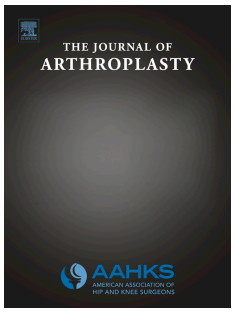

Factors associated with the risk of developing moderate to severe acute postoperative pain following primary total knee replacement: Results from the PAIN OUT registry

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Factors associated with the risk of developing moderate to severe acute postoperative pain following primary total knee replacement: Results from the PAIN OUT registry

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Highlights:

- Risk factors associated to acute pain after Total Knee Replacement

Category: Original article

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Abstract

Background: Total knee replacement (TKR) is one of the most common procedures in orthopaedic surgery and not always matches with patient's expectations of pain relief and function improvement. The aim of this study was to assess risk factors for developing moderate to severe acute postoperative pain (APOP) after TKR using the PAIN OUT Questionnaire.

Methods: Prospective, multicentre, international cohort study within the PAIN OUT PROJECT. Patients' outcomes were measured with 11-point numerical rating scales (0=null, 10=worst possible). Patient and analgesic/anaesthetic treatment were assessed. Odds ratio for moderate-severe pain were calculated for each variable and if they were statistically significant in the univariate logistic model, variables were fitted into a multivariate logistic regression model. The effect size was assessed by Cohen´s d coefficient.

Results: In total, 968 patients were evaluated. The multivariate model identified chronic preoperative pain ($p<0.001$), general anaesthesia ($p=0.020$), receiving chronic opioids before ($p=0.020$) or after the surgery ($p<0.001$) as factors associated with moderate-severe APOP. No protective factors were observed.

Conclusions Our model identified several risk factors for APOP. From our results, preoperative chronic pain, general anaesthesia and the use of opioid analgesics could be predictors for higher APOP. These findings may help establish new strategies for the treatment of pain in TKR. More studies should be carried out to identify acute pain predictors and to develop better strategies of pain management for risk patients.

Keywords

- Total Knee Replacement
- Pain management
- Questionnaire
- Postoperative pain
- Acute Pain
- Risk factors

Introduction

Total knee replacement (TKR), one of the most common procedures in orthopaedic surgery [1] is expected to rise [2]. Between 2005 and 2011 there was a 10-fold increase in TKR among the 35 countries included in the Organization for Economic Cooperation and Development (OECD) [2]. This trend could promote a four-fold demand for TKR in OECD countries by 2030 [3]. Primary TKR in USA is estimated to increase to 3–4 million/year, and TKR revision up to 270,000/year [4]. In the UK, from 1991 to 2006, the rates of TKR more than tripled: from 42.5 to 138.7 per 100,000 person-years for women, and from 28.7 to 99.4 per 100,000 person-years for men [5]. Reasons for the strong demand in TKR are multi-factorial: a longer life expectancy; an increasing body mass index (BMI); technological advances; greater patient awareness; and an increased surveillance for the disease, the latest factors possibly promoting the TKR at an earlier stage of disability compared to 15 years ago [5].

Although TKR is regarded as a highly successful procedure, it does not necessarily match with patient's expectations, and actual outcomes of pain and function impairment are well-known. Patients undergo a TKR for improving their quality of life, by reducing pain and resuming daily life activities. However, a systematic review of the literature indicates that 20% of patients remain with unfavourable long-term pain outcomes after TKR [6]. The recurrence and/or developing persistent pain after TKR, and its prognosis, are of concern for both patients and care providers. A high proportion of TKR patients experience chronic pain and receive opioids before surgery, both factors are associated with severe pain after surgery [7,8]. It is important to know how modifiable factors, such as BMI and comorbidities, could impact on pain following TKR. Factors such as these might help in identifying patients at risk for developing pain after TKR, so treatment before and after surgery can be tailored and optimized [6]. Besides promoting suffering, acute postoperative pain (APOP) has been associated with a delay in postsurgical recovery and an increase in the proportion of patients reporting chronic pain after surgery [9].

