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Epidemiology of persistent dry eye-like symptoms after cataract surgery:

Persistent post-surgical pain after cataract surgery

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Abstract

Purpose—To evaluate the frequency and risk factors for persistent post-surgical pain (PPP) after cataract surgery, defined as mild or greater dry eye (DE)-like symptoms 6 months after surgery.

Methods—The single center study population included 86 individuals who had cataract surgery between June-October 2016 and had DE symptom information available 6 months after surgery. Patients were divided into 2 groups: controls were defined as those without DE symptoms 6 months after surgery (defined by a Dry Eye Questionnaire 5 (DEQ5) score<6), cases were defined as those with mild or greater DE-like symptoms 6 months after surgery (DEQ5≥6).

Results—The mean age of the study population was 71 years±8.6; 95% (n=82) were male. DE-like symptoms were reported in 32% (n=27) of individuals 6 months after cataract surgery; 10% (n=8) reported severe symptoms (DEQ5≥12). Patients with DE-like symptoms after cataract extraction (CE) also had higher ocular pain scores, and specific ocular complaints (ocular burning, sensitivity to wind and light) compared to controls with no symptoms. A diagnosis of non-ocular pain increased the risk of DE-like symptoms after cataract surgery (OR 4.4, 95% confidence interval (CI) 1.58–12.1, P=0.005).

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Conclusions—Mild or greater PPP occurred in approximately 1/3 of individuals after cataract surgery. The prevalence of severe PPP is in line with that of refractive surgery, dental implants, and genitourinary procedures.

Keywords

cataract surgery; dry eye-like symptoms; persistent post-surgical pain; ocular pain; epidemiology

INTRODUCTION

Dry eye (DE) symptoms are a common patient complaint, with a frequency of approximately 50% among adults seen in an eye care clinic.[1] DE symptoms reduce quality of life as they affect the ability to perform activities of daily living and work. Additionally, they have a negative effect on mental health.[2] DE symptoms encompass sensations of dryness, but can also include other spontaneous and evoked sensations described as burning, aching, and sensitivity to wind and light. Some of these sensations are shared with those found in other pain conditions, specifically those with a presumed neuropathic etiology. In fact, an emerging concept in pain is that pain conditions tend to co-exist and likely share common underlying mechanisms. This idea is captured by the term chronic overlapping pain conditions (COPC).[3] DE symptoms seem to fit this pattern as we have found that patients with a high number of chronic pain conditions are more likely to have DE symptoms as compared to those with a lower number of chronic pain conditions.[4] Evaluating specific symptoms within DE, we found that individuals who reported ocular burning, sensitivity to wind, or sensitivity to light, had a more chronic symptom course[5] that was less responsive to topical therapy.[6] Furthermore, these individuals displayed somatosensory dysfunction in the form of hyperalgesia to air puff on the cornea[7] and to heat on the forearm.[8] This suggests that in some patients, DE resembles a chronic pain condition more closely than an ocular surface problem. In fact, DE symptoms often do not correlate with DE signs[1] (e.g. tear evaporation, tear production) and those with chronic non-ocular pain are the ones that most often have a disproportionate amount of DE symptoms compared to DE signs.[9, 10]

Another chronic pain condition that is thought to have a neuropathic etiology is persistent post-surgical pain (PPP). PPP can occur after any surgical intervention, and nerve injury is believed to be the major cause. Typically, this entity is considered to be present when the following criteria are met: (1) pain develops after surgery, (2) persists at least 3–6 months, (3) and occurs spontaneously with neuropathic qualities (burning, shooting, electric-like).[11] The incidence of PPP has a wide range (6–60%) depending on the type of surgery and definition of PPP. PPP is more frequent after breast surgery, amputation, and thoracotomy as compared to after dental implant surgery or knee arthroscopy.[11–16] Risk factors for the development of PPP include female gender, younger age, surgery type, and the presence of pre-operative pain.[14]

The epidemiology of PPP after ocular surgery is not well characterized, and that is likely because ocular sensations experienced after eye surgery often do not mirror cutaneous sensations after other surgeries. Specifically, many patients characterize their eye symptoms as dryness and/or discomfort. In fact, many patients report new or worse DE symptoms after

refractive corneal[17] and cataract surgery[18] which may reflect PPP in the eye. However, the epidemiology of this entity is not known as most studies have evaluated DE symptoms up to 3 months after cataract surgery, a time period in which acute post-operative changes may still be involved.[19, 20] To bridge this knowledge gap, in this study we ascertain the frequency of DE-like symptoms 6 months after cataract surgery, with a specific focus on descriptors associated with neuropathic pain, and evaluate risk factors associated with PPP after cataract surgery in our population.

