

Review

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Risk factors of chronic pain after inguinal hernia repair: a systematic review

DOI 10.1515/iss-2017-0017

Received March 15, 2017; accepted March 20, 2017; previously published online May 12, 2017

Abstract

Introduction: Chronic postoperative inguinal pain (CPIP) is the most common complication after inguinal hernia operation. Eighteen percent (range, 0.7%–75%) of patients suffered from CPIP after open inguinal hernia repair and 6% (range, 1%–16%) reported CPIP after laparoendoscopic groin hernia repair. The incidence of clinically significant CPIP with impact on daily activities ranged between 10% and 12%. Debilitating CPIP with severe impact on normal daily activities or work was reported in 0.5%–6% of the cases.

Materials and methods: PubMed, Medline, Embase, and the Cochrane Database were searched for studies on risk factors for chronic pain after open and endoscopic hernia repair. A systematic review of the literature was conducted using the grading of recommendations, assessment, development, and evaluations (GRADE) methodology.

Results: Risk factors for CPIP with strong evidence include female gender, young age, high intensity of preoperative pain, high early postoperative pain intensity, history of chronic pain other than CPIP, operation for a recurrent hernia, and open repair technique. Risk factors for CPIP with moderate evidence include postoperative complications, neurolysis, and preservation of the ilioinguinal nerve in Lichtenstein repair. Risk factors for CPIP with low evidence include genetic predisposition (DQB1*03:02 HLA haplotype), lower preoperative optimism, high pain intensity to tonic heat stimulation, inadequate suture/staple/clip mesh fixation, ignorance of the inguinal nerves, less experienced surgeon, sensory dysfunction in the groin, and worker's compensation.

Conclusion: Detailed knowledge of the risk factors, meticulous operative technique with profound knowledge of the anatomy, proper nerve identification and handling, optimization of prosthetic materials, and careful fixation are of utmost importance for the prevention of CPIP.

Keywords: chronic pain; chronic postoperative inguinal pain; groin hernia; inguinal hernia; inguinodynia; risk factor.

Introduction

It is well established that surgical trauma may lead to chronic pain. According to published trials with systematic data collection, the highest chronic pain rates are reported after leg amputation, thoracotomy, and breast surgery with 60%, 50%, and 30%, respectively [1]. The advent of open mesh repair and laparoendoscopic techniques led to a significant reduction of recurrences after groin hernia surgery. Although chronic postoperative inguinal pain (CPIP) is less prevalent after mesh repair, it is today the most frequent complication after inguinal hernia repair [2].

The first small case series on CPIP was reported in 1984 by Harms et al. [3]. In 1996, Cunningham et al. [4] published a prospective randomized trial of 315 patients comparing Bassini, McVay, and Shouldice repair with chronic pain, numbness, and recurrences as the primary outcome parameters. After 1 year, 63% of the patients reported inguinal pain and 12% of patients suffered from moderate to severe pain. After 2 years, chronic pain rates decreased only slightly to 54% and 11%, respectively. The predictors for long-term postoperative pain were the absence of a visible bulge before the operation ($p < 0.001$), the presence of numbness in the surgical area postoperatively ($p < 0.05$), and patient requirement of more than 4 weeks out of work postoperatively ($p < 0.004$). The finding that chronic pain is a very frequent late sequelae of open inguinal suture repairs sparked worldwide a very strong interest among hernia surgeons to prevent and further investigate this often complex complication. This

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systematic review gives an update on the risk factors of CPIP.

Materials and methods

Search strategy

PubMed, Medline, Embase, and the Cochrane Database were searched for studies on chronic pain after open and endoscopic hernia repair. The search terms were “chronic pain” and “inguinal hernia” or “groin hernia”, “chronic pain” and “inguinal hernia” or “groin hernia” and “risk” or “risk factor”, “inguinal hernia” or “groin hernia” and “meta-analysis”, “inguinal hernia” or “groin hernia” and “systematic review”, “chronic pain” and “inguinal hernia” or “groin hernia” and “Shouldice” or “suture repair”, “chronic pain” and “inguinal hernia” or “groin hernia” and “Lichtenstein” or “open mesh repair, and “chronic pain” and “inguinal hernia” or “groin hernia” and “TEP or TAPP”.

