Incidence of nonarteritic ischemic optic neuropathy following topical clear corneal cataract surgery: survey and meta-analysis

Edsel B. Ing, MD, FRCSC, MPH, CPH,* Joseph W.K. Kam, PhD,† Jasmine Z. Cheng, MD,‡ Samuel W.K. Wong, PhD,§ Hermina Strungaru, MD, FRCSC,‖ Allan Slomovic, MD, FRCSC,* Lawrence Weisbrod, MD, FRCSC,* Nurhan Torun, MD, FRCSC¶

ABSTRACT •

Objective: We estimate the incidence and characteristics of post-cataract-surgery nonarteritic ischemic optic neuropathy (PCNAION) after topical clear corneal cataract extraction (CCCE) in Canada.

Design: Canada-wide internet survey and meta-analysis

Participants: All certified Canadian ophthalmologists in the Canadian Ophthalmological Society directory, or belonging to a provincial ophthalmology internet group.

Methods: Identical surveys were distributed to 5 regions in Canada. CCCE surgeons were asked to estimate the number of CCCE they had performed in their career, and the number of PCNAION events that occurred within 1 year after CCCE. The results were analyzed using a random effects meta-analysis of proportions for rare events.

Results: The estimated survey response rate was 18%–32%. The 182 survey respondents performed a total of 1 499 694 CCCE with 107 events of PCNAION. Twenty-six percent of surgeons had at least one patient with PCNAION. Meta-analysis revealed a pooled estimate incidence of 2.8 PCNAION events (95% confidence interval 1.6–4.7) per 100 000 cataract procedures during the year after cataract surgery. Seventy-seven percent (82/107) of the PCNAION cases occurred within 3 weeks of surgery, and 7 patients had bilateral PCNAION.

Conclusions: PCNAION is a rare complication after topical CCCE. Its incidence is important to estimate for patient care and epidemiologic reasons.

Cataract surgery is a "low-risk, fast and effective" surgical procedure.[1] Commonly acknowledged serious adverse events after cataract surgery include endophthalmitis and retinal detachment, but post-cataract-surgery optic neuropathy [hereafter referred to as post-cataract-surgery nonarteritic ischemic optic neuropathy (PCNAION)] is rare and often not mentioned.[2,3]

PCNAION is attributed to ischemia of the retrolaminar optic disc supplied by the short posterior ciliary arteries, and may be exacerbated by increased intraocular pressure immediately after cataract surgery, and perhaps intraocular inflammation in later stages.[4] The incidence of PCNAION is important for patient counseling, epidemiologic, and medicolegal reasons. A recent report found that the incidence of PCNAION was 10.9 cases per 100 000 (95% confidence interval [CI] 1.3–39.4).[5] However, this was a single-institution retrospective series from a tertiary care centre in the United States, with numerous limitations[6] and a wide confidence interval. As such we sought to determine the incidence of PCNAION in Canada and ascertain a narrower confidence interval.

Methods

A survey of cataract surgeons with meta-analysis was chosen for the study design because (*i*) the rarity of PCNAION makes a prospective study time- and cost-prohibitive, (*ii*) the point estimate from a meta-analysis of rare events is more accurate than the average rare events where some contributing studies have a zero incidence, and (*iii*) the lack of an Ontario-wide electronic record system, or specific provincial billing code for nonarteritic ischemic optic neuropathy makes a retrospective study subject to even more deficiencies than those critiqued in a recent study.[6] In Toronto, Ontario, most cataract patients are examined in private offices, as are the neuro-ophthalmology consultations, with no common electronic record. In Canada 74% of ophthalmologists work in a private office or clinic.[7] A survey design allowed us to canvass cataract surgeons across Canada both academic and nonacademic.

