Persistent neuropathic pain after inguinal herniorrhaphy depending on the procedure (open mesh v. laparoscopy): a propensity-matched analysis

Patrick Niccolaï, MB
Lemlih Ouchchane, MD, PhD
Maurice Libier, MB
Fayçale Beouche, MB
Monique Belon, MB
Jean-Marc Vedrinne, MB
Bilal El Drayi, MB
Laurent Vallet, MB
Franck Ruiz, MB
Céline Biermann, MD
Pascal Duchêne, MB
Claudine Chirat, MB
Sylvie Soule-Sonneville, MS
Christian Dualé, MD, PhD
Claude Dubray, MD, PhD
Pierre Schoeffler, MD

Correspondence to:
C. Dualé
CPC / CIC, bâtiment 3C
CHU de Clermont-Ferrand
Rue Montalembert, BP69, 63003
Clermont-Ferrand Cedex 1, France
cduale@chu-clermontferrand.fr

Background: A greater incidence of persistent pain after inguinal herniorrhaphy is suspected with the open mesh procedure than with laparoscopy (transabdominal preperitoneal), but the involvement of neuropathy needs to be clarified.

Methods: We examined the cumulative incidence of neuropathic persistent pain, defined as self-report of pain at the surgical site with neuropathic aspects, within 6 months after surgery in 2 prospective subcohorts of a multicentre study. We compared open mesh with laparoscopy using different analysis, including a propensity-matched analysis with the propensity score built from a multivariable analysis using a generalized linear model.

Results: Considering the full patient sample (242 open mesh v. 126 laparoscopy), the raw odds ratio for neuropathic persistent pain after inguinal herniorrhaphy was 4.3. It reached 6.8 with the propensity-matched analysis conducted on pooled subgroups of 194 patients undergoing open mesh and 125 undergoing laparoscopy (95% confidence interval 1.5–30.4, p = 0.012). A risk factor analysis of these pooled subgroups revealed that history of peripheral neuropathy was an independent risk factor for persistent neuropathic pain, while older age was protective.

Conclusion: We found a greater risk of persistent pain with open mesh than with laparoscopy that may be explained by direct or indirect lesion of nerve terminations. Strategies to identify and preserve nerve terminations with the open mesh procedure are needed.

Contexte : On soupçonne que l'incidence de la douleur persistante à la suite d'une hernioplastie inguinale est plus élevée avec la mise en place d'un filet par voie ouverte qu'avec la laparoscopie (transabdominale prépéritonéale), mais encore faut-il clarifier le rôle de la neuropathie.

Méthodes : Nous avons mesuré l'incidence cumulative de la douleur neuropathique persistante, décrite comme une douleur au site opératoire accompagnée d'éléments neuropathiques déclarés par le patient dans les 6 mois suivant la chirurgie, auprès de 2 sous-cohortes prospectives d'une étude multicentrique. Nous avons comparé la mise en place d'un filet par voie ouverte et la laparoscopie à l'aide de différentes analyses, dont une analyse avec appariement des scores de propension, les scores de propension découlant d'une analyse multivariée générée à partir d'un modèle linéaire généralisé.

Résultats : En tenant compte de tout l'échantillon de patients (242 soumis à la mise en place d'un filet par voie ouverte c. 126 soumis à la laparoscopie), le rapport des cotes brut pour la douleur neuropathique persistante après l'hernioplastie inguinale était de 4,3. Il a atteint 6,8 à l'analyse par appariement des scores de propension réalisée auprès de sous-groupes réunis de 194 patients soumis à la technique ouverte avec treillis et 125 soumis à la laparoscopie (intervalle de confiance à 95 % 1,5–30,4, p = 0,012). Une analyse des facteurs de risque pour ces sous-groupes réunis a révélé que des antécédents de neuropathie périphérique constituaient un facteur de risque indépendant à l'égard de la douleur neuropathique persistante, tandis que l'avancée en âge a conféré un effet protecteur.

