Facteurs de risque de douleur postopératoire persistante après chirurgie urologique [Risk factors for persistent pain after urological surgery.]

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Facteurs de risque de douleur postopératoire persistante après chirurgie urologique

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Résumé

Objectif: En fonction du type de chirurgie, 10 à 50 % des patients ayant une douleur postopératoire sont à risque de chronicisation. Le but de cette étude était de déterminer l'incidence de la douleur postopératoire persistante (DPOP) et d'identifier les facteurs de risques après chirurgie urologique. ~~La relation entre les paramètres périopératoires et la DPOP a été évaluée par analyse multivariée.~~

Type d'étude : rétrospective observationnelle

Patients : 288 patients opérés de chirurgie urologique associée à une DPOP.

Méthodes : Les interventions urologiques associées à une DPOP ont été définies. Tous les patients ayant bénéficié d'une de ces interventions entre au cours de l'étude ont reçu par courrier un questionnaire au moins 3 mois après la chirurgie. Les dossiers de ces patients ont été étudiés rétrospectivement.

Résultats: Huit % des patients avaient une douleur préopératoire. En moyenne 6 mois après la chirurgie, 24 % des patients déclaraient ne DPOP. Parmi eux, 36% décrivaient une douleur neuropathique. Ils présentaient plus de douleur préopératoire et leur consommation postopératoire de morphine était augmentée. L'administration postopératoire d'AINS réduisait significativement la DPOP. Deux facteurs de risques indépendants de DPOP ont été identifiés: existence d'une douleur pré opératoire (OR = 21.6, 95% CI 6.7-69.5, $p < 0.0001$), consommation de morphine à 48 h postopératoire supérieure à 6 mg (OR = 2.3, 95% CI 1.2-4.3, $p = 0.0118$).

Discussion : Ces résultats confirment le rôle de la douleur préopératoire et de la consommation de morphiniques dans la genèse de la DPOP. La prise en charge périopératoire doit être ainsi individualisée.

Abstract

Objective: Ten to 50 % of patients with postsurgical pain develop chronic pain depending on the type of surgery. The objective of this study was to assess the incidence of persistent postsurgical pain (PPSP) and to identify risk factors following urology surgery. ~~Pre, intra and postoperative factors were assessed and their relationships wit PPSP were evaluated using multivariate analysis.~~

Design: retrospective observational study

Patients: 288 patients scheduled for urology surgery. Reasons for non-inclusions: patients who underwent a procedure not defined as being associated with PPSP.

Methods: Surgical urologic procedures potentially associated with PPSP were defined. All patients who had one of these procedures during the study period received a questionnaire by mail at least 3 months after the surgery. The files of these patients were retrospectively studied.

Results: Eight percent of the patients had preoperative pain. PPSP, assessed approximately 6 months after the surgery, was reported by 24 % of the patients. Twenty-five (36%) of them reported neuropathic pain. Patients with PPSP had significantly more preoperative pain and an increased postoperative morphine consumption. Postoperative NSAID administration led to less persistent pain. Multivariate logistic regression analysis identified two independent risk factors of developing persistent pain: preoperative pain (OR = 21.6, 95% CI 6.7-69.5, $p < 0.0001$), morphine consumption 48 hours after surgery higher than 6 mg (OR = 2.3, 95% CI 1.2-4.3, $p = 0.0118$).

Conclusion: These findings confirm the role of preoperative pain and morphine consumption in the genesis of PPSP and call for establishing clinical perioperative pathways tailored to the patient.

