Clinical Pain Research

Elisabeth Kjær Jensen*, Emmanuel Bäckryd, Jørgen Hilden and Mads U. Werner

Trajectories in severe persistent pain after groin hernia repair: a retrospective analysis

https://doi.org/10.1515/sjpain-2020-0104
Received June 25, 2020; accepted July 27, 2020; published online October 9, 2020

Abstract

Objectives: Severe persistent post-surgical pain (PPSP) remains a significant healthcare problem. In the third most common surgical procedure in the U.K., groin hernia repair, including 85,000 surgeries, estimated 1,500–3,000 patients will annually develop severe PPSP. While the trajectory of PPSP is generally considered a continuation of the acute post-surgery pain, recent data suggest the condition may develop with a delayed onset. This study evaluated pain-trajectories in a consecutive cohort referred from groin hernia repair-surgeons to a tertiary PPSP-center. Potential explanatory variables based on individual psychometric, sensory, and surgical profiles were analyzed.

Methods: Patients completed graphs on pain trajectories and questionnaires on neuropathic pain, pain-related functional assessments, and psychometrics. Surgical records and quantitative sensory testing profiles were obtained. Pain trajectories were normalized, and pre- and post-surgical segments were analyzed by a normalized area-under-the-curve (AUC) technique. Principal component analysis (PCA) was applied to the explanatory variables. Significant PCA-components were further examined using multiple logistic regression models.

Results: In 95 patients, the AUC identified groups of post-surgical pain trajectories (p<0.0001): group I (n=48), acute high-intensity pain progressing to PPSP; group II (n=28), delayed onset of PPSP; group III (n=7), repeat-surgery gradually inducing PPSP. Data from groups IV (n=3) and V (n=9) were not included in the statistical analysis due to small sample size and data heterogeneity, respectively. The PCA/logistic analyses indicated that neuropathic pain scores, composite pain scores, and pain-related functional assessments were explanatory variables for groups I and II.

Conclusions: Pain trajectories in PPSP after groin hernia repair are heterogeneous but can be classified into meaningful groups. Examination of pain trajectories, mirroring the transition from acute to severe persistent post-surgical pain, has the potential of uncovering clinically relevant pathophysiological mechanisms.

Keywords: chronic pain; groin; herniorrhaphy; physiopathology; postoperative.

Introduction

Severe persistent post-surgical pain (PPSP) is a prevalent and significant medical problem leading to impairment of physical and psychosocial functions in a large number of individuals [1]. Criteria for PPSP have recently been included in ICD-11 [2], although more elaborate criteria have been proposed (Table 1) [3]. Severe PPSP may significantly affect 2–8% of the surgical population, depending primarily on the surgical procedure and technique, but also on patient-related pre-surgical factors [1].

Groin hernia repair qualifies for PPSP-research due to a high surgical volume. While the surgery generally is considered a minor procedure with limited tissue damage, it is carried out in a delicate territory with abundant nerves and blood vessels and is involved in complex musculoskeletal functions, essential for locomotor actions. Persistent pain after groin hernia repair may develop after a
seemingly successful surgical procedure and is seen in a severe form in 2–4% of the patients associated with significant deterioration of the health-related quality of life [4].

The transition process from acute to persistent pain may be more complex than previously assumed, making the study of pain trajectories interesting [5, 6]. Based on our clinical experience from a nationwide research center specialized in the management of PPSP following groin hernia repair [7], it was hypothesized that patient-reported pain trajectories could be classified into pathophysiological relevant groups. The classification could become an essential part of future research criteria in PPSP. Furthermore, it was also hypothesized that the group structure could be substantiated by appropriate predictor variables, e.g., demographics, pain characteristics, psychometrics, and somatosensory profiles. The authors, therefore, decided first to perform an exploratory cohort study examining graphical pain charts. The charts were normalized using the area-under-the-curve (AUC) technique, attempting to construct a meaningful and valid statistical classification of the trajectories. Second, the association between the classification of the trajectories and potential explanatory variables, i.e., pain profiles, psychometrics, quantitative sensory testing (QST), and surgical procedure, were analyzed using principal component analysis (PCA) and logistic regression models.

Methods

Ethics approval and informed consent

The study protocol was approved by the Regional Committee on Health Research Ethics (H-2-2011-023) and the Danish Data Protection Agency (2012-41-0008). Patients referred to the center from 2014 to 2016 were consecutively offered to participate in the study at the first ambulatory visit. Patients were included after a signed, informed consent was obtained.