The aim of the present investigation was to assess risk factors for patients developing moderate to severe pain after TKR using the self-administered and validated International Pain Outcomes Questionnaire [10], and to compare the results with those obtained in previous studies. Data were obtained from a large, multi-centre cohort from the PAIN OUT PROJECT [11].

Material and Methods

Study design

The analysis presented here relies on data collected prospectively by hospitals who participated in the PAIN OUT registry and which had contributed fifteen or more records to the repository of patients who underwent TKR. All collaborators obtained approval for collecting non-identified patient data from their local ethics committees. The methodology used in PAIN OUT has been published elsewhere [12,13]. PAIN OUT is a web-based database that registers pain outcomes and management from hospitals at European and international level with the aim of improving clinicians' decision making and consequently postoperative outcomes [11]. It is registered at ClinicalTrials.gov (NCT02083835). The present study is a hypothesis generating study relying on data from the clinical routine.

Subjects

Inclusion criteria required that the patient: 1) underwent unilateral TKR (ICD9 81.54) as main surgery; 2) was of consenting age (18 years in general or 16 years in the United Kingdom) or older; 3) was on the first postoperative day (POD1) and back on the ward from the recovery room for at least 6 hours; and 4) agreed to participate in the survey. Consent could be oral or written, depending on requirements of the local ethics committee. Surgery for revision operations and bilateral operations were excluded. Epidural anaesthesia was also excluded given that it is not recommended for TKR [14].

Questionnaires

Data collection for each patient involved two questionnaires: 1) *Demographic and clinical*, obtained from the medical record by a surveyor, which comprises: gender, age (year of birth), weight, height, comorbidities that might interfere with the management of acute pain, administration of opioids before admission, administration of analgesics perioperatively, type of surgery, and type of anaesthesia; and 2) the *International Pain Outcomes* Questionnaire (IPO-Q) [10] which evaluates four domains: 1) *Severity of pain*, e.g. worst pain since surgery; 2) *Interference of pain:* e.g. with activities in bed such as turning, sitting up, and changing position, and affect due to pain specifically on anxiety and helplessness; 3) *Adverse Effects* (AEs): nausea, fatigue, dizziness, itch; and 4) *Perception of care*, assessed whether patients felt satisfied with the pain treatment provided; would have like to receive more pain treatment; participated in decisions concerning their treatment; and received information about pain treatment options. Patients also reported whether they had a persistent painful condition, and its severity, for three months of more before admission to hospital. Most items were scored using an 11-point numerical rating scale (0 = null, 10 = worst possible); and one item used a dichotomous yes /no scale. The questionnaire's psychometric properties have been assessed and validated [10]. As much as possible, patients received the questionnaire in their native language. It was available in nine different languages (English, French, German, Italian, Spanish, Serbian, Romanian, Russian and Ukrainian).

Data collection and storage

Surveyors were students, nurses, or medical residents who underwent training for approaching patients, collecting data, and entering the data into a web-based password secure portal. As far as possible, surveyors did not have clinical duties on wards from which they collected data. Patient's data was anonymised once the data was entered into the web-based mask; a randomized unique code was assigned to each patient file (unrelated to personal data, institution, or file number). The Institute for Medical Informatics, Statistics and Epidemiology at the University of Leipzig in Germany hosts and maintains the database.

Evaluation plan

Candidate variables, as predictors for developing moderate or severe postoperative pain (NRS≥4, Numerical Rating Scale) after TKR, included: 1) patient related factors: gender, age>65 years, BMI≥30 kg/m^2, chronic pain before surgery, anxiety; 2) treatment related: receipt of opioids before surgery at home, analgesic or anxiolytic premedication, general (GA) or regional (RA) anaesthesia, intraoperative opioids, RA in recovery and in the ward, intra-operative wound infiltration, opioids and non-opioids postoperatively, opioids given at any

perioperative time, multimodal analgesia (opioid+non-opioid). A cut-off of NRS>4 has been identified as the tolerable pain threshold above which patients require analgesic treatment [15].

