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Examination of psychological risk factors for chronic pain following cardiac surgery: Protocol for a prospective observational study

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ABSTRACT

Introduction: Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, and up to 56% will develop chronic post-surgical pain (CPSP). The primary aim of this study is to explore the association of pain-related beliefs and gender-based pain expectations on the development of CPSP. Secondary goals are to a) explore risk factors for poor functional status and patient-level cost of illness from a societal perspective up to 12 months following cardiac surgery; and b) determine the impact of CPSP on quality adjusted life years (QALY) borne by cardiac surgery, in addition to the incremental cost for one additional QALY gained, among those who develop CPSP compared to those who do not. **Methods and analyses**: In this prospective cohort study, 1,250 adults undergoing cardiac surgery, including coronary artery bypass grafting and open-heart procedures, will be recruited over a 3-year period. Putative risk factors for CPSP will be captured prior to surgery, at postoperative day 3 (in hospital) and 30 (at home). Outcome data will be collected via telephone interview at 6 and 12 months follow up. We will employ generalized estimating equations (GEE)
to model the primary (CPSP) and secondary outcomes (function and cost), while adjusting for pre-specified model covariates. Quality adjusted life years (QALYs) will be estimated by converting data from the Short Form-12(Version 2) to a utility score.

Ethics and dissemination: This protocol has been approved by the responsible bodies at each of the hospital sites and study enrollment began May 2015. We will disseminate our results through CardiacPain.Net, a web-based knowledge dissemination platform; presentation at international conferences, and publications in scientific journals.

Strengths and limitations of this study:

Strengths

- This is a prospective, multi-site study with a large cohort of cardiac surgery patients
- One year follow up is compliant with IMMPACT recommendations to standardize timing of outcome assessment for prognostic studies of CPSP.
- A robust analysis plan using generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-months and 1-year, while adjusting for pre-specified covariates.

- Assiduous follow up procedures will be adhered to, which have been proven effective in prior prospective observational studies

Limitations

- There is reliance on pain and quality of life self-report outcome measures, however rigorous criteria to define chronic post-surgical pain will be applied, and valid and reliable instruments will be used.

KEY WORDS: pain management, cardiac surgery, health economics

INTRODUCTION

Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, [4, 5] and these numbers are expected to rise as the population ages. [1-3] Despite the proven survival and symptom-related benefits of cardiac surgeries, mounting evidence suggests that chronic post-surgical pain (CPSP)—and related poor functional recovery—following these procedures are major clinical problems. [6-31] Moreover, the economic consequences of persistent pain and dysfunction remain uncertain. Identification of factors associated with the development of CPSP could facilitate efforts to improve outcomes among high risk patients, yet the majority of putative risk factors examined to date are not tenably modifiable in the perioperative context. Three psychological factors that do show promise as modifiable, potential risk factors for CPSP include pain-related beliefs, gender-based pain expectations, and somatic preoccupation and coping. The purpose of this study is to examine whether these factors are associated with transition to CPSP following cardiac surgery.

CPSP Following Cardiac Surgery

Due to conceptual and methodological differences in the assessment of pain, and conflicting opinions about the duration of "chronicity", there is no one accepted definition of CPSP. [32] However, there is consensus among experts, [32-38] that CPSP should meet the minimum criteria, set forth by Macrae and Davies [33] and others [34-40], as follows. It must a) have developed after the surgical procedure, b) be different from pain experienced prior to the procedure, c) not be caused by other factors (e.g., cancer recurrence, chronic infection), d) be present for at least 2-3 months, and e) interfere significantly with health-related quality of life. [34-40].

Open cardiac surgeries involve many pain-sensitive structures, as they require a median sternotomy, retraction of the ribs, and invasion of muscles and visceral tissues. In coronary artery bypass surgery (CABG), the grafting procedure requires harvesting at several sites including, most commonly, the internal mammary artery (IMA). The manipulation and retraction of the sternum as well as the use of electrocautery to dissect the IMA from the chest wall may result in nerve damage that leads to intercostal neuralgia. [41-44] The greater and lesser saphenous veins are also used as grafts in CABG surgery and require significant leg incisions. These procedures may result in pain that can last for variable periods, and may be inflammatory or neuropathic in

nature. CPSP in cardiac surgery patients is often experienced in the thorax and legs, but has also been described, to a lesser degree, in the shoulders, back, and neck. [10, 12, 45]. The pathophysiological pathways underlying CPSP are multi-factorial. Tissue damage leads to release of high concentrations of bradykinin, adenosine, lactate, and potassium in the peripheral microenvironment, thereby causing nociceptor activation. [46,47] These mediators activate capsaicin sensitive TRVP1 receptors, which serve as the primary transducer of the noxious stimulus. [47] Other neurochemicals, such as the neuropeptides Substance P and calcitonin generelated peptide, further augment pain. [47] These peripheral nociceptive processes, are modulated in the central nervous system by mechanisms involving selection, abstraction, and synthesis of information from the total sensory input. [48] The amount, quality, and nature of the pain experienced are therefore dynamic and multidimensional products of sensory-discriminative, cognitive-evaluative, and affective-motivational components. [48] Like any form of chronic pain, on-going pain after surgery can lead to pathological nervous system changes, collectively known as sensitization [47]—a function of what we now understand to be neuronal modifiability. [46] Sensitization of the nervous system may lead to increased pain sensitivity (hyperalgesia), augmentation of the normal duration (hyperpathia) and amplitude of pain, and abnormal perception of non-painful stimuli as painful (allodynia). [47,49]

As Katz and Seltzer argued, [32] critical to understanding the nature of CPSP is appreciating that in each case, the pain was once acute and involved a transition phase. There is much work to be done to continue to develop our understanding of risk factors, which predispose cardiac surgical patients to pain chronicity.

Prevalence and consequences

We reviewed 26 published/under review studies to date, across 14 countries, [6-31] which have examined the prevalence and/or factors associated with CPSP following cardiac surgery. Upon careful examination of the available data, it is important to recognize that cross-sectional and retrospective studies have generally reported higher prevalence rates (14%-56%) than those investigations with prospective designs (7.5 - 45%). In the recent (2013), large-scale Canadian CARDpain study (n=1,010), Choiniere, Watt-Watson et al. [28] reported CPSP prevalence rates of 40%, 22%, and 17% at 3, 6, and 12 months following cardiac surgery, respectively. Routledge

et al. (2009) [31] found similar prevalence rates of CPSP in their prospective extension (WREST-E) of a randomized clinical trial (WREST), (n=222) to examine the impact of a novel compression undergarment on women's recovery from median sternotomy (3 months post-op, 41%; 12 months post-op, 16.7%). In contrast to CARDpain and WREST-E, 1-year CPSP prevalence rates as high as 39% and 45% have been reported in prospective studies of patients following CABG in Turkey [27] and the Netherlands. [30] Aside from differences in study design, the observed variability in reported prevalence rates of CPSP after cardiac surgery may be explained by the use of point prevalence versus cumulative prevalence, variability with respect to the operational definitions of CPSP, timing of outcome measurement, and duration of follow up period.

CPSP has been associated with the development of anxiety and depressive disorders, [51-55] sleep disturbances and fatigue, [56-60] as well as poor self-rated health. [7, 51, 53, 61] For example, among those with CPSP in the CARDpain study, over 50% reported significant bodily pain pain-related interference with activities of daily living—including family and home responsibilities, recreation, and employment—at 3, 6 and 12 months following cardiac surgery. [28, 62]

Risk factors for CPSP

Several studies have attempted to establish risk factors for CPSP in cardiac surgery patients. Their limitations can be summarized [63] as: 1) many studies focused on univariate analyses, or were insufficiently powered to employ multivariate modeling techniques, 2) the vast majority of risk factors examined to date are not tenably modifiable in the peri-operative context, 3) psychological risk factors (affective and cognitive) are substantially understudied in comparison to demographic, clinical/surgical, and analgesic risk factors, constituting a major gap, 4) although retrospective and cross-sectional studies provide some insight on potential variables associated with CPSP, cross sectional studies lack the temporal orientation to make solid inferences about putative, causal relationships, and retrospective studies can be limited by availability and quality of data. In addition, even robust retrospective may be limited in terms of

risk factors explored and related data collection methods. Risk factors for CPSP can be classified into four categories: a) demographic, b) baseline clinical, technical-surgical, and hospitalization-related factors, c) acute post-operative pain, and d) psychological factors.

Demographic factors

Demographic factors examined include age, sex, level of education, body-mass index (BMI), and smoking history. Younger age has been positively associated with CPSP [7, 9, 12, 17, 20, 25, 28] in multiple retrospective, cross-sectional, and prospective studies, as observational data embedded within RCTs; significant odds ratios (OR) have ranged from 1.43-7.03 in cases where this outcome was dichotomized (i.e. younger vs. older patients). However, four of the more recent published studies to date (1 retrospective, [18] 1 cross-sectional, [30] 1 RCT, [50] 1 prospective [21]) have found no positive association between age and the development of CPSP. Conflicting findings have also been reported for sex. Although some studies indicate higher risk of CPSP with women, [21, 29, 30] multiple studies with divergent designs, [9, 12, 14, 48, 18, 20, 28] have reported no significant association between sex and the development of CPSP. Examination of BMI as a risk factor for CPSP has also produced mixed results. While two studies (1 cross-sectional, [7] 1 RCT (embedded observational data), [20] ORs =1.34 and 9.05, respectively) provided supportive evidence, other cross- sectional [17, 18] and prospective studies [9, 28] found no association between CPSP and BMI (OR range: 1.02-1.1). Finally, we are aware of 2 prospective studies to date which have examined the association of CPSP with formal level of education [28] and smoking history [14], respectively; no significant association was found in either case.

Baseline clinical, surgical and hospitalization-related factors

Among baseline clinical factors, neither a history of diabetes mellitus [9, 14, 17, 23, 24, 50] or peripheral arterial disease [24] have been significantly associated with the development of CPSP. However, pre- existing peripheral arterial disease has been examined as a risk factor in just one retrospective study [24] to date. Similar to diabetes mellitus, the majority of prospective studies [20, 21, 23] (including 1 RCT) [20] reported no predictive ability of baseline chronic pain conditions in the literature (OR=1.00-1.04, where reported). To date, CARDpain [28] is the only prospective examination to report that pre-existing chronic pain at baseline (non-anginal) is

positively associated with CPSP (adjusted OR=1.44, 95% confidence interval [CI]: 1.12 to 1.86). [28]

The evidence pertaining to the predictive value of pre-operative angina is also mixed. Two cross-sectional studies reported pre-operative angina that was positively associated with CPSP (OR, where reported=1.62) [7, 12] however, another cross-sectional [17] and two additional, large-scale prospective studies [14, 28] found no significant associations to infer that pre-operative angina is a significant risk factor for CPSP.

The majority of studies have reported no association [6, 12, 13, 17, 22, 28, 50] between a range of surgical factors, including a) type of surgical technique, b) number and type of bypass grafts per operation, c) harvesting technique, and d) total cross-clamp time (i.e., total time aorta is clamped to separate systemic circulation from cardiac outflow) and the development of CPSP. There is some evidence to suggest that not skeletonizing the internal thoracic artery harvest (i.e., harvesting it along with its surrounding pedicle of vascular tissue) is more likely to invoke CPSP; [64] those who have undergone left internal mammary artery harvesting may also be at higher risk. [13, 42] In general, post-operative complications and related adverse events (e.g., reoperation for bleeding, infections) have not been associated with CPSP, [9, 12, 14, 16, 20, 28] with the exception of 1 prospective study which identified postoperative re-sternotomy as a significant risk factor (OR=3.38). [21] Cardiac surgeries of longer duration (i.e. total OR time) [18, 20] also do not seem predictive of CPSP; in fact, the CARDpain [28] study found that the longer the OR time, the less likely CPSP was to develop. Finally, there seems to be no conclusive evidence to suggest that length of time in the ICU [18, 20, 28], or total duration of hospitalization [18] contribute to the development of CPSP after cardiac surgery.

Acute post-operative pain

Two prospective studies found that severe pain (i.e., Numeric Rating Scale ≥ 7/10) on postoperative (post-op) day 3 was a significant risk factor for CPSP at 1-year follow up, [21] as well as worst and average pain ratings at 2-years follow-up. [28] A third prospective study found that severe pain on post-op day 30 positively predicted CPSP at 3 months. [23] The association between analgesic therapy and CPSP is uncertain. [10, 11, 12, 18, 19, 21, 23, 27, 28]

Psychological factors

Only the CARDpain [28] study has examined the role of psychological risk factors in the development of CPSP and found that pre-surgical anxiety, as measured by the Hospital and Anxiety and Depression Scale (HADS-A), was a significant risk factor, with a 10% increase in the odds of developing CPSP for each unit increase in HADS-A scale scores (OR= 1.10, 95% CI, 1.06 to 1.14). Other psychological risk factors examined (catastrophizing, depression) demonstrated no association.

Genetic factors

Several members of this investigative team (e.g., Clarke, Katz,) are involved in studies investigating the influence of genetic polymorphisms on the development of CPSP after cardiac and other types of surgery. The science of pain genetics is evolving; investigations of this nature are complex, requiring extensive research infrastructure for genotyping and related proteomic methods. Controlling for the influence of genetic factors is beyond the scope this study.

