CHRONIC POST-SURGICAL PAIN AFTER NONCARDIAC SURGERY

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This thesis is dedicated to my older brother, Christopher Khan

ABSTRACT

Chronic post-surgical pain (CPSP) is a debilitating complication of surgery. Despite increasing attention in recent years, there is a paucity of data on the incidence of CPSP after noncardiac surgery and the risk factors that affect its development. The studies in this thesis inform current knowledge gaps in the literature. Chapter 2 describes the interim results of a large, international prospective cohort study on the incidence of chronic incisional pain, a type of CPSP specific to the incision site, and its associated risk factors. Chapter 3 describes the association between postoperative patient coping and expectations about recovery after traumatic tibial fracture repair and the development of CPSP and its interference on normal work. Chapter 4 outlines methodological issues with pain measurement in clinical trials and describes a protocol for a randomized controlled trial that compares electronic data collection to traditional data collection methods when investigating CPSP.

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DECLARATION OF ACADEMIC ACHIEVEMENT

I am the primary writer of all the chapters included in this thesis. I am also primarily responsible for the statistical analyses, interpretation, and reporting of the results. Patient data included in this thesis were collected by qualified research teams led by Dr. P.J. Devereaux and Dr. Mohit Bhandari for Chapters 2 and 3, respectively.

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ABBREVIATIONS

APAIS - Amsterdam Preoperative Anxiety and Information Scale
BMI – body mass index
BPI - Brief Pain Inventory
CI – Confidence interval
COX-2 – cyclo-oxygenase inhibitor sub-type 2
CPSP – Chronic post-surgical pain
IILI – intraoperative intravenous lidocaine infusion
IM - intramuscular
IQR – interquartile range
IV - intravenous
KW – kruskal-wallis
MPQ-2 - McGill Pain Questionnaire 2 (MPQ-2)
MVA – motor vehicle accident
NMDA – N-methyl-D-aspartate
NRS – Numeric Rating Scale
NSAIDs – nonsteroidal anti-inflammatory drugs
OHA – oral hypoglycemic agent
PCA – patient controlled analgesia
PCS – Pain Catastrophizing Scale
PHRI – Population Health Research Institute
PLAN - Pregabalin and lidocaine in breast cancer surgery to alter neuropathic pain
PLAN-ED – Pregabalin and lidocaine in breast cancer surgery to alter neuropathic pain: electronic data capture
RCT – randomized controlled trial
SC - subcutaneous
SD – standard deviation
SF-36 – Short form 36
SPOC – Somatic Preoccupation and Coping
SPRINT - Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures
VIF – variance inflation factor
VISION – Vascular events in noncardiac surgery patients cohort evaluation

CHAPTER 1

Introduction

Chronic pain is a major public health issue. An investigation of 25,916 consecutive patients attending a primary care clinic at 15 centres in 14 countries indicated that 22% of patients suffer from chronic pain.[1] Two large population-based surveys in Europe (n = 46,394) and Australia (n = 17,543) reveal a similar estimate of 19% for the prevalence of chronic pain.[2,3] Similar survey studies in the United States (n = 27,035) and in Canada (n = 2,012) report a prevalence of chronic pain of 31% and 29%, respectively, suggesting that chronic pain may be more prevalent in North America.[4,5] All of these surveys defined chronic pain as continual or intermittent pain over the previous 6 months.

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".[6] A key component to this definition is its recognition that pain is more than a physical sensation, it is a multi-dimensional process that has psychosocial consequences. Those living with constant pain tend to experience a variety of negative emotional responses such as anger, frustration, irritation, isolation, hopelessness, anxiety, and depression.[7] Often, these cognitive processes perpetuate and enhance the experience of pain, especially in the setting where a physical process or disease responsible for the pain does not exist.[7] Furthermore, there is a high co-occurrence of chronic pain and psychiatric disorders. About one third of those with chronic pain will suffer from major depression or an anxiety disorder, compared to a prevalence of 10-20% of depression and anxiety in the general population.[8,9] Those with chronic pain have also been found to have higher rates of suicidal ideation and suicide attempts.[10,11]

The burden of perpetual pain extends beyond biological and psychological impacts, and causes economic and financial strain on the patient, healthcare system, and society. Pain causes significant physical disability and is one of the top causes for work absenteeism and reduced productivity while at work.[12,13] Those with chronic pain are also seven-times more likely to quit their job than those without chronic pain.[14] Further, approximately 1 in 5 patients with chronic pain will lose their job because of their pain.[2] The direct costs of chronic pain are staggering — a study using a national electronic patient database found that chronic pain resulted in 4.6 million visits to a primary care physician for issues related to changing pain medications in the United Kingdom. This is equivalent to the time of 800 full time general practitioners and costs the system approximately £69 million ($100 million USD) a year.[15] The total cost of chronic pain due to direct healthcare expenditures and indirect costs associated with reduced work productivity is estimated to be in the billions of dollars each year, which approximates total costs from heart disease and cancer.[16,17]

Surgery appears to be a significant cause of chronic pain. Of 5,130 patients attending one of 10 chronic pain management clinics in North Britain, surgery was assessed to be the cause of pain in 1,154 patients (22.5%)[18]— ascertainment of the cause of chronic pain was performed by a pain physician based upon the patient's account, a clinical examination, and the review of patient records. Surgery was only deemed to be the cause of pain if the presenting pain complaint was not present prior to surgery. Other important identifiable causes of chronic pain found by this study included degenerative disease (34.2%) and trauma (18.7%). While this study was restricted to patients already diagnosed with chronic pain, a large population-based survey of 19,762 inhabitants of Norway (response rate = 65.7%) indicated that among those who had surgery greater than 3 months ago, 40.4% suffered from pain in the area of surgery, with 18.3%

suffering from moderate to severe pain.[19] Results of these studies indicate that surgery is not only a trigger for chronic pain but is also responsible for chronic pain in a sizeable proportion of the general population.

Chronic pain that is due to surgery is most commonly referred to as chronic post-surgical pain (CPSP). While a standardized definition for CPSP does not exist, the widely accepted and utilized definition includes four criteria: 1) the pain developed after a surgical procedure; 2) the pain is of at least 2 months duration; 3) other causes of pain should be explored and exclusions attempted; 4) the possibility that pain is continuous from a pre-existing problem has been explored and exclusions attempted.[20]

Although the pathophysiology of CPSP is not fully understood, the leading hypothesis is that peripheral nerve injury from surgery is likely the inciting trigger.[21,22] Complete axonal resection resulting from surgical incisions or injury due to surgical manipulation of large and small nerve fibres causes fundamental changes to the affected neuronal tissue.[23] Local mediators such as cytokines, prostaglandins, proteins, bradykinins, and other inflammatory molecules promote further neuronal irritation and hyper-excitability — these mechanisms are also responsible for acute postoperative pain experienced immediately after surgery.[24,25] For certain individuals, however, these nerves remain hyper-excitable and eventually undergo a process called sensitization, whereby the activation threshold is lowered and spontaneous ectopic impulses are produced, leading to hyperalgesia and allodynia.[26] Continuous impulses from the damaged peripheral nerves upregulates receptors and mediators along central pain pathways, ultimately leading to central neuroplastic changes and central sensitization.[27] Central and peripheral sensitization to pain contribute to the persistent nature of CPSP, and to the challenges associated with its management and treatment.[28]

The incidence of CPSP after noncardiac surgery varies in the literature. Studies have examined the development of CPSP within specific surgical populations and have found great variability. The occurrence of CPSP ranges from 11% to 57% after breast cancer surgery (mastectomy or lumpectomy), 19% to 63% after inguinal hernia repair, 25% to 60% after thoracotomy, and 5% to 32% after hysterectomy.[22,29–34] The majority of studies on CPSP utilize a cross-sectional study design on a group of patients who had previously undergone surgery. Thus, most studies document the prevalence, and not the incidence, of CPSP

The wide range of incidences found in the literature can be partly attributed to the absence of a standardized definition of CPSP. While the majority of studies use the aforementioned definition of CPSP, slight ambiguity in the criteria allows for subtle differences in definitions. For example, the proposed definition for CPSP does not specify that pain should be in the area of the surgical procedure. Hence, many studies that do not restrict assessment of new pain in and around the surgical area after surgery will inadvertently capture new pain after surgery that is unrelated to CPSP. Furthermore, there appears to be a natural history to CPSP pain and, depending on when an assessment is performed, different rates will be determined. A study that followed the same group of patients after a radical prostatectomy found that the incidence of CPSP to be 14.3% and 1.2% at 3 and 6 months after surgery, respectively.[35]

Various risk factors for the development of CPSP have been identified. Demographics such as younger age and female gender appear to be associated with chronic pain after surgery.[29,30,36] Certain psychological factors such as catastrophizing, somatization, and anxiety also appear to be risk factors for CPSP, as well as acute postoperative pain.[37–41] Given that many of these risk factors are not readily modifiable, further investigations on risk factors for CPSP are needed. Mounting evidence suggests that patients' expectation about recovery can predict long-

term clinical outcomes. A systematic review of 45 studies found that among studies rated as moderate to high quality, 94% indicated an association between positive expectations for recovery and improved clinical outcomes — suggesting that how well you think you will do influences how well you actually do.[42] Given the complex interactions between cognition, emotion, and mood with the perception of pain, it is plausible that patients' belief and expectation for recovery after surgery may be associated with the development of CPSP.[43] A few studies have suggested an association between these factors and acute postoperative pain, yet there are no studies assessing a relationship with CPSP.[44]

Clinical studies assessing pain interventions rely heavily upon the measurement of pain scores for outcome assessment. Hence, the accurate measurement of pain is critical to the validity of the results in a pain study. Current methods to collect pain-related data rely upon the use of pain diaries or telephoning the patient at home to inquire about pain scores over a period of time, usually the previous day. Prior investigations have indicated that the memory of pain may differ from the actual experience of pain.[45] Inaccuracies with the recall of pain has been suggested to be due to two cognitive heuristics, peak-end effect and duration neglect; the former relates to selectively recalling experiences that were most intense or closest to the time of reporting, and the latter describing how patients tend to forget the periods of time when they experienced no pain.[46] The advent of mobile electronic devices has provided the opportunity to capture real-time pain scores. In contrast to using conventional techniques, such as paper-based methods or telephoning the patient, electronic data capture allows for assessment of pain as it occurs, while improving the ease of data collection for both the patient and research personnel. While previous studies suggest that electronic data capture methods improve data quality and

reporting, there are no randomized trials comparing electronic to conventional data collection methods in a study that assesses chronic post-surgical pain.

This thesis dissertation addresses three important gaps in the chronic post-surgical pain literature. First, preliminary results of a large, international, prospective cohort study reports on the incidence and risk factors associated with chronic incisional pain 1-year after noncardiac surgery. Second, an analysis is presented describing the association between patients' beliefs and expectations after surgery and the development of chronic pain. Finally, this dissertation presents the protocol for a randomized controlled trial, which compares an electronic data capture system to traditional data collection methods in the context of a trial investigating CPSP.

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CHAPTER 2

Incidence and risk factors for chronic incisional pain after noncardiac surgery

Abstract

Introduction

Further data is needed regarding the incidence and risk factors for the development of chronic incisional pain after noncardiac surgery.

Methods

We explored the rate of chronic incisional pain at 1-year post-surgery among 10,481 patients enrolled in the VISION study (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation). Eligible patients were ≥ 45 years of age, undergoing a noncardiac procedure that required an overnight hospital stay, and received a general or regional anesthetic. We constructed multivariable logistic regression models to determine the association of preoperative and perioperative factors with the development of chronic incisional pain.

