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STUDY PROTOCOL

Evaluating the Predictive Value of a Short Preoperative Holistic Risk Factor Screening Questionnaire in Preventing Persistent Pain in Elective Adult Surgery: Study Protocol for a Prospective Observational Pragmatic Trial [PERISCOPE]

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Background: The global incidence of persistent pain after surgery is approximately 10%, with considerable clinical and socio-economic impacts. Despite identifying many risk factors in its development and the challenging management of the often neuropathic pain complaints, preoperative recognition of high-risk patients in various surgical populations using a standardized risk factor assessment questionnaire is lacking. This study evaluates the predictive value of a short holistic risk factor screening questionnaire as a first step in preventing and treating persistent pain in adults undergoing elective surgery.

Methods: This prospective observational pragmatic trial will include 560 adults undergoing elective surgery. The primary endpoint is the evaluation of the predictive value of the screening questionnaire, including the optimal cut-off determination in terms of sensitivity and specificity for inclusion in a perioperative high-vigilance program. Secondary endpoints are postoperative pain (intensity and characterization using the NRS and DN4), postoperative analgesic usage, and well-being using the EQ-5D-5 L. To assess the performance of the designed screening questionnaire in the identification of psychosocial pain aspects, HADs, and STAI-trait are being surveyed. Additionally, the multidimensional pain inventory (MPI, part 1) is being used to assess the impact of pain on daily life in patients.

Discussion: This pragmatic clinical trial will evaluate a short preoperative screening questionnaire to predict persistent postoperative pain after elective surgery in adults. Suppose high-risk patients could be identified earlier using this short preoperative holistic screening questionnaire. In that case, it might contribute to a more widespread implementation of standardized preoperative assessment and awareness for preventing persistent postoperative pain.

Trial Registration: Local ethics committee: B3002022000112. ClinicalTrials.gov identifier: NCT05526976. Registered on: 02 September 2022. Start of recruitment: 22 December 2022.

Trial Status: This paper is based on protocol version 4.0. The first patient was assigned to the research project on the 22 of December 2022. We anticipate including the last patient in October 2023 and plan to finalize the study by January 2024.

Keywords: persistent postsurgical pain, neuropathic pain, postoperative pain

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Introduction

Background Information

Over 230 million people undergo surgery each year worldwide.[1] The incidence of persistent postsurgical pain (PPSP) has been documented to be approximately 10% after all surgeries.[2,3] During the last decades, several authors described multiple risk factors in developing PPSP throughout the perioperative period. They concluded that to reduce this number, patients should be monitored closely and treated, if necessary, regardless of the surgery's complexity level.[4,5] Early identification of patients at risk for PPSP is an essential first step in preventing and treating this debilitating disease with significant clinical and socioeconomic implications.[5–7]

Rationale

Postoperative pain prevention should start as early as possible, ideally preoperatively, before the nociceptive trigger has happened. A review of the literature shows only two research groups that developed, implemented, and evaluated a practically valuable risk factor screening questionnaire for adults planned for elective surgery. Kalkman et al concluded that severe postoperative pain in the early postoperative phase can be predicted using a small set of variables that can be easily queried in the preoperative phase.[8] Alternatively, Althaus et al developed a risk index for predicting chronic postoperative pain.[9] Five predictors were as a result of this risk index identified, including severe postoperative pain. The results are promising in identifying high-risk patients who can benefit most from an optimized individual pain management strategy. Until today, no publications are found on external validation of these questionnaires, nor a preoperative questionnaire predicting PPSP.

Materials and Methods

Objectives and Purpose

The primary aim of this observational pragmatic trial is to assess the predictive value of a short preoperative holistic screening questionnaire for PPSP in adults defined as a pain intensity score of ≥3 on the NRS questionnaire at the surgical site, evaluated three months after elective surgery. The results will be analyzed, including the optimal cut-off determination regarding sensitivity and specificity for inclusion in a perioperative high-vigilance program. Secondary endpoints are postoperative pain intensity (numeric rating scale, NRS) and characterization (Douleur Neuropathic questionnaire, DN4), postoperative analgesic usage (opioid and antineuropathic drugs), and well-being using the EQ-5D-5L. To assess the performance of the designed screening questionnaire in identifying psychosocial pain aspects, the Hospital Anxiety and Depression questionnaire (HADs) and the State-Trait Anxiety Inventory (STAI-trait) are being surveyed. Supplementary, the Dutch version of the Multidimensional Pain Inventory (MPI, part 1) is being applied to patients with a score ≥3 on the NRS questionnaire, measuring the impact of pain on their daily life.