Conclusion : Nous avons observé un risque plus élevé de douleur persistante associée à la mise en place d'un filet par voie ouverte qu'avec la laparoscopie, ce qui pourrait s'expliquer par des lésions directes ou indirectes aux terminaisons nerveuses. Des stratégies s'imposent pour identifier et préserver les terminaisons nerveuses lors de la mise en place d'un filet par voie ouverte.

A recent systematic review estimated the risk of postsurgical persistent pain (PSPP) to be 7%–12% after inguinal herniorrhaphy, depending on the method of meta-analysis.[1] This finding may have relevant consequences for public health, as inguinal herniorrhaphy is one of the most frequently practised surgeries in industrialized countries. Furthermore, a proportion of the reported cases of PSPP after inguinal herniorraphy is suspected to be neuropathic, as nerve dysfunction has been reported after inguinal herniorrhaphy.[2] In addition, a literature-based estimation that took into account certain symptoms of persistent pain, such as numbness, paroxysmal pain or touch-evoked allodynia, stated that 30.5% of persistent pain was probably or definitely of neuropathic origin.[1] It has also been suggested that there is less risk of persistent pain with laparoscopic than with open inguinal hernia repair.[3] However, it is unknown whether this difference between the 2 techniques is maintained for neuropathic aspects of persistent pain. This mechanism is widely considered to be a factor of severity and chronicization.[4] In a recently published prospective open-ended French multicentric cohort study, the risk of persistent neuropathic pain in the 6 months following inguinal hernia repair was estimated at 12.4% for open mesh surgery and 3.2% for laparoscopic surgery.[5] We further studied these 2 subcohorts to assess the risk of persistent neuropathic pain associated with laparoscopic and open inguinal hernia repair. Our observational nonrandomized design resulted in unequal distributions of relevant covariates between comparison groups, but the level of evidence was improved by using an analysis based on propensity score.

METHODS

Our methodology is described in detail elsewhere.[5] Briefly, this multicentric French study was approved by the appropriate institutional research ethics boards (CCPPRB d'Auvergne and CPP Sud-Est VI for amendments), and the trial was registered on ClinicalTrials.gov (NCT00812734). In each centre, the study was coordinated by a referent anaesthetist and conducted by the anesthesiology team.

The study population consisted of prospective adult patients who, having given written informed consent, were scheduled in a recruitment centre for primary inguinal herniorrhaphy. We examined 2 procedures: open mesh and laparoscopy (transabdominal preperitoneal). The study centres were selected on the basis of their activity for these 2 procedures, aiming at a balance between them. The exclusion criteria for both procedures were planned laparotomy, reoperation, surgery for eventration, expected difficulty in the patient's ability to understand or complete the questionnaires and potential inability to reach the patient during the 6 months following surgery. The exclusion criterion specific to the open mesh procedure was a bilateral or intraperi-

toneal procedure. Laparoscopy had to be planned as such. Consecutive recruitment of patients was required.

The assessment of patients for inclusion in the study occurred 1–2 weeks before surgery. Patients completed a questionnaire about their working activities and history of previous pain, then the physician recorded information on potential symptoms of peripheral neuropathy and possible risk factors for peripheral neuropathy. The medical data sheet was completed on discharge from the surgical ward and included information on the strategies used for anesthesia, peri- and postoperative analgesia and the occurrence of early complications. At 3 and 6 months after surgery, patients received by mail a questionnaire in which they were asked to report whether they felt pain at the surgical site. If so, patients were asked to describe the intensity of this pain over the previous 48 hours using a visual analogue scale (VAS). Other questions concerned the time course of the pain since surgery and the clinical features; some questions were derived from the DN4 diagnostic questionnaire[6] and included within our questionnaire. If questionnaires were not completed and returned, we contacted the patients by telephone.

Postsurgical persistent pain was defined as self-reported pain at the surgical site; the pain was considered neuropathic in cases of 4 or more positive responses to the DN4 questions. Throughout the follow-up period, patients were able to visit a referent practitioner for analgesic treatment if required, or they could request a referral to the closest specialist pain centre. The primary outcome was the cumulative incidence of neuropathic postsurgical persistent pain, defined by occurrence at either the 3-month or 6-month follow-up. The primary end point was the effect of procedure type (open mesh v. laparoscopy) on the primary outcome, adjusted for covariates likely to influence either the occurrence of persistent pain or the choice of a given procedure.