Conceptual Underpinnings and Study Focus

To address the above noted gap in the research to date, our primary objective is to examine the potential influence of psychological factors on the development of CPSP after cardiac surgery. Clear justification for the specific putative risk factors to be measured requires that we first explicate the conceptual underpinnings of our study. Given the complexity of the multi-dimensional pain experience, there are many ways to conceptualize CPSP. [65] We are aligned with the bio-behavioural view of pain, espoused by international leaders in the science of the cognitive and learning aspects of pain, Flor and Turk. [65, 66] Fundamental to the bio-behavioural perspective is the assertion that people learn to predict future events based on prior learning experiences and information processing. As such, patients' behaviours elicit responses from significant others, including healthcare professionals, which can reinforce both adaptive and maladaptive modes of thinking, feeling and behaving. [65] With this understanding, patients' pain-related cognitions and behaviours are of chief concern with respect to identifying factors which may contribute to the transition from acute post-operative pain to chronic pain. In moving the science forward, we therefore give primacy to the cognitive-behavioural side of the global bio-behavioural view of pain, as the conceptual premise for our primary objective. According to the fundamental tenets of the cognitive-behavioural perspective of pain [65, 66]: a) behavior is

reciprocally determined by the person and environment, b) people can learn more adaptive ways of thinking and behaving, and c) people are capable of and should be involved as active agents in the change of maladaptive thoughts, amenable to intervention. [65] Our focus therefore will be on the contribution of patients' pain-related beliefs and expectations, as follows:

Pain-related beliefs

Decades of work [67-84] in the fields of post-operative pain and anesthesia has demonstrated that surgical patients have beliefs about pain and pain medication, which a) are based on incorrect information, and b) serve to block effective pain assessment and management. For example, one study found that among patients undergoing CABG surgery (n= 202), a majority (83%) reported that they would not voluntarily ask for pain medication when they needed it, although most reported unrelieved moderate-to-severe pain from post-operative day 2 (80%) until day 5 (69%). [67] As of 2013, data indicate that this unfortunate scenario remains largely unchanged. Cogan et al. [84] found that among cardiac surgery patients (n=564), 36% believed that "pain medication should be spared until the pain is very severe", 20% believed that "good patients do not speak of their pain", and 31% believed it is "very easy to become addicted to pain medication" while recovering from surgery. The particular role of these beliefs per se in the development of CPSP and has yet to be examined; we will do so in this study using the Pain Barriers Questionnaire (validated in multiple populations).

Gender-based pain expectations

As with a number of fields in the health sciences, the study of sex and gender, as they relate to pain, is evolving. Our comprehensive review of risk factors for CPSP after cardiac surgery revealed that thus far, investigation has been limited to the contribution of sex only as a risk factor. For the purposes of this study, we employ the following distinctions between sex and gender, set forth by Lips, [85] which have been adopted in a number of well-cited pain studies: [86-101] sex- the biologic distinction of being male or female; gender- learned masculinity or femininity, related to socially-constructed roles and behaviours attributed to men and women in society. [85, 86]

Emerging evidence suggests that gender-based pain expectations defined as "Sex-related stereotypic attributions about pain sensitivity, pain endurance, and willingness to report pain"

[89] may lead to important differences in the experience of pain and related response. Robinson et al. were among the first to investigate gender-based pain expectations, using the Gender Role Expectations of Pain Questionnaire (GREP). [89] Their study of pain cognitions in 156 men and 235 women found that men were perceived to be less willing to report pain than women, women were perceived to be more sensitive and less enduring of pain than men, and that men rated their pain endurance as higher than average. Further testing of the GREP by Wise et al. [96] found that after controlling for age, GREP scores accounted for 7%,11%, and 21% of the variance in pain threshold, tolerance, and pain unpleasantness scores, respectively, for women (n=87) and men (n=61) exposed to thermal testing. A recent meta-analysis by Alabas et al. (2012), for example, examined the role of gender-related cognitions in the experience of pain. [93] Pooling the results of 6 trials (406 men, 539 women), they found that those who considered themselves more masculine and less sensitive to pain, than the typical man, exhibited higher pain thresholds and tolerances in a variety of settings. Using the GREP, our study will be the first we know of to examine the role of gender-based pain expectations on the development of CPSP after cardiac surgery.

Health-related quality of life

Overwhelming evidence documents the deleterious impact of CPSP on health-related quality of life. [6-31, 50-62]

Cost of illness

We will examine the impact of CPSP on patient level-cost, calculated from a societal perspective, wherein all costs irrespective of payer are included thereby comprising private and public costs, using the Ambulatory Home Care Record. Data are available which indicate that from 20% to 30% of the occurrence of chronic pain is related to CPSP. [100, 101] Given the rates of cardiac surgery in Canada, [4, 5] literature has shown that CPSP contributes substantially to the $22.2 billion in direct and indirect costs borne by cardiovascular interventions and services annually. [15] With a view to comprehensive examination of the impact of CPSP, we will: a) estimate the extra cost, expressed in health care costs, for patients with CPSP compared to those without; and b) estimate an incremental cost-effectiveness ratio, i.e., the incremental cost for one additional quality-adjusted life year (QALY) gained, by virtue of cardiac surgery, among those

who develop CPSP compared to those who do not. QALY is a preference-based utility measure of health-related quality of life as perceived by the patient. [102, 103] QALYs incorporate both length of life and quality of life into a single measure and are calculated by combining health-related quality of life measures with data on health state duration. As such, QALY is the gold standard measure of effectiveness recommended for economic evaluation and represents a universally comparable outcome measure. QALY will be derived from our SF-12v2 data.

Study Objectives

Our primary objective is to examine the influence of pain-related beliefs and gender-based pain expectations on the development of chronic pain following cardiac surgery. Our secondary objectives and to a) examine the influence of pain-related beliefs and gender-based pain expectations on functional status and patient-level cost of illness following cardiac surgery; and b) to determine the impact of CPSP on the QALY borne by cardiac surgery, and the incremental cost for one additional QALY gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not.

METHODS AND ANALYSIS

Design

This study is a substudy of the Vascular Events In Surgery patIents cOhort evaluatioN - Cardiac Surgery study (https://clinicaltrials.gov/ct2/show/NCT01842568), examining 30 day all-cause mortality, myocardial injury, and related complications following cardiac surgery in 15,000 participants. In this substudy, we propose to prospectively follow a cohort of patients who have undergone cardiac surgery for one year. Data on potential predictors will be collected at baseline. The total follow-up period is 12 months, with pain, functional-status, and cost of illness-related data being collected at 6 and 12 months following cardiac surgery.

Patient and Public Involvement

We collected patient testimonials to articulate the nature of the chronic pain problem following cardiac surgery from the patient perspective and establish the need for this study. Following the completion of the study, we will debrief the patient panel with the results of our findings.

Study Population

The target population of 1,250 cardiac surgery patients will be recruited from participating hospital sites in Canada, The United States of America, and Hong Kong. Patients eligible for our study will be undergoing a first-time cardiac surgery involving a median sternotomy, including coronary artery bypass surgery (CABG) and all open heart procedures, such as valvular repairs/replacement. Eligible patients will also be able to read, speak and understand English and have a telephone allowing for follow-up. Patients will be ineligible if they: a) have undergone previous cardiac surgery, thoracotomy, or mastectomy, b) are scheduled for an isolated pericardial window procedure (due to malignancy), pericardectomy, permanent pacemaker, or defibrillator implantation, c) have a major cognitive disorder precluding participation, or d) have a hearing impairment or speech impediment precluding telephone-based follow up.

Cardiac surgery inpatients will be recruited in one of two ways: 1) from the hospital sites preoperative assessment clinic, if their surgery is pre-booked, or 2) from the cardiac surgical ward, if they have been admitted to hospital via the hospital's Emergency Department or the Heart Investigation Unit. A study nurse will obtain written, informed consent to participate among those willing and interested. The study enrollment period will conclude once the 1-year follow up telephone interview is complete.

Data Collection

Immediately following enrollment, standard baseline demographic, independent variable data (participants' age, sex, ethnicity, highest level of formal education, and marital and employment status) and data on baseline covariates (age and sex) will be collected by the study nurse via interview and chart audit. Post-operatively, the study nurse will collect data on surgical details via chart audit, and data on post-op day 3 cumulative analgesic dose and pain intensity scores via chart audit and \ participant interview, respectively. The study nurse will contact patients by phone at 30 days, and 6 and 12 months after surgery; the 30-day call will be for post-op pain monitoring, and the 2 subsequent calls will be for outcome assessment. Data on dependent variables will be measured at 6 and 12 months following cardiac surgery. Table 1 outlines this visit schedule. The timing of this follow up outcome measurement is in compliance with recommendations (2013) set forth by the Initiative for Methods, Measurement, and Pain

Assessment in Clinical Trials (IMMPACT) to standardize the timing of outcome assessment for prognostic studies of CPSP. [105]

Dependent variables

Chronic Post-Surgical Pain (CPSP)

The development of CPSP will be measured using a telephone structured interview protocol, defined as pain a) that developed after the surgical procedure, b) is different from pain experienced prior to the procedure (e.g. pre-op angina), c) is not be caused by other factors (e.g., cancer recurrence, chronic infection), d) is present for at least 2-3 months, and e) that interferes significantly with health-related quality of life. [34-40]

If participants answer in the affirmative to each of these questions, it will be indicated that 'Yes' they have developed CPSP; otherwise, it will be indicated that 'No' they have not. Among those deemed to have developed CPSP (i.e., 'yes') pain intensity, and its related interference with usual daily activities, will be measured via the Brief Pain Inventory-Short Form (BPI-SF). [105-109] The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measure "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), respectively, as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). As is common to studies of CPSP [28, 62, 67, 110-116] (including cardiac surgery), participants will be asked for their 'worst' pain intensity rating both upon rest and movement in the past 24 hrs. The BPI-SF interference subscale [105-109] will also be used, which measures the degree to which pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life (NRS for each item; 0=does not interfere, 10=completely interferes). A total interference score is taken by calculating the sum of these 7 items. The BPI-SF has strong psychometric properties with well-established reliability and validity across divergent surgical groups, [106-115, 117-122] including those reporting acute and chronic pain following cardiac surgery. [28, 62, 67, 112, 114-116] The BPI-SF also contains supplemental items, [105-109] for optional use (pain treatment, body diagram). Of these, only the body diagram will be used for descriptive purposes.

Functional status

Functional status will be measured with the Short-Form 12 version 2 (SF-12v2), an established reliable and validated health status measure. [123] It consists of 12 items taken from the SF-36, which is a widely accepted instrument that was developed from the Medical Outcomes Study. [124-126] The SF-12v2 was developed to reduce respondent burden. It can be administered by telephone interview and consists of two scales that measure physical and mental health status. The SF-12v2 comprises 8 domains, measured via 8 subscales: 1) physical functioning; 2) role limitations due to physical problems; 3) role limitations due to emotional problems; 4) bodily pain; 5) general health; 6) vitality; 7) social functioning; and 8) mental health. Results may be expressed as physical component summary (PCS) and mental component (MCS) summary scores. These scores range from 0 (worst) to 100 (best). [123]

Cost of illness

The Ambulatory and Home Care Record (AHCR) [127-137] will be used to measure patient-level cost of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers, such as family members and friends. Items in the AHCR can be categorized as publicly financed care (i.e., resources paid for by the public sector) or privately financed care (i.e., all out-of-pocket payments, third party insurance payments, and time costs incurred by caregiver). Face validity of the AHCR has been assessed by several health care providers, health economists, and administrators who work in the field of ambulatory and home-based care. [128 130] Reliability of the AHCR has been assessed via the level of agreement between self-reports of cost by cystic fibrosis care recipients and administrative data. [130] Moderate to almost perfect agreement was found between study participants' responses on the AHCR and administrative data (kappa=0.41-1.00). [130] The AHCR has since been used to evaluate various conditions, [129-137] including chronic cardiology patients who were interviewed over the phone. [136, 137] Additionally, the AHCR has been used to assess costs for an array of patients, including the elderly, middle-aged adults and children. [127-137] The AHCPR has been used in telephone and face-to-face interviews as well as in mailed form; it has been translated into several languages. [127-137]

Independent variables

Pain-related beliefs

Pain-related beliefs will be examined at baseline using the Pain Barriers Questionnaire (PBQ), [139 147] Version II (BQ-II). [148-152] The PBQ-II [148] includes 27 items divided into 4 subscales: erroneous beliefs regarding secondary effects of medication (12 items) and their harmful effects (6 items), fatalism about the control of pain (3 items), and attitudes regarding reporting pain to health professionals (6 items). Each item is rated on a 0 to 5 scale (0: totally disagree; 5: totally agree). A total score and scores for each subscale can be calculated by taking the sum of the items. The PBQ-II has established validity, internal consistency, and sensitivity to change, [116, 149, 151] and has recently been adapted and validated for use with cardiac surgical patients. [116]

Gender-based pain expectations

Gender-based pain expectations will be measured at baseline using the GREP. The GREP [89] measures stereotypic attributions regarding three constructs: pain endurance, pain sensitivity, and willingness to report of pain. Each construct includes four100-milimetre (mm) visual analog scales (VAS) regarding how women and men perceive themselves and the opposite sex, relative to a) their own sex, and b) the opposite sex with respect to how much pain can males/females endure, how sensitive to pain males/females are, and how willing males/females are to report pain; respondents indicate their views on a 100-mm line anchored by 0 (far less) and 100 (far more). An average score is derived for each construct; greater scores indicate more stereotypical views. The GREP has now been used in multiple pain investigations. [89, 91, 93-95, 152] Test-retest reliability is acceptable across items [89] (0.53 to 0.93) and internal consistency reliability testing has demonstrated high correlations (−0.71 to −0.81) between individual items which assess opposite perceived gender roles (e.g. typical masculine versus feminine orientation to pain endurance). [89]

Covariates

We will control for the following demographic, clinical and surgical covariates: sex, age, BMI, DM, PAD, pre- operative chronic pain and angina (Canadian Cardiovascular Society class), non-skeletonized ITA harvest, resternotomy, operating time. Additional covariates include baseline functional status, anxiety, and acute post-operative pain.