Concerning how the type of anaesthesia was assessed, we considered the GA group as those patients who received intravenous or inhalational anaesthetic drugs, or a combination of both. We classified under RA, those patients who underwent the surgery with spinal (intradural) anaesthesia. Patients with femoral or femoral plus sciatic nerve blocks were not included in the RA group. These techniques were considered as analgesic treatment applied after surgery (recovery room and/or ward) to lessen the postoperative pain, and not to anesthetize the lower extremities during surgery [16]. Therefore, the outcome of nerve blocks was evaluated independently from the type of anaesthesia.

Sample size

A sample size of 1076 TKR patients permits to recognize, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, a between-group statistically significant difference in pain intensity between GA or RA higher than or equal to 0.5 NRS points. The common standard deviation for pain assessment is 2.5 [17]. This sample size permits a loss up to 10% of patients in the data analysis.

Statistical analysis

Data are presented as proportions, median (interquartile range, IQ), and mean (standard deviation, SD) when appropriate. For items in the questionnaire using 0-10 (or 0-100%) numeric rating scales (NRS), median and interquartile range were reported. Differences among groups were assessed by ANOVA or Chi-squared tests. The effect size, a quantitative measure of the strength of a phenomenon for assessing the clinical significance of the findings, was assessed by Cohen´s d coefficient with confidence interval 95 (CI95) [18]. Cohen´s d is classified as small (d =0.2), medium (d =0.5) and large (d =0.8). These criteria are recommendations, and interpreting the response requires personal judgment regarding the practical or clinical importance of the effect. We classified variables that demonstrated a medium or large effect as being clinically meaningful, and outcomes with small effect sizes as academically interesting but without clinical significance.

To assess the predictive value of perioperative variables for developing moderate or severe postoperative pain (NRS≥4), multivariate logistic regression was performed. Odds ratios for moderate-severe pain were calculated for each variable. Variables which reached significance in the univariate logistic model, were then fitted into a multivariate logistic regression model. We considered $p<0.05$ to be statistically significant. We used IBM Statistics SPSS 18 (SPSS Inc, IBM, SAS Institute, Chicago, US 2009) for the analyses.

Results

From December 2009 to October 2013, surveyors approached 1076 patients in 10 hospitals in the following 8 countries: France, Italy, Israel, Germany (n=3), Spain, Sweden, Switzerland and United Kingdom. Hospitals contributed an average of 97 datasets (range 17-225) to the patients' sample. In total 968 patients were registered into the analysis (see Figure 1). Of the 1076 patients approached, 26 (2.4%) patients did not want to participate in the study and 1050 (97.6%) met the PAIN OUT inclusion criteria. Additionally, 3 patients were excluded because they answered less than half of the answers in the questionnaire, and 43 patients were excluded because the answer to "worst pain" was missing. Patients who underwent surgery under epidural anaesthesia were excluded (n = 36).

Patients' characteristics. Females represented 62% of the sample. Mean age and BMI was 68.4 (Standard Deviation (SD) 10.7) years and 30.1 (SD 5.7) kg/m^2, respectively. Indicating that half of the sample (48.8%), were obese ($BMI \geq 30 kg/m^2$) (WHO, 2000). Most patients (78.5%) had a comorbidity, the most frequent being cardiovascular (mainly hypertension) in 57% of patients, followed by respiratory (15%), affective disorder (8%) and/or gastrointestinal comorbidities (7%). 107 patients (11.0%) received opioid analgesics before admission to the hospital, without further information on the type and duration of the treatment.

Treatment processes. Significant variability among hospitals was observed concerning the type of anaesthesia used intra-operatively ($P<0.001$). The preferred method of anaesthesia was GA (60.6%), ranging from 11% to 97% between hospitals. Infiltration of the surgical incision with analgesics was carried out in 16% of patients. Nerve blocks were used in 605 patients (62.5%).

Perioperative (intra- and postoperative) administration of non-opioids analgesics was high, with 96.9% of patients receiving this type of medication. Paracetamol was the most commonly used non-opioid analgesic. Most patients (82.1%) received one or more analgesic opioids perioperatively, mostly morphine (55.2%). As for multimodal analgesia, 94% of patients received 2 or more different analgesics perioperatively. Details about patient characteristics and treatment are provided in Table 1 and Table 3.