The survey instrument was Survey Planet (https://surveyplanet.com/), and the survey questions are shown in Appendix A (available online). PCNAION was defined as abrupt onset vision loss with disc edema, relative afferent pupillary defect, and visual field defect within 1 year of cataract surgery, with no other cause for the vision loss. Clear corneal cataract procedures under topical anaesthesia were stipulated in our survey because local anaesthetic injections might contribute to eye injury or intraoperative pressure rise, and scleral tunnel procedures might have more inflammation. To prevent repetition or "double-counting" of cases, the survey software blocked multiple entries from the same electronic device

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or email address. Also, at the beginning of the survey participants were instructed to exclude any PCNAION cases they encountered as a resident or fellow. We specified that only cataract cases performed as the senior responsible surgeon be considered in the survey. The core survey questions included estimated number of topical clear corneal cataract surgeries, number of cases of NAION after cataract surgery with time of presentation. Early-onset NAION was defined as ≤3 weeks after cataract surgery. Later-onset NAION was defined as greater than 3 weeks but less than 1 year after cataract surgery. We determined whether there was a disc-at-risk morphology using Beck's definition of a cup-to-disc ratio of ≤0.35,[8] whether surgery was complicated by vitreous loss, and whether the intraocular pressure exceeded 28 mm Hg in the first 3 days postoperatively. The final question was essay format and asked about details of patient age, sex, medication use, and associated medical conditions.

To encourage survey participation, we kept the survey anonymous, avoided personal questions about age or years in practice, aimed for a survey completion time of less than 2 minutes, employed skip logic, frequently updated the number of cataract cases contributed by other participants, and used many of the other techniques recommended in Fan and Yan's paper, such as including a logo.[9] No financial incentives were offered.

Identical surveys were prepared for 5 regions in Canada: (*i*) British Columbia, (*ii*) Alberta, Manitoba, Saskatchewan, and North West Territories, (*iii*) Ontario, (*iv*) Quebec, and (*v*) the Maritime provinces. For the province of Quebec, the survey was accompanied by a French translation.

In August 2018, the surveys were sent to the individual e-mail addresses of all certified ophthalmologists in the Canadian Ophthalmological Society (COS) membership directory and to all available provincial internet ophthalmology discussion lines. Canvassing was repeated in September 2018 and December 2018. The survey was also advertised at a Canadian cataract conference on November 30, 2018.

Statistical analysis was performed with Stata 15.1 (StataCorp, College Station, TX). Meta-analysis is a well-known technique for combining data from multiple sources that is also applicable to surveys.[10] With respect to rare events, such as PCNAION, a meta-analysis of proportions using the conventional random effects model is subject to approximation bias[11]; the I^2 statistic is inappropriate because the incidence of NAION is too low. Therefore, we estimated the incidence of NAION among the surgeons with a random effects meta-analysis where proportions were pooled using a logistic-normal random-effects model, such that each surgeon's variability follows a binomial distribution. The metaprop_one routine of Stata was used to fit the model, and it correctly handled reports of 0% rates (i.e., surgeons who did not observe any PCNAION events) and provided appropriate confidence intervals for binomial data, both at the individual level and for the pooled estimate.[12]

The results from the 5 different regions of Canada are shown in Table 1. To determine whether our sample of survey responses was representative of the population, we tested for regional differences, comparing the response rate by region and the proportion of surgeons that observed PCNAION events by region using the Pearson χ^2 statistic.

Results

There were 186 survey respondents, 4 of who did not answer any survey questions, presumably because they were cataract surgeons but did not routinely perform clear corneal cataract extraction (CCCE) under topical anaesthesia, or because they were residents or fellows (see Table 1). The remaining 182 surgeons estimated that they performed 1 499 694 CCCE in their career with 107 events of PCNAION. Eighty-two cases (77%) of NAION occurred within the first 3 weeks after cataract surgery. The proportion of surgeon-recognized PCNAION occurrences in the first 21 days after surgery versus greater than 3 weeks postoperatively was statistically significant ($p < 0.001$; see Appendix B1 available online). Thirty-nine percent of the cases (32/82) were reported to have intraocular pressure >28 mm Hg in the first 3 days after cataract surgery. Forty-eight of the 182 surgeons (26%) reported at least one PCNAION event after cataract surgery, and hereafter are designated as "affected surgeons." Affected surgeons performed on average 8240 more CCCE than surgeons who did not report PCNAION ($p < 0.001$; see Appendix B2 available online). The maximum number of PCNAION reported per surgeon was 10 events, and this occurred in 2 individuals: one who performed 1000 CCCE and the other 18 000 CCCE (Fig. 1). The mean number of PCNAION encountered by affected surgeons was 2.2 ± 2.0 cases with a median 1.5 cases. There were 4 cases of bilateral PCNAION. An additional patient had a contralateral NAION, before developing PCNAION. The particulars for each province are shown in Table 2. Only 32 of the 182 surgeons completed the essay question, and no generalizations could be made.

