Chronic pain after surgery time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies

Chronic Pain After Surgery

Time for Standardization? A Framework to Establish Core Risk Factor and Outcome Domains for Epidemiological Studies

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Introduction and Objectives: Many studies have reported putative factors for the development of chronic pain after surgery. However, advances in knowledge about the etiology and prognosis of chronic postsurgical pain (CPSP) could be gained by improving methodology within studies of surgical pain. The purpose of this study was to review predictive factors and to propose core risk factor and outcome domains for inclusion in future epidemiological studies investigating CPSP.

Methods: Using the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials as a framework we reviewed risk factor and outcome domains, methodological issues and standardized measurement tools based on findings from narrative and systematic reviews, primary clinical and epidemiological studies and published guidelines for chronic pain clinical trials.

Results: Five "core" risk factor domains (demographic, pain, clinical, surgery-related, and psychological) and 4 outcome domains (pain, physical functioning, psychological functioning, and global ratings of outcome) were identified. Important methodological issues, related to the definition and timing of follow-up to assess transition from acute to chronic pain are discussed. We also propose the use of validated, standardized measurement tools to capture risk factor and outcome domains at multiple time points.

Discussion: There is potential to advance the field of CPSP research by striving for consensus among pain experts; this would advance current evidence by improving our ability to compare findings from different studies and would facilitate the aggregation of surgical cohort datasets to allow international comparisons. We propose these findings as a starting point to build a comprehensive framework for epidemiological studies investigating chronic pain after surgery.

Key Words: postoperative pain (MeSH subgroup epidemiology), pain measurement, surgery, risk factors, outcome assessment

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CHRONIC PAIN AFTER SURGERY

Acute postoperative pain is one of the most common complications associated with delayed recovery and discharge from hospital.[1] The prevalence of chronic postsurgical pain (CPSP), defined as pain persisting longer than 3 months after surgery, can be high especially after inguinal hernia surgery (30%) or thoracic surgery (50%).[2,3] CPSP adversely affects quality of life and delays return to usual activity.[2,4–8] Despite improvements in knowledge and awareness about the epidemiology and burden of disease from CPSP, less is known about risk factors for development or processes contributing to the transition from acute to chronic pain after surgery.[9]

Although the literature is extensive, conclusive evidence about the etiology and accurate prediction of patients most likely to develop CPSP is lacking. Recent narrative and systematic reviews have highlighted variation in definitions for CPSP, methodological differences in preoperative and postoperative assessment, and timing and conduct of follow-up.[10,11] Surgical epidemiological studies often lack data on preoperative health and pain status, or are limited by small patient samples from single surgical centers, with variation in measurement of predictor and outcome variables. These methodological shortcomings hamper our ability to combine findings across studies and limit accurate conclusions about definitive risk factors for CPSP. Lack of conclusive evidence about patient subgroups most at risk may ultimately delay the development of interventions to prevent or minimize the impact of CPSP. Other international groups have convened to agree on standardized measures for inclusion within pain studies.[12,13] The objectives of this review are to synthesize current evidence on risk factors for CPSP, to align CPSP-related outcomes with those proposed in the Initiative for Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT), and to initiate a process to develop a standardized approach to data collection of patient-reported and clinical outcomes for future epidemiological studies of CPSP.

MATERIALS AND METHODS

Search Strategy

A systematic search was undertaken to identify studies investigating predictors of chronic pain after any surgical procedure. Initial exploratory searches were undertaken on major bibliometric databases to identify medical subject headings (MeSH) and keywords relating to general surgical procedures and a subgroup of specific procedures (eg, inguinal hernia, breast cancer surgery, and orthopedic procedures). Given the breadth of the surgical postoperative pain literature, this strategy was revised to identify systematic and