The search detected 2013 abstracts. One hundred thirteen relevant papers were included in the review (Table 1). The grading of recommendations, assessment, development, and evaluations (GRADE) methodology was used for appraising studies and their level of evidence.

Definition of chronic pain

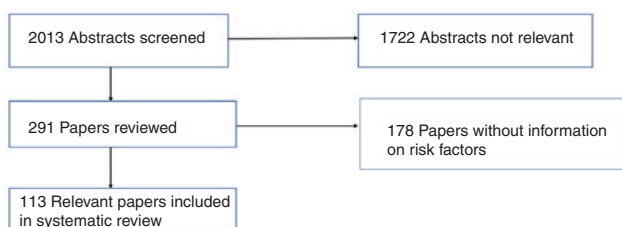
In 1986, the Association for the Study of Pain defined chronic pain as pain lasting more than 3 months [5]. This definition was used in the majority of studies on CPIP. However, some authors argued that inflammatory tissue reactions after mesh repair may lead to a prolonged healing process that may last longer than 3 months [4] and changed the definition of chronic pain to lasting longer than 6 months. In the absence of a more detailed definition, the results of the many trials on CPIP are difficult, if not impossible, to compare because there is no

uniform assessment of CPIP with regard to pain intensity, duration of pain episodes, impact on daily activities, physical activities, and impact on the quality of life. CPIP can also be classified according to its location. Most commonly, postherniorrhaphy pain is located in the groin. It may also cause symptoms in the genitals, thigh, and abdomen. Testicular pain (orchialgia) should be differentiated from scrotal skin pain. Moreover, inguinal hernia repair may also lead to pain-related sexual dysfunction, including dysejaculation [6, 7]. The HerniaSurge Group that has elaborated the first worldwide guidelines on inguinal hernia repair has defined CPIP as bothersome and at least moderate pain with impact on daily activities lasting 3 months or longer postoperatively [8].

Epidemiology of chronic pain

According to hernia registries, meta-analysis, and guidelines, 18% (range, 0.7%–75%) of the patients suffered from chronic pain after open inguinal hernia repair and 6% (range, 1%–16%) reported CPIP after laparoendoscopic groin hernia repair [1, 9, 10]. The incidence of clinically significant CPIP with impact on daily activities ranged between 2% and 12% [9–13]. Debilitating CPIP with severe impact on normal daily activities or work was reported in 0.5%–6% of the cases [9, 10, 13–15]. Also, 2%–3% of the patients suffered from chronic postoperative orchialgia. The large variance of reported chronic pain prevalence is due to inconsistent definitions and assessment of chronic pain in different trials. Whereas some trials defined any visual analog scale (VAS) score of pain >0 as chronic pain, other studies considered only VAS scores greater than 3 as chronic pain. In some publications, CPIP was defined as bothersome pain with impact on daily activities [12]. According to a 1-year questionnaire follow-up study of the Danish Hernia Database, 29% of the patients reported pain in the operated groin within the last month. Eleven percent suffered from work- or leisure-activity impairment and 4.5% of the patients needed medical treatment [16]. A 6-year long-term follow-up study of these chronic pain patients revealed an overall decrease of CPIP with less chronic pain in 76%, the same pain in 17%, and increased pain in 7% of the patients [14]. A trial from the Swedish Hernia Register on long-term CPIP (1–6 years after surgery) reported similar results: 29% of the patients reported pain within the last week and 6% suffered from pain interfering with daily activities [15]. The finding of the Swedish Hernia Register that chronic pain decreases over time [15] was not confirmed by a large prospective multiphase trial on 781 open primary inguinal hernia repairs (286

Table 1: Flow chart of the literature search.



Shouldice and 495 Lichtenstein operations). The chronic pain rate at 6 months and 5 years was 16% for both [17]. Current data of the German Hernia Registry “Herniamed”, which include 106,918 inguinal hernia repairs with 1-year questionnaire follow-up, reported chronic pain at rest, chronic pain during activities, and CPIP requiring any kind of treatment in 5.2%, 10.2%, and 3.2% of the cases, respectively. These data are in accordance with the results of Scandinavian hernia registers.

