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Review article

Evidence-based medicine in glaucoma surgery

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ABSTRACT

Evidence-based medicine (EBM) is a tool and guide for performing effective medical treatment. Here, as an example, EBM was applied to determine which between trabeculectomy and Baerveldt implant surgery would be more effective in a patient with a history of open-angle glaucoma. First, the author asked answerable clinical questions. Second, evidence using general search engines, such as the Cochrane Library or MEDLINE database, was collected. It was found that the Tube Versus Trabeculectomy (TVT) Study was a landmark study in determining optimum glaucoma surgical procedure. Third, the study's level of evidence was carefully examined. As the TVT Study was a prospective, randomized multicenter control study, its level of evidence was high. Fourth, the evidence to actual clinical decisions was applied, calculating the magnitude of the treatment effect using the results of the TVT Study. The event (surgical failure) rate in the control (trabeculectomy) and experimental (tube implant) groups (control event rate and experimental event rate, respectively) was obtained and the absolute risk reduction (ARR) was calculated by subtracting the experimental event rate from the control event rate. The inverse of ARR is the number needed to treat (NNT), which is the number of patients who must be treated to prevent a bad outcome. Using this method, it is possible to calculate the absolute risk (adverse event) increase (ARI) and the number needed to harm one more patient (NNH = 1/ARI). The balance of NNT and NNH is called the "likelihood of being helped and harmed." The practice of EBM integrates clinical expertise of individuals with the best available external clinical evidence from systematic research.

1. Introduction

Evidence-based medicine (EBM) is the conscientious, explicit, and judicious use of the optimal, current evidence to make decisions about the care of individual patients. The practice of EBM integrates individual clinical expertise with the optimal available external clinical evidence from systematic research.[1,2] EBM is a tool and guide for achieving effective treatment outcomes. To perform EBM studies, doctors are required to constantly gather new information. EBM is connected to lifelong learning and enhancing the performance of doctors. EBM was initially proposed more than 20 years before by Gordon Guyatt and is a well-recognized term in the medical field.[3–6] However, it is unclear how well doctors truly understand the concept of EBM. In this study, EBM is applied to a glaucoma patient and the specific steps used are discussed.

2. Case scenario

2.1. Patient and her medical history

The patient studied was an 82-year-old woman with a history of open-angle glaucoma for > 10 years. Her ophthalmologist gradually increased the dosage of eye drops due to deterioration in her visual function. She was currently using eye drops of a prostaglandin analogue, beta-blocker, carbonic anhydrase inhibitor, and alpha-2 stimulator in both eyes. Because of severe ocular surface damage, the patient also took hyaluronic acid to treat superficial keratopathy. She had a mildly high blood pressure level and required only one medication to maintain her blood pressure level within the normal range. She had no other systemic diseases, such as diabetes mellitus, heart disease, lung disease, or a malignant tumor. Her corrected visual acuity was 0.3 in the right eye and 0.5 in the left eye; intraocular pressure (IOP) was 22 mmHg and 28 mmHg in the

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right and left eyes, respectively. The mean deviation values according to the 30-2 program of the Humphrey visual field analyzer were −18.7 dB in the right eye and −25.0 dB in the left eye.

Superficial keratopathy was graded as A2D3 in both eyes (Figure 1).[7] She underwent cataract surgeries in both eyes by temporal clear corneal incision. Multiple antiglaucoma agents were suggested to be the possible cause of her ocular surface disease.

EBM consists of five parts, and these are detailed with respect to this patient in the following sections.

3. Step 1. Collecting answerable clinical questions.[1,5,6]

The clinical questions comprise the following four essential components: “P,” patients or population; “I,” intervention of exposure, test or other agents; “C,” comparison of interventions; and “O,” outcome(s) of clinical importance.

3.1. Patient

In 2013, the average life expectancy of a Japanese woman was 86.61 years.[8] Will this 82-year old-female patient die 4 years later? However, elderly people are anticipated to live a long, healthy life. An 82-year-old Japanese woman could live an additional 10.12 years.[8] The patient had mild blood hypertension, but no other severe diseases. Therefore, she might live an additional 10 years and possible up to 100 years. The patient's old age cannot be an excuse to ignore the therapeutic strategy.