Postoperative outcomes are shown in Table 1. Median worst pain intensity was 7 points in the NRS (interquartile range (IQR) 4-8). Median least pain intensity was 2 (IQR 0-3) points NRS. Patients reported to being about one third of the postoperative time in severe pain (median 30%, range 10-50%). Median interference of pain while doing activities in bed was 5 (IQR 2-8) and with sleep was 2 (IQR 0-6) points NRS. Pain relief, in any degree, was achieved in 70% (50-90%) of patients. The median satisfaction with pain the treatment was high, 9 points (IQR 7-10), although 20.4% of patients would have want more pain treatment. Also, 78.3% of patients reported that they received information about their pain treatment options, and positively valued their participation in these decisions, 8 (4-10) points NRS.

The most frequent adverse effect was drowsiness (in 57.4% of patients), followed by nausea, dizziness and itching, 43.9%, 37.9% and 14.4% respectively. Also, 50.3% of patients reported being anxious and/or helpless (45.8%) after the surgery.

Characteristics of patients according to the intensity of worst pain after surgery

After surgery, the proportion of patients who experienced moderate-severe pain (NRS ≥4, n=698, 71.9%) was greater than those with mild pain (NRS<4, n=272, 28.1%see Table 2.

The proportion of patients in the moderate-severe pain group reporting chronic pain was higher than in the mild one with a medium effect size (P<0.001, d=0.5), see Table 2. There were more females in the group with moderate-severe pain but with a small effect size (P=0.034, d=0.2). The groups did not differ regarding to age, weight or intensity of chronic pain.

Patients in the moderate-severe pain group received more opioids before surgery with a small effect size (P=0.001, d=0.22). Differences for the type of anaesthesia had a small-medium effect size with a higher proportion of patients with moderate-severe pain that underwent surgery with GA (P<0.001, d=0.4). Receiving opioids after surgery, in the recovery room or the ward, was more prevalent in the moderate-severe pain group (P<0.001), with a medium effect size (d=0.64). Also, 18% of patients either did not receive intraoperative opioids or it was not informed in the medical record.

Peripheral nerve blocks were performed in 605 patients (62.5%) intraoperatively or at the recovery room. Overall, there were no significant differences in the worst pain outcomes in patients with nerve blocks or without. Wound infiltration was recorded in 16% of the patients, making it difficult to observe a clear clinical benefit in worst pain related.

Patients' participation in decisions about their pain treatment was lower in patients with severe pain compared with mild pain [8 (7-10) and 10 (8-10), respectively, p <0.001 d=0.49].

Univariate and multivariate analyses

Results of the univariate analyses are shown in Table 3. Factors which were associated with an increase in moderate-severe postoperative pain were: female sex (p=0.034); chronic preoperative pain (p<0.001); GA (p<0.001); receipt of opioids before admission to hospital (p=0.002) or during surgery (p=0.001), or as postoperative analgesia (p<0.001), or in any part of the process (total opioids) (p<0.001). Factors which were protective for developing moderate-severe postoperative pain were: any type of analgesia premedication (p=0.042) and to have received a wound infiltration (p=0.049).

Results of the multivariate logistic regression model including all variables which were significant in the univariate analyses are shown in Figure 2. Of these, chronic preoperative pain (p<0.001), GA (p=0.020) and to have received opioids before surgery (p=0.020) or as postoperative analgesia (in recovery room or ward) (p<0.001) were associated with moderate to severe acute postoperative pain. No protective factors were observed in the multivariate model.

Discussion

In this study, we assessed risk factors for patients experiencing moderate to severe pain after TKR in a European, plus Israel, population of 968 individuals. From our results, two preoperative predictors: chronic pain and opioid administration before surgery, one intraoperative procedure: general anaesthesia, and a postoperative procedure: opioid administration on the ward were associated with moderate-severe APOP.

Orthopaedic surgery is considered one of the most painful surgeries [1,19] due to the fact that the periosteum has the lowest pain threshold of the deep somatic structures [20]. The demand for TKR is increasing worldwide and, despite the safety and the efficacy of the procedure, the control of APOP is a key factor for a rapid and safe recovery [21]. In our study, median worst acute postoperative pain was 7 (4-8), with a mean of 6.0±2.9. These data are similar to those reported in TKR studies in Portugal (mean 5.3) [22], and in Germany (means of 5.3 and 5.6) [17,23]. They are, however, higher than those reported in USA with a median resting pain intensity of 4 (IQR 1–10) and with movement of 12 (7–15), on postoperative day 2 for NRS 0-20 [24]. Another American observational study [8], found mean pain scores on postoperative day 1 of 2.3±2.0 at rest and 3.0±2.7 at movement (NRS 0-10).

