PROCEDURAL PAIN RESPONSES IN ACUTE AND CRITICALLY ILL PATIENTS

by

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DISSERTATION

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Dedication

I dedicate this dissertation to my beloved parents *Lulo Arroyo* and *Tere Novoa* for their unending love. They inspired me to be a good person and supported me in my decision to be a nurse. To *Papi*, a great father, who showed me how to take risks, to move beyond the fears and difficulties of life and who showed me the value of working hard. To *Mami*, the best mother, a decisive woman and dedicated mom who taught me Christian values, to respect human beings, and how to love. Although neither of you are any longer with me, you will be in my mind and in my heart forever.

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Research Advisor Statement

The publications represent research or scholarship comparable in scope and contribution to the portion of the standard dissertation it replaces.

The published material is substantially the product of the student's period of study at UCSF and was primarily written by the student.

Kathleen A. Puntillo

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Abstract

Procedural Pain Responses in Acute and Critically Ill Patients

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Acutely and critically ill patients are exposed to many therapeutic procedures that can produce painful experiences. Tracheal suctioning (TS) and wound care procedure (WCP) are frequently performed in these patients. The purpose of this dissertation was to evaluate pain responses during both TS and WCP and to determine the efficacy of a pharmacologic treatment to prevent pain during an open WCP.

The first report was a secondary data analysis of findings from a larger procedural pain study. A total of 755 patients underwent the TS procedure that was performed primarily in intensive care units (93%). Pain intensity mean (*SD*) scores were significantly greater during the TS procedure 3.96 (3.3) than prior to 2.14 (2.8) or after 1.98 (2.7). Few patients received analgesics prior to or during the procedure. Although mean pain intensity during TS was mild, almost the half of the patients who presented pain reported it as moderate to severe.

The second study was a randomized, cross-over design with the purpose to determine whether the addition of small doses of ketamine would potentiate morphine's analgesic effects and decrease WCP pain intensity. Patients were randomized to receive morphine plus saline (MS) IV or morphine plus ketamine (MK) IV before the WCP. When the WCP was repeated, patients were crossed-over to receive the alternate treatment.

Eleven patients from the Trauma Hospital of Puerto Rico participated in the study. Procedural pain intensity mean ranks during the WCP-MK was significantly less than during the WCP-MS ($p = .005$). Mean (*SD*) procedural pain intensity during the WCP-MK was 3.09 (3.27), while it was 6.82 (3.06) during the WCP-MS. However, 91% of patients had adverse effects during MK versus none during MS. In addition, mean (SD) diastolic BP was significantly higher during the WCP-MK than during WCP-MS and prior to WCP-MK, 84 (11.8), 73 (7.4), 72 (12.6), respectively.

Individualized pain management must be performed by healthcare providers in order to respond to patients' needs as they undergo painful procedures such as TS and WC. Further research is warranted to determine the dose of ketamine that is analgesic but causes minimal adverse effects during a WCP.

Approved by:

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Chapter I

Introduction

Introduction

Acute and critical care patients are exposed to painful situations, from simple therapeutic procedures such as intravenous cannulation to more aggressive interventions such as endotracheal intubation or wound care. Patients experience common painful diagnostic procedures such as arterial punctures for blood gases and pleural taps. They experience pain from surgical wounds, multiple traumatic injuries, and from simple activities such as coughing or more intense activities such as mobilization or turning.

Of those, endotracheal tubes and surgical or traumatic wounds are very common in acute and/or critical care patients. These require that patients be exposed frequently to procedures such as tracheal suctioning and wound care. The following chapters of this dissertation include three manuscripts related to pain in patients with endotracheal tubes and surgical or traumatic wounds. These chapters are followed with a conclusion. The first manuscript is a secondary analysis from a larger procedural pain study that examined several factors related to pain during tracheal suctioning. The principal aim for this secondary analysis was to describe and compare patients' pain perception and responses across different phases of the tracheal suctioning procedure. The sample consisted of 755 patients who underwent the tracheal suctioning procedure primarily in intensive care units. Pain intensity scores were significantly greater during the tracheal suctioning procedure than prior to or after tracheal suctioning and few patients received analgesics prior to the procedure.

The second manuscript is a literature review related to acute wound pain. A discussion of the causes, mechanisms and factors that contribute to acute wound pain and the management of acute wound pain are included. Patients with wounds experience pain at rest, and their pain intensity increases during wound care procedure. Wound pain can

be a consequence of one or several mechanisms and can benefit from a combination of analgesics. This literature review also revealed the paucity of pharmacological interventional studies to treat acute pain associated with traumatic or surgical open wounds.

Recognizing that many patients in trauma acute and critical care settings experience procedural pain related to wounds and the paucity of interventional studies, the third manuscript comprises the report of a study of the pharmacologic management of procedural wound pain. A clinical trial with a cross-over design was used to examine differences in patients' pain perceptions and hyperalgesia when receiving morphine with saline compared to morphine with a small dose of ketamine prior to an open wound care procedure. The main research aim of this study was to determine whether procedural wound pain intensity with morphine plus ketamine reduced procedural wound pain intensity more than morphine with saline. The sample consisted of 11 patients from the Trauma Hospital of the Puerto Rico Medical Center. When patients received morphine plus ketamine, their wound care procedural pain was significantly lower than when they received morphine plus normal saline.

Chapter II

Pain Related to Tracheal Suctioning in Awake
Acutely and Critically Ill Adults:
A Descriptive Study

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Abstract

The purpose of this secondary data analysis of findings from a larger procedural pain study was to examine several factors related to pain during tracheal suctioning. In addition to tracheal suctioning, other procedures studied included turning, wound drain removal, femoral catheter removal, placement of a central venous catheter, and wound dressing change. A total of 755 patients underwent the tracheal suctioning procedure that was performed primarily in intensive care units (93%). A 0 -10 numeric rating scale, a behavioral observation tool, and a modified McGill Pain Questionnaire-Short Form were used for pain assessment. Pain intensity scores were significantly greater during the tracheal suctioning procedure ($M = 3.96$, $SD = 3.3$) than prior to ($M = 2.14$, $SD = 2.8$) or after ($M = 1.98$, $SD = 2.7$) tracheal suctioning. Few patients received analgesics prior to or during the procedure. Surgical, younger, and non-white patients reported higher pain intensities. Although mean pain intensity during tracheal suctioning was mild, almost the half of the patients reported moderate to severe pain. Individualized pain management must be performed by healthcare providers in order to respond to patients' needs as they undergo painful procedures such as tracheal suctioning.

Introduction

Acutely and critically ill patients are exposed to many therapeutic or diagnostic procedures that can produce painful and/or distressing experiences. Tracheal suctioning is one of these procedures frequently performed by nurses and respiratory therapists. The presence of pain during tracheal suctioning has been demonstrated in earlier studies (Bergbom-Engberg & Haljamae, 1989; Hallenberg, Bergbom-Engberg, & Haljamae, 1990; Puntillo, 1994). Patients were asked 2 to 4 years after having been in an intensive care unit (ICU) and intubated about their recollection of their ICU stay, 57 (36% of the total sample) reported that pain associated with their ICU ventilator treatment had been a major problem for them (Bergbom-Engberg & Haljamae, 1989). Tracheal suctioning was specifically recalled as discomforting for 30% of these patients. In another study, even though 59 intubated ICU postoperative patients had received analgesics during their time of mechanical ventilation, 41% of them recalled having pain (Hallenberg et al., 1990). They reported that one cause of this pain was tracheal suctioning. Pain correlated significantly with suctioning ($r = .30$, $p < .001$). In a descriptive, correlational study, 45 post-operative awake adult cardiovascular surgical patients reported a mean pain intensity of 4.9 ($SD = 3.3$, median = 5.0) on a 0-10 numeric rating scale (NRS) from tracheal suctioning (Puntillo, 1994). While pain intensity scores ranged from 0-10, over one-third of the patients ($n = 17$) reported a suctioning pain intensity of 7 or greater.

In spite of the ubiquity of tracheal suctioning of ICU patients, these were the few studies to have explored pain associated with this procedure and study samples were small. More evidence is needed about pain perceptions and responses among patients from different ICU settings as well as factors that could influence pain with suctioning.

The American Association of Critical Care Nurses (AACN) supported the Thunder Project II®, a large research study in which pain perception and responses to tracheal suctioning, as well as five other procedures were evaluated (Puntillo et al., 2004; Puntillo et al., 2001). Although the data collection was completed in 2000, there have been no research reports on pain associated with tracheal suctioning or that suggest that pain management practices prior to tracheal suctioning have changed since then. Therefore, the aims of this secondary analysis were to: (1) describe and compare patients' pain perception and responses across different phases of the tracheal suctioning procedure; (2) examine relationships between patients' pain perceptions and responses to tracheal suctioning and the following factors: patient's age, diagnosis, gender, ethnicity, pre-and during-procedure analgesic and sedative use; and (3) relate physiological data and analgesic use to tracheal suctioning pain.

Method

A descriptive study design was used to examine the pain perceptions and responses of acutely or critically ill adults to tracheal suctioning. Study design and protocols were developed by the AACN Thunder Project II® task force (Puntillo et al., 2001).

Sample and Settings

A convenience sample of adults was recruited for the larger study (AACN Thunder Project II®) from 169 hospitals, 5 of which were outside the United States (3 from Canada, 1 from Australia, and 1 from the United Kingdom). Patients were enrolled if they were awake, alert, oriented, and medically stable enough to respond to questions; could understand and communicate in English; were able to hear and see; and if tracheal suctioning was part of their normal care. Patients who were receiving neuromuscular

blocking medication or had a disease process or injury that impaired sensory transmission from the procedure site were excluded from the study.

Instruments

Several instruments were used to measure a patient's pain responses to tracheal suctioning. Pain intensity was measured by 0-10 NRS and pain quality by the Thunder Study-Modified McGill Pain Questionnaire-Short Form (MPQ-SF). The modified MPQ-SF includes 20 words that describe pain qualities e.g. sharp, tender, fearful-frightening (Puntillo et al., 2001). Pain behavioral indices were identified by a behavioral observation tool. This tool consists of behaviors classified into three categories (body movement, facial, and verbal responses) (Puntillo et al., 2004). Concurrent and construct validities of the NRS have been established (Downie et al., 1978). Cronbach α for the modified MPQ-SF was .85 (Puntillo et al., 2001).

Procedure

A site coordinator at each study institution was responsible for obtaining institutional review board permissions; selecting patients; selecting and training nurses who acted as research associates through use of a detailed training program provided by the study investigators; and assuring the reliability and validity of study procedures in the institutions. Research associates were trained with use of a videotape that described the tracheal suctioning procedure and data collection protocol. Approval of institutional review board and patient consent were obtained in those institutions that required it. If informed consent was not required by the institution, patients were entered directly into the study. Data were collected immediately prior to suctioning (time-1), immediately after suctioning (time-2) and 10 minutes later (time-3) (see Figure 1). For those whose

heart rate (HR) and blood pressure (BP) were being continuously monitored, HR and BP data were obtained at time-2. Data regarding medications administered one hour pre- and during the procedure were obtained from patients' medical records.

Data Analysis

Descriptive statistics were used for sample demographics, pain intensity, pain quality, pain related behaviors, physiological measures, and pharmacological interventions. A repeated measures analysis of variance (ANOVA), with Huynh-Feldt correction, was conducted to assess whether there were differences between mean pain intensity scores across the 3-time periods of the tracheal suctioning procedure. Repeated measures ANOVA were also performed to evaluate the interaction of pain intensity with diagnostic groups, gender, physiologic responses, and pharmacologic interventions. The extremely large sample size justifies using the repeated measures ANOVA for the variable pain intensity with values that range between 0 and 10. Pearson correlations were used to examine relationships between patient pain intensity and age. Alpha level of $p < .05$ was considered to be statistically significant for all analyses.