It was difficult to determine the exact survey response rate for this anonymous survey for the following reasons: (*i*) the number of surgeons performing topical CCCE procedures is not definitively known; (*ii*) some provinces did not have a provincial ophthalmology discussion group (e.g., Alberta, Saskatchewan); and (*iii*) some provincial ophthalmology internet lines had multiple addresses for the same physician and retired physicians were not removed from the discussion group (e.g., Ontario).

Table 1—Number of topical, clear corneal cataract surgeons who responded per region in Canada

Region	No. of Survey Respondents	Percent
BC	17	9.3
AMSN	26	14.3
ONT	74	40.7
QC	49	26.9
MAR	16	8.8
Total	182	100.0

BC, British Columbia; AMSN, Alberta, Manitoba, Saskatchewan, and Northwest Territories; ONT, Ontario; QC, Quebec; MAR, Maritime Provinces.

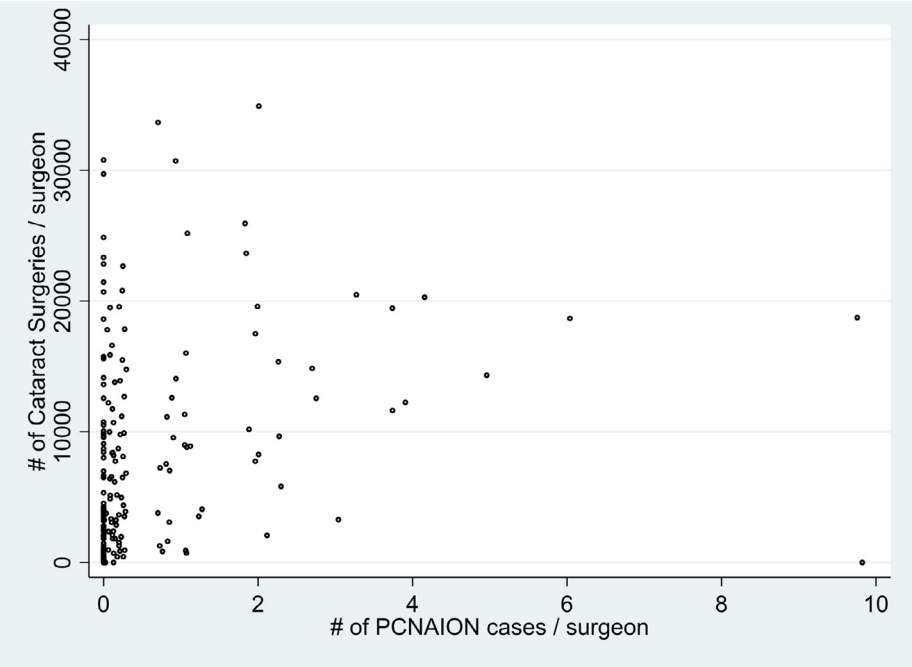

Fig. 1—The number of cases of post cataract nonarteritic ischemic optic neuropathy events versus the number of topical clear corneal cataract procedures per surgeon.