Introduction

Since Perkin's review published in 2000, persistent post surgical pain ~~(PPSP)~~ is considered as an outcome of surgery (1). The last publication by the American Committee on Advancing Pain Research, Care and Education reported that 10 to 50 % of patients with postsurgical pain develop chronic pain depending on the type of surgery (2). Thereby, identifying risk factors for (PPSP) can provide some basis for prevention (3). Trying to prevent the development of PPSP should be a cornerstone of perioperative medicine (4). Preoperative pain, nerve injury, severity of the immediate postoperative pain, opioid consumption are factors associated with increased risk of PPSP (5,6). The prevalence of PPSP may also vary depending on the type of surgery. Indeed, 25 to 60 % of the patients reported PPSP after thoracotomy (7), 50 to 80 % after amputation (8), 15% after inguinal hernia repair (9), 5 to 30 % after hysterectomy (10), 24 to 50 % after mastectomy (11) and 22 % after carpal tunnel surgery (12). Therefore, risk factors need to be clearly identified in different type of surgery. ~~This is critical because the identified risk factors of PPSP could depend on the type of surgery~~. For example, the international guidelines for prevention and management of PPSP following inguinal hernia repair strongly suggest that the identification of all three nerves plays an important role in reducing the risk of PPSP (13). The absence of such recommendations after urology surgery is probably due to the lack of data.

Therefore, our objective was to assess the incidence of PPSP, its characteristics (i.e neuropathic pain) and ~~the~~ its associated risk factors following urology surgery. We assessed pre, intra and postoperative factors and evaluated their relationship with PPSP.

Methods

Patients

This observational cohort study included all consecutive patients undergoing surgical urologic procedure in our university hospital between May 2009 and August 2010. Surgical procedures were classified into three categories according to the risk of PPSP. This risk stratification took into account surgery duration, the degree of invasiveness, and the surgery associated risk of postoperative pain and postoperative complications. The three categories were as follows: low (hernia, orchidectomy), intermediate (laparoscopic prostatectomy / complete nephrectomy / adrenalectomy) and high (pelvectomy, prostatocystetomy, cystectomy, open prostatectomy, open nephrectomy and partial nephrectomy). All patients received a questionnaire by mail at least 3 months after surgery (Appendix 1). This questionnaire was mailed only once. Patients who did not answer after 2 months were considered as being lost. The files of these patients were also retrospectively studied. The local ethics committee waived informed consent as it was a non-interventional study (number 12-25, on 12 march 2012).

Data collection

The following data were recorded: age, sex, type of surgery, type of anesthesia, pain preexisting the surgery, pre-, intra- and postoperative pain medication, morphine consumption 48 hours after the surgery, time between surgery and questionnaire administration. At the time of the questionnaire, the type of pain, the pain score (numerical rating scale from 0 to 10, where 0 = no pain and 10 = worst pain imaginable), and the use of pain medication were also collected. Neuropathic pain was defined using the DN4 “7 items” score (14). A DN4 score higher than 3 (on 7 items) was considered as positive for neuropathic pain. Pain preexisting the surgery was defined as pain of any type associated or not with the condition requiring surgery. In addition to the 7 items, the effect of “brushing”, which is part of the original complete DN4 questionnaire (10 items), was included as an 8th

item.

PPSP was considered present when the patient reported pain with a NRS of 3 or higher, in the area of the surgery.

Statistical analysis

Statistical analysis was performed with SAS software 8.02 (SAS Institute, Cary, N.C., USA). The normality of the variables was checked using a Shapiro-Wilk test. For continuous variables the mean (SD) is reported unless noted otherwise, and for categorical variables the number of patients in each category and the corresponding percentage are given. The characteristics of patients who developed PPSP and those who did not were compared using Student's *t* test or Wilcoxon rank sum test when appropriate for continuous variables, and the $\chi 2$ or Fisher's exact test when appropriate for categorical variables. To identify risk factors independently associated with the occurrence of PPSP, variables found to be significantly different ($p < 0.05$) between the two groups were entered into a forward stepwise logistic-regression model. All patients were entered in this model (no missing data). Each variable used in this logistic regression analysis was binary; therefore continuous variables were recoded using the median value of the distribution in the absence of a clinically defined cutoff point. All p values are two-sided and for all analysis, a p value < 0.05 was considered significant.