Results

Sample

A total of 755 patients underwent the tracheal suctioning procedure that was performed primarily in ICUs (n = 695, 93%). The majority of patients were male (n = 376, 52%) and white (n = 614, 82%); mean age was 64 years (SD = 14.4); and the patients' primary diagnoses were distributed among the following categories: medical (n = 357, 48%), surgical (n = 348, 47%), trauma/burn (n = 30, 4%), and other (n = 11, 2%).

Twenty-two percent (n = 165) of patients had tracheostomies, while the 78% (n = 555) had an endotracheal tube. Most patients (n = 643, 88%) were mechanically ventilated.

Tracheal Suctioning Pain

Pain intensity. The mean pain intensity score reported during tracheal suctioning (time-2) was 3.94 (SD = 3.32). For those who reported having pain ≥ 1 (73%), the most frequent scores were 5 (21%) and 10 (12%). Sixty-four percent had moderate (NRS = 5-6) or severe (NRS = 7-10) pain according to previously published criteria (Serlin, Mendoza, Nakamura, Edwards, & Cleeland, 1995) (see Figure 2). Results from repeated measures ANOVA indicated that patient pain intensity differed significantly across the 3-time periods, (F = 279.37, p < .0005). Pain intensity was greater during the tracheal suctioning procedure (M = 3.96, SD = 3.3) than prior to tracheal suctioning (M = 2.14, SD = 2.8) and after the procedure (M = 1.98, SD = 2.7).

Significant differences in pain intensity among diagnostic groups were also found, (F = 5.45, p = .004). A post hoc Scheffe comparison showed that surgical patients reported significantly higher tracheal suctioning pain intensity scores than did medical patients (p = .005) (see Table 1). For all three diagnostic groups, pain increased between time-1 and time-2 and then decreased from time-2 to time-3. There was an interaction between diagnostic group and time using the Huynh-Feldt correction, (F = 92.24, p < .0005). The increase in pain at time-2 was greater for both surgical and trauma groups than it was for the medical group.

Small but significant inverse associations between patient pain intensity and age were found at the 3-time periods of tracheal suctioning: prior, r = -.17, p < .0005; during, r = -.21, p < .0005; and after procedure, r = -.19, p < .0005. Older patients reported less

pain than younger patients at each of the 3-time periods. When differences in patient pain intensity according to gender was evaluated, a repeated measures ANOVA showed that the change in pain intensity over time did not depend on gender, ($F = .17$, $p = .81$), and the main effect of gender on pain intensity was not statistically significant, ($F = .48$, $p = .49$). On average across the 3-time periods non-white patients reported significantly higher pain intensity scores than white patients, ($F = 5.12$, $p = .024$) (see Table 2).

Pain quality. During suctioning, terms most frequently used by patients were "tender" (29%), "sharp" (26%), "aching" (24%), "tiring-exhaustive" (23%), "fearful-frightening" (23%), "bad" (21%), and "awful" (21%). The same pain quality terms were used most frequently at time-1 but at lower percentages. Only the terms "sharp" and "fearful-frightening" increased by more than 10% from time-1 to time-2 (see Table 3).

Other Responses to Tracheal Suctioning

Physiologic responses. HR and BP were measured in the 3-time periods as physiologic responses to tracheal suctioning. There were significant differences over the 3-time periods in HR, ($F = 117.71$, $p < .0005$); systolic BP (SBP), ($F = 103.06$, $p < .0005$); and diastolic BP (DBP), ($F = 43.73$, $p < .0005$). Simple contrasts showed that HR, SBP, and DBP at time-2 were significantly higher than at time-1 or time-3 (see Table 4). Mean DBP was significantly higher in patients who had moderate-to-severe (5 to 10) pain (DBP = 72) than in those who had no or mild (0 to 4) pain (DBP = 68) ($p = .02$).

Changes in observed pain behaviors. A 10% change in the frequency of observed pain behaviors between time-1 and time-2 was selected to evaluate behavioral responses. Those observed behaviors that increased by 10% or more were "grimace", "clenched

fists", "rigid", and "wince". Two behaviors "no movement" and "no facial responses" decreased by 10% or more (see Table 5).

Pharmacologic Interventions

A total of 39 out of 755 (5%) patients received medications (opioids, sedatives, and/or nonsteroidal anti-inflammatories) within one hour prior to tracheal suctioning, and seven patients received them for the procedure. Opioids were the type of medication administered most frequently prior to (n = 24) and during (n = 5) tracheal suctioning. Opioids were administered to 6% of surgical patients, 3% of trauma/burn patients, and in 1% of medical patients. The mean dose administered to these few patients, in equivalent doses of morphine, was 10.3 mg (SD = 9.1, median = 7.8 mg). The effect of opioids on pain intensity across the 3-time periods was evaluated using repeated measures ANOVA. Results indicated that both those who received opioids pre or during the procedure and those who did not receive any opioids had increased pain during tracheal suctioning. The pattern of change was not different between the two groups, (F = 1.34, p = .26). Interestingly those patients in the medicated group reported higher mean pain intensity scores across the 3-time periods than those who were not medicated, (F = 11.87, p = .001). Also, those who received opioids reported a higher mean pain intensity score (M = 4.13, SD = 3.2) prior to tracheal suctioning than those who did not receive it (M = 2.07, SD = 2.8) ($p < .0005$).

Discussion

This is the first report to examine the multiple dimensions of pain associated with tracheal suctioning and factors that influenced the patient's pain. Tracheal suctioning has been reported as a painful experience by acutely and critically ill patients (Bergbom-

Engberg & Haljamae, 1989; Hallenberg et al., 1990; Puntillo, 1994). More recently, two studies demonstrated significantly higher behavioral pain scale scores during tracheal suctioning when compared to rest and non-painful procedures (Aissaoui, Zeggwagh, Zekraoui, Abidi, & Abouqal, 2005; Payen et al., 2001). We found the overall pain intensity during tracheal suctioning to be mild. However, 64% of patients who did report having pain (≥ 1) had pain that was moderate-to-severe in intensity. In addition, surgical patients reported higher pain intensity scores compared to medical patients. The cough provoked by suctioning may produce pressure on thoracic, abdominal or other incisions (Puntillo, 1994) leading to higher pain scores in surgical patients. Previously 45 post-cardiac surgical patients reported a pain intensity of 4.9 during tracheal suctioning (Puntillo, 1994), which was a score similar to our surgical group. From these findings it appears that interventions for tracheal suctioning pain have not been instituted since pain in surgical patients undergoing tracheal suctioning has not decreased over time.

Younger patients reported higher pain scores, but there were no significant differences based on gender. These age and gender results were consistent with the report of procedural pain during wound care (Stotts et al., 2004). Age differences in postoperative pain intensity were not found in a study that compared pain intensity scales in younger and older surgical patients (Gagliese, Weizblit, Ellis, & Chan, 2005). Yet, while they reported that pain intensity did not differ by age on four of the pain five scales evaluated, older patients reported lower scores on the MPQ and self-administered fewer morphine doses. Until more evidence related to age and gender differences are found, greater attention must be given by health care providers to pain intensity during tracheal suctioning of all patients regardless of age and gender.

Non-white patients reported significantly higher pain intensity than whites. Previously, whites, African-American and Hispanics were interviewed during a phone survey about their chronic pain (Portenoy, Ugarte, Fuller, & Haas, 2004). White subjects in that study also reported less pain than those in each of the other ethnic groups. Since our sample consisted primarily of whites, further research is needed with a larger sample of other ethnic groups to better understand the contribution of ethnicity to a pain experience.

The first three of the most frequently selected pain quality terms (i.e., tender, sharp, and aching) to describe tracheal suctioning correspond to the sensory dimension of pain (Melzack, 1987). The selection of the word "sharp" increased over 10% from time-1 to time-2. The "sharp" feeling may be due to mechanical stimulation resulting from tracheal suctioning and increased activation of A delta fibers which contributes to the perception of incisive sensations (Puntillo et al., 2001). The other term that increased by more than 10% was "fearful-frightening" which can correspond to the affective dimension of pain (Melzack, 1987). Our findings about the qualitative nature of tracheal suctioning pain confirms previous descriptions that tracheal suctioning pain is "tender", "sharp", and "tiring-exhausting" (Puntillo, 1994). However, our patients did not include the pain descriptions "heavy" and "stabbing" noted in the earlier study. These terms can be useful to describe and assess pain quality during tracheal suctioning and give direction to interventions to decrease the sensory, affective, or both components of pain during suctioning. Such interventions could include pre-procedural teaching, medication, and use of distraction.

Changes in behavioral and physiological (BP and HR) responses can be utilized to assess pain in patients who cannot self-report. We saw statistically significantly higher increases in HR, SBP, and DBP during tracheal suctioning than prior to suctioning; however, the changes were not clinically significant. It may be that methods of measuring HR, SBP and DBP are not sensitive enough to capture the response to acute pain.

Increases in certain behaviors occurred during the procedure: grimace, clenched fists, rigid, wince, increase in movement, and increased facial responses. These findings were similar in a study of critically ill sedated patients on mechanical ventilation (Payen et al., 2001). Behavioral responses increased during painful procedures (tracheal suctioning or mobilization) as measured by the Behavioral Pain Scale. Furthermore their patients who underwent these procedures developed statistically significant (albeit, not clinically significant) increases in HR and BP, whereas patients who underwent non-painful procedures (compression stockings application or central venous catheter dressing change) did not have changes in hemodynamics when compared with data at rest. Gray, MacIntyre, and Kronenberger (1990) also found significant changes in physiological parameters (i.e., HR, BP, and respiratory rate) after tracheal suctioning. However, many factors besides pain can cause changes in physiological parameters such as cough, discomfort, hypoxemia, or anxiety. Further research is needed to understand the changes in physiological parameters from pain during tracheal suctioning while controlling for competing factors. Attention to changes in behavioral responses and physiological parameters could help health care providers to assess pain or discomfort in sedated patients or those who are otherwise unable to report their experiences during procedures.

Only 3% of the patients received opioids prior to or during the tracheal suctioning procedure. In fact, only 5% of the patients received any medications including analgesics, sedative, or nonsteroidal anti-inflammatories prior to tracheal suctioning. Consistent with these findings, Puntillo (1994) found that 40 of 45 ICU surgical patients did not receive analgesics for at least two hours prior to tracheal suctioning. Our patients who received opioids had significantly higher pain intensity during suctioning than those who did not receive them, but they also reported higher pain intensity at time-1. It may be that those patients with higher pain intensity scores prior to the procedure needed more opioids in general since they had higher background pain. Attention should be focused on a patient's present pain when a possibly painful procedure is planned. Otherwise, there exists the potential to create an exponential increase in pain that could have been prevented or minimized by analgesics.

Decisions not to administer analgesics prior to tracheal suctioning may be due to desensitization of health care providers to common procedures. Or, because of the short duration of the procedure, pre-medication may not be seen as necessary by providers (Puntillo et al., 2001). Another reason could be that providers underestimate pain intensity during tracheal suctioning. Although 27% of our sample did not report pain during tracheal suctioning, 64% reported moderate-to-severe pain intensity. These findings suggest that pre-medication should be individualized according to the needs of the patients. Further attention is required in terms of under-medication of ICU patients undergoing procedures such as tracheal suctioning.

Limitations

The sample was selected by convenience and, thus, those who did not participate could have different pain responses and perceptions to suctioning. We balanced that with our intention to enroll patients in multiple centers. Since this was a descriptive study and we did not intend to influence practice, the tracheal suctioning procedure was not standardized and was performed by the health care provider in charge of the patient. Although research assistants were trained and a protocol of the data collection process was established, this study could be subject to interobserver variability. Findings from our study should be generalized with caution to unconscious patients or to other patients unable to self-report their pain since those patients did not participate in this study.

Conclusion

Although the mean pain intensity score during tracheal suctioning suggests that the procedure is, on average, mildly painful, more than half of our patients with pain reported moderate-to-severe pain. Few patients received analgesics one hour prior to or during the procedure. Surgical, younger, and non-white patients reported higher pain intensities. Terms associated with both the affective and sensory dimensions of pain were used to describe pain quality during suctioning, and certain behavioral responses were prevalent during the procedure.