The 2018 Canadian Medical Association Physician Manpower report indicated there were 1249 ophthalmologists in Canada in 2018.[7] There were 818 members of the COS who practiced in Canada (personal communication with COS, August 2018). However, not all the ophthalmologists in the Canada manpower survey or the COS roster perform CCCE. In Ontario, Canada's most populous province, only 70% of ophthalmologists have a surgical practice.[13] Forty-five percent of ophthalmologists in Canada are subspecialists and 9.5% practice surgical retina and less likely to perform a high volume of cataract surgery.[14] Adjusting for these factors the most likely number of cataract surgeons in Canada is 1012 (see Appendix C1 available online). Of the 818 COS members in Canada, 106 had a primary practice focus of cataract and IOL, and 461 a secondary interest in cataract surgery with primary listing as comprehensive, anterior segment, glaucoma, or corneal specialists (see Appendix C2 available online).

Using the estimated number of cataract surgeons in the Canada Manpower study and COS directory, our survey response rate was between 18% (182/1012) and 32% (182/567), with a survey margin of error between 5.3% and 5.8% (see Appendix D available online).

Table 2—Number of cataract surgeries performed per region in Canada, and the number of cases of unilateral or bilateral nonarteritic ischemic optic neuropathy after cataract surgery

Region	No. of Cataract Surgeries	PCNAION	Bilateral PCNAION
BC	170 532	21	1
AMSN	209 286	6	0
ONT	639 719	40	4
QC	376 557	34	2
MAR	103 600	6	0
Total	1 499 694	107	7

BC, British Columbia; AMSN, Alberta, Manitoba, Saskatchewan, and Northwest Territories; ONT, Ontario; QC, Quebec; MAR, Maritime Provinces; PCNAION, postcataract nonarteritic ischemic optic neuropathy.

The random effects meta-analysis of proportions using logit binomial distribution suggested an incidence of 2.8 (95% CI 1.6−4.7) PCNAION events per 100 000 cataract procedures during the year after cataract surgery (see Appendix E available online). Funnel plots are not an accurate method to assess publication bias for meta-analyses of proportions[15] and were not applied to assess survey bias.

Compared with data from the 2018 *Canadian Medical Association Journal* (*CMAJ*) Ophthalmology Manpower report 7 and the 2017 Statistics Canada population figures,[16] our survey sample appears to be a representative sample of Canadian ophthalmologists and patients. There was no statistically significant difference in the proportion of (*i*) survey responses per region compared with the proportion of ophthalmologists in each region of the Canada Manpower report ($\chi^2 = 8.05$, $p = 0.090$) and (*ii*) affected surgeons in each survey region compared with the *CMAJ* regional distribution of ophthalmologists ($\chi^2 = 0.1.91$, $p = 0.753$). Furthermore, there was no statistically significant difference in the PCNAION cases from each survey region compared with the population per region using the Statistics Canada data ($\chi^2 = 1.89$, $p = 0.7561$) (see Appendix F available online).

Discussion

The unique features of our survey analysis include the large denominator of cataract surgeries from multiple surgeons across Canada, its focus on clear corneal topical anaesthetic

cataract procedure, and the application of a meta-analysis of proportions for rare events to the aggregate estimates provided by each individual survey surgeon.

Moradi et al's retrospective study was expansive but is based on 2 cases of PCNAION none of which occurred in the early postoperative period. The editorial accompanying their article cites the potential limitations of their study, including possible missing cases especially of early-onset PCNAION, the small sample size, wide confidence interval, and concerns about the temporal relationship analysis.[6] Our survey relies on surgeon recall and its anonymous design and brevity limit the detail we can report, as the survey was designed to optimize participation. Notwithstanding, this Canada-wide survey delineated a total of 107 cases of PCNAION from 1 499 694 topical CCCE cases (mean 7.1 events per 100 000) and is a much wider patient base than a single institution report of 2 cases of PCNAION from 18 361 cataracts (mean 10.9 events per 100 000).[5] A standard random effects meta-analysis of proportions would consider only the 48 affected surgeons and yields an incidence of 10.5 PCNAION per 100 000 cataract surgeries (95% CI 7.6−13.5) (see Appendix G available online), which is comparable to the Moradi results, but inaccurate because 74% of the surgeons who did not report PCNAION would have been excluded. Our random effects meta-analysis of proportions using a binomial distribution is better suited to rare events, accounts for heterogeneity between surgeons, and incorporates all the information, yielding a pooled estimate of 2.8 (95% CI 1.6−4.7) PCNAION events per 100 000 cataract procedures that is more representative of the true PCNAION rate among surgeons in Canada. Our confidence interval is much more precise and is compatible with and fully contained within the confidence interval reported by Moradi et al (95% CI 1.3−39.4 per 100 000 cataract surgeries).[5]

