specific diagnosis (11-14). Multiple factors within the acute phase might be responsible for the transition from acute to chronic pain. Factors known for their predictive validity after musculoskeletal injury are older age, being a woman, pre-injury anxiety or depression and severe pain in the acute post-injury period. In contrast, high-educated persons have a reduced risk (15).

Most studies investigating prognostic factors for chronic musculoskeletal pain post-injury had a retrospective design, or only two measurements were performed, i.e. at injury and follow-up. Therefore, it is difficult to determine the causality between prognostic factor and the process of chronification. Furthermore, the few current prospective studies included polytrauma patients and might have overestimated the incidence (5, 13, 16, 17).

The PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients (PROTACT)-study is a prospective follow-up study, with the aim to determine prognostic factors responsible for developing chronic pain after isolated musculoskeletal injury. These factors allow the identification of high-risk patients with the aim to provide these patients with appropriate treatment to prevent chronic pain.

PATIENTS AND METHODS

Study design and study population

This study is part of a one-year prospective follow-up study; the "PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients" (PROTACT). Ethics approval for the PROTACT-study was obtained from the regional Medical Research Ethics Committee on Research Involving Human Subjects (CCMO no. NL368.38044.11). Adult patients with isolated musculoskeletal extremity injury presenting at the ED of the level one trauma centre Medisch Spectrum Twente in Enschede, The Netherlands were invited to participate. The ED has a 24 hours a day, 7 days a week (24/7 ED) service. The ED is accessible for 264,000 individuals in the Twente region and treats approximately 27,000 patients annually.

Eligible patients were consecutively recruited when admitted to the ED from September 2011 until July 2013. Inclusion criteria were: patients (i) who had isolated musculoskeletal extremity injury caused by blunt trauma (ii) who had sufficient communication skills and a basic knowledge of the Dutch language; and (iii) aged 18 until 69 years. Exclusion criteria were: patients (i) with life or limb threatening conditions; (ii) with documented cognitive disability; (iii) suffering from hallucinations, delusions or suicidal ideation; (iv) with alcohol or drugs intoxication; and (v) living outside the 'catchment area' served by the hospital. During the 22 months inclusion period, 1994 adult patients with musculoskeletal extremity injury attended the ED and met the study criteria. Of these patients, 803 participants provided written informed consent. For current study, all patients who were followed until six months post-injury were included.

Data collection

During the ED admission, patients who met the study criteria were informed by a (triage) nurse about the purpose of the study. Participants were asked to provide informed consent and to complete a questionnaire. These were returned immediately while in the waiting room or send by mail. Eligible patients who were accidently not invited in the ED received an invitation and questionnaire by mail within one week after the ED visit. Six weeks, 3 months and 6 months after the initial ED visit, patients received a follow-up questionnaire by email or by mail, according to their stated preference. Subsequent reminders were sent one week later. If the questionnaire was not returned within 3-4 weeks patients were called to ask if they were still willing to fill in the questionnaire. If not, the average pain score in the last week was asked for and the reason for non-participation.

The questionnaires comprised six validated questionnaires that are frequently used in pain research (see below). Furthermore, questions about sociodemographics, self-reported lifestyle and health such as comorbidities, pain management and injury characteristics were included. Moreover, questions about who to blame for the injury and if patient applied for compensation status for bodily insurance were included.

In addition to the data obtained from the questionnaires, data from the ED electronic patient registry were used. Each event is recorded with a time-stamp for pre–specified ED events. The registry includes patient demographics (date of birth, sex), referrer, triage urgency level, triage pain score, type of analgesics, medical diagnoses (e.g. injury type and location), type of non-pharmacological pain management and timestamp of providing pain management.

The following six validated questionnaires were used:

Pain intensity

Pain intensity at ED admission and ED discharge were measured using Numerical Rating Scales (NRS). Patients were asked to fill in a number from 0 to 10, where 0 is "no pain" and 10 "the worst pain imaginable". The NRS was validated for use in the ED (18, 19) and retrospective one-week recall of pain intensity seems to be reliable and valid (20, 21).

Health-related quality of life

Health-related quality of life (HRQoL) was measured by using the validated Dutch language version of the 36-Item Short- Form Health Survey (SF-36, Corporation, Santa Monica, California USA) (22). The SF-36 is a general quality of life questionnaire with a 4-week recall period and assesses eight domains: physical functioning, social functioning, role limitations due to physical problems, and role limitations due to emotional problems, pain, mental health, vitality, and general health perception (23). For each domain, item scores were coded, summed, and transformed into a scale ranging from 0 to 100, where 100 was the highest best possible rating. Algorithms were used to produce the Physical Component Summary (PCS) scores for physical health status and Mental Component Summary (MCS) scores for mental health status (24). In the present study, the first quartiles of the obtained PCS (51.9) and MCS (49.9) scores were defined as the cut-off points for poor mental or physical health (25).

Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) The Dutch version was validated and was found to have good psychometric properties (26). The HADS is a screening tool used in a wide variety of clinical groups, such as emergency care patients (27) and chronic musculoskeletal patients (28). Patients were asked to recall a 7-days period about 14 items on a 4-point Likert scale; anxiety and depression sum scores were calculated (range 0–21), with a high score indicating a high level of anxiety or depression. In the present study, a sum score of >7 was used to indicate the presence of anxiety and depression.

Pain catastrophizing

Pain catastrophizing was measured by using a Dutch-language version of the Pain Catastrophizing Scale (PCS) consisting of 13 statements of pain experience; for example: "If I am in pain, I am afraid the pain will get worse." Patients were asked to indicate whether they agree with these statements by using a 5-point Likert scale. A PCS sum score was calculated from all items (range, 0–52), with a high score indicating a high level of pain catastrophizing. In this study, a score of >24 was used to indicate the presence of pain catastrophizing, because this cut-off point was found to be best associated with high follow-up pain ratings (29). Several studies support the validity and reliability of PCS (30).

Kinesiophobia

Kinesiophobia was measured by the Tampa Scale of Kinesiophobia (TSK). The TSK consists of 17 statements that reflect the notion that pain is a precursor for (re)injury because of physical activity or certain movements (31). Patients were asked whether they agree with these statements by using a 4-point Likert scale. A TSK sum score was calculated by using all items (range, 17–68). A score of 37 or higher was used to indicate the presence of kinesiophobia (32).The Dutch-language version TSK has been shown to be internally reliable and correlates with measures of other disability (32).

Pain experience during follow-up

Pain experience at 6 weeks, 3 and 6 months follow-up was measured using a few questions of the Brief Pain Inventory (BPI) – long version (33). The BPI is a self-reporting instrument to assess the multidimensional nature of pain, including pain intensity and pain interference on life activities. Pain intensity in patient's injured body part was measured four times: "worst pain last week", "least pain last week", "average pain last week", and "current pain", using the NRS related to their injury, where 0 is "no pain" and 10 "the worst pain imaginable". Patients also rated how much their pain interfered with daily activities and sleep during the past week, where 0 is "does not interfere" and 10 "interferes completely". BPI has a good reliability and validity for assessing pain intensity in patients with chronic non-malignant pain (34).

Primary outcome measure at follow-up

The primary outcome at six months post-injury was chronic pain. This was based on the BPI "rate your average pain last week". The cut-off score for chronic pain was set at NRS≥ 4 (35, 36). In addition, the pain intensity pattern over time in the post-injury period of each patient with a NRS≥ 4 was observed in order to determine if the pain was persistent after injury. If pain was not present during the whole period (NRS≥ 2 at 6 weeks, 3 months), patients were indicated as not having chronic pain. Secondary outcome at six months was pain interference with daily activities.

Potential prognostic factors

The following variables were analysed for their prognostic value (5, 6):

Demographics: Age; sex; educational level; marital status; income/employment status; and lifestyle factors (alcohol consumption and smoking).

Pain factors: Pain intensity at discharge measured with NRS; chronic pain in the past or at the time of filling in the questionnaire; pain interference with activities in the month before injury measured (none/little versus moderately/quite a bit/extremely) with SF-36; and the use of analgesics in the ED.

Psychosocial factors: Pre-injury anxiety and depression measured with HADS; catastrophizing measured with PCS; kinesiophobia measured with TSK; and mental health status measured with SF-36.

Injury and treatment factors: Type of injury; site of injury; previous injury on injured body part; urgency level; and surgery.

Clinical Factors: Physical health status measured with SF-36; self-reported comorbidities; and body mass index.

Others: Compensation status and blame of the injury.

Data analysis

For descriptive purposes, categorical data were characterized in terms of frequency (%), whereas continuous data were characterized as median with interquartile range (IQR, 25^{th} - 75^{th} percentile) or as mean ± standard deviation (SD). Generalized Linear Model (GLM) for repeated measures was used to investigate differences in pain scores over time between patients who developed chronic pain and those who did not. Pearson correlation coefficient between primary outcome pain intensity and pain interference with daily activities at six months was measured.

Associations between categorical variables and chronic pain six months post-injury were investigated using chi-squared tests. Odds ratios (ORs) and corresponding 95% confidence intervals (CI) were calculated and interpreted as the relative risk of the presence of a potential prognostic factor for chronic pain compared to the absence of that prognostic factor. Because pre-selection of prognostic factors based on p-values estimated from univariate analyses may result in unstable prediction models (37), all candidate variables were considered in the multivariate analysis. Backward stepwise selection of all candidate variables was applied using the likelihood ratio test with a p-value of 0.157 according to Akaike's Information Criterion. This Akaike variant is a measure of model fit that includes a penalty against large models and hence attempts to reduce overfitting (54). If multicollinearity between two variables was suspected, change of estimates, confidence intervals and p-values were evaluated when both variables were included in the model as compared to the inclusion of one variable. If the two variables were more or less equally associated with the

chronic pain we selected the variable most easily obtainable in clinical practice. The model's ability to discriminate non chronic from chronic pain patients was assessed by concordiance (c)-statistic. The c-statistic equals the area under the receiver operating characteristic (ROC) curve in logistic regression. The c-statistic, can range from 0.5 (no discrimination) to 1.0 (perfect) discrimination. The c-statistic for a prognostic model is typically between about 0.6 and 0.85 (38).

A bootstrapping procedure was used to assess the internal validity of the multivariate model. Two-hundred-fifty bootstrap samples were drawn from the data set. In each bootstrap sample, the modelling was repeated. This procedure produced a corrected model's c-statistic and a shrinkage factor. The regression coefficients (β) of the prognostic factors in the model were then multiplied by this shrinkage factor to prevent overfitting of the regression coefficients and optimism of the model when applied to new patients. The adjusted odds ratios (ORadj) and corresponding 95% CIs were calculated. In the final model, the R^2 Nagelkerke was used as a measure of the power of combined variables in predicting chronic pain. For the variables that turned out as independent prognostic factors, the observed and predicted proportions of patients reporting chronic pain were calculated. All data analyses were performed with SPSS version 21.0 (IBM Corporation, Armonk, NY) and R software version 3.0.3 (R foundation, Vienna, Austria).

RESULTS

Patients and pain characteristics

Between September 2011 and July 2013, 803 adult patients with musculoskeletal extremity injury provided written informed consent. Data on a total of 435 patients, who filled in baseline and follow-up questionnaires at 6 weeks, 3 and 6 months, were used for analysis. Distributions of age and sex among these 435 patients were slightly different from the 368 patients who did not fill in all four questionnaires; more women and an older age. Median age of the 435 patients was 50.0 years (IQR 36.0-60.0) and 60.5% were women (Table 1). The majority of 435 patients suffered a fracture (75.4%). Most common body parts where fractures occurred were wrist (n=69); ankle (n=56), elbow (n=31), metatarsalia (n=30) and hip (n=24).

Of all patients 43.9% had some degree of pain six months post-injury: 33.8% had minimal pain (NRS 1-3); 8.3% had moderate pain (NRS 4-6); and 1.8% reported severe pain (NRS≥7) (Fig. 1).

According to the cut-off score of chronic pain (NRS≥4), 44 out of 435 patients (10.1%) suffered chronic pain at 6 months post-injury. Most patients (77.5%) who reported some degree of pain also had pain interference during daily activities (Fig.1). The correlation between pain intensity and pain interference at six months post-injury was high ($r = 0.84$ $p<0.01$).

Table 1: Characteristics of 435 patients with musculoskeletal extremity injury

Sociodemographics		N (%)
Sex	Women	263 (60.5%)
Age (in years), median (IQR)		50.0 (36.0-60.0)
Educational level	High	144 (33.1%)
	Middle	227 (51.8%)
	Low	62 (14.3%)
Marital status	Married/domestic partnership	297 (68.8%)
	Divorced	13 (3.0%)
	Widowed	20 (4.6%)
	Single	103 (23.8%)
Work income	Modal	64 (14.7%)
	Lower than modal	100 (23.0%)
	Higher than modal	70 (16.1%)
	No (income out) of work	157 (36.1%)
	Prefers not to give this information	44 (10.1%)
Alcohol consumption before injury	Weekly or less	190 (44.0%)
	More than once a week	242(56.0%)
Smoking	Yes	62 (14.4%)
Pain factors		
Pain intensity at admission ED, mean (SD)		6.5 (2.4)
Used analgesics in the ED		160 (36.8%)
Pain intensity at discharge ED, mean SD		5.6 (2.5)
Pre-existing chronic pain		88 (20.2%)
Pain interferes with daily activities before injury	None/little	398 (91.5%)
	Moderately/quite a bit/extremely	37 (8.5%)
Psychological factors		
Anxiety before injury, mean (SD)		3.5 (2.9)
Depression before injury, mean (SD)		1.8 (2.6)
Kinesiophobia, mean (SD)		35.9 (6.8)
Pain catastrophizing, mean (SD)		8.4 (7.1)
Mental health before injury, mean (SD)		52.3 (8.4)
Injury and treatment factors		
Type of injury	Fracture	328 (75.4%)
	Dislocation	25 (5.7%)
	Sprains and strains	47 (10.8%)
	Contusion	24 (5.5%)
	Muscle rupture	10 (2.3%)
Site of injury	Lower extremities	215 (49.4%)
Urgency level	Standard	301 (69.4%)
	Urgent	114 (26.3%)
	Very urgent	19 (4.4%)
Earlier injury on injured body part	Yes	98 (22.5%)
Surgery	Yes	104 (23.9%)
Complications post-injury	Yes	22 (5.1%)

Table 1: Continued		
Clinical factors		
Physical health before injury, mean sum score		53.5 (8.4)
Comorbidity (self-reported)	Yes	131 (30.1%)
BMI, mean (SD)		25.2 (4.2)
Other		
Compensation status *	Yes	34 (7.9%)
Trauma caused	Self-injured	394 (90.6%)
	Third-party caused	41(9.4%)
Follow-up		
Follow-up in months, median IQR		6.3 (6.1-6.8)
Pain (NRS≥1) at 6 months follow-up		191 (43.9%)
Chronic pain (NRS≥4) at 6 months follow-up		44 (10.1%)
Pain disability (NRS≥4) with daily activity at 6 months follow-up		48 (11.0%)

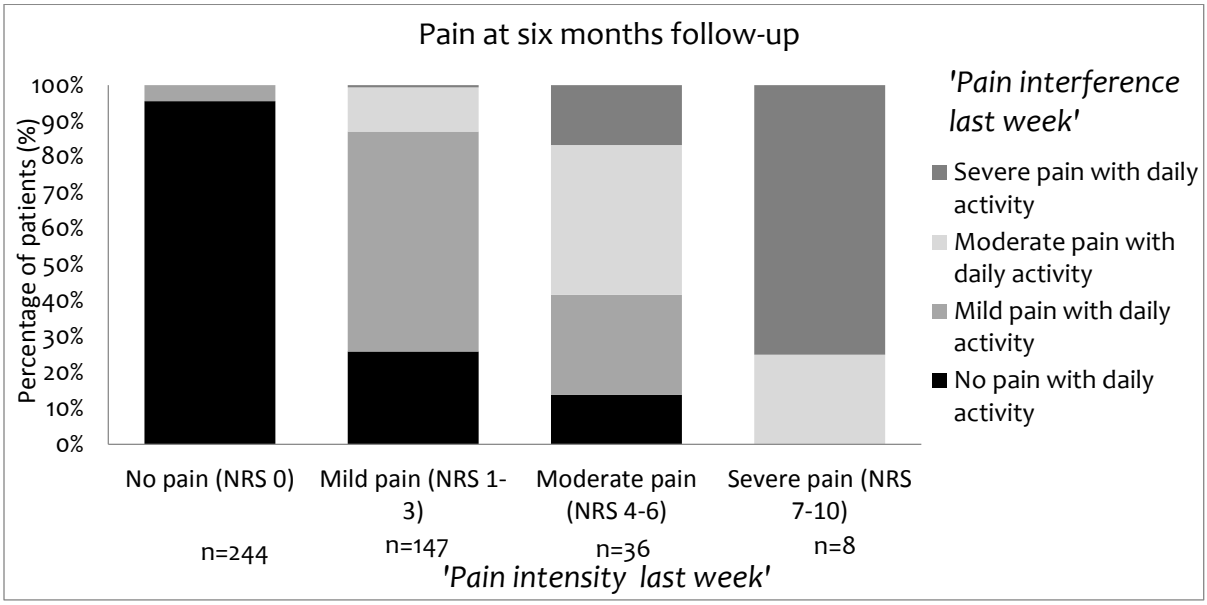

Figure 1. Percentage of patients with pain intensity and pain interference with daily activities at six months post-injury.

Fig. 2 shows the mean pain intensity over time from ED admission until 6 months post-injury separately for patients who developed chronic pain six months post-injury and for non-chronic pain patients. Chronic pain patients had a higher pain intensity score on ED admission ($p<0.01$). There was no difference in pain reduction over time from ED admission till discharge (GLM for repeated measures, $p=0.90$) and from discharge till 6 weeks follow-up (GLM for repeated measures, $p=0.53$) between patients who developed chronic pain and those who did not. After 6 weeks there was some increase in pain among chronic pain patients, in contrast to pain reduction in patients who did not develop chronic pain (GLM for repeated measures $p=0.16$). After 3 months the differences in pain experience over time between the two groups further increased significantly over time (GLM for repeated measures $p<0.01$).

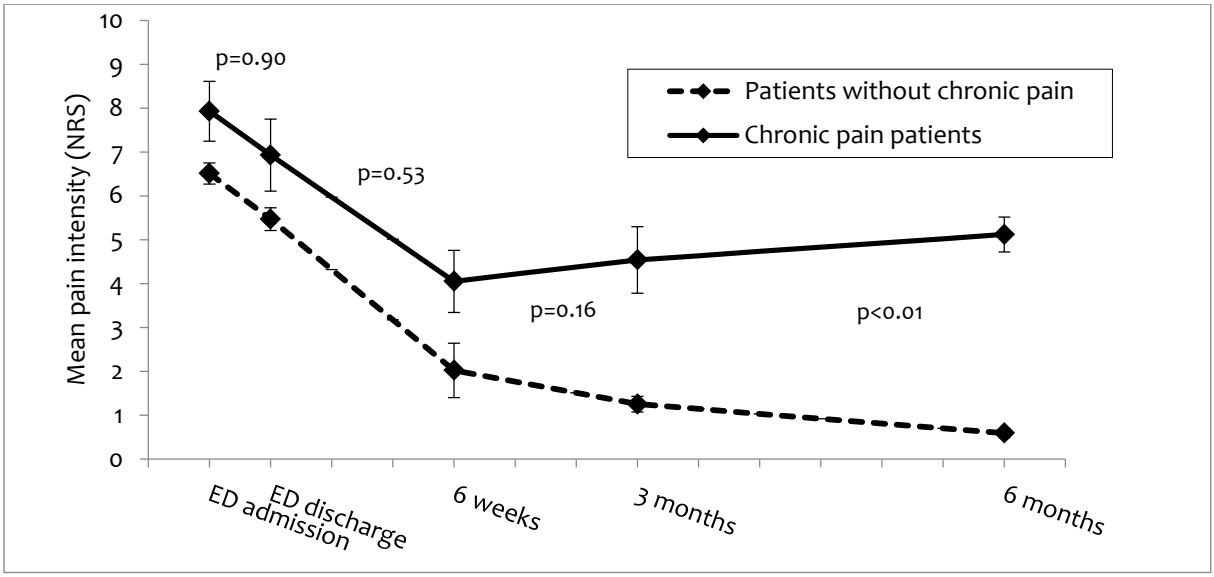

Figure 2: Mean (± 95% CI) pain intensity of chronic pain patients and patients without chronic pain over time. Differences were assessed with the General Linear Model method for analysing repeated measures.

Prognostic factors of chronic pain

To examine possible variables that account for developing chronic pain the association between potential prognostic factors and chronic pain at 6 months was investigated (Table 2). Most potential predictors were to some extent associated with chronic pain six months post-injury. All pain factors, an increased age, pain catastrophizing, having comorbidities, physical health before injury and urgency level are significantly associated with chronic pain.

Table 2 : Factors associated with chronic pain (NRS≥ 4) six months post-injury (N=435)

variable		chronic pain (n)	OR (95% CI)	p
Sociodemographics				
Sex	Men (ref.)	12/172	1	0.08
	Women	32/263	1.85 (0.93-3.70)	
Age in years	18 -39 (ref.)	6/128	1	<0.01
	40 - 49	4/83	1.03 (0.28-1.07)	
	50 - 59	16/111	3.43 (1.29-9.09)	
	60 - 69	54/113	3.85(1.47-10.08)	
Educational level *	High (ref.)	10/144	1	0.13
	Middle	24/227	1.58 (0.73-3.42)	
	Low	10/62	2.57 (1.01-6.55)	
Marital status*	Married/domestic partnership (ref.)	34/297	1	0.11
	Divorced	1/13	0.65 (0.08-5.11)	
	Widowed	4/20	1.93 (0.61-6.12)	
	Single	5/103	0.40 (0.15-1.04)	
Work income	Modal (ref.)	6/64	1	0.08
	Lower than modal	8/100	0.84 (0.28-2.55)	
	Higher than modal	3/70	0.43 (0.10-1.81)	
	No (income out) of work	24/157	1.74 (0.68-4.49)	
	Prefers not to give this info	3/44	0.71 (0.17-2.99)	
Alcohol consumption before injury*	Weekly or less (ref.)	23/190	1	0.19
	More than once a week	20/242	0.65 (0.35-1.23)	
Smoking*	No (ref.)	34/370	1	0.20
	Yes	9/62	1.68 (0.76-3.70)	

Table 2: Continued

Pain factors				
Used analgesics in the ED	No (ref.)	21/275	1	0.03
	Yes	23/160	2.03 (1.09-3.80)	
Pain level at discharge ED	No severe pain (ref.)	13/243	1	<0.01
	Severe pain [NRS≥7]	31/192	3.41 (1.73-6.71)	
Pre-existing chronic pain *	Absent or in the past (ref.)	20/345	1	<0.01
	Present	24/88	6.09(3.18-11.69)	
Pain interferes with daily activities before injury .	None/little (ref.)	35/398	1	<0.01
	Moderately/quite a bit/extremely	9/37	3.33 (1.46-7.62)	
Psychological factors				
Anxiety before injury *	No (ref.)	37/392	1	0.12
	Present	7/41	1.98 (0.82-4.77)	
Depression before injury *	No (ref.)	40/413	1	0.14
	Present	4/20	2.33 (0.74-7.31)	
Kinesiophobia ***	No (ref.)	18/227	1	0.09
	Present	24/184	1.74 (0.91-3.32)	
Pain catastrophizing **	No (ref.)	38/404	1	0.02
	Present	4/14	3.85(1.15-12.88)	
Mental health before injury *	Good (ref.)	30/325	1	0.28
	Poor	14/109	1.45 (0.74-2.85)	
Injury and treatment factors				
Type of injury	Fracture (ref.)	37/328	1	0.16
	Non-fracture	7/107	0.55(0.24-1.27)	
	Dislocation	3/25	1.07 (0.31-3.76)	
	Sprains and strains	3/47	0.54 (0.16-1.81)	
	Contusion	0/24	-	
	Muscle rupture	1/10	0.87 (0.11-7.09)	
Site of injury	Lower extremities (ref.)	24/215	1	0.47
	Upper extremities	20/220	0.80 (0.43-1.49)	
Urgency level	Standard (ref.)	23/301	1	0.01
	Urgent	16/114	1.97 (1.00-3.89)	
	Very urgent	5/19	4.03(1.34-12.07)	
Earlier injury on injured body part	No (ref.)	31/337	1	0.24
	Yes	13/98	1.51 (0.76-3.02)	
Surgery	No (ref.)	30/331	1	0.19
	Yes	14/104	1.56 (0.79-3.07)	
Complications post-injury	No (ref.)	40/413	1	0.20
	Yes	4/22	2.07 (0.67-6.42)	
Clinical factors				
Physical health before injury *	Good (ref.)	23/326	1	<0.01
	Poor	21/108	3.18 (1.68-6.02)	
Comorbidity	No (ref.)	21/304	1	<0.01
	Yes	23/131	2.87(1.53-5.40)	
BMI (international classification)*	Normal weight (ref.)	19/233	1	0.22
	Underweight	0/6	-	
	Overweight	17/143	1.52 (0.76-3.03)	
	Obesity	8/48	2.25 (0.92-5.50)	
Other				
Compensation status *	No (ref.)	38/397	1	0.14
	Yes	6/34	2.02 (0.79-5.20)	
Trauma caused	Self-injured (ref.)	42/394	1	0.24
	Third-party caused	2/41	0.43 (0.10-1.84)	

Only six prognostic factors (age ≥40 years, poor physical health status, pre-existing chronic pain before injury, pain catastrophizing, (very) urgent urgency level and severe pain at discharge) independently contributed to the prediction of chronic pain (Table 3). Other prognostic factors, which seemed relevant such as sex, kinesiophobia, comorbidities in univariate analyses, were not independent prognostic factors. Apparently, their predictive information was already provided by the remaining prognostic factors. The final model including the six prognostic factors showed a good calibration (Hosmer-Lemeshow test p=0.88) and discriminative ability (c-statistic 0.81; 95% CI 0.74-0.88). The final model is able to predict 19% of the chronic pain at six months post-injury. Internal validity was strong; the bootstrapping procedure yielded an optimism-corrected c-statistic of 0.80 (95% CI 0.73-0.88) and a shrinkage factor of 0.88. The best trade- off between sensitivity (no false negatives) and specificity (no false positives) was, respectively, 0.71 and 0.77 (figure 3). The presence of pre-existing chronic pain before injury was the strongest prognostic factor for developing chronic pain: patients who already had chronic pain were four-times (ORadj 3.99; 95% CI 2.07-7.69) more likely to develop chronic pain in the injured body part. Pain catastrophizing (ORadj 3.16; 95% CI 0.96-10.43) and severe pain at discharge (ORadj 1.89: 95% CI 0.98-3.66) are potential modifiable factors.