Results

A total of 458 patients (4.4%, 95% CI 4.0% to 4.8%) reported incisional pain at 1-year after surgery, with highest rates seen following pneumonectomy (11.1%, 95% CI 0.0% to 31.6%), complex bowel resection (8.5%, 95% CI 5.4% to 11.6%), and internal fixation of the femur (7.6%, 95% CI 3.1% to 12.1%). Approximately 41% rated their pain as mild (Numeric Rating Scale [NRS] 1-3), 33% as moderate (NRS 4-6), and 13% as severe (NRS 7-10). Fifty-nine percent of patients with incisional pain reported neuropathic pain characteristics. While increasing age was protective (OR 0.73 [in decades above 45], 95% CI 0.66 to 0.81), female

gender (OR 1.27, 95% CI 1.03 to 1.55), surgery for fracture (OR 1.97, 95% CI 1.34 to 2.90), and history of chronic pain (OR 2.21, 95% CI 1.72 to 2.83) were associated with an increased risk of chronic incisional pain. Open surgical techniques (OR 1.60, 95% CI 1.21 to 2.11), new administration of insulin on the day of surgery (OR 2.31, 95% CI 1.35 to 3.94), and COX-2 inhibitors withheld on the day of surgery (OR 2.55, 95% CI 1.53 to 4.24) were associated with an increased risk, whereas nitrous oxide use (OR 0.52, 95% CI 0.35 to 0.77), postoperative patient-controlled analgesia (OR 0.66, 95% CI 0.53 to 0.82), and postoperative epidural analgesia (OR 0.68, 95% CI 0.47 to 0.96) were associated with a decreased risk of chronic incisional pain.

Conclusion

Chronic incisional pain develops in one of 22 patients undergoing in-hospital noncardiac surgery which suggests 8.8 million new cases worldwide each year. Rigorous randomized controlled trials are urgently needed to establish whether modification of promising perioperative factors can reduce the rate of chronic incisional pain after non-cardiac surgery.

Introduction

The World Health Organization estimates the worldwide point prevalence of chronic pain at approximately 22%, defined as pain present most of the time for a period of ≥6 months during the prior year.[1] Chronic pain not only causes physical suffering but is associated with psychological, emotional, and social consequences.[2] Concurrent depression and anxiety is common and 10% of chronic pain patients will attempt suicide during their lifetime.[1,3–6] Furthermore, patients with chronic pain suffer greater economic hardships due to disability and reduced work productivity.[7]

Approximately 1 in 4 chronic pain patients report that their symptoms began following surgery.[8] Persistent pain after surgery has been designated chronic post-surgical pain (CPSP),[9] and has been suggested as pain that persists for more than 2 months after surgery.[10] Peripheral neuronal damage during surgery appears to be the dominant pathophysiological trigger in the development of CPSP.[11] CPSP will develop in approximately 11-57% of patients after mastectomy, 30-50% of those with leg amputations, and 10-20% of those with an inguinal hernia repair.[12–14] The use of varying follow-up times, regional surgical and perioperative practices, relatively small sample sizes (100 – 300 patients), and the lack of a consistent definition for CPSP contribute to this variability. Chronic incisional pain is a type of CPSP that is specific to the site of surgery. Only a limited number of investigations have focused on CPSP incisional pain, and thus the incidence and risk factors for persistent incisional pain are unknown. We analysed a large, international, prospective cohort study (the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation [VISION] Study; clinicaltrials.gov identifier NCT00512109) to inform these issues.

Methods

The VISION Study was an international, prospective cohort study of 40,000 patients undergoing noncardiac surgery. Patients were recruited, between August of 2007 to February 2014, from 33 centres in North and South America, Africa, Asia, Australia, and Europe. The primary aim of VISION was to determine the incidence of myocardial injuries and major vascular complications after noncardiac surgery. A secondary outcome was the rate of chronic incisional pain at 1-year follow up; however, questions regarding incisional pain were not added until June 2012. This study focusses on 10,481 patients who provided pain data.

Patients were included into VISION if they were ≥ 45 years of age, undergoing noncardiac surgery, and received a general or regional anesthetic. Patients were excluded from the study if they did not require at an overnight hospital admission after surgery, received only local infiltration (i.e., local anesthesia), if they were previously enrolled in VISION, or did not provide informed consent. Research Ethics Board/Institutional Review Board approval was obtained from each participating site.

Research personnel approached eligible patients in the preoperative assessment clinic, surgical wards, intensive care units, and in the preoperative holding area on the day of their surgery. For patients unable to provide consent preoperatively (i.e., emergent/urgent, night cases), consent was obtained within the first 24 hours after surgery. Eight centres used a deferred consent process that enrolled patients if consent was not obtained from the patient before surgery (i.e., sedated, intubated) or next of kin was unavailable. A representative sample of patients were recruited from each participating centre which included patients undergoing elective, urgent,

emergent cases during the day or night, on the weekday or weekends. If the clinical caseload of a centre exceeded the capacity of the research team, a recruitment schedule was created by either randomly selecting weeks to recruit patients or randomly selecting surgical services.

At the time of enrolment, patient information was collected including past medical history, medications, indications for surgery, and history of chronic pain. Research personnel also collected information regarding the type of surgery, anesthetic technique, and perioperative medications. Surgeries were categorized in VISION according to cardiovascular risk using 26 different categories. The major surgical categories were coded as: vascular surgery, general (abdominal) surgery, thoracic surgery, major urology and gynecology, major orthopedic surgery, major neurosurgery, and other surgeries (not otherwise specified). At 1 year follow-up, patients were asked about the presence or absence of persistent pain in or around their surgical incision that was not present prior to surgery. Those patients endorsing incisional pain were assessed for neuropathic pain characteristics, use of pain medications, severity of pain at its worst, least, and average pain over the past 24 hours, and pain at time of interview using the Numeric Rating Scale (NRS; 0 to 10, where 0 is no pain and 10 is worst possible pain), and impact of pain on aspects of daily living.

Assessment of neuropathic pain was performed by asking patients to gently rub the skin around their surgical incision and rate the presence of neuropathic characteristics (i.e., tingling, numbness, increased pain due to light touch) using a 0 to 10 scale, where 0 was none and 10 was worst possible. Similarly, patients were asked to rate the impact of pain on aspects of daily living (i.e., general activity, mood, walking activity, normal work, relations, sleep, and enjoyment of life) on a 0 to 10 scale, where 0 was no impact and 10 was complete interference. Research personnel at each site submitted patient data on case report forms directly to an online data

management system (iDataFax, McMaster University, Hamilton, Ontario, Canada). Data monitoring occurred through the use of iDataFax data system checks, statistical monitoring, and on-site monitoring for all participating centres.

Statistical analysis

All patients that were asked about chronic incisional pain at their 1-year follow-up were included in our analysis. We expressed the incidence of chronic incisional pain, across all noncardiac surgeries and per specific surgery categorized by VISION, as a percentage of patients affected over the total number of patients at follow-up assessed with a 95% confidence interval (CI).

We reported pain severity as assessed by the NRS as a mean and 95% CI. The proportion of patients with a specific neuropathic pain characteristic was determined by categorizing those who indicated 0 to the pain characteristic as having no neuropathic pain and those with a score greater than 0 as having neuropathic pain. Mean pain severity for those that reported neuropathic pain (score > 0) was then calculated with a 95% CI. Similarly, the proportion of patients who suffered interference on an aspect of daily living due to pain was determined by categorizing those who reported 0 on the interference scale as having no interference and those who reported a score greater than 0 as having pain interference. Mean degree of interference was determined in those expressing pain interference (score > 0) with the associated 95% CI.

We developed separate multivariable logistic regression models to identify preoperative and perioperative risk factors associated with the development of CPSP. Preoperative variables included 17 factors: patient demographics (i.e., age [in decades], sex, body mass index, ethnicity [8 categories: African ancestry; Arabic/Persian; Asian; South Asian/Indian ancestry; European;

Latin American; Native North/South American or Australian Aboriginal; Other ancestry]), co-morbidities (i.e., history of diabetes, history of chronic pain, active cancer, tobacco use within 30 days of surgery) and indications for surgery (i.e., surgery for cancer, surgery for fracture). We defined a history of chronic pain as daily pain for ≥3 months of which patients were taking one more of the following pain medications daily: tricyclic antidepressants, anticonvulsants, or opioids other than codeine.

Perioperative variables included: preoperative medications (i.e., aspirin, insulin, oral hypoglycemic drugs, COX-2 inhibitors, non-steroidal anti-inflammatories (NSAIDs), alpha-2 agonists) taken within 7 days and within 24 hours of surgery, just within 24 hours of surgery, or just within 7 days of surgery; intraoperative anesthetic technique (i.e., general, neuraxial block, regional block, nerve block, use of nitrous oxide); postoperative pain management modalities (i.e., epidural, patient-controlled analgesia [PCA]); and whether the surgery was open or endoscopic. The dependent variable in both models was chronic incisional pain at 1-year after surgery. The number of variables included in the model was limited to the number of events of chronic incisional pain using a ratio of 10 events for every variable included to ensure model stability and reduce over-fitting.[15] Variables were included into the model using forced-simultaneous entry. We tested for collinearity using the Variance Inflation Factor (VIF) and if two variables were highly correlated (VIF > 5), the least significant variable (lower coefficient) was dropped from the model.[16] The goodness-of-fit of the logistic regression models was assessed using the Hosmer-Lemeshow test.[17]

All statistical analyses were performed using SPSS v10 software or R Statistical Package. All tests were two-sided and significance was defined as $p < 0.05$.

Results

A total of 10,481 patients enrolled in the VISION study provided one year chronic pain data. The mean age of patients included into the analysis was 62.4 years old (SD 10.9), 49.6% were men, 21.2% had a history of diabetes, and 13.5% had active cancer. Approximately 10% of patients had chronic pain prior to surgery. The most common procedures were general (abdominal) surgery (19.9%), orthopedic surgery (19.0%), and urological-gynecological surgery (14.3%) (Table 1).

Chronic incisional pain was reported by 458 of 10,481 patients (4.4%, 95% CI 4.0% to 4.8%) at the 1-year follow-up. The incidence of incisional pain varied according to the type of surgical procedure. Pneumonectomies had the highest point estimate (11.1%, 95% CI 0.0% to 31.6%) followed by complex bowel resections (8.5%, 95% CI 5.4% to 11.6%), internal fixations of the femur (7.6%, 95% CI 3.1% to 12.1%), and major spine surgery (7.6%, 95% CI 5.3% to 10.0%). Surgical procedures with the lowest incidence of chronic incisional pain included: transurethral prostatectomies (0.6%, 95% CI 0.0% to 1.4%); radical prostatectomies (0.8%, 95% CI 0.0% to 1.9%); urological-gynecological cytoreductive surgeries (1.4%, 95% CI 0.0% to 4.1%); radical hysterectomies (1.9%, 95% CI 0.0% to 4.0%); and extracranial cerebrovascular surgeries (1.9%, 95% CI 0.0% to 4.5%) (Figure 1).

Among those with chronic incisional pain, mean worst pain was 5.0 (95% CI 4.8 to 5.3), mean least pain was 1.9 (95% CI 1.7 to 2.1), pain on average was 3.5 (95% CI 3.2 to 3.7), and mean pain at time of interview was 2.6 (95% CI 2.3 to 2.8). With regards to pain on average over the past 24 hours, 40.6% reported mild pain (NRS 1-3), 33% reported moderate pain (NRS 4-6), and 13.1% reported severe pain (NRS 7-10). Approximately 59% of patients reported one or

more neuropathic pain characteristics— 58.5% reported increased pain to touch (allodynia), 47.3% numbness, and 39.1% tingling pain (Table 2).