Individualized pain management must be performed by healthcare providers in order to respond to patients' needs. Future research should be focused on sedated and unconscious critically ill patients undergoing tracheal suctioning in order to explore their behavioral and physiological responses to this procedure since it is known to cause pain in patients who are able to self-report. Finally, interventional studies are needed to

determine the best pharmacologic and/or non-pharmacologic strategies for improving the pain associated with tracheal suctioning.

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Table 1

Pain Intensity Across the 3-time Periods of TS by Diagnosis

Diagnosis	**Frequency** ***n*** **= 707**	**Mean**	**(*SD*)**
Medical*	345		
Prior to TS		2.04	(2.91)
During TS		3.33	(3.30)
After TS		1.72	(2.63)
Surgical*	334		
Prior to TS		2.25	(2.68)
During TS		4.58	(3.21)
After TS		2.14	(2.58)
Trauma/Burn	28		
Prior to TS		2.00	(2.42)
During TS		4.36	(3.38)
After TS		2.46	(2.74)

* Mean difference is significant, p =.005. TS, tracheal suctioning; SD, standard deviation

Table 2

Pain Intensity Across the 3-time Periods of TS by Ethnicity

Period	**White (*n* = 592) Mean (*SD*)**	**Non-white (*n* = 132) Mean (*SD*)**
Prior to TS	2.1 (2.7)	2.4 (3.2)
During TS	3.8 (3.2)	4.7 (3.6)
After TS	1.9 (2.6)	2.4 (3.1)

TS, tracheal suctioning; SD, standard deviation

Table 3

Words Used to Describe the Quality of Pain at Time-1 and Time-2

Word	**Prior to tracheal suctioning (Time-1)**	**During tracheal suctioning (Time-2)**
Tender	23%	29%
Sharp*	14%	26%
Aching	26%	24%
Tiring-exhaustive	16%	23%
Fearful-frightening*	12%	23%
Bad	15%	21%
Awful	12%	21%
Stabbing	7%	16%
Throbbing	12%	15%
Hot-burning	9%	15%
Heavy	10%	14%
Sickening	7%	14%
Stinging	7%	13%
Dull	12%	11%
Shooting	5%	11%
Gnawing	11%	10%
Cramping	8%	10%
Punishing-cruel	5%	9%
Splitting	4%	8%
Numb	4%	5%

*Increased by more than 10% from time-1 to time-2

Table 4

Blood Pressure and Heart Rate Prior to, During, and After Tracheal Suctioning

Period	**Heart rate (*n* = 719) Mean (*SD*) mmHg**	**Systolic BP (*n* = 694) Mean (*SD*) mmHg**	**Diastolic BP (*n* = 688) Mean (*SD*) mmHg**
Prior to TS	94 (17)	126 (23)	65 (14)
During TS	100 (18)	135 (26)	70 (24)
After TS	94 (18)	126 (23)	64 (14)

SD, standard deviation; BP, blood pressure; TS, tracheal suctioning

Table 5

Percent of Patients with a Change in Observed Pain Behavior of 10% or More from Time-1 to Time-2

Pain behavior	**Prior to tracheal suctioning (Time-1)**	**During tracheal suctioning (Time-2)**
Grimace*	11%	52%
Clenched fists*	5%	24%
Rigid*	3%	23%
Wince*	5%	22%
No movement †	60%	19%
No facial response †	38%	4%

* Increased from time-1 to time-2; † decreased from time-1 to time-2

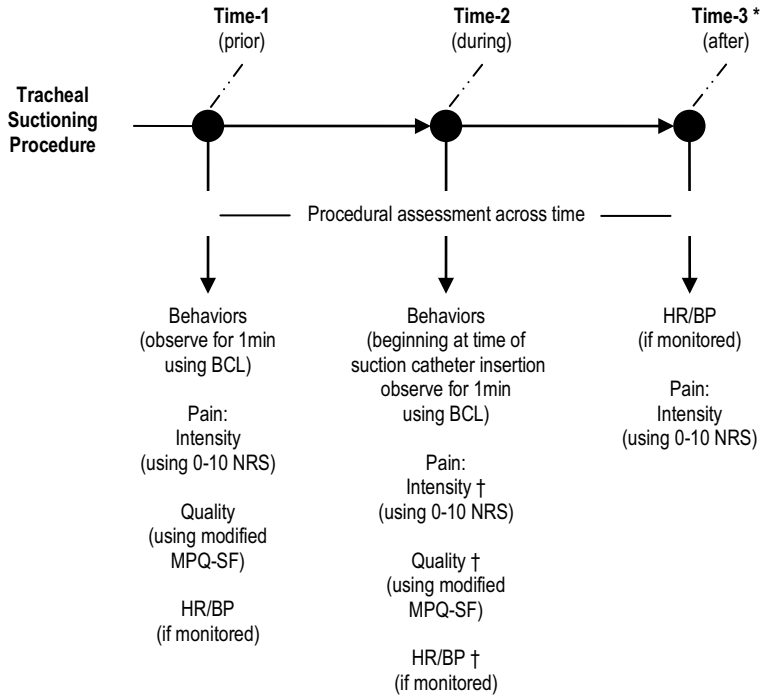

Figure 1. Tracheal suctioning procedure and data collection.

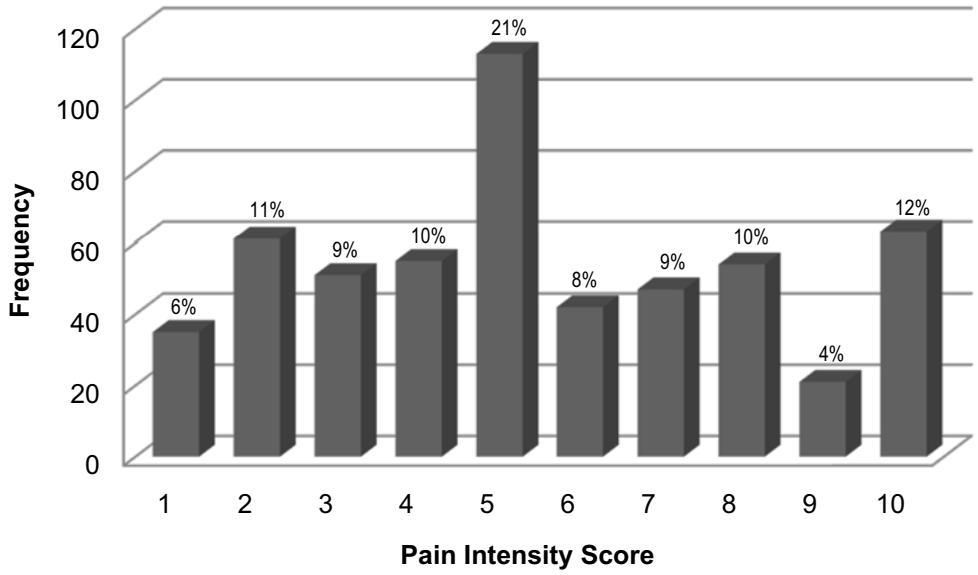

Figure 2. Pain intensity during tracheal suctioning.

Chapter III

Acute Wound Pain: Gaining a Better Understanding

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Introduction

Acute wounds that occur as a result of surgery or trauma are associated with moderate to severe pain (Apfelbaum, Chen, Mehta, & Gan, 2003; Meaume, Teot, Lazareth, Martini, & Bohbot, 2004; Shukla et al., 2005). Recent evidence suggests that unrelieved pain can interfere with the wound healing process. For example, women with higher pain intensity scores experienced delays in wound healing after elective gastric bypass surgery (McGuire et al., 2006). In addition, unrelieved postoperative pain and hyperalgesia may be risk factors for the development of chronic postsurgical pain (Lavand'homme, De Kock, & Waterloos, 2005; Perkins & Kehlet, 2000).

Despite the large numbers of patients who undergo surgery or experience traumatic injuries, the majority of the literature on wound pain is focused on chronic wounds. Therefore, this article will discuss the causes of acute wound pain; the mechanisms of and the factors that contribute to acute wound pain; and the management of acute wound pain.

Causes of Acute Wound Pain

Acute wounds heal in a timely manner (Lazarus et al., 1994) and most commonly are result of surgical or traumatic origin. Acute wound pain (i.e., pain at the site or around an acute wound) can occur spontaneously or result from an activity or procedure. The World Union of Wound Healing Societies (2004) categorized the causes of wound pain as background, incident, procedural, and operative.

Definitions and research findings on the causes of wound pain are summarized in Table 1. Not surprisingly, Table 1 shows that level of pain depends on the causes of pain. In both acute and chronic wounds, background pain (i.e., pain at rest) ranges from mild to

moderate. Incident pain (e.g., pain while coughing), procedural pain (e.g., pain during dressing removal), and operative pain (e.g., wound debridement) are worse than pain at rest.

Mechanisms of Wound Pain

Mechanisms that underlie the development of acute wound pain have been identified in experimental and clinical models of surgical wounds. Although many studies have attempted to determine the mechanisms involved in wound pain, these mechanisms remain poorly understood (Brennan, 2002). Apparently, more than one mechanism is involved in wound pain. For example, incisional pain may involve nociceptive, inflammatory, and neuropathic pain (Dahl & Kehlet, 2006). However, a recent review suggests that the ischemic pain mechanism may be responsible for incisional pain (Pogatzki-Zahn, Zahn, & Brennan, 2007). The following sections of this article will summarize the three major types of pain, the concepts of peripheral and central sensitization in relationship to acute wound pain, and factors that can contribute to acute wound pain.

Major Types of Pain

Nociceptive pain. As illustrated in Figure 1, nociceptive pain occurs immediately after exposure to a noxious stimulus (e.g., thermal, mechanical, chemical) and it is necessary to prevent further tissue damage (Woolf, 2004). Nociceptive pain is mediated through the peripheral (i.e., A-delta [A-δ] and C-fibers) and central nervous systems through the processes of transduction, transmission, modulation, and perception.

Transduction converts a peripheral noxious stimulus into electrical activity. The electrical signal is transmitted from the peripheral nervous system to the central nervous

system initiated by neurotransmitters found in the spinal cord, brain stem and thalamus, and cerebral cortex (Fields, 1987; Woolf, 2004).

Modulation refers to the facilitation or inhibition of pain impulses sent to the brain. Modulation occurs directly at the level of the spinal cord and through descending pathways from the midbrain periaqueductal gray region, pons, and medulla to the dorsal horn (Basbaum & Jessell, 2000; Hunt & Mantyh, 2001; Woolf, 2004). In addition to these areas, the thalamus and cortex are involved in pain modulation (Bushnell & Apkarian, 2006). Finally, perception refers to the interpretation of the nociceptive signal as pain (Dahl & Kehlet, 2006).

Inflammatory pain. Inflammatory pain arises when tissue damage occurs due to surgery, trauma, or other inflammatory conditions (Woolf, 2004). This pain usually resolves when the condition that provokes the inflammation is controlled (Woolf & Salter, 2000). Inflammation is characterized by redness (rubor), heat (calor), and swelling (tumor) (Basbaum & Jessell, 2000).

Inflammatory pain follows the same pathways and processes as nociceptive pain but is associated with peripheral sensitization and central sensitization (Woolf, 2004). According to Meyer, Ringkamp, Campbell, and Raja (2006) "sensitization is characterized by a decrease in threshold, an augmented response to suprathreshold stimuli, and ongoing spontaneous activity" (p. 14). As illustrated in Figure 2, peripheral sensitization occurs when tissue damage induces the release of chemical mediators from different cells and/or tissue- damaged sites that activate or sensitize the nociceptors (Basbaum & Jessell, 2000; Meyer et al., 2006; Scholz & Woolf, 2002; Woolf, 2004). As a consequence of nociceptor sensitization, the process of transduction is altered, and the

conduction of the electrical impulse increases (Dahl & Moiniche, 2004). In addition, the activation threshold of nociceptors decreases, which results in allodynia (i.e., pain caused by a stimulus that normally is not noxious) (Basbaum & Jessell, 2000; Julius & Basbaum, 2001). These physiologic processes result in primary hyperalgesia, a condition in which the site of injury or inflammation has increased sensitivity to pain (Meyer et al., 2006; Woolf, 2004).