Results

During the study period 523 patients were scheduled for one of the surgical procedures included in the 3 predefined categories. Amongst them 288 (55%) answered the questionnaire. Mean time from surgery to questionnaire response was 201 ± 53 days. Mean age was 64 ± 12 years. Three quarters of the patients were male. The majority of the patients underwent a procedure classified as intermediate (87 % vs high risk: 5% and low risk: 8%). The vast majority of the patients had a general anesthesia (table 1). Two patients (0,69 %) had a regional anesthesia (a TAP block) (Table 1). According to the institution protocol: the steroid administered was dexamethasone 8 mg peroperatively. If the patients had steroids before surgery, the prescription was continued; the NSAID administered was ketoprofen 50 mg every 6 hours; nefopam was administered every 6 hours (20 mg), paracetamol was systematically prescribed in all the patients (1g every 6 hours); lidocaine was administered preoperatively only (1,5 mg.kg.h-1); ketamine was administered at the dosage recommended (bolus 0,25 mg.kg-1 and then 0,2 mg.kg.h-1 continuously) (15).

Less than 8 % (n = 22) of the patients had preoperative pain. PPSP, assessed approximately from 3 to 11 months after the surgery, was reported by 24 % (n = 70) of the patients.

Very few patients answered the 8th item of the questionnaire. This did not allow any statistics.

Patients with PPSP

Among the 70 (24 %) patients describing PPSP, 30 (43 %) had sleep disturbance and 34 (49 %) used pain medication (Table 1). Twenty-five (36%) of them reported neuropathic pain (DN4 ≥3). The worst pain experienced within the week prior the questionnaire was higher than 5 on a 10-point scale in 28 (40 %) patients with PPSP.

Predictive factors of PPSP in univariate analysis

Preoperative pain, and postoperative morphine consumption were significantly associated with an increased risk of PPSP, whereas patients who received postoperative nonsteroidal anti-inflammatory drugs reported significantly less PPSP (Table 2). The ~~global~~ mean morphine consumption 48 hours after surgery was 13 ± 19 mg. In patients without PPSP, it was 10 ± 15 mg and this consumption doubled in patients reporting PPSP (22 ± 26 mg). The patients who received a preperitoneal continuous infiltration significantly undergone more procedures classified as high risk and their consumption of postoperative morphine was significantly higher ($p = 0.016$).

Predictive factors of PPSP in multivariate analysis

Multivariate logistic regression analysis identified two independent risk factors of developing PPSP: preoperative pain (OR = 21.6, 95% CI 6.7-69.5, $p < 0.0001$) and morphine consumption 48 hours after surgery higher than 6 mg (OR = 2.3, 95% CI 1.2-4.3, $p = 0.012$).

Discussion

In this study, 24% of the patients reported PPSP after urology surgery. Amongst them, 36 % reported neuropathic pain. The two independent risk factors associated with PPSP following urology surgery were: preoperative pain and postoperative morphine consumption.

The prevalence of PPSP of 24% 3 to 11 months after urology surgery is comparable with other studies. Recently published incidences vary between 14% 3 months after prostatectomy (16) and 26 to 28% 3 months after nephrectomy (17,18). In most previous studies the distinction between neuropathic and nociceptive pain was not described. The recent Tromso study reported an incidence of 24.5 % of sensory abnormalities after various type of surgery. This was strongly associated with PPSP (19). In our study, PPSP was classified as neuropathic pain in 36 % of the cases. This is higher than the 14 % of

neuropathic PPSP after nephrectomy reported by Owen et al (17). However, our results were not specifically focused on nephrectomy but on various urological surgeries.