Table 3. Independent factors associated with pain (NRS≥ 4) 6 months after trauma (n=397)#

		Reduced model		Extended (final) model	
		β	p	β*	ORadj* (95% CI)
Age	<40 years (ref.)				
	≥40 years	0.85	0.11	0.75	2.11 (0.85-5.26)
Pain at discharge	non severe(ref.)				
	severe	0.72	0.05	0.64	1.89 (0.98-3.66)
Pain catastrophizing	No (ref.)				
	Present	1.31	0.06	1.15	3.16 (0.96-10.43)
Chronic pain before injury	Absent or in the past (ref.)				
	Present	1.56	<0.01	1.38	3.99 (2.07-7.69)
Urgency level	Standard (ref.)				
	Urgent or very urgent	0.70	0.05	0.62	1.86 (0.98-3.51)
Physical health	Good (ref.)				
	Poor	0.61	0.11	0.54	1.72 (0.89-3.33)
Intercept		-4.32		-4.02	
C-statistic		0.81 (0.74-0.88).			0.80 (0.73-0.88)
Nagelkerke R^2		0.24			0.19

\# 38 missing values in multivariate analysis
Ref. reference group

*Regression coefficient and corresponding odds ratio after bootstrapping (i.e. adjusted for overfitting). The shrinkage factor was 0.8823

Probability of developing chronic pain= 1/ (1+exp (-(-4.02 + 0.75*(age_≥40 years) + 0.64* (pain at discharge_severe) + 1.15*(pain catastrophizing_present) + 1.38*(chronic pain before injury_present) +0.62* (urgency level_urgent or very urgent) + 0.54* (physical health_poor)).

With the risk score presented underneath Table 3, the risk of developing chronic pain six months post-injury can be calculated for each individual patient. The number of patients reporting chronic pain increases linearly with every additional prognostic factor. Patients who present at the ED with no or only one prognostic factor have a risk of 0% to 3% to develop chronic pain, patients with two prognostic factors have a risk of 6%, with three a risk of 17%, with four a risk 32% and patients with five prognostic factors have a risk of 50%. None of the patients had all six prognostic factors.

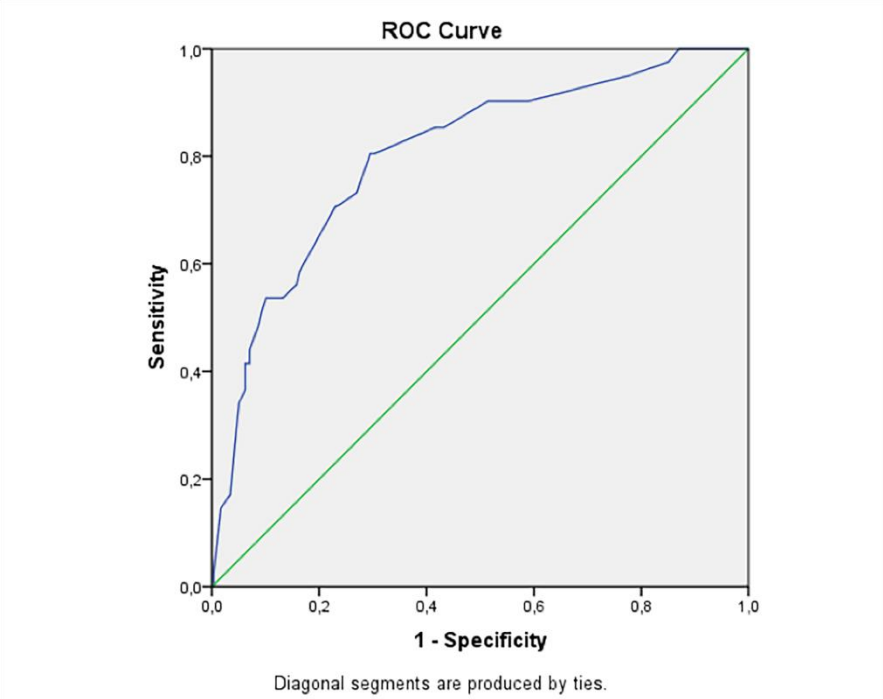

Figure 3: C-statistic (ROC area=0.80) of the final prediction model. Best trade-off for chronic pain prediction was with sensitivity 0.71 and specificity 0.77

DISCUSSION

In this prospective follow-up study ,43.9% of all 435 patients had some degree of pain and 10.1% had chronic pain six months after isolated musculoskeletal extremity injury. Patients aged over 40 years, in poor physical health and with chronic pain before injury, pain catastrophizing, (very) urgent urgency level and severe pain at discharge were more prone to develop chronic pain. Two prognostic factors, severe pain at discharge and pain catastrophizing, are potentially modifiable in the ED or within the first few days after discharge. Although the others factors are not modifiable, these can still be used to identify high-risk patients, which may have implications for patient information and the perspective of medical treatment and health care provision.

The question arises as to whether the potentially modifiable prognostic factors can contribute to a better clinical outcome and how. The PROTACT-study shows that patients with severe pain at ED discharge have an almost two times higher risk of developing chronic pain as patients who were not. Severe acute pain has already shown to be one of the most

consistent prognostic factors in developing chronic pain after surgery (39). Moreover, there is strong evidence that high pain intensity at discharge or early post-injury is associated with chronic pain (5). One of the theories postulated for this progression from severe acute to chronic pain is central sensitization, whereby the nociceptive neurons increase their response to non-painful stimuli and develop spontaneous activity (40).

One of the primary goals in the ED is the prompt, effective alleviation of pain. Acute pain relief is important for humanitarian reasons. Perhaps of equal, or arguably more importance, adequate and effective pain treatment may reduce or even terminate the progression from acute to chronic pain. The inadequate and ineffective pain treatment within the ED is a well-documented problem worldwide (41). The introduction of a pain protocol may improve pain management in the ED and decrease the percentage (44%) of patients discharged with severe pain. Studies have reported that such protocols improve the amount of and shortens the time to analgesic provision (42, 43).
Another potentially modifiable prognostic factor is pain catastrophizing, which is characterized by the tendency to magnify the threat value of a pain stimulus - to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of a painful experience (44). Pain catastrophizing has been associated with a number of important pain-related outcomes, including chronic pain (45, 46). The PROTACT-study confirms that patients who catastrophize their pain are three times more prone to develop chronic pain than patients who do not. Given pain catastrophizing is associated with different pain-related outcomes, as well as with neural, physiological, cognitive, affective and interpersonal factors associated with pain and suffering, it follows that a decrease of pain catastrophizing behaviour might reduce the development of chronic pain. Cognitive–behavioural techniques involving reducing catastrophizing and enhancing adaptive pain-coping skills are nowadays a core component of multidisciplinary pain treatment especially in chronic pain patients (44). These techniques might be useful to prevent progression from acute to chronic pain.

Other prognostic factors found in the PROTACT-study are older age, poor physical health, chronic pain before injury and a higher urgency level. These prognostic factors are not entirely consistent with the results of a recent systematic review on prognostic factors for chronic pain after orthopaedic trauma where patients who were older, women, or those who reported anxiety or depression before injury or severe pain in the acute post-injury period, were identified as more likely to develop chronic pain. High-educated persons had a reduced risk (15). Poor physical health, which the PROTACT-study identified as a prognostic factor, was earlier identified as a prognostic factor (17, 47). The same is true for having pre-existing chronic pain before injury (5, 13). In the PROTACT-study patients with pre-existing chronic pain were four times more likely to develop chronic pain at their injured body part. Moreover,

in 87.5% of these patients, the body part affected by pre-existing chronic pain was different from the affected body part at six months post-injury. A higher urgency level, indicative of a more severe injury, was a prognostic factor which is in agreement with a study of chronic pain after neck injuries (47).

Although many studies conclude that women are at higher risk of developing chronic pain (15, 48, 49), in the PROTACT-study this effect disappeared after using other factors in the model. Despite the fact that many psychological factors such as anxiety, depression (15, 17, 50) and kinesiophobia (51, 52) have been associated with developing chronic pain, the PROTACT-study only found pain catastrophizing to be associated with chronic pain in a model with other factors. Explanation for this might be that pain catastrophizing shares significant variance with these other negative affect-related constructs of pain (53).

Chronic pain after injury has received considerable attention the last decade yet there is no agreement regarding the definition or measurement. This explains some of the variation in incidence of chronic pain between studies. In our population almost 44% of the patients had some degree of pain six months post-injury, but only 1 out of 10 patients developed chronic pain defined as having a pain score of NRS≥4. This incidence of chronic musculoskeletal pain post-injury is lower than found in other studies, which ranges from 11 to 56%, and depends on specific diagnostic injury and time of assessing (11-14). Furthermore, differences in incidence between studies might be explained by in- or excluding polytrauma patients. An Australian study shows differences in pain outcomes between patients with isolated orthopaedic injury, patients with multiple orthopaedic injuries (without other injuries) and patients with single/multiple orthopaedic injuries and other injuries. The incidence of chronic pain in the latter was almost 1.5 times higher than the 32.5% found in patients with isolated injury (14). This suggests that studies which included polytrauma patients might overestimate the incidence of chronic musculoskelal pain.

The strength of the PROTACT-study is the application of a comprehensive set of potential prognostic factors in a prospective cohort design in a relatively large population of patients with isolated musculoskeletal injuries. Pain intensity was measured at different time points. Since there is no definition of chronic pain that distinguished it mechanically from acute pain than only by time course, knowledge in pain intensity pattern over time in the period post-injury is useful in order to determine if the pain intensity score at 6 months follow-up was really persistent pain. While pain intensity, quality of life, depression and anxiety were measured repeatedly, the analysis focused on the prognostic factors in pre-injury and acute pain phase, since this is the time period in which there is contact between patient and caregiver and modifiable prognostic factors can be intervened. Because some pre-injury factors are collected after injury, even though patients were asked to think of these in the

period before injury, one should be aware that these factors might be contaminated by the state of the patient after injury. The six prognostic factors in the PROTACT-study are able to predict one-fifth of the pain intensity at six months post-injury. Although many potential prognostic factors including sociodemographic characteristics, pain, clinical, injury- or treatment-related, and psychological factors were taken into account, other potential relevant prognostic factors, such as genetic predisposition and environmental factors were beyond the scope of present study.

Despite the fact all patients received reminders and were called by telephone, the PROTACT-study has a lost-to-follow-up of 45.8%. By calling non-responders, reasons for non-participation were collected from 235 out of the 368 non-responders (63.9%) and the primary outcome, the pain score at six months post-injury, was collected from 129 patients (35.1%). Most frequent reasons for non-participation were lack of time (30 %), received no questionnaire (22%), and not interested anymore (10%). It is unlikely that this influenced our results, as these are not associated with chronic pain. Of the non-responders 42.6% had some degree of pain (NRS≥1) six months post-injury comparable to 43.9% of all 435 included patients. Furthermore, 17.8% of the non-responders had chronic pain (NRS≥4), somewhat higher than the percentage of 10.1% in the included patients. This percentage in non-responders could be an overestimation as these patients may not have had persistent pain throughout six months, which is a criterion for the definition of chronic pain in the included patients. However, the incidence of chronic pain in the PROTACT-study might be underestimated, because age of the non-responders was slightly higher and age is a risk factor for chronic pain. It has to be noted that all our prognostic factors had a wide range of values, e.g. from young to old patients, men and women, standard to very urgent, in other words a variety in patients was included and thus enough information was available to assess prediction models.

In the present study we used internal validation to obtain more conservative estimates of the prognostic factors. Internal validation is helpful, but it cannot provide information about the model's performance elsewhere. Future research should continue to address the issue of generalizability of the prediction of chronic pain after isolated musculoskeletal injury by including larger samples of patients which makes external validation possible. Moreover, the present study focused only on the incidence and prognostic factors of chronic pain. The assessment of the consequences of chronic pain on physical and social function and healthcare utilization are relevant to determine the burden of chronic pain after musculoskeletal injury. With the global increase in health care costs, the costs of preventive interventions for chronic pain need to be carefully considered.

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Chapter 4

Short- and long-term health-related quality of life outcomes after isolated musculoskeletal extremity injury

This chapter has been submitted as:

Pierik J.G.J., Doggen C.J.M, Vollenbroek-Hutten M.M.R, Gaakeer MI, van Vugt A.B. and IJzerman M.J. Short- and long-term health-related quality of life outcomes after isolated musculoskelatal extremity injury.

ABSTRACT

BACKGROUND Physical disability and mental morbidity, whether or not in combination with developing chronic pain, are frequent and important complications of extremity injury posing sometimes serious consequences for the patient resulting in an impaired health-related quality of life (HRQoL). This study aims to investigate the impact of extremity injury on HRQoL during the first six months after extremity injury and the health impact of developing chronic pain.

METHODS A total of 390 adult patients with extremity injury admitted to an emergency department were studied. HRQoL (8 health dimensions, summary scores, and single index utility scores) was measured using the Short Form (SF)-36 Health Survey at 6 weeks, 3, and 6 months post-injury. When pain was still present at 6 months, also at 12 months post-injury. Pre-injury scores were measured at admission.

RESULTS In general, HRQoL dimensions changed over time in all dimensions, except general health. The highest decrease was seen immediately after injury in role limitation due to patient's physical functioning. Overall health status of patients at 6 months post-injury was lower than before injury; there was a significant decrease in physical health state dimensions vitality, bodily pain, physical functioning and role functioning physical. The impact of injury on HRQoL is the highest in patients with lower proximal injuries, both in acute phase and at 6 months. Distal injuries recover faster than proximal injuries. The mean single index measure of health in patients who developed chronic was both significant and clinical relevant lower than at pre-injury state and in comparison with the other 'healthy' patients. The physical health state was most affected.

CONCLUSIONS Patient's HRQoL is affected after extremity injury. The consequences of injury are present both in short- and long-term. In general, injury is affecting mostly the physical functioning, not the mental state in the first six months post-injury. The consequences of injury on HRQoL are the highest for patients with lower proximal injuries. The health impact of developing chronic pain following extremity injury is substantial; it causes impaired quality of life. Prevention of chronic pain is important.

BACKGROUND

Pain and musculoskeletal extremity injury are inevitably interrelated to each other. Acute pain following extremity injury is a frequent chief complaint of patients requiring emergency medical care (1-4), and a significant contributor to disability many months, or years after injury. Acute musculoskeletal pain may have many consequences including medical, psychosocial and economic problems. Risks include sequelae, disability and functional limitations, developing chronic pain, loss of independence, impaired health-related quality of life (HRQoL), substantial use of health services and large production losses (5-9).
Clinicians, but also policy makers, may not necessarily be aware of recovery patterns or residual impairment that may affect component of patient's quality of life because routine follow-up after injury treatment does not always occur. More information about the health status of injured patients increases the understanding of disability and impairment and might help clinicians to advice patients about likely recovery patterns.

Most follow-up studies who investigate disease burden on levels of functioning and disability after injury are performed in a broadly defined population of serious trauma patients (5, 10) or in patients with a specific serious injury (11-13). However, minor injuries which are highly prevalent and contribute also to this burden. The assumption has been made that patients with minor injuries generally make a good functionally recovery. However, a number of studies have suggested that a proportion of patients with minor musculoskeletal injuries continue to have functional problems, either physical, emotional or psychosocial in nature, long after normal healing time (14). This is not only seen in patients with fractures; the prevalence of residual problems for non-fracture injuries, like dislocation, sprains and strains, seems surprisingly as high as for fractures, at least in the lower extremities (15).
Not only the functional limitations after injury are substantial, in many patients pain persist. The incidence of chronic musculoskeletal pain after extremity injury is sizable; it varies from 10 to 56%, depending on the specific diagnosis of injury and time of assessing (6, 16-19). Chronic pain significantly affects patient's physical and mental health (8) and can delay functional recovery after injury (16, 20).
In addition to functional outcome parameters, HRQoL has become more important when it comes to evaluating outcome following injury and disease burden. HRQoL is increasingly being used to measure outcomes of the impact of injury on health from the patient's perspective. HRQoL seems to be substantially reduced after upper extremity injury, both in short- and long-term (9). There is a considerable variation in recovery of HRQoL in between patients and within injury types (15).

Extremity injury seems to be a serious problem maker; trauma patients with extremity injuries have more impairment of health-related quality of life than those without extremity

injury (21). Little is known about HRQoL pathways to recovery after isolated extremity injury or the lack of recovery, especially in combination with developing chronic pain, preventing a general understanding of HRQoL experienced in patients after injury.

The purpose of this study is to detect changes in patient's HRQoL over time caused by isolated extremity injury, - from pre-injury state to full recovery or to chronic pain or related disabilities to determine the impact of extremity injury on health. This will give insight into which dimensions of HRQoL are most affected. The health state of patients with different types of injury will be compared. Finally, health state of patients who will fully recover and who will develop chronic pain will be compared to determine the health impact of developing chronic pain following extremity injury. This will provide better reference about patient's health status for clinicians and policy makers over the period after routine follow-up managed care and the importance of prevention the transition from acute to chronic pain.

PATIENTS AND METHODS

Study design and study population

This study is part of a one-year prospective follow-up study; "PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients" (PROTACT). The study has obtained ethics approval from the regional Medical Research Ethics Committee on Research Involving Human Subjects (CCMO no. NL368.38044.11). Adult patients with isolated musculoskeletal extremity injury presenting at the emergency department (ED) of the level one trauma centre Medisch Spectrum Twente in Enschede, The Netherlands were invited to participate. The ED has a 24 hours a day, 7 days a week (24/7 ED) service. The ED is accessible for 264,000 individuals from the region and treats approximately 27,000 patients annually.

Eligible patients aged between 18 and 70 years were consecutively recruited when admitted to the ED between September 2011 and July 2013. Inclusion criteria for participation were (i) musculoskeletal isolated extremity injury caused by blunt trauma; (ii) sufficient communication skills and basic knowledge of the Dutch language. Exclusion criteria were (i) life or limb threatening conditions; (ii) documented cognitive disability; (iii) suffering from hallucinations, delusions or suicidal ideation and (iv) alcohol or drugs intoxication. During the 22 months inclusion period, 1994 adult patients with musculoskeletal extremity injury attended the ED and met the study criteria. Of these patients, 803 participants provided written informed consent. For the purpose of the current study all patients who were followed until 6 months post-injury and completed the health-related quality of life questionnaires in this follow-up period were included.

Procedures and data management

During ED admission, patients who met the study criteria were informed by the nurse about the purpose of the study. Participants were asked to provide informed consent and to

complete a questionnaire. Six weeks, 3 months and 6 months after the initial ED visit, patients received a follow-up questionnaire by email or by mail, according to their stated preference. Patients who had pain on injury site at 6 months post-injury, also received a questionnaire at 12 months follow-up.

The questionnaires included a validated tool to measure pain intensity, HRQoL, anxiety and depression as well as questions about injury-related and sociodemographic information like education level. Additionally, data from the ED electronic patient registration system were used. The registry is a fully electronic emergency medical record registry where each entry, order, or activity is automatically time-stamped for pre–specified ED events. The registry includes patient demographics (date of birth, sex), triage urgency level and medical diagnoses (e.g. injury type).

Measures and definitions

Health-related quality of life (HRQoL)

HRQoL was measured by using the validated Dutch-language version of the 36-Item Short-Form Health Survey (SF-36, Corporation, Santa Monica, California USA) (22). The SF-36 is a general quality of life questionnaire with a 4-week recall period and assesses eight domains: physical functioning; social functioning; role limitations due to physical problems; role limitations due to emotional problems; pain; mental health; vitality, and general health perception (23). For each domain, item scores were coded, summed, and transformed into a scale ranging from 0 to 100, where 100 was the highest best possible rating. Algorithms were used to produce scale scores for each domain; Physical Component Summary (PCS) scores for physical health status and Mental Component Summary (MCS) scores for mental health status. This is possible even when some data are missing (24). The SF-36 was measured at ED-admission (pre-injury state), 6 weeks, 3, 6 months and if patient's pain persisted also at 12 months.

Preference-based single index measure of health

The SF-36 was revised into a six-dimensional health state classification called the SF-6D. The six dimensions are physical functioning, role limitations, social functioning, pain, mental health and vitality. These six dimensions each have between two and six levels. An SF-6D "health state" is defined by selecting one level from each dimension. A total of 18,000 health states are defined. All responders to the original SF-36 questionnaire can be assigned a SF-6D score provided the 11 items used in the six dimensions of the SF-6D have been completed. The SF-6D preference-based measure can be regarded as a continuous outcome scored on a 0.29 to 1.00 scale, with 0.29 indicating 'worst possible health state' and 1.00 'best possible health state'(25).

Pain intensity in ED

Pain intensity at ED admission and ED discharge were measured using Numerical Rating Scales (NRS). Patients were asked to fill in a number from 0 to 10, where 0 is "no pain" and 10 "the worst pain imaginable". The NRS was validated for use in the ED (26) and retrospective one-week recall of pain intensity seems to be reliable and valid (27).

Pain intensity and experience during follow-up and chronic pain

Pain experience at 6 weeks, 3 and 6 months follow-up was measured using the Brief Pain Inventory (BPI) (28). The BPI is a self-reporting instrument to assess the multidimensional nature of pain, including pain intensity and pain interference on life activities. BPI has a good reliability and validity for assessing pain intensity in patients with chronic non-malignant pain (29). Chronic pain was defined as pain six months post-injury based on the BPI question "rate your average pain last week" using the NRS related to their injury, where 0 is "no pain" and 10 "the worst pain imaginable". The cut-off score for chronic pain was set at NRS≥ 4 (30). In addition, the pain intensity pattern over time in the post-injury period of each patient with a NRS≥ 4 was observed in order to determine if the pain was persistent after injury. If pain was not present during the whole period (NRS>1 at 6 weeks, 3 months), patients were indicated as not having chronic pain (31).