In a study concerning pain in TKR [25], females reported significantly higher pain at 24-48 hours postoperatively. Another study [19] reported age and sex as independent contributors for the development of severe postoperative pain defined as NRS ≥8.

From our results, however, neither gender nor BMI appear as major determinants for APOP after TKR. In our population, female sex had a significant relation with moderate-severe APOP only in the univariate analysis. Our results agree with those obtained in USA [8] and Portuguese populations [22,26] in the sense that a trend is observed, but significance is not reached. Sex could be a surrogate factor for anxiety in the preoperative state, and anxiety has been reported to worsen postoperative outcomes and be higher in women [22,27]. Preoperative anxiety can be managed through anxiolytic medication, among them benzodiazepines which have shown to reduce postoperative pain in several types of surgeries [28,29]. In our study, premedication was inversely related with APOP in univariate analyses. Both sex and premedication, however, lost their significance in the multivariate model.

Preoperative chronic pain is a recognized factor for moderate or severe APOP, both in TKR [7,8] and other types of surgeries [1,30–32]. Patients with chronic severe pain are more likely to receive chronic preoperative opioids, both factors being predictors for worsening pain after TKR in our analyses. The effect of chronic preoperative opioid administration on APOP could be partially explained by opioid induced hyperalgesia (OIH) [33]. Currently, given the concerns for OIH, the prescription of opioids for chronic non-cancer pain trends to be restrained [34]. Studies in preclinical models of post-incisional pain, have shown a dose-dependent nociceptive sensitization induced by opioids [35]. In clinical experimental studies [36], opioid dose and duration of treatment directly correlated with pain intensity. Previous clinical studies have reported an increase in postoperative pain hypersensitivity in patients receiving chronic opioids before surgery [37,38]. Chronic opioid consumption promotes opioid tolerance; therefore patients might require more opioids after TKR than opioid naïve ones.

In our survey, postoperative opioid administration was also associated with worst pain after TKR. However, in the *postoperative* period a causal relation between opioids and increased pain intensity cannot be assumed as the two factors are interrelated. In many patients, opioids after surgery are given on demand if patients have moderate or severe pain [16]; i.e., opioids are - at least partly - the consequence of (and not the reason for) increased pain.

Thus, chronic preoperative pain and chronic preoperative opioids are inter-twined phenomena associated with worse APOP after TKR surgery. In our survey, 14.7% of patients with moderate-severe postoperative pain received preoperative opioids, whereas 89.7% received opioids after surgery. Thus, in some of these patients, OIH and/or opioid tolerance could be present in the postoperative stage, in which case increasing the opioid doses do not reduce pain, even may increase it. In this context, guidelines from the American (APS, ASRAPM, ASA) [16], Australian-New Zealand [39], and French Pain Societies [40] recommend using analgesic techniques with opioid sparing effects, such as multimodal analgesia and nerve blocks (NB), for TKR.

The concern for the impact of anaesthesia modality on postoperative pain in TKR is growing lately. From our data, GA, appears as a determinant for moderate-severe APOP. Our results are in agreement with other reports which state that RA has significantly improved the perioperative pain, reduced opioids pain medication, and promoted a shorter rehabilitation in TKR patients [25,41,42]. The global postoperative quality of the immediate recovery after TKR has been shown to improve with peripheral NB with sedation versus GA in patients ≥65 years [43]. Recent studies with a large sample size (n=382,236 records) [44] show that in patients undergoing primary hip or knee arthroplasty, 11% were performed under neuraxial, 74.8% under GA, and 14.2% under combined neuraxial–GA [45]. Similarly, of 15,687 TKR procedures, 6.8% were performed under neuraxial, 80.1% under GA, and 13.1% under combined neural-GA [46]. In a retrospective study, 6,030 patients received spinal anaesthesia and 8,022 patients received GA [47]. In our survey GA was administered to 60.6% of the patients and RA to 39.4 %. However, although the global figures for GA administration in our study are similar or even lower than those reported above for TKR, a large diversity exists among our hospitals with percentages of GA from 11.1% to 96.9% in Europe, and with 92.3% in Israel. Diversity among hospitals concerning the use of GA has been also reported in USA studies. Liu et al. [8] in 897 patients undergoing primary hip or knee arthroplasty from 4 USA hospitals reported a range from 1% to 62% in GA administration. NB after TKR are recommended in pain management guidelines [40,48,49]. Our data support the need, when possible, to move from GA to RA practice for TKR pain management [8,48].