Statistical analysis

We performed our analyses using SAS software version 9.3 (SAS Institute Inc.). Results are expressed as means ± standard deviations for normally distributed data and as medians and interquartile ranges for non-normally distributed data. Categorical data are expressed as number of cases and percentage of the total. Type-I error was set at 5%. We conducted risk factor analyses on the pooled data from the 2 subcohorts. The covariates to be considered in the multivariate analyses were first defined on the basis of their likelihood to influence the dependent outcome. These covariates were age, sex, body mass index (BMI), the centre at which the surgery took place, Pain Catastrophizing Scale score,[7] type of surgery, location of preoperative pain (if any), history of peripheral neuropathy, report of a putative neurotoxic condition (see Dualé and colleagues[5] for a detailed description of these 2 preceding

composite outcomes), the use and time of use of locoregional anesthesia, the use of intraoperative opioids and of intra- or postoperative ketamine, and the report of any early postoperative complications. Owing to the large number of centres, the centre where surgery was performed was not retained in the analysis.

To assess the risk of persistent neuropathic pain depending of the type of surgery, we calculated odds ratios (ORs) and their 95% confidence intervals (CIs) using different methods with a presumed progressive level of relevance: raw univariate analysis; multivariate analysis with simple adjustment, selection of factors and propensity score adjustment; and propensity score matching. Open mesh surgery was considered to be the reference to which laparoscopy was compared. We conducted the multivariable risk factor analysis using a multistep approach: 1) reduction of the number of covariates either by eliminating those with very low variability or by building new composite variables with greater relevance; 2) transformation of the continuous variables into ordinal variables according to their terciles taken as cut-off values to avoid bias due to a nonlinear relation with the dependent outcome; 3) elimination of the covariates for which the p value of the univariate Wald test exceeded 0.25 (with the exception of centre, age and BMI, which were forced into the model regardless of the p value); and 4) logistic regression with an automated backward elimination procedure with a significance threshold of $p <$ 0.05 to stay in the model. We used a propensity score to represent the probability that a patient with particular background characteristics (i.e., preoperative outcomes) would undergo the open mesh technique instead of laparoscopy. This score was calculated using logistic regression, with type of surgery as the dependent variable and all background characteristics as explanatory variables, as selected on the basis of their putative association with either the dependent outcome or exposure to the surgical procedure.[8] These characteristics were sex, BMI, age, Pain Catastrophizing Scale score, history of peripheral neuropathy, putative neurotoxic condition and existence/location of preoperative pain. Continuous variables were separated in terciles. The hypothesis was that background characteristics in both groups would be similarly distributed within propensity score strata. We performed a multivariate analysis with propensity score adjustment for additional perioperative covariates. The final step consisted of constructing 2 samples of patients (1 in each subcohort), matched according to a 1:2 algorithm without replacement within 0.25 standard deviations of the logit of their estimated propensity scores. Conditional logistic regression, accounting for correlation within matched pairs, was used to compare the outcome of interest between patients who underwent the open mesh technique and those who underwent laparoscopy.

The sample size calculation was performed on the basis of the prevalence of persistent pain after inguinal herniorrhaphy, as reported in the literature. As different rates were reported in the literature, we estimated a 30% rate after pooling all the related studies available at the time of our study (see Dualé and colleagues[5] for details). With a risk a set at 5%, a precision measure set at 5% and a prediction of 20% loss to follow-up during the study, we planned an initial sample of 389 patients for each subcohort.