Criteria for referral

Patients were referred to the research center specialized in the management of PPSP following groin hernia repair, by a surgeon or a general practitioner on a nationwide basis, by the Danish Hernia Database's homepage (http://www.herniedatabasen.dk/; Supplementary file 1). The criteria for referral to the center were patients experiencing severe pain (activity-related or maximal pain intensity >7 NRS [numeric rating scale 0–10]) scores and PPSP-related serious impairment of working and social life.

Pre-visit questionnaires

Questionnaires were mailed to the patients before the first ambulatory visit (Supplementary file 2). The questionnaires covered the general pain characterization; pain intensity (numerical rating scale [NRS; 0–10], resting/average/activity-related/maximal), and pain localization. Specific validated questionnaires were as follows: the groin hernia-related Activities Assessment Scale (AAS); Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale (PCS); Self-reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), and painDETECT (Supplementary file 2).

Ambulatory visit

Medical history

The relevant medical and surgical history, including an evaluation of the physical and psychosocial consequences of the pain, was obtained by a senior physician specialized in pain management (MUW).

Pain trajectory outline

The patient made a drawing of the pain trajectory on paper, with a pre-marked x-axis of time (arbitrary units) and a y-axis of pain intensity (anchored by 0 [no pain] and 10 [worst possible pain]) from pre-surgery to the present, post-surgery level. The senior physician guided the process.

Table 1: Proposed criteria for persistent post-surgical pain (PPSP) [3].

| 1. | The pain develops after a surgical procedure or increases in intensity after the surgical procedure. |
| 2. | The pain should be of at least 3–6 months’ duration and significantly affect the health-related quality of life. |
| 3. | The pain is either a continuation of acute post-surgery pain or develops after an asymptomatic period. |
| 4. | The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome (after surgery in deep somatic or visceral tissues). |
| 5. | Other causes of the pain should be excluded, e.g., infection or continuing malignancy in cancer surgery. |
Quantitative sensory testing

Quantitative Sensory Testing (QST) is a standardized, graded activation of the sensory system by mechanical and thermal stimuli, with an assessment of the evoked psychophysical responses. Individual QST-profiles were obtained and correlated with the pain trajectory classification. Following a detailed clinical examination of the groin and genital areas, testing sites (2.5 × 5.0 cm²) were delineated in the pain area, centered at the point of maximum palpatory pain, corresponding to the superficial inguinal ring, and, mirrored on the contralateral side (Supplementary file 3). Assessments of mechanical and thermal, detection, and pain thresholds, in the groin areas and in a control area at the lower arm were performed (Supplementary file 4). Detailed descriptions of the QST-paradigms have previously been reported [7].

Testing paradigms

Since QST is ‘not recommended as a stand-alone test for the diagnosis of neuropathic pain’ [8], specific diagnoses inferred from the QST-data were avoided. Instead, the QST-findings were divided into inflammatory, neuropathic, mixed, or miscellaneous components (detailed description: Supplementary file 5).

1. An inflammatory component was substantiated by the finding of a decreased algometry pressure pain threshold (PPT) in the area compared to the contralateral groin area, i.e., potentially triggered by a deep inflammatory focus.

2. A neuropathic component, i.e., potentially triggered by nerve damage, was substantiated by at least three out of four tests of sensory dysfunctions (compared to contralateral groin area) including:
   - at least three out of four thermal thresholds were increased (warmth detection threshold [WDT], cool detection threshold [CDT], heat pain threshold [HPT], cold pain threshold [CPT])
   - a reduction in the difference between tactile pain threshold (TPT) and tactile detection threshold (TDT)
   - positive temporal summation phenomenon for dynamical and static responses to brush or polyamide filaments stimulation
   - positive athersensations following dynamical and static responses to stimulation by brush or polyamide monofilaments

3. A mixed component was defined as coexisting inflammatory and neuropathic components.

4. The miscellaneous component was ticked when no inflammatory or neuropathic components were observed.

Please, observe that an inflammatory or neuropathic component does not equate inflammatory and neuropathic pain, but only adheres to the authors QST-paradigm specifically developed for the groin region [7].