Functional status

We will control for baseline functional status using the SF12v2 PCS score. [123]

Baseline anxiety

We will control for anxiety at baseline using the Spielberger State-Trait Anxiety Inventory (STAI), a widely used, well-validated anxiety measure. [153-155] The STAI has forty items that comprise two domains; the State (STAI-S) and Trait (STAI-T) score, both ranging from 20 to 80, with higher scores representing higher levels of anxiety. The STAI-S measures the transitional emotional status evoked by a stressful situation, such as surgery. The STAI-T score reflects enduring individual differences in the likelihood of anxiety. [156] The STAI has been found reliable and valid among patients undergoing cardiac surgery (Cronbach's alpha = 0.94), [157] and is commonly applied in studies capturing preoperative anxiety among cardiac surgery patients. [158, 159]

Acute post-operative pain

Pain on post-op days 3 and 30 will be measured with the BPI. Cumulative 24-hour analgesic on post-op day 3, as an indication of analgesic dosing in hospital during recovery, will be determined via chart audit using a tool we have used in previous cardiac studies. [28, 62, 67] Opioid dosage will be converted into parenteral morphine-equivalents per day using standard dosage tables. [28, 62, 67]

Sample Size

The primary analysis for this study is the association of pain-related beliefs and gender-based pain expectations with CPSP at 6 and 12 month, while adjusting for a number of pre-specified covariates. Therefore, sample size was calculated based on the methods used by Hsieh and colleagues [160] for multivariable logistic regression. In this validated method, the sample size for a simple logistic regression modelling a single independent variable X_1 on the outcome is inflated by a variance inflation factor equal to $1 / (1-\rho_{2\ x2...xp})$, where $\rho_{2\ x2...xp}$ is equal to the proportion of the variance of X_1 explained by the regression relationship with $X_2...X_p$. [160] Additionally, sample size was inflated to account for the clustered nature of the data (i.e., 6 and 12 month measurements) by incorporating an additional design effect equivalent to 1+ (m-1)*ρICC, where m is the number of measurements per cluster (i.e., 2 time points) and ρICC represents the correlation of responses within clusters. A conservative scenario was assumed in

which the correlation between the two follow-up measurements could be as high as 0.60 and the variance of the independent variables explained by covariates (i.e., R_2) was 0.16, resulting in a requirement of 1250 participants to detect a significant change in the odds of post-operative pain of 5% (i.e., odds ratio of 1.05). This calculation allows the prevalence of CPSP to be as low as 10% (as found in some previous studies). Should the prevalence of CPSP be higher, the correlation between measurements be smaller, or the variance explained in the independent variables be smaller, 1,250 participants will provide > 80% power. [160]

Data Analyses

Categorical data (e.g., presence or absence of CPSP at 6 months and 1 year) will be summarized with frequencies and proportions. Continuous data (e.g., functional disability scores) will be evaluated for normality using Shapiro-Wilk tests of normality and summarized using measures of central tendency and dispersion (e.g., means and standard deviations for normally distributed factors and medians and interquartile ranges for non-normally distributed data). Generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-month and 1-year, while adjusting for pre-specified covariates. GEE models account for the lack of independence in outcome measurements introduced by multiple measurements. [161] We will enter all pre- specified variables in the model and retain them throughout the analysis. For each model the inclusion of an interaction term between the two independent variables of interest (pain belief scale and gender- based pain expectations) will be guided by 95% confidence intervals and likelihood ratio significance tests. Model diagnostics will consist of influential observation examination and Breslow-Day tests for goodness-of-fit. [162, 163] We will also assess for multi-collinearity in our model via assessment of condition indices. [162, 163]

Quality of adjusted life years (QALYs) [102, 103] will be estimated by converting SF-12v2 data collected in the study to utility score using a validated algorithm. [164] After estimating QALYs, we will analyze it as a dependent variable using regression to estimate the difference in expected QALYs between the two groups (i.e., those with CPSP versus those without). In addition, after calculating total cost from the AHCR, we will analyze it as a dependent variable using regression to estimate the difference in expected health care cost between the two groups (i.e., patients with

CPSP versus those without). Employing regression will allow for the adjustment of potential confounders. With a variety of different types of regression (i.e., ordinary least squares, generalized linear models), we will explore the impact of various modeling assumptions. In addition, we will compare parametric and non-parametric confidence intervals using bootstrapping. In theory, an ordinary least squares model produces unbiased estimates even if the data are skewed; however, different estimation methods (e.g., generalized linear models) and different uncertainty methods (e.g., non-parametric bootstrapping) will facilitate careful investigation of the impact that various assumptions have on our conclusions. [165-168] The regression models will provide estimates of differences in QALYs and costs for participants who develop CPSP versus those who do not develop CPSP, which will allow us to calculate incremental cost for one QALY gained. A cost-effectiveness acceptability curve and 95% confidence interval will be used to characterize the uncertainty of our findings. [168]

ETHICS AND DISSEMINATION

This protocol has been approved by the responsible bodies at each of the hospital sites. Both integrated and end-of-grant dissemination strategies will be implemented. Study progress and results will be disseminated on CardiacPain.Net, [169] a web-based pain resource centre (http://cardiacpain.onlinecjc.ca/) linked to Elsevier's global online readership, featuring active knowledge 'push' mechanisms including e-banner advertising and opt-in email blats. Final results will be presented at international conferences and published in scientific journals.

IMPLICATIONS

CPSP is an important socioeconomic problem with well-documented deleterious consequences on functional status for cardiac patients. We aim to investigate putative psychological risk factors that could be targeted for preventative intervention. We will also examine the economic consequences of CPSP comprehensively, including the impact on QALYs, with no additional data collection required. This study may contribute toward reducing the risk and impact of CPSP after cardiac surgery.

Authors' contributions: MM, PJD, JB, JCV, JK, AL, RW, SP, HC, SC, ND, HS, and NB contributed to the conception and design of the study. KB, JH, KG, and SH contribute to the

acquisition of data; data analyses and interpretation will be conducted by MHM, JB, PJD, SH, CO, PC, DG, JH, WI, JK, SI, JM, HC, GM, JCV, SY, JP, IG, MTVC, MC, JWW, KHQ, AM. MM, JB, JK, and PJD wrote the first draft of the protocol. JCV, JK, AL, MC, RW, SP, KB, HS, and JWW revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published. The authors wish to thank our patient advisors for their testimonials, which served to establish the need for this study.

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Competing interests:

MM and PJD are members of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions. Based on study questions, PJD has originated and grants he has written, he has received grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. PJD has participated in an consultancy advisory board meeting for Boehringer Ingelheim

SH, JB, CO, JK, MC, AL, RW, SP, JH, KG, KB, ND, SY, JP, DDS, IG, NB, HS, SLC, PCC, SE, WI, DG, JH, JK, JMD, GM, JCV, JWW, KHQ, AM, MC, HC have no competing interests to declare.

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Table 1. Visit Schedule

	Baseline	Post-op day 3	Day 30	6 Months	1 Year
Pain Barriers Questionnaire (PBQ)	X				
Gender Based Pain Expectations	X				
Somatic Pre-Occupation and Coping (SPOC)	X				
State-Trait Anxiety Inventory (STAI)	X				
Hospital Depression Scale (HADS-D)	X				
Short Form-12 (SF-12)	X		X	X	X
CPSP Related Disability	X			X	X
Analgesic Chart Audit		X			
Brief Pain Inventory (BPI)		X	X	X	X
Ambulatory Home Care Record (AHCR)				X	X

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Examination of psychological risk factors for chronic pain following cardiac surgery: Protocol for a prospective observational study

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Examination of psychological risk factors for chronic pain following cardiac surgery: Protocol for a prospective observational study

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ABSTRACT

Introduction: Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, and up to 56% will develop chronic post-surgical pain (CPSP). The primary aim of this study is to explore the association of pain-related beliefs and gender-based pain expectations on the development of CPSP. Secondary goals are to a) explore risk factors for poor functional status and patient-level cost of illness from a societal perspective up to 12 months following cardiac surgery; and b) determine the impact of CPSP on quality adjusted life years (QALY) borne by cardiac surgery, in addition to the incremental cost for one additional QALY gained, among those who develop CPSP compared to those who do not. **Methods and analyses**: In this prospective cohort study, 1,250 adults undergoing cardiac surgery, including coronary artery bypass grafting and open-heart procedures, will be recruited over a 3-year period. Putative risk factors for CPSP will be captured prior to surgery, at postoperative day 3 (in hospital) and 30 (at home). Outcome data will be collected via telephone interview at 6 and 12 months follow up. We will employ generalized estimating equations (GEE)
to model the primary (CPSP) and secondary outcomes (function and cost), while adjusting for pre-specified model covariates. Quality adjusted life years (QALYs) will be estimated by converting data from the Short Form-12(Version 2) to a utility score.

Ethics and dissemination: This protocol has been approved by the responsible bodies at each of the hospital sites and study enrollment began May 2015. We will disseminate our results through CardiacPain.Net, a web-based knowledge dissemination platform; presentation at international conferences, and publications in scientific journals.

Strengths and limitations of this study:

Strengths

- This is a prospective, multi-site study with a large cohort of cardiac surgery patients
- One year follow up is compliant with IMMPACT recommendations to standardize timing of outcome assessment for prognostic studies of CPSP.
- A robust analysis plan using generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-months and 1-year, while adjusting for pre-specified covariates.

- Assiduous follow up procedures will be adhered to, which have been proven effective in prior prospective observational studies

Limitations

- There is reliance on pain and quality of life self-report outcome measures, however rigorous criteria to define chronic post-surgical pain will be applied, and valid and reliable instruments will be used.

KEY WORDS: pain management, cardiac surgery, health economics

INTRODUCTION

Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, and these numbers are expected to rise as the population ages [1-5]. Despite the proven survival and symptom-related benefits of cardiac surgeries, mounting evidence suggests that chronic post-surgical pain (CPSP)—and related poor functional recovery—following these procedures are major clinical problems [6-31]. Moreover, the economic consequences of persistent pain and dysfunction remain uncertain. Identification of factors associated with the development of CPSP could facilitate efforts to improve outcomes among high risk patients, yet the majority of putative risk factors examined to date are not tenably modifiable in the perioperative context. Three psychological factors that do show promise as modifiable, potential risk factors for CPSP include pain-related beliefs, gender-based pain expectations, and somatic preoccupation and coping. The purpose of this study is to examine whether these factors are associated with transition to CPSP following cardiac surgery.

CPSP Following Cardiac Surgery

Due to conceptual and methodological differences in the assessment of pain, and conflicting opinions about the duration of "chronicity", there is no one accepted definition of CPSP [32]. However, there is consensus among experts, [32-38] that CPSP should meet the minimum criteria, set forth by Macrae and Davies [33] and others [34-40], as follows. It must a) have developed after the surgical procedure, b) be different from pain experienced prior to the procedure, c) not be caused by other factors (e.g., cancer recurrence, chronic infection), d) be present for at least 2-3 months, and e) interfere significantly with health-related quality of life [34-40].

Open cardiac surgeries involve many pain-sensitive structures, as they require a median sternotomy, retraction of the ribs, and invasion of muscles and visceral tissues. In coronary artery bypass surgery (CABG), the grafting procedure requires harvesting at several sites including, most commonly, the internal mammary artery (IMA). The manipulation and retraction of the sternum as well as the use of electrocautery to dissect the IMA from the chest wall may result in nerve damage that leads to intercostal neuralgia [41-44].The greater and lesser saphenous veins are also used as grafts in CABG surgery and require significant leg incisions. These procedures may result in pain that can last for variable periods, and may be inflammatory or neuropathic in

nature. CPSP in cardiac surgery patients is often experienced in the thorax and legs, but has also been described, to a lesser degree, in the shoulders, back, and neck [10, 12, 45]. The pathophysiological pathways underlying CPSP are multi-factorial. Tissue damage leads to release of high concentrations of bradykinin, adenosine, lactate, and potassium in the peripheral microenvironment, thereby causing nociceptor activation [46,47]. These mediators activate capsaicin sensitive TRVP1 receptors, which serve as the primary transducer of the noxious stimulus [47]. Other neurochemicals, such as the neuropeptides Substance P and calcitonin gene-related peptide, further augment pain [47]. These peripheral nociceptive processes, are modulated in the central nervous system by mechanisms involving selection, abstraction, and synthesis of information from the total sensory input [48]. The amount, quality, and nature of the pain experienced are therefore dynamic and multidimensional products of sensory-discriminative, cognitive-evaluative, and affective-motivational components [48]. Like any form of chronic pain, on-going pain after surgery can lead to pathological nervous system changes, collectively known as sensitization [47]—a function of what we now understand to be neuronal modifiability [46]. Sensitization of the nervous system may lead to increased pain sensitivity (hyperalgesia), augmentation of the normal duration (hyperpathia) amplitude of pain, perception of non-painful stimuli as painful (allodynia) [47,49], and abnormal, unpleasant hypersensitivity (dysesthesia) [50].