RESULTS

We had some difficulty recruiting patients for the laparoscopy cohort; the results of an intermediate analysis of the primary outcome undertaken in September 2009 showed a cumulative incidence clearly inferior to the expected one, and the recruitment was discontinued at 40% of the initial objective. For the open mesh cohort, the same intermediate analysis showed a cumulative incidence slightly inferior to the expected one, and the recruitment was discontinued at 96% of the initial objective. A total of 530 patients were included (156 in the laparoscopy group, 374 in the open mesh group), and the surgeries took place between June 2006 and December 2008. Our analyses included only the patients for whom complete information on the studied outcomes was available: 126 patients who underwent laparoscopy and 242 who underwent open mesh repair, representing 80.7% and 64.7%, respectively, of all patients. The demographic and clinical characteristics of both subcohorts are summarized in Table 1; a full description is available elsewhere.[5] Ten patients were taking medication for pain 6 months after surgery, and 4 of them were considered to have neuropathic pain based on positive responses to the DN4 diagnostic questionnaire. When graded according to the World Health Organization's (WHO) analgesic ladder, 4 patients had a first-step and 3 had a second-step treatment, and 1 was treated for neuropathic pain (antidepressant plus gabapentin).

The centre where surgery was undertaken was not retained as a factor in the multivariate analysis, because the number of centres was too large and the number of patients per centre was too small and because, overall, each centre predominantly performed 1 of the 2 types of surgery. The intraoperative use of systemic opioids was the only factor representing the anesthetic practice that was retained for analysis, as it was less associated with the type of surgery and represented both the practice of general anesthesia and the time course of locoregional anesthesia (e.g., systemic opioids are not given for a surgery performed under successful spinal anesthesia). Two factors facilitating the incidence of neuropathic pain were identified by the stepwise logistic regression model: open mesh surgery (Table 2) and history of neuropathic event (OR 3.19, 95% CI 1.45–7.05, $p = 0.004$). Age older than the third tercile was found to be a protective factor (OR 0.18, 95% CI 0.06–0.53, $p = 0.049$). Table 2 shows the different ORs for the risk of occurrence of postsurgical persistent

Table 1. Demographic and clinical characteristics of the study sample

Characteristic	Group, no. (%)*	
	Laparoscopy, *n* = 126	Open mesh, *n* = 242
Male sex	122 (96.8)	219 (90.5)
Age (mean ± SD), yr	55.9 ± 12.4	59.5 ± 14.2
Weight (mean ± SD), kg	75.5 ± 9.2	74.5 ± 11.4
Height (mean ± SD), cm	174.7 ± 6.4	172.5 ± 7.8
Body mass index (mean ± SD)	24.7 ± 2.7	25.0 ± 3.4
Recruiting centre		
HR-1	23 (18.3)	10 (4.1)
HR-2	0 (0)	18 (7.4)
HR-3	0 (0)	26 (10.7)
HR-4	0 (0)	44 (18.2)
HR-5	10 (7.9)	0 (0)
HR-6	0 (0)	3 (1.2)
HR-7	44 (34.9)	1 (0.4)
HR-8	0 (0)	82 (33.9)
HR-9	0 (0)	44 (18.2)
HR-10	1 (0.8)	1 (0.4)
HR-11	2 (1.6)	0 (0)
HR-12	0 (0)	3 (1.2)
HR-13	46 (36.5)	0 (0)
HR-14	0 (0)	10 (4.1)
Catastrophizing Pain Score (preoperative), median [IQR]	9.5 [3 –17]	9 [3 –18]
Preoperative pain		
No pain	46 (36.5)	86 (35.5)
Elsewhere	18 (14.3)	35 (14.5)
Unknown location	24 (19.0)	44 (18.2)
Close to the site of surgery	33 (26.2)	74 (30.6)
At the site of surgery	5 (4.0)	74 (30.6)
History of peripheral neuropathy	30 (23.8)	74 (30.6)
Putative neurotoxic condition	3 (2.4)	34 (14.0)
Perioperative outcomes		
General anesthesia	124 (98.4)	185 (76.4)
Intraoperative use of systemic opioids	124 (98.4)	180 (74.4)
Locoregional anesthesia		
None	109 (86.5)	79 (32.6)
Postoperative only	12 (9.5)	11 (4.5)
Peroperative only	5 (4.0)	106 (43.8)
Peri- and postoperative	0 (0)	46 (19.0)
Perioperative use of ketamine	80 (63.5)	50 (20.7)
Postoperative complication	5 (4.0)	10 (4.1)
Persistent pain at 3 mo†		
All cases	29 (21.0)	55 (21.7)
Positive response to DN4	4 (2.9)	29 (11.4)
Pain score (VAS out of 10), median [IQR]		
DN4 (–)	2.3 [1.6 – 2.9]	1 [0.8 – 2.5]
DN4 (+)	Missing data§	2.4 [1.5 – 3.2]
Persistent pain at 6 mo‡		
All cases	18 (14.0)	60 (18.3)
Positive response to DN4	1 (0.8)	26 (7.9)
Pain score (VAS out of 10), median [IQR]		
DN4 (–)	1.5 [0.8 – 2.1]	1.1 [0.6 – 1.9]
DN4 (+)	Missing data¶	2.3 [1.4 – 5.1]
Report of persistent neuropathic pain, any time	4 (3.2)	30 (12.4)