As part of inflammatory pain, central sensitization can occur. In this process, dorsal horn neurons are activated through the release of neurotransmitters from primary afferent nociceptors (Scholz & Woolf, 2002; Woolf, 2004). These neurotransmitters stimulate dorsal horn neurons to become hyperresponsive to noxious stimuli, leading to an increase in pain transmission (Woolf, 2004). N-methyl-D-aspartate (NMDA)-type glutamate receptors participate in the hyperresponsiveness of second-order neurons (Basbaum & Jessell, 2000). With central sensitization, secondary hyperalgesia and allodynia occur in uninjured areas surrounding the site of injury (Meyer et al., 2006).

Neuropathic pain. Neuropathic pain is caused by lesions in the peripheral or central nervous systems (Woolf & Salter, 2000). Similar to inflammatory pain, both peripheral and central sensitization occur, which are characterized by primary and secondary hyperalgesia, respectively (Woolf, 2004). Neuropathic pain can occur spontaneously or be provoked by an external stimulus (Woolf, 2004). However, unlike inflammatory pain, temporary or permanent changes can occur within the peripheral and central nervous systems, and this can result in chronic pain (Perkins & Kehlet, 2000; Woolf & Salter, 2000).

Role of Peripheral and Central Sensitization in Acute Wound Pain

Although it remains a topic of debate, recent studies suggest that both peripheral and central sensitization contribute to the symptoms of primary and secondary hyperalgesias associated with incisional pain (Dahl & Kehlet, 2006; Pogatzki-Zahn et al., 2007). Sensitization can contribute to increases in the severity of wound pain owing to augmentation of noxious inputs (Wilder-Smith & Arendt-Nielsen, 2006). Both primary and secondary hyperalgesias were demonstrated in a rat model of incisional pain (plantar aspect of the foot) (Zahn & Brennan, 1999) and in human experimental models (small incision through the skin, fascia, and muscle) (Kawamata et al., 2002). In addition, secondary hyperalgesia was found in the area surrounding an incision in patients who underwent nephrectomy (Stubhaug, Breivik, Eide, Kreunen, & Foss, 1997) and abdominal hysterectomy (Dirks, Moiniche, Hilsted, & Dahl, 2002).

The mechanisms that underlie the development and maintenance of peripheral and central sensitization (i.e., primary and secondary hyperalgesias) are not well understood. Kawamata et al. (2002) established that secondary hyperalgesia is mediated by peripheral sensitization. After an incision is performed, A-δ and C-fibers are sensitized and generate spontaneous activity that amplify the responses of dorsal horn neurons (Pogatzki, Gebhart, & Brennan, 2002). Silent nociceptors, which normally do not respond to noxious stimuli, can become activated and contribute to the development of both primary and secondary hyperalgesia (Kawamata et al., 2002; Zahn, Pogatzki, & Brennan, 2002). Finally, an innocuous stimulus can be transformed to evoke allodynia through an increase in the responses of nociceptors, sensitization of silent nociceptors, and an increase in the receptive field of A-δ and C-fibers (Brennan, Zahn, & Pogatzki-

Zahn, 2005). While the specific mechanisms remain unclear, both peripheral and central mechanisms may contribute to the maintenance of secondary hyperalgesia (Kawamata et al., 2002). A comparison of the type of pain, characteristic of pain, and clinical symptoms among the four causes of wound pain is presented in Table 2.

Factors that Contribute to Acute Wound Pain

Many factors can contribute to the development of both peripheral and central sensitization and, consequently, wound pain. These factors can be categorized as "wound-direct" and "wound-indirect" (Figure 3).

Wound-direct factors. Brennan (2002) suggested that factors associated with the surgical wound contribute to the development of sensitization. Wound-direct factors include acidosis at the wound site, infection, inflammation, size, and location of the wound. Recent findings suggest that acidosis at the site of the wound induces sensitization of nociceptors (Kim, Freml, Park, & Brennan, 2007; Woo, Park, Subieta, & Brennan, 2004). In a rodent model, the development of tissue acidosis after an incision resulted in increased pain behaviors. Rodent pain behaviors decreased when tissue pH levels became normal (Woo et al., 2004). Kim et al. (2007) suggested that both a decrease in pH levels and increase in tissue lactate concentration after incision contributed to incisional pain through the induction of ischemia.

Acute wounds are at risk for infection, and wound infection is usually associated with increased pain at the site of the wound. In fact, one criterion for diagnosis of an acute wound infection is pain (Center for Disease Control and Prevention, 1999). Infection-causing bacteria produce endotoxins and exotoxins, both of which injure tissue (Rote & Huether, 2006) and may contribute to sensitization. Infection leads to an

inflammatory response that releases the inflammatory soup (i.e., the several chemical mediators) that induces nociceptor sensitization.

The association between pain and wound size is not well studied. However, in one study patients with larger acute wounds reported higher pain intensity scores (Meaume et al., 2004). It is possible that if the area of the wound is large, more nociceptors are activated and sensitized.

The location of the wound is another factor that is associated with differences in pain intensity. Some wounds are located in areas that involve major peripheral nerves (e.g., thorax, breast, groin). These nerves can be damaged during surgical procedures, and this damage can contribute to the development of neuropathic pain as well as hyperalgesia and allodynia (Kehlet, Jensen, & Woolf, 2006).

Wound-indirect factors. A variety of indirect factors can contribute to pain in acute wounds including repetitive stimuli, cleansing solutions, the primary dressing (i.e., dressing applied directly to the wound bed), and the length of time from injury. Repetitive stimulation associated with respiratory movements and coughing, especially following thoracic or abdominal surgery, may contribute to peripheral and central sensitization (Kawamata et al., 2002). In addition, wound care which includes removal of the dressing, local care applied to the wound, and reapplication of a dressing may also stimulate or traumatize the wound area and enhance sensitization. Trauma to the wound during local care can be done by mechanical (i.e., scrubbing or high-pressure irrigation) or chemical (i.e., toxic cleansing solutions) means (Rodeheaver & Ratliff, 2007).

Numerous solutions are available to clean a wound. However, some solutions (e.g., povidone-iodine, acetic acid, hydrogen peroxide, sodium hypochlorite) have antiseptic

properties that are toxic to wound cells (Lineaweaver et al., 1985; Wilson, Mills, Prather, & Dimitrijevich, 2005) and may lead to sensitization of nociceptors. Some of these solutions, as well as other products, are often used as part of the primary dressing. Jurczak et al. (2007) found that the overall ability to manage open surgical or traumatic wound pain was rated significantly ($p < .01$) better in patients using a hydrofiber with silver dressing than in patients using providone-iodine gauze as the primary dressing. Patients with open wounds from excision of a pilonidal sinus treated with hydrocolloids reported significantly less pain ($p = .05$) compared to those treated with providone-iodine gauze (Viciano et al., 2000). In the study by Meaume et al. (2004), 95% of patients reported no pain or less pain during dressing removal when they were treated with a lipido-colloid contact layer dressing compared to wet, dry, or paraffin gauze. The use of wet or dry gauzes and gauzes impregnated in antiseptic solutions (e.g., sodium hypochlorite and providone-iodine) as primary dressings enhance wound pain (Krasner, Shapshak, & Hopf, 2007). These dressings often dry out and adhere to the wound bed, traumatizing it when they are removed, thereby sensitizing nociceptors.

The length of time from injury is another factor that contributes to sensitization and wound pain. Wounds are more painful during the inflammatory phase of healing than during the active repair phases (Krasner et al., 2007; van Rijswijk, 1999). Mechanisms that may contribute to increased pain include inflammation, wound hypoxia, and exposed nerve endings (Krasner et al., 2007). Patients with acute wounds reported severe pain when the wound had less time from injury ($p < .001$) (Meaume et al., 2004). Patients who underwent a hysterectomy were evaluated preoperatively and at different postoperative times for pain intensity using a 0 to 100 mm visual analogue scale. Pain

intensity at rest was significantly higher at four hours (42 mm), six hours (22 mm), and first day (21 mm), decreasing gradually to 0 mm by the fourth postoperative day (Moiniche, Dahl, Erichsen, Jensen, & Kehlet, 1997). Their pain intensity during coughing gradually decreased (88 mm at four hours, 85 mm at eight hours, 51 mm at first day, 45 mm at fourth day), but was still significantly higher up to the eighth day (33 mm) when compared with preoperative pain intensity (0 mm).

Pain Management for Acute Wounds

Pain management for acute wounds should focus on the use of strategies that will attenuate modifiable factors that contribute to wound pain such as infection, repetitive stimuli, cleansing solution, and primary dressing (Table 3). These strategies involve both pharmacologic and non-pharmacologic interventions that need to be individualized. Pharmacologic treatments will vary based on the different types, causes, and severity of the pain. Whereas moderate to severe nociceptive pain is usually managed with opioids (e.g., morphine, fentanyl, oxycodone with acetaminophen), inflammatory pain responds better to nonsteroidal anti-inflammatory drugs (NSAIDs). However, clinicians need to exercise caution with the use of NSAIDs, specifically selective COX-2 inhibitors, which may increase the risk for cardiovascular events in some patients (Antman et al., 2007). Neuropathic pain is treated with co-analgesics, such as antidepressants and anticonvulsants. Nonetheless, because acute wound pain may involve multiple mechanisms, the use of a combination of analgesics is recommended (Dahl & Kehlet, 2006).

Ketamine, another pharmacologic agent, has been a focus of study to prevent or treat central sensitization (i.e., decrease secondary hyperalgesia) in the postoperative

period (De Kock & Lavand'homme, 2007; Stubhaug et al., 1997). Ketamine is a NMDA noncompetitive receptor antagonist which has antihyperalgesic and analgesic properties at sub-anesthetic doses (i.e., small doses). In several clinical trials (Dahl, Ernoe, Steen, Raeder, & White, 2000; Suzuki et al., 1999; Weinbroum, 2003), small doses of ketamine in combination with opioids decreased postoperative pain. Although ketamine has been associated with psychomimetic side effects (White, Way, & Trevor, 1982), in a systematic review (Subramaniam, Subramaniam, & Steinbrook, 2004) of randomized double-blinded clinical trials of perioperative pain management, the incidence of central nervous system side effects did not differ between patients who received an opioid with a small dose of ketamine compared to patients who received only an opioid.

It is imperative to consider the causes of wound pain in order to provide adequate pain management. Because background pain can be continuous, the administration of analgesics "around the clock" is recommended, instead of as "needed," to maintain a steady analgesic level (American Pain Society, 2003). In addition to an analgesic given to decrease background pain, it is necessary to administer rescue doses for incident pain. In terms of procedural and operative pain, it is critical to know the pharmacokinetics (i.e., time to peak analgesic effect; duration of analgesia) of the various analgesics to determine the correct time to administer the agents to prevent pain.

Conclusion

Acute wound pain is common in patients with surgical and traumatic wounds. The principal causes of acute wound pain are background, incident, and procedural pain. Different mechanisms underlie acute wound pain including nociceptive, inflammatory,

neuropathic, and ischemic. Wound pain can be a consequence of one or all of these mechanisms.

Research has advanced our knowledge of pain mechanisms. Nevertheless, there are still gaps in the research that require further attention. For example, clinical studies could target wound-direct and indirect factors. Such studies could contribute to the understanding of the perception of pain as well as to the development of clinical symptoms such as hyperalgesia and allodynia. Furthermore, research could investigate the best pharmacologic therapies to treat background, incident, and procedural wound pain. Acute wound pain is not only distressing; it can develop into chronic pain if ineffectively treated.

Pain research can contribute to a better understanding of the mechanisms involved in different clinical situations that evoke wound pain as well as promote the development of new pharmacologic therapies to improve a patient's pain experience. The translation of these research findings into clinical practice can contribute to the improvement of wound pain assessment and management, eventually achieving better patient outcomes.