Elderly patients with vision loss can readily develop cognitive damage. Nursing a man with dementia and vision loss is challenging for the caregiver and society. Therefore, maintaining good IOP and visual function in elderly people throughout their entire lifespan is a primary concern of ophthalmologists.

3.2. Intervention

The patient's visual field in both eyes indicated end-stage glaucoma. Antiglaucoma eye drops could not sufficiently control IOP and caused ocular surface damage. Although additional laser therapy might decrease her IOP, IOP reduction alone would be insufficient to protect her visual function.[9,10] Therefore, glaucoma surgery appeared to be necessary to achieve low IOP levels.[11]

3.3. Comparison

It is common to perform trabeculectomy in patients with uncontrollable primary open-angle glaucoma. Recently, the results of the Tube Versus Trabeculectomy (TVT) Study were published. The study demonstrated the superiority of Baerveldt implantation over trabeculectomy with mitomycin C (MMC) in controlling IOP.

3.4. Outcome

Which is better for this patient: Baerveldt implantation or trabeculectomy with MMC?

4. Step 2. The next step in EBM is “Collecting the necessary information.”

First, the guidelines for glaucoma were reviewed.

The European Glaucoma Society published the *Terminology and Guidelines for Glaucoma* in 2014.[12] The use of long-tube devices, such as those described by Molteno, Krupin, Baerveldt, Ahmed, or Schocket, are generally reserved for patients with risk factors for a poor outcome following trabeculectomy with antimetabolites (weak recommendation, very low evidence), although recent trials have established their efficacy and safety in primary surgical procedures (weak recommendation, moderate evidence[12]). Factors that decrease the chance of successful trabeculectomy and make tube surgery attractive include previous failed filtering surgery with antimetabolites, excessive conjunctival scarring due to previous ocular surgery with severe conjunctival or surface disease, active neovascular disease, pediatric aphakia, or cases where filtration surgery will be technically difficult (weak recommendation, very low evidence).

The guidelines proposed by the Japan Glaucoma Society[13] also presented a similar standard for tube surgeries. Both recommendations were graded as weak recommendation, very low evidence.

Information from medical search engines and textbooks were once recommended as informative sources. However, many believe that textbooks should be avoided for EBM, as the information in textbooks may be outdated due to long durations before publication.[1] Nonetheless, textbooks remain useful to obtain standard background information.

The PubMed/MEDLINE and The Cochrane Library databases must be continually checked. For this work, when “tube versus trabeculectomy” was entered as a search term in the PubMed database, 29 manuscripts, published until the end of October 2015, were identified. The TVT Study was a landmark study for determining the glaucoma surgical procedure.[14,15] When the search term “Baerveldt glaucoma implant” was entered in the Cochrane Library database, similar results were obtained.

The TVT Study found that tube shunt surgery had a higher success rate than trabeculectomy with MMC during a 5-year

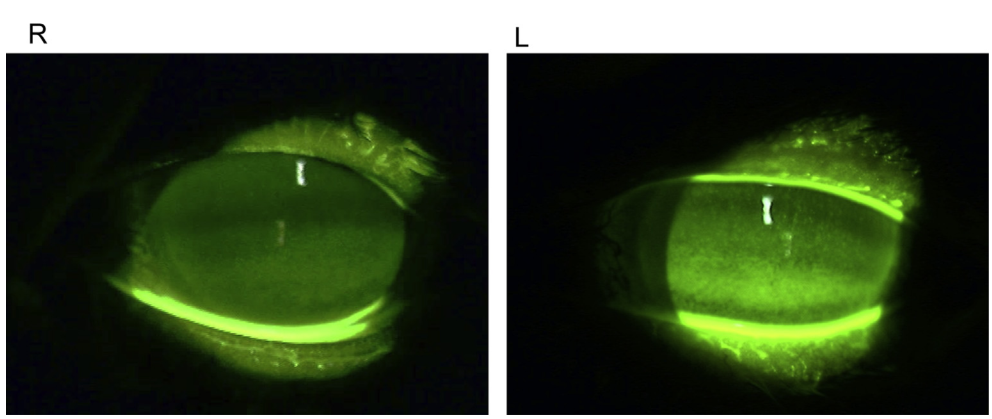

Figure 1. Fluorescein staining in the cornea. L = left; R = right.