Characterization and mechanisms of CPIP

There are several overlapping causes and mechanisms of pain after prior inguinal hernia repair [1–3]. Preoperative and other non-surgery-related causes of CPIP have to be considered and differentiated. Nociceptive pain is mediated by tissue damage and (chronic) inflammation without damage of nerve structures. It can be related to recurrence, muscle or ligamentous strain, perineural fibrosis, scarring with or without from mesh, meshoma pain (related to wrinkling, migration, or folding of mesh), and suture or fixation material. Nociceptive pain is characterized as a dull ache over the groin area commonly described as gnawing, tender, pulling, or throbbing.

Neuropathic pain may be caused by direct nerve injury or nerve entrapment related to mesh, staples, tacks, suture material, scar tissue, neuroma, or tumor formation. Nerve destruction can also be caused by severe inflammation or infection. Neuropathic pain is described as stabbing, burning, shooting, or pricking, aggravated by walking or sitting. It often also characterized by paraesthesia (burning, pricking, or tingling sensation), hypoesthesia (reduced sensation), allodynia (pain from a nonpainful stimulus), and hyperalgesia (increased sensitivity to pain). The majority of pain experts believe that nerve damage is the most common cause of CPIP.

No studies have investigated whether nociceptive pain can be reliably distinguished from neuropathic pain and there is considerable overlap in symptoms, presentation, and findings. The classification of neuropathic and nociceptive pain has limited practical significance because there is no reproducible diagnostic method of differentiation between them. It has to be acknowledged that every skin incision in open hernia repair leads to damage of branches and subbranches of the inguinal nerves and thus implies the risk of neuropathic pain. Visceral pain may also confound the picture and contribute to the overall presentation of pain.

Risk factors and prevention of CPIP

Surgery-related (intraoperative and postoperative) risk factors have to be differentiated from those not related to surgery (Table 1) [9, 10]. Probably the most important but presently insufficiently analyzed risk factor of CPIP is the hernia surgeon. The most detailed analysis of risk factors for CPIP was published in the guidelines for the laparoendoscopic treatment of inguinal hernia of the International Endohernia Society (IEHS) [9, 10].

Risk factors for CPIP with strong level of evidence

According to several meta-analyses, guidelines, and register data on inguinal hernia repair, there is strong evidence that the risk of acute pain, CPIP, and numbness is significantly lower and the return to normal activities is faster after laparoendoscopic procedures compared to open mesh and nonmesh techniques [9, 10, 18–24]. The most likely explanation for the better outcome after totally extraperitoneal (TEP) repair and transabdominal preperitoneal (TAPP) repair is the minimal access trauma. Moreover, in laparoendoscopic groin hernia repair, the inguinal nerves remain in their natural embedding and are separated from the plane of dissection by a fascial layer. In open repair, the skin incision always implies nerve damage. Additionally, open mesh implantation often interferes with the ilioinguinal nerve (IIN). The risk of chronic pain after TAPP and TEP is the same. Open posterior mesh repair seems to be related to less CPIP than open anterior mesh implantation: a meta-analysis of randomized trials reported more chronic pain after Lichtenstein compared to preperitoneal repair [25]. The use of mesh seems to reduce the risk of CPIP [4, 9, 10, 21, 23, 26–28].

Several meta-analysis, register data, and guidelines have demonstrated that young age (age below median 40–50 years), female gender, high level of preoperative inguinal pain, high level of early postoperative pain intensity, history of chronic pain other than inguinal, and operation for a recurrent hernia are strong preoperative risk factors for CPIP (Table 1) [9, 10, 17, 27–30]. The causative mechanisms of these findings remain unclear and need further investigation.

Risk factors for reoperation for CPIP

Patients with strong risk factors for CPIP may also have a higher risk for reoperation for severe chronic pain that is

refractory to nonsurgical treatment. According a recent publication of the Swedish Hernia Register, 218 patients (0.13%) after 166,760 primary inguinal hernia repairs had to be reoperated for CPIP. Risk factors for being reoperated due to chronic pain include age below median, female gender, a direct hernia, a previous Lichtenstein or plug repair, bilateral repair, and postoperative complications [31].

CPIP risk factors with moderate or low evidence

Neurolysis and preservation of the IIN in Lichtenstein repair is significantly associated with chronic pain after 5 years [17] (see nerve management chapter; moderate level of evidence).