Data management

Pain trajectories

The pain trajectory graphs were individually inspected, and, depending on the graphical characteristics classified, into the groups I–V; in group I, the acute post-surgical pain continued into PPSP with unchanged high-intensity pain; in group II, the acute post-surgical pain decreased significantly to low-intensity levels, but pain recurred developing into high-intensity PPSP; in group III, repeat-surgery precipitated high-intensity PPSP; and in group IV, presurgical high-intensity pain continued unchanged post-surgically. If a pain trajectory was not classifiable into any of the groups, it was allocated to the “miscellaneous” group V.

The pain trajectory graphs were manually processed in a vector-based drawing program (Canvas 12.0, ACD Systems International, BC, Canada). A 10 × 10 grid was superimposed on individual graphs and fitted to the post-surgery timeline (x-axis) and the post-surgery pain intensity NRS-scores (y-axis), respectively. Each box in the grid corresponded to an arbitrary x-value of 1.0 and a y-value of 0.1. Application of the grid normalized the data-points, making comparisons between groups possible: the coordinate (x/y = 0.0/1.0) corresponding to the NRS-score at the time of surgery; while the coordinate (x/y = 10/NRS_normalized) corresponded to the normalized NRS-score at the right temporal margin of the trajectory. The timeline for the post-surgery data thus was from 0 to 10, and the normalized NRS-scores were ≥0 using 1.0 at the time of surgery. For the pre-surgical data, the identical procedure was performed; however, using a timeline from −10 to 0. All data-points were calculated from the grid and transferred for processing to a standard spread-sheet.

In group II, the temporary decrement in post-surgical pain intensity was calculated as the span, in real-time, between the 50% intensity decrease of the downward slope of the immediate post-surgical pain and the 50% increase of the upward slope of high-intensity PPSP.
Statistics

General measures

Due to the exploratory nature of the study, an *a priori* sample size estimate was not done. Data normality was examined by standardized residual plots and the Kolmogorov–Smirnov test (SPSS IBM Software 22.0, IL; MedCalc Software 16.4.3, Mariakerke, Belgium). Data were analyzed with SAS (SAS Institute Inc., 9.4, NC).

Explanatory variables

Data regarding demographics (age, gender, surgical procedure), pain intensities, and AAS, HADS, PCS, S-LANSS, and painDETECT were processed as continuous or ordinal variables. QST-data (*inflammatory, neuropathic, mixed,* and *miscellaneous* components) were processed as nominal variables. The correlation pattern of the variables was examined by a simple correlation matrix.

Group analyses

The normalized pain trajectory data for groups I, II, and III were analyzed using a summed measure, calculating the AUC by the trapezoidal rule. Data from groups IV and V were not included in the statistical analysis due to inadequate sample size and data heterogeneity, respectively. Pre-surgery and post-surgery data were analyzed separately. The Kruskal–Wallis H-test with post-hoc analysis and the Mann–Whitney test were used comparing groups I, II, and III.

Principal component analysis

Orthogonal PCA was performed on the raw explanatory data in order to organize and reduce the amount of variables into a number of artificial variables (components). SAS procedure FACTOR was employed. All components obtained by the PCA were then used as regressors in the subsequent explanatory analyses.

Multiple logistic regression

In the explanatory analyses, multiple logistic regression models were used to estimate the association between the explanatory variables and group affiliation. All components obtained by the PCA and the demographic variables were used in a logistic regression with a binary dependent outcome variable (two groups of pain trajectory graphs compared, e.g., group I vs. group II) at a time.

Significance levels

The Bonferroni correction was applied in multiple comparisons (Mann–Whitney tests). A significance level of 5% was considered significant.

Results

General

The total number of referred patients (August 21, 2014 to November 10, 2016) was 109 (Figure 1). Time from the groin hernia repair, resulting in severe persistent pain, to the ambulatory visit, was in median (95% CI) 2.1 (1.7–2.6) years. The total number of obtained pain trajectory graphs was 99, and from these 95 trajectory graphs were eligible for further analysis. Demographics, QST-findings, and scores from PCS, HADS, summed pain scores, AAS, S-LANSS, and painDETECT are presented in Table 2. The "cut-off" limits were reached for PCS in 29% (27/94), HADS-A in 22% (21/94), HADS-D in 13% (12/94), S-LANSS in 48% (44/92), and painDETECT in 28% (26/93) of the patients. The AAS has no "cut-off" limits but is a relative scale applied during recovery after groin hernia repair.

Data acquisition

Eight patients were not included in the PCA and the ensuing multiple logistic regression, due to incompletely answered questionnaires.

