Is the observed lowering of intraocular pressure due to treatment?

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Objective: Use Bayes' theorem to estimate the intraocular pressure (IOP) lowering effect of medical treatment initiated for glaucoma and determine if IOP comparisons to the baseline IOP of the same eye is clinically useful. **Materials and Methods:** The probability that treatment with prostaglandin is responsible for an observed 20% decrease in IOP with prostaglandin treatment was calculated using Bayes' theorem using the following available information: the probability of a 20% decrease in IOP given treatment with prostaglandin, the probability of a treatment effect using prostaglandin and the overall probability of a 20% decrease in IOP. The calculations were repeated to account for a possible 2 mmHg overestimation of effect caused by measurement error in performing applanation tonometry. **Results:** The probability that treatment is responsible for an observed 20% decrease in IOP following initiation of treatment with a prostaglandin was 99%. After adjusting for measurement error this probability was 98%. Obtaining two IOP measurements marginally increased the probability. **Conclusion:** Following initiation of treatment with prostaglandin, Bayes' theorem allows us to infer that treatment effect is the most likely explanation for an observed 20% decrease in IOP from the baseline; this inference remains even after adjusting for known measurement error. The high probability of a treatment effect is due to the high prior odds of treatment effect and the high likelihood ratio for prostaglandin producing such an effect. If data is available, similar calculations can be used for other percentage decreases, other medications and for the monocular trial.

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Published preferred practice for the initiation of medical treatment for glaucoma recommends the use of a monocular trial.[1] The monocular trial is used to distinguish the intraocular pressure (IOP) lowering due to the medication from that caused by spontaneous variation. In the monocular trial, one eye is treated while the fellow eye serves as a control. The effect of medication is determined by "adjusting" the treated eye for the change in IOP measurement in the control fellow eye. While sound in theory the practical value of such a trial has been questioned and some experts suggest comparison to baseline IOP rather than adjusting for the IOP in the fellow eye.[2] The latter essentially implies that treatment can be initiated in both eyes without going through the time consuming process of a monocular trial. The debate is ongoing and the best method of assessing the IOP-lowering effect of medical treatment initiated for glaucoma is still uncertain.[3,4] A recent publication using data from the Ocular Hypertension Treatment Study (OHTS) and the accompanying editorial highlighted this continuing clinical debate[5,6] The article concluded that neither the adjusted or unadjusted method were really good enough. The editorial recommended multiple measurements of IOP over several visits, both pre and post-therapy, but acknowledged that the optimal number of such measurements have not been established.[6] There is a practical limitation to the number of IOP measurements that can be obtained prior to and after initiation of treatment and a monocular trial adds to the logistical complexity.

Following initiation of medical treatment we observe a certain decrease in IOP. However, the information that we actually need is the probability that this decrease is in fact due to the medication. This is a problem in inverse probability that can be solved using Bayes' theorem.[7] We have recently applied the theorem to selected ophthalmic situations, and addressed the question of IOP-lowering efficacy of medical treatment as well.[8,9] Before we decide to continue lifelong treatment the practical clinical question is how sure we want to be that the observed decrease in IOP is fact due to the medication? We can never be 100% certain, but are most clinicians likely to act on an 80-90% probability that an observed 20% drop in IOP was due to the medication? Herein, we further elaborate on how Bayes' theorem can be used to calculate this probability, adjust for measurement error, as well as determine the change in this probability if more IOP measurements were obtained. This information and an understanding of the underlying logic permit informed clinical decision making for initiating continuation of medical treatment for glaucoma.

Materials and Methods

Like the recent OHTS article, we restricted our calculations to treatment with a prostaglandin and an observed 20% decrease in IOP compared to baseline.[5] Compared to the baseline IOP a 20% decrease in IOP is observed following initiation of treatment with a prostaglandin. The information we actually need is the probability that it is in fact the treatment that is responsible for the observed 20% decrease in IOP. This probability will be denoted as P (RxE|IOP20) where RxE is treatment effect, the sign "|" means *given*. Here *given* (|) indicates that we are concentrating only on those with an IOP decrease of 20% which is denoted as IOP20. The right side of

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the "given" sign is the "universe" we are examining.

For the example above, Bayes's theorem takes the following form:

P (RxE|IOP20) = P (IOP20|RxE) × P (RxE) ÷ P (IOP20).[7]

Where

P (RxE|IOP20): probability of a treatment effect *given* that there is a 20% decrease in IOP

P (IOP20|RxE): probability of a 20% decrease in IOP *given* that there is a treatment effect

P (RxE): probability of a treatment effect

P (NoRxE): probability of no treatment effect

P (IOP20): probability of a 20% decrease in IOP.

Further, P (IOP20) = P (IOP20 and RxE) plus P (IOP20 and NoRxE).[7] To put this in words, the probability of a 20% decrease in IOP comprises the probability of a 20% decrease in IOP AND a treatment effect PLUS the probability of a 20% decrease in IOP AND no treatment effect. These can be calculated as:

P (IOP20 and RxE) = P (IOP20|RxE) × P (RxE)

P (IOP20 and NoRxE) = P (IOP20|NoRxE) × P (NoRxE)

The (inverse probability) information that we need, P (RxE|IOP20), can be calculated from available information.

Prostaglandins are known to produce an IOP reduction of >25% about 83% of the time.[10] For P (IOP20|RxE), we used a conservative estimate of 80% (0.8).

In the study quoted above, less than 1% of patients did not respond to prostaglandin and 2.7% demonstrated just a 10% decrease in IOP.[10] For P (RxE), probability of a treatment effect with prostaglandin we use a conservative estimate of 90% or 0.9. If we consider the probability of a treatment effect as 0.90, then the probability of no treatment effect, P (NoRxE) is = 0.1.