METHODS

Population

A total of 204 individuals had cataract surgery at the Miami Veterans Affairs (VA) Medical center between June and October 2016. Of these, 82 had available information on DE-like symptoms 6 months after surgery and were included in the study. Of note, we use the term "DE-like" throughout the manuscript as an ocular surface examination was not performed at the time of symptom assessment and as such, it is not known whether tear film and ocular surface disruptions accompanied symptoms. Demographic characteristics were similar between those with and without available symptom data.

At the VA, all patients begin topical medication after cataract surgery. On average, polymyxin/trimethoprim is used four times a day for 1 week, ketorolac tromethamine 0.5% four times a day for 2–3 weeks, and prednisolone acetate 1% in a tapering schedule for 4 weeks after surgery. Miami VA Institutional Review Board (IRB) approval was granted (IRB number 3011.01) to allow the retrospective evaluation of patient charts. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Declaration of the World Medical Association.

Data collection

All information was collected six months after cataract surgery via chart review and standardized questionnaires obtained over the phone. Information collected from the clinical chart included: demographics, presence of ocular and non-ocular co-morbidities that have been reported to associate with DE (glaucoma, diabetes, depression, sleep apnea, autoimmune disease, headache, low back pain, etc.), and topical and systemic medications. The time point at which co-morbidities and medications were noted were further recorded as prior to or after surgery.

Information collected via phone interview using a standardized questionnaire included: presence of DE symptoms prior to surgery (assessed by the question *Did you have dry eye symptoms (sensations of dryness, burning, aching, irritation, discomfort, etc. prior to cataract surgery?*), course of DE symptoms in the operated eye since surgery (assessed by the question *How do your dry eye symptoms (discomfort/dryness) compare to before surgery?* Answer choices included "no symptoms", "no change", "worse", or "better"), current DE symptomology (assessed with the validated Dry Eye Questionnaire 5 (DEQ5)[21], range 0–22), current ocular pain (assessed by a numerical rating scale (NRS), *How would you describe the overall intensity of your ocular pain on average during the last week?*,

range 0–10), and specific descriptors of eye pain (burning, eye pain caused or worsened by wind and/or light, range 0–10).[22] A 0–10 NRS has been validated as a measure of pain intensity across multiple populations and has been recommended for use as the primary outcome metric in clinical trials for chronic pain.[23] In addition, we have used criterion validity to examine the utility of specific eye symptoms in predicting behavior consistent with neuropathic pain outside the eye. For example, neuropathic pain tends to be chronic and less responsive to local treatment[24] and in the eye, we found that specific descriptors (spontaneous burning pain, sensitivity to light, wind) predicted a more severe and chronic DE course[5] that was less responsive to artificial tears.[6]

Statistical Methods

The main outcome measure was the frequency of mild or greater DE-like symptoms after cataract surgery. We chose the prevalence of DE symptoms (DEQ5≥6) as our primary outcome as it could be assessed using a validated metric without being subjected to recall bias. Nevertheless, when considering post-operative pain, it is important to consider pre-operative pain and the post-operative time course of the pain. Similar to other PPP studies[25–27], we additionally assessed DE symptom course as a secondary outcome, ascertaining the development of new or worsening DE symptoms post-operatively.

Patients were therefore divided into 2 groups: controls were defined as those without DE symptoms (DEQ5 score less than 6) 6 months after cataract surgery while cases were defined as those with mild or greater DE-like symptoms (DEQ5 score 6 or greater). Secondary measures included course of DE-like symptoms after surgery and risk factors for symptoms. Logistic regression analysis was used for risk factor analysis. All statistical analyses were performed using SPSS 22.0 (SPSS Inc, Chicago, IL) statistical package.