Group analyses

Comparison of pre-surgical AUC-data for the pain trajectories of groups I, II, and III did not demonstrate any statistical differences between the groups (p=0.27, Kruskal–Wallis H-test), as confirmed by simple rank tests (p=0.33; Mann–Whitney with Bonferroni correction). Comparison of the post-surgical AUC-data for the trajectories of groups I, II, and III demonstrated a highly statistically significant difference between the groups (Figure 2; p<0.0001, Kruskal–Wallis H-test). A *post-hoc* test (p<0.005) and simple rank tests confirmed this finding (group I vs. II: p<0.001; group I vs. III: p<0.002; group II vs. III: p<0.005; Mann–Whitney with Bonferroni correction). In group II, the
duration of the temporary post-surgical decrement in pain intensity was median (95% CI) 6.9 (4.0–16.0) months (Figure 2).

Correlations between primary explanatory variables

The explanatory variables (age, gender, surgical procedure, pain intensities, AAS, HADS, PCS, S-LANSS, painDETECT, and QST-components) “clustered” around psychometrics, neuropathic pain questionnaires, and groin hernia repair related persistent pain and its functional consequences (Figure 3). The within “cluster” correlations were of moderate strength with R² ranging from 0.29 to 0.42. The between “cluster” correlations were of weaker strength with R² ranging from 0.16 to 0.24. The correlation between the QST-findings (neuropathic + mixed component) vs. painDETECT-scores showed a statistically significant, albeit a weak correlation (ρ=0.23; 0.03 to 0.41; p=0.03). Corresponding analysis for S-LANSS did not attain statistical significance (p=0.08).

Principal component analysis

PCS, HADS-A, HADS-D, summated pain intensity scores, AAS, S-LANSS, and painDETECT yielding seven variables were subjected to a PCA using 1.0 as prior communality estimates. The method arranged data into a number of components. All initial seven components were retained by the NFACTOR criterion and had eigenvalues ranging from 3.11 to 0.27. An item was said to load on a given component if the component loading had an absolute value ≥0.38 (default setting; Supplementary file 6).

Explanatory analyses

All components obtained by the PCA and the variables age, gender, and type of surgery were used in a logistic regression with a binary dependent outcome. The likelihood ratio of the logistic regression model was statistically significant (p=0.016). The analysis of maximum likelihood estimates demonstrated that components 3 (component with strong loadings of the variables summated pain score, AAS score, and S-LANSS) and 4 (component with strong loading of the variable AAS) were statistically significant (p=0.004 and p=0.022, respectively) indicating that summated pain score, AAS score, and S-LANSS score had an influence in predicting the group membership of groups I or II as presented in Figure 4.

