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Epidemiological and Health Economical Evaluation of Intraoperative Antibiosis as a Protective Agent against Endophthalmitis after Cataract Surgery

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Abstract
Objective: To evaluate risk factors for endophthalmitis after cataract surgery and to retest recent findings on the protective effect of intraoperative antibiosis and the promoting effect of the clear corneal as compared to sclerocorneal incision. In addition, the economics of intraocular intraoperative antibiosis as a prophylaxis in cataract surgery are asketched.
Design: survey study
Participants: five hundred thirty-eight ophthalmosurgical centres in Germany
Main Outcome Measure: epidemiological evaluation: responder specific endophthalmitis incidence in year 2000; economical evaluation: direct cost analysis based on incidence data and local cost estimates (health service's perspective)
Results: A total of 310 (58%) questionnaires were computed resulting in an overall count of 404,356 cataract surgeries and 291 self-reported endophthalmitis cases (crude rate 0.072%). The risk of postoperative endophthalmitis for sclerocorneal versus clear corneal incisions was not significantly reduced (relative risk 0.97, 99% confidence interval 0.69-1.38). The hypothesis of a protective effect of intraocular antibiosis could be confirmed by a significantly decreased risk ratio of 0.69 (99% confidence interval 0.48-0.99) indicating a significant benefit from intraoperative intraocular antibiosis. A similar tendency was observed for an intraoperative periocular antibiosis with a significantly reduced risk ratio of 0.68 (99% confidence interval 0.49-0.96). These risk estimates had been adjusted for the size of the surgical centre: a significantly reduced risk ratio of 0.70 (99% confidence interval 0.49-0.98) for postoperative endophthalmitis was observed for local centres. Cost evaluation for the prophylactic use of intraocular intraoperative antibiosis in cataract surgery revealed an economically relevant decrease in direct endophthalmitis associated costs.
Conclusions: Whereas this 2000 appraisal of a recent survey in 1996 could not reproduce the benefit of sclerocorneal incision, the protective effect of intraoperative intraocular antibiotic propylaxis could be confirmed. However, the results of this survey have to be interpreted with care, since it is not based on individual case information, but rather on aggregate questionnaire data.

Key words: cataract surgery, endophthalmitis, antibiotic prophylaxis, direct costs

Introduction

Endophthalmitis is a dreaded condition in ophthalmology, which can occur after ophthalmic surgery [1], posttraumatically or endogenously. At the beginning of the 20th century its annual incidence after intraocular surgery was estimated [1] about 1%. Meanwhile it appears reduced [2, 3, 4, 5, 6, 7] to about 0.05% to 0.5% because of better knowledge about antibiotic prophylaxis. The multicenter "Endophthalmitis Vitrectomy Study" provided guidelines [4] on case management [8] in case of postoperative infection. However, standardized procedures for infection prophylaxis are of increasing interest.

Therefore a survey on putative risk factors for endophthalmitis after cataract surgery and possible protective strategies had been performed in Germany [9] based on the German surgeons' self-reported counts of cataract surgeries and subsequent endophthalmitis cases in 1996. This survey revealed some promising results both concerning incision techniques [9, 10, 11, 12, 13] as well as the impact of antibiotic prophylaxis [9, 14, 15, 16, 17, 18, 19, 20]: According to the surgeons' self-reported data in this survey the sclerocorneal incision was associated with a 65% reduction in risk for endophthalmitis when compared to the clear cornea approach. Furthermore, the intraocular application of antibiotics showed a 35% reduction in endophthalmitis risk.

To retest these findings the German study group decided to perform a similar survey in 2000. In addition, an estimation of the direct endophthalmitis associated costs was performed in order to evaluate the economical impact of a possible guideline for intraocular antibiosis.

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Material and Methods

Epidemiological Study

In August 2001 a questionnaire was mailed to each opthalmosurgical centre and university hospital in Germany, and chairmen were asked to send it back in an anonymous envelope. The questionnaire focused on pre-, intra- and postsurgical prophylaxis (antibiotics and steroids) as well as on details on incision techniques and postoperative complications. Centre chairmen and local surgeons were asked to report their site's overall number of cataract surgeries in 2000 as well as the overall number of endophthalmitis cases among patients, who became known until August 2001.