The majority of patients reported interference of pain on nearly all aspects of daily living. Approximately 57-66% of patients reported interference of pain on general activities, normal work, walking, mood, sleep, and enjoyment of life; roughly 39% reported interference with relationships with others. With regards to pain interference with general activities, 22.7% reported mild interference (inference scale 1-3), 20.9% reported moderate interference (interference scale 4-6), and 19.9% reported severe interference (interference scale 7-10). The greatest interference of pain occurred with walking (5.3 [1-10 scale], 95% CI 5.0 to 5.6), normal work (5.2, 95% CI 4.8 to 5.5), and general activity (5.0, 95% CI 4.7 to 5.4) (Table 3).

Approximately 51% of patients with chronic incisional pain report taking a pain medication for relief of their incisional pain. Those taking pain medication suffered significantly greater interference on all aspects of daily living compared to those who were not taking pain medication for their incisional pain (Table 4).

In the multivariable logistic regression model of preoperative risk factors associated with the development of chronic incisional pain, four independent predictors were identified: age (OR 0.73 [per decade over 45], 95% CI 0.66 to 0.81), female gender (OR 1.27, 95% CI 1.03 to 1.55), surgery for fracture (OR 1.97, 95% CI 1.34 to 2.90), and history of chronic pain (OR 2.21, 95% CI 1.72 to 2.83) (Table 5).

The multivariable logistic regression model of perioperative interventions revealed six interventions that were associated with chronic pain. Intraoperative nitrous oxide use (OR 0.52, 95% CI 0.35 to 0.77), postoperative PCA (OR 0.66, 95% CI 0.53 to 0.82), and postoperative epidural analgesia (OR 0.68, 95% CI 0.47 to 0.96) were associated with a decreased risk in

chronic incisional pain. Open surgical technique over endoscopic technique (OR 1.60, 95% CI 1.21 to 2.11), new administration of insulin less than 24 hours prior to surgery (OR 2.31, 95% CI 1.35 to 3.94), and COX-2 inhibitors given the week prior to surgery but withheld on the day of surgery (OR 2.55, 95% CI 1.53 to 4.24) were associated with an increased risk of incisional pain (Table 6).

Discussion

Among our international cohort of 10,481 patients that underwent noncardiac surgery, the incidence of chronic incisional pain at 1-year was 4.4%. More than 200 million major noncardiac surgeries occur worldwide each year,[18] which suggests that approximately 8.8 million patients will develop chronic incisional pain on an annual basis. Our findings suggest that this complaint is associated with moderate pain intensity and interferes across a broad range of activities of daily living.

Our study also revealed that patients who were taking an analgesic medication for chronic incisional pain experience significantly greater interference on all aspects of daily living compared to those who were not. While treatment with pain medication may be indicative of patients suffering from more severe pain, side-effects of pain medications may also limit function and quality of life due to side-effects. Opioids are often prescribed for chronic pain, but long-term therapy is associated with reduced health-related quality of life, higher occurrence of depression and catastrophizing, and side-effects such as nausea and constipation.[19,20] Other pain medications such as anti-convulsants or anti-depressants are also associated with adverse effects such as dizziness, somnolence, gait disturbances, and peripheral edema.[21]

There are a several limitations to this study. First, although this study included a large cohort of patients undergoing a diverse set of surgical procedures, it was restricted to patients requiring an overnight hospital stay, and as such, ambulatory surgical procedures were not represented. Secondly, we were not able to conduct in-person assessments with patients which may have helped in accurately characterizing neuropathic features of incisional pain — standardized assessments exists to determine areas of hyperalgesia, and allodynia. Finally, given that VISION sought to determine the incidence of perioperative vascular complications after

noncardiac surgery, certain baseline and postoperative variables relevant to the development of chronic pain were not collected. For example, preoperative catastrophizing and acute postoperative pain have been suggested to be associated with CPSP, however, these data were not collected and thus not adjusted for in the analyses.

Our study focused on persistent pain in and around the incision after surgery, which may explain our lower incidence of CPSP compared to previous investigations. Previous studies have typically used broad definitions for CPSP, and were not specific to the surgical site. Apart from specifying for incisional pain in our study, differences in our incidence of chronic pain to that of the literature may be also due to several reasons. Previous studies have used varying study designs and varying follow-up times after surgery. Follow-ups that occur close to the date of surgery will report a higher rate of chronic pain —among the same group of patients who underwent a radical prostatectomy, 14.3% and 1.2% reported chronic pain at three and six months after surgery, respectively.[22] Furthermore, this study included surgeries that required an overnight hospital stay, thus certain ambulatory surgeries typically associated with higher rates of chronic pain (i.e., breast, inguinal hernia) repair were not included. Finally, previous studies have focused on elective patients undergoing a high-risk (for CPSP) surgery, whereas our sample included a representative contemporary sample of patients undergoing elective or urgent/emergent surgery, during the day or at night, on the weekend or weekdays.

We found that patients undergoing surgery for a fracture were 1.7 times more likely to develop chronic incisional pain. Patients suffering a fracture likely sustain extensive neuronal damage due to both the surgery and trauma, which has been associated with the development of chronic post-surgical pain.[23] Furthermore, in contrast to most elective procedures, fractures tend to be associated with severe acute preoperative pain, and mounting evidence suggests that

preoperative pain in the area of surgery is associated with CPSP, and likely incisional pain.[24] We also found that younger age was associated with the development of chronic pain, which is consistent with previous investigations.[25–27] Evidence suggests that advanced age causes diminution and progressive loss of primary afferent pain fibres, leading to an elevated threshold and decreased sensitivity to pain.[28,29] Changes in the pain threshold may also explain why females are at higher risk of chronic pain.[30] Positron emission tomography analyses indicate that females also have greater activation of their prefrontal cortex during heat-induced pain compared to men.[31] Females are also more prone to catastrophizing, which is an independent predictor of CPSP.[32]

We also found evidence that nitrous oxide is associated with a 48% reduction in the odds of developing chronic incisional pain. Nitrous oxide has been demonstrated to cause endogenous release of opioids and possess an antagonistic effect on the N-methyl-D-aspartate receptor (NMDA), which is thought to play a critical role in the central sensitization of pain.[33,34] Further, animal studies indicate that nitrous oxide can prevent hyperalgesia induced by opioids, inflammation, and incisional pain.[35] Postoperative PCA and epidural analgesia were also associated with a reduction in chronic incisional pain, an effect likely mediated through improved postoperative pain[36,37] — postoperative pain scores within 24 hours after thoracic surgery was associated the presence of chronic post-surgical pain 1.5 years after surgery.[38]

Open surgery, in contrast to endoscopic surgery, was associated with greater risk of chronic incisional pain — possibly due to increased neuronal damage due to larger incisions and more invasive techniques.[23] A COX-2 inhibitor taken the week prior to surgery and withheld on the day of surgery was also associated with chronic pain. Sudden discontinuation of a pain medication taken regularly likely contributes to increased acute postoperative pain intensity, a

predictor of CPSP.[38] However, the lack of association between discontinuing a standing dose of a NSAID prior to surgery and chronic pain may relate to the superior analgesic effect of COX-2 inhibitors over NSAIDs.[39]

Our most novel finding from the logistic regression was that the use of insulin given within 24 hours prior to surgery was associated with the development of chronic incisional pain; however, diabetes, insulin given the week prior to and on the day of surgery, and insulin given the week prior to surgery but withheld on the day of surgery was not associated with the chronic pain. It is not entirely clear why initiation of insulin prior to surgery is associated with chronic pain, but there is evidence to suggest that abrupt improvements in glycemic control in the context of chronic hyperglycemia is associated with a treatment-induced neuropathy referred to as insulin neuritis. An observational study of 954 patients with poorly-controlled diabetes were followed after acute improvements in glycemic control with insulin.[40] Approximately 11% developed treatment-induced neuropathy, with a higher risk of neuropathy for those with larger improvements in Hemoglobin A_1C. Insulin neuritis is likely a result of improved neuronal transmission from nerves that were previously damaged from chronic hyperglycemia — sensory input from previously damaged nerves are then interpreted as pain. Thus, abrupt improvements in glycemic control prior to surgery may be a causative factor in CPSP.

Chronic incisional pain is an important complication after noncardiac surgery. Given that over 200 million patients undergo noncardiac surgery annually, 8.8 million patients will develop chronic incisional pain worldwide each year. Chronic incisional pain is associated with pain of mild to moderate intensity, has neuropathic pain characteristics, and results in substantial interference on one's daily activities. Randomized controlled trials are needed on potential perioperative interventions that aim to reduce the risk of chronic incisional pain.

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Tables

Table 1: Patient Characteristics (n = 10,481)

Variables	
Age, mean in years (SD)	62.4 (10.9)
Sex, male/female*	5171/5246
Body mass index, mean (SD)	27.7 (9.7)
History of diabetes, no. (%)	2206 (21.2%)
Active cancer, no. (%)	1400 (13.5%)
History of chronic pain, no. (%)	1048 (10.1%)
Surgeries, no (%)	
General surgery	2077 (19.9%)
Orthopedic surgery	1986 (19.0%)
Urological-gynecological surgery	1495 (14.3%)
Neurosurgery	685 (6.6%)
Vascular surgery	519 (5.0%)
Thoracic surgery	174 (1.7%)
Other surgery	3793 (36.4%)

* missing data for 64 patients

Table 2: Neuropathic pain characteristics in those with chronic incisional pain (n = 458)

Pain Characteristic	**Number reporting pain, no. (%)**	**Scale 1-10, mean, (95% CI)**
Increased pain to touch	268 (58.5%)	2.70 (2.41 to 2.99)
Numbness	217 (47.3%)	1.90 (1.65 to 2.15)
Tingling Pain	179 (39.1%)	1.78 (1.53 to 2.04)

Table 3: Interference of pain on aspects of daily activities (n = 458)

Daily Activity	**Number with interference, no. (%)**	**Scale 1-10, mean, (95% CI)**
General activity	300 (65.5%)	5.04 (4.73 to 5.35)
Normal work	298 (65.1%)	5.15 (4.82 to 5.47)
Walking activity	289 (63.1%)	5.31 (5.00 to 5.62)
Mood	274 (59.8%)	4.66 (4.34 to 4.98)
Sleep	269 (58.7%)	4.96 (4.61 to 5.30)
Enjoyment of life	263 (57.4%)	4.80 (4.48 to 5.13)
Relations with other people	180 (39.3%)	4.69 (4.28 to 5.10)

Table 4: Impact of medications for incisional pain on aspects of daily life

Aspect of daily life	Medications for incisional pain?	Scale 1-10, mean (SD)
General activity	Yes	5.64 (2.68)*
	No	3.92 (2.36
Mood	Yes	5.17 (2.77)*
	No	3.76 (2.24)
Walking activity	Yes	5.87 (2.68)*
	No	4.31 (2.40)
Normal work	Yes	5.80 (2.71)*
	No	3.98 (2.62)
Relations with other people	Yes	5.25 (2.73)*
	No	3.52 (2.42)
Sleep	Yes	5.40 (2.67)*
	No	4.16 (2.90)
Enjoyment of life	Yes	5.43 (2.65)*
	No	3.69 (2.21)