Anxiety and depression

Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS). The Dutch version was validated and was found to have good psychometric properties (31). The HADS is a screening tool used in a wide variety of clinical groups, such as emergency care patients (32) and chronic musculoskeletal patients (33). Patients were asked to recall a 7-days period about 14 items on a 4-point Likert scale; anxiety and depression sum scores were calculated (range 0–21), with a high score indicating a high level of anxiety or depression. The HADS was measured at ED-admission (pre-injury state), 3 and 6 months and if patient's pain persisted also at 12 months.

Data analysis

For descriptive purposes, categorical data were characterized in terms of frequency (%), whereas continuous data were characterized as median with interquartile range (IQR, 25^{th} - 75^{th} percentile) or as mean ± standard deviation (SD). Preliminary analyses determined whether HRQoL scores were skewed or contained outliers.

Paired t-test was used to detect differences in HRQoL scores between pre-injury state and 6 weeks (acute phase) or 3 till 6 months post-injury (sub-acute phase) or 6 till 12 months post-injury (chronic phase).

Multivariate ANOVA (GLM) for repeated measures was used to investigate differences in HRQoL scores over time with a one within-subjects factor design with the eight health domains as the within-subject variables. To assess changes in the patients' HRQoL dimension over time, repeated measures analyses of variance (MANOVAs) with the pre-injury and the follow-up HRQoL scores as dependent variables. Additionally, we examined group differences over time in post-injury HRQoL. In these analyses the follow-up HRQoL scores were entered as dependent variables and the pre-injury HRQoL scores were included as a covariate (repeated-measures MANCOVAs). The between-subject factors concerned chronic pain and injury type. All data analyses were performed with SPSS version 21.0 (IBM Corporation, Armonk, NY).

RESULTS

Patients' characteristics

Between September 2011 and July 2013, 803 adult patients with musculoskeletal extremity injury provided written informed consent. Data on a total of 390 patients, who completed HRQoL questionnaire in baseline, at 6 weeks, 3 and 6 months, were used for analysis. Median age of these patients was 50 years (IQR 37-60) and 62.1% were women (Table 1). The majority of 390 patients suffered a fracture (76.4%). Of the patients, most had distal injuries; 33.6% had distal injuries of the lower extremities and 28.5% had distal injuries of the upper extremities.

Table 1: Characteristics of 390 patients with musculoskeletal extremity injury

	N	(%)
Sociodemographics		
Sex		
Women	242	(62.1%)
Age (in years), median (IQR)	50.0 (37.0-60.0)	
Education level		
High	131	(33.8%)
Middle	202	(52.1%)
Low	55	(14.1%)
Pain intensity at ED admission, mean (SD)	6.6	(2.3)
Type of injury		
Fracture	298	(76.4%)
Dislocation	20	(5.1%)
Sprains and strains	40	(10.3%)
Contusion	22	(5.6%)
Muscle rupture	10	(2.6%)
Site of injury		
Upper extremity injury		
Proximal injuries	83	(21.3%)
Distal injuries	111	(28.5%)
Lower extremity injury		
Proximal injuries	65	(16.7%)
Distal injuries	131	(33.6%)

Health-related Quality of Life after injury

The repeated-measures MANOVAs that were applied to investigate changes in HRQoL dimensions over time revealed significant time effects for 7 of the 8 dimensions, except for the general health dimension. The mean values measured at baseline, 6 weeks, 3 and 6 months of all dimension scales are shown figure 1 and table 2. Time effect was the highest in physical functioning dimension with a significant main effect of time [$F(2.57) = 256.5$, $p < 0.01$, partial $\eta^2 = 0.40$]. This partial Eta squared is the variance in outcome which can be explained by the time effect. For the physical functioning the explained variance is 40%.

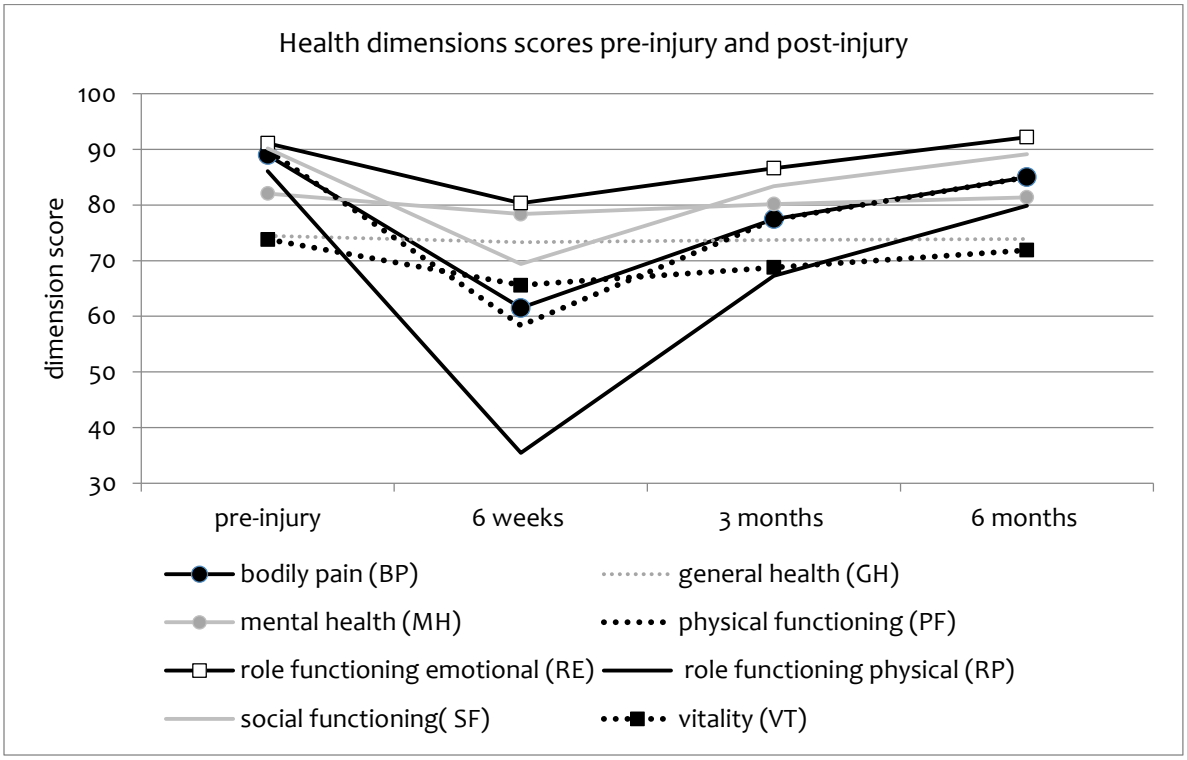

Figure 1: Health dimensions scores measured with SF-36 at several time points

The effect of injury, the difference between 6 weeks score and pre-injury state, was present in almost all dimensions, except for general health ($p=0.07$). All scores decreased. The highest effect of injury in this acute phase was seen in the role limitations due to physical functioning; the mean decrease between pre-injury state and 6 weeks post-injury was 50.7 (SD=46.7) from 86.1 to 35.4 ($p<0.01$). At 6 months post-injury, there was compared with pre-injury state, still a significant decrease in the dimensions vitality, bodily pain, physical functioning and role functioning physical (Table 2).

After aggregating the scores from the 8 dimensions in two distinct higher-order summary scores: Physical Component Summary (PCS) and Mental Component Summary (MCS), it is shown that only the physical component is significant changing over time ($F(2.64) = 295.9$, $p<0.01$, partial $\eta^2 = 0.43$). The mental component is not changing over time ($F(2.78) = 0.68$,

p=0.56, partial η^2 <0.01) (Table 2). The mean physical component score of all patients decreased from 53.4 points at pre-injury to 39.9 in the first 6 weeks after injury, but returns after this period slowly back to pre-injury state. At 6 months post-injury the physical score is 51.4, which was significantly lower than pre-injury state level (p<0.01).

Table 2: HRQoL after injury in 390 patients

	pre-injury		6 weeks		3 months		6 months		P time	partialη^2
	mean	SD	mean	SD	mean	SD	mean	SD		
Bodily pain (BP)	89.0	19.2	61.5	23.5	77.5	20.8	85.0	19.0	<0.01	0.38
General health (GH)	74.5	19.5	73.3	19.2	73.7	19.7	73.9	19.7	0.43	<0.01
Mental health (MH)	82.1	14.4	78.4	15.3	80.2	15.0	81.4	14.5	<0.01	0.03
Physical functioning (PF)	89.9	18.6	58.3	29.5	77.3	24.6	85.0	20.3	<0.01	0.40
Role functioning emotional (RE)	91.1	25.7	80.4	36.5	86.6	32.1	92.2	23.1	<0.01	0.05
Role functioning physical (RP)	86.1	31.8	35.4	41.4	67.3	43.2	79.9	35.9	<0.01	0.36
Social functioning (SF)	90.2	17.3	69.4	29.2	83.4	22.1	89.1	18.6	<0.01	0.25
Vitality (VT)	73.8	16.7	65.6	18.7	68.8	17.5	71.9	16.7	<0.01	0.09
Physical Component (PCS)	53.4	8.4	39.9	10.7	48.1	10.6	51.4	9.3	<0.01	0.43
Mental Component (MCS)	52.4	8.5	52.5	10.2	52.2	9.2	52.8	8.3	0.56	<0.01
Single index measure of health	0.83	0.12	0.67	0.13	0.77	0.13	0.81	0.12	<0.01	0.40

The single index of health state of 390 patients changes over time (F (2.61) =249.0 p<0.01, partial η^2 =0.40); it decreased from a mean score of 0.83 at pre-injury stateto 0.67 in the first six weeks after injury. At 6 months post-injury it increased to 0.81. This score was significantly lower than during pre-injury state (p=0.02).

Differences in recovery pattern

To examine whether reduced scores in physical or mental component of HRQoL could be observed for specific groups of patients, repeated-measures MANCOVAs were performed with the pre-injury state scores as covariate.

Injury site

For the physical component a significant difference over time F(5.45)=3.01, p<0.01, partial η^2=0.023) between the groups with different sites of injury was seen. In post-injury period till 3 months, there was no difference in recovery between the injury groups (p=0.86), but between 3 and 6 months a difference was observed (p<0.01). Distal injuries, of both upper and lower extremities, recovering faster than proximal injuries. Notably is the physical function in patients with proximal injuries of the lower extremities which is significantly lower

in both acute as well as at 6 months post-injury compared to the other injuries. For the mental component summary no significant differences over time were found between injury groups (F (5.54=0.33, p=0.91, partial η^2=0.003) (figure 2A).

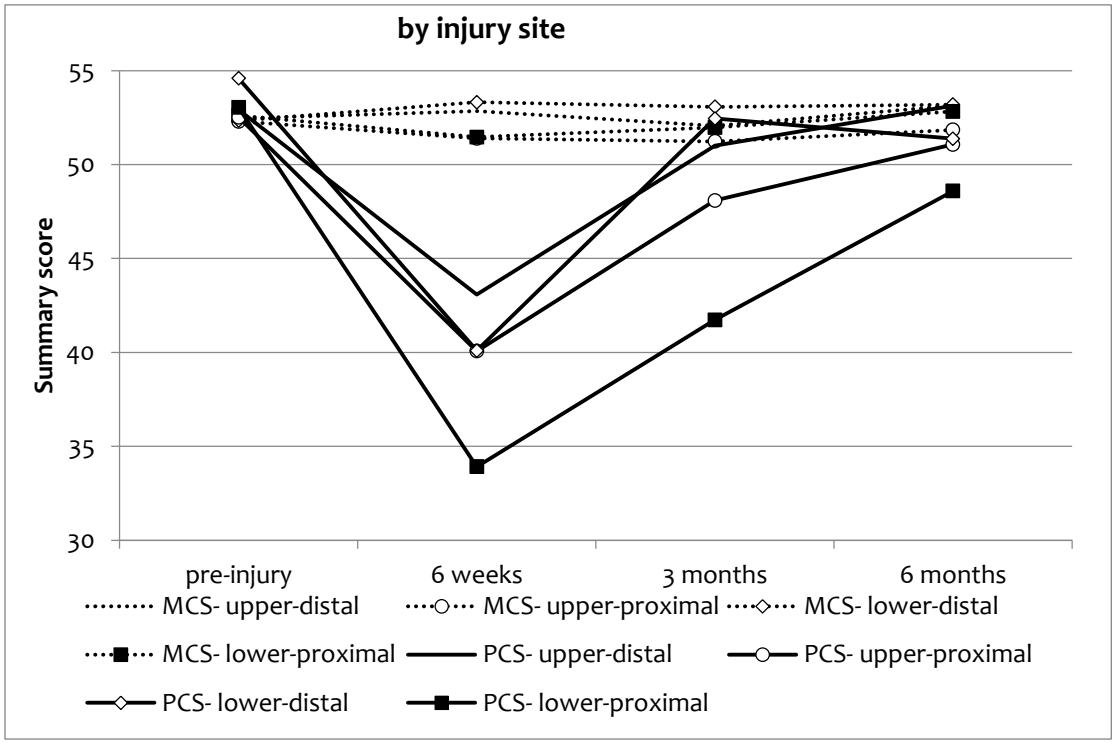

Figure 2A: Mental and Physical summary scores by injury site measured SF-36 at several time points

Chronic pain

Of the 390 patients, 43 developed chronic pain. Pre-injury physical health state of patients who developed chronic pain was lower than in those patients who did not (p<0.01). Pre-injury mental health was comparable between both groups (p=0.47).

The mean single index measure of health, with 0.29 indicating 'worst possible health state' and 1.00 'best possible health state' was at pre-injury state in the group of patients who developed chronic pain little lower than in the other patients; 0.78 vs. 0.83. (Table 3). In the patients who developed chronic pain health scores decreased during injury like in the other patient group, but after 6 or 12 months the health state was still significant lower than before injury (p<0.01). Also the mean single index score of health at 6 months post-injury is in patients with chronic pain significantly lower than in the other patients; 0.83 vs 0.65. Between 6 and 12 months there was a small improvement from 0.65 to 0.70 in health score of the chronic pain patients (Table 3). For the physical component of health a significant difference over time F(1.85)=305.4, p<0.01, partial η^2=0.019) was found between patients who developed chronic pain and those who did not. This time effect was seen in the first 3 months, recovery pattern over time between 3 and 6 months were comparable (p=0.22). Notable is that the scores of chronic patients are lower during the whole post-injury period.

The mean score at 6 months post-injury was significantly lower in chronic pain patients, 38.9 vs. 52.9 ($p<0.01$) (figure 2B). For the mental component of health there was a difference between patients who developed chronic pain and those who did not at 6 months-post injury ($p=0.04$), but no significant difference over time $F(1.85)= 56.9$, $p=0.26$, partial $\eta^2 =<0.01$) was found (figure 2B). A sub-analyse with anxiety and depression scores in chronic patients showed also no significant change over time, but both scales showed substantial increase in score in the subacute phase till 3 months post-injury, but decreased afterwards. Mean anxiety score at 6 months post-injury was higher than at pre-injury ($p<0.01$), for depression the score was somewhat higher ($p=0.30$). During the 6 and 12 months post-injury period the both scores nearly changed.

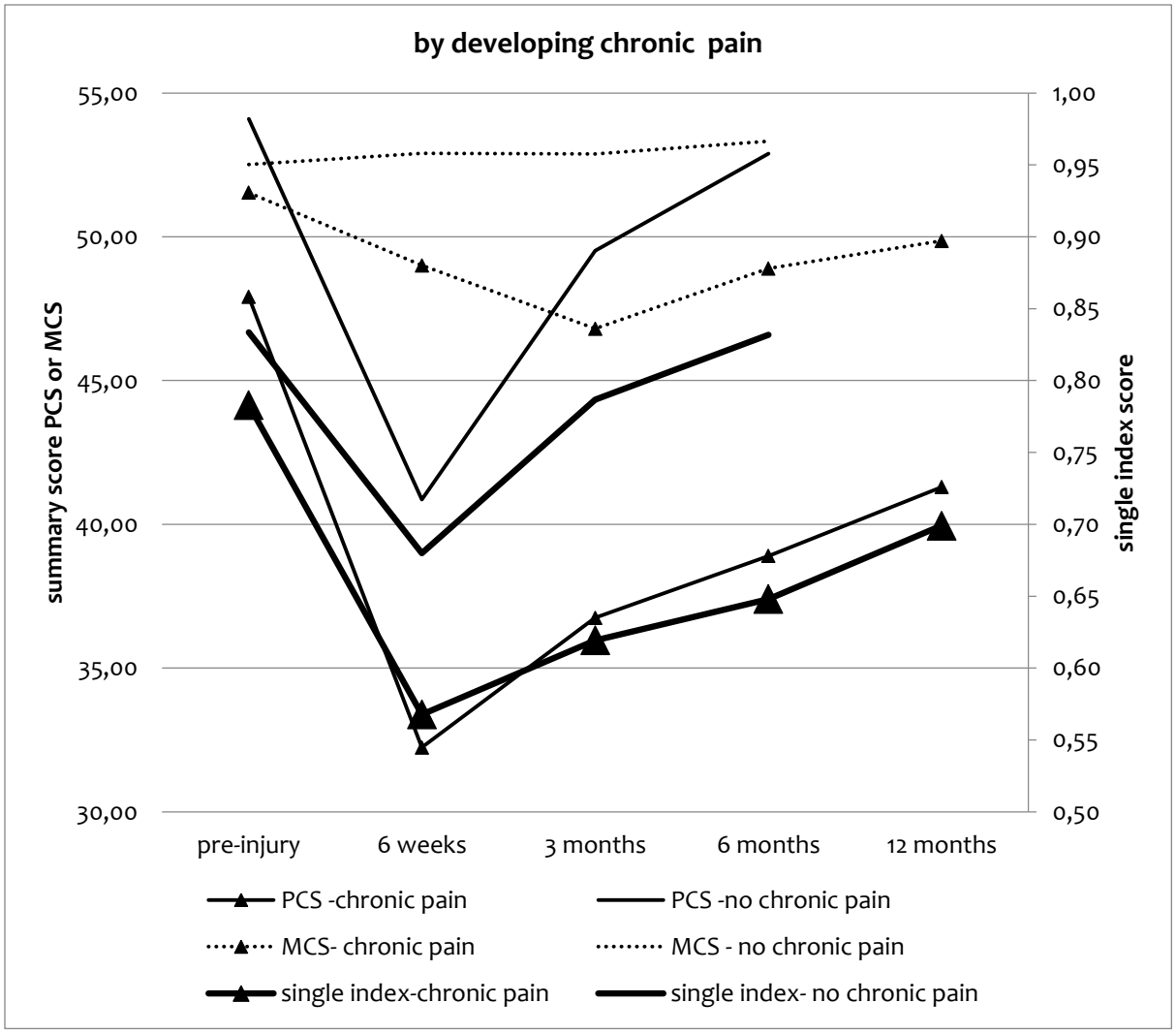

Figure 2B: Mental and Physical component summary score measured SF-36 and the single index of health state at several time points in patients who developed chronic pain at 6-months follow-up vs. those who did not. For patients who developed chronic pain the scores at 12 months were included.

Table 3: HRQoL after injury in patient who developed chronic pain vs. no chronic pain.

	pre-injury	6 weeks	3 months	6 months	12 months
Chronic pain					
Physical Component Summary (PCS)	47.9	32.2	36.8	38.9	41.3
Mental Component Summary (MCS)	51.5	49.0	46.8	48.9	49.9
Single index measure of health state	0.78	0.57	0.62	0.65	0.70
No Chronic pain					
Physical Component Summary (PCS)	54.1	40.9	49.5	52.9	
Mental Component Summary (MCS)	52.5	52.9	52.9	53.3	
Single index measure of health state	0.83	0.68	0.79	0.83	

DISCUSSION

The primary aim of this study was to detect changes in patient's HRQoL over time caused by isolated extremity injury - from pre-injury state to full recovery or to chronic pain or related disabilities- to determine the impact of extremity injury. This gives insight into which dimensions of HRQoL are most affected by injury and pain.

There is ample evidence that injuries are painful and cause significant interruption to quality of life in the early post-injury phase. Changes in HRQoL dimensions over time after extremity injury revealed significant time effects for 7 of the 8 dimensions, except for general health which is recalled over the last year. The highest effect of injury in the acute phase was seen in the role limitations due to physical functioning.

At 6 months post-injury, there was a significant decrease in the dimensions vitality, bodily pain, physical functioning and role functioning physical compared to pre-injury state. These four dimensions were aggregated as part of the physical component summary, which is changing over time. The mental component is not changing over time. However, the mean health state of the 390 patients at 6 months post-injury is somewhat lower than at pre-injury state.

In addressing pain and physical disability outcomes, assessment of a minimal clinically important difference is an important aspect in verifying the clinical relevance of the results. In this study, there were significant physical impairments in the early post-injury phase, but also significant improvements between 3 months and 6 months assessment in physical health. However, it seems unlikely that these differences in functioning would be clinically relevant to all patients on the long-term. The threshold values for a clinical relevant difference for physical component of health vary between 3.2 and 6.1 points (34). The mean of the physical score of all 390 patients is at 6 months post-injury only two points lower than pre-injury state, so it is interesting to find out which specific patients have clinical relevant impairments.

Injury type

The consequences on HRQoL are the most important for patients with lower proximal injuries, both in the early post-injury phase and at 6 months. The impact of injury between different injury types was only seen on the physical component of health. The results are in line with earlier findings that lower extremity injuries had the highest impact on HRQoL. This study found that patients with upper extremity injuries made larger improvements in the first 3 months post-injury versus patients with lower extremities whose improvements extended over the first 6 months (35).

In the PROTACT-study a distinction between distal and proximal injuries was made. Distal injuries of both upper and lower extremities recover faster than proximal injuries. This was seen before in patients with upper extremity injuries (9). In the PROTACT-study patients with distal extremity injury improved during the first 3 months and nearly reached their pre-injury health state within this period. This is in line with a study of HRQoL in which most patients with upper extremity injuries who were not hospitalized recovered within two months after injury (5). In this PROTACT-study no distinction was made between hospitalized and non-hospitalized patients. It seems that for upper extremity injury non-hospitalized patients had substantial loss of HRQoL at 2.5 months which improved by 9 months post-injury to the same level as the general population norms. Nevertheless, hospitalized patients remained far below the general population norms, even after two years of follow-up (9).

Consequences of developing chronic pain

The assessment of the consequences of chronic pain on HRQoL, the physical and mental function, are relevant to determine the disease burden after extremity injury. In total 43 of the 390 patients developed chronic pain 6 months post-injury. The PROTACT-study already revealed that pain intensity and pain interference with daily activities at six months post-injury were highly correlated (6), which suggested the presence of pain has also an effect on patient's HRQoL. Time effects of the physical recovery between patients who developed chronic pain and those who did not were only seen in the first 3 months. Remarkably, the physical health state of patients who developed chronic pain were lower both during the pre-injury as well as during post-injury period in comparison with patients in whom pain did not persist. Poor physical health at pre-injury was already found to be one of the six risk factors for developing chronic pain in this study population (6).

Pain is the most common physical symptom-based condition and anxiety and depression are the most common psychological conditions reported in the general population (36) (37). Additionally, pain, anxiety and depression frequently co-occur and have both additive and adverse effects on HRQoL and functional limitations (38). Surprisingly, in this study no time effect on the mental component during the first 6 months post-injury was found. At 6 months post-injury the anxiety levels in chronic pain patients were higher, but depression levels were not. Nearly half of the patients with chronic musculoskeletal pain in primary care

had anxiety symptoms, which in turn were adversely associated with impairment across multiple domains of HRQoL (39), which may suggest follow-up time till twelve months is too early to evaluate final outcomes on the impact of mental health. The results of a two-year cohort study of lower extremity trauma patients on longitudinal relationships between anxiety, depression, and pain suggest that in the early phase after injury pain predicts anxiety and depression, but the magnitude of these relationships are smaller than the longitudinal relationship from anxiety to pain over this period. Pain intensity weakly predicted depression symptoms during the first year after injury, but did not predict depression symptoms beyond a year (40).