We acknowledge the numerous sources of potential bias in this survey, including limited sample size, selection bias from sampling bias, and information biases, including nonresponse bias, response bias, surgeon recall bias, and response inconsistency.

It is unlikely that we can increase the number of online survey respondents. The COS publishes an annual cataract surgery practice pattern based on its members,[17] and in the last decade, the maximum number of cataract surgeon respondents was 123 with an average of 96 respondents. Our survey with 182 respondents exceeds the maximum number of responses in the annual COS cataract survey by 1.5 times[18] and our survey margin of error rate approached 5%. Our best estimated survey response rate was 18%−32%, which is better than the 10%−15% response rate of many external surveys.[19]

Recall bias and response bias are difficult to eliminate from a retrospective survey. It is difficult for surgeons to accurately recall the postoperative intraocular pressure years later. Our incidence rate of NAION would be too low if the survey respondents overestimated the number of cataract surgeries they performed or underestimated the number of NAION events. Mild cases of PCNAION with spontaneous recovery of vision may not have been diagnosed or recognized. If PCNAION patients were not followed by the primary surgeon, under-reporting would also have occurred. Further, it is difficult to determine whether surgeons who did and did not respond to the survey had different NAION incidence rates and characteristics, or systematic differences that may have led to nonresponse bias. If present, such bias could preclude the generalization of results to the entire population of Canadian cataract surgeons. The response profile in our survey was consistent across the 5 regions of Canada, indicating that regional factors, such as language in Quebec, did not have significant impact on the efficacy of the survey instrument. This consistency would be expected of a representative sample, though we note that formal assessment of other sources of bias would require additional follow-up study, with different methodology, which lies outside the scope of the current survey.

In this study, there was heterogeneity among the surgeons and wide variation in cataract numbers with $\tau^2 = 2.551$ ($p < 0.001$). Therefore, the usual sample mean and standard error of the mean were inappropriate methods for analysis and construction of confidence intervals. The random effects meta-analysis of proportions for rare events accounts for the heterogeneity between surgeons and further mitigates the limited survey numbers by coherently pooling the results. This study is the largest series estimate for NAION after cataract surgery, and its nation-wide perspective and meta-analysis technique enhance validity.

Immediate-onset PCNAION is attributed to increased intraocular pressure[4] and perhaps intraoperative systemic hypotension. Later-onset NAION after 3 weeks may be due to intraocular inflammation.[4] In our series 77% of the cases of NAION were in the first 3 weeks post-op; in half of these cases the surgeons indicated that there was associated increased intraocular pressure, but this figure is prone to recall bias. The 77% incidence of early PCNAION differs markedly from the 13.6% figure in the Moradi paper, and may reflect recall bias from the surgeon, or follow-up bias if patients with later-onset NAION did not return to their cataract surgeon with vision complaints. The paucity of early-onset PCNAION was a criticism of the Moradi study.[5] If the predominance of NAION events in the first 3 weeks after surgery is not a follow-up bias, a possible causal relationship between cataract surgery and optic nerve ischemia might possibly be inferred.

Moradi et al concluded that PCNAION was not more common than NAION events in the noncataract population.[5] The estimated annual incidence of NAION in the United States has been quoted from 10.2/100 000 in Rochester, MN,[20] to as high as 82/100 000 in diabetic Medicare beneficiaries over the age of 68 years.[21] The incidence of NAION in Korean patients 40 years of age or older was 11.35 per 100 000 person-years.[22] We preferred to report the risk of NAION per cataract procedure in the year after cataract surgery, as it is easier for patients who are contemplating cataract extraction to understand. Although our incidence figures for NAION were calculated by cataract procedure, and are not directly comparable with the

aforementioned incidence figures, the incidence of PCNAION does not seem to be higher than the incidence of NAION in the general population. To estimate the comparable person-year incidence rate of PCNAION, we require the rate of cataract procedures in the general population, which is approximately 700 to 1110 procedures per 100 000 persons per year in developed countries.[23] Multiplying this cataract surgery rate by our incidence rate per procedure suggests that PCNAION contributes a minuscule 0.02−0.03 occurrences per 100 000 persons per year to the overall incidence rate.