RESULTS

Study population

The study population consisted of predominantly older, white, males (Table 1). 13 individuals had cataract surgery in the right eye, 22 in the left eye, and 51 in both eyes at the time of their 6 month follow up appointment. In the majority of individuals, co-morbidities and medications listed in Table 1 were present prior to surgery. For example, 20/22 individuals had a diagnosis of depression, 23/26 were on an anti-depressant, 9/11 were on an anxiolytic, 15/17 were on an anti-histamine, and 3/6 were on glaucoma medication prior to surgery. The exception to this was the use of artificial tears. Of 39 individuals on artificial tears, 28 started the therapy after cataract surgery.

Dry eye-like symptoms and ocular pain

Six months after cataract surgery, 32% (n=27) reported mild or greater DE-like symptoms, with 10% (n=8) reporting severe symptoms (DEQ5 score ≥12). Not surprisingly, those with mild or greater DE-like symptoms also had higher ocular pain intensity scores, including higher ratings of ocular burning and sensitivity to wind and light compared to those without DE symptoms. (Table 2) Of the 35 individuals who had cataract surgery in only 1 eye, mean

ocular pain scores in the operated eye (1.2 SD 2.3) were higher than the non-operated eye (0.31 SD 1.3), p=0.06.

52% (n=45) of individuals recalled having DE-like symptoms prior to cataract surgery, 28% (n=24) of which were diagnosed as having DE by an eye care professional. Of these 45 individuals, 89% (n=40) reported stable or improved symptoms 6 months after surgery while 11% (n=5) reported worse symptoms. Of the 41 individuals without DE-like symptoms prior to surgery, 17% (n=7) reported new symptoms 6 months after cataract surgery. Individuals with new or worse symptoms (n=12) were more likely to start artificial tears after surgery (67%, n=8) compared to those without (21%, n=7) or with stable symptoms (33%, n=13), p=0.02.

Risk factors for persistent DE-like symptoms 6 months after cataract surgery

A non-ocular pain diagnosis was significantly associated with an increased risk of any and severe DE-like symptoms 6 months after cataract surgery (odds ratio (OR) 4.4, 95% confidence interval (CI) 1.58–12.1, p value 0.005 for any symptoms, Table 3). Self-reported DE symptoms prior to surgery was also associated with an increased risk of any DE-like symptoms after surgery (OR 3.9, 95% CI 1.4–10.8, p=0.008). Sleep apnea imparted a 6.8 fold risk of severe DE-like symptoms after surgery. Several other factors, including depression, PTSD, and the use of an anti-depressant or anxiolytic medication, had an elevated OR (range 1.3–4.5) but did not reach statistical significance. Not surprisingly, those with DE-like symptoms were more likely to use artificial tears. In a multivariable analysis, the presence of non-ocular pain remained significantly associated with any DE-like symptoms when considering all other co-variables in the model.

DISCUSSION

To conclude, we found that 32% of individuals had PPP 6 months after cataract surgery, defined as any DE-like symptom (discomfort, dryness), with 10% reporting severe symptoms. 17% of individuals without prior symptoms noted new symptoms after surgery. In addition, several individuals were started on artificial tears after surgery. Individuals with PPP also reported higher levels of ocular pain, including features of neuropathic ocular pain, as compared to their counterparts with no symptoms. A diagnosis of non-ocular pain portended a 4.4 fold increased risk of PPP after cataract surgery.

The frequency of PPP after cataract surgery is more in the range of what has been reported after dental implant procedure (8.5–36%)[15], vasectomy (15%)[28], caesarean section (11.2%)[29], and lower than that reported after mastectomy (10%–50%),[28] limb amputation (30–81%),[28] and thoracotomy.[30] Interestingly, our data are similar to PPP after laser refractive surgery. Using PROWL data, 14% of individuals had new DE symptoms (mild or greater using the ocular surface disease index) 6 months after LASIK surgery.[31] Similar to our study, many previous reports identified co-morbid pain disorders as a risk factor for PPP.[16, 28] Among patients undergoing hysteroscopic sterilization, a co-morbid chronic pain disorder conferred an increased risk of developing chronic postoperative pain (OR 6.15, 95% CI 2.10–18.10)[32], and among patients undergoing transvaginal mesh revision, pre-existing chronic pelvic pain was associated with significantly lower odds of achieving postoperative