As Katz and Seltzer argued, [32] critical to understanding the nature of CPSP is appreciating that in each case, the pain was once acute and involved a transition phase. There is much work to be done to continue to develop our understanding of risk factors, which predispose cardiac surgical patients to pain chronicity.

Prevalence and consequences

We reviewed 26 published/under review studies to date, across 14 countries, [6-31] which have examined the prevalence and/or factors associated with CPSP following cardiac surgery. Upon careful examination of the available data, it is important to recognize that cross-sectional and retrospective studies have generally reported higher prevalence rates (14%-56%) than those investigations with prospective designs (7.5 - 45%). In the recent (2013), large-scale Canadian CARDpain study (n=1,010), Choinière, Watt-Watson et al. [28] reported CPSP prevalence rates

of 40%, 22%, and 17% at 3, 6, and 12 months following cardiac surgery, respectively. Routledge et al. (2009) [31] found similar prevalence rates of CPSP in their prospective extension (WREST-E) of a randomized clinical trial (WREST), (n=222) to examine the impact of a novel compression undergarment on women's recovery from median sternotomy (3 months post-op, 41%; 12 months post-op, 16.7%). In contrast to CARDpain and WREST-E, 1-year CPSP prevalence rates as high as 39% and 45% have been reported in prospective studies of patients following CABG in Turkey [27] and the Netherlands [30]. Aside from differences in study design, the observed variability in reported prevalence rates of CPSP after cardiac surgery may be explained by the use of point prevalence versus cumulative prevalence, variability with respect to the operational definitions of CPSP, timing of outcome measurement, and duration of follow up period.

CPSP has been associated with the development of anxiety and depressive disorders, [51-55] sleep disturbances and fatigue, [56-60] as well as poor self-rated health [7, 51, 53, 61]. For example, among those with CPSP in the CARDpain study, over 50% reported significant pain-related interference with activities of daily living—including family and home responsibilities, recreation, and employment—at 3, 6 and 12 months following cardiac surgery [28, 62].

Risk factors for CPSP

Several studies have attempted to establish risk factors for CPSP in cardiac surgery patients. Their limitations can be summarized [63] as: 1) many studies focused on univariate analyses, or were insufficiently powered to employ multivariate modeling techniques, 2) the vast majority of risk factors examined to date are not tenably modifiable in the peri-operative context, 3) psychological risk factors (affective and cognitive) are substantially understudied in comparison to demographic, clinical/surgical, and analgesic risk factors, constituting a major gap, 4) although retrospective and cross-sectional studies provide some insight on potential variables associated with CPSP, cross sectional studies lack the temporal orientation to make solid inferences about putative, causal relationships, and retrospective studies can be limited by availability and quality of data. In addition, even robust retrospective may be limited in terms of

risk factors explored and related data collection methods. Risk factors for CPSP can be classified into four categories: a) demographic, b) baseline clinical, technical-surgical, and hospitalization-related factors, c) acute post-operative pain, and d) psychological factors.

Demographic factors

Demographic factors examined include age, sex, level of education, body-mass index (BMI), and smoking history. Younger age has been positively associated with CPSP [7, 9, 12, 17, 20, 25, 28] in multiple retrospective, cross-sectional, and prospective studies, as observational data embedded within RCTs; significant odds ratios (OR) have ranged from 1.43-7.03 in cases where this outcome was dichotomized (i.e. younger vs. older patients). However, four of the more recent published studies to date (1 retrospective, [17] 1 cross-sectional, [18] 1 RCT, [50] 1 prospective [21]) have found no positive association between age and the development of CPSP. Conflicting findings have also been reported for sex. Although some studies indicate higher risk of CPSP with women, [21, 29, 30] multiple studies with divergent designs, [9, 12, 14, 18, 20, 28, 48] have reported no significant association between sex and the development of CPSP. Examination of BMI as a risk factor for CPSP has also produced mixed results. While two studies (1 cross-sectional, [7] 1 RCT (embedded observational data), [20] ORs =1.34 and 9.05, respectively) provided supportive evidence, other cross- sectional [17, 18] and prospective studies [9, 28] found no association between CPSP and BMI (OR range: 1.02-1.1). Finally, we are aware of 2 prospective studies to date which have examined the association of CPSP with formal level of education [28] and smoking history [14], respectively; no significant association was found in either case.

Baseline clinical, surgical and hospitalization-related factors

Among baseline clinical factors, neither a history of diabetes mellitus [9, 14, 17, 23, 24, 50] or peripheral arterial disease [24] have been significantly associated with the development of CPSP. However, pre-existing peripheral arterial disease has been examined as a risk factor in just one retrospective study [24] to date. Similar to diabetes mellitus, the majority of prospective studies [20, 21, 23] (including 1 RCT) [20] reported no predictive ability of baseline chronic pain conditions in the literature (OR=1.00-1.04, where reported). To date, CARDpain [28] is the only prospective examination to report that pre-existing chronic pain at baseline (non-anginal) is

positively associated with CPSP (adjusted OR=1.44, 95% confidence interval [CI]: 1.12 to 1.86) [28].

The evidence pertaining to the predictive value of pre-operative angina is also mixed. Two cross-sectional studies reported pre-operative angina that was positively associated with CPSP (OR, where reported=1.62) [7, 12] however, another cross-sectional [17] and two additional, large-scale prospective studies [14, 28] found no significant associations to infer that pre-operative angina is a significant risk factor for CPSP.

The majority of studies have reported no association [6, 12, 13, 17, 22, 28, 50] between a range of surgical factors, including a) type of surgical technique, b) number and type of bypass grafts per operation, c) harvesting technique, and d) total cross-clamp time (i.e., total time aorta is clamped to separate systemic circulation from cardiac outflow) and the development of CPSP. There is some evidence to suggest that not skeletonizing the internal thoracic artery harvest (i.e., harvesting it along with its surrounding pedicle of vascular tissue) is more likely to invoke CPSP; [64] those who have undergone left internal mammary artery harvesting may also be at higher risk. [13, 42] In general, post-operative complications and related adverse events (e.g., reoperation for bleeding, infections) have not been associated with CPSP, [9, 12, 14, 16, 20, 28] with the exception of 1 prospective study which identified postoperative re-sternotomy as a significant risk factor (OR=3.38). [21] Cardiac surgeries of longer duration (i.e. total OR time) [18, 20] also do not seem predictive of CPSP; in fact, the CARDpain [28] study found that the longer the OR time, the less likely CPSP was to develop. Finally, there seems to be no conclusive evidence to suggest that length of time in the ICU [18, 20, 28], or total duration of hospitalization [18] contribute to the development of CPSP after cardiac surgery.

Acute post-operative pain

Two prospective studies found that severe pain (i.e., Numeric Rating Scale ≥ 7/10) on postoperative (post-op) day 3 was a significant risk factor for CPSP at 1-year follow up, [21] as well as worst and average pain ratings at 2-years follow-up. [28] A third prospective study found that severe pain on post-op day 30 positively predicted CPSP at 3 months. [23] The association between analgesic therapy and CPSP is uncertain. [10, 11, 12, 18, 19, 21, 23, 27, 28]

Psychological factors

Only the CARDpain [28] study has examined the role of psychological risk factors in the development of CPSP and found that pre-surgical anxiety, as measured by the Hospital and Anxiety and Depression Scale (HADS-A), was a significant risk factor, with a 10% increase in the odds of developing CPSP for each unit increase in HADS-A scale scores (OR= 1.10, 95% CI, 1.06 to 1.14). Other psychological risk factors examined (catastrophizing, depression) demonstrated no association.

Genetic factors

Several members of this investigative team (e.g., Clarke, Katz,) are involved in studies investigating the influence of genetic polymorphisms on the development of CPSP after cardiac and other types of surgery. The science of pain genetics is evolving; investigations of this nature are complex, requiring extensive research infrastructure for genotyping and related proteomic methods. Controlling for the influence of genetic factors is beyond the scope this study.

Conceptual Underpinnings and Study Focus

To address the above noted gap in the research to date, our primary objective is to examine the potential influence of psychological factors on the development of CPSP after cardiac surgery. Clear justification for the specific putative risk factors to be measured requires that we first explicate the conceptual underpinnings of our study. Given the complexity of the multi-dimensional pain experience, there are many ways to conceptualize CPSP [65]. We are aligned with the bio-behavioural view of pain, espoused by international leaders in the science of the cognitive and learning aspects of pain, Flor and Turk [65, 66]. Fundamental to the bio-behavioural perspective is the assertion that people learn to predict future events based on prior learning experiences and information processing. As such, patients' behaviours elicit responses from significant others, including healthcare professionals, which can reinforce both adaptive and maladaptive modes of thinking, feeling and behaving. [65] With this understanding, patients' pain-related cognitions and behaviours are of chief concern with respect to identifying factors which may contribute to the transition from acute post-operative pain to chronic pain. In moving the science forward, we therefore give primacy to the cognitive-behavioural side of the global bio-behavioural view of pain, as the conceptual premise for our primary objective. According to the fundamental tenets of the cognitive-behavioural perspective of pain [65, 66]: a) behavior is

reciprocally determined by the person and environment, b) people can learn more adaptive ways of thinking and behaving, and c) people are capable of and should be involved as active agents in the change of maladaptive thoughts, amenable to intervention [65]. Our focus therefore will be on the contribution of patients' pain-related beliefs and expectations, as follows:

Pain-related beliefs

Decades of work [9, 67-82] in the fields of post-operative pain and anesthesia has demonstrated that surgical patients have beliefs about pain and pain medication, which a) are based on incorrect information, and b) serve to block effective pain assessment and management. For example, one study found that among patients undergoing CABG surgery (n= 202), a majority (83%) reported that they would not voluntarily ask for pain medication when they needed it, although most reported unrelieved moderate-to-severe pain from post-operative day 2 (80%) until day 5 (69%) [67]. As of 2013, data indicate that this unfortunate scenario remains largely unchanged. Cogan et al. [82] found that among cardiac surgery patients (n=564), 36% believed that "pain medication should be spared until the pain is very severe", 20% believed that "good patients do not speak of their pain", and 31% believed it is "very easy to become addicted to pain medication" while recovering from surgery. The particular role of these beliefs per se in the development of CPSP and has yet to be examined; we will do so in this study using the Pain Barriers Questionnaire (validated in multiple populations).

Gender-based pain expectations

As with a number of fields in the health sciences, the study of sex and gender, as they relate to pain, is evolving. Our comprehensive review of risk factors for CPSP after cardiac surgery revealed that thus far, investigation has been limited to the contribution of sex only as a risk factor. For the purposes of this study, we employ the following distinctions between sex and gender, set forth by Lips, [83] which have been adopted in a number of well-cited pain studies: [84-99] sex- the biologic distinction of being male or female; gender- learned masculinity or femininity, related to socially-constructed roles and behaviours attributed to men and women in society [83, 84].

Emerging evidence suggests that gender-based pain expectations defined as "Sex-related stereotypic attributions about pain sensitivity, pain endurance, and willingness to report pain"

[87] may lead to important differences in the experience of pain and related response. Robinson et al. were among the first to investigate gender-based pain expectations, using the Gender Role Expectations of Pain Questionnaire (GREP) [87]. Their study of pain cognitions in 156 men and 235 women found that men were perceived to be less willing to report pain than women, women were perceived to be more sensitive and less enduring of pain than men, and that men rated their pain endurance as higher than average. Further testing of the GREP by Wise et al. [94] found that after controlling for age, GREP scores accounted for 7%,11%, and 21% of the variance in pain threshold, tolerance, and pain unpleasantness scores, respectively, for women (n=87) and men (n=61) exposed to thermal testing. A recent meta-analysis by Alabas et al. (2012), for example, examined the role of gender-related cognitions in the experience of pain. [91] Pooling the results of 6 trials (406 men, 539 women), they found that those who considered themselves more masculine and less sensitive to pain, than the typical man, exhibited higher pain thresholds and tolerances in a variety of settings. Using the GREP, our study will be the first we know of to examine the role of gender-based pain expectations on the development of CPSP after cardiac surgery.