In this study there were 7 patients with bilateral PCNAION. Moradi et al suggest that patients with NAION in one eye had *no* increased risk of contralateral NAION after uncomplicated cataract surgery in the fellow eye.[5] In contrast, Lam et al found that "cataract extraction in the fellow eye increased the risk of NAION occurrence in the fellow eye by 3.6-fold (Cox regression, $p = 0.001$)"[24] and concluded that if a patient with prior NAION is considering cataract surgery in the contralateral eye, surgery should be avoided until activities of daily living are compromised.

Predispositions for NAION and likely PCNAION include the small cup-disc of "disc at risk" morphology, diabetes, hypertension, hypercholesterolemia, and obstructive sleep apnea.[25] Other possible associations include disc drusen, nocturnal hypotension, smoking, anemia, hypercoagulable states, migraine, and medications such as phosphodiesterase-5 inhibitors and amiodarone.

Because there is no definitive treatment for NAION supported by high-grade evidence, prevention and optimization of the modifiable risk factors is a priority. If cataract surgery is required, topical anaesthesia is preferred to local anaesthetic injection.[5] Although unproven, it would be prudent to treat pre-operative anemia and avoid intraoperative hypotension. In patients at risk for PCNAION and obstructive sleep apnea, compliance with ventilation treatment with continuous positive airway pressure should be encouraged.[25] The role of nocturnal hypotension in NAION is controversial,[26] but in patients on antihypertensives and at risk for NAION, medication regimens can be adjusted to minimize nocturnal troughs in blood pressure. Aspirin may decrease the short-term risk of contralateral NAION, but as of yet we do not have any reliable neuroprotective agents for NAION.

Past treatments for NAION with limited or no efficacy include prednisone 80 mg with tapering doses,[27] megadose corticosteroids,[28] erythropoietin,[29] and levodopa/carbidopa.[30] Optic nerve sheath fenestration, intravitreal triamcinolone, and intravitreal bevacizumab have shown no treatment benefit.[31,32] Intravitreal erythropoietin and at least one intravitreal small interfering RNA anti-apoptotic agents (anticaspase) are undergoing investigation.[33]

In summary, our survey estimate suggests that the incidence of NAION after topical clear corneal cataract surgery is 2.8 (95% CI 1.6−4.7) per 100 000 procedures, during the year after cataract surgery. The incidence of NAION after topical clear corneal cataract surgery is rare, but when it occurs, 77% of cases may be within the first 3 weeks after surgery. This study is limited by its retrospective survey design and surgeon recall bias but provides the largest estimate to date on the incidence of postoperative NAION after modern cataract surgery methods, and is useful for patient counselling and epidemiologic considerations.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjo.2019.06.006.

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Footnotes and Disclosure:

The authors have no proprietary or commercial interest in any materials discussed in this article.

This article includes online-only material. Appendices A–G can be found on the CJO web site at http://pubs.nrc-cnrc.gc.ca/cjo/cjo.html. It is linked to this article in the online contents of the xxx 20xx issue.

From the *University of Toronto, Toronto, Ont.; †McGill University, Montreal, Que.; ‡University of British Columbia, Vancouver, B.C.; §University of Waterloo, Waterloo, Ont.; ‖University of Alberta, Edmonton, Alta.; ¶Harvard University, Boston, MA

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Correspondence to Edsel Ing, MD, Michael Garron Hospital, 650 Sammon Ave, K306, Toronto, Ont. M4C 5M5. edingLidStrab@gmail.com