Preoperative pain was the strongest independent risk factor with an odds ratio of 21.6 (95% CI 6.7-69.5). Recent reviews have described preoperative pain as being a typical risk factor of PPSP (4). Some studies have indeed reported a link between preoperative pain and PPSP after amputation (20), hernia repair (21), hysterectomy (10,22) and thoracotomy (23). Some studies did not report a statistically significant link especially after thoracotomy (7). Indeed, the authors of a systematic review published in 2009 were not able to draw a conclusion because of the inconsistencies of the data (24). These discrepancies could be due to interindividual variability described by some authors (25). Our results showed a strong link and add more data into this field. The likelihood of PPSP in patients with preoperative pain was so high in our study that it called for establishing specific clinical perioperative pathways in these patients.

In our study, morphine consumption higher than 6 mg 48 hours after the surgery was also associated with an increased risk of PPSP. Opioid-induced hyperalgesia had been first described with remifentanil (26). Since this article, it has also been identified with fentanyl and with morphine. Chronic use of opioid can also increase the risk of hyperalgesia (27). Within the perioperative context, a study showed that opioid-induced hyperalgesia with a high dose of remifentanil was associated with a higher incidence of PPSP after thoracotomy (28). Preventing hyperalgesia (inflammation-induced and opioid-induced hyperalgesia) can prevent post surgical pain 6 months to one year after surgery (29). This was shown with ketamine or epidural (29,30). Overall, it seems that preventing high opioid consumption would prevent opioid-induced hyperalgesia and PPSP. However, high postoperative morphine consumption is always associated with intense acute postoperative pain. Indeed, acute postoperative pain *per se* has also been linked with the risk of PPSP (31) even in patients who did not receive any morphine (12). The need for additional clinical studies on surgical-induced and opioid-induced hyperalgesia was recently underlined (32). Therefore

our study brings more evidence in confirming the hypothesis that opioid consumption including postoperative morphine consumption is linked to the risk of PPSP.

No other data were significantly associated with the risk of PPSP in our study. In particular, perioperative administrations of ketamine, gabapentine or pregabaline were not protective against PPSP. Only a very small fraction of the patients received gabapentinoids. However, the most recent meta analysis on the subject did not suggest any reduction in chronic pain with gabapentinoids (33). Ketamine was often administered (57%) in our study but the administration was only very rarely continued after the end of surgery. The most recent meta analysis reported that ketamine could reduce PPSP 3 months after surgery if the administration was prolonged for 24 hours (33). This could explain our negative results.

Our study has several limitations. It is an observational study that did not include the elements of the ideal study design of PPSP as defined by Kehlet et al. (34). The minimum of three months period was chosen according to the literature. Although the IASP-published definition several years ago was 2 months (35), some authors have proposed 3 months (34). In our study, the mean time between surgery and completing the questionnaire was 201 days with a wide range (92-336). However, this elapsed survey period was statistically similar between the two groups. Our study was neither randomized nor controlled and the patients who received a local anesthetics infiltration significantly undergone more procedures classified as high risk and their consumption of postoperative morphine was significantly higher. This was not the case for ketamine or gabapentinoids administration. Finally, we did not record the preoperative morphine consumption, which could influence the postoperative consumption.

In conclusion, our study confirmed that preoperative pain and morphine consumption are strong risk factors of PPSP after urology surgery. These findings bring evidences in the role of preoperative pain and morphine consumption in the genesis of PPSP and could suggest the need to establish clinical perioperative pathways tailored to the patient.