Subsequent logistic analyses showed that high PCS-scores were statistically significant in predicting groups III, IV, and V (p=0.042). A potential indicator of neuropathic pain, assessed by painDETECT and S-LANSS, had a near-significant influence in predicting membership in groups I and II (p=0.062). The type of primary surgery did not influence the prediction of group membership. Patients with a neuropathic component, according to QST-criteria, demonstrated statistically significantly lower mean PCS-scores (p=0.026) than patients with an inflammatory component.
Table 2: Demographics, quantitative sensory testing (QST) findings, and scores for Pain Catastrophizing Scale (PCS), Hospital Anxiety and Depression Scale – Anxiety Subscale (HADS-A), Hospital Anxiety and Depression Scale – Depression Subscale (HADS-D), summed pain scores, Activities Assessment Scale Total Score (AAS), Self-reported Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS), and questionnaire evaluating neuropathic pain (painDETECT) for subjects with persisting pain after inguinal herniorrhaphy.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>95</td>
<td>48</td>
<td>28</td>
<td>7</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Gender ratio (M/F)</td>
<td>82/13</td>
<td>45/3</td>
<td>22/6</td>
<td>5/2</td>
<td>3/0</td>
<td>7/2</td>
</tr>
<tr>
<td>Age, years</td>
<td>47.8 (45.4–50.3)</td>
<td>47.2 (43.9–50.5)</td>
<td>48.6 (43.9–53.3)</td>
<td>43.4 (25.7–61.1)</td>
<td>60.0 (42.0–60.0)b</td>
<td>50.2 (41.3–59.1)</td>
</tr>
<tr>
<td>Primary surgery (number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open surgery</td>
<td>57</td>
<td>20</td>
<td>11</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>38</td>
<td>28</td>
<td>17</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>QST-findings (number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory component</td>
<td>11</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Neuropathic component</td>
<td>25</td>
<td>16</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mixed component</td>
<td>32</td>
<td>12</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Miscellaneous component</td>
<td>27</td>
<td>16</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>PCS (points)</td>
<td>23.3 (21.1–25.5)</td>
<td>21.0d (18.2–23.7)</td>
<td>24.1 (19.5–28.8)</td>
<td>36.2 (29.6–42.9)</td>
<td>22.0f (1.0–34.0)b</td>
<td>24.7 (16.8–32.6)</td>
</tr>
<tr>
<td>HADS-A (points)</td>
<td>6.5e (6.0–8.0)</td>
<td>7.7 (6.5–8.9)</td>
<td>5.0f (3.0–7.0)</td>
<td>8.6 (5.1–11.9)</td>
<td>8.0f (1.0–14.0)b</td>
<td>7.4 (2.8–12.0)</td>
</tr>
<tr>
<td>HADS-D (points)</td>
<td>4.0g (3.0–6.0)</td>
<td>4.0h (2.0–7.0)</td>
<td>4.4 (2.8–6.1)</td>
<td>6.7 (2.8–10.6)</td>
<td>3.0f (0.0–12.0)b</td>
<td>5.6 (0.6–10.7)</td>
</tr>
<tr>
<td>Summated pain (NRS-scores)</td>
<td>25.8 (24.5–27.0)</td>
<td>24.9 (23.3–26.6)</td>
<td>26.9 (24.6–29.2)</td>
<td>29.7h (26.3–33.0)</td>
<td>33.0i (14.0–35.0)b</td>
<td>23.3 (18.1–28.5)</td>
</tr>
<tr>
<td>AAS (points)</td>
<td>12.0 (11.0–13.0)</td>
<td>11.8 (10.6–12.9)</td>
<td>12.0i (11.0–13.8)</td>
<td>13.2 (10.2–16.2)</td>
<td>15.0f (7.0–16.0)b</td>
<td>11.4 (9.3–13.5)</td>
</tr>
<tr>
<td>S-LANSS (points)</td>
<td>14.0 (13.0–14.9)</td>
<td>14.5 (13.0–16.0)</td>
<td>11.7 (9.4–14.6)</td>
<td>14.1 (7.2–21.0)</td>
<td>18.0f (5.0–19.0)b</td>
<td>10.7 (5.7–15.7)</td>
</tr>
<tr>
<td>painDETECT (points)</td>
<td>14.0 (12.0–15.0)</td>
<td>13.0 (11.0–15.2)</td>
<td>13.4 (10.8–15.9)</td>
<td>15.8 (9.5–22.2)</td>
<td>21.0f (4.0–32.0)b</td>
<td>12.2 (8.9–15.5)</td>
</tr>
</tbody>
</table>

In PCS a total score of ≥20 pts indicates signs of pain catastrophizing behavior. In HADS-A and HADS-D a total score of ≥11 pts indicates anxiety or symptoms of depression. Summed pain indicates pain intensity scores (numerical rating scale [NRS]) at rest, during activity, on average and maximally, during the previous week. The pain intensity scores were indicated on a horizontally held NRS (numeric rating scale) anchored by no pain (=0) and worst imaginable pain (=10). In the statistical analyses the NRS scores were summated (min = 0; max = 40). AAS is a measure of the impact of pain on activity-of-daily-living (ADL); the higher the AAS score, the higher the negative impact on ADL-function. S-LANSS evaluates neuropathic pain symptoms. A score >12 pts suggests pain of predominantly neuropathic origin. The painDETECT evaluating neuropathic pain symptoms. A total score ≥18 pts indicates that the pain probably is of neuropathic origin. *p<0.05; **p<0.01; aChi-squared test was used on the variables: gender, age, primary surgery and QST-diagnosis. One-way ANOVA/Kruskal-Wallis test was used in group comparisons. Unless otherwise indicated no statistically significant difference between groups were found. Values are presented as mean (95% CI) or median (95% CI) depending on data distribution; bRange; cMedian; dCompared to group IV; eCompared to group V.
The main findings of the present study are, in patients experiencing severe, persistent pain after groin hernia repair, that an examination of the long-term post-surgical pain trajectories revealed a clinically interpretable and statistically supported group classification. Examining the associations between the classification-groups, and the potential explanatory variables, based on individual pain profiles, psychometrics, results of QST, and surgical

Discussion

Summary of findings

The main findings of the present study are, in patients experiencing severe, persistent pain after groin hernia repair, that an examination of the long-term post-surgical pain trajectories revealed a clinically interpretable and statistically supported group classification. Examining the associations between the classification-groups, and the potential explanatory variables, based on individual pain profiles, psychometrics, results of QST, and surgical
procedure used, even using advanced, multivariate statistics, were largely unsuccessful.