According to a clinical trial from Sweden, there seems to be a genetic predisposition for postoperative chronic. HLA DRB1 genotyping of 189 patients with or without CPIP revealed that significantly more patients with chronic pain were carrying DRB1*04 compared to patients in the pain-free group. Additional typing of the DQB1 gene further strengthened the association; carriers of the DQB1*03:02 allele together with DRB1*04 displayed an increased risk of postsurgery pain with an odds risk of 3.16 (1.61–6.22) compared to noncarriers. Similar results were found in patients with chronic pain after lumbar disk surgery [32] (low level of evidence).

Other risk factors for CPIP with low level of evidence include lower preoperative optimism, inadequate use of sutures, staples, and clips, nerve-ignoring operation technique, less experienced surgeon, sensory dysfunction in the groin, postoperative complications (hematoma, infection), and worker's compensation (Table 2) [9–11, 18–22].

Quantitative sensory testing (QST)

A systematic review of predictive experimental pain studies of QST investigated mechanical, thermal, and electrical stimuli and concluded that there is no simple reliable prognostic assessment method for postoperative pain [33]. Preoperative QST may help to identify patients with lowered threshold for experimentally induced tonic heat stimulation who seem to have a higher risk to suffer from CPIP (low level of evidence) [24].

Mesh

The use of mesh seems to reduce the risk of CPIP compared to suture repair [4, 9, 10, 21, 23, 27, 28, 34]. Many

Table 2: Risk factors for CPIP.

Preoperative risk factors
Female gender (strong)
Young age (strong)
High intensity of preoperative pain (strong)
History of chronic pain other than CPIP (strong)
Operation for a recurrent hernia (strong)
Genetic predisposition (DQB1*03:02 HLA haplotype) (low)
Lower preoperative optimism (low)
High pain intensity to tonic heat stimulation (low)
Worker's compensation (very low)
Intraoperative risk factors
Open repair technique (strong)
Preservation of the IIN in Lichtenstein repair (moderate)
Inadequate suture/staple/clip mesh fixation (low)
Mesh type: heavyweight mesh in open repair (low)
Ignorance of the inguinal nerves (low)
Less experienced surgeon (low)
Postoperative risk factors
High early postoperative pain intensity (strong)
Postoperative complications (hematoma, infection) (moderate)
Sensory dysfunction in the groin (low)

trials have investigated the question whether lightweight meshes (LWM) may reduce the risk of CPIP. The interpretation of these studies is difficult due to the large variety of mesh materials and mesh properties such as weight, pore size, tensile strength, weaving pattern, and elasticity [9, 10, 27, 28].

Open surgery

Short-term follow-up studies comparing heavyweight mesh (HWM) and LWM in Lichtenstein repairs reported a lower incidence of pain [35–38] and foreign body sensation [35, 39–41] in the LWM group [29]. Four longer-term follow-up trials (3–5 years) found no difference in chronic pain between LWM and HWM repairs [37, 39, 42, 43]. One randomized controlled trial (RCT) reported a lower incidence of chronic pain with LWM [40]. Long-term studies did not report a difference in the incidence of recurrence [37, 39, 40]. Notably, the absence of a significant difference is due to the small numbers of recurrences in the studies cited [29].

Laparoendoscopic inguinal hernia repair

Several RCTs have analyzed discomfort, foreign-body feeling, and acute and chronic pain after laparoendoscopic hernia repair (TAPP and TEP) with either HWM or

LWM. The use of LWM seems to improve the early postoperative convalescence and may be associated with less early CPIP. However, in medium- and long-term follow-up trials, there is no difference in chronic pain and recurrences after the use of LWM and HWM [9, 10, 43–50]. In contrast to the results of previous trials, a recent RCT on 950 patients with primary inguinal hernias comparing LWM and HWM in TEP reported statistically significant more chronic pain and recurrences in the lightweight cohort [51].

A recommendation resting solely on mesh weight cannot be supported by evidence as varying pore sizes and diverse other mesh properties are not considered in any available study.