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Table 1

Definitions and Research Findings on the Causes of Pain Associated with Acute Wounds

Causes of Pain	Definition	Research Findings
Background	Pain from wound areas that is felt at rest	Shukla et al (2005) • Sample Acute wound (n = 26) Chronic wound (n = 24) • Presence of background pain Patients with acute wounds (100%) Patients with chronic wounds (83.3%) • Background pain intensity Mild to moderate pain (88%) • Pain course Intermittently (72%) Continuous (28%) Meaume et al (2004) • Sample Acute wound (n = 2890) • Presence of background pain (83%) • Pain course Continuous in traumatic wounds (16%) Continuous in burns (24%)
Incident	Pain that occurs at the wound site during routine activities (e.g., mobilization, turning, sitting, walking, coughing)	Shukla et al (2005) • Movement increased background pain (37%) Gilron et al (2002) • Sample Hysterectomy patients (n = 25) • Pain intensity during sitting (21.5 mm) and coughing (26.1 mm) was significantly ($p < .05$) higher than pain at rest (10.5 mm) measured on a 0 to 100 mm VAS
Procedural	Pain that patients experience during routine wound care procedures such as wound dressing removal and wound cleansing	Shukla et al (2005) • Dressing changes increased background pain (60%) Meaume et al (2004) • Pain intensity during wound care procedure Moderate to severe pain (79.9%) • Most painful procedure Dressing removal (85%) Stotts et al (2004) • Sample (n = 412) • Pain intensity during wound care procedure M = 4.4 measured on a 0 to10 NRS • 23% received analgesic treatment one hour before and during the procedure
Operative	The pain caused by interventions such as wound debridement	Stotts et al (2004) • Pain intensity during debridement (n = 15) M = 8.2 measured on a 0 to 10 NRS

NRS, numeric rating scale; VAS, visual analogue scale; *M*, mean

Table 2

Overview of Wound Pain

Causes of Pain	**Types of Pain (Mechanism-based)**	**Characteristic of Pain**	**Clinical Symptom**
Background	Neuropathic Inflammatory	Spontaneous	Pain
Incident	Inflammatory	Evoked	Allodynia Pain
Procedural	Nociceptive Inflammatory	Evoked	Hyperalgesia Pain
Operative	Nociceptive Inflammatory	Evoked	Hyperalgesia Pain

Table 3

Strategies Directed at Attenuating Modifiable Wound Factor

Modifiable Wound Factor	**Strategies**
Infection	Debride devitalizing tissue
	Drain of purulent fluid collection
	Use systemic antibiotics
Repetitive stimuli	Reduce frequency of wound local care and dressing change if not contraindicated (using more absorbent dressings)
	Use wound irrigation instead of scrubbing technique
Cleansing solution	Avoid toxic cleansing solutions such as povidone-iodine, acetic acid, hydrogen peroxide, sodium hypochlorite unless wound's condition requires their use
Primary dressings	Use moisture-retentive dressings
Acidosis	Do not alter wound acidosis milieu since it is necessary for acute wound-healing process

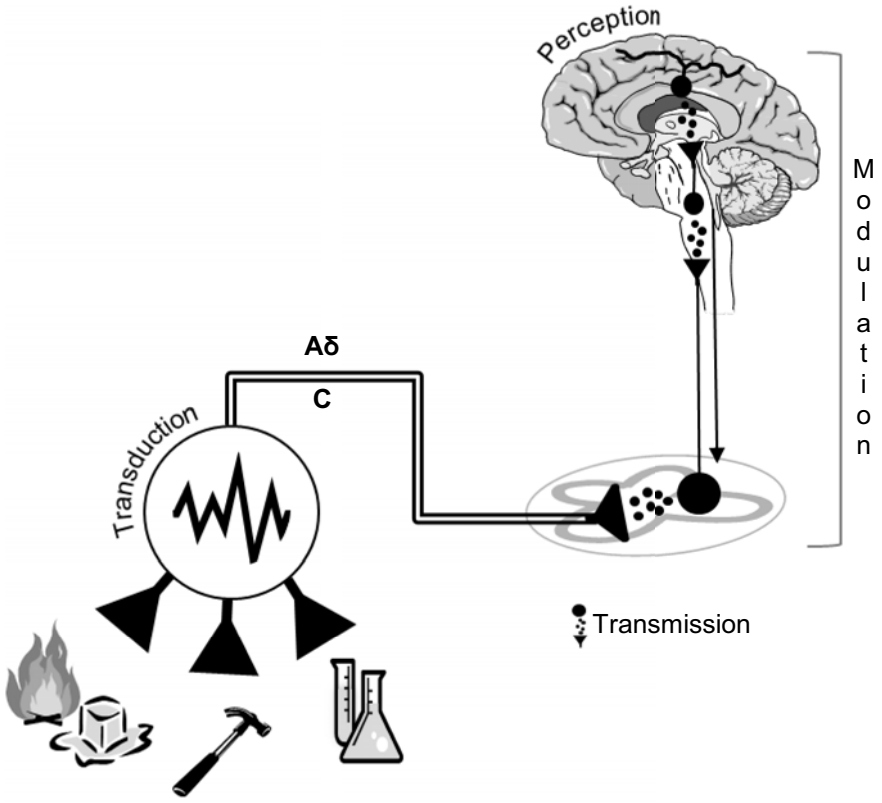

Figure 1. Nociceptive pain mechanism. Aδ; A-delta fibers; C, C fibers.

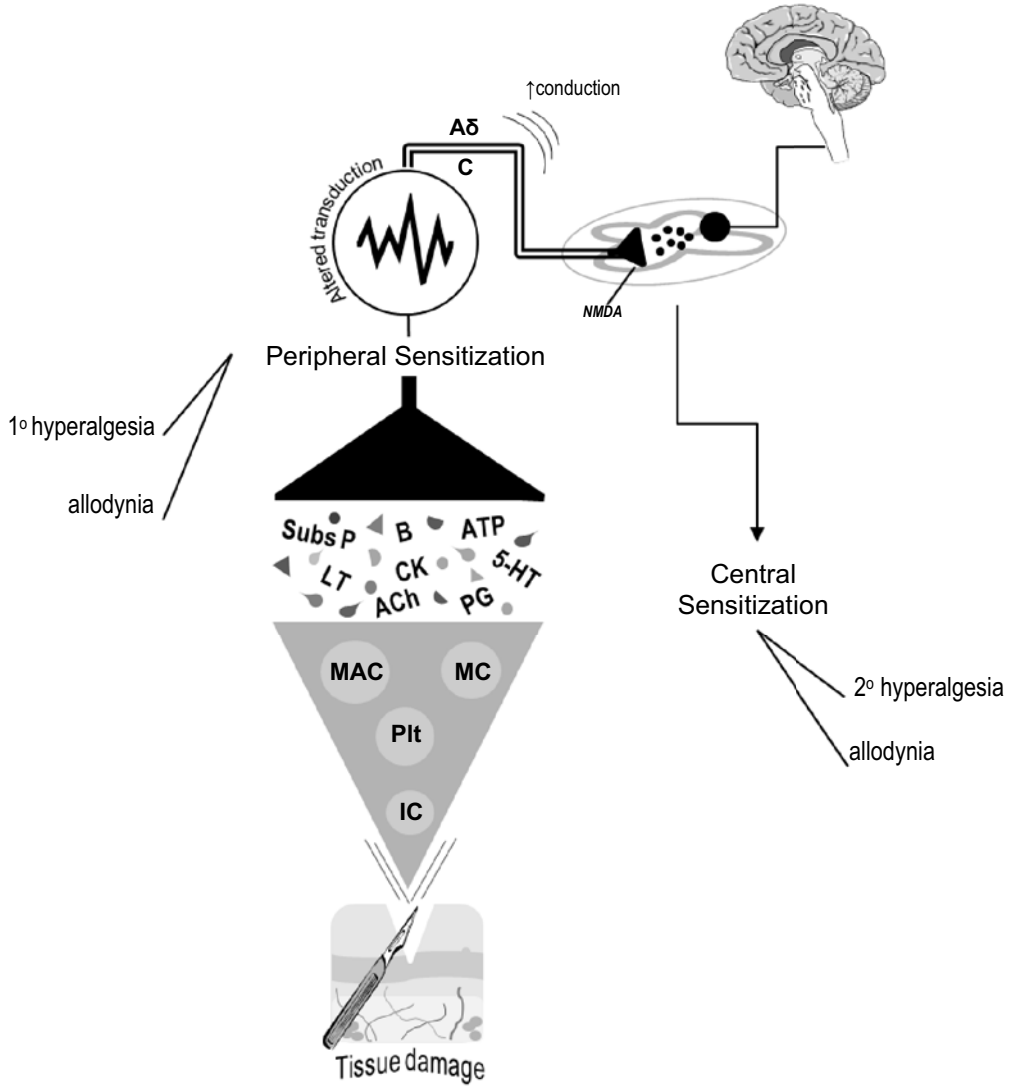

Figure 2. Peripheral and central sensitization mechanisms. ↑, increase; Aδ, A-delta fibers; C, C fibers; NMDA, N-methyl-D-aspartate receptors; Subs P, substance P; B, bradykinin; ATP, adenosine triphosphate; LT, leukotrienes; CK, cytokines; 5-HT, serotonin; Ach, acetylcholine; PG, prostaglandins; MAC, macrophages; MC, mast cells; Plt, platelets; IC, immune cells; 1^{o}, primary; 2^{o}, secondary.

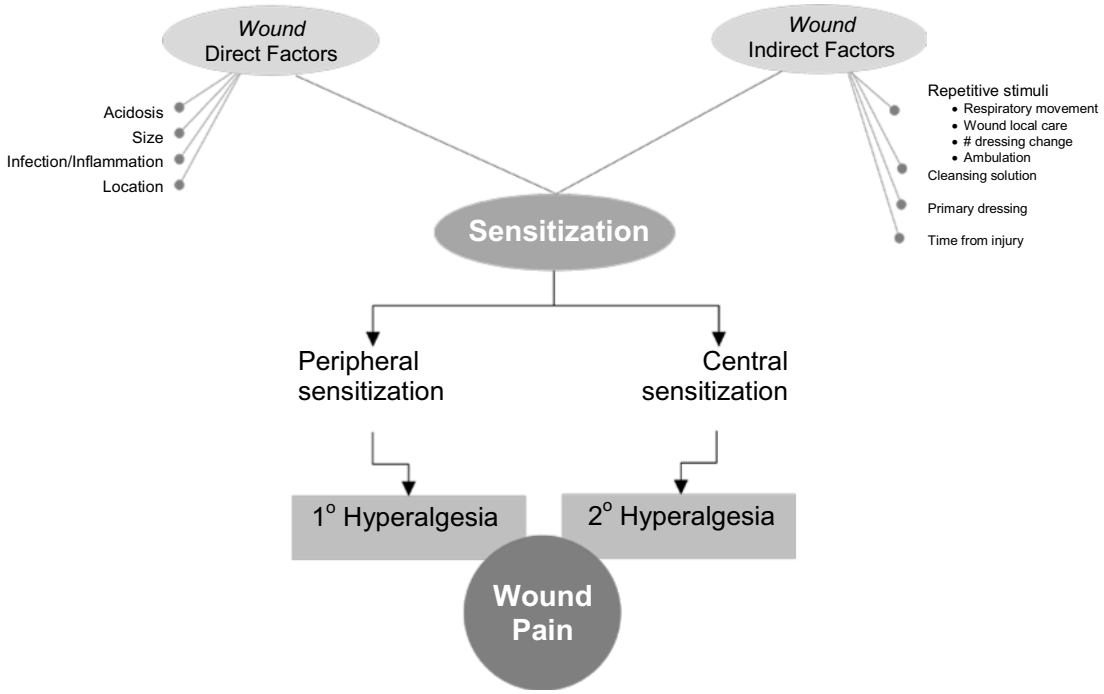

Figure 3. Factors that contribute to acute wound pain. #, number; 1^{o}, primary; 2^{o}, secondary.