In patients who developed chronic pain, both mental and physical components scores were decreased at 6 and 12 months post-injury related to pre-injury state, suggesting a considerable loss in HRQoL by developing chronic pain. The single index of health (utility score), a score that can contribute to a composite health outcome measure, is decreased with 0.135 points in comparison with pre-injury state to 0.65 at 6 months follow-up and 0.085 points to 0.70 at one year follow-up. This difference is higher than the minimum important difference for the utility score measured SF-6D, which is 0.041 (41). The utility score decreased with at least two times the minimally important difference; a change in outcome that a patient would identify as important. Moreover, the utility score at six month of 0.65 found in patients who developed chronic pain is substantially lower than in the rest of the study population (0.83). These patients will regain their pre-injury level of function. One reason that indicates prevention of chronic pain is necessary.

It is known chronic pain significantly affects both patients' physical and mental functioning (8) and can delay functional recovery after injury (16, 20). The impact of chronic pain can be major. One study showed an impressive finding that non-cancer patients with long-lasting pain admitted at a multidisciplinary pain centre reported even worse HRQoL than dying cancer patients (42).

The term HRQoL has been developed to describe aspects of an individual's subjective experience that relate both directly and indirectly to health, disease, disability and impairment. In this study HRQoL was measured with a generic health status instrument. One limitation of a generic instrument like the SF-36 is the inability to translate the information into limitations in activities of daily living and the perceived effects on patient's quality of life (43). The terms quality of life and health status are often used interchangeably, assuming that a fully healthy life is identical to a high quality of life and vice versa. But patients with significant health impairments do not necessarily have a poor quality of life. In future studies, the perceived level of satisfaction is important to add to quality of life measurements in addition to the appraisal level of functioning measured with SF-36. In this study the impact of health-related factors might be overestimated or conversely, may seriously undervalue the

effect of non-medical subjects such as well-being, social contacts, which are actually also referring to the perceived health of the patients.

Despite best efforts, a number of study limitations were apparent. The results might be subject to response bias and recall bias, particularly in the reporting of pre-injury health. However, in a study considering other health status outcomes, persons' recalled pre-injury health status was (re-)attained when they also reported having recovered, suggesting reasonable recall of pre-injury states (44). Furthermore, both the mean physical and mental scores of all patients were before injury comparable with Dutch population norms (45, 46). Moreover, the non-responders of the PROTACT-study seem to be comparable with the studied population (6).

The strength of our study is the inclusion of a comprehensive population, with both patients who were hospitalized and who were not. Further, many injury outcome studies have focused on very specific injury types (e.g. traumatic brain injury or hip fracture) or causes (e.g., falls, road crashes), rather than all types of extremity injuries due to blunt trauma.

CONCLUSION

In general, substantial loss of HRQoL was observed in the acute phase measured within the first 6 weeks after injury, followed by improvements in the recovery after this period. High prevalences of health problems were found. Almost all dimensions of HRQoL were affected by injury, however only time effects were seen on physical health, not on mental health. However, the mean health state of 390 patients was 6 months post-injury significantly lower than pre-injury state. The impact on HRQoL is the highest for patients with lower proximal injuries, both in the early post-injury phase and at 6 months.

That pain plays a crucial role in our daily life is revealed by the impact of developing chronic pain on HRQoL. The impact of HRQoL is much higher in patients who developed chronic pain post-injury. Patients who developed chronic pain had a considerable loss both on physical and mental health state. This revealed the health impact of chronic pain following extremity injury. Pain treatments are, once chronic pain has been established, relatively ineffective. Therefore prevention of the transition from acute to chronic pain is important.

These findings contribute to the growing body of knowledge about the consequences of injury in order to provide better reference about patient's health status for clinicians and policy makers over the period after routine follow-up managed care, wherein the focus of attention is generally only on physical recovery.

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Chapter 5

A nurse-initiated pain protocol in the ED improves pain treatment in patients with acute musculoskeletal pain

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ABSTRACT

BACKGROUND While acute musculoskeletal pain is a frequent complaint, its management is often neglected. An implementation of a nurse-initiated pain protocol based on the algorithm of a Dutch pain management guideline in the Emergency Department might improve this.

METHODS A pre–post intervention study was performed as part of the prospective PROTACT follow-up study.

RESULTS During the pre- (15 months, n=504) and post-period (6 months, n=156) patients self-reported pain intensity and pain treatment were registered. Analgesic provision in patients with moderate to severe pain (NRS≥4) improved from 46.8% to 68.0%. Over 10 %of the patients refused analgesics, resulting into an actual analgesic administration increase from 36.3% to 46.1%. Median time to analgesic decreased from 10 to 7 min ($p<0.05$), whereas time to opioids decreased from 37 to 15 min ($p<0.01$). Mean pain relief significantly increased to 1.56 NRS-points; in patients who received analgesic treatment even up to 2.02 points.

CONCLUSION The protocol appeared to lead to an increase in analgesic administration, shorter time to analgesics and a higher clinically relevant pain relief. Despite improvements, suffering moderate to severe pain at ED discharge was still common. Protocol adherence needs to be studied in order to optimize pain management.

BACKGROUND

While acute musculoskeletal pain is a frequent complaint among patients in the Emergency Department (ED), its management is often neglected, placing patients at risk of oligoanalgesia.

During the past decade, there has been an explosion of research on both acute and chronic pain, with significant advances in understanding its etiology, assessment, and treatment. Improvements in pain assessment and management have combined to facilitate care improvements in the ED (1). However, inadequate pain management has still not been fully eliminated. Although pain is the most prevalent and chief complaint for visiting the ED (2-4), acute pain appears undertreated worldwide which is reflected by the high prevalence of moderate to severe pain at discharge and the low percentage of patients receiving analgesics. The proportion of adults receiving analgesics for painful conditions varies between 19% and 64% (2, 5-8). Moreover, the percentage of patients discharged with moderate to severe pain ranges from 52% to 74% (2, 4, 6).

Adequate pain management is important, not only from the perspective of good patient care and patient satisfaction, but also from a physiologic point of view. Adverse physiological effects can result from unrelieved acute pain, such as cardiovascular side-effects and negative effects on respiratory function (9, 10). Failure to relieve acute pain may also result in increasing anxiety, inability to sleep, demoralization, a feeling of helplessness, loss of control, and inability to think and interact with others, and therefore it is likely to result in longer rehabilitation, decreased productivity and diminished quality of life (11). The early and effective management of acute pain is obviously of critical importance in the short term, but also important in the long term: unrelieved pain is associated with the likelihood of developing chronic pain (12, 13)

Although the importance of timely pain management in the ED is acknowledged, it is also recognized that there are barriers to effective pain relief, such as inadequate inter- and multidisciplinary communication, workload and attitude problems, lack of patient input, knowledge deficits, and misconceptions on the need for effective pain management (14, 15). Different strategies to enhance pain management have been developed in response to inadequate pain relief, such as pain management protocols or clinical guidelines and staff educational interventions (16-22). Pain management protocols have been shown to be useful. Studies indicate that a pain protocol shortens the time to analgesic administration (18-21), improves the percentage of patients who received analgesics (16, 20), increases pain relief (16, 17) and shortens ED length of stay (LOS) (23). Despite these efforts to increase awareness of the importance of timely and adequate pain management, inadequately managed pain is still a persistent problem.

With the implementation of a nurse-initiated pain protocol, emergency nurses are allowed to administer analgesics, including opioids, according to a pre-defined protocol, without the patient being first assessed by an ED-physician. This is important because depending on the workload of the ED staff, there can be a considerable delay between the patient's presentation and being seen by an ED-physician, and even a longer time to analgesic administration (24). Timely analgesic administration is required because patients become increasingly more sensitive to painful stimuli if pain is uncontrolled for a longer period of time.

Musculoskeletal injuries are not only highly prevalent in ED, they are usually very painful (2, 25). Especially in patients presenting to the ED with minor acute musculoskeletal injuries, a nurse-initiated pain protocol might be useful to optimize pain treatment. These patients are usually triaged to a low (semi-urgent) triage category, which typically results in an extended waiting time for pain relief or even oligoanalgesia (26).

The aim of this pre–post intervention study is to evaluate the effect of implementation of a nurse-initiated pain protocol based on the Dutch evidence-based guideline regarding analgesic provision, actual administration, time to first analgesic or opioid, ED LOS, and patient satisfaction in patients with acute musculoskeletal pain. Second, effectiveness of pain management will be determined in terms of clinically relevant pain relief. Finally, protocol deviation will be assessed.

PATIENTS AND METHODS

Study design and setting

A pre–post intervention study was performed as part of the prospective "PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients" (PROTACT) follow-up study. Adult patients with musculoskeletal isolated extremity injury attending the ED of the level one trauma center Medisch Spectrum Twente in Enschede, The Netherlands, were invited to participate. The ED functions continuously 24 hours a day, 7 days a week (24/7 ED), has a catchment area of 264,000 individuals and treats approximately 27,000 patients annually. Ethical approval for the PROTACT study was obtained from the regional Medical Research Ethics Committee on Research Involving Human Subjects (CCMO No. NL368.38044.11). All participants provided written informed consent.

Study population

Eligible patients between 18 and 70 years were consecutively recruited when admitted to the ED between September 2011 and July 2013. Inclusion criteria for participation were (i) musculoskeletal isolated extremity injury caused by blunt trauma; and (ii) sufficient communication skills and a basic knowledge of the Dutch language. Exclusion criteria were (i) life or limb threatening conditions; (ii) documented cognitive disability; (iii) suffering from hallucinations, delusions or suicidal ideation; and (iv) alcohol or drugs intoxication. For the purpose of this study, patients who did not provide pain scores on both ED admission and discharge were excluded

Intervention

The pain protocol, an algorithm for pain assessment and pharmacological treatment in the ED, (figure 1) was implemented in January 2013. The protocol was based on the Dutch evidence-based guideline 'Pain management for trauma patients in the chain of emergency care', which was developed to provide pain management recommendations for trauma patients (27). The new protocol leads to an important change in the current operating procedure of the ED. The structural measurement and registration of a pain score was not yet standard procedure. Major change for pain management in the ED is that with the implementation of the protocol, nurses are allowed to administer analgesics, including opioids, without the patient being first assessed by a physician. Paracetamol is the treatment of first choice, if necessary with additional use of non-steroidal anti-inflammatory drugs (NSAIDs) or opioids. Because of the implementation, this study was divided into two data collection periods separated by a one-month interval. In the pre-period from September 2011 until December 2012 (15 months) there was no standardized pain protocol available, so nurses were not allowed to give opioids on nurse's own initiative. Paracetamol was provided by nurse's own judgment. There was no structural measurement and registration of pain in this period. In the one-month interval, time was allowed for the active and passive distribution of the protocol among ED staff. The staff was informed about the new protocol and operating procedure, and the protocol and relevant important leaflets were available at the ED. During the intervention period from February 2013 until July 2013 (6 months), patients should be given analgesics according to the algorithm of the implemented protocol.

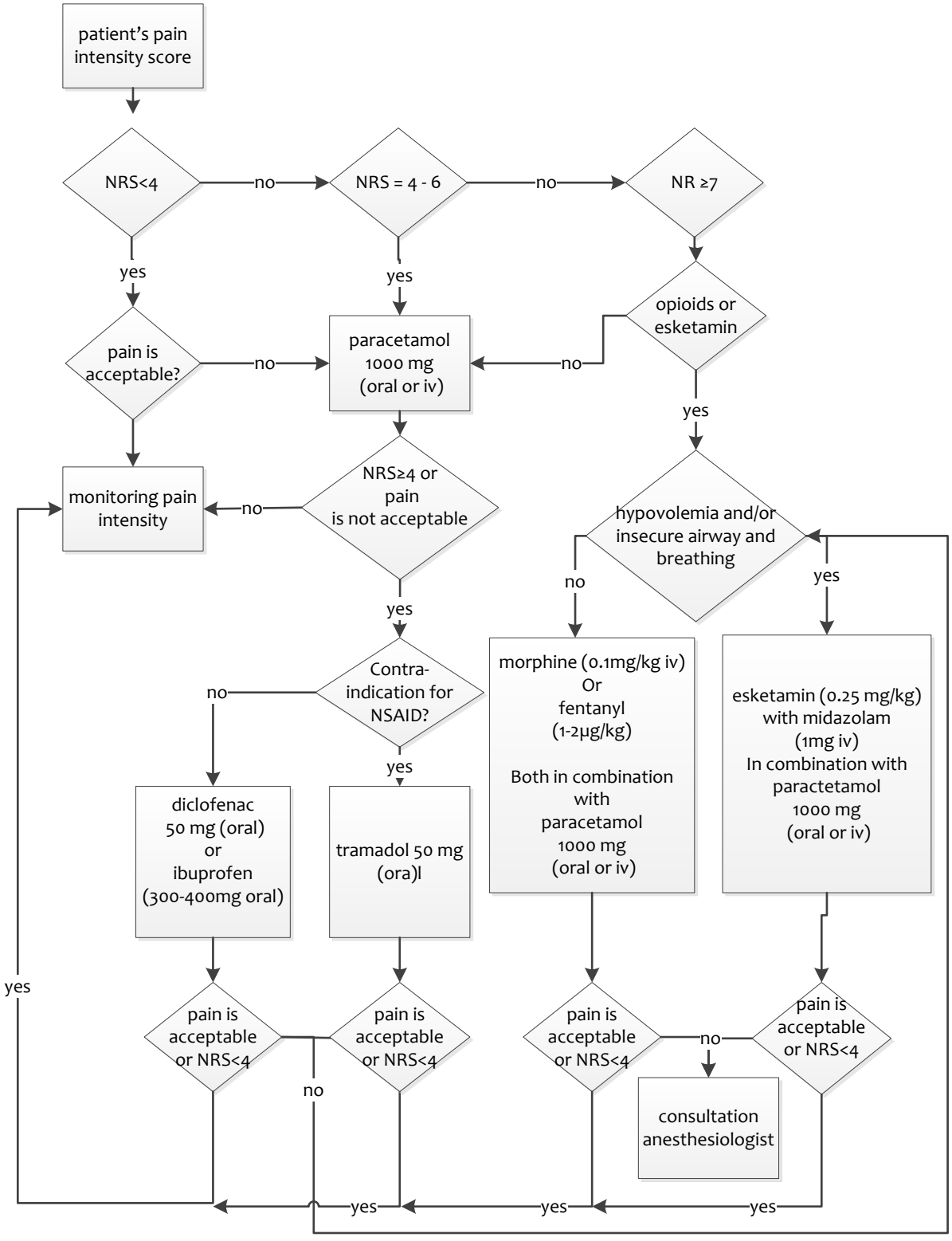

Figure 1: Algorithm for analgesic pain management in the ED.

Procedures and data management

Patients who met the study criteria were informed by the nurse about the purpose of the study. Participants were asked to provide informed consent and to complete a questionnaire. The questionnaire included a validated tool to measure pain intensity and questions about educational level, pre-hospital analgesic use and patient satisfaction (yes or no). Additionally, data from the ED patient registration system were used. The registry is a fully electronic emergency medical record registry where each entry, order, or activity is automatically time-stamped for pre-specified ED events. The registry includes patient demographics (date of birth, sex), urgency level, medical diagnoses (e.g. injury type), type of analgesics, type of non-pharmacological injury treatment, time of providing pain management and analgesic refusal. If patients arrive by ambulance, data on pre-hospital analgesic use were retrieved from the regional emergency medical service (EMS) registry.

Measures and definitions

Pain intensity in the ED

Pain intensity was measured using the Numerical Rating Scale (NRS). The NRS of acute pain was validated for use in the ED (28, 29). Patients were asked to fill in a number from 0 to 10 to represent their pain severity, where 0 is "no pain" and 10 "the worst pain imaginable," in response to the questions "How severe was your pain on ED admission?" and "How severe was your pain at ED discharge?" NRS scores were converted to categorical groups in line with the algorithm of the protocol: (i) no pain to mild pain (NRS <4); (ii) moderate pain (NRS 4–6); and (iii) severe pain (NRS ≥7).

Analgesics in the prehospital phase and ED

Data regarding the prehospital analgesic use were collected by questionnaire and from the EMS registry. Analgesic administration in the ED was obtained from the electronic patient registry. The type of analgesic administered (if any) was categorized as follows: (i) no analgesics; (ii) paracetamol; (iii) non-steriodal anti-inflammatory drug (NSAID) such as diclofenac; (iv) mild opioids such as tramadol; (v) major opioids such as morphine and fentanyl; and (vi) others including esketamine. Analgesic provision means either administration or refusal of offered analgesics occurred.

The time of analgesic administration was obtained from the ED registry. Time to analgesic represents the time recorded from triage to administration of the first analgesic and was reported in minutes. Because a major change after implementation involves opioid provision, time from triage to first opioid administration was also obtained.

ED LOS

Patients' length of stay was obtained from the ED registry. The duration represents the time recorded from admission to discharge and was reported in minutes.

Pain relief during ED-stay and clinically relevant pain relief

Pain relief was defined as the difference between the NRS scores on admission and discharge. Clinically relevant pain relief was defined as 33% or more decrease in NRS score of an individual patient during ED-stay (30) or when the patient in pain was discharged with NRS<4.

Data analysis

Descriptive data are presented as means with standard deviations (SD) for continuous variables, as medians with interquartile ranges (IQR, 25th–75th percentile) for time variables, and as frequencies for categorical variables. Comparisons between the pre- and post-intervention groups were made using Pearson's Chi-squared test for categorical variables and two-tailed student's t-test or non-parametric Mann–Whitney U-test for continuous variables, depending on whether the data met the assumptions of normality. Differences and corresponding 95% confidence intervals (CIs) in pain relief between the pre- and post-intervention period were analyzed using two-tailed Student's *t*test. Differences between proportions of non-pharmacological use, analgesic use and analgesic provision and pain relief between the pre- and post-intervention period were analyzed by Pearson's Chi-squared. Differences and corresponding 95% CIs of the median times to analgesics were calculated with the median test. A p-value < 0.05 (95% CI does not include *zero*) is considered statistically significant. Based on a pilot study with an analgesic administration of 35%, at least 134 patients are needed in the post-intervention period to detect an increase in analgesic administration of 50% or more with a power of 80% at the 5% significance level. All data were analyzed using SPSS version 21.0 (IBM Corporation, Armonk, NY).

RESULTS

In total 660 patients were included in this pre–post intervention study with the aim to evaluate the effect of the implementation of a nurse-initiated pain protocol on pain management in patients with acute musculoskeletal pain. Patients enrolled during the pre- (n = 504) and post- (n = 156) intervention period were similar with regard to pain intensity at admission (Table 1) The majority of patients suffered a fracture, most frequently in the ankle (n = 148) and wrist (n = 104). Almost 85% of the patients had moderate to severe pain (NRS ≥4) on admission. These patients should receive analgesics after protocol implementation.

Table 1: Baseline characteristics of the pre- and post-intervention groups

	Pre (n=504)	Post (n=156)	Difference (95%	*p*
Age, median (IQR)	44.2(28.7-56.6)	50.6 (37.8-	+ 4.4 (0.7↔8.2)	0.05
Sex (women)	276 (54.8%)	87 (55.8%)	+1.0% (-8.0↔10.0)	0.84
Educational level *				0.41
High	135 (27.6%)	50 (32.5%)	+4.9% (-3.4↔13.1)	
Medium	285 (57.1%)	80 (51.9%)	-5.2% (-14.1↔3.9)	
Low	78 (15.3%)	24 (15.6%)	-0.2% (-6.8↔6.3)	
Injury type, (fracture)	344 (68.3%)	113 (72.4%)	+4.2% (-4.1↔12.5)	0.32
Analgesic use before ED presentation	187 (37.1%)	69 (44.2%)	+7.1% (-1.6↔15.9)	0.11
Pain intensity at admission, mean (SD)	6.4 (2.4)	6.5 (2.6)	+0.0 (-0.5↔0.4)	0.91
NRS<4 at admission	72 (14.3%)	28 (17.9%)	+3.6% (-1.6↔15.9)	0.42
NRS 4-6 at admission	136 (27.0%)	36 (23.1%)	-3.9% (-11.8↔4.0)	
NRS≥7 at admission	296 (58.7%)	92 (59.0%)	+0.2% (-8.9↔9.1)	

*6 missing

The provision, refusal and actual administration of analgesics in the ED

Before protocol implementation, 46.8% of the patients with moderate to severe pain were offered analgesics. This percentage increased after implementation to 68%, a difference of 21.2% [95% CI 11.5–30.9, p < 0.01] (Table 2). Analgesic refusal increased after implementation from 10.2% to 21.9%, resulting into an actual analgesic administration increase from 36.6% to 46.1%, a difference of 9.5% [95% CI 0.0–19.1, p = 0.05]

In the subgroup of patients with severe pain (NRS ≥7), the percentage of analgesic provision increased with 18.0% from 52.7% to 70.7% (p < 0.01). Moreover, analgesic provision increased with 27.3% from 33.8% to 61.6% (p < 0.01) in patients with moderate pain (NRS 4–6). In the subgroup of patients with no to mild pain (NRS <4), the percentage of analgesic provision increased with 18.1% from 31.9% to 50.0% (p = 0.09).