narrative reviews focusing on predictors of pain-related outcomes after surgery. Studies eligible for inclusion were systematic and narrative reviews that examined the role and quantification of preoperative and intraoperative factors on the development of postoperative pain with a follow-up period of at least 3 months after surgery, as per the International Association for the Study of Pain (IASP) definition for chronic pain.[14] Studies only reporting pain prevalence were excluded (eg, cross-sectional surveys), as were those with postoperative follow-up of <3 months. Searches were undertaken on MEDLINE and EMBASE using different combinations of the following MeSH terms and textwords: chronic pain; postoperative pain; chronic postoperative pain; surgery; general surgery; surg$.tw; risk factor$,tw; predictive factor$,tw; predict$.tw. A predesigned filter was applied to identify review articles (review; meta-analysis; meta-analys$; systematic adj5 review$; integrative research review, etc.). Articles published between 1966 and 2010, in English, German, French, or Dutch languages were eligible for inclusion; duplicate abstracts were removed. Twenty review articles were identified and critically appraised, of which 15 satisfied the criteria of including preoperative predictive factors for CPSP. Of the 15 included articles, 8 studies reviewed risk factors for surgical procedures in general,[3,9,10,15–19] 5 studies concerned specific surgical procedures (ie, lumbar disk surgery,[20,21] thoracic surgery,[22,23] and hysterectomy[24]), and 2 articles reviewed the predictive power of preoperative experimental pain testing.[25,26]

The most recently published systematic reviews included searches for primary studies published up to 2007. We therefore conducted an additional search to identify primary studies of CPSP, with follow-up of at least 3 months, published between 2007 and 2010. This additional search was conducted to identify whether "new" risk factors had been reported in recent studies (not already identified from previous reviews, etc.). This search identified 218 abstracts of primary studies investigating chronic pain after surgery; of these 163 were excluded because of nonprospective design, did not have the required length of follow-up or did not investigate risk factors for CPSP. A total of 55 primary studies were shortlisted for inclusion and critically appraised (search strategies and full bibliography available from authors on request). In our final proposed core set, we only included risk factors that were repeatedly reported in the review papers or that were identified as a significant predictor in at least 2 primary studies published since 2007.

RESULTS

Risk Factors for CPSP

We have organized the findings of our literature review of risk factors for CPSP using the following 5 domains: demographic, pain, clinical, surgery-related, and psychological. These domains were derived from review papers reporting multidimensional risk factors.[3,9,16,19,24,27,28] Two additional risk domains have been reported in the CPSP literature: genetic predisposition and preoperative response to experimentally induced pain.[9,25,26] These factors have already been comprehensively reviewed and although we acknowledge their importance, they are beyond the scope of the present study. Genetics and laboratory-based experimentally induced pain are specialist topic areas that use different methodologies and in general, use standardized measurement tools and outcomes that differ from the patient-completed questionnaires used in epidemiological studies of CPSP.

Demographic Factors

Multiple demographic factors have been investigated as risk factors for CPSP, including age, sex, education, marital status, socioeconomic status, and lifestyle factors (ie, smoking). Younger age is one of the most consistently reported factors associated with increased risk of development of CPSP[3,15]; however, 1 recent primary study found increased prevalence of CPSP after knee arthroscopy in patients over 50 years.[29] Education and lower socioeconomic status have also been identified as risk factors for CPSP.[21,24] There is mixed evidence for sex, employment status, marital status, and workers compensation.[3,9,15,16,20,21] Few studies have explored lifestyle factors; although 1 recent study found smoking to be associated with a poor recovery after surgery for sciatica.[30]

Pain

Presence of preoperative pain, either at the site or unrelated to the site of surgery, and duration of preoperative pain, are predictive for the development and persistence of CPSP.[3,9,15,16,21,24] One of the most consistent predictors of CPSP is the presence of severe acute pain in the first week after surgery.[3,9,15,16] Location and character of the pain is important to establish whether pain assessed at follow-up is a continuation of an existing pain problem (prevalent pain), or whether it is a new pain condition (incident CPSP).