Mesh fixation in inguinal hernia repair

Mesh fixation methods in open inguinal hernia repair were analyzed in several RCTs and systematic reviews with poor or moderate quality. One systematic review involved 12 RCTs with 1992 open primary inguinal hernia repairs [52]: 4 studies compared n-butyl-2 cyanoacrylate (NB2C) glues to sutures, 2 trials self-fixing meshes to sutures, 4 RCT fibrin sealant to sutures, 1 study tacks to sutures, and 1 trial absorbable sutures to nonabsorbable sutures. The trials' level of evidence using GRADE classification was rated poor to moderate mostly due to the lack of power calculations, small subject numbers, short follow-up periods, and poorly matched groups (for age, hernia size, and comorbidities). Different definitions of chronic pain were used. Chronic pain was measured at different time intervals ranging from 3 to 12 months. Nine studies reported no significant difference in chronic pain between fixation methods. Three trials identified a significant short-term chronic pain reduction with NB2C glue [53] or FS [54, 55] compared to sutures. A recent systematic review of 12 trials with poor to moderate level of evidence (GRADE) comparing suture and glue fixation reported comparable short-term outcomes for chronic pain and recurrences after Lichtenstein inguinal hernioplasty [56].

In open inguinal and femoral hernia repair, suture and atraumatic mesh fixation (e.g. fibrin glue, cyanoacrylate, and self-fixating meshes) have a comparable risk of recurrence, acute, and chronic postoperative pain. The use of self-fixating meshes is feasible in all hernia types and sizes without raising the risk for recurrence, whereas glue fixation in the Lichtenstein technique should not be performed in L3 and M3 groin hernias (EHS classification) [9, 10, 27–29, 52, 56].

Laparoendoscopic inguinal hernia repair

A recent meta-analysis of four RCTs (430 patients) and a systematic review of six non-RCTs (8637 patients) comparing fibrin glue to tacker mesh fixation in TAPP showed no significant difference in seroma or hematoma formation, recurrence, and chronic pain [57]. A recent register trial from the Danish Hernia Database, which included 1421 patients who had a TAPP repair with either fibrin glue or tacker mesh fixation, reported no significant difference in CPIP and recurrences after a medium follow-up of 35 months (range, 12–62 months). A register study from the Swedish Hernia Register including 1110 patients compared the impact of permanent fixation to no fixation/nonpermanent fixation of mesh on chronic pain after TEP primary inguinal hernia repair. The trial detected no significant difference of chronic pain and recurrences and concluded that mesh fixation in TEP is safe but not necessary [58].

In TEP and TAPP, inguinal and femoral hernia repair mesh fixation is only recommended in large medial defects (M3 EHS classification). If fixation is used, atraumatic fixation techniques (fibrin glue, cyanoacrylate) should be considered to minimize the risk of acute postoperative pain. Penetrating mesh fixation should only be performed in safe anatomical areas where no nerves are at risk (i.e. Cooper's ligament).

Penetrating mesh fixation with the risk of nerve injury must strictly be avoided in all open and laparoendoscopic groin hernia repairs [8–10, 27–29, 59].

Nerve management in open and laparoendoscopic groin hernia repair

A detailed knowledge of the anterior and posterior inguinal nerve anatomy is of utmost importance for every hernia surgeon. In every open and laparoendoscopic groin hernia operation, the surgeon should be aware of the nerve anatomy and pay attention to the nerves. A nerve-ignoring operation is not acceptable by any means.

In a properly performed TAPP and TEP repair, the nerves remain untouched in their natural embedding. A fascial layer protects the nerves from direct mesh contact. Nonfixation or adequate atraumatic mesh fixation minimizes the risk of nerve injury. A recent cadaver study on the retroperitoneal course of the lumbar plexus nerves revealed that the territory where the inguinal nerves can be damaged during laparoendoscopic and open preperitoneal inguinal hernia repair is larger than previously anticipated. The territory of pain extends to at least 2 cm

cranially of the iliopubic tract and 2 cm circumferentially around the inguinal ring [8].

In open groin hernia repair, the nerves are commonly encountered in the operation field and often interfere with the steps of the operation.

Many trials on nerve management in open groin hernia repair have been conducted. The surgical options include the preservation of the nerves with or without its mobilization, prophylactic neurectomy, or pragmatic neurectomy.

A prospective nonrandomized multicenter of Alfieri et al. [60] compared 310 open mesh repairs with identification and preservation of the iliohypogastric nerve (IHN), IIN, and genital branch of the genitofemoral nerve (GB) to 189 cases in which the nerves were divided. After 6 months, there was significantly more moderate to severe pain in the nerve-dividing group (4.7% vs. 0%; $p < 0.02$). The authors concluded that the three inguinal nerves should be identified and preserved.