* $p < 0.05$

Table 5: Adjusted odds ratios of preoperative variables to predict CPSP

Variable	Adjusted Odds Ratios (95% CI)	p-value
Age	0.73 (0.66 to 0.81)	< 0.001*
Female sex	1.27(1.03 to 1.55)	0.024*
History of chronic pain	2.21(1.72 to 2.83)	< 0.001*
Surgery for fracture	1.97 (1.34 to 2.90)	0.001*
Active cancer	1.14 (0.79 to 1.66)	0.48
Arabic/Persian	0.16 (0.01 to 2.76)	0.21
Asian ethnicity	2.08 (0.27 to 16.27)	0.49
African ancestry	0.54 (0.07 to 4.42)	0.57
BMI	1.00 (0.99 to 1.01)	0.73
European	0.60 (0.08 to 4.70)	0.63
History of diabetes	1.07 (0.83 to 1.37)	0.63
Latin American	0.15 (0.02 to 1.26)	0.08
Native American/Australian	0.18 (0.02 to 1.55)	0.12
Other ancestries	0.19 (0.02 to 2.24)	0.19
Smoking within 30 days	1.27 (0.96 to 1.67)	0.09
South Asian	0.15 (0.02 to 1.24)	0.08
Surgery for cancer	0.81 (0.60 to 1.10)	0.17

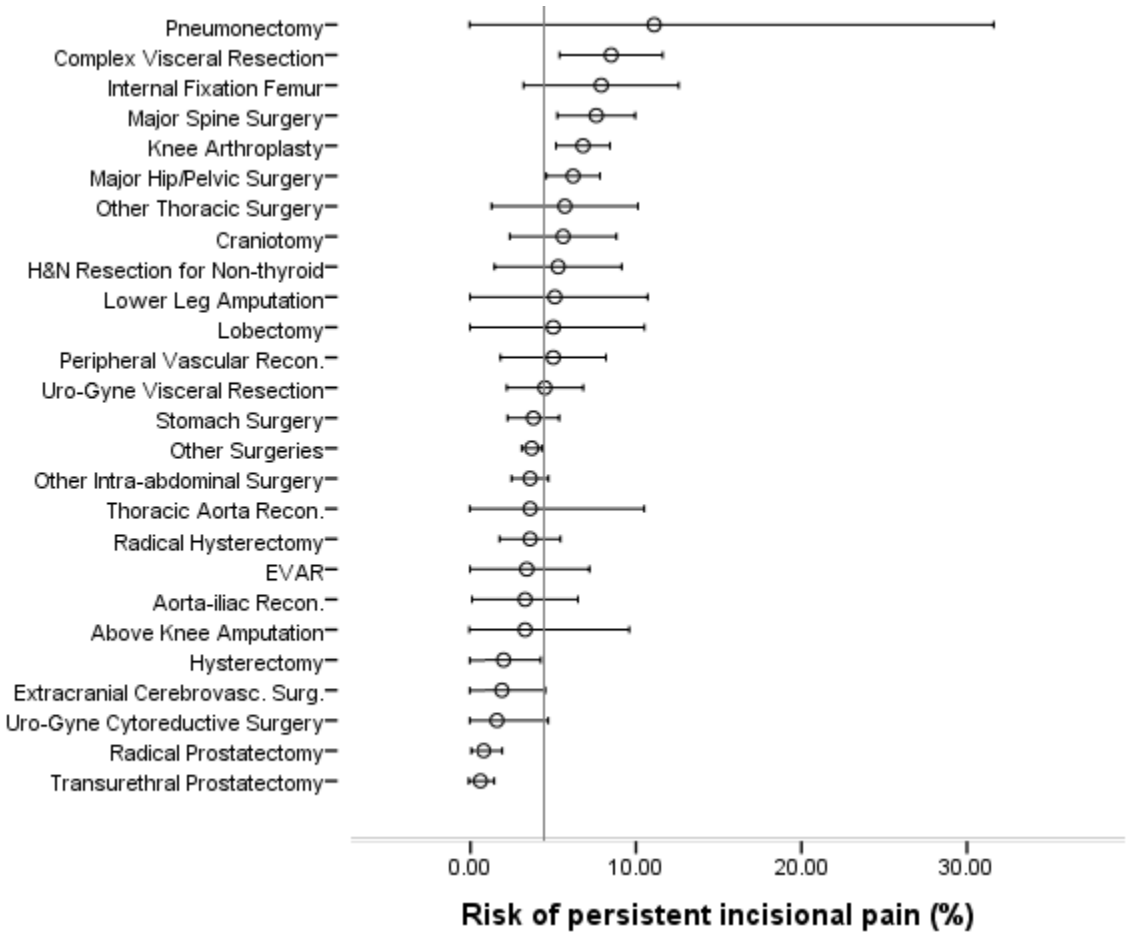
BMI – body mass index, * $p < 0.05$

Table 6: Adjusted odds ratios of perioperative variables to predict CPSP

Variable	Adjusted Odds Ratio (95% CI)	p-value
COX-2 1-7 days only	2.55 (1.53 to 4.24)	<0.001*
Insulin < 24 hours	2.31 (1.35 to 3.94)	0.002*
Intraop. nitrous oxide	0.52 (0.35 to 0.77)	0.001*
Open surgical technique	1.60 (1.21 to 2.11)	0.001*
Postoperative epidural	0.68 (0.47 to 0.96)	0.03*
Postoperative PCA	0.66 (0.53 to 0.82)	<0.001*
Alpha-2 agonist < 24h hours to 7 days	0.86 (0.20 to 3.60)	0.83
Alpha-2 agonist 1-7 days only	1.75 (0.23 to 13.57)	0.59
Aspirin < 24 hours	2.59 (0.59 to 11.45)	0.21
Aspirin < 24 hours to 7 days	0.84 (0.53 to 1.33)	0.46
Aspirin 1-7 days only	0.73 (0.51 to 1.04)	0.08
COX-2 < 24 hours	0.92 (0.22 to 3.85)	0.91
COX-2 < 24 hours to 7 days	1.71 (0.73 to 3.98)	0.22
Insulin < 24 hours to 7 days	0.86 (0.53 to 1.39)	0.53
Insulin 1-7 days only	0.49 (0.18 to 1.35)	0.17
Intraoperative general anesthesia	1.53 (0.95 to 2.46)	0.08
Intraoperative nerve block	1.22 (0.82 to 1.83)	0.33
Intraoperative spinal	1.24 (0.77 to 2.01)	0.38
NSAID < 24 hours	1.11 (0.68 to 1.82)	0.67
NSAID < 24 hours to 7 days	0.78 (0.46 to 1.32)	0.36
NSAID 1-7 days only	1.16 (0.73 to 1.86)	0.53
OHA < 24 hours to 7 days	0.76 (0.45 to 1.25)	0.28
OHA 1-7 days only	1.266 (0.87 to 1.85)	0.22
Postoperative IM/IV/SC opioids	1.00 (0.82 to 1.23)	0.99
Postoperative nerve block	0.60 (0.31 to 1.19)	0.15

IM – intramuscular; IV – intravenous; NSAID – non-steroidal anti-inflammatory drugs; OHA – oral hypoglycemia agents; PCA – patient-controlled analgesia; SC- subcutaneous, * $p < 0.05$. OHA< 24 hours and Alpha-2 agonist < 24 hours incalculable due to low frequencies and dropped from model.

Figure 1: Incidence of CPSP in specific surgical populations



CHAPTER 3

Patient coping and expectations about recovery predict the development of chronic post-surgical pain and pain interference after traumatic tibial fracture repair

Abstract

Introduction

Chronic post-surgical pain (CPSP) is a common and often debilitating complication of surgery. Patient expectations about recovery have been shown to affect several clinical outcomes, yet there are no studies evaluating their association with CPSP.

Methods

Patients enrolled in the SPRINT trial were asked to complete the Somatic Preoccupation and Coping (SPOC) Questionnaire 6 weeks after surgical repair for a traumatic tibial fracture. The SPOC instrument measures patients' somatic complaints, coping, and optimism about their recovery. We explored the association of SPOC scores with chronic post-surgical pain (CPSP; defined as ≥ mild pain) and interference of pain (defined as ≥ moderate interference) at 1-year after surgery, adjusting for age, sex, smoking status, fracture type (open vs. closed), and the presence of multi-trauma.

Results

Of 267 patients in this study, a total of 147 (55.1%) reported CPSP at 1-year, with 73 (27.3%) reporting moderate and 26 (9.7%) ≥ severe pain. The incidence of chronic pain in those with low (≤ 40), intermediate (41- 80), and high (> 80) SPOC scores were 37.6%, 54.1%, and 81.7%, respectively. Patients with high and medium SPOC scores were also at greater risk of more severe pain, and greater interference of pain on daily activities, than those with low scores ($p < 0.001$). Our adjusted analysis to predict CPSP had a c-statistic of 0.70 (95% CI 0.64 to 0.77) and indicated that smoking status (odds ratio [OR] 2.10, 95% CI 1.17 to 3.77) and increasing SPOC scores (score > 80: OR 6.56, 95% CI 2.90 to 14.81) were associated with an increased risk. Similarly, our adjusted model for pain interference had a c-statistic of 0.77 (95% CI 0.71 to 0.83) and indicated that smoking status (OR 2.54, 95% CI 1.39 to 4.67), open fracture (OR 2.24, 95% CI 1.24 to 4.03), and increasing SPOC scores (scores > 80: OR 10.10, 95% CI 4.26 to 23.96) were associated with increased risk.

Conclusions

Patients' coping and expectations of recovery, as measured by the SPOC 6 weeks after surgery, is a powerful predictor of CPSP and pain interference after traumatic tibial fracture. Future studies should explore whether these beliefs can be modified and improve prognosis.

Introduction

In North America, chronic pain affects approximately 30% of the population, with similar rates in Europe and Australia.[1–5] Surgery and trauma are frequently cited as triggering events responsible for the development of chronic pain. A survey of 5,130 patients attending 10 outpatient clinics located throughout North Britain found that 41% attributed their pain to a traumatic event or surgery.[6] Rates of chronic post-surgical pain (CPSP) range from 0.1% to 65% with higher rates associated with cardiac, breast, and orthopedic surgeries.[7,8]

Surgical repair of long bone fractures constitute the majority of emergent surgical procedures at trauma centres, of which traumatic tibial fractures are the most common.[9] A systematic review of 20 observational studies of traumatic tibial fracture repairs determined a mean incidence of 47.4% (range: 10% to 86%) of CPSP at a mean follow-up time of 23.9 months after surgery.[10]

Although several risk factors for CPSP have been identified, many are non-modifiable and thus not amendable to intervention.[8] However, there are emerging data that suggest patients' beliefs may be associated with long-term clinical outcomes.[11,12] A previous study from our group found that patients' coping and expectations regarding recovery at 6 weeks after a traumatic tibial fracture repair were strongly associated with short form-36 (SF-36) physical component summary scores and return to work at 1 year.[13] Although no studies have examined the influence of patient coping and recovery expectations and the development of CPSP, the interaction between mood and emotions and the perception of pain, as described by the gate theory of pain, suggests a plausible biological mechanism.[14] Further, there is indirect evidence from other

clinical populations— positive expectations for recovery after an episode of acute low back pain are associated with improved recovery and reduced disability due to pain.[15]

The purpose of this study was to determine whether patients' coping abilities and expectations regarding recovery 6 weeks after traumatic tibial fracture repair are associated with CPSP.