Table 2: Differences in pre-and post-intervention outcomes, by severity of pain

	Pre (n=504) N	Post(n=156) N	Difference	(95% CI)
Moderate to severe pain (NRS ≥4)	**432**	**128**		
Offered analgesics, N (%)	202 (46.8%)	87(68.0%)	+21.2% *	(11.5↔30.9)
Refused analgesics, N (%)	44 (10.2%)	28 (21.9%)	+11.7% *	(5.1↔18.2)
Received analgesics, N (%)	158 (36.6%)	59 (46.1%)	+ 9.5%	(0.0↔19.1)
Time to analgesic, median (IQR)	10.0 (3.0-48.5)	7.0 (2.0-17.0)	- 4.0 *	(-9↔-1)
Time to opioid, median (IQR)	37.0 (23.0-71.0)	15.0 (9.0-34.0)	-22.0*	(-38↔-5)
Pain relief during ED-stay, mean (SD)	-1.00 (1.77)	-1.56 (1.91)	- 0.56 *	(-0.92↔-0.21)
With analgesic treatment	-1.46 (1.90)	-2.02 (2.22)	-0.55*	(-1.20↔-0.09)
Clinically relevant pain relief N (%)	91 (21.1%)	40 (31.3%)	+10.2%*	(1.8↔18.5)
With analgesic treatment	42 (26.6%)	21 (35.6%)	+9.0%	(-5.3↔23.3)
ED LOS (min), mean (SD)	111.2 (52.0)	104.8 (53.4)	- 6.5	(-16.8↔3.8)
Nonpharmacological pain interventions N (%)	337 (78.0%)	107 (83.6%)	+ 5.6%	(-2.4↔13.6)
Severe pain (NRS ≥7)	**296**	**92**		
Offered analgesics, N (%)	156 (52.7%)	65 (70.7%)	+18.0% *	(6.4↔29.5)
Refused analgesics, N (%)	26 (8.8%)	16 (17.4%)	+ 8.6% *	(1.3↔15.9)
Received analgesics, N (%)	130 (43.9%)	49 (53.3%)	+ 9.3%	(-2.3↔-21.0)
Paracetamol	75	28		
Paracetamol + NSAID	13	1		
Paracetamol + tramadol	2	1		
NSAID	13	3		
Paracetamol + opioid	2	7		
Opioid	23	7		
Paracetamol + NSAID + opioid	2	2		
Time to analgesics, median (IQR)	10.0 (3.0-51.5)	7.0 (2.0-17.0)	- 4.0 *	(-11↔ 0)
Time to opioid, median (IQR)	35.0 (23.0-67.0)	15.0 (9.0-34.0)	-20.0*	(-35↔3)
Pain relief during ED-stay, mean (SD)	-1.22 (1.79)	-1.74 (1.98)	-0.52 *	(-0.95↔-0.09)
With analgesic treatment	-1.58 (1.92)	-2.20 (2.28)	-0.62*	(-1.36↔-0.10)
Clinically relevant pain relief, N (%)	55 (18.6%)	24 (26.1%)	+7.5%	(-2.6↔17.7)
With analgesic treatment	22.3%	34.7%	+12.4%	(-3.1↔27.9)
ED LOS (min), mean (SD)	109.1(51.3)	107.7 (54.0)	- 1.4	(-136↔10.7)
Nonpharmacological pain interventions N(%)	226 (76.4%)	75 (81.5%)	+5.1%	(-4.6↔15.0)
Moderate pain (NRS 4-6)	**136**	**36**		
Offered analgesics, N (%)	46 (33.8%)	22 (61.1%)	+27.3% *	(9.6↔45.0)
Refused analgesics, N (%)	18 (13.2%)	12 (33.3%)	+20.1% *	(6.3↔33.9)
Received analgesics, N (%)	28 (20.6%)	10 (27.8%)	+ 7.2%	(-8.2↔22.6)
Paracetamol	19	8		
Paracetamol + NSAID	3	2		
Paracetamol + tramadol	1	0		
NSAID	1	0		
Paracetamol + opioid	1	0		
Opioid	3	0		

Table 2: Continued				
Time to analgesics (min), median (IQR)	10.0 (3.3-45.0)	5.0 (1.5-29.3)	-4.0	(-19↔4)
Time to opioid, median (IQR)	66.0 (38.0-78.0)	-		
Pain relief during ED-stay, mean (SD)	-0.52 (1.56)	-1.11 (1.55)	-0.59 *	(-1.16↔-0.01)
With analgesic treatment	-	-1.10 (1.66)	-0.17	(-1.48↔-1.14)
Clinically relevant pain relief, N(%)	36 (26.5%)	16 (44.4%)	+18.0%	(-0.6↔36.5)
With analgesic treatment	13(46.3%)	4(40%)	-6.4%	(-44.5↔31.7)
ED LOS (min), mean (SD)	115.9 (53.4)	97.3 (51.6)	- 18.6	(-38.2↔1.0)
Nonpharmacological pain interventions, N(%)	111 (81.6%)	23 (88.9%)	+ 7.3%	(-6.6↔21.2)
No to mild pain (NRS <4)	**72**	**28**		
Offered analgesics, N (%)	23 (31.9%)	14 (50.0%)	+18.1%	(-3.1↔39.3)
Refused analgesics, N (%)	14 (19.4%)	7 (25.0%)	+ 5.6%	(-12.5↔23.7)
Received analgesics, N (%)	9 (12.5%)	7 (25.0%)	+12.5%	(-3.6↔28.7)
Paracetamol	*8*	5		
Paracetamol + NSAID	*0*	*1*		
Opioid#	*1*	*1*		
Time to analgesics (min), median (IQR)	7.0 (4.0-33.0)	6.0 (4.0-61.0)	-2.0	(-54↔5)
Time to opioid, median	61	47	-14	
Pain relief during ED-stay, mean (SD)	+0.44 (1.72)	+0.21 (0.96)	-0.23	(-0.77↔0.31)
ED LOS (min), mean (SD)	108.3 (48.3)	107.8 (51.4)	-0.5	(-22.2↔21.2)
Nonpharmacological pain interventions, N (%)	76.4%	78.6%	+2.2%	(-16.6↔21.0)

#patients were administered esketamine and the short-acting opioid fentanyl in ambulance prior ED admission; *p<0.05

Time to analgesics

Before protocol implementation, the median time to analgesics in patients with moderate to severe pain was 10 minutes (IQR 3–48.5). After implementation median time decreased to 7 minutes (IQR 2–17) ($p < 0.05$) (Table 2). A high percentage of patients were administered analgesics within 10 minutes after triage, 51.9% before and 66.1% after protocol implementation. In patients with no to mild pain median time to analgesics decreased from 7 (IQR 4–33) to 6 (IQR 4–61) minutes ($p = 0.92$). The median time to first opioid administration improved from 37 minutes (IQR 23–71) to 15 minutes (IQR 9–34) ($p < 0.01$).

Clinically relevant pain relief

Mean pain relief in patients with moderate to severe pain increased after implementation from 1.00 to 1.56 point on NRS; a difference of 0.56 [95% CI (0.21-0.92), p<0.01] (Table 2). In patients with no to mild pain there was no pain relief, but in both periods there was a slight increase in mean pain intensity. In patients who received analgesic treatment mean pain relief increased from 1.46 to 2.02 points, a difference of 0.55 [95% CI (0.09–1.20), $p < 0.05$]. In patients who received only nonpharmacological injury treatment, pain relief increased from 0.74 to 1.26, a difference 0.52 [95% CI (0.04–0.98), $p < 0.05$] (Table 3). Mean pain relief did not change between pre- and post-period in patients who did not receive any pain treatment.

Before implementation clinically relevant pain relief (33%) was achieved in 21.1% of the individually patients. After implementation, this percentage increased to 31.3%, a difference of 10.2% [95% CI (1.8–18.5), p < 0.05 (Table 2). In patients who received analgesic treatment, this percentage increased from 26.6% to 35.6% (p = 0.16). In patients with only nonpharmacological injury treatment, this increased from 17.6% to 29.3% (p = 0.08) (Table 3).

Moreover, before protocol implementation 77% of the patients suffered moderate to severe pain at discharge. After implementation this percentage decreased by 7.8% [95% CI (0.0–15.5), p < 0.05] to 69.2%.

Table 3: Pain management and (clinically relevant) pain relief in patients with moderate to severe pain

	Pre (n=432) N	Post (n=128) N	Difference	(95% CI)
Pain management, N (%)				
Analgesic treatment	158 (36.6%)	59 (46.1%)	+ 9.5%	(0.0↔19.1)
Analgesic only	42 (9.7%)	10 (7.8%)	-1.9%	(-7.7↔3.8)
Analgesic and nonpharmacological	116 (26.9%)	49 (38.3%)	+11.4%*	(1.9↔20.9)
Nonpharmacological injury treatment only	221 (51.1%)	58 (45.3%)	-5.8%	(-15.7↔4.0)
No pain treatment	53 (12.3%)	11 (8.6%)	-3.7%	(-9.5↔2.1)
Pain relief during ED-stay, mean (SD)	-1.00 (1.75)	-1.56 (1.89)	- 0.56 *	(-0.92↔-0.21)
Analgesic treatment	-1.46 (1.90)	-2.02 (2.22)	-0.55*	(-1.20↔-0.09)
Analgesic only	-1.69(2.34)	-2.10(2.28)	-0.41	(-2.14↔1.32)
Analgesic and nonpharmacological	-1.37(1.72)	-2.00 (2.22)	-0.62	(-1.33↔0.09)
Nonpharmacological injury treatment only	-0.74 (1.66)	-1.26 (1.48)	-0.52*	(-0.98↔-0.04)
No pain treatment	-0.68 (1.34)	-0.73 (1.27)	- 0.05	(-0.93↔0.86)
Clinically relevant pain relief N (%)	91 (21.1%)	40 (31.3%)	+10.2%*	(1.8↔18.5)
Analgesic treatment	42 (26.6%)	21 (35.6%)	+9.0%	(-5.3↔23.3)
Analgesic only	10 (23.8.4%)	2 (20%)	-3.8%	(-34.1↔26.5)
Analgesic and nonpharmacological	32 (27.6%)	19 (38.8%)	+11.1%	(-5.1↔27.5)
Nonpharmacological injury treatment only	39(17.6%)	17(29.3%)	+11.7%	(-1.3↔24.7)
No pain treatment	10 (18.9%)	2 (18.2%)	-0.7%	(-27.0↔25.6)

*p<0.05

ED LOS

Mean ED LOS in patients with moderate to severe pain decreased by 6.5 minutes [95% CI (−3.8 – 16.8), p= 0.22] from 111.2 to 104.8 minutes (Table 2). In patients with no to mild pain mean ED LOS did not change after implementation (p= 0.97).

Patient satisfaction

The percentage of patients with moderate to severe pain who were satisfied with their treatment increased with 4.0% from 92.0 in the pre-period to 96.0% after implementation ($p = 0.11$). In patients with analgesic treatment these percentages increased from 92.4% to 95.7% ($p = 0.44$).

Protocol deviation

Of all patients with moderate to severe pain who according to the protocol algorithm should receive analgesics, 68% were offered analgesics, resulting in a protocol deviation of 32%. The type of analgesic administered was consistent with the protocol for the specific pain score in 83% of the patients. The other 17% of the patients received opioids or NSAIDs without paracetamol. Out of the 49 patients with severe pain who received analgesics, 7 patients received only opioids and 3 patients received only NSAIDs. Moreover, 30 patients received paracetamol with or without NSAID or tramadol instead of an opioid in combination with paracetamol, which should have been given according to the protocol.

DISCUSSION

This pre–post intervention study shows that the implementation of a nurse-initiated pain protocol in the ED appears to lead to an increase in analgesic provision, a shorter time to analgesics and a higher clinically relevant pain relief in acute musculoskeletal patients. However, adequate pain management remains a major challenge. Despite improvements in pain management, a high percentage of patients did not receive analgesics while in pain and a high percentage was still discharged with moderate to severe pain.

In order to improve pain management, a nurse-initiated protocol based on the algorithm of the Dutch evidence-based guideline for pain management in trauma patients was implemented. Before protocol implementation a pain protocol was lacking in half of all Dutch EDs (31). The absence may not necessarily imply there was no care for pain relief and the other way around; the presence of a protocol does not mean that a protocol is used accordingly.

In this study there is a discrepancy between the content of the protocol and modus operandi. Although the analgesic provision was highly improved after implementation, only 68% of the patients with moderate to severe pain, who should receive analgesics according to the protocol, were offered analgesics. Actual analgesic administration increased from 36.6% to 46.1%. Also other studies have shown that pain protocols improve analgesic administration, even more than in our study. A Swiss study showed an increase in analgesic administration from 40% to 63% in patients with acute pain by any cause (16). Furthermore, a study in the US showed an improvement from 45% to 70% in patients with extremity and back pain (20).

The type of analgesic administered was consistent with the protocol in 83% of the cases. Remarkably, more than three-fifths of the patients with severe pain were downgraded to use paracetamol or NSAIDs instead of opioids. Yet the reluctance of nurses to use opioids could also be partly explained by the study population, patients with musculoskeletal injury, who often will be discharged home. The use of more potent analgesics could result in longer ED LOS and the inability to be discharged home safely. Another reason for protocol deviation might be due to discrepancies in pain assessment between patients and emergency nurses. These discrepancies were identified as the most powerful predictor for poor pain management (32).

Furthermore, it is notable that a relatively high percentage of patients refuse to take analgesics. Of course patients may decline analgesics, but physicians and nurses should make sure that analgesic refusal is only made after the patient has had the opportunity to comprehend the possible consequences. Explanation regarding harmful effects of prolonged, untreated pain and side effects of analgesics leads to a decrease in analgesic refusal (33).

The protocol improved mean pain relief in patient with moderate to severe pain from 1.00 to 1.56 points on NRS, a statistically significant difference. In patients who received analgesic treatment, mean relief increased even up to 2.02 points. Because a statistically significant difference in pain relief is mostly a matter of sample size, it is more important to know whether this difference is clinically relevant. A pain relief of 2 points on NRS or 33% decrease in pain is defined as clinically important changes (30). In patients treated with analgesics this clinically important change of 2 points was achieved. Furthermore, the percentage of patients who achieved clinically relevant pain relief during ED-stay increased from 21.0% before protocol implementation to 31.3% after implementation.

Especially in patients with minor acute musculoskeletal injuries, a nurse-initiated pain protocol might be useful to optimize pain management. These patients are usually triaged to a low triage category, which results in an extended waiting time for assessment by an ED-physician. This study confirms the protocol shortens the time to analgesics; the median time to analgesics significantly reduced from 10 to 7 minutes. In both periods, before and after protocol implementation analgesics were given relatively quickly after triage. Remarkable is the high percentage of patients who received analgesics within 10 minutes of triage. Even before protocol implementation this percentage was 51.9%, suggesting that nurses routinely provided over-the-counter analgesics during triage in the pre-intervention period. After implementation nurses were allowed to give opioids according to the pre-defined protocol. This shortened the median time to first opioid from 37 to 15 minutes.

Moreover, the pain protocol seemed to lead to a reduced ED-stay especially in patients with moderate pain, which is in line with a Canadian study which revealed that reduced time to analgesics was associated with a shorter duration of ED-stay (23).

The strength of this study is its prospective design in a relatively large homogeneous population of patients with isolated musculoskeletal injuries. Furthermore, pre- and post-intervention periods were separated by a one-month interval to be able to implement the pain protocol in daily practice before measuring the potential effects. During the study period no other programs for improved pain management were distributed in the Netherlands or in the hospital, which may have had an effect on study results. Another strength is the use of patients' self-reporting pain intensity instead of the documented pain scores assessed by nurses. A potential bias in data collection was limited by giving patients a written questionnaire as opposed to a verbal one.

The quasi-experimental design used in this pre–post intervention study is not the best design to evaluate the benefits of an implementation of pain protocol. A randomized controlled trial is generally considered to have the highest level of credibility with regard to assessing causality. However, randomization was not logistically feasible. Hence, the statistical association found in this study does not directly imply causality. There are a number of important potential confounding factors, e.g. severity of injury, knowledge and experience of pain management, which were not measured and may have differed in both periods. No adjustments could be made. Yet the pre-intervention period provides data about what pain management would have been had the intervention not occurred.

Another possible limitation is the Hawthorne effect, alteration of behaviour of ED-staff as a response to their awareness of being observed. This may well surface in this kind of study design and is difficult to avoid. However, this effect would have been present during both study periods because the staff was subject to observation in both periods. This supports that the observed beneficial effect is the result of the intervention.

Pain management involves assessment, documentation, treatment, and evaluation. Reassessment of pain following analgesic administration and checking if the right analgesic doses were given was not part of this study. Because acute pain is dynamic, frequent assessment over time is necessary to make adjustments in analgesic doses or multimodal analgesic treatment strategies. In this study pain intensity was measured only twice, at ED admission and discharge, without additional assessments that might more accurately reflect the impact of analgesic treatment.

The percentage of patients who were actually administered analgesics might be underestimated. Even though the ED staff was instructed to list all medications, some may have neglected to do so, especially for over-the-counter analgesics. Moreover, prehospital analgesic use might have influenced the use and choice of analgesics by the nurse and may improve pain relief. However, no difference in pain relief in patients who used prehospital analgesics between the two periods was found.

CONCLUSION

The implementation of a nurse-initiated pain protocol in the ED appears to lead to an increase in analgesic provision, a shorter time to analgesics and a higher clinically relevant pain relief in acute musculoskeletal patients. Adequate pain management remains a major challenge for ED staff. Despite improvements in pain management, many patients did not receive analgesics. Moreover, the percentage of patients with moderate to severe pain at ED discharge is still high. The adherence to the protocol, especially in terms of analgesic doses and reassessment of pain after analgesic administration, needs to be studied in order to further optimize pain management

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Chapter 6

Painful discrimination in the emergency department: risk factors for underassessment of patient's pain by nurses

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ABSTRACT

BACKGROUND AND AIMS Unrelieved acute musculoskeletal pain continues to be a reality of major clinical importance, despite advancements in pain management. Accurate pain assessment by nurses is crucial for effective pain management. Yet, inaccurate pain assessment is a consistent finding worldwide in various clinical settings including the emergency department. In this study, pain assessments between emergency nurses and patients with acute musculoskeletal pain following extremity injury will be compared to assess discrepancies. A second aim is to identify patients of whom pain is likely to be under assessed by emergency nurses.

METHODS The prospective PROTACT-study included 539 adult patients who were admitted to the emergency department with pain following extremity injury. Data on pain assessment and characteristics of patients including demographics, pain, and injury, psychosocial and clinical factors were collected using questionnaires and hospital registry.

RESULTS Nurses significantly underestimated patient's pain with a mean difference of 2.4; 95% CI (2.2-2.6) on an 11-points NRS. Agreement between nurses' documented and patients' self-reported pain was only 27%, while 63% of the pain was under assessed. Pain was in particularly underassessed in women, in persons with a lower educational level, in patients who used prehospital analgesics, in smokers, in patients with injury to the lower extremities, in anxious patients and in patients with a lower urgency level.

CONCLUSIONS Underassessment of pain by emergency nurses is still a major problem. This might result in under-treatment of pain if the emergency nurses rely on their assessment to conduct further pain treatment. Strategies focusing on awareness among nurses of which patients are at high-risk for underassessment of pain are needed.

BACKGROUND

Pain is a multidimensional phenomenon in which pain experience of the patients is determined by the interactions of physical, psychological, cultural and sociodemographic factors (1). Patients vary markedly in the intensity of their pain in response to an identical procedure, injury, or noxious condition. Due to the subjective nature of pain, it can be very difficult to quantify patients' pain. A clinically, objective measurement for the experience of pain is not available. Therefore, the assessment of this inherently subjective symptom relies on patients' self-report. Underassessment of pain may occur when clinicians, like emergency nurses, attempt to calculate the severity of patients' pain experiences thereby placing patients at risk of inadequate pain relief (2, 3).

Although pain is the most prevalent chief complaint for patients visiting the emergency department (4-6), undertreatment of acute pain appears worldwide which is reflected by the high prevalence of moderate to severe pain at discharge and the low percentage of patients receiving analgesics. The proportion of adults receiving analgesics varies between 19% and 64% (4, 7-11). Moreover, the percentage of patients discharged with moderate to severe pain ranges from 52% to 74% (4, 6, 8, 11).

Accurate assessment of pain is a crucial step in providing effective pain management. Discrepancies between patients' and clinicians' assessment are identified as the most powerful predictor of poor pain management (12, 13). The consequences of inaccurate assessment are substantial. Underassessment of pain can lead to inadequate pain management, unnecessary suffering and delay in recovery, while overassessment of pain can lead to over-treatment and potentially to iatrogenic disease (14). Major underestimations in pain assessment are noted in patients with musculoskeletal pain, where the discrepancy in assessment of pain between patients and clinicians is considerable (2, 3, 15). As a result, insufficient pain relief occurs frequently in these patients (4, 16-18).

Given the multidimensional nature of pain and the complexity of pain assessment, it is likely that different clinician, patient and environmental characteristics are involved in accurate pain assessment (14). Several studies found that experienced clinicians have a tendency to underestimate patients' pain. However, a study which investigated the agreement of pain assessment between patients and emergency nurses revealed that characteristics such as nurse's sex, age, ED experience, nursing grade and previous attendance to pain management courses were not associated with inaccurate pain assessment (2).

Patients' behaviour and characteristics may have an influence on the assessment. However, except for some demographic characteristics like age and sex, not much is known which characteristics play a role in pain assessment. Our goal is to identify patients of whom pain is likely to be under assessed by emergency nurses. Identifying risk factors for underassessment of pain might reduce pain rating discrepancies, optimize pain management and as a result reduce unnecessary suffering and improve recovery and patient outcome.

PATIENTS AND METHODS

Study design and setting

This study is part of a prospective follow-up study; the "PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients" (PROTACT). The PROTACT-study includes adult patients with isolated musculoskeletal extremity injury who attended the emergency department of Medisch Spectrum Twente in Enschede, The Netherlands. This is a 24/7 emergency service which is accessible for 264,000 individuals in the Twente region and treats approximately 27,000 patients annually. This study was approved by the regional Medical Research Ethics Committee on Research Involving Human Subjects (CCMO no. NL368.38044.11). Written informed consent was obtained from each participant.

Study population

Eligible patients aged 18 to 69 years were consecutively recruited in the study when admitted to the emergency department during a 22 months period from September 2011 until July 2013. Inclusion criteria for participation were (i) musculoskeletal isolated extremity injury caused by blunt trauma; (ii) sufficient communication skills and a basic knowledge of the Dutch language. Exclusion criteria were (i) life or limb threatening conditions; (ii) documented cognitive disability; (iii) suffering from hallucinations, delusions or suicidal ideation and (iv) alcohol or drugs intoxication. For the purpose of this study, patients who did not filled in the questionnaires at ED admission and six weeks follow-up were excluded.

Procedures and data management

Patients admitted to the emergency department who met the study criteria were informed by a (triage) nurse about the purpose of the study. Participants were asked to provide informed consent and to complete a questionnaire. Six weeks after the initial ED visit, patients received a follow-up questionnaire by (e)mail, according to their stated preference. The questionnaires comprised validated questionnaires that are frequently used in pain research (see below). Furthermore, questions about sociodemographic, lifestyle, injury and treatment were included. Additional data from the ED electronic patient registration system were used. The registry is a fully electronic emergency medical record registry where each entry, order, or activity is automatically time-stamped for pre–specified ED events. The registry includes patient demographics (date of birth, sex), triage urgency level, nurses pain score and medical diagnoses e.g. injury type and location. If patients arrived by ambulance, additional data regarding the use and type of analgesic pain management were retrieved from the registry of the regional ambulance services.

The following validated questionnaires were used:

Pain intensity

Pain intensity at ED admission was measured using a Numerical Rating Scales (NRS). Patients were asked to fill in a number from 0 to 10 to represent their pain intensity, where 0 is "no pain" and 10 "the worst pain imaginable". The NRS was validated for use in the emergency department (19). During triage, the nurse also registered a pain intensity score in the patient's medical record.

Pre-injury physical and mental health status

Physical and Mental health was measured using the validated Dutch-language version of the 36-Item Short- Form Health Survey (SF-36, Corporation, Santa Monica, California USA) (20). The SF-36 is a general quality of life questionnaire with a 4-week recall period and assesses eight domains e.g. physical functioning, pain, mental health, vitality, and general health perception (21). Algorithms were used to produce the Physical Component Summary (SF-36 PCS) scores for physical health status and Mental Component Summary (SF-36 MCS) scores for mental health status (22). In the present study, the first quartiles of the obtained SF-36 PCS (<51.7) and SF-36 MCS (<49.7) scores were defined as the cut-off points for poor physical or mental health (23).

Pre-injury anxiety and depression

Anxiety and Depression were measured using the Hospital Anxiety and Depression Scale (HADS). The validated Dutch version was found to have good psychometric properties (24). The HADS is a screening tool for assessment in a wide variety of clinical groups, such as emergency care patients (25). Patients were asked to recall a 7-days period about 14 items on a 4-point Likert scale; seven items for each subscale of anxiety and depression. The anxiety and depression sum scores were calculated (range 0–21), with a high score indicating a high level of anxiety or depression. In the present study, a sum score of >7 was used to indicate the presence of anxiety and depression (24)

Pain catastrophizing

Pain catastrophizing is conceptualized as a negative cognitive–affective response to anticipated or actual pain and was measured by using a Dutch-language version of the Pain Catastrophizing Scale (PCS) consisting of 13 statements of pain experience; for example: "If I am in pain, I am afraid the pain will get worse." Patients were asked to indicate whether they agree with these statements by using a 5-point Likert scale. A PCS sum score was calculated from all items (range 0–52), with a high score indicating a high level of pain catastrophizing. In the current study, a score of 24 of higher was used to indicate the presence of pain catastrophizing. This cut-off point was found to be highly associated with high follow-up pain

ratings (26). Several studies have supported the validity and reliability of PCS (27). The PCS was measured at 6 weeks follow-up.

Kinesiophobia

Kinesiophobia, or fear of movement, refers to the anxiety that many individuals in pain have regarding engaging in activities or physical movements and was measured by the Tampa Scale of Kinesiophobia (TSK). The TSK consists of 17 statements that reflect the notion that pain is a precursor for (re)injury because of physical activity or certain movements (28). Patients were asked whether they agree with these statements by using a 4-point Likert scale. A TSK sum score was calculated by using all items (range 17–68); a high score indicates a high level of kinesiophobia. A score of 37 or higher was used to indicate the presence of kinesiophobia (29). The Dutch-language version TSK has been shown to be internally reliable and correlates with measures of other disability (29). The TSK was measured at 6 weeks follow-up.