Note that there was no individual case data available from the responders' questionnaire, but rather overall indications on their usual performance and on the overall counts of endophthalmitis cases among their patients. Therefore the primary endpoint of this epidemiological study is the "responder specific rate" (RSR) of endophthalmitis cases, which is the ratio of self-reported cases related to the number of self-reported cataract surgeries for each responder. The RSR therefore represents a responder's 2000 endophthalmitis incidence.

Statistical Analysis of the questionnaires mainly focused on the RSR, which was correlated to the putative risk factors by fitting multiple Poisson regression models [21]. Results are summarized as hazard ratios, which estimate the relative endophthalmitis risk (RR). RR is smaller than 1.0, as soon as a surgical strategy turns out protective (1.0-RR indicates the order of reduction in the endophthalmitis risk). If 1.0 is not contained in the 99% confidence interval, then the risk reduction is proven statistically significant at the 1% significance level [9, 21]. Additionally, the correpsonding Wald test [21] p value was provided; a p value < 1% indicates local statistical significance. All numerical analysis was drawn out using SAS® (Release 6.8 for Windows) [21], data entry and graphical representation was drawn out using SPSS® (Release 10.0 for Windows) [22].

Health Economical Evaluation

The RSR data is the basic input parameter for the cost analysis: From the estimated reduction in risk by applying intraocular antibiotics, the reduction in costs due to avoided cases can be derived. However, each unavoided endophthalmitis case will cause fix costs of about 107.92 € and additional 165.76 € each day under hospitalisation (standard case rates). Assuming a mean hospitalisation time of 14 days per endophthalmitis case, each case will cause direct costs of about 3831.47 € . The individual direct costs for the antibiotic prophylaxis can be estimated as follows: According to the experiences at the Ophthalmology Department of the University Hospital in Mainz, 20 portions of Gentamicin 40 Hexal® (500 ml) can be regarded sufficient for about 60 surgeries. This results in direct costs of 0.68 € per eye under antibiotic prophylaxis.

Results

Epidemiological Study

A total of 310 (58%) questionnaires were returned. Their analysis revealed an overall count of 404,356 cataract surgeries and of 291 self reported endophthalmitis cases (crude endophthalmitis incidence rate 0.072% as compared to 0.078% in the 1996 survey [9]). Figure 1 displays the bivariate distribution of the responders' self reported number of cataract surgeries in 2000 versus their endophthalmitis counts.

The hypothesis of different endophthalmitis rates between sclerocorneal (n = 201 responding centres) and clear cornea incisions (n = 92 responding centres) could not be verified: the risk of postoperative endophthalmitis after sclerocorneal incision was 0.97 (99% confidence interval 0.69-1.38). The second hypothesis of a protective effect of intraoperative intraocular antibiosis could be confirmed by a significantly decreased risk ratio of 0.69 (0.48-0.99) indicating clinically and statistically significant benefit from intraoperative intraocular antibiosis (n = 170 versus n = 125 responders). Most surgeons (81%), who usually perform such prophylaxis, indicate regular use of gentamicine derivates. A similar tendency was observed for an intraoperative periocular antibiosis (n = 136 versus n = 131 responders) with a significantly reduced risk ratio of 0.68 (0.49-0.96). Furthermore, the protective effect of an intraocular antibiosis is strongly associated with conjunctival iodine prepping (by installation of iodine solution), showing a significantly reduced risk [23, 9, 24] of 0.56 (0.34-0.94). Furthermore, a difference in endophthalmitis indicedences was observed between local surgical centres (n = 203) versus larger clinical departments (n = 87) with a significantly reduced risk ratio of 0.70 (0.49-0.98; the latter indicates larger endophthalmitis rate in larger clinical centres. Table 1 summarizes the information on the above confirmatory risk factors' evaluation and also displays the underlying mean endophthalmitis counts.

Table 2 presents the results for the exploratory risk factors assessed by the questionnaire. Surprisingly none of these items turned out statistically significant, nor did any of the relative risk estimates indicate clinical relevance. Table 2 provides slight prophylactic evidence for the postoperative application of periocular steroids and antibiotics, but the duration of the prophylaxis should exceed one week after surgery (relative risks 1.23 and 1.11 for cancellation within one week, respectively). Whereas the application of intraoperative periocular steroids seems protective (relative risk 0.83), the local application of steroids 1 day before and at the day of surgery appears promoting for the development of an endophthalmitis (risk estimates 1.19 and 1.11, respectively). The same tendency was observed for local antibiotics (risk estimates 1.05 and 1.15, respectively). Finally it was observed that patients undergoing outpatient surgery showed a reduction in risk for postoperative endophthalmitis (relative risk for surgeons with more than 20% outpatient surgery 0.76).