Methods

This investigation utilized data from the Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures (SPRINT) trial.[16] A multicenter, randomized controlled trial that assessed the efficacy of reamed or unreamed intramedullary nailing for patients ≥ 18 years old with an open or closed tibial fracture. Exclusion criteria included neurovascular deficits, pathologic fractures, excessive surgical delay (>12 hours from time of injury for open fractures, > 3 weeks from time of injury for closed fracture), and associated fractures in the foot, ankle, or knee. From July 2000 to September 2005, 1,339 patients were enrolled into this trial from 29 clinical sites in Canada, United States, and the Netherlands. The last follow-up visit occurred in September 2006, with final outcomes adjudicated by January 2007. A detailed protocol of the SPRINT trial has been published elsewhere.[9]

During the conduct of the trial, centers with high recruitment rates were approached to administer the Somatic Pre-Occupation and Coping (SPOC) questionnaire at 6 weeks following surgical fixation, regardless of group assignment. Three-hundred and fifty-nine consecutive patients agreed to complete the SPOC questionnaire, 316 provided complete data. The SPOC questionnaire is a 27-item questionnaire that assesses patients' somatic complaints, coping, energy, and optimism about their recovery. The SPOC instrument produces a single score on a scale of 0 to 162, with higher scores representing greater somatic preoccupation, worse coping, and pessimism about recovery. Full details on the development and validation of the SPOC questionnaire have been published,[13] as has a re-validation study in a separate population of lower limb trauma patients.[17]

The SPRINT trial administered the SF-36, a generic health status and quality of life instrument, at hospital discharge, 2 weeks, 6 weeks, and 3, 6, 9, and 12 months post-surgery. The

SF-36 has been validated in surgical and non-surgical populations and demonstrates good validity, reliability, and internal consistency.[18–20] Questions 7 and 8 of the SF-36 capture information regarding the degree of bodily pain and interference of pain on daily activities experienced during the last 4 weeks prior to survey completion.

Pain must be present >2 months after surgery to be considered CPSP [21]; however, we believe that patients are more likely to be concerned about pain that persists for a longer duration of time. Accordingly, our primary outcome was the presence of pain at 1-year after surgery. Secondary outcomes were the severity of pain and interference of pain on normal work.

Missing or incomplete data for responses to the SF-36 at 1-year were imputed using the last value carried forward from the six-month follow-up date — we found a 90% concordance between patient-reported pain at 6 months and at 1-year. We did not impute missing 1-year data from the 3 month follow-up as there was only 64% concordance in pain data. Accordingly, patients that did not provide SF-36 data at the 6 month or later after surgery were excluded from the analysis. Another criteria of CPSP is the lack of previous chronic pain in the area of surgery. To uphold this criteria, we excluded any patients who were on two or more pain medications (e.g., acetaminophen, anti-inflammatory, opioids, anti-convulsants) prior to surgery.

Statistical Analysis

We generated frequencies for all collected data. We reported the mean and standard deviation (SD) of continuous variables, and the number of occurrences with proportions represented as percentages for categorical variables. The presence of chronic pain was determined by responses to question 7 of the SF-36 at 1-year follow-up, which provides six

response options: none; very mild; mild; moderate; severe; or very severe. We dichotomized responses to this question — none and very mild pain versus other response options, as we found that 27.1% of the 48 patients with mild pain at 1-year reported $\geq$ moderate interference compared to 3.8% (3 of 80) of patients with very mild pain (Appendix). Responses to question 8 of the SF-36 on the interference of pain on normal work included five response options: none; a little bit; moderately; quite a bit; and extremely. Responses were also dichotomized — none and a little bit versus other response options. We believed pain that moderately interfered with normal work would be important to patients.

We categorized patients into 3 groups based upon their 6-week post-surgery SPOC scores. We used the interquartile range (IQR) to create tertiles as the Shapiro-Wilk test indicated the data was not normally distributed ($p<0.001$). We calculated risk differences for chronic pain and pain interference at 1-year in the intermediate and high SPOC score groups, in reference to the low-score group, expressed as odds ratios (ORs) with 95% confidence intervals (CI). We used the Kruskal-Wallis (KW) test to explore for differences in the severity of pain and degree of interference across the three categories of SPOC scores. If KW test was significant, we used the Wilcoxon ranked-sum test was used to test for differences in the medium and high-score group in reference to the low-score group.

We constructed multivariable logistic regression models to explore the association between SPOC scores at 6-weeks following surgery, and the presence of chronic pain or interference of pain with daily activities at 1-year. We selected 5 additional variables that we judged may be associated with CPSP, and predicted the direction of anticipated effects: female gender, younger age, open fractures, the presence of multi-trauma, and currently a smoker – all associated with worse outcomes. We assessed collinearity between each variable included in our

regression models with the variance inflation factor (VIF) and if the VIF > 5, then the least important variable was removed (variable with the smaller coefficient).[22] We constructed our regression models with and without SPOC scores and calculated the concordance statistic (c-statistic) and associated 95% CI for each model to quantify the change in predictive power with the addition of SPOC scores— a c-statistic of 0.5 indicates that the model is no better than chance at predicting the outcome, c-statistic of 0.7-0.8 is considered reasonable prediction, and ≥ 0.8 is considered strong prediction.[23] SPOC scores were added to the model as a categorical variable based upon a patients SPOC group (low, intermediate, and high SPOC groups). We assessed the goodness-of-fit of our logistic regression models with the Hosmer-Lemeshow test.[23] We explored over-fitting of our regression models by calculating optimism of the model using boot-strapping methods of 400 cycles— optimism is a measure of over-fitting in a model and should be as small as possible.[24]

All statistical analyses were performed using R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided and $p < 0.05$ was considered statistically significant.

Results

Of 1,339 patients in the SPRINT trial, 359 patients received the SPOC questionnaire; 316 patients provided complete SPOC data at 6-weeks after surgery. Of these patients, 224 had complete SF-36 data at 1 year. We imputed outcome data for an additional 43 patients from their 6 month follow-up visit. The remaining 49 patients only reported pain scores at 3 months or less and were not included in our analyses. Baseline characteristics of patients are depicted in Table 1. The mean age of patients was 38.7 years old (SD 16.2) and most were male (74.9%). The majority of patients presented with a closed tibial fracture, most often resulting from a fall, motor-vehicle accident, or motor-cycle accident.

A total of 147 patients (55.1%) reported mild to very severe chronic pain after surgery, and 94 (35.2%) reported pain that interfered, moderately to extremely, with their daily activities (Table 2). Low SPOC scores were defined as ≤40, intermediate scores from 41 to 80, and high scores as > 80. The presence and severity of chronic pain and pain that interfered with activities at 1-year following surgery increased with higher SPOC scores (Tables 3-4). Compared to those in the low-score group, patients reporting an intermediate SPOC score at 6-weeks after surgery were twice as likely to report pain (OR 1.95; 95% CI 1.11 to 3.44) and three times more likely to report pain that interfered with activities (OR 3.43, 95% CI 1.68 to 7.01) at 1-year. Patients reporting a high SPOC score at 6-weeks were 7 times as likely to report chronic pain (OR 7.38, 95% CI 3.36 to 16.22) and 10 times more likely to report pain that interfered with activity (OR 10.51, 95% CI 4.70 to 23.51) at 1-year.

The multivariable logistic regression model to predict CPSP limited to adjustment variables (no SPOC scores) produced a c-statistic of 0.61 (95% CI 0.55 to 0.68), with an optimism of 0.072. When the SPOC groups were added to the model with the low (≤40 scores)

group used as the reference, the model indicated a significant association with the development of chronic pain with those in the medium (OR 1.84, 95% CI 1.02 to 3.31) and high group (OR 6.56, 95% CI 2.90 to 14.81). The c-statistic of the model improved to 0.70 (95% CI 0.64 to 0.76, $p = 0.005$) and optimism decreased to 0.052. Smoking status was also found to be a significant predictor of CPSP with an odds ratio of 2.10 (95% CI 1.17 to 3.77).

The model to predict interference of pain on normal work limited to adjustment variables produced a c-statistic of 0.68 (95% CI 0.61 to 0.74), and an optimism of 0.050. When SPOC groups were added to the model, the intermediate (OR 3.15, 95% CI 1.49 to 6.69) and high SPOC groups (OR 10.10, 95% CI 4.26 to 23.96) were significant predictors (Table 6) and improved the c-statistic to 0.79 (95% CI 0.73 to 0.84, $p < 0.001$) and reduced optimism to 0.0417. Open fracture (OR 2.24, 95% CI 1.24 to 4.03) and smoking status (2.54, 95% CI 1.39 to 4.67) were also associated with an increased risk of pain interference at 1-year. The Hosmer-Lemeshow test was non-significant for all regression models.

Discussion

Our study suggests that patients' coping abilities, beliefs, and expectations about recovery, as operationalized by the SPOC instrument, is a strong predictor of chronic pain, its severity, and its interference with daily activities 1-year after a traumatic tibial fracture repair. This is the first investigation to document an association between patients' beliefs and expectations for recovery and the development of chronic post-surgical pain.

There are also several limitations to our study. First, this analysis was performed in the same sample population used to develop and validate the SPOC instrument. Second, pain outcomes were measured by only two questions from the SF-36. These questions were also not specific to pain in or around the incision site, and thus, may have captured pain unrelated to a patient's trauma or surgery and introduced noise into the analysis. Third, we were unable to control for other potential prognostics factors (i.e., preoperative catastrophizing, depression) in our adjusted analyses.

Strengths of this study includes using a validated instrument to assess patient coping and expectations, adjusting for a variety of patient demographics and injury characteristics, and constructing models that were not over-fitted. Another strength of this investigation is its application to clinical practice. The divisions in SPOC scores that placed patients into low, intermediate, and high-risk groups are easy-to-remember (≤ 40, 41-80, ≥ 80) and allows for greater adoption into the clinical setting.

Findings from our study add to a growing body of evidence on the impact of cognitive processes and expectations on clinical health outcomes. A systematic review found 45 studies assessing the relationship of patient expectations for recovery in a variety of clinical conditions

ranging from myocardial infarctions to alcoholism.[11] Of the studies rated as moderate to high quality, 94% indicated an association between positive expectations and improved outcomes; 73% of these studies indicated a moderate to high effect size. While the majority of these studies did not control for other prognostic factors, the studies that conducted statistical adjustment found similar results, suggesting an independent effect of patient expectations.

The concept of psychological factors influencing outcomes is not novel to the area of pain medicine. It is generally believed that the experience of pain is an interplay of the biomedical with the cognitive, affective and behavioral.[25] Catastrophizing is an exclusively cognitive process that has been shown to be associated with both acute postoperative and chronic pain, irrespective of the degree of physical injury.[26–28] The impact of catastrophizing does not only lead to greater pain intensity, but results in greater disability and reduced rate of return to work.[26,28] Other psychological factors, such as depression, have also been shown to influence the degree of pain and analgesic requirements after surgery.[29] However, the effect of patient beliefs and expectations on chronic pain is an immensely under-investigated area. A recent systematic review on measures of patient expectations on recovery found only four studies in the perioperative setting of which none examined the relationship with chronic post-surgical pain.[12]

Our study provides the first evidence that poor coping and low patient expectations are associated with the development of chronic pain after surgery. In contrast to patient characteristics, underlying biology, and other prognostic factors that are otherwise non-modifiable, patient beliefs and expectations are potentially amendable and thus allow for an opportunity to reduce the risk of chronic pain. Interventions aimed at improving patients' coping abilities, optimism, and outlook on their recovery will need to be developed and assessed in randomized controlled trials. Non-clinical studies on healthy adults provide evidence about the

potential effectiveness of such strategies to reduce pain levels. Self-instruction, which is the process of identifying negative cognitions and replacing them with positive cognitions, appear to improve pain thresholds in catastrophizing males.[30]

While it has been suggested that increasing a patient's outlook on recovery after surgery may lead to unrealistic expectations and possible disappointment, previous studies do not support this notion. A prospective cohort study of 120 patients undergoing lumbar surgery, were interviewed about their expectation of postoperative pain, recovery, and return to work status prior to surgery and their disappointment levels in relation to their expectations after surgery.[31] Patients who did not expect to have any postoperative pain, had less disappointment than those who did expect postoperative pain— although, there were no differences between groups in their rate of recovery or return to work.