Primary outcome measure

The primary outcome was disagreement in pain severity rating between self-reported pain intensity by the patient and documented pain intensity by the nurse. Pain disagreement was present if the ratings differed by ≥33%. A difference of 33% represents clinical significance (30). The difference in pain ratings was calculated by subtracting the nurse's rating from the patient's rating, divided by the patient self-reported pain rating * 100%. The focus of this study was on the underassessment of patient's pain.

Potential risk factors for underassessment of patients' pain

The following variables were analysed for their prognostic value, because these may play a role in pain signalling, transition, perception or modulation.

Demographics: Age; sex; educational and lifestyle factors (alcohol consumption and smoking).

Pain factors: pre-existing chronic pain (pain longer than 3 months before injury); and the use of analgesics in the prehospital phase;

Psychosocial factors: pre-injury anxiety and depression measured with HADS; catastrophizing measured with PCS; kinesiophobia measured with TSK; and mental health status measured with SF36.

Injury factors: Type of injury; site of injury; time between injury and ED admission; and urgency level;

Clinical Factors: Physical health status measured with SF-36, self-reported comorbidities; and body mass index (BMI).

Data analyses

For descriptive purposes, categorical data were characterized in terms of frequency (%), whereas continuous data were characterized as median with interquartile ranges (IQR, 25^{th} - 75^{th} percentile) or as mean ± standard deviation (SD). Spearman correlation coefficients and Bland–Altman plots were used to give a graphical demonstration of the relationship between nurse's pain score and patient's self-reported pain scores. For the purpose of this study, the primary outcome disagreement was dichotomized into no underassessment <33% and underassessment ≥33%. The potential association between categorical variables and underassessment were investigated using chi-squared tests. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated.

Because pre-selection of risk factors based on p-values estimated from univariate analyses may result in unstable prediction models (31), all potential risk factors were considered in the multivariate analysis. Backward stepwise selection of all potential risk factors was applied using the likelihood ratio test with a p-value of 0.157 according to Akaike's Information Criterion. If multicollinearity between two variables was suspected, change of estimates, confidence intervals and p-values were evaluated when both variables were included in the model as compared to the inclusion of one variable.The model's ability to discriminate accurately assessed patients from the under assessed patients was ascertained by concordance (c)-statistic which can range from 0.5 (no discrimination) to 1.0 (perfect) discrimination. A bootstrapping procedure (250 samples) was used to assess the internal validity of the multivariate model. This procedure produced a corrected model's c-statistic and a shrinkage factor. The regression coefficients (β) of the risk factors were then multiplied by this shrinkage factor to prevent overfitting and optimism of the model when applied to new patients. The adjusted odds ratios (ORadj) and corresponding 95% CIs were calculated. In the final model, the R^2 Nagelkerke was used as a measure of the power of combined variables in predicting underassessment. All data analyses were performed with SPSS version 21.0 (IBM Corporation, Armonk, NY) and R software version 3.0.3 (R foundation, Vienna, Austria).

RESULTS

Patients' characteristics

Between September 2011 and July 2013, 803 adult patients with isolated musculoskeletal extremity injury provided written informed consent. Data of 541 patients, who filled in both ED- and follow-up questionnaire were used for analyses. Of two patient's, the nurse's pain score was not registered and therefore excluded from analyses. Median age of the 539 patients was 45.9 years (IQR 33.9-59.2) and 57.9% were women (Table 1). Pain prevalence at admission was high; 533 out of 539 patients (98.9%) reported pain. Most patients (73.1%) had a fracture; common injury sites were wrist (16.8%) and ankle (21.6%). Before injury ,5.2% of the patients had symptoms of depression and 9.6% symptoms of anxiety. Furthermore, 3.9% had

symptoms of pain catastrophizing and symptoms of kinesiophobia were present in 40.4% of patients.

Table 1: Characteristics of 539 patients with acute musculoskeletal injury

Variable		N (%)
Sociodemographics		
Age (in years), median (IQR)		45.9 (33.9-59.2)
Sex	*Women*	313 (57.9%)
Educational	level	78 (14.5%)
	Medium	286 (53.1%)
	High	172 (31.9%)
Pain factors		
Prehospital analgesic use		200 (37.1%)
Pain at admission		533 (98.9%)
Injury factors		
Injury type	*Fracture*	394 (73.1%)
	Luxation	26 (4.8%)
	Distortion	66 (12.2%)
	Contusion	42 (7.8%)
	Muscle rupture	11 (2.0%)
Site of injury	*lower*	278 (51.6%)
Urgency Level		375 (69.6%)
	Urgent	143 (26.5%)
	Very urgent	21 (3.9%)
Time between injury and ED admission	*<2 hours*	255 (47.3%)
	≥2 and ≤24 hours	202 (37.5%)
	>24 hours	82 (15.2%)
Clinical factors		
RAND 36, Physical Component Score, median (IQR)		56.4 (51.7-58.7)
	Poor physical health (<51.7)	134 (24.9%)
Psychosocial factors		
RAND 36, Mental Component Score, median (IQR)		54.5 (49.7-57.3)
	Poor mental health (<49.7)	134 (24.9%)
HADS score depression, mean (SD)		3.5 (3.1)
	Symptoms of depression (>7)	28 (5.2%)
HADS score anxiety, mean (SD)		1.9 (2.8)
	Symptoms of anxiety (>7)	52 (9.6%)
Pain Catastrophizing Scale score, mean (SD)		8.4 (7.3)
	Symptoms of pain catastrophizing (≥24)	21 (3.9%)
Tampa Scale for Kinesiophobia score, mean (SD)		35.7 (6.4)
	Symptoms of kinesiophobia (≥37)	218 (40.4%)

Disagreement in pain assessment

The average patients' self-reported pain score was NRS 6.5 (95%CI 6.3-6.7) and the nurses' pain score was NRS 4.0 (95%CI 3.9-4.1), a difference of 2.4 (95%CI 2.2-2.6) ($p<0.01$). A comparison nurses' and patients' self-reported pain scores gives a spearman correlation coefficient between the two measures of 0.36.

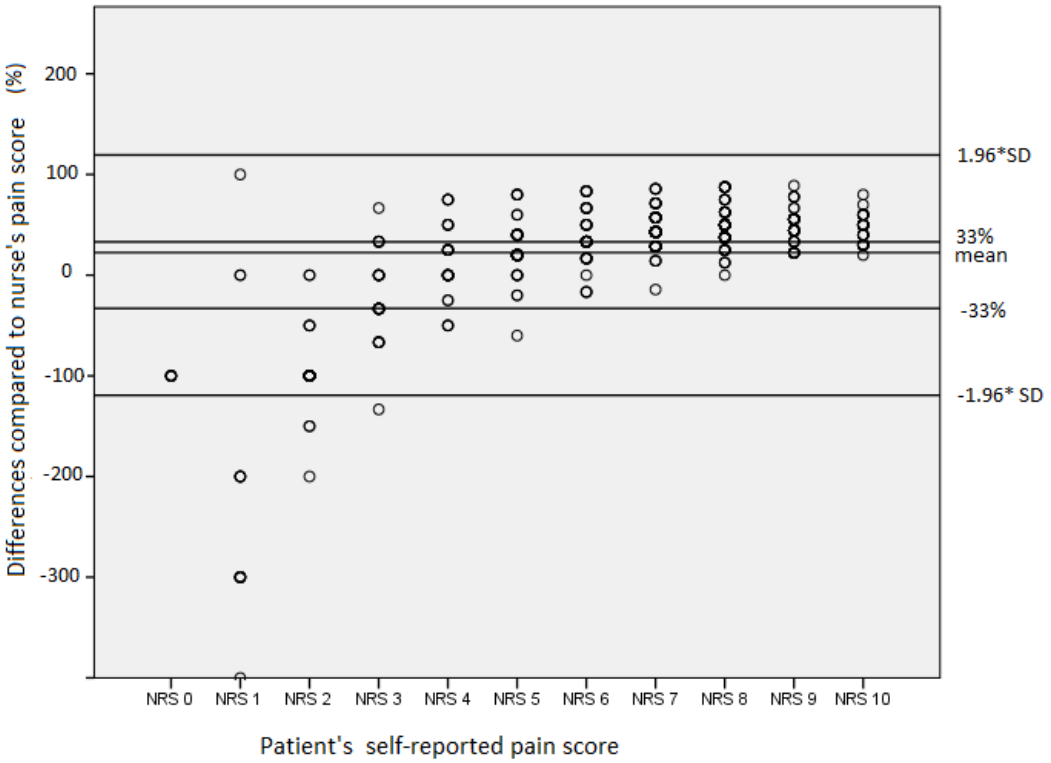

Figure 1: Bland–Altman plot of the differences between nurse's and patient's self-reported pain scores. The area within the lines of 33% and -33%, represents no clinically relevant difference on a NRS for acute pain. It is evident that many data points lie outside this range.

A Bland–Altman plot of the differences in pain measures is shown in Figure 1. The plot includes the mean and 1.96 SD lines, as well as reference lines depicting 33% and -33%. Pain score discrepancies between -33% and 33% represent a difference that is not clinically relevant. Many data points are outside this range. The agreement between nurse's and patient's self-reported pain score was only 27%. Sixty-three percent of nurses rated the patient's pain level as less intense than patients' self-reported level and almost 10% of nurses over assessed patients' pain.The figure shows how more severe the patient's pain is, how more often pain is under assessed by the nurse. However, the margin of error in pain assessment is higher when patients reported mild pain.

Table 2: Potential risk or protective factors predictors of underestimation of patient's pain by the nurse (n=539)

Potential risk and protective factors				
		Pain intensity at ED admission		
variable		Underestimation (n)	OR (95% CI)	p
Sociodemographics				
Age (in years)	*18-29(ref.)*	72/112 (64.3%)	1	0.98
	30-39	43/66 (65.2%)	1.04 (0.55-1.96)	
	40-49	64/105 (61.0%)	0.87 (0.50-1.50)	
	50-59	80/129 (62.0%)	0.97 (0.54-1.53)	
	60-69	81/127 (63.8%)	0.98 (0.58-1.66)	

Table 2: Continued				
Sex	Men *(ref.)*	129/227 (56.8%)	1	
	Women	211/312 (67.6%)	1.59 (1.11-2.26)	0.01
Educational level[1]	*High (ref.)*	99/172 (57.6%)	1	0.17
	Medium	186/286 (65.0%)	1.37 (0.93-2.02)	
	Low	53/78 (67.9%)	1.56 (0.89-2.75)	
Alcohol consumption	*weekly or less (ref.)*	160/246	1	0.37
	More than once a week	175/286	0.85 (0.60-1.21)	
Smoking	*No (ref.)*	297/444	1	0.07
	Yes	64/89	1.62 (0.98-2.67)	
Pain factors				
Pre-existing chronic pain[1]	*No (ref.)*	261 /425 (61.4%)	1	0.14
	Yes	76/110 (69.1%)	1.41 (0.90-2.20)	
Prehospital analgesics *use*	*No (ref.)*	199/335 (59.4%)	1	0.02
	Yes	139/200 (69.5%)	1.56 (1.07-2.26)	
Injury factors				
Type of injury	*Fracture (ref.)*	242/394 (61.4%)	1	0.02
	Luxation	12/26 (46.2%)	0.54 (0.24-1.20)	
	Others	86/119 (72.3%)	1.64 (1.04-2.57)	
Site of injury	*Upper limb (ref.)*	150/261 (57.5%)	1	0.01
	Lower limb	190/278 (68.3%)	1.60 (1.12-2.27)	
Urgency Level	*Standard(ref.)*	265/375 (70.7%)	1	<0.01
	Urgent	72/143 (50.3%)	0.42 (0.28-0.63)	
	Very Urgent	3/21 (14.3)	0.07 (0.02-0.24)	
Time between injury and ED-visit	*>24 hours (ref).)*	55/82 (67.7%)	1	0.07
	≥2 and ≥24 hours	137/202 (67.8%)	1.04 (0.60-1.79)	
	< 2 hours	148/255 (58.0%)	0.68 (0.40-1.15)	
Clinical factors				
Physical Health status	*Good (ref.)*	250/401 (62.3%)	1	0.40
	Poor	89/134 (66.4%)	1.20 (0.79-1.80)	
BMI[2]	*Normal weight (ref.)*	174/284	1	0.84
	Underweight	5/8	1.05(0.25-4.50)	
	Overweight	117/179	1.19 (0.81-1.76)	
	Obesity	37/59	1.14 (0.64-2.05)	
Comorbidity	*No (ref.)*	234/379	1	0.33
	Yes	106/160	1.21 (0.83-1.79)	
Psychosocial factors				
Anxiety before injury [2]	*No (ref.)*	294/482 (61.0%)	1	<0.01
	Yes	43/52 (82.7%)	3.44(1.58-7.47)	
Depression before injury[2]	*No (ref.)*	315/505 (62.4%)	1	0.18
	Yes	21/28 (75.0%)	1.81 (0.76-4.34)	
Pain catastrophizing[3]	*No (ref.)*	307/486 (63.2%)	1	0.10
	Yes	17/21 (81.0%)	2.47(0.82-7.48)	
Kinesiophobia[3]	*No (ref.)*	177/285 (62.1%)	1	0.42
	Yes	143/218 (65.6%)	1.16 (0.81-1.68)	
Mental Health status	*Good (ref.)*	246/402 (61.2%)	1	0.07
	Poor	93/133 (69.9%)	1.47 (0.97-2.25)	

[1] Missing 1 ≤5 [2] Missing 5 ≤10 [3] Missing 10 ≤ 40 ref.= reference group

Risk factors for underassessment of pain

Most potential risk factors were in univariate models to some extent associated with underassessment by nurse except for age, BMI, kinesiophobia and physical health (Table 2). However, only seven risk factors including sex, educational level, prehospital analgesic use, site of injury, smoking, anxiety and urgency level, independently contributed to the prediction of underassessment (Table 3). Other risk factors, which seemed relevant in univariate models such as type of injury and time between injury and ED-visit were not independent risk factors. Apparently, their predictive information was already covered by the remaining factors. The reduced model including the seven predictors showed good calibration (non-significant Hosmer–Lemeshow test p=0.99) and discriminative ability (c-statistic 0.72; 95%CI 0.66-0.76). Internal validity was good; the bootstrapping procedure yielded an optimism-corrected c-statistic of 0.70 and a shrinkage factor of 0.86. Urgency level (ORadj=11.51; 95%CI 4.61-63.56) and anxiety (ORadj=2.22; 95%CI 1.08-5.95) were strong prognostic factors for underassessment of patient's pain levels. With the risk score presented underneath Table 3, the risk of underassessment can be calculated for each individual patient.

Table 3: Reduced and extended (final) model to predict underassessment of patient's pain by the nurse

	Reduced model		Extended (final) model	
	β	p	β *	ORadj (95%CI)*
Sociodemographic factors				
Sex, Women	0.43	0.04	0.37	1.45 (1.03-2.33)
Educational level Middle (versus High)	0.20	0.37	0.18	1.19 (0.79-1.91)
Educational level Low (versus High)	0.72	0.04	0.62	1.85 (1.05-4.00))
Smoking	0.58	0.05	0.49	1.64 (0.98-3.21)
Pain-related factors				
Analgesics use before admission	0.38	0.08	0.33	1.38 (0.95-2.24)
Biomedical factors				
Site of injury, lower extremity	0.47	0.02	0.40	1.50 (1.07-2.39)
Psychosocial factors				
Anxiety	0.93	0.03	0.80	2.22 (1.08-5.95)
Others				
Urgency Level. Urgent (versus very	1.72	0.01	1.48	4.38 (1.48-
Urgency Level. Standard (versus very	2.84	<0.01	2.44	11.51 (4.61-
Intercept	-2.83		-2.35	
C-statistic	0.72			
Nagelkerke R^2	0.19		0.15	

*****Regression coefficient and corresponding odds ratio after bootstrapping (i.e. adjusted for overfitting). The shrinkage factor was 0.86

\# 53 missing values in multivariate analysis

DISCUSSION

Assessment of pain is difficult as pain is a highly subjective and personal experience, which is hardly clinically measurable with objective criteria. In the PROTACT study, nurses significantly underassessed patient's pain with a mean difference of 2.4 on an 11-points NRS. More

important than a statistical significant difference between both assessments is the issue of clinical relevant difference. Earlier findings have demonstrated that a difference of 33% in acute pain scores is clinically relevant (30), so pain assessments between nurses and patients are deemed to be accurate if the differences between the two scores are even or less than 33%. In a majority of 63 percent patient's pain was under assessed by the emergency nurse and in almost 10% the nurse over assessed patients' pain intensity. Pain was in particularly under assessed in women, in persons with a lower educational level, in patients who used prehospital analgesics, in smokers, in patients with injury to the lower extremities, in anxious patients and in patients with a lower urgency level.

The literature already suggested that clinicians including nurses have a tendency to under assess patient's pain (14). Discrepancies between patients' self-reported pain intensity and the documented pain intensity by clinicians were described in different clinical settings (2, 3, 14, 32-34). These discrepancies are remarkably consistent across different patient diagnoses and clinical settings (14). Of concern is the trend to under assess patients' pain, especially in patients who report severe pain (14). In present study,the pain of patients with severe pain were more often under assessed while the pains of patients with mild pain were more often over assessed.

In the emergency department, the percentage of underassessment of pain is high, ranging from 40% to 77%. The highest underassessment of pain levels are noted in patients with musculoskeletal injuries and abdominal pain (2, 3). One study revealed the percentage of underassessment in patients with musculoskeletal injuries, fractures or dislocations to be even up to 79% (3). This PROTACT-study found a percentage of 63% underassessment in a musculoskeletal pain population, which included patients with severe injuries like complex fractures as well as patients with mild injuries such as small contusions. This percentage seems to be reliable, but is difficult to compare with other studies because of variation in methodologies (e.g. different cut off points for accurate assessment and discrepancy) and study population. The present study found a moderate correlation assessment of 0.36 between patient's and nurse's assessment. This is in line with earlier correlations ranging between 0.21 and 0.38 (33, 35, 36).

It seems there is a lack of good pain assessment. Because pain cannot be proved or disproved, patient's pain intensity self-reports should be accepted as the gold standard and takes precedence over patient's behaviour and vital signs. However, earlier findings show that observations of patients pain behaviour is the most potent factor in decision making related to pain (37). The discrepancies in this study also show that nurses don't rely on patient's self-reported pain and documented a pain score which is in most cases (63%) less

intense. One reason might be that nurses often belief that patients exaggerate reports of pain (36).

The PROTACT-study revealed an association for several sociodemographic factors with underassessment of pain. Women are at higher risk for underassessment of their pain levels than men. Differences in pain perception between men and women have been reported before in emergency departments (38-41). Women experience pain more intense and are more sensitive to pain, both in a clinical as in an experimental settings (42). Moreover, a prospective study found that women were 13 to 25% less likely than men to receive analgesics (43). Difference in educational level is a commonly used marker for social inequality. In current study, patients with a lower educational level are at high-risk for underassessment. This is in contrast with a study in surgery patients with abdominal pain in which educational level was unrelated with difference between nurses 'assessment and patients 'assessment (33).

In the PROTACT-study, one-third of the patients had already used analgesics before attending the emergency department; somewhat less than 44% found in previous studies (5). Patients who already used analgesics in the prehospital phase had a higher risk to be rated as having less severe pain by the nurse. The analgesics may not yet fully work between the time of injury onset and ED admission, but nurses might take the analgesic use, the lagging possible pain relief, into account during their assessment of pain. Furthermore, the ability to assess patients' severity of injury was in this study limited to ED-assigned triage urgency categories. A low urgency level seems to be a really strong predictor for underestimation of patient's pain, suggesting the pain of patients with mild injuries will be more under assessed.

Many psychological factors have been indicated as potential prognostic factors for individual pain experiences, like kinesiophobia, anxiety (44, 45) and catastrophizing (46). Of all psychological measures, anxiety is the only independent risk factor for underestimation of pain. The positive relationship between anxiety and pain is a common experience in clinical settings. Anxiety levels have been shown to predict pain severity and pain behaviour in acute pain patients (47). Anxiety can also exacerbate the pain sensation (48). Studies have confirmed the enhancing effect of anxiety on pain for different components and measures of pain, e.g. ratings of pain intensity and pain discrimination (44, 45).

The implications of cigarette smoking to the practice of pain medicine are complex and not well understood. Smoking a nicotine-containing cigarette nearly doubled the pain awareness thresholds in an experimental setting and pain tolerance thresholds were also elevated. On the other hand is nicotine showed to have analgesic properties. The complex relationship between the multiple factors for example psychosocial factors associated with smoking needs to be explored to elucidate the mechanisms responsible for the interaction (49)

The low value of explained variance in the prediction model means that the independent risk factors can only explain a small fraction of variance between the individual patients. Variables

might have been missed that play a role in the complexity of pain and influence discrepancies in pain assessment between patients and nurses, such as patient-nurse interaction, nurse and environmental characteristics. Studies are needed which include all these possible factors.

Implications for emergency nurses

Knowing which factors can increase risk for discrepancies in pain assessment is a necessary first step towards optimizing pain management and pain relief. Nurses should be aware in which patients they usually underassess the pain. Underestimation of patients' pain can have negative effects if appropriate treatment is withheld. Not only in terms of patient suffering, but unrelieved pain may also lead to adverse physiological effects such as cardiovascular side-effects and negative effects on respiratory function, coagulation and immune function (50, 51).

Pain assessment is the keystone of adequate pain management. Unfortunately, the PROTACT-study shows inaccurate assessments are more rule than exception. This may highlight a need for better education for nurses about pain and pain assessment. An unwritten assumption that is evident within the literature is that pain management would improve if pain assessment tools were used routinely in clinical practice. By drawing attention to patients' self-reported pain and minimizing assumptions, and the routinely use pain assessment tools, pain management in the ED might improve.

In summary, there are several issues that can be learned and built on from this study. Inaccurate assessment of pain is still a problem. This results in under-treatment of clinically unacceptable pain if nurses rely only on their own assessment of pain to provide pain treatment. This might lead to unnecessary suffering and delay in recovery of the patient. Strategies focusing on awareness among nurses of which patients are at high-risk for underassessment of pain are needed. From a clinical point of view, further studies are needed to examine whether more accurate pain assessment improves pain management and other patient outcomes.

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Chapter 7

General Discussion

Acute musculoskeletal pain following extremity injury is one of the primary complaints of patients in the Emergency Department (ED). Multiple factors may be responsible for transition from acute to chronic pain and research into the origin and development of chronic pain is extremely important to prevent progression. For instance, once pain is chronic the treatment options are limited and relative ineffective. Chronic pain has been shown to be a major health problem. Moreover, chronic pain often leads to psychosocial problems, work disability and health care overutilization (1). Therefore chronic pain is not only a disease burden, but also a substantial economic burden (2).

The primary aim of this thesis was to determine prognostic factors involved in the transition from acute to chronic pain after extremity injury. This will give the ability to target high-risk patients in the emergency setting and to intervene and to modify the presence of these factors thereby preventing the development of chronic pain. Furthermore, secondary objectives were to determine the current state of pain management following extremity injury and the consequences of extremity injury and developing chronic pain post-injury in terms of quality of life.

In this general discussion the findings of the PROTACT- study will be put into the perspective of current knowledge, and further elaborate on conceptual and methodological issues concerning pain management in emergency care and predictions and patient outcomes in terms of persistence of pain and quality of life. Finally, recommendations for further research will be formulated and the implications for clinical practice and education will be described, and main conclusions will be drawn.

DISCUSSION OF THE MAIN FINDINGS

Incidence and prognostic factors for chronic pain

The link between acute and chronic pain has been subject of investigation in many studies (3, 4). The large variation on incidence of chronic after musculoskeletal injury (11 to 56%) in literature (5-8) is probably due to differences in study design, patient populations, and definitions of chronic pain. In the PROTACT-study, a prospective follow-up study including a large population of patients with both minor and major isolated musculoskeletal extremity injuries, a comprehensive set of potential prognostic factors was used to determine incidence and to identify prognostic factors for chronic pain. At 6 months post-injury, 43.9% of the patients in the PROTACT-study had still some degree of pain and 10.1% had developed chronic pain, defined as persisting pain with a pain score ≥4 on the site of injury (Chapter 3). This percentage of chronic pain was similar to other studies reporting these figures and confirm chronic pain as common complication after extremity injury. Patients aged over 40 years, in poor physical health, with pre-injury chronic pain, pain catastrophizing, high urgency level (as surrogate for injury severity) and severe pain at discharge were found to be at high risk for

developing chronic pain. Only two prognostic factors, severe pain at discharge and pain catastrophizing, are potentially modifiable variables.