DN4 = DN4 diagnostic questionnaire; IQR = interquartile range; SD = standard deviation; VAS = visual analogue scale.
*Unless otherwise indicated.
†*n* = 138 in the laparoscopy group and *n* = 254 in the open mesh group.
‡*n* = 128 in the laparoscopy group and *n* = 328 in the open mesh group.
§The 3 available pain scores were 1.2, 2.2 and 2.4 /10.
¶The pain score was 10/10 for the only case.

neuropathic pain (open mesh v. laparoscopy). For the multivariate analysis with propensity-score adjustment, the use of perioperative ketamine and the occurrence of postoperative complications were taken as additional perioperative covariates. The ORs were quite stable regardless of the method of analysis used with the exception of propensity-matched analysis, which had a lower precision owing to a smaller sample size. The OR tended to increase with the level of evidence, reaching a value slightly inferior to 7 for the propensity-matched analysis.

DISCUSSION

The main result of the present substudy is the strong difference in risk of occurrence of persistent neuropathic pain, with a nearly 7-fold greater risk of pain associated with open mesh compared with laparoscopic surgery. On the other hand, the risk of persistent pain, regardless of the suspected mechanism, was not substantially greater after open mesh than laparoscopic surgery (Table 1). This information adds to the debate about the optimal technique for herniorrhaphy, as a neuropathic mechanism is considered a factor of severity and chronicization of postsurgical persistent pain.[4,9] In addition, the role of preoperative history of peripheral neuropathy in the occurrence of persistent neuropathic pain, as shown previously,[5] was confirmed in our subcohorts. In addition, we observed no protective role of locoregional anesthesia, probably because this technique acts to block central sensitization rather than neuropathic processes.

Since both open mesh and laparoscopic surgery were developed in the late 1990s as an alternative to meshless herniorrhaphy, the issue of long-term complications of these 2 concurrent techniques has been addressed. Two meta-analyses conducted by the European Hernia Society, which covered the publication periods before and after May 2008, respectively,[10,11] failed to show a different risk of persistent pain between the 2 techniques. However, a recent review suggested a 3-fold greater risk (18% v. 6%) with open surgery than with laparoscopy,[12] and this finding is supported by a focus on the most prominent randomized trials[13–17] or well-sized prospective cohort studies.[18–20] It must be noted that pain was not the primary outcome in the trials and that none of these studies quantified the neuropathic aspect of pain. More information was recently provided by a prospective study of persistent pain 6 months after herniorrhaphy in 244 patients who underwent Lichtenstein and and 198 who underwent laparoscopic procedures, respectively, with clinical and psychophysical examination.[3] The adjusted OR for persistent pain was 0.45 (95% CI 0.23–0.87) for the laparoscopic compared with the Lichtenstein procedure (i.e., open mesh doubled the risk). The study also showed that patients who underwent open mesh surgery exhibited increased thresholds to warm and hot sensations in the groin area, a symptom suggesting nerve lesion.[2,21] It must be noted that, in that study, each centre offered only 1 type of surgery, but no adjustment based on propensity score was performed. Such adjustment reduces the bias due to factors that could influence the likelihood for each patient to undergo one procedure over another.[22]