Clinical Factors

Recent primary studies identified medical comorbidity[31] and number of preoperative comorbidities[32,33] as being predictive of pain-related outcomes. In addition, preoperative disability is associated with outcome, especially in terms of persisting disability.[20,21,32] The evidence for height, weight, and body mass index (BMI) is conflicting; some primary studies report an association[34,35] but others examining BMI as a risk factor for CPSP find no association.[8,36]

Surgery-related Factors

The following relevant surgery-related factors were identified as increasing the risk of CPSP: longer duration of surgery[9,15] and specific surgical techniques used (eg, open vs. laparoscopic surgery, type of implant).[3,9,15,16] These factors may be related to the extent of surgical trauma or inflammatory processes.[9] Mixed evidence is found for the role of the anesthetic (eg, regional anesthesia) and analgesic regimens (eg, preemptive analgesia, epidural analgesia)[3,15,16,24] and for experience of the surgeon.[9,15,16]

Psychological Factors

Psychological factors include both cognitive (eg, how patients think about their pain) and emotional (eg, what patients feel) functioning. Several review papers have provided evidence for the role of depression as an important predictive factor for CPSP.[10,17,20,24] There is also good evidence for the role of trait anxiety and specific surgical fears in CPSP, with higher preoperative anxiety and/or surgical fear increasing the risk of persistent CPSP.[9,20,21,32,37–39] Other factors identified less frequently included somatization/hypochondriasis,[20,21] avoidant coping,[20,21] psychological vulnerability/neuroticism,[10,16] and low expectation of

return to work.[40] More recently, pain catastrophizing has been studied as a risk factor for CPSP and was reported by 1 review as a potential predictor of persistent pain.[9] Recent primary studies give additional evidence for pain catastrophizing as a risk factor for CPSP after knee arthroplasty[33,41–43] and shoulder surgery.[44]

Core Outcomes in CPSP Studies

The overview of pain-related outcomes pertinent to CPSP studies was guided by the IMMPACT guidelines, which recognizes the multidimensional nature of chronic pain and provides recommendations for selected core outcome domains for inclusion within clinical trials investigating efficacy of chronic pain treatments.[13] We present our findings using the following 4 domains selected from IMMPACT: pain, physical function, psychological function, and global ratings of outcome,[13] plus a fifth domain which we have added to cover other factors specifically relevant to CPSP. We reviewed the most relevant constructs within these broader domains and considered their applicability for future epidemiological studies of CPSP.

Pain

Measurement of pain intensity/severity is recommended by the IMMPACT group. Other recommended pain outcomes include pain quality, temporal aspects of pain, and usage of rescue analgesia.[45] For CPSP, routine analgesia usage might also be an important outcome to consider. Pain quality and character is particularly important for the surgical population as it can elucidate the characteristics of CPSP which may be important for treatment, for example, whether neuropathic or nociceptive pain. Many studies have demonstrated that at least some CPSP is neuropathic in character.[6,36,46] Obtaining information on pain location can clarify whether CPSP is located adjacent to or distant from the surgical site and is useful when determining attribution.

Physical Functioning

The degree to which pain interferes with activity of daily living and adversely affects functioning is an important component of chronic pain. Moreover, there is much evidence that pain severity and physical functioning are only modestly associated.[47] The IMMPACT recommends inclusion of disease specific as well as generic measures of physical functioning.[45] Generic measures of physical functioning and/or pain interference would allow comparisons across surgical procedures and different indications, whereas disease-specific instruments would capture outcomes relevant to specific surgical procedures (eg, in the case of lumbar spine or breast cancer surgery).

Psychological Functioning

The IMMPACT recommendations for outcomes of pain treatment studies have stressed the importance of emotional functioning and recommend capturing depression as a core outcome.[45] In addition, they recommend a more general assessment of emotional well-being. No recommendations regarding cognitive functioning are made by IMMPACT although pain may also negatively affect this aspect of psychological functioning.[48] However, reliable assessment of cognitive functioning requires a comprehensive battery of tests which is beyond the scope of most epidemiological studies.