Pain trajectories: previous research

Several studies examining short-term (days) post-surgical pain trajectories have identified explanatory variables in the development of PPSP [9–12], chronic pain [13], preoperative opioid use [13, 14], psychometrics [3, 9], and severe acute postoperative pain [11, 14]. However, to the best of our knowledge, only three studies have presented detailed analyses of long-term (months to years) post-surgical pain trajectories. The first study, in hip preservation procedures (n=369) [15], classified three trajectory “solutions” from pre-surgery to 2-year post-surgery into “low pain” (31%), “pain improvement” (50%) and “high pain” (19%). In the latter group, characterized by the development of PPSP, “high-intensity” pain was seen pre-surgery and, following a slight improvement at 6-month post-surgery, a recurrence of “high-intensity” pain at 1- and 2-year post-surgery. Impaired physical functioning and reduced quality of life scores were explanatory pre-surgery variables. However, confounding issues cannot be excluded, since the general responder rate was low (21–41%), and the pain intensity ranges were overlapping between the three trajectory-‘solutions’.

The second study, in patients undergoing hysterecomy (n=170), by open abdominal hysterectomy (72%), vaginal hysterectomy (18%), or laparoscopically assisted vaginal hysterectomy (10%) [16], analyzed pain trajectory data from pre-surgery to 5-year post-surgery. The classifications into “no PPSP” (52%), “prolonged post-surgical pain” (31%) and “PPSP” (17%) revealed that psychological factors, i.e., anxiety, pain catastrophizing, illness perception, and, the acute pain characteristics, predicted an unfavorable pain trajectory. In the PPSP-group at 5-year post-surgery, the worst and average pain intensities (mean [SD]) were 3.2 (1.7) and 1.9 (0.9), respectively, indicating that most of the patients, did experience low to moderate intensity pain. The questionnaires, however, indicated pain-related impairments in activity, general mood, and work, in 43–58% of the patients.

The third study, a secondary analysis, included healthy individuals (n=260) undergoing cesarean sections that were followed-up by questionnaires at 3-, 6-, and 12-months post-surgery [17, 18]. The questionnaires included the Short-Form Brief Pain Inventory (BPI). The number of individuals experiencing moderate to severe pain after 3-, 6-, and 12-months were 26% (61/231), 21% (48/228), and 13% (29/215), respectively. Severe acute postoperative pain was an independent predictor of the development of PPSP up to 6-month post-surgery. Interestingly, preoperative anxiety, i.e., surgery conducted on psychological/maternal request (37% of all surgeries), was not a predictor of PPSP at 3-, 6-, or 12-month post-surgery.

Pain trajectories: potential pathophysiological mechanisms

Group I trajectories (Figure 2) demonstrated high intensity acute post-surgical pain, which is a consistent explanatory factor in the literature concerning PPSP [1, 19]. The potential pathophysiological mechanisms behind the continuation of high-intensity acute pain are surgical nerve-damage due to the tissue dissection, inadvertent placement of sutures or tacks near nerve structures, or the implantation procedure of the mesh per se, either directly or indirectly, affecting outcome by an acute or chronic foreign body inflammatory reaction. However, groin hernia recurrence or a surgical complication, e.g., seroma, hematoma, or a post-surgical infection, should always be excluded as a potential pain generator [3]. In the present study, all patients prior to referral had been examined by a groin hernia surgeon, often including ultrasound scans, or CT-scans, who did not find any indication for surgical re-exploration.