Chapter IV

The Efficacy of Small Doses of Ketamine
with Morphine on Decreasing Procedural Pain Responses
During Open Wound Care

Abstract

Patients with open wounds frequently undergo painful wound care procedures (WCP) to prevent wound infection and promote wound healing. Hyperalgesia around the wound may increase the pain intensity during a WCP. Ketamine in small doses has antihyperalgesic and analgesic properties.

A randomized, cross-over design was used to determine whether the addition of small doses of ketamine would potentiate morphine's analgesic effects and decrease WCP pain intensity. Patients were randomized to receive either 0.1 mg/kg of morphine (maximum dose of 8 mg) plus saline (MS) IV or 0.05 mg/kg of morphine (maximum dose of 4 mg) plus ketamine 0.25 mg/kg (MK) IV before the WCP. When the WCP was repeated, patients were crossed-over to receive the alternate treatment.

Eleven patients from the Trauma Hospital of Puerto Rico participated in the study, all male with a mean (*SD*) age of 32 (7.8). Wound pain intensity was measured with a 0-10 numeric rating scale prior to and during the WCP. A Friedman test showed a statistically significant overall difference among the mean ranks of wound pain intensity, χ^2 (3, N =11) = 8.45, p =.038. Wilcoxon tests showed that the contrast between procedural wound pain intensity during the WCP-MK and during the WCP-MS was significant (p = .005). Mean (*SD*) of the procedural wound pain intensity during the WCP-MK was 3.09 (3.27), while it was 6.82 (3.06) during the WCP-MS. However, 91% of patients had adverse effects during MK versus none during MS. The most common adverse effects were hallucinations (n = 4, 36%), blurred vision (n = 4, 36%), and a strange sensation (n = 6, 55%). In addition, mean (*SD*) diastolic BP was significantly higher during the WCP-MK than during WCP-MS and prior to WCP-MK, 84 (11.8), 73

(7.4), 72 (12.6), respectively. There was no difference in hyperalgesia between MK or MS treatments.

In conclusion, ketamine with morphine significantly reduced procedural wound pain intensity during a WCP yet produced more adverse effects and higher, without consequences, diastolic BP. Further research is warranted to determine the dose of ketamine that is analgesic but causes minimal adverse effects during a WCP.

Introduction

Many patients in critical and acute care settings have open wounds that are due to traumatic injuries or surgical procedures. Wound pain can be perceived at rest (i.e., background pain) or evoked by any activity (i.e., incident pain) or procedure (i.e., procedural pain) (World Union of Wound Healing Societies, 2004). Patients with open wounds frequently undergo wound care procedures (WCP) to promote wound healing and prevent infection, and pain intensity increases during a WCP (Shukla et al., 2005; Stotts et al., 2004).

Although it is a known fact that open wounds are painful, the mechanisms involved in wound pain are not yet well understood (Brennan, 2002). Injury to superficial or deep tissues may provoke an inflammatory response that induces the release of chemical mediators. Peripheral neurons are activated and neurons located in the dorsal horn of the spinal cord are sensitized by the release of transmitters from the nociceptors. This process can result in central sensitization, which provokes the neurons in the dorsal horn to become hyperresponsive to noxious stimuli, leading to an increase in pain transmission (Scholz & Woolf, 2002; Woolf, 2004). As a result, uninjured areas surrounding the injury become hyperalgesic; that is, secondary hyperalgesia occurs (Meyer et al., 2006). N-methyl-D-aspartate (NMDA) glutamate receptors participate in the process of hyperresponsiveness of neurons in the dorsal horn (Basbaum & Jessell, 2000).

Although the contribution of hyperalgesia to postoperative pain has not been well established, it is thought that hyperalgesia may increase the intensity of pain (Wilder-Smith & Arendt-Nielsen, 2006). Ketamine is an NMDA antagonist which has antihyperalgesic and analgesic properties at small doses. In patients who underwent

nephrectomies (n = 20), small doses of ketamine reduced the area of secondary hyperalgesia around the surgical incision (Stubhaug et al., 1997).

Several studies have evaluated the effect of intravenous (IV) small dose ketamine given as a single bolus in addition to IV opioids on postoperative pain intensity. Two studies found that ketamine administered at the end of surgery (i.e., hysterectomy, n = 89 and laparoscopic cholecystectomy, n = 60) after receiving opioids for surgery induction resulted in significantly lower pain intensity scores postsurgery, when compared with patients who received ketamine or saline before skin incision (Dahl et al., 2000; Mathisen, Aasbo, & Raeder, 1999). Weinbroum (2003) evaluated the effect of a single dose of ketamine on pain intensity in postoperative patients (n = 245) who had morphine-resistant pain (i.e., pain which did not resolve with morphine 0.1mg/kg within a 30 minute period). Overall pain intensity during two hours in the postanesthesia care unit was significantly lower in the 131 patients in the ketamine group ($p < .001$). In addition, an immediate (i.e., < 10 minutes) and significant decrease in pain intensity was found among these patients.

Contrary to these studies, Menigaux and colleagues (2000) found no difference in pain intensity scores among patients (n = 45) who received ketamine at different times during an arthroscopic anterior ligament repair surgical procedure. In another study (n = 41) investigators failed to demonstrate the analgesic effect of a single dose of ketamine on patients' postoperative pain (Gillies, Lindholm, Angliss, & Orr, 2007). Trauma patients with severe pain who received small doses of ketamine and morphine (n = 33) in a hospital emergency room had no significant difference in pain intensity score compared to those who received placebo and morphine (n = 32) (Galinski et al., 2007). However,

morphine consumption was significantly less in the ketamine group.

In an experimental human study, Arendt-Nielsen and colleagues (1995) concluded that a small dose of ketamine has a hypoalgesic effect on high intensity electrical and mechanical stimuli. Based on this conclusion, as well as those from some clinical studies in which small doses of ketamine significantly reduced pain intensity, it seems reasonable to test its effect on procedural wound pain intensity during a WCP (i.e., a nociceptive stimulus).

Method

A randomized, double-blind, cross-over design was used to examine differences in patients' pain perceptions and hyperalgesia when receiving morphine with saline (MS), compared to morphine and a small dose of ketamine (MK) prior to an open WCP. The research design had four conditions: (1) prior to WCP-MS, (2) during or immediately after WCP-MS, (3) prior to WCP-MK, and (4) during or immediately after WCP-MK. The cross-over design allows for a small sample size, in permitting each patient to serve as his/her own control, thereby minimizing the potential for confounding results (Grady, Cummings, & Hulley, 2007).

The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus and the Committee of Human Research of the University of California, San Francisco approved the study. ClinicalTrials.gov identifier for this study is NCT00701909.

Aims

The aims of this cross-over clinical trial were to: (a) examine differences in wound pain intensity between patients who received MK and those who received MS, measured

prior to (i.e. background pain) and during (i.e. procedural pain) a WCP; (b) examine differences in wound pain quality prior to and during a WCP; (c) examine differences in the area of secondary punctuate mechanical hyperalgesia prior to and immediately after a WCP; (d) examine differences in the levels of drowsiness prior to and immediately after a WCP; (e) compare the occurrence of adverse effects such as nausea, vomiting, hallucinations, and a strange sensation; (f) examine differences in physiological measures prior to and during the WCP; and (g) examine differences in procedural wound pain intensity during the "screening" WCP between patients who received analgesics 1 hr before the "screening" WCP and those who did not receive analgesics. The "screening" WCP was that which occurred at the time that the patient was screened for eligibility and enrolled in the study.

Power Analysis

To determine the possible effect size, results from two previous studies were used that explored whether ketamine plus morphine caused a significant reduction in pain intensity when compared to morphine plus saline in postoperative patients (Gillies et al., 2007; Weinbroum, 2003). One of these studies found an extremely large effect size of 2.081 (Weinbroum, 2003) and the other one a medium effect size of .541 (Gillies et al., 2007).

Using n-Query Advisor 5.0 for calculation of power analysis for the main hypothesis, a sample size of 42 patients would have 80% power to detect a medium effect size of .541 versus six patients to detect a large effect size of 2.081 using Friedman test with matched-pair Wilcoxon contrasts at a .0125 two-sided significance level. The significance criteria are corrected using the Bonferroni method based on four principal

contrasts that will be discussed in the data analysis part. To be conservative, the sample size of 42 patients obtained from the medium effect was selected.

Sample and Settings

Patients from the Trauma Hospital (Trauma Intensive Care Unit and Trauma Intermediate Care Unit) and Hyperbaric Unit of the Puerto Rico Medical Center were screened for their eligibility for the study. The inclusion criteria consisted of patients who: (a) were between the ages of 21 and 65, (b) had an open surgical or traumatic wound with duration of no more than 10 days, (c) would be able to self-report their pain, and (d) had a wound pain intensity score greater than three on a 0 to 10 numeric rating scale (NRS) during the "screening" WCP. A score greater than three has been categorized as moderate pain according to a study of acute postoperative pain (Dihle, Helseth, Paul, & Miaskowski, 2006). Patients who had an injury that impaired their sensation in the wound area; who were allergic to morphine or ketamine; and/or who had not received morphine previously were excluded from the study.

Measures

Two instruments were used to measure a patient's pain responses to WCP. Wound pain intensity was measured by a 0 to 10 NRS, where 0 equaled to no pain and 10 equaled the worst pain imaginable. Wound pain quality was measured with the short-form McGill Pain Questionnaire (SF-MPQ), administered in the Spanish version for the Puerto Rican population. The SF-MPQ is comprised of 15 adjectives that describe pain, with a scale to rate them as mild, moderate, or severe. Doctor Ronald Melzack gave permission for its use by e-mail communication. The NRS is useful to describe pain intensity and the effectiveness of pain treatment. Concurrent and construct validities of

the NRS have been well-established (Berthier, Potel, Leconte, Touze, & Baron, 1998; Downie et al., 1978). The SF-MPQ has good psychometrics properties when it is used to measure different types of pain (Melzack, 1987).

Level of drowsiness (sleepiness) and strange sensation were also measured by a 0 to 10 NRS. For drowsiness, 0 meant not sleepy at all and 10 meant extremely sleepy. For strange sensation, 0 meant no unpleasant sensation at all, and 10 meant an extremely unpleasant sensation. Physiological measures of blood pressure (BP), heart rate, and oxygen saturation were obtained from a non-invasive monitor (Accuttorr Plus™, Datascope Patient Monitoring, Mahwah, NJ).

A von Frey filament of size 5.46 (target force of 26 g or 254.09 mN) was used to test the presence of secondary hyperalgesia around the wound. This instrument has been used in previous studies to test hyperalgesia around closed surgical incisions (Lavand'homme et al., 2005; Stubhaug et al., 1997). The surface area of both wound and hyperalgesia was calculated using a wound measurement system (VISITRAK™ Digital, Smith and Nephew, England, UK). Accuracy of the VISITRAK™ Digital to measure wound area has been established (Haghpanah, Bogie, Wang, Banks, & Ho, 2006; Sugama et al., 2007).

Procedure

All patients with open wounds who reported a procedural wound pain intensity score greater than three in the "screening" WCP were asked to participate and sign a written, informed consent form. The analgesic therapy regimen given before that "screening" WCP was obtained from the patient's clinical record.

Before the administration of the study's drugs and WCP, the following variables

were measured: (a) background wound pain intensity (i.e., “now”), (b) background wound pain quality, (c) area of punctuate secondary hyperalgesia around the wound (after removing the secondary dressing), and (d) level of drowsiness.

The presence of secondary hyperalgesia was obtained by stimulating the area around the wound with a von Frey filament from the periphery towards the wound until the patient reported a distinct change in perception. The first point where a “painful,” “sore,” or “sharper” feeling occurred was marked, and the distance to the wound was measured. When no change in perception occurred, stimulation was stopped 0.5 cm from the wound (Lavand'homme et al., 2005; Stubhaug et al., 1997). The area of hyperalgesia was determined by testing along radial lines at a distance of approximately 5 cm around the wound and then calculating the surface area (Lavand'homme et al., 2005).