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Legends

Table 1: Demographics of the studied population

Age, years: mean, (SD, range)	64 (12, 16–87)
Sex F/M (%)	25/75
Preoperative pain, n (%)	22 (8)
Type of surgery, *n* (%)	
Laparoscopic/open nephrectomy	59 (20)/27 (9)
Laparoscopic/open prostatectomy	78(27)/3 (1)
Adenomectomy	34 (12)
Cystectomy	2 (0.7)
Prostatocystectomy	13 (4.5)
Laparoscopic/open surrenalectomy	10 (3.5)/1 (0.3)
Hernia	2 (0.7)
Orchidectomy	7 (2.4)
Renal transplant	38 (13)
Pelvectomy	8 (3)
Laparoscopic promontofixation	6 (2)
High risk surgery, n (%)	23 (8)
Intermediate risk surgery	250 (87)
Low risk surgery	15 (5)
General/spinal anesthesia, n (%)	280 (97)/8 (3)
Preoperative, n (%)	
Gabapentin, pregabalin	7 (2.4)
Dose of peroperative sufentanil per hour (microg): mean (SD)	14 (23)
Dose of peroperative remifentanil per hour (μg): mean (SD)	47 (154)
Peroperative, n (%)	
Steroids	68 (24)
NSAID	100 (35)

Ketamine	165 (57)
Nefopam	178 (62)
Lidocaine	3 (1)
Postoperative, n (%)	
Steroids	47 (16)
NSAID	91 (32)
Ketamine	5 (2)
Nefopam	236 (82)
Regional anesthesia (TAP block)	2 (1)
LA continuous infiltration	40 (14)
Morphine consumption at h48 (mg): mean (SD)	13 (19)
Patients with persistent pain (> 3 months), n (%)	70 (24)

Table 2: Characteristics of the patients with persistent pain

Actual pain, mean (SD)	3.57 (1.53)
Mildest pain per week, mean (SD)	1.77 (1.84)
Worst pain per week, mean (SD)	4.44 (2.28)
Worst pain per week > 5/10, *n* (%)	28 (40)
Worst pain per week > 7/10, *n* (%)	12 (17)
Neuropathic pain (DN4 ≥ 3), *n* (%)	25 (36)
Sleep disturbance, *n* (%)	30 (43)
Use of pain medication, *n* (%)	34 (49)

Table 3: Comparison between patients with and without persistent pain: NSAID: non steroidal anti-inflammatory drugs

	Patients with persistent pain (*n* = 70)	**Patients without persistent pain (*n* = 218)**	***P***
Age > 65 years, n (%)	29 (41)	118 (54)	0.064
Sex F (%)	29	24	0.427
Time from surgery to questionnaire response (mean,	202 (55)	201 (53)	0.8473

	Patients with persistent pain (*n* = 70)	**Patients without persistent pain (*n* = 218)**	***P***
SD)			
Preoperative pain, n (%)	18 (26)	4 (2)	< 0.0001
General anesthesia, n (%)	69 (99)	211 (97)	0.684
High risk surgery, n (%)	6 (8.6)	17 (8)	0.261
Intermediate risk surgery	63 (90)	187 (86)	
Low risk surgery	1 (1.4)	14 (6)	
Preoperative, n (%)			
Gabapentin, pregabalin	2 (3)	5 (2)	1.000
*Dose of peroperative sufentanil per hour (*µg*) (mean, SD)*	12 (7)	14 (27)	0.774
*Dose of peroperative remifentanil per hour (*µg*) (mean, SD)*	54 (175)	45 (146)	0.905
Peroperative, n (%)			
Steroids	20 (29)	48 (22)	0.261
NSAID	19 (27)	81 (37)	0.125
Ketamine	39 (56)	126 (58)	0.759
Nefopam	42 (60)	136 (62)	0.721
Lidocaine	0	3 (1)	1.000
Postoperative, n (%)			
Steroids	14 (20)	33 (15)	0.338
NSAID	15 (21)	76 (35)	0.035
Ketamine	1 (1)	4 (2)	1.000
Nefopam	59 (84)	177 (81)	0.558
Regional anesthesia (TAP block)	0	2 (1)	1.000
LA continuous infiltration	18 (26)	22 (10)	0.001
Morphine consumption at h48	23 (26)	10 (15)	0.0002

	Patients with persistent pain (*n* = 70)	Patients without persistent pain (*n* = 218)	*P*
(mg): mean (SD)			

NSAID: non-steroidal anti-inflammatory drugs.

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