Group II trajectories (Figure 2) were characterized by normal post-surgical recovery followed by the late development of PPSP. Time-related changes in post-surgical pain phenotype have been demonstrated in a long-term follow-up groin hernia repair study (n=588) [5]. In the preoperatively pain-free cohort (241/588 [41%]) at the 6-month control and the 5-year control, 49 (20%) patients and 52 (22%) patients, respectively, experienced PPSP. A pain phenotype shift was seen in 33/49 (67%) patients experiencing PPSP at the 6-month control but not at the 5-year control. Interestingly, a reciprocal pain phenotype shift was seen in 36/52 (69%) patients experiencing PPSP at the 5-year control but not experiencing pain at the 6-month control, indicating that more than two-thirds of the patients undergoing groin hernia repair had developed persistent pain with a delayed onset. A similar trend in time-related change of pain phenotype has been demonstrated in long-term follow-up studies of patients following breast cancer surgery, as well as in general and thoracic surgery [6, 20, 21].

In group II, the time profile of the temporary post-surgical decrement in pain intensity (median 6.9 month; Figure 2) may support several different pathogenic mechanisms associated with this phenotype shift. First, nerve
injury, caused by surgery or the reactive inflammatory process following mesh implantation, is known to be associated with a delayed onset of neuropathic pain symptoms [19, 22]. An implant procedure may lead to the shrinkage, partial dehiscence, or dislocation of the inguinal mesh or development of an inflammatory “meshoma” leading to painful mechanical or inflammatory irritation of the surgically altered tissues in the groin. Recently, a histopathological study in explanted meshes demonstrated neo-innervation by nerve fibers and a significantly higher nerve fiber density in specimens obtained due to re-surgery for groin hernia repair related persistent pain than for non-pain hernia recurrence [23]. Furthermore, the reactive fibrosis may impinge upon or compress the spermatic cord leading to movement-related pain and dysejaculation [24]. Second, short-lasting, non-specific, anticipated advantageous, placebo, or Hawthorne effects may occur in surgical procedures, called the “honeymoon period”. Thus, the post-surgical pain ratings and the post-surgical functional performance may improve in the short-term, but may eventually deteriorate, leading to delayed onset of PPSP.

Third, recent animal studies suggest that tissue inflammation produces a state of latent sensitization masked by signaling of the endogenous opioid system for months, even after complete behavioral recovery and re-establishment of normal pain thresholds [25]. Unmasking or disruption of the process with the administration of high-dose μ-opioid-receptor (MOR) inverse agonists reinstates pain and precipitates nocifensive behavior for 30–120 min. Since disruption of the latent sensitization mechanism could be a tentative pathophysiological factor in the development of PPSP, translational studies in humans have been carried out. A preliminary translational study from rodent to man indicates that the mechanism seems to be active also in humans [26], but the pathophysiological role needs to be elucidated.

Group III trajectories (Figure 2), precipitated by repeat-surgery, likely present neuroplasticity changes in the CNS. The maladaptive responses include the development of excessive hyperalgesia and increased pain perception due to central sensitization, facilitated by a compromised descending inhibitory pain modulation [27].

Group IV trajectories (Figure 2), demonstrating a presurgical high-intensity pain unchanged by surgery, the likely causative mechanisms are either irreversible tissue injury due to the groin hernia per se, e.g., compression or dislocation of nerve structures or the spermatic cord, or, more likely to unrelated causes; adductor muscle-related pathology, femoro-acetabular impingement, or “athletes” groin pain.

Pain trajectories: quantitative sensory testing and questionnaires

The weak statistical association observed between the QST-findings and the neuropathic pain questionnaires brings into question the clinical relevance of these research methods. Although recently published, high-powered peri-surgical QST-studies, have contributed to a heightened knowledge base regarding post-surgical pain outcomes [28], the QST-method seems an experimental measure supplementing the clinical assessments [29]. Our data corroborate recent findings on post-surgical neuropathy reporting no or sparse association between a neuropathic questionnaire, QST-findings, and PPSP [20]. Interestingly, in this recent study, 61% of the PPSP patients demonstrated “probable” neuropathic components assessed by QST, which corresponds to the present study with 57/95 (60%) patients demonstrating neuropathic components (Table 2) [20]. Furthermore, in selected neuropathic pain patients, moderate concordance rates between dynamic QST-assessments and neuropathic pain questionnaires were demonstrated [30]. The authors concluded that since questionnaires mostly evaluate the ongoing pain experience while QST mirrors sensory functions, both methods are complementary for pain assessments.