Table 1. Confirmatory risk factors: column 2 displays mean endophthalmitis counts (EO). Column 3 presents the risk factors' hazard ratio (RR), column 4 shows the RR's 99% confidence interval (99% CI), column 5 displays the corresponding Wald test p value.

size of surgical centre	mean EO count	relative risk	99% CI	p (Wald test)
local surgeons (n = 203)	0.66			
larger centres / university hospitals (n = 87)	1.72			
		RR = 0.70	0.49-0.98	p = 0.007
incision mode	mean EO count	relative risk	99% CI	p (Wald test)
clear corneal (n = 92)	1.32			
sclerocorneal (n = 201)	0.84			
		0.97	0.69-1.38	p = 0.845
intraocular antibiotics applied	mean EO count	relative risk	99% CI	p (Wald test)
yes (n = 170)	0.75			
no (n = 125)	1.27			
		0.69	0.48-0.99	p = 0.009
periocular antibiotics applied	mean EO count	relative risk	99% CI	p (Wald test)
yes (n = 136)	0.90			
no (n = 161)	1.02			
		0.68	0.49-0.96	p = 0.004
participation in 1996 survey	mean EO count	relative risk	99% CI	p (Wald test)
yes (n = 245)	1.00			
no (n = 32)	0.34			
		0.47	0.21-1.07	p = 0.020

Table 2. Exploratory risk factors; column 2 displays the sub groups' sizes, column 3 the risk factors' hazard ratio (RR, 99% confidence interval in brackets), column 4 the correponding Wald test p value

risk factor	frequency “yes” / “no”	RR (99% CI)	p (Wald test)
> 20% outpatient surgery?	123 / 171	0.76 (0.55-1.04)	0.022
ECCE involved in incicion?	14 / 285	2.12 (0.58-7.77)	0.139
incision (postero)limbal?	45 / 43	0.80 (0.49-1.29)	0.222
incision width larger than 3 mm?	16 / 75	1.51 (0.81-2.81)	0.087
local antibiotic prophylaxis			
1 day before surgery?	106 / 193	1.05 (0.77-1.44)	0.674
at day of surgery?	72 / 227	1.15 (0.80-1.65)	0.334
local steroid prophylaxis			
1 day before surgery?	258 / 41	1.19 (0.77-1.86)	0.303
at day of surgery?	161 / 138	1.11 (0.81-1.50)	0.396
conjunctival iodine preppping?	288 / 19	0.66 (0.37-1.17)	0.059
covering lashes' environment?	289 / 8	1.15 (0.36-3.70)	0.750
intraoperative periocular steroids?	188 / 109	0.83 (0.61-1.14)	0.134
postoperative prophylaxis			
local steroid application?	226 / 73	0.69 (0.26-1.87)	0.342
duration less than 1 week?	148 / 153	1.23 (0.90-1.68)	0.083
local antibiotic application?	233 / 60	0.95 (0.65-1.41)	0.756
duration less than 1 week?	119 / 114	1.11 (0.78-1.59)	0.447

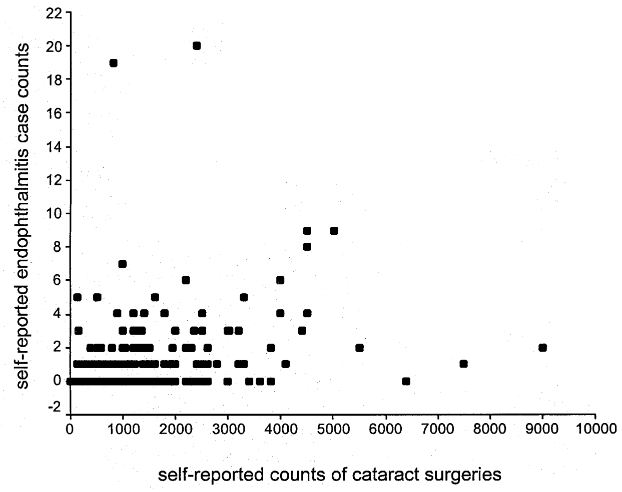

Fig. 1. Scattergram of the bivariate distribution of self reported numbers of cataract surgeries and endophthalmitis cases in 1998.