pain relief (OR 0.28, 95% CI 0.12–0.64, p=0.003).[25] Another shared-risk factor is the presence of mood disorders[16, 28, 33], which increased the risk of PPP after cataract surgery but did not meet statistical significance. Psychological distress, accounting for heightened symptoms of depression and anxiety, elevated the risk of developing persistent postoperative pain in a cross-sectional study of nonspecific surgical cases (OR 1.94, 95% CI 1.44–2.61, p<0.001)[34], and in a meta-analysis assessing the association between chronic postsurgical pain and preoperative anxiety and catastrophizing, the overall pooled odds ratio varied from 1.55 (95% CI 1.10–2.20) to 2.10 (95% CI 1.49–2.95).[35] Several prior reviews noted younger age and female gender as risk factors for PPP[16, 33]; however, we could not replicate these findings in our older, predominantly male population.

We are not the first to report that DE parameters, including symptoms, worsen after cataract surgery. Several studies have investigated this question, evaluating patients up to 3 months. While some studies reported a return to baseline symptoms by 3 months,[36] many others reported persistent symptoms.[20, 37–39] Based on the available data, it is not possible to extract the percent of patients with new or worse symptoms. It is not surprising, however, that persistent DE symptoms after surgery were associated with dissatisfaction after surgery.[18]

There is biological plausibility that PPP would develop in some patients after cataract surgery. Cataract surgery typically involves making two incisions at the limbus, one approximately 2.5 mm in length and one approximately 1.5 mm in length, with localized damage to corneal nerves in those areas. The cornea is one of the most densely innervated organs in the body[40], embedded with a variety of nerve types that sense different environmental signals. Polymodal nerves are the most abundant sub-type and respond to a variety of stimuli (capsaicin, mechanical, pH). Polymodal nerves have been found to easily sensitize when exposed to inflammatory mediators[41], as occurs with surgical trauma, displaying spontaneous firing and firing at decreased thresholds.[41] However, only a minority of patients report PPP after cataract surgery, suggesting that nerve and ocular surface integrity is restored in most individuals. Many factors may underlie persistence of DE symptoms after cataract surgery in a minority of individuals, including psychological factors (catastrophizing, anxiety, depression, fear of surgery), pain perception, and/or genetic predisposition, as these have been found to be shared risk factors for PPP after multiple different surgeries.[28]

In our patients, topical corticosteroids and nonsteroidal anti-inflammatory agents (NSAID) are used in the first month after cataract surgery. As acute post-op pain is a risk factor for PPP[42], decreasing acute pain after cataract surgery may decrease the frequency of PPP. In fact, the addition of oral ketorolac to narcotic analgesics decreased pain scores compared to patients receiving only narcotic analgesics after lumbar disc surgery.[43] Another preventive therapy used to reduce PPP after surgery is the use of a gabapentinoids in the perioperative period. Gabapentin and pregabalin are first line therapies in the treatment of neuropathic pain. They bind to the regulatory alpha-2 delta (α2δ) subunit of N-type voltage gated calcium channels in dorsal root ganglia, in the dorsal horn and periaqueductal gray, and reduce calcium-dependent excitatory neurotransmission.[11] Evidence also exists for antagonism of the NMDA receptor which plays a critical role in central sensitization.

Gabapentin also reduces discharge from injured peripheral nerves.[44] Schmidt et al. summarized that gabapentin decreased the incidence of persistent post-operative pain after many, but not all, surgical procedures in randomized, placebo-controlled trials.[45] A similar strategy has not been tested in cataract surgery but may be a future direction of study to reduce the frequency of new or worsening unpleasant ocular sensations after surgery.

Our findings need to be considered keeping in mind the limitations of the study, which include a predominantly male population, the ascertainment of specific DE, ocular, and non-ocular pain symptoms, and the retrospective nature of the study. Due to this design, we focused our primary outcome measure on DE-like symptoms 6 months after surgery, a metric assessed in real time and therefore not subject to recall bias. On the other hand, our secondary outcomes measure, course of symptoms, was subject to potential recall bias. A prospective study is thus needed to replicate our findings. In addition, we focused our study on DE symptoms as a marker of PPP. It is well known that there is a lack of correlation between DE symptoms and signs, and thus we cannot comment on ocular surface parameters in our patients. As such, it is important to note that in this study we did not assess for the presence of DE, which would require signs of disease, but only for the presence of symptoms, in order to assess the frequency of persistent post-operative ocular pain following uncomplicated cataract surgery. Despite these limitations, this study shows that a sub-set of patients experience PPP after cataract surgery, in line with post-LASIK surgery and dental procedures. More information is needed on the epidemiology of PPP after cataract surgery in other populations, including risk factors, with a future focus on preventative and therapeutic strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics, comorbidities, and medications of the study population (n=86)