Furthermore, the weak statistical association, also evident between the three “clusters” (Figure 3), neuropathic pain questionnaires, psychometrics, and groin hernia repair related persistent pain intensity and its functional consequences, are interesting. The within “cluster” statistical associations obviously confirmed a closer correlation than in the between “cluster” associations but examining the coefficients of determination (R²) of the within “cluster” associations; the independent variable could only explain 29–42% of the variance for the dependent variable.

Limitations of the study

First, it could be argued that the statistical analysis of group membership comparing post-surgical AUC-trajectory data is subjected to circular reasoning: the trajectories were a priori divided into groups using a graphical discrimination paradigm, and then the groups were subjected to statistical analysis (i.e., graphical discrimination is valid because a statistical difference has been demonstrated; statistical discrimination is valid because a graphical difference has been demonstrated). The authors, at least partially, concede to the flaw of circular reasoning. However, the intention of the statistics was to investigate the
discriminative strength of the group outcomes. Interestingly, the PCA discriminated unambiguously between groups I and II, corroborating the validity of the observed group outcomes. Second, the study had a limited number of participating patients (n=95), increasing the potential risk of a type II error. Third, incompletely answered questionnaires from 8/95 patients were excluded from the PCA analysis. Imputations were not performed, thus reducing the volume of the original database with 8.4%. Fourth, the fairly large number of predictive variables (n=11) used in the analyses increased the overall risk of a type I error. Furthermore, no attempts at estimating sample or effect sizes were made. The authors can only justify this by the hypothesis-generating nature of the study; by the research issue itself, nearly devoid of previous scientific data; and by the multivariate data analyses, like PCA and multiple logistics regression analyses, required to potentially decipher the multifactorial etiological mechanisms in PPSP. Fifth, another limitation is, while the pain trajectory graphs were based on self-perceived and self-reported data, the data are likely to be subjected to retrospective recall bias: influenced by the inherent temporal variation in cognitive, emotional, sensory, and social awareness by the subject. In future studies, data replicability should be tested, i.e., testing the month-to-month variance in the perceived pain trajectories [31]. Sixth, a limitation, however, that in certain aspects also could be recognized as a strength, is that only patients with severe pain intensity (NRS > 7) were included. Our data, thus, cannot directly be extrapolated to patients with less severe pain states. However, from a methodological standpoint, focusing on patients with severe pain intensities, the likelihood of finding essential differences between the groups, e.g., functional indices and psychometrics, may increase. In this hypothesis-generating study, it is thus reasonable to assume that high-intensity pain per se has a “contrast-enhancing” effect of potential value in characterizing the groups for future intervention studies. In chronic pain trials of analgesics, the recommended inclusion-range of patients’ pain intensities are NRS 5–9 in order to increase the assay sensitivity [32, 33].

**Strengths of the study**

Several advantages of the present study are noticeable compared to other SSPS-studies. First, the study recruited, on a nationwide basis, a procedure-specific consecutive cohort of patients with severe pain after groin hernia repair, with impaired psychosocial and physical functions. Second, data sampling was prospective and consecutive. Third, the patients were comprehensively evaluated by standardized clinical examinations and QST-assessments and, validated questionnaires, minimizing the data variability. All assessments were performed by two investigators (EKJ and MUW), minimizing the data variability.

**Implications of the study**

Examination of pain trajectories, mirroring the transition from acute to severe persistent post-surgical pain, has the potential of uncovering clinically relevant pathophysiological mechanisms. The findings of this study corroborate previous studies [5, 6], suggesting that the transition process may be more complex than hitherto assumed. Several studies have suggested that acute pain trajectories provide a superior assessment of pain experience, capturing the variability of pain better than conditional pain measurements [9, 34] and thus may improve identification of subjects at risk for development of severe persistent post-surgical pain.

**Research funding:** The authors state no funding involved.

**Authors’ contributions:** EKJ and MUW conceived the idea and designed the study. EKJ and MUW acquired the clinical test-data. EKJ managed the study database. EKJ conducted statistical analyses under guidance from JH (biostatistician) and MUW. Analyses and interpretation of study data were by MUW, EKJ, EB, and JH. EKJ wrote the first draft of the manuscript. All authors revised the manuscript and approved the present version of the manuscript.

**Competing interest:** The authors state no conflict of interest.

**Informed consent:** Informed consent has been obtained from all individuals included in this study.

**Ethical approval:** The research related to human use complied with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board or equivalent committee.

**Data availability:** Data are available upon request to the corresponding author.

**References**


Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/j_sjpain-2020-0104).

DE GRYTER