Our investigation has also found that smoking is a strong predictor of chronic pain and interference of pain at 1-year after traumatic tibial fracture. Epidemiological data has also demonstrated a link between smoking and the development of chronic pain.[32] The relationship between smoking and chronic pain is complex and is related to the interaction of biological, psychological, and social factors.[33] Smoking is known to cause impaired oxygen perfusion through hypoxia and increased carboxyhemoglobin levels, which leads to decreased wound healing, impaired bone formation, and increased rates of non-union—a study in patients with open and closed tibial fractures demonstrated that smokers have clinically and radiographically prolonged periods needed for union.[33–35] Further, those who smoke have higher rates of mood disturbances such depression and anxiety, which are also associated with chronic pain.[36] Additionally, in our study, those with an open fracture were at higher risk of developing

interference of pain. This association is likely a reflection of the severity of injury and the greater disability of those with open tibial fractures over those with closed fractures.[37]

Results of our study suggest a mediating influence of negative beliefs and pessimism in the pathogenesis of CPSP. This relationship further supports a biopsychosocial model as a framework to understand and study chronic pain. Future investigations are needed to evaluate the relationship of SPOC scores and chronic pain in other surgical populations and determine, for elective procedures, whether SPOC scores obtained prior to surgery are also prognostically important. Randomized controlled trials are needed to determine whether patient beliefs and expectations can be modified and whether this results in improved prognosis.

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Table 1: Patient characteristics (n=267)

Variable	
Age, mean in years (SD)	38.7 (16.2)
Sex, male/female	200/67
Smoking history, no. (%)	87 (32.6)
Fracture type, open/closed	98/169
Isolated fracture, no. (%)	154 (57.7)
Mechanism of injury (n, %)	
Crush injury	11 (4.1)
Direct trauma (blunt)	22 (8.2)
Direct trauma (penetrating)	3 (1.1)
Fall	63 (23.6)
Motorcycle accident	39 (14.6)
MVA (driver/passenger)	60 (22.5)
MVA (pedestrian)	59 (22.1)
Twist	6 (2.2)
SPOC score (mean, SD)	57.2 (28.6)

MVA – motor vehicle accident; SPOC – Somatic Preoccupation and Coping; SD – standard deviation

Table 2: Patient-reported chronic pain and pain that interferes with normal work at 1-year, stratified by SPOC scores acquired 6-weeks after surgery (n= 267)

SPOC Score Category	**None to Very Mild Pain (n)**	**Mild to Severe Pain (n)**	**Risk (95% CI)**	**None to a Little Pain Interference (n)**	**Moderate to Extreme Pain Interference (n)**	**Risk (95% CI)**
Low (≤ 40)	53	32	37.6% (27.3% to 47.9%)	73	12	14.1% (6.7% to 21.5%)
Intermediate (41 - 80)	56	66	54.1% (45.3% to 62.9%)	78	44	36.1% (27.6% to 44.6%)
High (> 80)	11	49	81.7% (71.9% to 91.5%)	22	38	63.3% (51.1% to 75.5%)

Table 3: Distribution of pain severity at 1-year stratified by SPOC scores acquired 6-weeks after surgery (n=267)

SPOC Category	None to Very Mild	Mild	Moderate	Severe	Very Severe
Low (≤ 40)	53 (62.4%)	16 (18.8%)	15 (17.1%)	1 (1.2%)	0 (0.0%)
Intermediate (41 - 80)	56 (45.9%)	24 (19.7%)	33 (27.0%)	8 (6.6%)	1 (0.8%)
High (> 80)	11 (18.3%)	8 (13.3%)	25 (41.7%)	12 (20.0%)	4 (6.7%)
Total	120 (44.9%)	48 (20.0%)	73 (27.3%)	21 (7.9%)	5 (1.9%)

Table 4: Distribution of pain interference at 1-year stratified by SPOC scores acquired 6-weeks after surgery (n=267)

SPOC Category	Not at all to a little bit	Moderately	Quite a bit	Extremely
Low (≤ 40)	73 (85.9%)	11 (12.9%)	1 (1.2%)	0 (0.0%)
Intermediate (41 - 80)	78 (63.9%)	25 (20.5%)	13 (10.7%)	6 (4.9%)
High (> 80)	22 (36.7%)	15 (25.0%)	13 (21.7%)	10 (16.7%)
Total	173 (64.8%)	51 (19.1%)	27 (10.1%)	16 (6.0%)

Table 5: Variables associated with chronic pain at 1-year (n=267)

Variable	**Adjusted model without SPOC scores**	**Adjusted model with SPOC scores**
	Odds ratio (95%CI)	Odds ratio (95%CI)
Sex	1.02 (0.56 to 1.83)	1.01 (0.54 to 1.88)
Age	1.09 (0.93 to 1.27)	1.13 (0.96 to 1.34)
Open	1.11 (0.66 to 1.88)	1.00 (0.58 to 1.73)
Multi-trauma	1.54 (0.92 to 2.56)	1.30 (0.76 to 2.24)
Smoker	2.41 (1.38 to 4.20)	2.10 (1.17 to 3.77)
SPOC		
Low		reference
Intermediate		1.84 (1.02 to 3.31)
High		6.56 (2.90 to 14.81)

Age in decades

Table 6: Variables associated with pain interference at 1 year (n= 267)

Variable	**Adjusted model without SPOC scores**	**Adjusted model with SPOC scores**
	Odds ratio (95%CI)	Odds ratio (95%CI)
Sex	0.75 (0.39 to1.43)	0.69 (0.34 to 1.37)
Age	1.11 (0.93 to 1.32)	1.20 (0.99 to 1.45)
Open	2.28 (1.32 to 3.95)	2.24 (1.24 to 4.03)
Multi-trauma	1.34 (0.78 to 2.30)	0.99 (0.55 to 1.79)
Smoker	2.38 (1.60 to 4.99)	2.54 (1.39 to 4.67)
SPOC		
Low		reference
Intermediate		3.15 (1.49 to 6.69)
High		10.10 (4.26 to 23.96)

Age in decades

Appendix: Cross-tabulation of 1-year pain severity with pain interference

		Pain Severity						
		None	**Very Mild**	**Mild**	**Moderate**	**Severe**	**Very Severe**	**Total**
Pain Interference	**Not at all**	37	42	12	4	0	0	95
	A little bit	2	35	23	18	0	0	78
	Moderately	0	2	13	32	4	0	51
	Quite a bit	1	1	0	14	11	0	27
	Extremely	0	0	0	5	6	5	16
	Total	40	80	48	73	21	5	267

CHAPTER 4

Pregabalin and Lidocaine in breast cancer surgery to Alter Neuropathic pain: Electronic Data Capture (PLAN-ED) Sub-study

Introduction

Pain is an unpleasant sensory and emotional experience unique to the individual it afflicts. Pain is also a dynamic process, fluctuating from second-to-second, and subject to the influences of a variety of internal cognitive processes such as mood, emotions, previous experiences, as well as external stimuli such as physical movement.[1–4] The measurement of pain is of utmost importance to clinicians and researchers. The most commonly used method of measuring pain in the clinical and research setting is the use of self-report questionnaires. While a variety of questionnaires are used to measure pain intensity, its impact on emotions and mood, and its interference on daily activities, the current method in which these questionnaires are employed may impair the validity of the data they provide.

In clinical trials, pain measurements are usually performed at baseline and compared to measurements after an intervention to assess for a change and a response to therapy. These assessments are typically performed using paper-based questionnaires or telephoning the patient at home. These methods of data collection require the patient to recall their pain symptoms over the past 24 hours, previous few days or even the past few weeks. However, in contrast to measuring pain in the moment (i.e., real-time measurement or ecological monitoring), this type of data collection, may cause validity issues with the collected data.[5,6] The memory of pain is vulnerable to distortion due to physical and psychological contextual factors and the selective

coding and retrieval of memories. In other words, the memory of pain may be different than the actual experience of pain.[7]

The recall of pain is vulnerable to two known cognitive heuristics, namely peak-end effect and duration neglect.[7] Peak-end effect is the notion that patients selectively recall intense experiences or those that occur close to the time of reporting. Duration neglect means that patients tend to forget the periods of time when they were without pain. Both of these cognitive biases lead to the overestimation of the severity of the reported pain. For example, in the same cohort of patients with rheumatoid arthritis and fibromyalgia, the average intensity of recalled pain as measured on a 100-point visual analog scale for the previous week was 57, whereas the average of several pain scores taken routinely during the week was 44.[8]Although short recall periods are often used to minimize recall bias, studies have shown that a recall period of even the last 24 hours may be vulnerable to these biases.[9,10]

The momentary assessment of pain (i.e., obtaining pain scores in reference to the present time) can overcome cognitive biases associated with recalling pain. However, momentary assessments using traditional data collection methods can be cumbersome. Telephoning the patient at home to obtain daily pain scores is burdensome to both the patient and research team. Paper-based pain diaries have been proposed to reduce excessive contact while collecting multiple pain scores per day, yet studies suggest that patients are notoriously non-compliant with completing a symptom diary and will tend to quickly fill in missing values prior to submission.[11] Furthermore, transferring data from the pain diary to the desired electronic database creates the opportunity for data-entry errors.

The advent of mobile electronic devices has allowed for novel opportunities to collect patient reported outcomes for clinical or research purposes. Since paper diaries and telephone-

interviewing are impractical for real-time data collection and contain inherent limitations, electronic mobile devices allow investigators to perform momentary assessments through electronic data capture systems.[12] Data collection performed using an electronic mobile device has been used in a variety of research settings including mood disorders, asthma, tobacco cessation programs, urinary incontinence, brain injury, diabetes, and pain research.[13] Electronic data capture systems have also been advocated in collecting data on physiological parameters, such as blood pressure or heart rate, given the dynamic nature of these variables and the desire to have multiple measurements rather than a single value.

Electronic data capture systems have become increasingly popular within health research over the past two decades. However, a question that arises is whether data collected from electronic sources is similar to data collected using traditional methods. Correlation between recalled pain scores used paper-based methods and averaged momentary pain using electronic data capture is estimated to be 0.75[7]— however, the scatterplot of the association between recalled pain and averaged momentary pain reveals systematically higher pain scores for recalled pain, likely relating to cognitive distortions of memories about pain.[7] However, when paper and electronic methods are both used to capture momentary pain, there appears to be a greater correlation ($r = 0.91$).[14]

Mounting evidence suggests that data collected via electronic methods may be more accurate and contain less errors than traditional methods. A study of 198 participants assessing sexual health practices compared paper-based data collection to an electronic data capture system using a Personal Digital Assistant (PDA) and found that paper-based methods had a significantly higher number of data inconsistencies. The number of inconsistencies per patient for the paper method was 1.93 (SD 1.98) and for PDA was 0.08 (SD 0.54, $p < 0.0001$).[15] This study also

reported a higher mean number of missing values with the paper format (0.85, SD 1.35) in comparison to PDA format (0.29, SD 1.02, p=0.001).[15] Furthermore, a crossover randomized controlled trial of 35 patients with overactive bladders compared self-reported data collected by patients using an electronic diary versus a paper-based diary. Data errors such as incomplete events, inappropriate times of reporting, and incorrect data were detected in 80% of those using the paper-based diary, whereas no such errors were detected in the electronic diary group — this difference occurred due to on-screen prompts in the electronic diary that prevented any incomplete or inappropriate data entries.[16]

Studies that use telephone follow-ups typically gather all required study information in a single phone call. The aim is to obtain as much information as possible without the need to contact the patient again. Electronic data capture systems allow for increased reporting without being overly burdensome to study participants. A randomized trial of 92 patients allocated patients to four groups—three groups were assigned to use an electronic data capture system with increasing levels of reporting (3 times a day, 6 times a day, and 12 times a day), while the fourth group used paper-based methods for weekly reporting of data.[17] Other than patients in the 12 times a day electronic reporting group, patients all had similar levels of burden and interference with daily life with their reporting requirements. It appears that obtaining multiple measurements per day using an electronic device is not more bothersome to patients than weekly measurements of pain using traditional follow-ups. Furthermore, several studies have indicated a strong patient preference for the electronic data collection citing portability and ease of use as appealing factors.[13]

Electronic data capture systems may also aid in improving patient adherence to a clinical trial protocol. Numerous studies have documented the effective use of text-message reminders to

improve patient adherence to medications in the clinical setting.[18,19] However, few studies have explored the use of text-message reminders for adherence to study medications in a clinical trial. If an electronic data capture system provided two-way communication between research personnel and patients, text-messages could be sent to patients to remind them to take study medications or complete an electronic follow-up visit.