Global Ratings of Outcome

A global rating of improvement or satisfaction in clinical trials is recommended by IMMPACT. A global rating gives participants the opportunity to aggregate the various components of their condition (pain, physical, and emotional functioning) into 1 overall score.[45] For studies of CPSP, a global assessment of overall recovery from the operation or satisfaction with the procedure would be a suitable alternative.

Other Relevant Outcomes

Other important outcomes listed in the IMMPACT recommendation include adverse effects and complications.[13,45] Complications during the perioperative and postoperative periods may confound the relationship between risk factor and outcome (eg, surgical site infection and further surgery). Other potential relevant outcomes include health care use[49] and work-related variables.[12]

DISCUSSION

Chronic pain after surgery has received considerable attention recently yet there is no agreement regarding the definition or measurement of risk factors and pain-related outcomes. The purpose of this study was to conduct an overall review of factors predictive of CPSP and to identify potential risk factor and outcome domains for inclusion in future prospective epidemiological studies investigating surgical pain. Findings from narrative and systematic reviews, recent primary studies and published guidelines for chronic pain clinical trials (IMMPACT) were reviewed and critically appraised. On the basis of the results of our review and consideration of the IMMPACT recommendations, we propose core risk factor and outcome domains as a basis for discussion by the CPSP community. Other research groups may build upon these recommendations and expand upon risk factors or particular aspects of CPSP, for example, measurement of pain quality and character. We discuss key domains based on factors most frequently identified in our literature review and list some potential measurement tools for consideration in future CPSP studies. We also discuss important methodological issues relating to the definition, timing, and measurement of chronic pain after surgery. Table 1 presents a proposed data collection schedule for future epidemiological studies investigating pain after surgery.

Proposed Core Set

Pain

At the simplest level, pain intensity can be captured using a visual analogue scale or a numerical rating scale.[50] More comprehensive assessments of preoperative and postoperative pain, at rest and on movement, can be captured using other standardized tools, such as the Brief Pain Inventory[51] or Short Form McGill Pain Questionnaire.[52] For the immediate, acute, postoperative period, visual analogue scale or numerical rating scale could be used to measure pain intensity at rest and on movement.[53] Assessments should be made on multiple days (ie, up to 1 week) after surgery and at multiple times during the day. For assessment of neuropathic pain, one of several neuropathic pain scales could be used, such as the Douleur Neuropathique 4 Questions, Neuropathic Pain Scale, Self-report Leeds Assessment of Neuropathic Signs and Symptoms , or other similar tool.[54–56] Patients identified as potentially having

TABLE 1. Proposed Domains, Constructs, and Measurement Tools for Inclusion in Future Studies of CPSP

Domain	Construct	Timing			Potential Measurement Tools/Source
		Preoperative	Perioperative/ Acute	Chronic	
Demographic	Age	✓			
	Sex	✓			
	Education	✓			Clinical record BPI-LF
	Marital status (circumstance of living)	✓			
	Employment status	✓			
Pain	Intensity and character	✓	✓*	✓	VAS, NRS, BPI-LF and SF, SF-MPQ, DN4, NPS, S-LANSS
	Location (at or remote to surgical site)	✓	✓	✓	
	Duration	✓	✓	✓	
Clinical factors	Comorbidities	✓			
	BMI	✓			Clinical record SF-36
	Disability	✓		✓	
Surgery related	Duration of surgery		✓		
	Surgical technique		✓		
	Analgesia regimen	✓	✓		Clinical record
	Anesthesia		✓		
	Complications		✓		
Psychological†	Depression	✓		✓	
	Anxiety/surgical worry/fear	✓			CES-D and STAI or HADS, PCS, SF-36
	Pain catastrophizing	✓			
Physical functioning		✓		✓	SF-36, BPI, or MPI interference scale
Global ratings of outcome				✓	GSR