Patients were randomized to receive either 0.1 mg/kg of morphine (maximum dose of 8 mg) plus saline IV or 0.05 mg/kg of morphine (maximum dose of 4 mg) plus ketamine 0.25 mg/kg IV before the WCP. The principal investigator (CMA), patients, and orthopedics technicians in charge of the wound care procedure were blinded to the study drugs. One of the co-investigators (MIF) was responsible for the randomization of the treatments, whereas the study drugs were prepared and administered by the nurse in charge of the patient. Morphine was administered 20 minutes prior to the WCP, based on morphine’s pharmacokinetic properties (i.e., peak analgesia is at 20 minutes) (Gutstein & Akil, 2006). Ketamine or saline was administered in a separate syringe five minutes before the WCP. This timing was based on Weinbroum's (2003) study that found a decline on pain intensity in less than 10 minutes after ketamine and morphine administration. The WCP was done by orthopedic technicians in charge of wound care in

the Trauma Hospital.

Immediately after the WCP the following were measured: (a) "worst" procedural wound pain intensity, (b) procedural wound pain quality, (c) level of drowsiness (sleepiness), (d) adverse effects (nausea, vomiting, hallucinations, and a strange sensation), (e) punctuate secondary hyperalgesia around the wound, and (f) length of the WCP (i.e., from the removal of the primary dressing until reapplication of a primary dressing) was measured in minutes using a stop watch. Patients were crossed over to receive the alternate treatment during the next WCP. All measures were repeated a second time. Heart rate, BP, oxygen saturation, and respiratory rate were measured before and during the procedure to assess the patient's clinical condition.

Data Analysis

Descriptive statistics were used for sample demographics, wound descriptions, analgesic treatment in the "screening" WCP prior to the experiment, and adverse effects. Paired *t* test was used to compare the length of the WCP between treatments. A Friedman test was conducted in order to analyze the main research aim, i.e., whether procedural wound pain intensity under the MK treatment was less than procedural wound pain intensity under the MS treatment. The Friedman test was followed up with matched-pair Wilcoxon tests to determine where differences resided. Four post-hoc contrasts using the Bonferroni correction to the overall alpha level were performed. The significance criterion for each of the contrasts mentioned above was .0125 (.05/4). Wound pain quality, hyperalgesia, and level of drowsiness were examined, also using Friedman, followed up with Wilcoxon tests. Repeated measure analysis of variance (RM-ANOVA) was used to examine differences in physiological measures using the

same significance criterion of .0125. The Mann-Whitney test was used to examine differences in procedural wound pain intensity between patients who received analgesics one hour before the "screening" WCP and those who did not receive analgesics prior to the experiment. Statistical analysis was performed using SPSS version 16.0.

Results

Patients were recruited between July 29, 2008 and January 20, 2009. Allocation of patients according to randomization is shown in Figure 1. A total of 11 patients from the Trauma Hospital completed the study. An interim evaluation was performed because the majority of patients (10 out of 11) developed adverse effects after ketamine administration. These effects were mild to moderate (patients did not require any treatment), expected, and were described in the consent form. The study was stopped due to this concern by the Data and Safety Monitoring Committee comprised of members of the dissertation committee of the principal investigator.

All patients were male with a mean (*SD*) age of 32 (7.8) years. Wounds were of surgical or traumatic origin (54.5% and 45.5%, respectively), located in the leg (82%) or arm (18%), with a mean (*SD*) size of 109.5 cm^2 (63.1).

Wound Pain Intensity and Analgesics Prior to the Experiment

Procedural wound pain intensity during the "screening" WCP was an average of 7.27 (*SD* = 2.10). Only 36% of those patients received morphine IV prior to the "screening" WCP and 64% did not receive any analgesic within one hour before the "screening" WCP. However, the morphine administered prior the WCP was not given for procedural pre-medication indeed coincided with the scheduled analgesic order.

Differences in procedural wound pain intensity between those patients who received morphine and those who did not were not significant ($p = 78$).

Wound Pain Intensity Prior to and During the WCP

During the experiment, a statistically significant overall difference in wound pain intensity was found among the four conditions, χ^2 (3, $N = 11$) = 8.45, $p = .038$. The contrast between procedural wound pain intensity during WCP-MS and during WCP-MK was found to be significant ($p = .005$). However, the other three contrasts were not significant. The significant contrast indicated that procedural wound pain intensity was less in patients treated with MK than those treated with MS. Although these non-parametric statistics use mean ranks to test differences, Figure 2 presents means of wound pain intensity within the four conditions for a better description. Length of WCP did not differ ($p = .71$) between treatments: a mean (*SD*) of 7.45 (3.08) minutes for the MS treatment and a mean (*SD*) 7.73 (3.77) minutes for the MK treatment.

Wound Pain Quality Prior to and During the WCP

Overall difference between the mean ranks in wound pain quality among the four conditions was not significant. However, when each word of the SF-MPQ was independently evaluated, an overall difference among the four conditions in the adjective "tender" was significant, χ^2 (3, $N = 11$) = 10.76, $p = .013$. Wilcoxon tests showed that the word "tender" to describe procedural wound pain quality during WCP-MS was rated significantly higher than during WCP-MK ($p = .011$). Table 1 shows the adjectives used to describe wound pain quality among the four conditions by more than 50% of patients. Background wound pain quality was described using adjectives from both sensory and affective dimensions. However, the majority of patients used adjectives from the sensory

dimension to describe procedural wound pain quality, and fewer adjectives were used during WCP-MK.

Hyperalgesia and Adverse Effects

The overall difference in both hyperalgesia and levels of drowsiness among the four conditions was not statistically significant. Overall differences in physiological measures were not statistically significant, except for diastolic BP, F (3, 30) = 6.64, p = .001. Diastolic BP was significantly higher during WCP-MK compared with both during WCP-MS and prior WCP-MK (see Figure 3).

Ninety-one percent (n = 10) of patients that received MK had adverse effects, versus none when treated with MS. The most common adverse effects were hallucinations (n = 4, 36%), blurred vision (n = 4, 36%), and a strange sensation (n = 6, 55%). Of those who presented the latter, three patients described it as an unpleasant sensation; two of them rated it as 10 (i.e., an extremely unpleasant sensation) and one as three. Patients' strange sensations are described in Table 2.

Discussion

To our knowledge, this is the first study to explore the effect of small doses of ketamine with morphine on wound pain intensity during a WCP. When ketamine was used to examine reduction in pain intensity during dressing change with burn patients (Owens et al., 2006; Tosun, Esmaoglu, & Coruh, 2008; Zor, Ozturk, Bilgin, Isik, & Cosar, 2009), it was always administered in larger doses. The majority of studies using small doses of ketamine explored pain in the perioperative period.

Our study demonstrated that small doses of ketamine (0.25mg/kg) plus morphine (0.05mg/kg) reduced procedural wound pain intensity during a WCP more than double

the dose of morphine (0.1mg/kg) plus saline in traumatically injured male patients. Using Dihle and colleagues' (2006) criteria for severity of pain, patients under the MK treatment developed mild procedural pain (i.e., < 4 in a 0-10 NRS) versus severe procedural pain (i.e., > 6) for those under the MS treatment. Morphine (0.1mg/kg) alone did not produce adequate analgesia, as occurred with emergency patients in severe pain (Bijur, Kenny, & Gallagher, 2005). This suggests that the effect of the combination of ketamine with morphine is a synergistic interaction between the two types of analgesics with different pharmacodynamic properties (Bossard et al., 2002).

The administration of ketamine produced a significant increase in diastolic BP in our study. Ketamine is associated with increases in blood pressure due to sympathetic stimulation (Takki, Nikki, Jaattela, & Tammisto, 1972). In a cross-over study of healthy volunteers, ketamine was given at 0.1mg/kg and 0.5mg/kg in addition to placebo (Krystal et al., 1994). The results showed a significant dose-dependent increase in diastolic BP from baseline. Yet, in contrast to our findings, a recent study showed significant increases in systolic BP in patients with bone fractures who were administered ketamine (Johansson, Kongstad, & Johansson, 2009). Their systolic BP was significantly higher at the time of hospital admission if they received low doses of ketamine during a pre-hospital intervention rather than morphine alone. Although the time to return of the diastolic BP to baseline was not quantified in our study, a transient effect was observed. A transient increase in BP with ketamine administration has been documented in a study review (Grossman & Messerli, 1995). No consequences derived from the increase of the diastolic BP were found in our study. However, in future studies using ketamine, a systematic evaluation of BP and its consequences is warranted.

Ketamine also induced psychomimetic adverse effects in our study. The majority of the studies with a single small dose of ketamine administration in postoperative patients did not report significant psychomimetic adverse effects (Gillies et al., 2007; Subramaniam et al., 2004). However, in emergency room trauma patients mentioned earlier (Galinski et al., 2007), those in the small dose ketamine group developed significantly more psychomimetic adverse effects than those who received saline. Similar findings were reported in a group of patients with a chronic pain syndrome (i.e., complex regional pain) who received an infusion of ketamine in an outpatient clinic when compared with those who received saline infusion (Sigtermans et al., 2009). However, in a second study, when patients with complex regional pain were pre-medicated with both clonidine and midazolam, no significant differences in the development of psychomimetic effects were found between ketamine infusion and saline infusion groups (Schwartzman et al., 2009). Apparently, the differences in the development of psychomimetic effects is that residual anesthesia (Gillies et al., 2007; Subramaniam et al., 2004) or pre-medication (Schwartzman et al., 2009) may reduce these effects.

The area of secondary hyperalgesia around the wound was not lower after ketamine administration in our study contrary to findings by Stubhaug and colleagues (1997). They noted a significant reduction in the area of secondary hyperalgesia around an incision in patients who underwent nephrectomy while receiving ketamine. A possible explanation of this finding is that the WCP could traumatize the wound area, provoking nociceptors sensitization as well hyperalgesia. We did not measure hyperalgesia between the study drugs' administration times and the WCP. Doing so could have shown the effect of the study drugs on hyperalgesia before the WCP. In addition, it is important to

mention that hyperalgesia measurement in our patients was challenging and subject to error for two reasons. First, the wounds in our study were opened with an irregular shape, located in extremities, and almost half were of traumatic origin. Prior measurement of hyperalgesia has been done in closed incisions (Lavand'homme et al., 2005; Stubhaug et al., 1997). Second, the procedure to measure hyperalgesia was difficult to perform when patients were in pain because it required movement of the extremity involved, which stimulated pain.

Although pain intensity was significantly different between treatments, pain quality was not. Lack of significance could be due to the small sample size. Therefore, consideration of a larger sample size is warranted. Notwithstanding, the adjective "tender" was rated significantly less during the WCP-MK. This could be possible due to the effect of ketamine on hyperalgesia. Tenderness has been used as an indicator of hyperalgesia in a previous study (Ilkjaer, Bach, Nielsen, Wernberg, & Dahl, 2000). However, this is a contradictory conclusion because of our non-significant finding on hyperalgesia measurement.

Prior to the experiment, patients reported severe pain during the "screening" WCP. However, more than the half of these patients did not receive any analgesic prior to the "screening" WCP. Moreover, those who received analgesics tended to be under-treated (i.e., reported higher pain intensity score than those that were not treated). Unfortunately, inadequate analgesia practices have not changed much through the years. Stotts and colleagues (2004) found that only 23% of patients received any medication, and only 18% received opioids prior to a WCP.

Limitations

It is important to acknowledge some limitations. The sample size was small and all patients were male. Yet, it was sufficiently powered to find significant differences in wound pain intensity between those who received ketamine with morphine and those only received morphine. Blinding was difficult to assure when patients demonstrated adverse effects that suggested a response to ketamine. In addition, the WCPs were done by different orthopedic technician and, consequently, the procedure could be subject to variability in the technique used and may influence differences in patients' pain response.

Conclusion

In conclusion, small doses of ketamine with morphine reduced procedural pain intensity during an open wound care; yet ketamine produced more adverse effects and higher diastolic BP. Further research is warranted to more accurately determine the dose of ketamine necessary to provide analgesia but cause only minimal adverse effects during a WCP. Future studies could also include the administration of a benzodiazepine to mitigate the psychomimetic effects.