Study Design and Registration

This pragmatic prospective observational monocentric trial is being performed following the Declaration of Helsinki (Fortaleza, Brazil; October 2013) and Good Clinical Practice (GCP) guidelines. The study has been approved by the ethics committee at Antwerp University Hospital, Edegem, Belgium (reference: B3002022000112). The trial has been prospectively registered at https://www.clinicaltrials.gov (reference: NCT05526976) and is being monitored by the clinical trial centre (CTC) of Antwerp University Hospital. Table 1 displays the schedule of enrolment, interventions, and assessments. In this pragmatic trial, included patients will receive an analgesic regimen prescribed for postoperative pain by the attending anaesthesiologist according to the surgery specific anaesthesia guidelines as performed in our centre.

Participation

Adult patients (≥18y) scheduled for elective surgery in the tertiary 600-bed University Hospital of Antwerp, will be preoperatively asked for informed consent by a study team member. The recruitment started at the preoperative consultation in December 2022 and will close when the anticipated number (n = 560) of patients has been reached.

Considering the critical role of the type of surgery in the development of PPSP, which was shown in previous publications,[6,7,10] our surgical population will be stratified based on the surgical risk factor characteristics into three groups: (1) major procedures with high risk, (2) minor procedures with high risk, and (3) other procedures. Allocation in these groups will be executed as follows: (1) limb amputation, knee-hip or shoulder prosthetic surgery, craniotomy, spinal fusion of 3 or more levels, mastectomy, open cardiac surgery, thoracotomy, laparotomy; (2) laparoscopy (including cholecystectomy and inguinal hernia repair), open inguinal hernia repair, laminectomy/fusion less than three levels, hand and foot surgery, tonsillectomy.

Exclusion criteria are as follows: patients aged <18 years, patients not able to complete the questionnaires (due to mental incompetence or cognitive deficit and insufficient knowledge of the Flemish language), planned elective examinations under general anesthesia, or sedation without additional surgical intervention (such as bronchoscopy, hysteroscopy, gastroscopy, and colonoscopy), patients' refusal/no informed consent.

Assessments

The PERISCOPE study starts with a preoperative evaluation of combined risk factors in developing PPSP using the PERISCOPE screening battery, including a modified questionnaire based on the Althaus and Kalkman questionnaires. This preoperative screening survey will only be collected at the preoperative time point. Additionally, patients are questioned postoperatively at fixed time points (Table 1).

All questionnaires listed below are being surveyed at all three time points. Pain intensity will be evaluated using the 11-level numeric rating scale (NRS, 0 means no pain and 10 maximum pain) and categorized into three groups according to Cho et al classified as mild (NRS ≤ 5/10), moderate (NRS 6–7/10) or severe (NRS ≥ 8/10) pain.[11] A NRS pain intensity score of 3 or more, at the surgical site, three months after surgery (v4) is defined as PPSP. The DN4 questionnaire will be used to diagnose pain characteristics (neuropathic pain).[11,12] Postoperative use of analgesics will

Table 1 Schedule of Enrolment, Interventions, and Assessments (Spirit Figure)

	Study Period			
	Enrolment			**Close-Out**
Timepoint	**V1 Preoperative Enrolment**	**V2 Postoperative (Day 0 ± 1 Day)**	**V3 Postoperative (Day 30 ± 3 Days)[d]**	**V4 Postoperative (Day 91 ± 3 Days)[d]**
ENROLMENT:				
Eligibility screening	x			
Informed consent	x			
Demographic[a] and medical history[b]	x			
Concomitant medication[c]	x		x	x
Surgical procedure details	x			
INTERVENTION:				
Periscope screening battery	x			
ASSESSMENTS:				
NRS	x	x	x	x
EQ-5D-5L	x		x	x
HADS, STAI-trait, MPI Part 1, DN4 [e]	x		x	x

Notes: [a]Age, sex, length, weight, education level, place of residence. [b]Psychiatric comorbidities (focusing on questioning depressive and/or anxiety disorders), presence of preoperative chronic pain, cancer history, surgical history. [c]Analgesic usage (opioids and non-opioids) and concomitant psychotropic usage. [d]Contact by telephone to monitor the development of severe/persistent pain complaints. [e]MPI and DN4 will only be questioned when the pain intensity measured on the 11-level NRS score is three or more.