While the PROTACT-study was recruiting patients, two systematic reviews have documented prognostic factors for chronic pain after orthopaedic injury (9, 10). The first review, based on ten studies showed strong evidence supporting the association of women, older age, high pain intensity, pre-injury anxiety or depression, and lower level of education with persistent pain outcomes (9). Moreover, there was moderate evidence supporting the association between early post-injury depression and anxiety with persistent pain. Injury severity was not a risk factor for ongoing pain. Due to the limited number of studies, the use of different constructs to measure the same factor, and the methodological limitations associated with many of the studies, the review was, according to the authors, only able to reliably identify a limited set of factors that predicted the development of chronic pain. In the second systematic review, major findings included a trend towards strong association between lower extremity injuries and chronic pain, but as in the previous review, a weak relationship with injury severity (10). Frequently cited prognostic factors for chronic pain post-injury were symptoms of anxiety and depression, patient perception that the injury was attributable to external sources (i.e. they themselves were not at fault), cognitive avoidance of distressing thoughts, alcohol consumption prior to injury, lower educational status, being injured at work, eligibility for compensation, pain at initial assessment, and older age. Also these authors concluded that perhaps the most striking finding from the synthesis was the wide variability of results, which was likely due to many factors such as variation in study designs and populations.

Remarkably, pain catastrophizing, one of the most powerful prognostic factors of the PROTACT-study was not found in both systematic reviews. However, only a few studies analysed the association between pain catastrophizing with chronic pain as outcome of injury. A study conducted in patients with single wrist or ankle fracture patients with higher levels of pain catastrophizing had an increased, almost 6-fold risk of poorer strength recovery at 6 months (11). Also a recent 'state of the art' article concluded pain catastrophizing as significantly contributing to the development of chronic pain post-injury (12). Further understanding of the link between psychological health and the development of chronic by exploring the role of pain catastrophizing has already been suggested by experts (13), suggesting the potential importance of this factor in the transition from acute to chronic pain.

Both reviews identified no studies of prognostic factors of chronic pain following non-life-threatening, less serious, injuries. The results of the PROTACT-study as a large, prospective follow-up study of a heterogeneous patient population with both minor and major injuries will add knowledge in understanding the risk factors for persisting pain in patients following less serious, minor orthopaedic or extremity injury. Furthermore, the choice of which and

how much potential factors would be included in the study might be crucial in finding good prognostic factors for the development of chronic pain. In the PROTACT-study we included wide range of factors found in earlier studies about prognostic factors for persistence of pain after injury, acute back/neck pain, whiplashes and surgery. Remarkably, almost all measured potential prognostic factors were in univariate analyses associated with the persistence of pain, confirming the complexity of pain.

Unfortunately, there are potential important factors for developing chronic pain which were not included due to the fact that the study was conducted in the emergency setting and because the study aimed to identify factors that are easily measurable to use it as a 'simple, non-invasive screening tool'. First of all, the genetic predisposition. Given the complexity of pain, many genes might contribute to the transition of chronic pain. There is a genetic basis for individual variations in pain perception and the development of chronic pain (14). Also the nociceptive stimulus processing and sensory function of the patients, with can be measured with psychophysical quantitative sensory testing (QST), is promising to identify high-risk patients. The estimation of sensory thresholds can be used to identify nociceptive disease as happens in chronic pain development. This QST is a potentially useful tool for the prediction of post-surgery chronic pain (15, 16). However, the application of QST as prediction tool immediately following injury is unusable because patients are already in pain.

Consequences of extremity injury and developing chronic pain on patient's quality of life

Pain and musculoskeletal extremity injury are inevitably interrelated to each other. Acute musculoskeletal pain may have many consequences including medical, psychosocial and economic problems. Risks include sequelae, disability and functional limitations, loss of independence and development of chronic pain (1, 17-19). In addition to these outcome parameters, Health-related Quality of Life (HRQoL) has become more important when it comes to evaluating outcome following injury and disease burden. HRQoL is increasingly being used to measure outcomes of the impact of injury on health from the patient's perspective. HRQoL encompasses those aspects of health and well-being valued by patients, specifically, their physical, emotional, and cognitive function, and their ability to participate in meaningful activities within their family, workplace, and community. It is important to obtain greater insight into HRQoL, functional outcome and recovery patterns, of injured patients to quantify the impact of injury on health over time.

In the PROTACT-study there is ample evidence that injuries are painful and cause significant interruption to quality of life in the early post-injury phase (Chapter 4). High prevalences of health problems were found. Changes immediately after injury are seen for 7 of the 8 HRQoL dimensions, except for general health which is recalled over the last year. The highest effect of injury in the acute phase was seen in role limitations due to patient's physical health; patients are limited in their physical activity by injury and are disabled to do their daily activities.

Also in the long-term the consequences of injury are present. The overall health state of injured patients at 6 months post-injury was significantly lower than before injury. A significant decrease was present in physical health state dimensions vitality, bodily pain, physical functioning and physical role functioning. It was already known extremity injury could be a serious problem maker in impairment of quality of life (20). Unfortunately, the large variation in use of HRQoL instruments, study populations, and time points of assessment in current studies impedes comparison of HRQoL scores of the PROTACT-study with other studies.

Measuring the impact of extremity injury in general is particularly challenging due to the large variation in injury type, severity and patient outcomes. To examine whether reduced scores of HRQoL could be observed for specific groups of patients, recovery pattern by injury type and patterns between patients who developed chronic pain and those who did not were compared. HRQoL is, both in short- and long term, the highest decrease was seen in patients with lower proximal injuries, suggesting these patients are suffering the most from the consequences of injury. This is in line with the findings that patients with orthopaedic injuries, particularly injuries of the lower limb, have poor functional outcomes and quality of life (21, 22). It will be interesting to determine the cause for the observed reduced quality of life of these injured patients and to suggest injury-specific treatment adaptations to optimize their quality of life.

That perception of pain plays a crucial role in our daily life, is revealed by the impact of developing chronic pain on HRQoL. The impact on HRQoL is much higher in patients who developed chronic pain post-injury. Patients who developed chronic pain had a considerable loss in HRQoL both on physical and mental health state. This revealed the health impact of chronic pain following extremity injury. The single index of health (utility score), a score that contributes to a composite health outcome measure, is decreased with 0.135 points in comparison with pre-injury state to 0.65 at 6 months follow-up. At 12 month, the score is little improved to 0.70. This difference is higher than the minimally important difference for the utility score measured SF-6D, which is 0.041 (23). Moreover, the utility score at six month of 0.65 found in patients who developed chronic pain is substantially lower than in the rest of the study population (0.83). These latter patients will regain their pre-injury level of function. One other reason that indicates prevention of chronic pain is necessary. The utility score are important for the development of future interventions and policy makers, because these can be used in health economic evaluations as a basis of cost-utility analysis, the most common type of health economic evaluation used in health technology assessment.

Improving pain management following extremity injury

The inadequate and ineffective pain treatment in emergency care is a well-documented problem worldwide (24) The PROTACT-study shows that oligoanalgesia (inadequate pain relief) is to be a serious problem in patients with acute musculoskeletal pain following

extremity injury (Chapter 2). The prevalence of pain following extremity injury is high: 4 out of 5 patients presented to the emergency department (ED) with moderate to severe pain. And even though sixty percent of the patients used analgesics somewhere in the chain of emergency care, more than two-third of the patients still suffered moderate to very severe pain at discharge from the ED. Paradoxically, many patients who report having moderate or severe pain at discharge are satisfied with their pain treatment. Thus, the extent to which patients who indicate moderate pain really suffer remains uncertain. In the ED, approximately forty percent of the patients received analgesics. The importance of administration of this pain medication in the ED is reflected by the significant and clinically relevant higher reduction of pain. And as pain is a primary motive of the patients to present themselves to the ED, pain relief should be one of the primary foci of emergency care provision. Based on the current results and knowledge of previous research we might conclude it is not and that there is still room for improvement in acute pain management following extremity injury.

Severe pain at discharge is found to be one of the prognostic factors for the transition from acute to chronic pain. This arose the question whether and how this potentially modifiable prognostic factor can contribute to a better clinical outcome.

One of the theories postulated for the progression from severe acute to chronic pain is central sensitization, whereby the nociceptive neurons increase their response to non-painful stimuli and develop spontaneous activity (25). This suggests if acute pain is treated adequately, central sensitization will not occur. Furthermore, it is known patients become increasingly more sensitive to painful stimuli if pain is uncontrolled for a longer period of time (26), thus timely and adequate treatment of pain might intervene the progression from acute to chronic pain and thereby reduce the risk of developing chronic pain.

Although the importance of timely and adequate pain management in the ED is acknowledged, it is also recognized that there are many barriers for effective pain relief in the emergency setting, such as workload and attitude problems, lack of patient input, knowledge deficits and misconceptions on the need of effective pain management (27, 28). Worldwide, different strategies to enhance pain management have been developed in response to inadequate pain relief such as pain management protocols or clinical guidelines and staff educational interventions (29-35).

The efficacy of a pain protocol in EDs seems persuasive. Therefore, during the execution of the PROTACT-study, a nurse-initiated pain protocol (36) was implemented in the ED. With the implementation of this protocol, emergency nurses are allowed to administer analgesics, including opioids, according to a pre-defined protocol, without the patient being first assessed by an ED-physician. This is important because depending on the workload of the ED staff, there can be a considerable delay between the patient's presentation and being seen by an ED-physician, and even a longer time to analgesic administration (37). Especially in patients presenting to the ED with minor extremity injuries, a nurse-initiated pain protocol might be useful to optimize pain treatment. These patients are usually triaged to a low (semi-

urgent) triage category which typically results in an extended waiting time for pain relief or even oligoanalgesia (38).

The pre–post intervention comparison shows that the implementation of a nurse-initiated pain protocol in the ED appears to lead to an increase of analgesic provision, a shorter time to analgesics and a higher (clinically relevant) pain relief in patients with acute musculoskeletal pain following extremity injury (Chapter 5). Although the results showed that the amount of severe pain can be reduced, the prevention of chronic pain if effective pain treatment is provided was not definitely demonstrated.

Moreover, despite improvements in pain management by the implementation of the protocol, a high percentage of patients was still discharged with moderate to severe pain. This could be partly explained by protocol adherence, which was not optimal. For instance, there was a discrepancy between the content of the protocol and modus operandi. Although the analgesic provision was highly significantly improved, only 68% of the patients with moderate to severe pain who should receive analgesics according to the protocol were actually offered these analgesics.

Accurate assessment

Remarkably, after protocol implementation many patients with severe pain did not receive opioids but were downgraded to use paracetamol or NSAIDs instead of opioids. A reason for this kind of protocol deviation might be due to discrepancies in pain assessment between patients and nurses. In the overall PROTACT-study patients' self-reporting pain intensity was used instead of the documented pain scores assessed by nurses. Because a clinically, objective measurement for the experience of pain is not available, the gold standard of pain assessment relies on patients' self-report. "Pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does" (39). The nature of pain itself complicates the assessment and subsequent management of pain. The perception of pain is not simply a function of the amount of physical injury, it is also influenced by factors such as past experience, attention, expectation and anxiety, as well as the meaning of the situation in which pain occurs.These factors have influence on patient's suffering and pain behaviour.

Inaccurate pain assessment is a consistent finding worldwide in various clinical settings including the ED. Nurses are not always rely on patient's self-reported pain and apparently make their own assessments of patients' pain based on a combination of nonverbal cues, such as type of and time since injury or patient behaviour (40). Due to the subjective nature of pain, it can be very difficult to quantify patients' pain (41). In the emergency setting, also the fact that pain is a discriminator of the Manchester triage system (MTS), the system which was used to determine the urgency level of patients in the ED, might be a reason to under assess patient's pain in the sometimes overcrowded ED.

Underassessment of pain may occur when nurses attempt to calculate the severity of patients' pain experiences thereby placing patients at risk of inadequate pain relief. In the

PROTACT study nurses significantly under assessed patient's pain with a mean difference of 2.4 points on an 11-points NRS (Chapter 6). This can result in under-treatment of pain if the emergency nurses rely on their assessment to conduct further pain treatment. Discrepancies in assessment are identified before as the most powerful predictor of poor pain management (42, 43). Accurate pain assessment by nurses is crucial for effective pain management.

As health care becomes more and more patient-centred, healthcare providers must explore patients' preferences and provide them with information that helps them to make the right decisions (44). Therefore, nurses have to try to understand patients' pain and determine their pain management needs. In our population, pain was in particularly under assessed by nurses in women, in persons with a lower educational level, in patients who used prehospital analgesics, in smokers, in patients with injury to the lower extremities, in anxious patients and in patients with a lower urgency level (surrogate for minor injuries). There should be awareness among nurses that these patients are at high-risk for underassessment.

Pain experts have stated that pain scores should be seen as the fifth vital sign and pain assessment also received extra attention of policy makers during the last decade. With the implementation of the Dutch National Patient Safety Programme (VMS), wherein one of the goals is the prevention of unnecessary patient suffering as a result of pain, there is nowadays more and more attention to pain on the workplaces, especially to assessment and evaluation of pain. This trend will contribute to an improvement in pain management and outcomes after extremity injury.

FUTURE PERSPECTIVES

Recommendations for further research

Intervention for risk factor pain catastrophizing

In the PROTACT-study, pain catastrophizing has been demonstrated to be a potential modifiable risk factor for chronic pain after extremity injury. Cognitive-behavioural interventions, techniques such as graded increases in activity, activity scheduling, relaxation training, and cognitive therapy for individuals with acute or subacute pain, have been recognized to address prognostic factors such as pain catastrophizing, while being acknowledged as the most effective treatments in the chronic pain context (45). These interventions promote individuals positive perception of their ability to function and supporting them to develop self-care behaviours (e.g. skills to manage) even when patients experience pain.

Some empirical evidence revealed that cognitive-behavioural intervention could prevent the transition from acute to chronic pain several months post-injury. Reductions in levels of catastrophizing have been achieved through targeted interventions, and have been shown to prospectively predict improvements in pain intensity (46-48). However, no such interventions have yet been developed nor studied in patients with acute pain following extremity injury.

Accordingly, a cognitive-behavioural intervention applied in the acute phase of pain, which could limit the development of chronic pain appears to be promising.

More unified methodologies

The variation in methodology between studies which aimed to determine incidence rates and identify prognostic factors for chronic pain leads to the recommendation that future research studies in this field use a more common and systematic approach in order to better identify the scope and magnitude of those at high-risk of developing chronic pain following extremity injury. This can be accomplished by utilizing study designs that explore the transition from acute to chronic pain over time (i.e. prospective, longitudinal), with an emphasis on obtaining initial assessments as close to the time of the injury as possible to ensure that the results are able to consider patient presence of pain prior to the injury. Moreover, it is important to use during initial and follow-up assessment comprehensive and validated measures for pain following components of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) guidelines (49). These include measurement of pain intensity, assessed by a 0 to 10 numerical rating scale. Moreover, it includes a general measure of physical functioning and/or pain interference, which are important components of chronic pain. The IMMPACT group recommends the SF-36 to assess physical functioning and either the interference items of the Brief Pain Inventory or the Multidimensional Pain Inventory interference scale. The use of these generic measures of physical functioning and pain interference allow comparisons across different injury groups. Furthermore, the IMMPACT recommendations for outcomes of pain studies have stressed the importance of emotional functioning and recommend capturing depression as a core outcome. Although the IMMPACT group recommends the use of the Beck Depression Inventory for measuring depressive symptoms, the Hospital Anxiety and Depression Scale (HADS) may be more appropriate in epidemiological studies which investigate the transition from acute to chronic pain in large cohorts (50). HADS is a very brief screening instrument, and it measures besides depression also anxiety and is therefore recommended in studies following injury. Finally, the IMMPACT group recommends ratings of overall improvement, assessed by the Patient Global Impression of Change scale. This scale offers a flexible, quick, and simple method of charting self-assessed clinical progress and correlates with pain, disability, and quality-of-life measures (51).

One other important feature to consider in studies is the timing of follow-up to assess the transition from acute to chronic pain. Generally, it is accepted that pain that persists beyond the expected period of time for tissue healing is considered to be chronic pain. However, the specific timeframe constituting an expected healing period is variable and often difficult to ascertain. Timing of follow-up within studies ranged from months to years, making it difficult to compare results. Most studies use the IASP criteria for "chronicity" as pain persisting for 3 months or more. In the PROTACT-study (Chapter 5), a small improvement in pain and HRQoL

in some patients is seen between 6 to 12 months after extremity injury. Therefore, a period of at least 12 months follow up is recommended. Furthermore, future studies of prognostic factors for chronic pain after orthopaedic or extremity should at least include prognostic factors found in studies which were included in both systematic reviews (9, 10). And when interventions are designed on a specific prognostic factor to intervene the transition from acute to chronic pain, not only the effect on reducing this single risk factor, but also the effect on chronic pain development at follow-up is required and should be studied, if possible, in a randomized control trial.

Another important issue for future research is the extent to which the prognostic factor involved in the transition to chronicity differs from those involved in the maintenance of already established chronic pain. This approach highlights the importance of assessing outcomes at multiple time points after injury and implies that the transition to chronic pain and related psychosocial and functional dysfunction is a dynamic process that evolves over time. In the PROTACT-study, chronic pain outcomes were assessed at a single follow-up point at 6 months post-injury, assuming chronic pain is established in these patients. However, a small improvement in some patients was seen at 12 months post-injury (chapter 4). An analysis of prognostic factors for pain at different time points between injury and established chronic pain will lead to better examination of whether the factors involved in the transition to chronicity differ from those involved in the maintenance of already established chronic pain.

Better diagnosing chronic pain

In most studies, like the PROTACT-study, chronic pain is determined with patient's self-reported pain intensity at site of injury. But chronic pain is pain without a clear somatic substrate**.** In future epidemiological studies, once chronic pain in the patient is established, physical examinations in combination with quantitative sensory testing (QST) can be used to better diagnose chronic pain. With addition of physical examination to the patient's self-reported data, it can be determined if any other underlying pathology causes the experienced pain and with the use of quantitative sensory testing (QST) sensory changes in injured body parts can be quantified.

Clinical implications

Although pain is acknowledged as a major public health issue, the gap between the increasing knowledge of pain, treatment and the effective application of it is large (52). In the last decades there has been a shift from using only clinical outcome assessment to the development and validation of patient-reported outcome measures. Self-reported data from the patient's perspective provide additional insight into health outcomes and are needed to improve quality of care. In the PROTACT-study some important findings give opportunities to improve patient outcomes and quality of care following extremity injury.

Patient education to improve pain management

As one of the prognostic factors for chronic pain following extremity is pain severity in acute pain phase, the effective management of pain seems important to improve patient outcomes both on short-term and long-term. The PROTACT-study demonstrated a relative high percentage of patients who refused pain medication. It is desirable to educate patients about the importance of communicating unrelieved pain and the use of pain medication. Of course patients may decline these analgesics, but physicians and nurses should make sure that analgesic refusal is only made after the patient has had the opportunity to comprehend the possible consequences. Explanation regarding harmful effects of prolonged, untreated pain and side effects of pain medication leads to a decrease in analgesic refusal (53). This education also might stimulate the patient in self-management of taking pain medication at home.

More accurate pain assessment to improve pain management

Pain assessment is the keystone of adequate pain management. Unfortunately, the PROTACT-study shows inaccurate assessments are more rule than exception. This may highlight a need for better education for nurses about pain and pain assessment. An unwritten assumption that is evident within the literature is that pain management would improve if pain assessment tools were used routinely in clinical practice. By drawing attention to patients' self-reported pain and minimizing assumptions, and the routinely use pain assessment tools, pain management in the ED might improve.

Screening of high-risk patients for chronic pain

First of all, in the PROTACT-study six prognostic factors for the development of chronic pain following extremity injury were found. Of these factors, pain severity in acute pain phase and pain catastrophizing are potentially modifiable. Although the other factors are not modifiable, these can still be used to identify high-risk patients, which may have implications for patient information and the perspective of medical treatment and health care provision. Early risk factor screening has been implicated as one strategy to identify patients who may be at risk for poor clinical outcomes and as a potential method to improve the efficiency and effectiveness of care. Recently, there has been a surge of interest in using brief risk screening tools that include assessment of prognostic factors, to identify individuals at high-risk for chronic pain and to stratify treatment based on risk (54).

Currently, one such screening tool to prevent the transition of acute to chronic pain after acute back pain will be implemented in the Dutch GP-setting (by the author) and might be an example of future clinical implications of findings of the PROTACT-study. This so called STarT Back Tool combines nine repeatedly identified physical or modifiable psychosocial prognostic factors for the persistence of pain. The treatment intervention following screening is targeted on kinesiophobia and pain catastrophizing. Patients with low risk of an unfavourable

outcome will be reassured and encouraged to resume normal activities, but high-risk patients will receive near standard physiotherapy, also physiotherapy which is addressed on the psychosocial obstacles to recovery (55).

Although this work is still in its infancy, current findings contribute to identify repeatedly physical (e.g. older age) and modifiable psychosocial factors as input for the development of such a screening tool for extremity injuries. Questionable is whether the ED, which is often overcrowded, is the best place to conduct the screening or if it should be integrated in primary care. A possible new form of treatment in which injury rehabilitation and prevention of chronic care can be provided is e-health. E-health applications can be made accessible to many patients at low cost, and the content can be individualized (56). The development of web-based programs, home telemonitoring systems or mobile phone and tablet applications, for regular measurement of important outcomes such as pain intensity or movement patterns, or to measure treatment responses, offer considerable promise in improving patient care and outcomes.

CONCLUSION

In this thesis the results of a prospective follow-up study are presented, and confirmed chronic pain to be a common complication following injury. Six prognostic factors for the development of chronic pain following extremity injury were found, of which only pain severity in the acute phase and pain catastrophizing are potentially modifiable and thus useful to prevent chronic pain. This arises the question whether and how these findings can contribute to a better clinical outcome. To reduce inadequate pain relief in the ED, the implementation of a nurse-initiated pain protocol was studied. This implementation appears to lead to an increase of analgesic provision, a shorter time to analgesics and a higher (clinically relevant) pain relief in patients with acute pain following extremity injury. Although implementation showed that severe pain can be reduced, the prevention of chronic pain is not definitely demonstrated. Despite improvements in pain management, the results reflected by the amount of patients discharged with moderate to severe pain showed that there is still room for improvement in pain management. Accurate pain assessment by nurses is crucial for effective pain management. Following extremity injury, nurses significantly under assessed patient's pain. By drawing attention to patients' self-reported pain and minimizing assumptions, and the routine use of pain assessment tools, pain management might further improve. Furthermore, it is desirable to educate patients about the importance of communicating unrelieved pain and the use of pain medication. Due to the limited number of studies which identify prognostic factors for chronic pain following extremity injury and the different methodology which were used only a limited set of factors that predict the development of chronic is available. When future research studies use a more common and systematic approach in order to better identify the scope and magnitude of those at high-risk of developing chronic pain following extremity injury, this will, together with current findings,

contribute to identify repeatedly physical and modifiable psychosocial factors as input for the development of a brief risk screening tool for injured patient to the extremities.

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Summary

Samenvatting

SUMMARY

Acute pain is a frequent complaint of patients requiring emergency medical care. Acute pain as a result of (potential) tissue damage warns and protects the body from (further) damage. Normally, acute pain disappears along with the healing process. However, in some cases, persisting pain outlasts the healing process and no longer serves as a protecting mechanism. This pain without any useful biological function is called chronic pain. Chronic pain is prevalent and has an impact that often extends well beyond the pain itself. Chronic pain and related disability often leads to complex social and psychological maladaptations affecting patient's quality of life, leads to health care overutilization, as well as many other substantial costs for example due to productivity loss. It is increasingly recognized that acute and chronic pain represent a continuum rather than distinct entities. Chronic pain patients often relate their pain onset to acute injury such as surgery or trauma, drawing attention to the need to prevent the progression from acute to chronic pain. The transition from acute to chronic pain is still a complex and poorly understood developmental process. A range of injury-, psychosocial-, socio-environmental and patient-related factors has been associated with the persistence of pain.