Given the scarcity and competition for research funding, it is imperative that clinical trial investigators are frugal and fiscally responsible. To that end, in addition to improving data quality, reporting, and patient adherence, electronic data capture systems may also be a more cost-effective tool than traditional data collection methods. Despite overhead costs associated with purchasing an electronic data system, there may be cost savings through the reduction in time research assistants spend collecting patient data. Specifically, in a pain clinical trial, the multitude of questionnaires used may require research assistants to spend several hours with each patient over the course of a study. Electronic data capture systems could reduce the amount of time needed to spend with each patient, allowing research personnel to attend to other pertinent study tasks. Furthermore, in the age of smartphones, investigators no longer need to purchase mobile electronic devices for each study participant and could rely upon patients' own device or home computer.

There may be several benefits associated with an electronic data capture system. However, few randomized trials have assessed these benefits over traditional methods for pain measurements. Furthermore, there are no randomized trials comparing these data collection methods for acute and chronic pain measurements within the perioperative setting.

Summary

Pain is a dynamic sensory experience and its measurement is critical to the validity and statistical power of a clinical research study. While conventional techniques for the measurement of pain are still widely used, they may reduce the quality of data collected through errors, incomplete data, missing data, and recall bias. Electronic data capture systems can potentially improve data quality and frequency of reporting. Furthermore, if a two-way electronic data capture system is employed, electronic reminders could potentially improve patient adherence to the study protocol. While the benefits of an electronic system have been documented in the literature, there is a paucity of randomized controlled trials directly comparing an electronic system to traditional methods in a pain clinical trial.

We plan to undertake a randomized controlled trial (RCT) comparing an electronic data collection system to traditional data collection methods in the Pregabalin and Lidocaine in breast cancer surgery to Alter Neuropathic Pain (PLAN) Pilot Trial. The proposed RCT will be known as PLAN-ED Sub-study (PLAN Electronic Data Capture Sub-study).

TRIAL DESIGN

The PLAN-ED Sub-study will be an open randomized controlled trial assessing the use of an electronic data capture system to traditional methods of data collection (i.e., paper-based and telephone-interviewing) within the context of a randomized controlled trial assessing the use of two perioperative interventions to reduce chronic post-surgical pain, the PLAN Pilot Trial.

The PLAN Pilot Trial is a 2X2 factorial design randomized controlled trial that will assess the use of perioperative pregabalin and intraoperative intravenous lidocaine infusion to reduce the development of post-mastectomy pain syndrome after breast cancer surgery

(lumpectomy or mastectomy). Patients are randomized to one of four different groups: IILI/pregabalin, IILI/pregabalin placebo, IILI placebo/pregabalin, and IILI placebo/pregabalin placebo. We will test the feasibility of comparing IILI to placebo and pregabalin to placebo in patients undergoing breast cancer surgery to establish the foundation for a larger, multicentre, clinical trial. Patients, health care providers, data collectors, and data analysts will be blinded to treatment allocation.

STUDY OBJECTIVES

PLAN-ED Sub-study Objectives

The purpose of this study is to compare the use of an electronic data capture system to traditional data collection methods in the PLAN Pilot Trial. Objectives of this study are to determine the impact of an electronic data collection method on:

a) data quality;

b) patient protocol adherence;

c) patient and research assistant satisfaction; and

d) resource requirements.

PLAN Study Objectives

The primary study objectives of the PLAN Pilot Trial include the following:

1. determine the feasibility of recruiting patients undergoing breast cancer surgery into a factorial-designed randomized controlled trial (RCT) of intraoperative intravenous lidocaine infusion versus placebo and perioperative pregabalin versus placebo for the prevention of post-mastectomy pain syndrome;

2. determine clinical site compliance with trial protocol;
3. determine time, resources, and management issues related to conducting a larger study

HYPOTHESES

Our hypotheses for this study is that the use of an electronic data capture system compared to traditional data collection methods in the PLAN Pilot Trial will allow for: a) improved data quality and accuracy; b) improved patient adherence to the study as it relates to drug compliance, retention, and completion of study outcome measures; c) greater patient and research assistant satisfaction with data collection; and d) lower financial costs.

ELIGIBILITY CRITERIA

Inclusion Criteria

- Enrolled in the PLAN Pilot Trial
- Have access to a computer with internet access at home or have a capable smartphone with internet access (i.e., iPhone 3G or above, iPad 1st generation or above, LG L7, Sony Xperia Z, Samsung Galaxy III or Nexus, Blackberry Z10, HTC Desire or ONE, Blackberry Q10, Nokia Lumnia 920)
- Agree to enrol into the sub-study

Exclusion Criteria

- Patient does not provide informed consent

TRIAL DESIGN

The PLAN-ED Sub-study will utilize the infrastructure created by the PLAN Pilot Trial. The PLAN Pilot Trial is a multicentre factorial-design, blinded, randomized controlled trial. Patients will be recruited from Juravinski Hospital in Hamilton, Ontario and from the Sunnybrook Health Sciences Centre in Toronto, Ontario. PLAN will randomize patients to receive either perioperative pregabalin or placebo and intraoperative intravenous lidocaine infusion or placebo. The PLAN-ED Sub-study will randomize patients who are included in the PLAN Pilot Trial upon informed consent for the main trial and sub-study.

PATIENT RECRUITMENT AND INFORMED CONSENT

Patients undergoing a unilateral or bilateral mastectomy or partial-mastectomy (i.e., breast conserving surgery), for prophylactic (e.g. family history or BRCA gene mutation) or isolated (non-metastatic) cancerous lesions will be recruited into the PLAN Pilot Trial. Patients will be recruited at the breast surgeon's office or in the pre-assessment clinics prior to their operation. Patients who meet the eligibility criteria and agree to participate in the PLAN-ED Sub-study will subsequently be enrolled.

INTERVENTION

Patients that are eligible and provide informed consent will be enrolled in the PLAN-ED Sub-study. They will be randomized to either the electronic data capture system or standard data collection methods:

a) <u>Electronic data capture system:</u>

The electronic data capture system has been developed and programmed by InputHealth for specific use in the PLAN-ED Sub-study. Electronic questionnaires to capture study data can be sent to the patient via text-message or email — patients will be asked about their preference to receive prompts via text-message or email for data collection at the start of the study. Patients will click on the link on their phone or computer and complete the requested questionnaire. The link is encrypted and personalized to each patient and submitted data will be recorded under their study ID in the database. If patients are in-hospital during the study period, research assistants will provide patients with an iPad and study data will be collected directly into the electronic database.

The electronic data capture system abides by privacy regulations in accordance with the Personal Health Information Protection Act. Such regulations include: strong password policy; authorized log-in and two-factor authorization; severs that utilize anti-sniff/anti-spoof firewall defenses with advanced 24/7 monitoring and multi-level intrusion prevention, anti-spam, anti-malware, and anti-virus implementations; all data stored in Canada; all online interactions are encrypted using 256-bit SSL technology and the databases are stored in an encrypted fashion using AES-256-CBC technology; and there is no storage of information on the electronic device.

b) Standard data collection methods:

Standard methods to collect patient data in a clinical trial include paper-based methods for in-person visits or telephone calls for follow-up visits at home.

Data collection in this study will be completed during three time periods: baseline, immediate postoperative period, and three-month follow-up visit. A description of the data collection used in the intervention and control groups are outlined below:

Baseline

Preoperatively, patients are expected to fill out the Numeric Rating Scale (NRS), Pain Catastrophizing Scale (PCS), Amsterdam Preoperative Anxiety and Information Scale (APAIS), and the Somatic Pre-occupation and Coping (SPOC) scale.

Patients in the electronic data capture arm will fill out these questionnaires in-hospital or at home. If patients are in-hospital, they will fill out these questionnaires on an iPad which will be provided to them by a PLAN Research Assistant. If they are at home, they will be sent the questionnaires via email or through a text-message if they have a capable smartphone.

If the patient is in the control group, they will complete questionnaires by paper methods in-person or over the telephone if they are at home.

Immediate Postoperative Period

Postoperatively, patients will be expected to report pain scores twice a day, opioid and non-opioid pain medication use, and adverse side-effects on postoperative days 1-3 and 9. No data is collected during postoperative days 4-8.

In the electronic data capture arm, patients will be sent an email or text-message to report on study outcomes on days 1, 2, 3 and 9. With regards to pain scores, patients will fill out an electronic version of the NRS pain scale regarding current pain in the morning and in the evening. For the morning pain score, patients will receive an electronic data request sent to them

at 8am and will have until 12pm to complete it. Similarly, an electronic request will be sent at 8pm to obtain the evening pain score and patients will have until 12am to complete the request — the evening data request will also contain questions regarding opioid and non-opioid medication use and adverse-effects for that day. Both the morning and evening data requests will also have a brief reminder for the patient to take daily study medications. If the patient does not complete the morning and evening data request by 11am or 11pm, respectively, an electronic reminder will be sent to the patient. If the patient does complete the request by the specified time, an automated electronic notification will then be sent to the research team. A research personnel will then contact the patient by phone to obtain study data — the need to use traditional methods (i.e., telephoning the patient) to collect study data due to failure of the electronic system will be documented. During postoperative days 4-8, there will be no data requests but patients in the electronic arm will receive an electronic reminder to take morning and evening study medications.

For patients in the electronic arm that remain in hospital during the immediate postoperative period and have a smartphone with internet access, they will receive the same schedule for morning and evening electronic requests as described above. However, if the patient does not have a smartphone with internet access, the patient will be given an iPad by the research team and will be responsible for completing the questionnaires as required.

Patients in the control group will be given a paper pain diary that will ask the patient to record their pain scores, medication use, study drug compliance, and adverse events in the morning and evening on postoperative days 1-3 and 9. Research personnel will call patients at home on postoperative days 1, 4, and 10 to obtain data from the paper diary. The phone call on postoperative day 1 will collect data about the morning of day 1, postoperative day 4 phone call

will collect data about day 1 evening, day 2, and day 3. The postoperative day 10 phone call will collection data about day 9. There will be no reminders in the control group during postoperative days 4 – 8, as this is not the standard practice using traditional data collection methods in a clinical trial. Patients in the control group who remain in hospital postoperatively will be visited by the research team on the hospital ward to collect study data.

Three-month Follow-up

In the PLAN Pilot Trial, patients will be followed up three months after their surgery to collect information on the primary outcome. Patients will be required to fill out a PLAN pain questionnaire, the McGill Pain Questionnaire 2 (MPQ-2), Brief Pain Inventory (BPI), and the Short Form 36 (SF-36).

In the electronic data capture arm, patients will be sent an email or text-message to fill out these questionnaires, whereas in the control group, patients will be called at home.

After all study data is collected via electronic or traditional methods, outcome measures will be transferred into the PHRI iDataFax system. Outcome measures in this sub-study relating to data quality will be determined once all data is inputted into the iDataFax sysem.