Health-related quality of life

Overwhelming evidence documents the deleterious impact of CPSP on health-related quality of life. [6-31, 50-62]

Cost of illness

We will examine the impact of CPSP on patient level-cost, calculated from a societal perspective, wherein all costs irrespective of payer are included thereby comprising private and public costs, using the Ambulatory Home Care Record. Data are available which indicate that from 20% to 30% of the occurrence of chronic pain is related to CPSP [98, 99]. Given the rates of cardiac surgery in Canada, [4, 5] literature has shown that CPSP contributes substantially to the $22.2 billion in direct and indirect costs borne by cardiovascular interventions and services annually [15]. With a view to comprehensive examination of the impact of CPSP, we will: a) estimate the extra cost, expressed in health care costs, for patients with CPSP compared to those without; and b) estimate an incremental cost-effectiveness ratio, i.e., the incremental cost for one additional quality-adjusted life year (QALY) gained, by virtue of cardiac surgery, among those

who develop CPSP compared to those who do not. QALY is a preference-based utility measure of health-related quality of life as perceived by the patient [100, 101]. QALYs incorporate both length of life and quality of life into a single measure and are calculated by combining health-related quality of life measures with data on health state duration. As such, QALY is the gold standard measure of effectiveness recommended for economic evaluation and represents a universally comparable outcome measure. QALY will be derived from our SF-12v2 data.

Study Objectives

Our primary objective is to examine the influence of pain-related beliefs and gender-based pain expectations on the development of chronic pain following cardiac surgery. Our secondary objectives and to a) examine the influence of pain-related beliefs and gender-based pain expectations on functional status and patient-level cost of illness following cardiac surgery; and b) to determine the impact of CPSP on the QALY borne by cardiac surgery, and the incremental cost for one additional QALY gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not.

METHODS AND ANALYSIS

Design

This study is a sub-study of the Vascular Events In Surgery patIents cOhort evaluatioN - Cardiac Surgery study (https://clinicaltrials.gov/ct2/show/NCT01842568), examining 30 day all-cause mortality, myocardial injury, and related complications following cardiac surgery in 15,000 participants. In this sub-study, we propose to prospectively follow a cohort of patients who have undergone cardiac surgery for one year. Data on potential predictors will be collected at baseline. The total follow-up period is 12 months, with pain, functional-status, and cost of illness-related data being collected at 6 and 12 months following cardiac surgery.

Patient and Public Involvement

We collected patient testimonials to articulate the nature of the chronic pain problem following cardiac surgery from the patient perspective and establish the need for this study. Following the completion of the study, we will debrief the patient panel with the results of our findings.

Study Population

The target population of 1,250 cardiac surgery patients will be recruited from participating hospital sites in Canada, The United States of America, and Hong Kong. Patients eligible for our study will be undergoing a first-time cardiac surgery involving a median sternotomy, including coronary artery bypass surgery (CABG) and all open heart procedures, such as valvular repairs/replacement. Eligible patients will also be able to read, speak and understand English and have a telephone allowing for follow-up. Patients will be ineligible if they: a) have undergone previous cardiac surgery, thoracotomy, or mastectomy, b) are scheduled for an isolated pericardial window procedure (due to malignancy), pericardectomy, permanent pacemaker, or defibrillator implantation, c) have a major cognitive disorder precluding participation, or d) have a hearing impairment or speech impediment precluding telephone-based follow up.

Cardiac surgery inpatients will be recruited in one of two ways: 1) from the hospital sites preoperative assessment clinic, if their surgery is pre-booked, or 2) from the cardiac surgical ward, if they have been admitted to hospital via the hospital's Emergency Department or the Heart Investigation Unit. A study nurse will obtain written, informed consent to participate among those willing and interested. The study enrollment period will conclude once the 1-year follow up telephone interview is complete.

Data Collection

Immediately following enrollment, standard baseline demographic, independent variable data (participants' age, sex, ethnicity, highest level of formal education, and marital and employment status) and data on baseline covariates (age and sex) will be collected by the study nurse via interview and chart audit. Post operatively, the study nurse will collect data on surgical details via chart audit, and data on post-op day 3 cumulative analgesic dose and pain intensity scores via chart audit and \ participant interview, respectively. The study nurse will contact patients by phone at 30 days, and 6 and 12 months after surgery; the 30-day call will be for post-op pain monitoring, and the 2 subsequent calls will be for outcome assessment. Data on dependent variables will be measured at 6 and 12 months following cardiac surgery. Table 1 outlines this visit schedule. The timing of this follow up outcome measurement is in compliance with recommendations (2013) set forth by the Initiative for Methods, Measurement, and Pain

Assessment in Clinical Trials (IMMPACT) to standardize the timing of outcome assessment for prognostic studies of CPSP [102].

Dependent variables

Chronic Post-Surgical Pain (CPSP)

The development of CPSP will be measured using a telephone structured interview protocol, defined as pain a) that developed after the surgical procedure, b) is different from pain experienced prior to the procedure (e.g. pre-op angina), c) is not be caused by other factors (e.g., cancer recurrence, chronic infection), d) is present for at least 2-3 months, and e) that interferes significantly with health-related quality of life [34-40].

If participants answer in the affirmative to each of these questions, it will be indicated that 'Yes' they have developed CPSP; otherwise, it will be indicated that 'No' they have not. Among those deemed to have developed CPSP (i.e., 'yes') pain intensity, and its related interference with usual daily activities, will be measured via the Brief Pain Inventory-Short Form (BPI-SF) [103-107].The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measure "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), respectively, as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). As is common to studies of CPSP [28, 29, 62, 67, 108-113] (including cardiac surgery), participants will be asked for their 'worst' pain intensity rating both upon rest and movement in the past 24 hrs. The BPI-SF interference subscale [103-107] will also be used, which measures the degree to which pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life (NRS for each item; 0=does not interfere, 10=completely interferes). A total interference score is taken by calculating the sum of these 7 items. The BPI-SF has strong psychometric properties with well-established reliability and validity across divergent surgical groups, [29, 103-117] including those reporting acute and chronic pain following cardiac surgery [28, 29, 62, 67, 112,113]. The BPI-SF also contains supplemental items, [103-106] for optional use (pain treatment, body diagram). Of these, only the body diagram will be used for descriptive purposes.

Functional status

Functional status will be measured with the Short-Form 12 version 2 (SF-12v2), an established reliable and validated health status measure [118]. It consists of 12 items taken from the SF-36, which is a widely accepted instrument that was developed from the Medical Outcomes Study. [119-121] The SF-12v2 was developed to reduce respondent burden. It can be administered by telephone interview and consists of two scales that measure physical and mental health status. The SF-12v2 comprises 8 domains, measured via 8 subscales: 1) physical functioning; 2) role limitations due to physical problems; 3) role limitations due to emotional problems; 4) bodily pain; 5) general health; 6) vitality; 7) social functioning; and 8) mental health. Results may be expressed as physical component summary (PCS) and mental component (MCS) summary scores. These scores range from 0 (worst) to 100 (best). [118]

Cost of illness

The Ambulatory and Home Care Record (AHCR) [122-132] will be used to measure patient-level cost of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers, such as family members and friends. Items in the AHCR can be categorized as publicly financed care (i.e., resources paid for by the public sector) or privately financed care (i.e., all out-of-pocket payments, third party insurance payments, and time costs incurred by caregiver). Face validity of the AHCR has been assessed by several health care providers, health economists, and administrators who work in the field of ambulatory and home-based care [122,125]. Reliability of the AHCR has been assessed via the level of agreement between self-reports of cost by cystic fibrosis care recipients and administrative data [125]. Moderate to almost perfect agreement was found between study participants' responses on the AHCR and administrative data (kappa=0.41-1.00) [125]. The AHCR has since been used to evaluate various conditions, [124-132] including chronic cardiology patients who were interviewed over the phone [131, 132] Additionally, the AHCR has been used to assess costs for an array of patients, including the elderly, middle-aged adults and children [122-132] The AHCPR has been used in telephone and face-to-face interviews as well as in mailed form; it has been translated into several languages [122-132].

Independent variables

Pain-related beliefs

Pain-related beliefs will be examined at baseline using the Pain Barriers Questionnaire (PBQ), [76, 77] Version II (BQ-II) [74, 76-79, 133] The PBQ-II [134] includes 27 items divided into 4 subscales: erroneous beliefs regarding secondary effects of medication (12 items) and their harmful effects (6 items), fatalism about the control of pain (3 items), and attitudes regarding reporting pain to health professionals (6 items). Each item is rated on a 0 to 5 scale (0: totally disagree; 5: totally agree). A total score and scores for each subscale can be calculated by taking the sum of the items. The PBQ-II has established validity, internal consistency, and sensitivity to change, [113, 135, 136] and has recently been adapted and validated for use with cardiac surgical patients [113].

Gender-based pain expectations

Gender-based pain expectations will be measured at baseline using the GREP. The GREP [87] measures stereotypic attributions regarding three constructs: pain endurance, pain sensitivity, and willingness to report of pain. Each construct includes four100-milimetre (mm) visual analog scales (VAS) regarding how women and men perceive themselves and the opposite sex, relative to a) their own sex, and b) the opposite sex with respect to how much pain can males/females endure, how sensitive to pain males/females are, and how willing males/females are to report pain; respondents indicate their views on a 100-mm line anchored by 0 (far less) and 100 (far more). An average score is derived for each construct; greater scores indicate more stereotypical views. The GREP has now been used in multiple pain investigations [87, 89, 91-93, 137,138]. Test-retest reliability is acceptable across items [87] (0.53 to 0.93) and internal consistency reliability testing has demonstrated high correlations (−0.71 to −0.81) between individual items which assess opposite perceived gender roles (e.g. typical masculine versus feminine orientation to pain endurance) [87].

Covariates

We will control for the following demographic, clinical and surgical covariates: sex, age, BMI, DM, PAD, pre- operative chronic pain and angina (Canadian Cardiovascular Society class), non-skeletonized ITA harvest, re-sternotomy, operating time. Additional covariates include baseline functional status, anxiety, and acute post-operative pain.

Functional status

We will control for baseline functional status using the SF12v2 PCS score [118].

Baseline anxiety

We will control for anxiety at baseline using the Spielberger State-Trait Anxiety Inventory (STAI), a widely used, well-validated anxiety measure [139,140]. The STAI has forty items that comprise two domains; the State (STAI-S) and Trait (STAI-T) score, both ranging from 20 to 80, with higher scores representing higher levels of anxiety. The STAI-S measures the transitional emotional status evoked by a stressful situation, such as surgery. The STAI-T score reflects enduring individual differences in the likelihood of anxiety [141]. The STAI has been found reliable and valid among patients undergoing cardiac surgery (Cronbach's alpha = 0.94), [142] and is commonly applied in studies capturing preoperative anxiety among cardiac surgery patients [143, 144].

Acute post-operative pain

Pain on post-op days 3 and 30 will be measured with the BPI. Cumulative 24-hour analgesic on post-op day 3, as an indication of analgesic dosing in hospital during recovery, will be determined via chart audit using a tool we have used in previous cardiac studies [28, 62, 67]. Opioid dosage will be converted into parenteral morphine-equivalents per day using standard dosage tables [28, 62, 67].

Sample Size

The primary analysis for this study is the association of pain-related beliefs and gender-based pain expectations with CPSP at 6 and 12 month, while adjusting for a number of pre-specified covariates. Therefore, sample size was calculated based on the methods used by Hsieh and colleagues [145] for multivariable logistic regression. In this validated method, the sample size for a simple logistic regression modelling a single independent variable X_1 on the outcome is inflated by a variance inflation factor equal to $1 / (1-\rho_{2\ x2...xp})$, where $\rho_{2\ x2...xp}$ is equal to the proportion of the variance of X_1 explained by the regression relationship with $X_2...X_p$. [145] Additionally, sample size was inflated to account for the clustered nature of the data (i.e., 6 and 12 month measurements) by incorporating an additional design effect equivalent to $1+ (m-1)*\rho ICC$, where m is the number of measurements per cluster (i.e., 2 time points) and ρICC represents the correlation of responses within clusters. A conservative scenario was assumed in

which the correlation between the two follow-up measurements could be as high as 0.60 and the variance of the independent variables explained by covariates (i.e., R_2) was 0.16, resulting in a requirement of 1250 participants to detect a significant change in the odds of post-operative pain of 5% (i.e., odds ratio of 1.05). This calculation allows the prevalence of CPSP to be as low as 10% (as found in some previous studies). Should the prevalence of CPSP be higher, the correlation between measurements be smaller, or the variance explained in the independent variables be smaller, 1,250 participants will provide > 80% power [145].

Data Analyses

Categorical data (e.g., presence or absence of CPSP at 6 months and 1 year) will be summarized with frequencies and proportions. Continuous data (e.g., functional disability scores) will be evaluated for normality using Shapiro-Wilk tests of normality and summarized using measures of central tendency and dispersion (e.g., means and standard deviations for normally distributed factors and medians and interquartile ranges for non-normally distributed data). Generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-month and 1-year, while adjusting for pre-specified covariates. GEE models account for the lack of independence in outcome measurements introduced by multiple measurements [146]. We will enter all pre- specified variables in the model and retain them throughout the analysis. For each model the inclusion of an interaction term between the two independent variables of interest (pain belief scale and gender- based pain expectations) will be guided by 95% confidence intervals and likelihood ratio significance tests. Model diagnostics will consist of influential observation examination and Breslow-Day tests for goodness-of-fit [147,148]. We will also assess for multi-collinearity in our model via assessment of condition indices [147,148].