Against this background, the PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients (PROTACT)-study was designed. The PROTACT-study was initiated as a one year prospective follow-up study with the primary aim to determine prognostic factors involved in the transition from acute to chronic pain after extremity injury. This will give the ability to target high-risk patients in the emergency setting and to intervene on one or more of these factors thereby preventing the development of chronic pain. Secondary objectives were to describe the current state of pain management following extremity injury and to determine the consequences of extremity injury and developing chronic pain post-injury in terms of quality of life. The PROTACT-study was conducted in adult patients, aged 18 until 69 years, who presented themselves to the emergency department (ED) of Medisch Spectrum Twente in Enschede with isolated musculoskeletal extremity injury caused by blunt trauma. During the 22 months inclusion period, 1994 adult patients with extremity injury attended the ED and met the study criteria. Of these patients, 803 participants provided written informed consent. Participants were asked during the follow-up period to complete 4 or 5 questionnaires. Data from the emergency medical services (EMS), ED and hospital electronic patient registry were collected. Collected data included potential prognostic factors, injury and pain-related characteristics, pain management and patient's perspective of their quality of life.

The inadequate and ineffective pain treatment in emergency care is a well-documented problem worldwide. **Chapter 2** shows that oligoanalgesia (inadequate pain relief) is a serious problem in patients with acute musculoskeletal pain following extremity injury. The

prevalence of pain following extremity injury is high: 4 out of 5 patients presented themselves to the ED with moderate to severe pain. And even though sixty percent of the patients used analgesics (pain medication) somewhere in the chain of emergency care, more than two-thirds of the patients still suffered moderate to very severe pain at discharge from the ED. The importance of analgesics in the ED is reflected by the significant and clinically relevant higher reduction of pain in patients who were administered pain medication.

Chapter 3 represents the outcome of the primary aim of the study. In the PROTACT-study, a comprehensive set of potential prognostic factors was used to determine incidence and to identify prognostic factors for chronic pain following both minor and major isolated musculoskeletal extremity injuries. At 6 months post-injury, 43.9% of the patients still had some degree of pain and 10.1% developed chronic pain, defined as persisting pain with a pain score ≥4 on the site of injury. Patients aged over 40 years, in poor physical health, with pre-injury chronic pain, pain catastrophizing, high urgency level (as surrogate for injury severity) and severe pain at discharge were found to be at high-risk for developing chronic pain. Only two prognostic factors, severe pain at discharge and pain catastrophizing, are potentially modifiable.

Acute musculoskeletal pain following extremity injury may have many consequences including medical, psychosocial and economic problems. Health-related quality of life (HRQoL) has become more important when it comes to evaluating outcome following injury and disease burden. In **chapter 4** the impact of extremity injury and chronic pain on health from the patient's perspective is described. There is ample evidence that extremity injuries are painful and cause significant interruption to quality of life in the early post-injury phase. High prevalences of health problems were found. Changes immediately after injury are seen for 7 of the 8 HRQoL dimensions, except for general health which is recalled over the last year. Also on the long-term the consequences of injury are still present. Overall health state of the injured patients at 6 months post-injury was significantly lower than before injury. A significant decrease was present in physical health state dimensions vitality, bodily pain, physical functioning and role limitations due to physical functioning.

That pain plays a crucial role in our daily life is revealed by the impact of developing chronic pain on HRQoL. The impact on HRQoL is much higher in patients who developed chronic pain post-injury; these patients had a considerable loss in HRQoL both on physical and mental health state. The single index of health (utility score) decreased with at least two times the minimally important difference; a change in outcome that a patient would identify as important. Moreover, the utility score at six months in patients who developed chronic pain is substantially lower than in the rest of the study population. These latter patients will regain their pre-injury level of function. One other reason that indicates prevention of chronic pain is necessary.

It is assumed timely and adequate treatment of pain intervenes the progression from acute to chronic pain and thereby reduce the risk of developing chronic pain. Worldwide, different strategies to enhance pain management have been developed in response to inadequate pain relief such as pain management protocols or clinical guidelines and staff educational interventions. The pre-post intervention study in **chapter 5** aims to evaluate the effect of a nurse-initiated pain protocol in the ED. With the implementation, emergency nurses were allowed to administer analgesics, including opioids, according to a pre-defined protocol, without the patient first being assessed by an ED-physician. This is important because there can be a considerable delay between the patient's presentation and being seen by an ED-physician, and even a longer time to analgesic administration. Especially in patients presenting to the ED with minor extremity injuries this protocol might be useful to optimize pain treatment, because these patients are usually triaged to a low (semi-urgent) triage category which typically results in an extended waiting time to physician's assessment.
The pre–post intervention comparison shows that the implementation of the protocol lead to an increase of analgesic provision, a shorter time to analgesics and a higher (clinically relevant) pain relief in patients with acute musculoskeletal pain following extremity injury. Despite these improvements in pain management, a relatively high percentage of patients was still discharged with moderate to severe pain.

Inaccurate pain assessment is a consistent finding in various clinical settings including the ED. Accurate pain assessment is crucial for effective pain management. Nurses not always rely on patients' self-reported pain and apparently make their own assessments of patients' pain based on a combination of nonverbal cues, such as type of and time since injury or patient behaviour. Due to the subjective nature of pain, it can be very difficult to quantify patients' pain. In **chapter 6** the discrepancies in pain assessment between patients and nurses were analysed. In the PROTACT-study nurses significantly underassessed patients' pain with a mean difference of 2.4 points on an 11-points numeric rating scale. Even more important is the issue of clinically relevant differences (33%) between both assessments. In a majority of 63% patients' pain was clinically relevant under assessed. In our population, pain was in particularly under assessed by nurses in women, in persons with a lower educational level, in patients who used prehospital analgesics, in smokers, in patients with injury to the lower extremities, in anxious patients and in patients with a lower urgency level (surrogate for minor injuries). There should be awareness among nurses that these patients are at high-risk for underassessment. Underassessment can result in under-treatment of pain if the emergency nurses rely on their assessment to conduct further pain treatment.

In **chapter 7** the impact and implications of the main findings of the PROTACT-study were discussed. Chronic pain is confirmed to be a common complication following extremity injury. The health impact of developing chronic pain is substantial; it causes impaired quality of life.

Six prognostic factors for the development of chronic pain were found. Of these factors, pain severity in acute pain phase and pain catastrophizing are potentially modifiable. A nurse-initiated pain protocol, which was implemented to reduce inadequate pain relief in the ED, appears to lead to an increase of analgesic provision, a shorter time to analgesics and a higher (clinically relevant) pain relief. Although this showed that severe pain can be reduced, the prevention of chronic pain is not investigated. Despite improvements in pain management, the results reflected by the amount of patients discharged with moderate to severe pain showed that there is still room for improvement. Accurate pain assessment is crucial for effective pain management. Nurses significantly underassessed patient's pain. By drawing attention to patients' self-reported pain and minimizing assumptions, and the routinely use of pain assessment tools, pain management might further improve. Furthermore, it is desirable to educate patients about the importance of communicating unrelieved pain and the use of pain medication.

Due to the limited number of studies which identified prognostic factors for chronic pain following extremity injury and the different methodology used only a limited set of consistently found factors that predict the development of chronic is available. When future studies use a more common and systematic approach in order to better identify the scope and magnitude of those at high-risk of developing chronic pain, this will contribute, together with current findings of the PROTACT-study, to identify (modifiable) physical and psychosocial prognostic factors as input for a brief risk screening tool that includes assessment of prognostic factors to identify injured patients at high-risk for chronic pain in the early acute pain phase and to stratify treatment based on their risk.

SAMENVATTING

Acute pijn is een veel voorkomende klacht bij mensen die medische hulp nodig hebben. Acute pijn als gevolg van (potentiële) weefselschade waarschuwt en beschermt het lichaam tegen (verdere) schade. Deze acute pijn verdwijnt normaal gesproken tijdens het helingsproces. Echter, in sommige gevallen, blijft de pijn na het genezingsproces aanwezig en verliest het zijn waarschuwende functie. Deze pijn zonder bruikbare, biologische functie heet chronische pijn. Chronische pijn komt relatief veel voor en heeft een impact die vaak veel verder reikt dan de pijn zelf. Chronische pijn en daaraan gerelateerde beperkingen leiden vaak tot complexe sociale en psychologische maladaptatie die invloed hebben op kwaliteit van leven. Daarnaast leidt chronische pijn tot een verhoogde consumptie van de gezondheidszorg, evenals vele andere aanzienlijke kosten bijvoorbeeld door het verlies van arbeidsproductiviteit.
Meer en meer wordt aangenomen dat acute en chronische pijn deel uitmaken van een continuüm eerder dan ze te zien als afzonderlijke entiteiten. Chronische pijn patiënten relateren hun pijn vaak aan het ontstaan van een acuut letsel zoals tijdens een operatie of bij trauma. Dit heeft gewezen op de noodzaak om de progressie van acute naar chronische pijn te voorkomen. De overgang van acute naar chronische pijn is echter nog steeds een complex en slecht ontrafeld proces. Een reeks van letsel-, psychosociale-, sociodemografische en patiënt gerelateerde factoren worden in verband gebracht met het persisteren van de pijn.

Met dit in gedachten is de " PROgnostic factors for the Transition from Acute to Chronic pain in Trauma patients (PROTACT)- studie" ontworpen. De PROTACT-studie is geïnitieerd als een prospectieve studie waarbij patiënten een jaar lang worden gevolgd om de prognostische factoren die invloed hebben op de overgang van acute naar chronische pijn als gevolg van extremiteitenletsel te bepalen. Dit geeft de mogelijkheid om hoogrisicopatiënten te identificeren en in de acute fase te behandelen door op één of meerdere risicofactoren te interveniëren zodat de ontwikkeling van chronische pijn voorkomen kan worden. Andere doelstellingen waren om de huidige stand van zaken rond pijnbehandeling bij extremiteiten in kaart te brengen en de consequenties van extremiteitenletsel en het ontwikkelen van chronische pijn op de kwaliteit van leven te bepalen.
De PROTACT-studie is uitgevoerd bij volwassen patiënten van 18 t/m 69 jaar die zich presenteerden op de spoedeisende hulp (SEH) van het Medisch Spectrum Twente in Enschede met geïsoleerd musculoskeletaal extremiteitenletsel veroorzaakt door stomp trauma. Gedurende een inclusieperiode van 22 maanden voldeden 1994 patiënten aan de inclusiecriteria, waarvan uiteindelijk 803 patiënten hun toestemming gaven om deel te nemen aan het onderzoek. Deze deelnemers werden tijd de follow-up periode gevraagd enkele (4 of 5) vragenlijsten in te vullen en er werden gegevens uit de ziekenhuisregistratie verzameld. De gegevens die verzameld werden waren o.a. potentieel prognostische factoren, letsel- en pijn-gerelateerde gegevens, gegevens over pijnbehandeling en over de kwaliteit van leven.

De inadequate en ineffectieve pijnbehandeling in de spoedzorg is wereldwijd een alom bekend probleem. In **hoofdstuk 2** blijkt dat oligoanalgesia (onderbehandeling van pijn) een ernstig probleem is bij patiënten met acute musculoskeletale pijn als gevolg van extremiteitenletsel. De prevalentie van pijn na een extremiteitletsel is hoog: 4 van de 5 patiënten presenteert zich op de SEH met matige tot ernstige pijn. En hoewel zestig procent van de patiënten ergens in de spoedzorgketen analgetica (pijnmedicatie) gebruikt blijkt dat ruim twee derde van de patiënten bij vertrek van de SEH nog steeds matige tot zeer ernstige pijn heeft. Het belang van analgetica in de SEH wordt onderschreven door de significante en klinisch relevante vermindering van pijn bij patiënten die pijnmedicatie ontvangen.

In **hoofdstuk 3** worden de resultaten van de primaire doelstelling van de PROTACT-studie gepresenteerd. In de PROTACT-studie wordt door middel van een uitgebreide set van potentieel prognostische factoren gekeken naar welke factoren belangrijk zijn in de ontwikkeling van chronische pijn met als doel hoogrisicopatiënten te kunnen identificeren. Zes maanden na het ontstaan van extremiteitenletsel had 43,9% van de patiënten nog pijn en 10,1% van de patiënten had chronische pijn ontwikkeld, gedefinieerd als persisterende pijn (NRS pijnscore ≥4) op de plaats van het letsel. Patiënten ouder dan 40 jaar, in een slechte fysieke gezondheid, die al chronische pijn hadden voor het letsel, die pijn catastroferen, met een hoge urgentie (als surrogaat voor de ernst van letsel) en met ernstige pijn bij vertrek SEH blijken een hoog risico te hebben voor het ontwikkelen van chronische pijn. Slechts twee prognostische factoren, ernstige pijn bij vertrek SEH en pijn catastroferen, zijn potentieel modificeerbaar.

Aan acute musculoskeletale pijn als gevolg van extremiteitenletsel kunnen vele vervelende consequenties kleven, zoals medische, psychosociale en economische problemen. Gezondheidsgerelateerde kwaliteit van leven (HRQoL) is een steeds belangrijkere uitkomstmaat geworden als het gaat om het meten van uitkomsten na letsel en ziektelast. In **hoofdstuk 4** wordt de impact van extremiteitenletsel en het ontwikkelen chronische pijn op de gezondheidsgerelateerde kwaliteit van leven vanuit het perspectief van de patiënt beschreven. Er is voldoende bewijs dat de extremiteitenletsels pijnlijk is en in de acute fase een significante invloed heeft op de kwaliteit van leven van de patiënt. Direct na het ontstaan van het letsel worden in 7 van de 8 dimensies van kwaliteit van leven veranderingen gezien, met uitzondering van de algehele gezondheidstoestand waar naar de verandering ten opzichte van het voorgaande jaar wordt gevraagd. Ook op de lange termijn zijn de gevolgen van extremiteitenletsel nog aanwezig. De algemene gezondheidstoestand gemeten na zes maanden na het ontstaan van het letsel is significant lager dan voor het ontstaan van het letsel. Een significante daling is voornamelijk aanwezig in de fysieke component van kwaliteit van leven; in de dimensies vitaliteit, lichamelijke pijn, fysiek functioneren en de rol beperkingen als gevolg van fysiek functioneren.

Dat pijn een cruciale rol speelt in ons dagelijks leven wordt bevestigd door de impact van chronische pijn op de kwaliteit van leven. De impact van letsel op de gezondheidsgerelateerde kwaliteit van leven is veel groter bij patiënten die chronische pijn ontwikkelen. Deze patiënten hebben een aanzienlijk verlies in kwaliteit van leven, zowel fysiek als mentaal. De *single-index* van hun gezondheidsgerelateerde kwaliteit van leven (utiliteitsscore) daalde met tenminste twee keer het minimaal klinisch relevante verschil; het kleinste gunstige effect dat waardevol is voor de patiënt. Bovendien ligt de utiliteitsscore van de patiënten die chronische pijn ontwikkelen aanzienlijk lager dan in de rest van de onderzoekspopulatie. De patiënten die geen chronische pijn ontwikkelen zullen hun niveau van kwaliteit van leven van voor het ontstaan van het letsel terug krijgen. Nog een reden die de noodzaak van de preventie van chronische pijn aangeeft.

Er wordt verondersteld dat tijdige en adequate behandeling van pijn de progressie van acute naar chronische pijn en daarmee het risico op het ontwikkelen van chronische pijn kan verminderen. Wereldwijd zijn er verschillende strategieën ontwikkeld om de pijnbehandeling te verbeteren zoals het gebruik maken van pijnprotocollen of klinische richtlijnen en educatieve interventies voor zorgprofessionals. De pre-post interventiestudie die in **hoofdstuk 5** wordt beschreven is gericht op het effect van een pijnprotocol op de SEH te evalueren. Met de implementatie van dit protocol mogen SEH-verpleegkundigen de patiënten pijnmedicatie, ook opioïden, toedienen volgens een vooraf bepaald protocol, zonder dat de patiënt eerst beoordeeld hoeft te worden door een arts. Dit is belangrijk aangezien het lang kan duren voordat de patiënt echt beoordeeld wordt door een arts. Vooral bij patiënten die naar de SEH komen met relatief klein letsel lijkt de implementatie van het pijnprotocol nuttig om de pijnbehandeling te optimaliseren omdat deze patiënten meestal getrieerd worden tot een lage (semi-spoed) urgentiecategorie en daardoor meestal lang dienen te wachten totdat ze worden beoordeeld door een arts. Uit de pre-post interventiestudie blijkt dat de implementatie van een pijnprotocol leidt tot een toename in pijnmedicatie, een korte toedieningsduur, een hogere (klinisch relevante) pijnafname bij patiënten met acute musculoskeletale pijn. Ondanks deze verbetering in pijnmanagement, werd nog steeds een relatief groot percentage patiënten ontslagen met matige tot ernstige pijn.

Inaccurate pijnbeoordelingen zijn een consistente bevinding in verschillende klinische settingen, ook in de SEH. Accurate pijnbeoordeling is van cruciaal belang voor een effectieve pijnbehandeling. Verpleegkundigen vertrouwen niet altijd op de patient's zelfgerapporteerde pijnscore maar beoordelen de pijn blijkbaar gebaseerd op een combinatie van non-verbale signalen, zoals de duur en soort pijn of het (pijn)-gedrag van de patiënt. Omdat pijn subjectief is blijkt het zeer moeilijk om pijn te kwantificeren. In **hoofdstuk 6** worden de verschillen in pijnbeoordeling tussen de patiënten en verpleegkundigen geanalyseerd. In de PROTACT-studie wordt de pijn van de patiënten significant lager ingeschat door verpleegkundigen met gemiddeld een verschil van 2,4 punten op een 11-puntsschaal. Nog belangrijker zijn de

klinische relevante verschillen (>33%) tussen beide beoordelingen. Bij ruim 63% van de patiënten werd de pijn met een 'klinisch relevante waarde' onderschat. In onze studiepopulatie werd de pijn voornamelijk onderschat bij vrouwen, bij lager opgeleiden, bij patiënten die al pijnmedicatie hadden gehad, bij rokers, bij patiënten met letsel aan de onderste extremiteiten, bij angstige personen en bij patiënten met een lage urgentielevel (surrogaat voor kleine letsels). Verpleegkundigen moeten zich er van bewust zijn dat ze deze patiëntengroepen een hoogrisico hebben op onderschatting. Onderschatting van pijn kan resulteren in onvoldoende pijnbehandeling wanneer het beleid wordt afgestemd op de pijnmeting.

In **hoofdstuk 7** wordt de impact en de implicaties van de belangrijkste bevindingen van de PROTACT-studie besproken. Chronische pijn blijkt een veelvoorkomende complicatie te zijn van extremiteitenletsel. De impact van chronische pijn op iemands gezondheid is aanzienlijk, chronische pijn leidt tot een verminderde kwaliteit van leven. In totaal blijken zes prognostische factoren verantwoordelijk voor de ontwikkeling van chronische pijn. Van deze factoren blijken er slechts twee modificeerbaar: ernstige pijn in de acute pijnfase en pijn catastroferen. Een pijnprotocol dat werd geïmplementeerd om de pijnbehandeling te optimaliseren leidde tot een verhoging van pijnmedicatie, een snellere toediening en een hogere (klinische relevante) pijnvermindering. Hoewel het pijnprotocol zorgt voor meer pijnvermindering en het aantal patiënten dat met ernstige pijn vertrekt afneemt is in de studie het effect hiervan op het ontwikkelen van chronische pijn niet onderzocht. En ondanks dat het aantal patiënten dat met matige tot ernstige pijn de SEH verliet verminderde, is er nog steeds veel ruimte voor verbetering. Accurate pijnbeoordeling is cruciaal voor een effectieve pijnbehandeling. Helaas wordt de pijn van de patiënten vaak onderschat. Door de aandacht te vestigen op de patient's zelfgerapporteerde pijnscore, aannames in pijn te minimaliseren en routinematig gebruik te maken van pijnmetinginstrumenten zal de pijnbehandeling verbeterd kunnen worden. Verder is het gewenst om patiënten goed voor te lichten over het belang van pijnmedicatie en de mogelijke risico's van slechte pijnbehandeling. Vanwege het beperkte aantal studies naar prognostische factoren van chronische pijn als gevolg van extremiteitenletsel en de verschillende methodes die gebruikt worden, zijn er weinig consistent aanwezige risicofactoren in de literatuur gevonden. Wanneer bij toekomstige studies meer gebruik wordt gemaakt van een uniforme, systematische aanpak om de scope en de omvang van patienten met een verhoogd risico op het ontwikkelen van chronische pijn te onderzoeken, zal dit -samen met bevindingen van de PROTACT-studie- kunnen bijdragen tot het identificeren van meer consistente, modificeerbare fysieke en psychosociale factoren Deze kunnen vervolgens als input dienen voor een screeningsinstrument om hoogrisicopatiënten in de acute pijnfase te identificeren en te stratificeren op basis van risico naar een bepaalde behandelingsmethode.

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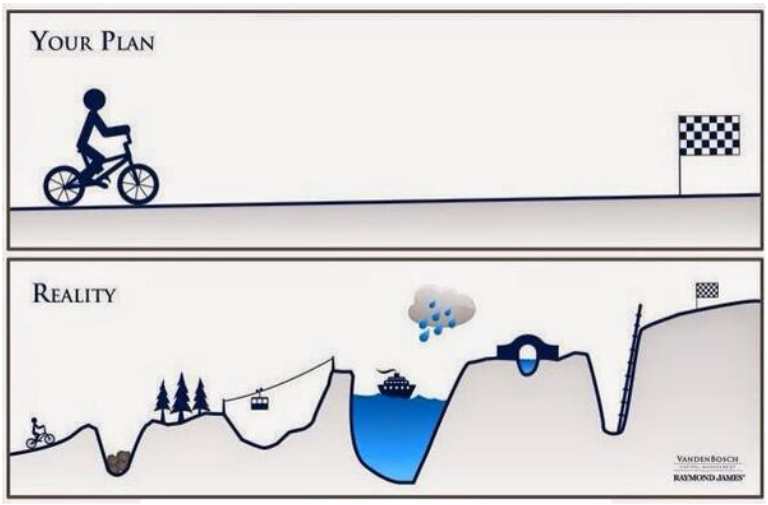

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Curriculum Vitae and Publications

CURRICULUM VITAE

Jorien Pierik was born on June 28, 1985 in Hengevelde (Ambt Delden), the Netherlands. She attended the Athenaeum of Twickel College in Hengelo and obtained her secondary school diploma in 2003. The same year she started studying the interfaculty bachelor programme Life Science and Technology at the University of Groningen. In 2010, she received her Master of Science degree in Medical Pharmaceutical Science in the Management and Policy Track. Her Master thesis was a feasibility study on the introduction of a tetravalent measles mumps rubella varicella vaccine on the Dutch Market. During this study she also did epidemiological research about the incidence and disease burden of the varicella zoster virus in the primary care setting in the Netherlands, of which the results were published in BMC infectious diseases (2012). Since September 2010 Jorien started her PhD at the department Health Technology and Services Research of the University of Twente. Her PhD project was about finding prognostic factors involved in the transition from acute to chronic pain after extremity injury that will give the ability to target high-risk patients in the emergency setting and to intervene on (one or more) of this factors thereby preventing the development of chronic pain. From June 2014 until December 2015 she combined her PhD project with an assignment at the Radiotherapiegroep. From January 2015 until October 2016 she worked as quality and policy advisor in the primary care setting at Federatie Eerstelijnzorg Almelo e.o. She was involved in the policy of general practitioners regarding integrated care programmes for chronic disease management, innovation and substitution of healthcare. In January 2016, she started working as policy advisor in the emergency care setting at Bureau Acute Zorg Euregio. She contributes to the development and evaluation of regional emergency care policy in Twente, Oost Achterhoek and the regional cross-border emergency care with Germany.

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