RANDOMIZATION

At the time of informed consent, patients will be randomized to either the electronic or traditional data collection group using an electronic centralized randomization service (i.e., ROME). Patients will be randomized to the drug arms in the PLAN Trial the day before their surgery using the same electronic centralized randomization service.

FOLLOW-UP AND DATA COLLECTION

Patients will be followed-up in the PLAN-ED Sub-study in the same schedule used in the PLAN Pilot Trial. Patients will be followed during their hospitalization, immediate postoperative days, and three months after their procedure. Data collection for those in the electronic arm will occur on days 1, 2, 3, and 9, and at 3 months after surgery. Data collection for those in the control group occur on days 1, 4, and 10 and at 3 month after surgery.

TRIAL OUTCOMES

Assessment of the effectiveness of the electronic data capture system will be evaluated using the following outcomes:

Data Quality

A. Total Number of Queries

   The number of queries in the iDataFax system after the 3 month follow-up visit will be determined for each patient in the sub-study. Queries relate to data that is inappropriate, missing, incongruent for the specified field, contains an error, or needs clarification. Queries are posted by the Study Coordinator who is blind to patient group allocation in the sub-study and corrected by the research assistant.

B. Queries requiring intervention

   The number of queries relating to data fields in iDataFax that require the research assistant to change or correct a specified data field for each patient will be calculated after 3 month follow-up visit. Not all data queries posted by the Study Coordinator

require correction but the ones that do typically represents a data error. The number of queries requiring intervention will denote data error rate in each group.

C. Queries denoting missing data

The number of queries relating to a missing data fields in iDataFax for each patient will be calculated after the 3 month follow-up visit.

Protocol Adherence

A. Drug Compliance

This is the proportion of patients who took study medications as directed in the protocol during the study period. Patients will be asked about their compliance with study drugs during the clinical trial. This outcome relates only to compliance with the perioperative pregabalin study medications since the intraoperative intravenous lidocaine infusion is administered by the attending Anesthesiologist. This outcome will be a patient self-reported outcome and will be assessed on day 9 in the electronic arm and day 10 in the control arm.

B. Patient Retention

This outcome relates to the proportion of patients who remain in the study until study completion (i.e., the total number of patients randomized minus those lost to follow-up and withdrawals). Patient retention in the study will be determined at the end of the study completion.

Patient and Research Assistant Satisfaction

A. Patient Satisfaction

At the end of the immediate postoperative period and at the three month follow-up, patients will be asked: "On a scale of 0 to 100, 0 being not satisfied and 100 being extremely satisfied, how satisfied were you with your experience filling out study data using paper-based (or electronic-based) methods?"

B. Research Assistant Satisfaction

At the end of the study, PLAN Research Assistants will be asked about their satisfaction working with these two different data collection methods. They will specifically be asked: "If you had a choice between paper-based methods and electronic data collection for a study, which one would you chose?" and "On a scale of 0 to 100, 0 being not satisfied and 100 being extremely satisfied, how satisfied were you with working with patients in the paper-based (or electronic-based) group?"

Resource Requirements

A. Research Assistants' Time

The cumulative time a research assistant spends with a patient on collecting patient data in the PLAN Pilot Trial will be determined in minutes. At baseline, the length of time a research assistant spends collecting baseline information as well as training patients on the type of data collection method will be determined. During the postoperative days and at the 3 month follow-up, the length of time spent on the phone with the patient or setting up electronic questionnaires will be recorded. Any time spent by the research assistant troubleshooting technical difficulties with the electronic system will also be recorded, in addition to telephoning the patient if the electronic system fails. Further, if a patient

reports any issues completing questionnaires, the research assistant will record the nature of the issue, time allotted to rectify the issue and action taken.

B. Costs Analysis

A cost analysis will be performed comparing the use of the electronic data capture system provided by InputHealth and traditional data collection methods. Research assistants' time will be added to the cost analysis by determining how much time (in hours) they spent performing data collection for each patient and then using their hourly wage to calculate the associated cost in Canadian dollars. The cost of the electronic data capture system will include costs associated with the InputHealth service, iPads, research assistant's time, and other incidental fees. The costs associated with the control group will be only the research assistant's time, stationary, and costs for printing paper diaries. The average cost per patient according to their data collection group will be calculated and compared.

SAMPLE SIZE

Based upon an internal analysis of a similar pilot randomized controlled trial conducted at the Population Health Research Institute, the average number of queries per patient was 25 with a standard deviation of 5. With an alpha of 0.05 and 80% power, we would need at least 32 patients in total to identify a reduction in queries from a mean of 25 to a mean of 20. The PLAN Pilot Trial aims to recruit 100 patients across the Juravinski Hospital in Hamilton and Sunnybrook Health Sciences Centre in Toronto. We anticipate that 90% of patients enrolled in PLAN Pilot Trial will be eligible for the PLAN-ED Sub-study — those undergoing breast cancer surgery are typically young and have access to a computer or smartphone. Aiming for an 80%

recruitment rate of those eligible for the Sub-study, we anticipate an enrolment of 72 patients into the PLAN-ED Sub-study, a sample size sufficient to meet our power calculation.

STATISTICAL ANALYSIS

Continuous outcomes such as total queries, queries requiring intervention, queries for missing data, patient and research assistant satisfaction, research assistant's time, and costs (in Canadian dollars) will be performed using a t-test. Outcomes of proportions such as drug compliance and patient retention will be performed using a test of proportions. Pearson's r correlation between postoperative days 1-3 acute pain scores between the electronic and traditional data collection methods will be determined. All statistical analyses will be performed using SPSS software version 20 (Armonk, NY). All tests will be two-sided and significance will be considered at $p < 0.05$.

SIGNIFICANCE

Previous studies suggest that the use of an electronic data capture system in a pain clinical trial can improve data quality and reporting. However, despite the potential benefits, there has been a low adoption rate of this data collection method in pain clinical trials. This will be one of the first randomized controlled trials comparing an electronic data capture system to traditional methods on data quality, patient adherence, patient and research assistant satisfaction, and resource requirements in a trial assessing chronic post-surgical pain. Results from this study can inform the value of an electronic data capture system into pain clinical trial design and methodology.

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CHAPTER 5

Conclusion and future directions

This thesis explored the issue of chronic post-surgical pain after noncardiac surgery. The included studies informed the incidence and risk factors for chronic incisional pain after noncardiac surgery from data of a large prospective observational study, identified the association between patient beliefs and expectations for recovery and the incidence of chronic pain after traumatic tibial fracture, and the potential effect of data collection technique on data quality and reporting in a pain clinical trial.

Incidence and risk factors for chronic post-surgical pain

A preliminary analysis of the data collected by the VISION Study on the development of chronic incisional pain at 1-year after noncardiac surgery was reported. This was an analysis of 10,481 patients of a larger group of approximately 20,000 patients who were queried about chronic pain among the VISION cohort. Approximately 4.4% of patients undergoing noncardiac surgery will suffer from chronic incisional pain 1-year after their procedure. Identified risk factors for the development of chronic incisional pain included female gender, younger age, surgery for fracture and preoperative chronic pain. Several interventions given around the time of surgery were also found to be associated with chronic pain including lack of postoperative PCA and epidural analgesia, lack of nitrous oxide, open surgical technique, the withdrawal of daily COX-2 inhibitors and new administration of insulin on the day of surgery — the last being a particularly novel finding of this study and deserving of further exploration in the main analysis. While outcome data on the remaining patients in the VISION study is currently being collected, it is likely that the final results will not substantially differ from that of the interim analysis.

Our study provides an estimate of chronic incisional pain, a type CPSP specific to the incision site. This is in contrast to previous studies that have typically used broad definitions for CPSP. This study also provides incidences specific to a diverse group of surgical populations, many of which have not been studied for the development of chronic pain previously. Given that approximately over 200 million adult patients undergo noncardiac surgery each year, this study suggests that an overwhelming number of patients will develop chronic incisional pain on an annual basis. Implications of this study will also inform future risk prediction models and potential randomized controlled trials that aim to reduce the development of chronic post-surgical pain.

Somatic pre-occupation and coping and chronic pain after traumatic tibial fracture

Secondary data collected by the SPRINT trial was used to determine an association between patient beliefs and expectations for recovery and the development of chronic pain after traumatic tibial fracture. Patient beliefs and expectations about recovery were operationalized by the SPOC instrument, with higher scores reflecting greater pre-occupation and pessimism. We found that higher SPOC scores were strongly associated with chronic pain. While patient beliefs and expectations had previously been shown to predict functional outcomes, this is one of the few studies to identify an association with pain. Findings from this study also support the shift towards a biopsychosocial model as a framework to understand the development of CPSP.

This study has potential implications for risk stratification and non-pharmacological risk reduction strategies. If SPOC scores are evaluated in a broader surgical population and continue to demonstrate a strong association with chronic pain, SPOC scores could be used to identify those at highest risk for CPSP. Effective interventions could then be selectively administered to

these high-risk patients — unselective administration of interventions is the current approach used in clinical practice and unnecessarily exposes low-risk patients to potential side-effects and adverse events. Furthermore, while many of the previously identified factors associated with chronic pain after surgery, including psychological factors (i.e., catastrophizing, depression), are not tenably modifiable in the perioperative period, patient expectations are potentially modifiable and thus may provide an opportunity to reduce the risk of chronic pain. Certainly, it will first need to be demonstrated that patient beliefs and expectations for recovery can be altered, followed by a randomized controlled trial to see if a modification intervention can reduce CPSP. If such a trial is positive, we would have evidence for a non-pharmacologic approach to the reduction of CPSP.

Electronic data capture on data quality and reporting in a pain clinical trial

A protocol for a randomized controlled trial to assess the effect of electronic data collection methods compared to traditional methods in a pain clinical trial was presented. This study is currently underway and is expected to finish recruitment in August,2015. Results of this study will be an important advancement in the methodology of pain measurement in clinical studies. Electronic data collection methods using mobile devices or home computers potentially allow for improved data quality and increased frequency of reporting with less disturbance to the patient. These methods may also improve patient adherence of study drug medications and may offer a cost-effective option for researchers. Although there has been low uptake of electronic data collection methods in clinical research, this trial will indicate the potential benefits of such a technique and inform its use in pain clinical study design and methodology.

Future Directions

Findings from these studies have inspired subsequent investigations that I am currently undertaking. From the VISION analysis, it is clear that different surgical populations have different risks for chronic pain — specific surgical techniques, perioperative considerations, and patient populations may all contribute to varying rates. An analysis specific to orthopedic procedures using the VISION data is currently planned with hopes of identifying specific risk factors, surgical techniques, or interventions that are associated with chronic pain in this surgical population. Additionally, I will be exploring the association between SPOC scores and risk of chronic pain in those after breast cancer surgery. I am currently undertaking a pilot trial of 100 patients undergoing breast cancer surgery (mastectomies and lumpectomies) to assess the use of perioperative pregabalin and intraoperative intravenous lidocaine on chronic pain. All patients enrolled in this study are required to complete the SPOC instrument prior to surgery. This sub-study will provide evidence of the association between preoperative SPOC scores and the development of chronic pain after breast cancer surgery. Furthermore, in developing the PLAN-ED protocol, I was inspired to conduct a systematic review on the benefits of electronic data collection methods for the measurement of pain for clinical and research purposes. We are currently in the process of completing the full-text review of 162 articles and hope to complete the entire review by the fall of 2015.

I believe that the articles included in this thesis advance our collective knowledge and understanding of chronic post-surgical pain. As it has inspired me to pursue subsequent studies, I hope that it also inspires others to do the same. Chronic pain is an under-recognized and under-appreciated complication of surgery. CPSP is a significant source of morbidity for those it

affects. Further research is needed on this important issue to reduce suffering and improve safety of all patients undergoing surgery.