P (IOP20|NoRxE), the probability of a 20% decrease in IOP given no treatment, (due to variation and other causes) is available from a recent publication = 0.05.[11]

As detailed above P (IOP20) = {P (IOP20|RxE) × P (RxE) + P (IOP20|NoRxE) × P (NoRxE)}. From the information provided above, this can be calculated as:

(0.8 × 0.9) + (0.05 × 0.1) = 0.72 + .005 = 0.725

Using Bayes' theorem the probability of a treatment effect given a 20% decrease in IOP, P (RxE|IOP20) = P (IOP20|RxE) × P (RxE) ÷ P (IOP20)

= (0.8 × 0.9) ÷ {(0.8 × 0.9) + (0.05 × 0.1)}

= 0.72 ÷ .725 = 0.99 = 99%

The measurement error inherent in applanation tonometry is 2 mmHg.[12] Adjustment for this error in measurement can be performed as follows. Considering an initial IOP of 24 mmHg, a 20% decrease with treatment is 4.8 mmHg. In our example underestimation would not matter, but if we overestimate the decrease in IOP by this error of 2.0 mmHg, the P (IOP20|RxE) has to be adjusted downwards. The corrected decrease in IOP, 2.8 mmHg (4.8 minus 2.0) is 12% of the 20% reduction from the baseline of 24 mmHg. Accordingly we decrease our estimate of P (IOP20|RxE) by 12% from 0.8 to 0.68 (0.8 minus 0.12). Similarly we decrease our estimate of P (RxE) from 0.9 to 0.78 (0.9 minus 0.12); this increases the P (NoRxE) to 0.22 (1 minus 0.78). We use these revised estimates that incorporate the possible overestimation to calculate

P (IOP20|RxE) = 0.68 × 0.78 ÷ {(0.68 × 0.78) + (0.05 × 0.22)}

= 0.979 = 97.9%.

Discussion

Provided the information used for the calculations is accurate, we can be 99% sure that the observed 20% decrease from baseline pressures following initiation of treatment with a prostaglandin is associated with use of the medication. If the probability of such an IOP decrease (or any other cut off) compared to the fellow eye and the effect of prostaglandin compared to the fellow eye were available we could perform similar calculations for a monocular trial. There are several accepted advantages to the use of a monocular trial and if both methods show a drop this will increase our certainty to theological levels; most clinicians, however, are likely to act on an 80 – 90 +% probability that the medication works.

Bayes theorem expressed in another form, the "odds" form, helps us understand why the probability for the observed effect being associated with medication (rather than spontaneous variation) is so high as well as appreciate the factors involved.[7] The prior odds of a treatment effect P (RxE) ÷ P (NoRxE) = (0.9 ÷ 0.1) = 9 are high to start with. The likelihood ratio P (IOP20|RxE) ÷ P (IOP20|NoRxE) that a treatment effect produced the observed 20% reduction (0.8 ÷ .05) = 16 is also high. Multiplying the prior odds (9) by the likelihood ratio (16), the posterior odds of a treatment effect given a 20% decrease in IOP is 145:1. As probability = odds ÷ (odds + 1), this translates into the 99.3% probability obtained earlier.

It seems counter intuitive that the probability of a treatment effect remains so high even after adjusting for a 2 mmHg overestimation due to measurement error. This is, however, easily understood by again considering the prior odds and the likelihood ratio for this scenario. The prior odds of treatment effect after adjusting for a 2-mm overestimation (0.78 ÷ 0.22 = 3.5) remains high as does the likelihood ratio (0.68 ÷ 0.05 = 13.6). Multiplying this prior odds by the likelihood ratio results in the posterior odds of 47.6, which is a posterior probability of 97.9% (47.6 ÷ 48.6). It is important to remember that this high likelihood ratio is not only due to the high probability of a 20% decrease in IOP with treatment, but also because such a quantum of decrease rarely occurs without treatment.[11]

As the prior odds and likelihood ratios are so high, even if the probability of an IOP reduction of 20% is only 50%, the probability that the observed decrease is associated with a treatment effect is still 98%. If the data is available, similar calculations can be performed for other percentage decreases in IOP from different baseline levels and for other drugs. This can help make routine clinical decisions in other clinical scenarios.

We may need a specified level of accuracy for the measured decrease in IOP.[6] Using a 2.0 mmHg standard deviation for IOP measurements, in order to achieve a 1 mmHg error margin, we would need four measurements pretreatment and a similar number following initiation of treatment.[13] Even more readings would be required if we are trying to estimate the accuracy of the difference in IOP measurements. Obtaining such a number of measurements is not currently possible even in a research setting, let alone in clinical practice.

We estimated the effect of measurement error on our probability calculations to determine if this might induce a

change in our probability calculations that is large enough to make us question our clinical decision. As we showed, if measurement error overestimates the IOP by 2 mmHg, we can still be 98% sure that the 20% decrease in IOP was associated with the treatment. Taking two measurements should decrease the measurement error to 1.4 mmHg ($2 \div \sqrt{2}$) and make us adjust our estimate by about 5% instead of 12%. While this will further increase the probability, it is already at a level most clinicians would be comfortable with continuation of treatment and hence should not impact the decision to continue treatment.

In summary, Bayes's theorem can be used to calculate the probability that the observed IOP decrease is in fact associated with treatment provided. We used published data for treatment with a prostaglandin and a 20% decrease in IOP for the calculations. For most prostaglandins started at the levels of IOP used in this example, a single (technically well performed) applanation IOP that demonstrates a 20% decrease in IOP from baseline can be clinically interpreted as the effect of the medication. If data are available, it should be possible to apply similar calculations to a monocular trial, most baseline IOP's and percentage IOP decreases using any medication; it should be possible to automate this process for clinical use.

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