THE USE OF EPIDEMIOLOGICAL TECHNIQUES TO ASSESS RISK: THE EPIDEMIOLOGY OF MICROBIAL KERATITIS

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SUMMARY

The role of the three principal epidemiological study designs – descriptive, cohort and case–control studies – for the evaluation of risk, is illustrated by describing their use for the investigation of microbial keratitis. Descriptive studies have identified potential risk factors and causes of microbial keratitis by both case reports and case series; trauma, ocular surface diseases and, latterly, contact lenses have been identified as potential risk factors. These studies have also shown that *Pseudomonas aeruginosa* and *Acanthamoeba* are particularly associated with contact lens wear. However, these studies are limited because they cannot be used to quantify risk. Cohort studies, in which the number of cases of a disease developing in a defined and initially unaffected population are identified, are usually inappropriate for assessing rare conditions because the size of the study often has to be too large, and follow-up too long, to generate sufficient numbers of cases. Some of the disadvantages of this study type can be overcome by sampling techniques and have been successfully carried out to obtain incidence figures for microbial keratitis. Case–control studies use multivariable analyses to examine the risk of microbial keratitis associated with various factors. This is an economical study design for investigating rare diseases because a group of subjects with the disease is compared with a control group from the same population who are unaffected. The selection of an appropriate control group is a difficult problem in epidemiology but this study design has been crucial in identifying risk factors and potential causes of microbial keratitis.

Epidemiological study designs can be used to evaluate risk factors and their magnitude for a disease.[1,2] The three principal types of epidemiological study – descriptive, cohort and case–control – have all been used to investigate risk factors and identify potential causes of microbial keratitis. The advantages and limitations of these techniques are illustrated by this review of the use of these methods in the investigation of this disease.

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DESCRIPTIVE STUDIES

The initial identification of potential major risk factors for keratitis has resulted from case reports and simple case series. Before the widespread introduction of contact lenses (CLs), case series had established that microbial keratitis occurred principally in eyes with existing disorders of the ocular surface: corneal surgery, trauma and ocular surface disease (principally post-herpetic corneal disease, bullous keratopathy, corneal anaesthesia, corneal exposure and the dry eye).[3–5] Until the late 1970s CL wearers made up only a small proportion of patients with microbial keratitis. Since 1977 case reports have appeared reporting the association of microbial keratitis with CLs.[6,7] The size of this problem was established by the reporting of larger series of keratitis cases from major ophthalmic institutions, where over 30% were shown to be related to CL wear. These studies identified that a substantial problem was emerging in CL wearers which was of concern because, unlike the other causes, it was potentially avoidable. In addition these case series identified that a higher proportion of patients than anticipated were using overnight wear soft lenses.[8-10] Lastly it was also noted that the use of CLs was associated with a different spectrum of organisms compared with the other causes: *Pseudomonas* occurs more frequently among CL users[7,9,10] and, more recently, it has been shown that 85% of *Acanthamoeba* cases are in CL users.[11]

These reports and studies have been valuable for identifying the emergence of new risk factors for keratitis. However, this study design cannot provide

information about the magnitude of the associated risk, such as CL wear (known as an 'exposure'), or the significance of the risk factor to the population as a whole. This is because the prevalence of CL use in the population, from which the cases are derived, is usually unknown (the denominator). Any attempt to extrapolate from hospital-based studies to the situation in the community must be done with caution. Failure to do so when interpreting data has led to widely differing conclusions; for example, regarding the risks of extended wear lenses for microbial keratitis, 'the risk of ulcer formation may be just as great for daily wear as for extended wear'[12] and conversely represent an 'alarming increase in complications . . . for extended wear lenses'.[13]

In addition to these limitations the descriptive study can generally identify only the presence of potential associations. Some observed associations may be real while others could be spurious due to confounding by other factors. For example the association of CLs with keratitis might be unrelated to the lens itself but to the type of disinfection system, or lack of it, associated with lens wear.

Descriptive studies have frequently been used for clinical trials of CLs. These have provided incidence data for various complications resulting from exposure to a particular CL type. The weakness of these studies has been the lack of a comparison group. Data from such clinical trials, often carried out as pre-marketing approval studies in the United States where CLs must be licensed, has provided little information about the risks for keratitis. Analysis of the pooled results of 48 consecutive pre-market approval studies (clinical trials) on 22 739 CL users for the US Food and Drug Administration has provided annualised incidence rates for keratitis of 6.8:10 000 ($n = 3907$) for gas-permeable daily CL wear, 5.2:10 000 ($n = 3591$) for daily wear soft CL wear and 18.2:10 000 ($n = 1276$) for reusable extended wear soft CL wear.[14] These studies were

Table I. Comparison of cohort and case–control studies

(a) Cohort (or longitudinal) study

A group (A_x) who are initially disease free (i.e. users of contact lens x) and followed over time to establish those who develop a disorder (D_x) (i.e. keratitis) and those remaining free of the disorder (C_x) (examples assume no losses to follow-up):