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Table 1

Adjectives Used to Describe Wound Pain Quality with Over 50% Frequency

Condition	**Adjective**	**%**
Background Wound Pain Quality MS	Sharp	64%
	Heavy	64%
	Aching	55%
	Tiring-Exhausting	55%
Background Wound Pain Quality MK	Hot-Burning	82%
	Throbbing	64%
	Aching	64%
	Heavy	64%
	Tender	55%
	Tiring-Exhausting	55%
Procedural Wound Pain Quality MS	Aching	82%
	Tender	82%
	Sharp	73%
	Throbbing	64%
	Heavy	64%
	Shooting	55%
	Cramping	55%
	Hot-Burning	55%
Procedural Wound Pain Quality MK	Aching	64%
	Throbbing	55%
	Hot-Burning	55%

MS, morphine plus saline; MK, morphine plus ketamine

Table 2

Descriptions of Strange Sensations

Classification	**Rate**	**Description**
		Patient felt like if he was:
Unpleasant	10	in a rocket
Unpleasant	10	in a tunnel
Unpleasant	3	in the air
Pleasant	0	inside a computer
Pleasant	0	in the operation room
Un-classified	0	in a train

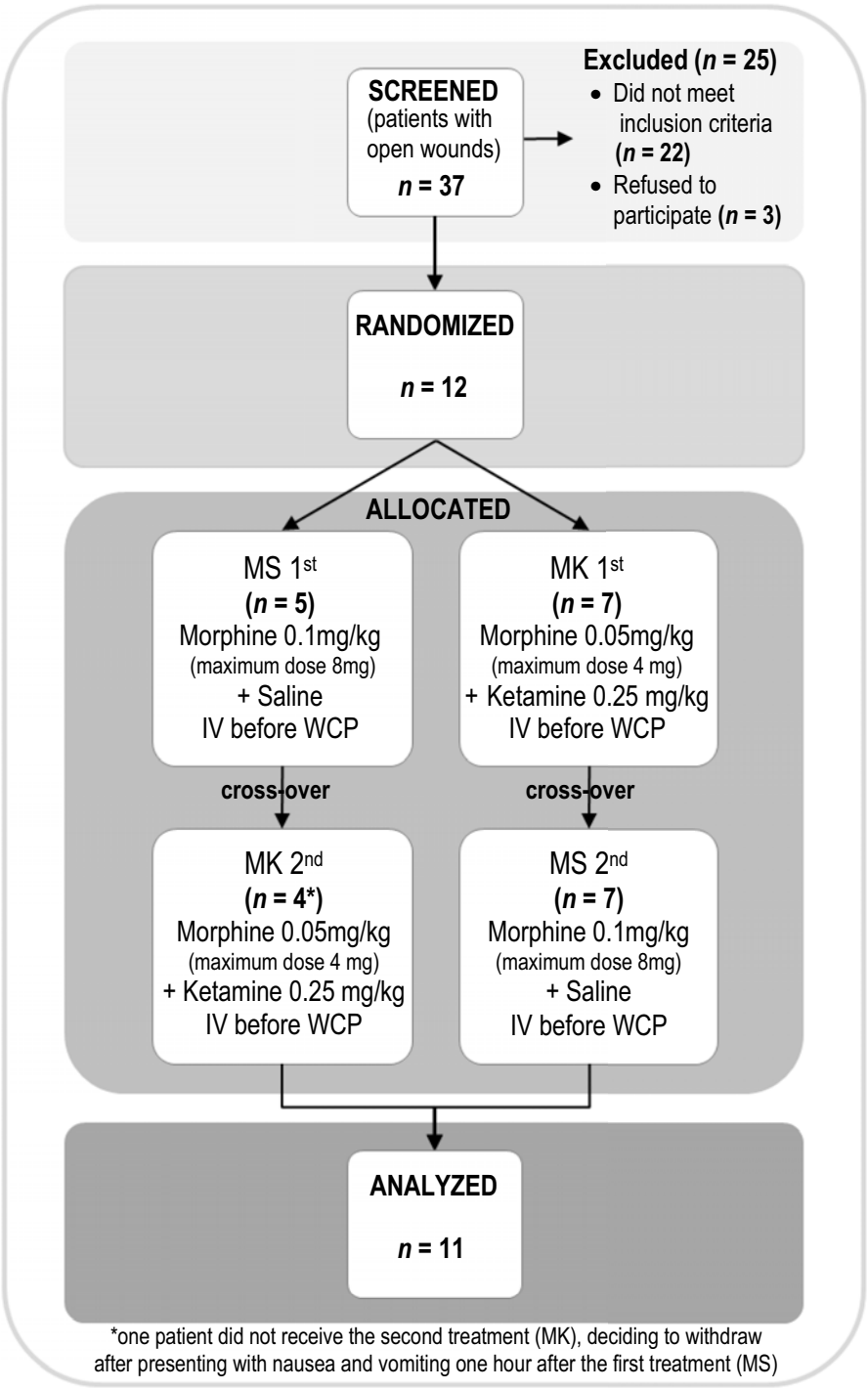

Figure 1. Flow diagram of the study. MS, morphine plus saline treatment; MK, morphine plus ketamine treatment; IV, intravenous; WPC, wound care procedure

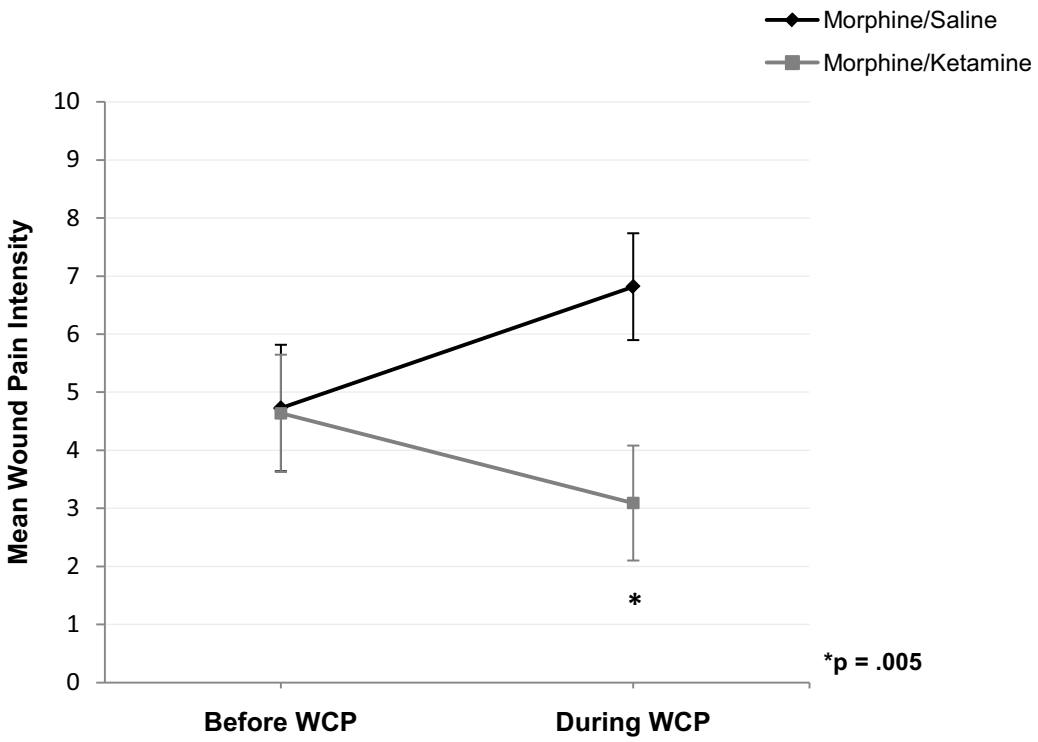

Figure 2. Mean of wound pain intensity among the four conditions. Standard error of the mean (SEM) are represented by error bars. Statistical differences were found between mean ranks of procedural wound pain using matched-pair Wilcoxon test.

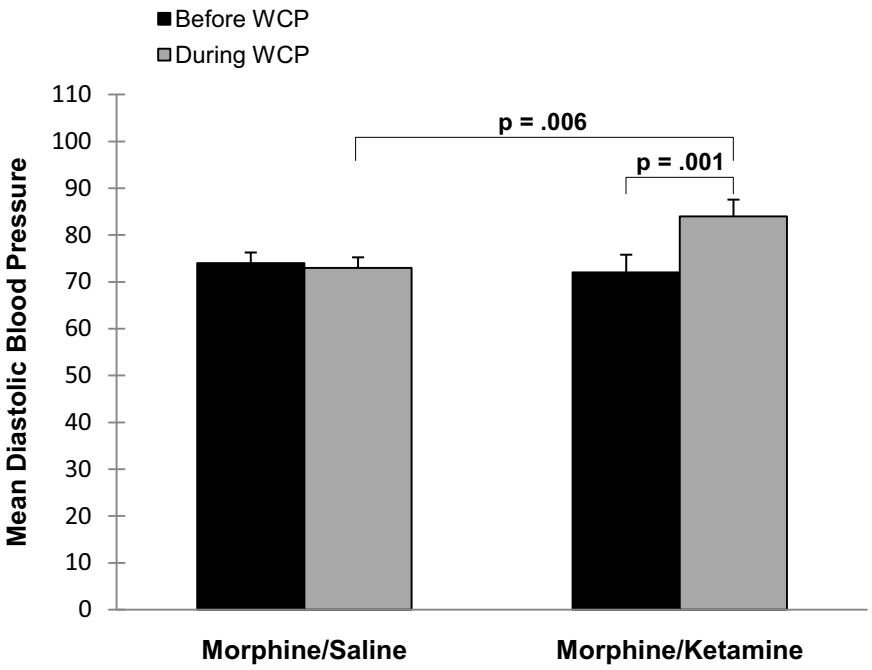

Figure 3. Mean of diastolic blood pressure among the four conditions. Standard error of the mean (SEM) are represented by error bars. WCP, wound care procedure.

Chapter V

Conclusion

Conclusion

Procedural pain is commonly experienced by acute and critical care patients. Unrelieved pain can contribute to the development of several multi-systemic effects. However, despite many years of research into the subject, current analgesic practices are inadequate for controlling procedural pain. Patients have a right to receive adequate pain management, which has been ignored for many years. The two research reports in this dissertation demonstrated that analgesic practices have not changed through the years and patient procedural pain often remains undertreated.

The first report explored pain responses during tracheal suctioning, one of the most common procedures performed to critically ill patients. Results showed that more than half of the patients reported moderate-to-severe pain and few patients received analgesics one hour prior to or during the procedure. Decisions not to administer analgesics prior to tracheal suctioning may be due to desensitization of health care providers to common procedures, short duration of the procedure, or that providers underestimate pain intensity during this procedure. Individualized pain management must be performed by healthcare providers in order to respond to patients' needs.

According to the literature review, wound pain intensity increased with wound care procedure; however, there are not enough intervention studies that address pharmacologic strategies for reducing wound procedural pain. Consequently, the second study was designed to examine a combined pharmacologic approach to address pain during wound care, one of the most common procedures experienced by trauma acute and critical care patients. Although the findings showed better procedural pain management with morphine plus ketamine, with a significant reduction in pain intensity, a final

recommendation in favor of using this combination as a standard practice cannot be given since psychomimetic effects were demonstrated when some patients received morphine plus ketamine.

Both reports demonstrated the need for intervention studies to determine the best pharmacologic strategies to improve pain associated with tracheal suctioning and with a wound care procedure. Based on the research findings of the second study, further research is needed to more accurately determine the dose of ketamine necessary to provide analgesia while causing only minimal adverse effects. A second alternative of exploration is to examine if the addition of a benzodiazepine could mitigate the psychomimetic effects of ketamine. Future research should focus on more interventional studies to explore the best pharmacologic and non-pharmacologic therapies for relief of pain related to other common procedures such as tracheal suctioning. Translation of these research findings into clinical practice is needed.

APPENDICES

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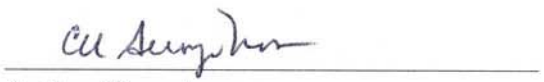

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