*Includes in the first week postoperatively.
†Includes emotional and cognitive.
BPI-LF indicates Brief Pain Inventory-Long Form; BPI-SF, Brief Pain Inventory-Short Form; CES-D, Center for Epidemiologic Studies Depression Scale; DN4, Douleur Neuropatique 4 Questionnaire; GSR, Global Surgical Recovery; HADS, Hospital Anxiety Depression Scale; MPI, Multidimensional Pain Inventory; NPS, Neuropathic Pain Scale; NRS, numeric rating scale; PCS, Pain Catastrophizing Scale; SF-36, Short-Form 36 Health Survey; SF-MPQ, Short Form McGill Pain Questionnaire; S-LANSS, Self-report Leeds Assessment of Neuropathic Signs and Symptoms; STAI, State Trait Anxiety Inventory; VAS, visual analogue scale.

pain of neuropathic origin on one of the screening tools could be followed up with detailed clinical examination.

Clinical and Surgical Factors

Most clinical and surgical risk factors, such as duration of surgery, American Surgical Association grade, BMI, comorbidity, anesthetic, and analgesic regimen can be obtained from clinical records. In some cases there is only moderate evidence for these factors being important predictors of CPSP (eg, BMI) and the quality of reporting may be variable (eg, comorbidities). However, we recommend these factors be recorded when available. The American Surgical Association grade has been reported to be predictive of pain-related outcome,[31,37] and it may be relatively straightforward to extract from anesthesia records. Surgical experience may be more challenging to capture and therefore we recommend it only be collected if this is a specific objective of the study. Assessment of comorbidity may be poorly reported and cumbersome to extract from clinical records. One option may be to screen for self-reported number of comorbidities and determine whether these are painful or not.

Physical Functioning

The IMMPACT group recommends the Short Form-36 Health Survey (SF-36)[57] to assess physical functioning and either the interference items of the Brief Pain Inventory or the Multidimensional Pain Inventory interference scale.[58] The SF-36 may also be relevant for studies on CPSP as a measure of physical function and a generic measure of HRQOL.

Psychological Functioning

The IMMPACT group recommends the use of the Beck Depression Inventory for measuring depressive symptoms.[45] However, the Center for Epidemiologic Studies Depression Scale[59] or the Hospital Anxiety and Depression Scale[60] may be more appropriate in epidemiological studies. An advantage of the Hospital Anxiety and Depression Scale over the Center for Epidemiologic Studies Depression Scale is that despite it being a very brief screening instrument, it measures both depression and anxiety. The State Trait Anxiety Inventory,[61] although a longer instrument, has also been frequently used to assess anxiety before surgery. In addition, instruments to measure pain catastrophizing

and specific surgical fears and worries could be considered. Two studies found evidence that preoperative surgical fear was predictive of CPSP.[37,39] However, they both used tailor made and nonvalidated instruments. Nevertheless, surgical-related fear and worry might offer an interesting venue for further research. The Pain Catastrophizing Scale (PCS) is the most widely used instrument to measure pain catastrophizing in studies of chronic pain and because pain catastrophizing was found to be predictive of CPSP, this instrument may be considered in future studies of CPSP.[33,41,42,44] The mental health domain of the SF-36 could be used as a generic measure of emotional functioning.

Other Risk and Outcome Factors

The IMMPACT group recommends global rating of improvement, however for surgical studies, global rating of recovery may be more appropriate. A good candidate might be the single item Global Surgical Recovery index (percentage recovery).[31,37,62] Studies should consider potential confounding factors that might affect outcome, such as repeat or new surgery and intercostobrachial nerve handling. Where possible, these should be controlled for in the statistical analysis. Depending on the purpose of the study, other outcome variables might be included, such as health care utilization and work-related factors (eg, sick leave, disability pension, work retention, time to return to work). These are important outcomes for studies incorporating cost-benefit or cost-utility analyses.