Demographics	
Age, mean (SD)	71 (8.6)
Gender, n (%) male	82 (95%)
Race, n (%) white	58 (67%)
Ethnicity, n (%) Non-Hispanic	69 (80%)
Co-morbidities	
Diabetes Mellitus, n (%)	32 (37%)
Depression, n (%)	22 (26%)
Post-traumatic stress disorder, n (%)	12 (14%)
Sleep apnea, n (%)	20 (23%)
Non-ocular pain (headache, migraine, low back pain, fibromyalgia), n (%)	24 (28%)
Glaucoma, n (%)	12 (14%)
Medications	
Anti-depressant, n (%)	26 (30%)
Anxiolytic, n (%)	11 (13%)
Antihistamine, n (%)	17 (20%)
Artificial Tears, n (%)	39 (45%)
Glaucoma medications, n (%)	6 (7%)

SD=standard deviation

Table 2

Ocular pain complaints between those with persistent post-surgical pain (PPP) after cataract surgery, defined as mild or greater dry eye-like symptoms 6 months after surgery compared to controls with no DE symptoms.

	Mild or greater DE-like symptoms (n=27)	**No DE symptoms (n=57)**	**p-value**
Average ocular pain over 1 week recall, mean (SD)	3.2 (2.7)	0.17 (1.07)	<0.0005
Spontaneous ocular burning, mean (SD)	1.2 (2.2)	0.0 (0.0)	<0.0005
Sensitivity to wind, mean (SD)	1.9 (3.0)	0.42 (1.5)	0.002
Sensitivity to light, mean (SD)	3.1 (3.1)	1.2 (2.5)	0.003

SD=standard deviation

Table 3

Risk factors for DE symptoms 6 months after cataract surgery

	Risk factors for mild or greater DE-like symptoms			Risk factors for severe DE-like symptoms		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Demographics						
Age, years	0.99	0.94–1.04	0.62	0.95	0.87–1.03	0.22
Gender	—	—	—	—	—	—
Race, Black/white	1.58	0.55–4.52	0.40	0.90	0.17–4.82	0.90
Ethnicity, Hispanic (H)/Non-H	1.20	0.39–3.66	0.76	1.36	0.25–7.40	0.73
Co-morbidities (Y/N)						
Diabetes Mellitus	1.01	0.39–2.60	0.99	3.21	0.71–14.5	0.13
Depression	1.29	0.47–3.6	0.62	3.22	0.73–14.2	0.12
PTSD	2.43	0.70–8.40	0.16	4.47	0.91–21.9	0.07
Sleep apnea	2.09	0.74–5.90	0.16	6.78	1.4–31.6	0.02
Glaucoma	0.77	0.19–3.15	0.71	0.94	0.11–8.50	0.96
Self-reported DE symptoms prior to surgery	3.93	1.43–10.8	0.008	3.00	0.57–15.8	0.20
DE diagnosis by physician prior to surgery	2.32	0.87–6.24	0.09	2.80	0.64–12.3	0.17
Non-ocular pain *	4.36	1.58–12.1	0.005	5.37	1.12–24.7	0.03
Medications (Y/N)						
Anti-depressant	1.93	0.73–5.07	0.19	4.37	0.96–19.9	0.06
Anxiolytic	1.48	0.38–5.75	0.57	1.06	0.12–9.67	0.96
Antihistamine	1.46	0.50–4.32	0.49	2.44	0.52–11.4	0.26
Artificial Tears	3.40	1.31–8.84	0.01	11.4	1.33–97.0	0.03
Glaucoma medication	—	—	—	—	—	—

OR=odds ratio; CI=confidence interval; DE=dry eye, PTSD=post traumatic stress disorder; Y/N=yes/no

— unstable estimates due to low number in one group

* headache, migraine, low back pain, fibromyalgia, etc.