	A_x	=	D_x	+	C_x
For example:	1000		100		900

The *incidence* of the disorder in this group is then:

D_x/A_x

For example:

100/1000 or 0.1
(Risk A_x)

For a second group (A_y) (i.e. users of contact lens y):

	A_y	=	D_y	+	C_y
For example	1000		200		800

The *incidence* of the disorder is then:

D_y/A_y

For example:

200/1000 or 0.2
(Risk A_y)

The *relative risk* of developing the disorder between these two groups having different exposures (i.e. using different contact lens types) is the ratio of the incidence for each group:

$$\frac{\text{Risk } A_y}{\text{Risk } A_x} \quad \text{is } 0.2/0.1 = 2 \text{ times}$$

(b) Case–control study

An initial group with a disorder (D) (i.e. keratitis) is collected and compared with a control group (C) who are derived from the same population as those with the disorder but who do not have it. The numbers with the disorder and controls using the referent contact lens, x ($D_{x\text{ref}}$,$C_{x\text{ref}}$), and those with the alternative (test) contact lens, y (D_y,C_y), are determined:

	D	=	$D_{x\text{ref}}$	+	D_y
	All CL users with the disorder		Referent lens users with the disorder		Alternative lens users with the disorder
For example:	30		10		20
	C	=	$C_{x\text{ref}}$	+	C_y
	All CL users without the disorder (controls)		Controls using referent lens		Controls using alternative lens
For example:	120		100		20

The *odds ratio* (used as an estimate of relative risk for the alternative contact lens y compared with the referent contact lens $x$ref is then the product of the proportions of the users of each lens type in the diseased and control groups:

$$y{:}x\text{ref} = \frac{D_y/D_{x\text{ref}}}{C_y/C_{x\text{ref}}}$$

For example

$$\frac{20/10}{20/100} = \frac{2}{0.2} = 10 \text{ times}$$

carefully carried out but were not comparative and were on carefully monitored volunteer users giving informed consent. For these reasons they may not be representative of the population of CL users in the real post-marketing situation. Although the information they give is valuable, the individual studies were too small to give precise estimates of the incidence of these less common but severe complications of lens wear and failed to alert the licensing authority to the potential problems associated with the use of continuous wear soft CLs.

COHORT STUDIES

In the cohort study design a representative group of subjects with different exposures (such as different CL types) is selected for follow-up. The annualised incidence for each complication can be simply calculated from the proportion who develop it over time. In addition the relative risk of developing a complication, for one exposure compared with another, can be calculated for a complication by dividing the proportion developing the complication for one exposure by the proportion developing the complication for the referent exposure (the referent is usually chosen as an exposure for which the level of risk is likely to be lowest or best established). An example is shown in Table Ia.

This design is usually inappropriate for the study of rare conditions, such as microbial keratitis, because the size of the cohort may need to be too large to be practical. This is demonstrated by the use of this type of study for the evaluation of the risks of different CL types for aphakic correction.[15] Although this might indicate that the problem is too small to be of concern, this is not the case when there is a very large population exposed or when the disease is severe.

This problem has been successfully addressed for estimating the incidence of ulcerative keratitis associated with CL wear in New England. This was achieved by completing the study in an area with a small potential for cross-border treatment of keratitis and identifying all cases of keratitis occurring within this area in a defined period (the numerator). The number of CL users at risk in this area (the denominator) was then established by sampling the population by telephone, to establish the penetrance of different lens types in the population, using a structured questionnaire. This study estimated an annual incidence for ulcerative keratitis in the United States of 20.9 (15.1–26.7):10 000 for extended wear soft CL use compared with 4.1 (2.9–5.2):10 000 for daily wear soft CL use.[16] This study did not have the power to identify differences between rigid and soft lens type.

The cohort study design has the advantage of simplicity in conception. It is ideal for assessing the incidence and risks of common complications. The principal disadvantages are that rare complications cannot be evaluated when the incidence is too low to allow the use of a manageable cohort size. These studies can be carried out prospectively or retrospectively. The advantages of a prospective design are that comprehensive data sets can be collected. Retrospective collection of data for cohort studies restricts the data sets that can be collected for analysis. However, data about clinically significant complications can often be extracted from clinical records. This can be an economical study design for obtaining data on both incidence and, in comparative cohort studies, relative risk.

CASE–CONTROL STUDIES

The case–control design has recently been used to overcome some of the problems of cohort studies, and to resolve the uncertainties arising from the results of descriptive studies, in the assessment of risk. The case–control study design has provided quantitative data on differences in risk for different lens types and other causes of keratitis. It has also been used to investigate, by multivariable analysis, the influence of additional factors associated with the use of different CL types and which might contribute to the risk of keratitis.