be monitored and classified as opioid (strong and weak), nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, antineuropathic drugs (tricyclic antidepressants (TCA), serotonin-norepinephrine reuptake inhibitor (SNRI), and gabapentinoids), or other. Quality of life (EQ-VAS) and global well-being will be measured using the EQ-5D-5L questionnaire. The EQ-VAS is a subjective assessment of generic health ranging from 0 to 100. Patients representing a better health experience will enter higher scores. The validated EQ-5D-5L questionnaire evaluates the quality of life in 5 domains: mobility, self-care, daily activities, pain or discomfort, and anxiety or depression. For each factor, five levels of scoring are available.[13] Furthermore, symptoms of anxiety, depression, and fear predisposition will be assessed in more detail using the Hospital Anxiety and Depression Scale (HADS)[12] and the State-Trait Anxiety Inventory (STAI-trait) questionnaire.[14] To examine the impact of persistent pain on patients' lives, part 1 of the Multidimensional Pain Inventory (MPI-1) will be used.[15] Part I includes five scales designed to measure different dimensions of the chronic pain experience: life interference, support, life control, pain severity, and affective distress.[12]

Data Collection

After informed consent has been obtained, patients' demographic data will be collected during the inclusion assessment. Patients will be asked to complete the abovementioned questionnaires at three different time points digitally: preoperative, one month postoperative, and three months postoperative (Table 1). For patients undergoing day surgery instead of hospitalization, the NRS questionnaire must also be completed digitally one day after the surgery. For hospital-admitted patients, the NRS score reported by the ward nurse and collected in the electronic patient record will be used. Paper versions of the questionnaires are available when digital submission is not possible. All data, including online and paper questionnaire results, will be collected in REDCap® (Research Electronic Data Capture, Version 13.6.1, Vanderbilt University, Nashville, Tennessee, USA). The members of the preoperative evaluation department, the attending anaesthesiologist, and the surgical ward nurses will collect data during the hospital stay. The study coordinator contacts the patient by phone one and three months after surgery to monitor the development of severe/persistent pain complaints and any changes in (pain) medication. All data will be processed anonymously.

Sample Size

A logistic regression model will be developed to predict the probability of PPSP three months after surgery correctly. The estimated probability from this model can then be used to construct a ROC curve (receiver operating characteristic) to discriminate between PPSP and non-PPSP and determine the optimal cut-off value regarding maximal sensitivity and specificity.

The sample size calculation is based on an area under the curve (AUC) from the ROC curve. To construct a 95% confidence interval for the AUC with a width of 0.2 and assuming an AUC of 0.7, we need at least a group of 56 patients with chronic pain.[16] Based on the available scientific evidence of a mixed incidence of PPSP of 10%, 560 subjects will be included in this study.[2–4]

Analysis of the Endpoints/Statistics

Baseline characteristics, including demographics, will be summarized. For categorical variables, frequencies and percentages will be described. As appropriate, continuous variables will be reported as the mean with standard deviation or median with interquartile range. The summary measures of the assessments (NRS, EQ-5D-5L, HADS, STAI-trait, MPI, DN4) at the different time points will be described numerically and with a line plot.

R software version 4.1.2 will be used for statistical analysis. PPSP at three months will be defined as a pain NRS score of at least 3. A logistic regression model for PPSP at three months will be considered using the Periscope screening (Kalkman and Althaus score) as predictors. We will see if other variables such as age, sex, BMI, education level, type of surgery (major high risk, minor high risk, and other), preoperative NRS, EQ-5D-5L (index and/or VAS), HADS, and STAI-trait improve the prediction. It will be explored whether the associations with PERISCOPE screening scores differ depending on the type of surgery. The AUC under the ROC curve will be calculated using the predicted probabilities of the logistic regression model. The Youden index can then be used to determine the optimal cut-off regarding sensitivity and specificity. To study the association between the PERISCOPE screening and the outcomes at three months (NRS,

EQ-5D-5L, HADS, STAI-trait), a linear regression model will be used to allow correction for other variables. The NRS, categorized into three categories (mild, moderate, severe), can also be studied with an ordinal regression model. As these outcomes (NRS, EQ-5D-5L, HADS, STAI-trait) are also measured repeatedly, a linear mixed effects model with subject as a random effect can be considered to model their evolution over time. In the model for NRS, we can correct for postoperative analgesic use.