Several randomized trials have studied prophylactic neurectomy versus the preservation of the IIN. Three meta-analyses concluded that there was no significant difference in chronic pain [61–63]. The most recent meta-analyses reported more sensory loss 6 months and 1 year after neurectomy of the IIN [63]. Two RCTs on preservation versus neurectomy of the IHN revealed no difference in chronic pain but more numbness after neurectomy. There are no RCTs comparing preservation and neurectomy of the GB.

According to relevant trials, meta-analyses, and guidelines, a general prophylactic neurectomy in open inguinal hernia repair cannot be recommended as it does not reduce the risk of CPIP and adds sensory loss, which is in itself a risk factor for chronic pain [17, 61–63].

In recent years, the term “pragmatic neurectomy” has been coined for the resection of nerves being damaged by the hernia, scar tissue, surgical trauma, or nerves being at risk for damage mainly due to interference with mesh [64, 65]. Although no RCTs have been conducted on this issue and the term “nerve at risk” has not been clearly defined, the pragmatic neurectomy approach is currently favored by the majority of specialized hernia surgeons. Currently, it is considered good surgical practice to preserve only intact nerves that are unlikely to cause chronic pain.

The pragmatic neurectomy approach is strongly supported by a prospective nonrandomized two-phase trial of 781 patients with primary inguinal hernias who had a Shouldice operation (LI, LII, and MI inguinal hernias) or Lichtenstein repair (LIII, MII, and MIII hernias) [17]. After 5 years, Lichtenstein repair with mobilization and preservation of the IIN was an independent significant risk factor for chronic pain. Eleven of 12 patients with relevant

chronic pain (VAS > 3) at 5 years had Lichtenstein repair with mobilization of the IIN. The conclusion of this study was that mesh contact with a nerve removed from its natural bed should be avoided, supporting the notion that nerve resection is superior to leaving an injured nerve *in situ* or allowing mesh/nerve contact to occur [17].

Conclusion

The avoidance of chronic pain is a primary concern in inguinal hernia repair and may be considered the most important clinical outcome. This problem preceded modern mesh-based techniques; however, as recurrence rates have decreased, pain has become the more prevalent and important complication. Understanding the causative mechanisms and risk factors of inguinodynia help to prevent, diagnose, and treat this condition. Groin pain, especially in the absence of a bulge, often needs interdisciplinary diagnostics and no operation. Detailed diagnostics, meticulous operative technique with profound knowledge of the anatomy, proper nerve identification and handling, optimization of prosthetic materials, and careful fixation are of utmost importance. Further research on how to avoid CPIP and explore the effectiveness of treating it is necessary.

Author Statement

Research funding: Authors state no funding involved. Conflict of interest: Authors state no conflict of interest. Informed consent: Informed consent is not applicable. Ethical approval: The conducted research is not related to either human or animals use.

Author Contributions

Wolfgang Reinbold: Investigation; Methodology; Validation; Writing (original draft).

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Supplemental Material: The article (DOI: 10.1515/iss-2017-0017) offers reviewer assessments as supplementary material.

Reviewer Assessment

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Wolfgang Reinpold*

Risk factors of chronic pain after inguinal hernia repair: a systematic review

DOI 10.1515/iss-2017-0017

Received March 15, 2017; accepted March 20, 2017

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Reviewers' Comments to Original Submission

Reviewer 1: anonymous

Mar 15, 2017

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	80
Custom Review Questions	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	N/A
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	3
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a nicely presented topic of a highly significant clinical issue. It shows, that many potential risk factors for chronic pain after inguinal hernia repair exist. Although some of the risk factors are well known, the paper gives a comprehensive overview so that hopefully many surgeons who treat these patients will benefit from the data. Additionally, it shows that in particular in open surgery a meticulous surgical technique is crucial to identify and preserve the nerves.

Reviewer 2: Timm Franzke

Mar 18, 2017

Reviewer Recommendation Term: Accept
Overall Reviewer Manuscript Rating: N/A

Custom Review Questions

	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	4
Are the experimental methods/clinical studies adequate?	3
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

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