Quality of adjusted life years (QALYs) [100, 101] will be estimated by converting SF-12v2 data collected in the study to utility score using a validated algorithm [149]. After estimating QALYs, we will analyze it as a dependent variable using regression to estimate the difference in expected QALYs between the two groups (i.e., those with CPSP versus those without). In addition, after calculating total cost from the AHCR, we will analyze it as a dependent variable using regression to estimate the difference in expected health care cost between the two groups (i.e., patients with

CPSP versus those without). Employing regression will allow for the adjustment of potential confounders. With a variety of different types of regression (i.e., ordinary least squares, generalized linear models), we will explore the impact of various modeling assumptions. In addition, we will compare parametric and non-parametric confidence intervals using bootstrapping. In theory, an ordinary least squares model produces unbiased estimates even if the data are skewed; however, different estimation methods (e.g., generalized linear models) and different uncertainty methods (e.g., non-parametric bootstrapping) will facilitate careful investigation of the impact that various assumptions have on our conclusions [150-153]. The regression models will provide estimates of differences in QALYs and costs for participants who develop CPSP versus those who do not develop CPSP, which will allow us to calculate incremental cost for one QALY gained. A cost-effectiveness acceptability curve and 95% confidence interval will be used to characterize the uncertainty of our findings [153].

ETHICS AND DISSEMINATION

This protocol has been approved by the responsible bodies at each of the hospital sites. Both integrated and end-of-grant dissemination strategies will be implemented. Study progress and results will be disseminated on CardiacPain.Net, [154] a web-based pain resource centre (http://cardiacpain.onlinecjc.ca/) linked to Elsevier's global online readership, featuring active knowledge 'push' mechanisms including e-banner advertising and opt-in email blats. Final results will be presented at international conferences and published in scientific journals.

IMPLICATIONS

CPSP is an important socioeconomic problem with well-documented deleterious consequences on functional status for cardiac patients. We aim to investigate putative psychological risk factors that could be targeted for preventative intervention. We will also examine the economic consequences of CPSP comprehensively, including the impact on QALYs, with no additional data collection required. This study may contribute toward reducing the risk and impact of CPSP after cardiac surgery.

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and SH contribute to the acquisition of data; data analyses and interpretation will be conducted by MHM, JB, PJD, SH, CO, PCC, SE, DG, JH, WI, JKa, SI, JM, HC, GM, JCV, SY, JP, IG, MTVC, MC, JWW, KHQ, AM. MM, JB, JKh, and PJD wrote the first draft of the protocol. JCV, JKa, AL, MC, RW, SP, KB, HS, and JWW revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published. The authors wish to thank our patient advisors for their testimonials, which served to establish the need for this study.

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Competing interests:

MM and PJD are members of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions. Based on study questions, PJD has originated and grants he has written, he has received grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. PJD has participated in an consultancy advisory board meeting for Boehringer Ingelheim

SH, JB, CO, JKa, MC, AL, RW, SP, JH, KG, KB, ND, SY, JP, DDS, IG, NB, HS, SLC, PCC, SE, WI, DG, JH, JKh, JMD, GM, JCV, JWW, KHQ, AM, MC, HC have no competing interests to declare.

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Table 1. Visit Schedule

	Baseline	Post-op day 3	Day 30	6 Months	1 Year
Pain Barriers Questionnaire (PBQ)	X				
Gender Based Pain Expectations	X				
Somatic Pre-Occupation and Coping (SPOC)	X				
State-Trait Anxiety Inventory (STAI)	X				
Hospital Depression Scale (HADS-D)	X				
Short Form-12 (SF-12)	X		X	X	X
CPSP Related Disability	X			X	X
Analgesic Chart Audit		X			
Brief Pain Inventory (BPI)		X	X	X	X
Ambulatory Home Care Record (AHCR)				X	X

Examination of psychological risk factors for chronic pain following cardiac surgery: Protocol for a prospective observational study

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ABSTRACT

Introduction: Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, and up to 56% will develop chronic post-surgical pain (CPSP). The primary aim of this study is to explore the association of pain-related beliefs and gender-based pain expectations on the development of CPSP. Secondary goals are to a) explore risk factors for poor functional status and patient-level cost of illness from a societal perspective up to 12 months following cardiac surgery; and b) determine the impact of CPSP on quality adjusted life years (QALY) borne by cardiac surgery, in addition to the incremental cost for one additional QALY gained, among those who develop CPSP compared to those who do not. **Methods and analyses**: In this prospective cohort study, 1,250 adults undergoing cardiac surgery, including coronary artery bypass grafting and open-heart procedures, will be recruited over a 3-year period. Putative risk factors for CPSP will be captured prior to surgery, at postoperative day 3 (in hospital) and 30 (at home). Outcome data will be collected via telephone interview at 6 and 12 months follow up. We will employ generalized estimating equations (GEE)
to model the primary (CPSP) and secondary outcomes (function and cost), while adjusting for pre-specified model covariates. Quality adjusted life years (QALYs) will be estimated by converting data from the Short Form-12(Version 2) to a utility score.

Ethics and dissemination: This protocol has been approved by the responsible bodies at each of the hospital sites and study enrollment began May 2015. We will disseminate our results through CardiacPain.Net, a web-based knowledge dissemination platform; presentation at international conferences, and publications in scientific journals.

Strengths and limitations of this study:

Strengths

- This is a prospective, multi-site study with a large cohort of cardiac surgery patients
- One year follow up is compliant with IMMPACT recommendations to standardize timing of outcome assessment for prognostic studies of CPSP.
- A robust analysis plan using generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-months and 1-year, while adjusting for pre-specified covariates.

- Assiduous follow up procedures will be adhered to, which have been proven effective in prior prospective observational studies

Limitations

- There is reliance on pain and quality of life self-report outcome measures, however rigorous criteria to define chronic post-surgical pain will be applied, and valid and reliable instruments will be used.

KEY WORDS: pain management, cardiac surgery, health economics

INTRODUCTION

Approximately 400,000 Americans and 36,000 Canadians undergo cardiac surgery annually, and these numbers are expected to rise as the population ages [1-5]. Despite the proven survival and symptom-related benefits of cardiac surgeries, mounting evidence suggests that chronic post-surgical pain (CPSP)—and related poor functional recovery—following these procedures are major clinical problems [6-31]. Moreover, the economic consequences of persistent pain and dysfunction remain uncertain. Identification of factors associated with the development of CPSP could facilitate efforts to improve outcomes among high risk patients, yet the majority of putative risk factors examined to date are not tenably modifiable in the perioperative context. Three psychological factors that do show promise as modifiable, potential risk factors for CPSP include pain-related beliefs, gender-based pain expectations, and somatic preoccupation and coping. The purpose of this study is to examine whether these factors are associated with transition to CPSP following cardiac surgery.

CPSP Following Cardiac Surgery

Due to conceptual and methodological differences in the assessment of pain, and conflicting opinions about the duration of "chronicity", there is no one accepted definition of CPSP [32]. However, there is consensus among experts, [32-38] that CPSP should meet the minimum criteria, set forth by Macrae and Davies [33] and others [34-40], as follows. It must a) have developed after the surgical procedure, b) be different from pain experienced prior to the procedure, c) not be caused by other factors (e.g., cancer recurrence, chronic infection), d) be present for at least 2-3 months, and e) interfere significantly with health-related quality of life [34-40].

Open cardiac surgeries involve many pain-sensitive structures, as they require a median sternotomy, retraction of the ribs, and invasion of muscles and visceral tissues. In coronary artery bypass surgery (CABG), the grafting procedure requires harvesting at several sites including, most commonly, the internal mammary artery (IMA). The manipulation and retraction of the sternum as well as the use of electrocautery to dissect the IMA from the chest wall may result in nerve damage that leads to intercostal neuralgia [41-44]. The greater and lesser saphenous veins are also used as grafts in CABG surgery and require significant leg incisions. These procedures may result in pain that can last for variable periods, and may be inflammatory or neuropathic in

nature. CPSP in cardiac surgery patients is often experienced in the thorax and legs, but has also been described, to a lesser degree, in the shoulders, back, and neck [10, 12, 45]. The pathophysiological pathways underlying CPSP are multi-factorial. Tissue damage leads to release of high concentrations of bradykinin, adenosine, lactate, and potassium in the peripheral microenvironment, thereby causing nociceptor activation [46,47]. These mediators activate capsaicin sensitive TRVP1 receptors, which serve as the primary transducer of the noxious stimulus [47]. Other neurochemicals, such as the neuropeptides Substance P and calcitonin gene-related peptide, further augment pain [47]. These peripheral nociceptive processes, are modulated in the central nervous system by mechanisms involving selection, abstraction, and synthesis of information from the total sensory input [48]. The amount, quality, and nature of the pain experienced are therefore dynamic and multidimensional products of sensory-discriminative, cognitive-evaluative, and affective-motivational components [48]. Like any form of chronic pain, on-going pain after surgery can lead to pathological nervous system changes, collectively known as sensitization [47]—a function of what we now understand to be neuronal modifiability [46]. Sensitization of the nervous system may lead to increased pain sensitivity (hyperalgesia), augmentation of the normal duration (hyperpathia) amplitude of pain, perception of non-painful stimuli as painful (allodynia) [47,49], and abnormal, unpleasant hypersensitivity (dysesthesia) [50].

As Katz and Seltzer argued, [32] critical to understanding the nature of CPSP is appreciating that in each case, the pain was once acute and involved a transition phase. There is much work to be done to continue to develop our understanding of risk factors, which predispose cardiac surgical patients to pain chronicity.

Prevalence and consequences

We reviewed 26 published/under review studies to date, across 14 countries, [6-31] which have examined the prevalence and/or factors associated with CPSP following cardiac surgery. Upon careful examination of the available data, it is important to recognize that cross-sectional and retrospective studies have generally reported higher prevalence rates (14%-56%) than those investigations with prospective designs (7.5 - 45%). In the recent (2013), large-scale Canadian CARDpain study (n=1,010), Choinière, Watt-Watson et al. [28] reported CPSP prevalence rates

of 40%, 22%, and 17% at 3, 6, and 12 months following cardiac surgery, respectively. Routledge et al. (2009) [31] found similar prevalence rates of CPSP in their prospective extension (WREST-E) of a randomized clinical trial (WREST), (n=222) to examine the impact of a novel compression undergarment on women's recovery from median sternotomy (3 months post-op, 41%; 12 months post-op, 16.7%). In contrast to CARDpain and WREST-E, 1-year CPSP prevalence rates as high as 39% and 45% have been reported in prospective studies of patients following CABG in Turkey [27] and the Netherlands ~~.~~ [30]. Aside from differences in study design, the observed variability in reported prevalence rates of CPSP after cardiac surgery may be explained by the use of point prevalence versus cumulative prevalence, variability with respect to the operational definitions of CPSP, timing of outcome measurement, and duration of follow up period.

CPSP has been associated with the development of anxiety and depressive disorders, [51-55] sleep disturbances and fatigue, [56-60] as well as poor self-rated health ~~.~~ [7, 51, 53, 61]. For example, among those with CPSP in the CARDpain study, over 50% reported significant ~~bodily pain~~ pain-related interference with activities of daily living—including family and home responsibilities, recreation, and employment—at 3, 6 and 12 months following cardiac surgery~~.~~ [28, 62].

Risk factors for CPSP

Several studies have attempted to establish risk factors for CPSP in cardiac surgery patients. Their limitations can be summarized [63] as: 1) many studies focused on univariate analyses, or were insufficiently powered to employ multivariate modeling techniques, 2) the vast majority of risk factors examined to date are not tenably modifiable in the peri-operative context, 3) psychological risk factors (affective and cognitive) are substantially understudied in comparison to demographic, clinical/surgical, and analgesic risk factors, constituting a major gap, 4) although retrospective and cross-sectional studies provide some insight on potential variables associated with CPSP, cross sectional studies lack the temporal orientation to make solid inferences about putative, causal relationships, and retrospective studies can be limited by availability and quality of data. In addition, even robust retrospective may be limited in terms of

risk factors explored and related data collection methods. Risk factors for CPSP can be classified into four categories: a) demographic, b) baseline clinical, technical-surgical, and hospitalization-related factors, c) acute post-operative pain, and d) psychological factors.

Demographic factors

Demographic factors examined include age, sex, level of education, body-mass index (BMI), and smoking history. Younger age has been positively associated with CPSP [7, 9, 12, 17, 20, 25, 28] in multiple retrospective, cross-sectional, and prospective studies, as observational data embedded within RCTs; significant odds ratios (OR) have ranged from 1.43-7.03 in cases where this outcome was dichotomized (i.e. younger vs. older patients). However, four of the more recent published studies to date (1 retrospective, [~~18~~17] 1 cross-sectional, [18~~30~~] 1 RCT, [50] 1 prospective [21]) have found no positive association between age and the development of CPSP. Conflicting findings have also been reported for sex. Although some studies indicate higher risk of CPSP with women, [21, 29, 30] multiple studies with divergent designs, [9, 12, 14, ~~48,~~ 18, 20, 28, 48] have reported no significant association between sex and the development of CPSP. Examination of BMI as a risk factor for CPSP has also produced mixed results. While two studies (1 cross-sectional, [7] 1 RCT (embedded observational data), [20] ORs =1.34 and 9.05, respectively) provided supportive evidence, other cross- sectional [17, 18] and prospective studies [9, 28] found no association between CPSP and BMI (OR range: 1.02-1.1). Finally, we are aware of 2 prospective studies to date which have examined the association of CPSP with formal level of education [28] and smoking history [14], respectively; no significant association was found in either case.