Health Economical Evaluation

Since there was an obvious preference for gentamicine in the surgeons' answers (59%, plus 22% in combination with vancomycine), the subsequent cost analysis will be based on the assumption of an overall prophylactic application of gentamicine.

According to the above epidemiological data 400,000 cataract surgeries per year are assumed for Germany. Establishment of the prophylaxis will reduce the total number of endophthalmitis cases per year from the reported 291 to 214 cases per year. Each of the remaining unavoided cases will cause direct costs of 3 831.47 €, cumulating to overall costs of 819 934.58 € per year. This must now be corrected for the cumulate costs of 272 000 € for the assumed 400 000 prophylactic intervention at a rate of 0.68 € per eye. This results in annual costs of 1 091 934.58 €. The above must now be compared with the opposite scenario, when antibiotic prophylaxis is omitted by all surgeons. The observed number of 291 endophthalmitis cases may then increase up to 399 cases per year, resulting in cumulate costs of 399 x 3 831,47 = 1 528 756.53 € per year.

Summarizing global recommendation of an intraocular intraoperative antibiotic prophylaxis based on gentamicine would then result in a maximum annual gain of about 436 822 €. Even compared to the recent status quo (58% of the surgeons reporting regular use of antibiotics) the annual gain would amount to about 183 465 €.

Discussion

The main intention of this evaluation was to reproduce recent epidemiological findings on putative risk factors [25, 11] for endophthalmitis after cataract surgery. The main confirmatory hypotheses generated from a German survey [9] in 1996 stated the protective effect of intraoperative intraocular antibiosis [6] and the promoting effect of the clear cornea incision mode. The size of the ophthalmosurgical centre and a participation in the 1996 survey were regarded as confounders and introduced into the multivariate analysis.

There was neither a statistically nor clinically relevant indication for an increased endophthalmitis risk of patients undergoing clear corneal incision. This may be explained by an increased familarity with the clear corneal procedure and an increased awareness of its risk potential for postoperative complications [9].

Note that the underlying data base includes some crucial limitations, which must be emphazised when interpreting the results at hand: First, both the 2000 and the 1996 survey are only based on aggregate *self-reported* information instead of clinically monitored case data, i.e. surgeons only report their *usual* ways of surgery and their *overall* numbers of cataracts: Maybe there have occurred rare, but systematic, deviations from this *usual* surgical strategies just in those few cases, which ended up with an endophthalmitis. The resulting misclassification could lead to severe bias and therefore even to adverse results concerning the risk factors under consideration. The validity of self-reported endophthalmitis counts has to be questioned as well, since some of the responders may have "corrected" their endophthalmitis counts. Others (presumably non-responders) may have produced remarkable endophthalmitis rates, which they would never like to commit even in an anonymous questionnaire. In addition, only the sites' chairmen were asked for their site's overall endophthalmitis counts; their answers may not necessarily represent the whole site. Furthermore, the self-reported data is due to some obvious "digital preference": surgeons may have truncated their reported counts of cataract surgeries to "round numbers" such as 5000 or 1500 (Fig. 1). Since this effect will hardly be relevant for the endophthalmitis counts, the RSR values may be biased by this truncation process. On the other hand, any of the recent survey studies on the epidemiology of endophthalmitis [2, 3, 4, 5, 6, 7, 9] will underly these limitations.

To evaluate the impact of the above sources of bias, a sensitivity analysis of the main statistical results was performed, where all reported cataract counts were randomly corrected for truncation. None of the results changed notably. In summary, the protective effect of intraoperative antibiosis has been strictly confirmed.

An additional cost analysis for the putative prophylaxis was performed. Of course this analysis can only be based on very crude assumptions concerning the costs and the numbers of avoidable endophthalmitis cases. Nevertheless, even an extensive sensitivity analysis for the economical input data still confirmed the overall result, that the prophylaxis is economically beneficial. The ethical benefit of an antibiotic prophylaxis would be obvious, regarding the large number of vitrectomies [26] and enucleations caused by endophthalmitis. On the other hand, extensive microbiological research seems necessary to obtain information on the risk of increasing resistance [27, 28] of the infectious agent: Whereas the variation of infectious agents seems unlimited, the range of effective antibiotics is certainely restricted and maybe soon exhausted.

Of course, the results of an incidence-based health economical evaluation cannot be regarded sufficient for health policy decisions – the above epidemiological and health economical results were rather provided as part of a rationale for the overall evidence based discussion [6] on endophthalmitis prophylaxis.

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