As stated in the sample size estimation, based on the available literature we expected a 30% rate of persistent pain, regardless of the neuropathic features, at least for open mesh surgery. The rates observed in the present study were lower than expected, although this did not alter the statistical precision in estimating the risk. This is also consistent with a recent meta-analysis of 89 studies that estimated a 7%–12% risk of persistent pain after herniorrhaphy, regardless of the technique performed.[1] This decrease in global risk over the years may be explained either by an improvement in surgical techniques or by better precision in assessing pain. The authors also estimated that 30.5% of the pain reported was probably or definitely neuropathic, which is consistent with the observation of raw prevalence rates of pain at 6 months after open mesh surgery (18.3% for all pain and 7.9% for neuropathic pain). The lack of literature related to the association between neuropathic pain and laparoscopy makes any comparison with the present results difficult. The internal validity of the present study is supported by the results of the risk factor analysis, as a protective role of older age has been previously suggested in inguinal herniorraphy.[18]

Table 2: Analyses of persistent neuropathic pain following open mesh versus laparoscopic surgery						
	No. of patients					
Method	All	Laparoscopy	Open mesh	Reporting neuropathic pain	OR (CI 95%)*	p value
Univariate analysis	368	126	242	34	4.3 (1. 5–12.5)	0.007
Multivariate analysis, adjusted	368	126	242	34	5.0 (1.4–17.1)	0.011
Multivariate analysis, selected	368	126	242	34	4.6 (1.5–13.8)	0.006
Multivariate analysis, PS-adjusted	368	126	242	34	4.1 (1.3–13.0)	0.016
PS-matched analysis	319	125	194	30	6.8 (1.5–30.4)	0.012

CI = confidence interval; OR = odds ratio; PS = propensity score.
*OR estimated following 5 different techniques (see the Methods section).

Limitations

The present study has some methodological limitations. First, self-report screening questionnaires for neuropathic pain do not have a 100% sensitivity and specificity, and diagnosis should be confirmed by clinical examination.[23] Second, details of the precise location of neuropathic pain were not collected, although this information is important to estimate which nerve termination(s) may be involved. Third, information about the device used for open mesh repair (e.g., flat mesh, plug, bilayer) was not recorded. Techniques of nerve preservation were not noted either, as they had not been identified as a standard technique at the time of survey administration; there was no notion during our study period of any practice of intentional neurectomy for herniorrhaphy in France.

In addition, the incidence rates reported here do not imply that all cases will turn into chronic pain with relevant consequences on daily life. Severe cases of reported pain made up only about 4% of the whole cohort (18/458) 6 months after surgery, and few patients had treatment beyond the first step of the WHO analgesic ladder. This is in accordance with the literature, with respective rates of 2%–7% for severe persistent pain and 1%–3% for need for a treatment.[20,24–26] It cannot be ruled out that pain spontaneously resolved in some patients, as some studies with longitudinal follow-up showed a decrease in the rate of persistent pain with postsurgical delay.[27–29] At this point, only long-term cohorts who undergo clinical examinations can help to obtain relevant information.

CONCLUSION

The results of the present study are not sufficient to recommend the systematic use of laparoscopic surgery instead of open mesh for inguinal herniorrhaphy. First, laparoscopic repair may have disadvantages, such as a longer duration of the procedure and a higher rate of serious complications, including visceral and vascular injuries.[19] Second, the surgeons' experience, the patients' preference and their confidence in the team are well-known factors influencing the quality of the results. A recent review conducted by a collective of expert surgeons pointed out the challenge in developing strategies to identify and encourage the correct handling of the nerves involved in this surgery (i.e., ilioinguinal, iliohypogastric and genitofemoral nerves). There is still no high-level evidence to recommend a particular nerve-preserving technique.[30] It must be added that intraoperative nerve lesion is not the only possible mechanism of neuropathic pain. In patients who experience neuropathic pain and have been reoperated for this reason, examination has revealed not only cases of transection, neuroma or entrapment by sutures, but also entrapment in the fibrosis around the sutured mesh.[31,32]

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