Table II. Principal advantages and disadvantages of cohort and case–control studies

Cohort studies	Case–control studies
Advantages	
Simple concept	Appropriate for measuring odds ratios (relative risks) for rare diseases and for assessing the effect of multiple factors on the risks
Both incidence and relative risks can be established in comparative studies	
The evolution of disorders in the study group can be assessed	
Disadvantages	
Disorders with a low incidence cannot be evaluated with a manageable size of study population	More difficult concept and statistical handling
Subjects and follow-up regime may be highly selected and unrepresentative	Control group may not be appropriate – the greatest problem with this study design
	Incidence cannot be adequately estimated unless the total population at risk is known

In case–control designs a group of subjects having the disorder is compared with a group of controls derived from the same population but who do not have the disorder. The controls are ideally collected concurrently with the cases. The odds ratio (or relative risk – the odds ratio is used to give a close estimate of relative risk) of one CL type can be calculated for each complication as shown in Table Ib.

This study design has the advantage over a cohort study that it can be used for the assessment of rare complications because diseased cases are collected with appropriate controls (summarised in Table II). This is in contrast to the cohort study which starts with a healthy population all of whom must be followed up in order to identify the diseased cases. This difference can result in a cohort study with 2200 in each group having comparable power to a case–control study with only 20 cases and 120 controls to demonstrate an equal difference in risk.[17] The disadvantages are that the concept is more difficult to understand and that selection of an appropriate control group is critical to the success of the study. The selection of appropriate controls for a case–control study presents one of the greatest difficulties in epidemiology.

Case–control studies can be carried out either retrospectively or prospectively. They are often carried out using retrospective ascertainment of exposure to various risk factors. However, the information must be collected systematically, with a standardised method, for cases and controls. Clinical case records are usually inadequate.

The case–control study of microbial keratitis in the United Kingdom has shown that CLs are now the major associated cause of microbial keratitis in London, with a risk that is significantly higher than that for corneal trauma.[18] The relative risk (RR) of keratitis associated with CL wear was 80 (95% CI 38–166), and 14 (95% CI 6–32) for trauma compared with cases without an identifiable predisposing factor (the referent, with a baseline risk of 1.0). CL wear, principally of soft CLs, was also shown to be responsible for 65% of all new microbial keratitis cases at this centre, where no serious cases attributable to this cause had been reported a decade earlier. This study also showed that, compared with hard CLs, the risk for extended wear soft CLs was ×21 (7–60) and for daily wear soft CLs ×3.6 (1–14). Continuous periods of extended wear of more than 6 days were associated with a further increase in the risk of keratitis. This study confirmed the results both of a previous pilot study carried out in London[19] and of an independent case–control study of ulcerative keratitis, carried out in multiple centres in the United States, which showed that the risk of using extended wear soft CLs was 9–15 times higher than that for daily wear soft CLs, and that the risk was incrementally related to the period of extended wear. The RRs for hard CLs could not be assessed.[20]

Disposable CLs were recently introduced as a solution to some of the problems associated with reusable daily and extended wear lenses. The investigation of the risks associated with this new type of lens illustrates well the use of different study types for investigating problems. Several studies have reported a low incidence of adverse reactions.[21–23] However, as already discussed, these study designs are unlikely to identify less common, but serious disorders such as keratitis for which a relatively low incidence becomes important only when there is a large population at risk. Case series and reports have shown that keratitis may occur in disposable CL wear.[14] A case–control study design is ideally suited to investigating whether there are differences in risks between lens types, allowing comparison of new types of lens and lens-wearing regimes with those for which the level of risk is better established. Small case–control studies using this methodology suggest that risks for microbial keratitis may be as great or greater with disposable lenses than for conventional soft lens wear;[24,25] failure to comply with recommended lens care and wear regimes may be one cause of this, rather than the lenses themselves.[25] Case–control studies, including a multivariable analysis of factors that may be associated with these differences in risk, can be expected to determine whether it is a failure to comply with the recommended regimes for disposable CLs that is resulting in higher than expected risks of keratitis or whether some other factor, related to the care system or the lens, might be responsible. This approach has been used to identify the use of home-made saline solutions, swimming in CLs and irregular disinfection as risk factors for *Acanthamoeba* keratitis in the United States, although no differences could be shown for the different CL types.[26]

DISCUSSION

All the principal epidemiological study designs have been used in the assessment of risk factors for microbial keratitis. Investigation of this disease provides an example of how these study designs can be utilised to investigate any potential cause of disease and how risks can be quantified. Simple descriptive studies have often identified associations that may be potential causes of disease. The cohort study design allows precise estimates of incidence and, in comparative studies, of relative risk. It is appropriate for the evaluation of common disorders. However, this type of study cannot be used to evaluate rare events, such as keratitis, unless the study numbers are very large. Relatively rare

disorders may become apparent only when very large numbers of individuals are exposed to a risk. Case–control studies are useful for evaluating relatively rare disorders and can provide precise estimates of relative risk as well as having the power to evaluate the effect of multiple associated factors on the risk.

All these different study designs have their role in the investigation of disease. An understanding of the methodology, advantages and limitations of these designs has become increasingly important for both evaluating and planning research into the causes of disease.

Key words: Case–control study, Cohort study, Descriptive study, Epidemiology, Microbial keratitis, Study design.

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