Baseline clinical, surgical and hospitalization-related factors

Among baseline clinical factors, neither a history of diabetes mellitus [9, 14, 17, 23, 24, 50] or peripheral arterial disease [24] have been significantly associated with the development of CPSP. However, pre-existing peripheral arterial disease has been examined as a risk factor in just one retrospective study [24] to date. Similar to diabetes mellitus, the majority of prospective studies [20, 21, 23] (including 1 RCT) [20] reported no predictive ability of baseline chronic pain conditions in the literature (OR=1.00-1.04, where reported). To date, CARDpain [28] is the only prospective examination to report that pre-existing chronic pain at baseline (non-anginal) is

positively associated with CPSP (adjusted OR=1.44, 95% confidence interval [CI]: 1.12 to 1.86) [28].

The evidence pertaining to the predictive value of pre-operative angina is also mixed. Two cross-sectional studies reported pre-operative angina that was positively associated with CPSP (OR, where reported=1.62) [7, 12] however, another cross-sectional [17] and two additional, large-scale prospective studies [14, 28] found no significant associations to infer that pre-operative angina is a significant risk factor for CPSP.

The majority of studies have reported no association [6, 12, 13, 17, 22, 28, 50] between a range of surgical factors, including a) type of surgical technique, b) number and type of bypass grafts per operation, c) harvesting technique, and d) total cross-clamp time (i.e., total time aorta is clamped to separate systemic circulation from cardiac outflow) and the development of CPSP. There is some evidence to suggest that not skeletonizing the internal thoracic artery harvest (i.e., harvesting it along with its surrounding pedicle of vascular tissue) is more likely to invoke CPSP; [64] those who have undergone left internal mammary artery harvesting may also be at higher risk. [13, 42] In general, post-operative complications and related adverse events (e.g., reoperation for bleeding, infections) have not been associated with CPSP, [9, 12, 14, 16, 20, 28] with the exception of 1 prospective study which identified postoperative re-sternotomy as a significant risk factor (OR=3.38). [21] Cardiac surgeries of longer duration (i.e. total OR time) [18, 20] also do not seem predictive of CPSP; in fact, the CARDpain [28] study found that the longer the OR time, the less likely CPSP was to develop. Finally, there seems to be no conclusive evidence to suggest that length of time in the ICU [18, 20, 28], or total duration of hospitalization [18] contribute to the development of CPSP after cardiac surgery.

Acute post-operative pain

Two prospective studies found that severe pain (i.e., Numeric Rating Scale ≥ 7/10) on postoperative (post-op) day 3 was a significant risk factor for CPSP at 1-year follow up, [21] as well as worst and average pain ratings at 2-years follow-up. [28] A third prospective study found that severe pain on post-op day 30 positively predicted CPSP at 3 months. [23] The association between analgesic therapy and CPSP is uncertain. [10, 11, 12, 18, 19, 21, 23, 27, 28]

Psychological factors

Only the CARDpain [28] study has examined the role of psychological risk factors in the development of CPSP and found that pre-surgical anxiety, as measured by the Hospital and Anxiety and Depression Scale (HADS-A), was a significant risk factor, with a 10% increase in the odds of developing CPSP for each unit increase in HADS-A scale scores (OR= 1.10, 95% CI, 1.06 to 1.14). Other psychological risk factors examined (catastrophizing, depression) demonstrated no association.

Genetic factors

Several members of this investigative team (e.g., Clarke, Katz,) are involved in studies investigating the influence of genetic polymorphisms on the development of CPSP after cardiac and other types of surgery. The science of pain genetics is evolving; investigations of this nature are complex, requiring extensive research infrastructure for genotyping and related proteomic methods. Controlling for the influence of genetic factors is beyond the scope this study.

Conceptual Underpinnings and Study Focus

To address the above noted gap in the research to date, our primary objective is to examine the potential influence of psychological factors on the development of CPSP after cardiac surgery. Clear justification for the specific putative risk factors to be measured requires that we first explicate the conceptual underpinnings of our study. Given the complexity of the multi-dimensional pain experience, there are many ways to conceptualize CPSP [65]. We are aligned with the bio-behavioural view of pain, espoused by international leaders in the science of the cognitive and learning aspects of pain, Flor and Turk [65, 66]. Fundamental to the bio-behavioural perspective is the assertion that people learn to predict future events based on prior learning experiences and information processing. As such, patients' behaviours elicit responses from significant others, including healthcare professionals, which can reinforce both adaptive and maladaptive modes of thinking, feeling and behaving. [65] With this understanding, patients' pain-related cognitions and behaviours are of chief concern with respect to identifying factors which may contribute to the transition from acute post-operative pain to chronic pain. In moving the science forward, we therefore give primacy to the cognitive-behavioural side of the global bio-behavioural view of pain, as the conceptual premise for our primary objective. According to the fundamental tenets of the cognitive-behavioural perspective of pain [65, 66]: a) behavior is

reciprocally determined by the person and environment, b) people can learn more adaptive ways of thinking and behaving, and c) people are capable of and should be involved as active agents in the change of maladaptive thoughts, amenable to intervention [65]. Our focus therefore will be on the contribution of patients' pain-related beliefs and expectations, as follows:

Pain-related beliefs

Decades of work [9, 67-824] in the fields of post-operative pain and anesthesia has demonstrated that surgical patients have beliefs about pain and pain medication, which a) are based on incorrect information, and b) serve to block effective pain assessment and management. For example, one study found that among patients undergoing CABG surgery (n= 202), a majority (83%) reported that they would not voluntarily ask for pain medication when they needed it, although most reported unrelieved moderate-to-severe pain from post-operative day 2 (80%) until day 5 (69%) [67]. As of 2013, data indicate that this unfortunate scenario remains largely unchanged. Cogan et al. [824] found that among cardiac surgery patients (n=564), 36% believed that "pain medication should be spared until the pain is very severe", 20% believed that "good patients do not speak of their pain", and 31% believed it is "very easy to become addicted to pain medication" while recovering from surgery. The particular role of these beliefs per se in the development of CPSP and has yet to be examined; we will do so in this study using the Pain Barriers Questionnaire (validated in multiple populations).

Gender-based pain expectations

As with a number of fields in the health sciences, the study of sex and gender, as they relate to pain, is evolving. Our comprehensive review of risk factors for CPSP after cardiac surgery revealed that thus far, investigation has been limited to the contribution of sex only as a risk factor. For the purposes of this study, we employ the following distinctions between sex and gender, set forth by Lips, [835] which have been adopted in a number of well-cited pain studies: [846-99101] sex- the biologic distinction of being male or female; gender- learned masculinity or femininity, related to socially-constructed roles and behaviours attributed to men and women in society [835, 846].

Emerging evidence suggests that gender-based pain expectations defined as "Sex-related stereotypic attributions about pain sensitivity, pain endurance, and willingness to report pain"

[879] may lead to important differences in the experience of pain and related response. Robinson et al. were among the first to investigate gender-based pain expectations, using the Gender Role Expectations of Pain Questionnaire (GREP) [879]. Their study of pain cognitions in 156 men and

235 women found that men were perceived to be less willing to report pain than women, women were perceived to be more sensitive and less enduring of pain than men, and that men rated their pain endurance as higher than average. Further testing of the GREP by Wise et al. [946] found that after controlling for age, GREP scores accounted for 7%,11%, and 21% of the variance in pain threshold, tolerance, and pain unpleasantness scores, respectively, for women (n=87) and men (n=61) exposed to thermal testing. A recent meta-analysis by Alabas et al. (2012), for example, examined the role of gender-related cognitions in the experience of pain. [913] Pooling the results of 6 trials (406 men, 539 women), they found that those who considered themselves more masculine and less sensitive to pain, than the typical man, exhibited higher pain thresholds and tolerances in a variety of settings. Using the GREP, our study will be the first we know of to examine the role of gender-based pain expectations on the development of CPSP after cardiac surgery.

Health-related quality of life

Overwhelming evidence documents the deleterious impact of CPSP on health-related quality of life. [6-31, 50-62]

Cost of illness

We will examine the impact of CPSP on patient level-cost, calculated from a societal perspective, wherein all costs irrespective of payer are included thereby comprising private and public costs, using the Ambulatory Home Care Record. Data are available which indicate that from 20% to 30% of the occurrence of chronic pain is related to CPSP [98100, 99101]. Given the rates of cardiac surgery in Canada, [4, 5] literature has shown that CPSP contributes substantially to the $22.2 billion in direct and indirect costs borne by cardiovascular interventions and services annually [15]. With a view to comprehensive examination of the impact of CPSP, we will: a)

estimate the extra cost, expressed in health care costs, for patients with CPSP compared to those without; and b) estimate an incremental cost-effectiveness ratio, i.e., the incremental cost for one additional quality-adjusted life year (QALY) gained, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not. QALY is a preference-based utility measure of health-related quality of life as perceived by the patient. [1002, 1013]. QALYs incorporate both length of life and quality of life into a single measure and are calculated by combining health- related quality of life measures with data on health state duration. As such, QALY is the gold standard measure of effectiveness recommended for economic evaluation and represents a universally comparable outcome measure. QALY will be derived from our SF-12v2 data.

Study Objectives

Our primary objective is to examine the influence of pain-related beliefs and gender-based pain expectations on the development of chronic pain following cardiac surgery. Our secondary objectives and to a) examine the influence of pain-related beliefs and gender-based pain expectations on functional status and patient-level cost of illness following cardiac surgery; and b) to determine the impact of CPSP on the QALY borne by cardiac surgery, and the incremental cost for one additional QALY gained for patients, by virtue of cardiac surgery, among those who develop CPSP compared to those who do not.

METHODS AND ANALYSIS

Design

This study is a sub-study of the Vascular Events In Surgery patIents cOhort evaluatioN - Cardiac Surgery study (https://clinicaltrials.gov/ct2/show/NCT01842568), examining 30 day all-cause mortality, myocardial injury, and related complications following cardiac surgery in 15,000 participants. In this sub-study, we propose to prospectively follow a cohort of patients who have undergone cardiac surgery for one year. Data on potential predictors will be collected at baseline. The total follow-up period is 12 months, with pain, functional-status, and cost of illness-related data being collected at 6 and 12 months following cardiac surgery.

Patient and Public Involvement

We collected patient testimonials to articulate the nature of the chronic pain problem following cardiac surgery from the patient perspective and establish the need for this study. Following the completion of the study, we will debrief the patient panel with the results of our findings.

Study Population

The target population of 1,250 cardiac surgery patients will be recruited from participating hospital sites in Canada, The United States of America, and Hong Kong. Patients eligible for our study will be undergoing a first-time cardiac surgery involving a median sternotomy, including coronary artery bypass surgery (CABG) and all open heart procedures, such as valvular repairs/replacement. Eligible patients will also be able to read, speak and understand English and have a telephone allowing for follow-up. Patients will be ineligible if they: a) have undergone previous cardiac surgery, thoracotomy, or mastectomy, b) are scheduled for an isolated pericardial window procedure (due to malignancy), pericardectomy, permanent pacemaker, or defibrillator implantation, c) have a major cognitive disorder precluding participation, or d) have a hearing impairment or speech impediment precluding telephone-based follow up.

Cardiac surgery inpatients will be recruited in one of two ways: 1) from the hospital sites preoperative assessment clinic, if their surgery is pre-booked, or 2) from the cardiac surgical ward, if they have been admitted to hospital via the hospital's Emergency Department or the Heart Investigation Unit. A study nurse will obtain written, informed consent to participate among those willing and interested. The study enrollment period will conclude once the 1-year follow up telephone interview is complete.

Data Collection

Immediately following enrollment, standard baseline demographic, independent variable data (participants' age, sex, ethnicity, highest level of formal education, and marital and employment status) and data on baseline covariates (age and sex) will be collected by the study nurse via interview and chart audit. Post-operatively, the study nurse will collect data on surgical details via chart audit, and data on post-op day 3 cumulative analgesic dose and pain intensity scores via chart audit and \ participant interview, respectively. The study nurse will contact patients by phone at 30 days, and 6 and 12 months after surgery; the 30-day call will be for post-op pain

monitoring, and the 2 subsequent calls will be for outcome assessment. Data on dependent variables will be measured at 6 and 12 months following cardiac surgery. Table 1 outlines this visit schedule. The timing of this follow up outcome measurement is in compliance with recommendations (2013) set forth by the Initiative for Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to standardize the timing of outcome assessment for prognostic studies of CPSP [10245].

Dependent variables

Chronic Post-Surgical Pain (CPSP)

The development of CPSP will be measured using a telephone structured interview protocol, defined as pain a) that developed after the surgical procedure, b) is different from pain experienced prior to the procedure (e.g. pre-op angina), c) is not be caused by other factors (e.g., cancer recurrence, chronic infection), d) is present for at least 2-3 months, and e) that interferes significantly with health-related quality of life [34-40].