Although peripheral nerve blocks are recommended in international guidelines for pain management after TKR [40,48,49] our model did not reflect a protective effect of this technique against APOP. Due to the way in which the data were recorded the NB administered during surgery or as rescue analgesia at the postoperative period were assessed together, we do not have an accurate explanation for this fact. Therefore, we could have patients who after suffering intense pain were administered with a rescue NB. Due to this, a certain bias, related to the time of the application of nerve blocks and the appearance of intense pain, could appear. Another possible explanation for the underperformance of NB could be that the analgesic effect of the intraoperative NB was worn off, and patients suffered APOP at some degree at the moment of the survey.

Additionally, the performance of nerve blocks requires a learning curve and a certain failure rate is expected; especially if the effectiveness of the blockade is not evaluated [50].

As for local infiltration analgesia of the wound, it was performed in a small percentage of patients (16%), and showed a minor protective effect for developing moderate-severe postoperative pain in univariate analysis. The low percentage of infiltrations registered, and the lack of data regarding the anaesthetics used, the doses and the techniques used limit the validity of this variable as a risk factor. However, our multivariate model accepted the low percentage of and that is why we used it. Wound infiltration as part of multimodal analgesia is recommend in several publications [51,52], therefore it is expected that if a higher percentage of patient had received local infiltration, we could have seen its beneficial effect within the multivariate model.

At this point, we would like to compare our results with those obtained by Baca et al., 2019 in a study similar within the PAIN OUT Project [53]. In their predictive model with 1008 patients that underwent spinal surgery Baca et al. identified the following predictors of pain on POD1: female sex, preoperative chronic pain, intraoperative use of volatile anaesthetics, intraoperative use of remifentanil and ketamine, surgery duration and opioid use in the recovery room. Moreover, the intraoperative administration of non-opioid analgesics strongly predicted decreased pain on POD1. Considering the differences in the type of surgery and the nature of predictive model, our findings concur in the preoperative chronic pain and the use of perioperative opioids. Nevertheless, in their multivariate model chronic opioid use before surgery was not predictive of pain on POD1 [53].

Our study has strengths and limitations. As limitations, participation from the hospitals and patients was voluntary, and that can produce a bias toward a willingness for assessing pain outcomes. The data was obtained from few centres, in a variety of countries, and so the findings cannot be generalized. Pain was evaluated once, on the first postoperative day, thus, answers could be influenced by the analgesic schedule of the specific ward and the level of pain experienced while filling in the questionnaire. There was no homogeneity in the number of patients by hospital and this could affect the generalization of the results. Among strengths, we used the IPO questionnaire which consistency, reliability, construct, and discriminant validity has been validated [10]. Self-administration of the questionnaire reduces the bias which occurs when external interviewers are involved [16,54]. Also, data collection was carried out trained personnel, and registered in a protected and monitored database, thus, ensuring data homogeneity across study centres.

Conclusions

In summary, our multivariate logistic regression model identified chronic preoperative pain, GA and to have received opioids before surgery or as a postoperative analgesia associated with moderate to severe acute postoperative pain. Mechanisms for the identified predictors are speculative and its justification out of the scope of this observational study. However, chronic preoperative pain and home use of opioids before surgery may reflect a greater severity of the underlying pathology, pain sensitization or opioid induced hyperalgesia in some patients. Additional studies should be carried out to identify acute pain predictors that may involve and additional effort in the pain management in certain patients.