Dissemination Policy

The trial results will be submitted to a high-impact peer-reviewed journal considering the meaningful clinical impact of the findings.

Discussion and Conclusion

Worldwide, more than 230 million surgical procedures are performed annually for diverse reasons.[1] Although acute pain is almost ubiquitous after surgery, it can usually be controlled well and will mostly resolve after a few days.[3] The suboptimal treatment of postoperative pain is widely recognized as a significant delaying factor in postoperative recovery, rehabilitation, and hospital discharge. In many of these patients, postoperative pain complaints will persist beyond the expected healing time. Consequently, chronic or persistent postsurgical pain (PPSP) arises as it is defined as pain that lasts for more than three months after surgery.[6,17] The variability in PPSP incidence is a function of multiple risk factors throughout the preoperative, intraoperative, and postoperative periods containing psychosocial and surgical factors.[18] Despite the increasing knowledge of these risk factors, the incidence of chronic pain after surgery is still high,[3] with a significant influence on daily functioning and well-being, as well as the emergence of socioeconomic hurdles.[19] Therefore, in preventing PPSP, many surgical procedures have evolved in nerve-sparing techniques,[20,21] but nerve damage cannot always be avoided. Furthermore, preoperative anxiety, fear, and need for information can also contribute to delayed recovery, increased postoperative pain, and PPSP.[22] The reason for anxiety can be fear of anesthesia, the surgical procedure, postoperative pain, or several other aetiologies.[23] To date, the global prevalence of preoperative anxiety is still high in surgical patients.[24–26] Protocols for systematically evaluating these various predictors are challenging to implement in daily routine practice. Nevertheless, early identification of at-risk patients may benefit the most from early management strategies.

This study presents a protocol for a predictive value evaluation of a short preoperative holistic risk factor screening questionnaire to prevent persistent pain in elective adult surgery. The strength of this study is that it includes all types of elective surgery and is not limited to specific surgical protocols. Also, risk factor screening takes place before surgery is performed. Furthermore, as there are discrepancies in pain score and risk factor evaluation between patients and different caregivers, the patient's perspective will be respected as patients fill out the questionnaires themselves.[27,28] Moreover, they complete the questionnaires whenever they want, within a defined time zone. If this easy-to-use PERISCOPE questionnaire (digital and paper versions available) can be used in the early allocation of patients at risk for PPSP to appropriate care pathways, the PPSP incidence may decrease.

Abbreviations

AUC, area under the curve; CTC, Clinical Trial Centre; DN4, Douleur neuropathic; GCP, good clinical practice; HADS, Hospital Anxiety and Depression Scale; MPI, Multidimensional Pain Inventory; NRS, Numeric Rating Scale; NSAIDs, Nonsteroidal anti-inflammatory drugs; PPSP, Persistent postsurgical pain; REDCap®, Research Electronic Data Capture; STAI, State Trait Anxiety Inventory; SNRI, Serotonin-norepinephrine reuptake inhibitor; TCA, Tricyclic antidepressants.

Data Sharing Statement

The PI, statistical analyst, and data manager will have access to the final trial dataset. Data of participants will be collected in Redcap in the context of this study only and will be owned by the current researchers.

Ethics Approval and Consent

This study was approved by the UZA Ethics Committee, Edegem, Belgium, with reference B3002022000112. Written, informed consent to participate will be obtained from all participants.

Consent for Publication

We are willing to provide a model informed consent form upon request.

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Author Contributions

DW is the principal investigator (PI). She participated in study conception, design, execution and interpretation. She wrote, revised and reviewed the article. IM contributed to the study's design and will contribute to the study result interpretation. She critically reviewed the manuscript. IV, EW and LVL contributed to the conception and study design and data collection. They drafted and substantially revised the manuscript. ER is involved as a statistician in the study design and analysis and interpretation of the study results. She critically reviewed and revised the manuscript. LVDV contributed to data collection and reviewed the article. RD, VS, and GH contributed to the design, organization, and draft preparations and will also contribute to the study results interpretation. Moreover, they are involved in revising the manuscript. All authors have read and approved the final draft of the study protocol. Furthermore, they have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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