If participants answer in the affirmative to each of these questions, it will be indicated that 'Yes' they have developed CPSP; otherwise, it will be indicated that 'No' they have not. Among those deemed to have developed CPSP (i.e., 'yes') pain intensity, and its related interference with usual daily activities, will be measured via the Brief Pain Inventory-Short Form (BPI-SF) [10345-107 1089]. The BPI-SF includes four 11-point numeric rating scales (NRS) of pain intensity, which measure "average", "least", and "worst" pain intensity in the past 24 hours (hrs.), respectively, as well as pain intensity "now" (0= no pain, 10= pain as bad as you can imagine). As is common to studies of CPSP [28, 29, 62, 67, 108110-1136] (including cardiac surgery), participants will be asked for their 'worst' pain intensity rating both upon rest and movement in the past 24 hrs. The BPI-SF interference subscale [1035-1079] will also be used, which measures the degree to which pain interferes with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life (NRS for each item; 0=does not interfere, 10=completely interferes). A total interference score is taken by calculating the sum of these 7 items. The BPI-SF has strong psychometric properties with well-established reliability and validity across divergent surgical groups, [29, 103-117107, 109 106- 115, 117-122] including those reporting acute and chronic pain following cardiac surgery [28, 29, 62, 67, 112, 112,1134-

116]. The BPI-SF also contains supplemental items, [10345-10689] for optional use (pain treatment, body diagram). Of these, only the body diagram will be used for descriptive purposes.

Functional status

Functional status will be measured with the Short-Form 12 version 2 (SF-12v2), an established reliable and validated health status measure .-[11823]. It consists of 12 items taken from the SF-36, which is a widely accepted instrument that was developed from the Medical Outcomes Study. [124-126119-121] The SF-12v2 was developed to reduce respondent burden. It can be administered by telephone interview and consists of two scales that measure physical and mental health status. The SF-12v2 comprises 8 domains, measured via 8 subscales: 1) physical functioning; 2) role limitations due to physical problems; 3) role limitations due to emotional problems; 4) bodily pain; 5) general health; 6) vitality; 7) social functioning; and 8) mental health. Results may be expressed as physical component summary (PCS) and mental component (MCS) summary scores. These scores range from 0 (worst) to 100 (best). [11823]

Cost of illness

The Ambulatory and Home Care Record (AHCR) [1227-1327] will be used to measure patient-level cost of illness from a societal perspective. This approach gives equal consideration to health system costs and costs borne by patients and unpaid caregivers, such as family members and friends. Items in the AHCR can be categorized as publicly financed care (i.e., resources paid for by the public sector) or privately financed care (i.e., all out-of-pocket payments, third party insurance payments, and time costs incurred by caregiver). Face validity of the AHCR has been assessed by several health care providers, health economists, and administrators who work in the field of ambulatory and home-based care. [122,8-12530]. Reliability of the AHCR has been assessed via the level of agreement between self-reports of cost by cystic fibrosis care recipients and administrative data [125. [130]. Moderate to almost perfect agreement was found between study participants' responses on the AHCR and administrative data (kappa=0.41-1.00). [130125]. The AHCR has since been used to evaluate various conditions, [12429-1327] including chronic cardiology patients who were interviewed over the phone .-[1316, 1327] Additionally, the AHCR has been used to assess costs for an array of patients, including the elderly, middle-aged adults

and children .-[1227-1327] The AHCPR has been used in telephone and face-to-face interviews as well as in mailed form; it has been translated into several languages. [127-137] [122-132].

Independent variables

Pain-related beliefs

Pain-related beliefs will be examined at baseline using the Pain Barriers Questionnaire (PBQ), [139-14776,77] Version II (BQ-II) [74,. [148-152 76-79, 133] The PBQ-II [13448] includes 27 items divided into 4 subscales: erroneous beliefs regarding secondary effects of medication (12 items) and their harmful effects (6 items), fatalism about the control of pain (3 items), and attitudes regarding reporting pain to health professionals (6 items). Each item is rated on a 0 to 5 scale (0: totally disagree; 5: totally agree). A total score and scores for each subscale can be calculated by taking the sum of the items. The PBQ-II has established validity, internal consistency, and sensitivity to change, [1136, 13549, 13651] and has recently been adapted and validated for use with cardiac surgical patients .-[1136].

Gender-based pain expectations

Gender-based pain expectations will be measured at baseline using the GREP. The GREP [879] measures stereotypic attributions regarding three constructs: pain endurance, pain sensitivity, and willingness to report of pain. Each construct includes four100-milimetre (mm) visual analog scales (VAS) regarding how women and men perceive themselves and the opposite sex, relative to a) their own sex, and b) the opposite sex with respect to how much pain can males/females endure, how sensitive to pain males/females are, and how willing males/females are to report pain; respondents indicate their views on a 100-mm line anchored by 0 (far less) and 100 (far more). An average score is derived for each construct; greater scores indicate more stereotypical views. The GREP has now been used in multiple pain investigations. [879, 8991, 913-935, 13752] Test-retest reliability is acceptable across items [879] (0.53 to 0.93) and internal consistency reliability testing has demonstrated high correlations (−0.71 to −0.81) between individual items which assess opposite perceived gender roles (e.g. typical masculine versus feminine orientation to pain endurance). [879].

Covariates

We will control for the following demographic, clinical and surgical covariates: sex, age, BMI, DM, PAD, pre- operative chronic pain and angina (Canadian Cardiovascular Society class), non-skeletonized ITA harvest, resternotomy, operating time. Additional covariates include baseline functional status, anxiety, and acute post-operative pain.

Functional status

We will control for baseline functional status using the SF12v2 PCS score [118. [123].

Baseline anxiety

We will control for anxiety at baseline using the Spielberger State-Trait Anxiety Inventory (STAI), a widely used, well-validated anxiety measure .[13853-14055]. The STAI has forty items that comprise two domains; the State (STAI-S) and Trait (STAI-T) score, both ranging from 20 to 80, with higher scores representing higher levels of anxiety. The STAI-S measures the transitional emotional status evoked by a stressful situation, such as surgery. The STAI-T score reflects enduring individual differences in the likelihood of anxiety. [14156] The STAI has been found reliable and valid among patients undergoing cardiac surgery (Cronbach's alpha = 0.94), [14257] and is commonly applied in studies capturing preoperative anxiety among cardiac surgery patients .[14358, 14459].

Acute post-operative pain

Pain on post-op days 3 and 30 will be measured with the BPI. Cumulative 24-hour analgesic on post-op day 3, as an indication of analgesic dosing in hospital during recovery, will be determined via chart audit using a tool we have used in previous cardiac studies. [28, 62, 67]. Opioid dosage will be converted into parenteral morphine-equivalents per day using standard dosage tables .[28, 62, 67].

Sample Size

The primary analysis for this study is the association of pain-related beliefs and gender-based pain expectations with CPSP at 6 and 12 month, while adjusting for a number of pre-specified covariates. Therefore, sample size was calculated based on the methods used by Hsieh and colleagues [14560] for multivariable logistic regression. In this validated method, the sample size for a simple logistic regression modelling a single independent variable X_1 on the outcome is

inflated by a variance inflation factor equal to 1 / (1-$\rho_{2\ x2...xp}$), where $\rho_{2\ x2...xp}$ is equal to the proportion of the variance of X_1 explained by the regression relationship with $X_2...X_p$. [14560] Additionally, sample size was inflated to account for the clustered nature of the data (i.e., 6 and 12 month measurements) by incorporating an additional design effect equivalent to 1+ (m-1)*ρICC, where m is the number of measurements per cluster (i.e., 2 time points) and ρICC represents the correlation of responses within clusters. A conservative scenario was assumed in which the correlation between the two follow-up measurements could be as high as 0.60 and the variance of the independent variables explained by covariates (i.e., R_2) was 0.16, resulting in a requirement of 1250 participants to detect a significant change in the odds of post-operative pain of 5% (i.e., odds ratio of 1.05). This calculation allows the prevalence of CPSP to be as low as 10% (as found in some previous studies). Should the prevalence of CPSP be higher, the correlation between measurements be smaller, or the variance explained in the independent variables be smaller, 1,250 participants will provide > 80% power. [14560]

Data Analyses

Categorical data (e.g., presence or absence of CPSP at 6 months and 1 year) will be summarized with frequencies and proportions. Continuous data (e.g., functional disability scores) will be evaluated for normality using Shapiro-Wilk tests of normality and summarized using measures of central tendency and dispersion (e.g., means and standard deviations for normally distributed factors and medians and interquartile ranges for non-normally distributed data). Generalized estimating equations (GEE) will be used to model the primary analysis: the association between pain-related beliefs and gender-based pain expectations with the development of CPSP at 6-month and 1-year, while adjusting for pre-specified covariates. GEE models account for the lack of independence in outcome measurements introduced by multiple measurements. [14661]. We will enter all pre- specified variables in the model and retain them throughout the analysis. For each model the inclusion of an interaction term between the two independent variables of interest (pain belief scale and gender- based pain expectations) will be guided by 95% confidence intervals and likelihood ratio significance tests. Model diagnostics will consist of influential observation examination and Breslow-Day tests for goodness-of-fit [147,148. [162, 163]. We will also assess for multi-collinearity in our model via assessment of condition indices [147,148]. [162, 163]

Quality of adjusted life years (QALYs) [1002, 1013] will be estimated by converting SF-12v2 data collected in the study to utility score using a validated algorithm [149. [164]. After estimating QALYs, we will analyze it as a dependent variable using regression to estimate the difference in expected QALYs between the two groups (i.e., those with CPSP versus those without). In addition, after calculating total cost from the AHCR, we will analyze it as a dependent variable using regression to estimate the difference in expected health care cost between the two groups (i.e., patients with CPSP versus those without). Employing regression will allow for the adjustment of potential confounders. With a variety of different types of regression (i.e., ordinary least squares, generalized linear models), we will explore the impact of various modeling assumptions. In addition, we will compare parametric and non-parametric confidence intervals using bootstrapping. In theory, an ordinary least squares model produces unbiased estimates even if the data are skewed; however, different estimation methods (e.g., generalized linear models) and different uncertainty methods (e.g., non-parametric bootstrapping) will facilitate careful investigation of the impact that various assumptions have on our conclusions . [165-168150-153]. The regression models will provide estimates of differences in QALYs and costs for participants who develop CPSP versus those who do not develop CPSP, which will allow us to calculate incremental cost for one QALY gained. A cost-effectiveness acceptability curve and 95% confidence interval will be used to characterize the uncertainty of our findings . [15368].

ETHICS AND DISSEMINATION

This protocol has been approved by the responsible bodies at each of the hospital sites. Both integrated and end-of-grant dissemination strategies will be implemented. Study progress and results will be disseminated on CardiacPain.Net, [15469] a web-based pain resource centre (http://cardiacpain.onlinecjc.ca/) linked to Elsevier's global online readership, featuring active knowledge 'push' mechanisms including e-banner advertising and opt-in email blats. Final results will be presented at international conferences and published in scientific journals.

IMPLICATIONS

CPSP is an important socioeconomic problem with well-documented deleterious consequences on functional status for cardiac patients. We aim to investigate putative psychological risk factors that could be targeted for preventative intervention. We will also examine the economic consequences of CPSP comprehensively, including the impact on QALYs, with no additional data collection required. This study may contribute toward reducing the risk and impact of CPSP after cardiac surgery.

Authors' contributions: MM, PJD, JB, JCV, JKa, AL, RW, SP, HC, SC, ND, HS, and NB contributed to the conception and design of the study. KB, JH, KG, DDS and SH contribute to the acquisition of data; data analyses and interpretation will be conducted by MHM, JB, PJD, SH, CO, PC, DG, JH, WI, JKa, SI, JM, HC, GM, JCV, SY, JP, IG, MTVC, MC, JWW, KHQ, AM. MM, JB, JKh, and PJD wrote the first draft of the protocol. JCV, JKa, AL, MC, RW, SP, KB, HS, and JWW revised the protocol critically for important intellectual content. All authors have read and approved the final version of the manuscript to be published. The authors wish to thank our patient advisors for their testimonials, which served to establish the need for this study.

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Competing interests:

MM and PJD are members of a research group with a policy of not accepting honorariums or other payments from industry for their own personal financial gain. They do accept honorariums/payments from industry to support research endeavours and costs to participate in meetings. Based on study questions. Based on study questions, PJD has originated and grants he has written, he has received grants from Abbott Diagnostics, Boehringer Ingelheim, Covidien, Octapharma, Philips Healthcare, Roche Diagnostics and Stryker. PJD has participated in an consultancy advisory board meeting for Boehringer Ingelheim

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	Baseline	Post-op day 3	Day 30	6 Months	1 Year
Pain Barriers Questionnaire (PBQ)	X				
Gender Based Pain Expectations	X				
Somatic Pre-Occupation and Coping (SPOC)	X				
State-Trait Anxiety Inventory (STAI)	X				
Hospital Depression Scale (HADS-D)	X				
Short Form-12 (SF-12)	X		X	X	X
CPSP Related Disability	X			X	X
Analgesic Chart Audit		X			
Brief Pain Inventory (BPI)		X	X	X	X
Ambulatory Home Care Record (AHCR)				X	X

Table 1. Visit Schedule