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Table 2. Characteristics of the sample according the intensity of worst pain

Variable (%)	Intensity of worst pain			
	Mild (NRS <4) (N= 272)	Moderate-Severe (NRS ≥ 4) (N = 696)	**P value**	**Effect size**
Sex, *Female %*	56.6	64.0	0.034	0.17
Age ≥65, *years %*	71.1	66.6	0.180	0.14
BMI ≥30, *%*	50.5	48.0	0.561	0.05
Chronic preoperative pain, *%*	77.0	88.9	**<0.001**	**0.31**
General Anesthesia, *yes %*	47.8	65.6	**<0.001**	**0.39**
Intrathecal Reg. Anesth., *yes%*	52.2	34.5	**<0.001**	**0.39**
Local infiltration analgesia, *%*	19.8	14.4	**0.048**	**0.35**
Nerve blocks, *%*	61.8	62.7	0.788	0.13
Opioids, *%*				
Chronic before surgery	6.3	14.4	0.001	0.22
During surgery (intra-op)	75.0	84.5	<0.001	0.27
Postoperative	68.4	87.5	**<0.001**	**0.64**
Non-Opioid analgesics, *%*	97.8	96.6	0.318	0.08

NRS, numeric rating scale from 0-10. Cohen´s d coefficient was used to estimate the effect size. Significant effect sizes (>0.3) are shown in **bold**. N, number of patients who answered the item. When the summation of both categories (of any given factor) does not reach the total number of patients in the sample (968) is because there are missing values in the registry. OR, Odds ratio; 95%CI, confidence interval 95%.

Table 3. Univariate analysis for the association between risk factors and moderate-severe postoperative worst pain (≥4, NRS).

	N (%)	OR	95%CI	P value
Gender				
Men	368 (38.0)			
Women	600 (62.0)	1.36	(1.02 – 1.81)	0.034
Age				
<65 years	309 (32.1)			
≥65 years	653 (67.9)	0.81	(0.60 – 1.10)	ns
Body mass index				
<30	330 (51.2)			
≥30	314 (48.8)	0.69	(0.44 – 1.09)	ns
Preoperative chronic pain				
No	139 (14.4)			
Yes	823 (85.6)	2.38	(1.65 – 3.45)	<0.001
Preoperative chronic opioids				
No	779 (87.9)			
Yes	107 (12.1)	2.47	(1.42 – 4.30)	0.002
Comorbidities				
No	195 (20.4)			
Yes	761 (79.6)	1.06	(0.75 – 1.50)	ns
Anxiety				
No	882 (92.3)			
Yes	74 (7.7)	1.22	(0.70 – 2.11)	ns
Premedication				
No	136 (14.5)			
Yes	801 (85.5)	0.63	(0.40 – 0.98)	0.042
Type of anaesthesia				
Intrathecal	382 (39.5)			
General	586 (60.5)	2.08	(1.57 - 277)	<0.001
Intraoperative opioids				
No	176 (18.2)			
Si	792 (81.8)	1.82	(1.29 – 2.56)	0.001
Nerve Block				
No	363 (37.5)			
Yes	605 (62.5)	1.04	(0.78 – 1.39)	ns
Wound infiltration				
No	747 (84.0)			
Yes	142 (16.0)	0.70	(0.47 – 0.99)	0.049
Postoperative opioids				
No	173 (17.9)			
Yes	795 (82.1)	3.24	(2.31 – 4.56)	<0.001
Postoperative non-opioids				
No	30 (3.1)			
Yes	938 (96.9)	0.63	(0.26 – 1.57)	ns
Opioids (total)				
No	34 (3.5)			
Yes	934 (96.5)	3.41	(1.71-6.82)	<0.001
Analgesic combination				
1 analgesic	58 (6.0)			
≥2 analgesics	910 (94.0)	1.07	(0.60 – 1.91)	ns

NRS, numeric rating scale from 0-10. Cohen´s d coefficient was used to estimate the effect size. Significant effect sizes (>0.3) are shown in **bold**. N, number of patients who answered the item. When the summation of both categories (of any given factor) does not reach the total number of patients in the sample (968) is because there are missing values in the registry. OR, Odds ratio; 95%CI, confidence interval 95%.