Methodological Issues

Timing

One important feature to consider in surgical studies is the timing of follow-up to assess the transition from acute to chronic pain. Timing of follow-up within the reviewed studies ranged from hours to years after surgery, making it difficult to compare results and virtually impossible to combine data from studies with similar surgical cohorts. Our review revealed differences in the definition and timing of "CPSP" ranging between 2, 3, and 6 months,[2,14] although most studies use the IASP criteria for "chronicity" as pain persisting for 3 months or more, beyond expected healing time.[14] Macrae and Davies[2] proposed specific criteria for CPSP, in that the pain must be of at least 2-month duration, must develop after surgery, other causes should be excluded and the possibility that the pain is a continuation from a preexisting problem be explored and exclusion attempted. Although more specific to surgery than the broader IASP definition, the "Macrae" definition has been criticized for the short duration of follow-up given that inflammatory processes may continue for up to 8 weeks postoperatively.[27]

It is important to conduct further follow-up to assess the trajectory and prognosis of CPSP, for example, subsequent postoperative assessment quarterly or semiannually for the first postoperative year, then annually thereafter. This extended postoperative assessment goes beyond the usual timeline of other clinical studies, for example, many randomized-controlled trials comparing efficacy of perioperative interventions are completed within 6 weeks. There are practical issues to consider with this extended follow-up, such as patient (and researcher) burden from prolonged repeated questionnaire assessment.

Study Design

The modest associations and sometimes conflicting results in studies of CPSP may in part, be because of the sampling and variability of surgical procedures across studies, the complexity of relationships between multiple risk factors and outcomes, and the lack of statistical power to test outcomes beyond the primary exposure and outcome variables. Epidemiological studies of CPSP should be prospective rather than cross-sectional in design, with detailed assessment of preoperative variables and repeated assessment of pain measures throughout the postoperative period to capture pain trajectory. Wherever possible, cohort studies should attempt to distinguish between prevalent pain (existing) and incident (new onset) pain. There is no additional benefit to be gained from the publication of small single-center cross-sectional studies reporting pain prevalence, which are often misreported as incident pain; larger studies incorporating detailed assessment of preoperative and perioperative factors with long-term follow-up will enhance our understanding of the factors associated with CPSP.

Limitations

It should be acknowledged that the results of this review are limited by the fact that current evidence about risk factors for CPSP are mostly derived from small samples of surgical patients from single centers (often with < 100 patients) and, therefore, may not necessarily report the most important putative risk factors. Moreover, there are several areas that may be of particular importance for future studies on CPSP that we have not included in our review. These include genetics (including epigenetics), assessment of preoperative nociceptive functional status, brain imaging, the influence of chronic opioid use presurgery and postsurgery, management of acute postoperative pain, and the role of protective resilience factors. These areas are beyond the scope of the current paper; however, there is emerging evidence in these areas that may significantly change the future landscape of chronic pain and CPSP.

Conclusions and Future Directions

We propose that the time has come for an interdisciplinary, international task force of CPSP experts to focus on development of definitions and instruments for selected common surgical procedures. Difficulties with sample size and measurement challenges are not unique to surgical pain epidemiology: other "task force" groups within the chronic pain community[12] and other clinical conditions (eg, diabetes[63]) have successfully convened to standardize measurement and methodology. Although initiatives have been established for acute postoperative pain,[64] these are limited in the measures they use and the short duration of postoperative follow-up. Furthermore, there is a need to develop and validate surgery-specific definitions and measurement instruments for capturing CPSP as this would improve methodology. Although a number of instruments are available, formal assessment of validity, reliability, and repeatability using surgical populations has yet to be undertaken.

Multidisciplinary teams with expertise in chronic pain after specific surgical procedures, (eg, breast cancer surgery task force, hernia surgery task force) could convene to test and validate pain data collection tools and agree on "core" confounding variables specific to those surgeries (eg, intercostobrachial nerve handling). In addition, because of

the nature of epidemiologic studies, data in many cases are collected before and after surgery away from the point of care, for example, in the patient's home by mail, electronic, or phone questionnaire, where direct observation is not possible. Direct observation such as performance tests or diagnostic assessments may be captured in future trials. Establishing a core minimum dataset for future epidemiologic studies will facilitate aggregation of CPSP risk and outcome data from different centers/studies. This will allow for comparisons across surgical populations from different geographical and health care settings. These larger datasets will increase statistical power and lead to improved prediction models for the development of CPSP.

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