Table 1. Postoperative outcomes

	N (%)	Median (IQ) or %
Related with pain		
Worst pain, *NRS*	968 (100)	7 (4-8)
Least pain, *NRS*	957 (98.8)	2 (0-3)
How often in severe pain?, *%*	908 (93.7)	30 (10-50)
Interference with in bed activities, *NRS*	871 (89.9)	5 (2-8)
Interference with breathing deeply or coughing, *NRS*	649 (67.0)	0 (0-0)
Interference with sleep, *NRS*	674 (69.6)	2 (0-6)
Have you been out of bed? (yes), *%*	697 (71.9)	39.3
Interference with out of bed activities, *NRS*	400 (41.3)	6 (3-8)
Pain relief, *%*	826 (85.2)	70 (50-90)
*Adverse Events, %**		
Anxiety	946 (97.7)	50.3%
Helplessness	942 (97.3)	45.8%
Nausea	957 (98.9)	43.9%
Drowsiness	952 (98.3)	57.4%
Itching	952 (98.3)	14.4%
Dizziness	952 (98.3)	37.9%
Perception of care		
Would you have liked MORE pain treatment? (yes), *%*	951 (98.1)	20.4
Information on your pain treatment options (yes), *%*	955 (98.6)	78.3
Allowed to participate in decisions on your pain treatment. (yes), *NRS*	849 (87.6)	8 (4-10)
Satisfaction with the results of your pain treatment, *NRS*	897 (92.6)	9 (7-10)
Did you use or receive non-medical treatments for pain? (yes), *%*	962 (99.3)	64.3

N, number of patients with a registered answer. IQ, interquartile range. NRS, numeric rating scale from 0-10.

*Adverse Events are presented as % of patients with ≥1 NRS.

Figure 1. Study Overview (patient inclusion diagram).

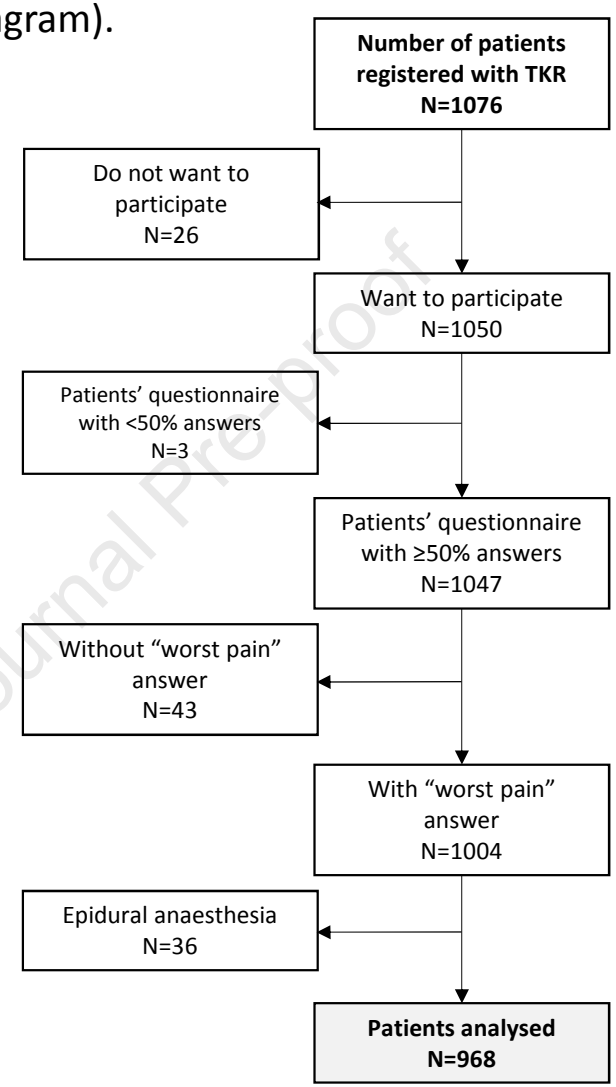

Figure 2. Multivariate analyses of the association between moderate-severe chronic pain (NRS>4, scale from 0-10) and variables which reached significance in the univariate analyses.