follow-up. Both procedures were associated with similar IOP reduction and the use of supplemental medical therapy at 5 years.[14]

A substantial number of surgical complications were observed in the TVT Study; however, most were transient and self-limited.[16] The incidence of early postoperative complications was higher following trabeculectomy with MMC than tube shunt surgery. The rates of late postoperative complications, reoperation for complications, and cataract extraction were similar in both surgical procedures after 5 years of follow-up. Baerveldt implantation could control IOP better than trabeculectomy with less frequent complications at the early postsurgical period.

5. Step 3. A study's level of evidence must be carefully examined.

To reduce study bias, a randomized control study is recommended. Concealing the treatment information from the observer is also important to avoid observation bias.[1,2] In a study to examine the surgical effect, it is often difficult to conceal the surgical methods to the observer, because the observer can instantly recognize the surgical method upon examining the patients. Masking the treatment procedure from the patients is also recommended to reduce bias (double-blinded study).[1,2] All the patients must provide their informed consent before surgery and receive adequate explanation about the type of surgery they will undergo and its potential adverse events. Therefore, a double-blinded procedure is often difficult in this situation.

A dropout rate less than 20% is one standard for a highly ranked study. Some journals automatically reject studies with a dropout rate over 20%.[1] Another classification standard requires a sample size greater than 200 and a follow-up period longer than 5 years.[17]

A grading system to rank the level of evidence in a study has been established (Table 1).[1,2] A randomized trial is assigned a high level, whereas observational studies are assigned a low level. Expert opinion is ranked at the lowest level. The method of expert consensus is referred to as the GOBSAT: Good Old Boys Sat Around the Table.[1]

The TVT Study was a prospective, randomized multicenter control study.[14,15,18] Its level of evidence was ranked at Level 1b, and had a dropout rate of 32%. The authors observed 212 patients for more than 5 years.

6. Step 4. The following step is "Applying evidence for actual clinical decisions."

This is the most difficult step in EBM. When applying evidence to an actual patient, the following must be considered: (1) evidence; (2) patient status; (3) patient value and circumstances; and (4) expert judgment.

This patient had a long history of glaucoma treatment. She and her family understood the concept of glaucoma and recognized that she had end-stage glaucoma. The use of four types of eye drops could not adequately control her IOP. In fact, the eye drops caused severe damage to her ocular surface. She felt discomfort using the eye drops and wished for an alternative treatment. Although she did not wish to undergo ocular surgery, she and her family recognized that glaucoma surgery was necessary to maintain visual function.

The doctor treating this patient completed a glaucoma fellowship and worked as a glaucoma specialist for more than 20 years at a major hospital in the city. He had performed more than 1000 trabeculectomies and 150 tube surgeries. He had sufficient skills and experience to perform both procedures. There was no reason to hesitate to perform Baerveldt implant surgery or trabeculectomy in this patient.

One approach would be to insist that the patient should satisfy all the inclusion criteria for the study.[1] The inclusion criteria of the TVT Study were as follows[18]: patient between 18 years and 85 years of age and IOP range from 18 mmHg to 40 mmHg, and had already received cataract or glaucoma surgeries. Patients without light perception, pregnant woman, aphakic eyes, and those with active neovascular disease and uveitis were excluded from the study.

This patient satisfied all the inclusion criteria of the TVT Study. However, she had one demographic difference. Although the main patents in the TVT Study were white, black, and Hispanics, she was of Asian ethnicity. However, the results of the TVT Study showed that ethnic difference did not affect the surgical effect of their results. Thus far, the effect of racial difference on surgical failure after tube surgery has not yet been reported. A review by Husain et al[19] mentioned that trabeculectomy with antimetabolites in an East Asian population was associated with a lower success rate and a higher complication rate than in other populations.

7. What is the magnitude of the treatment effect?[1,5,6]

Knowledge of basic calculus of EBM is necessary to evaluate the magnitude of the treatment effect (Table 2).

In the TVT Study, trabeculectomy was regarded as the standard modality (control group) and the tube surgery group was set as the experimental group. The main outcome was IOP control. When IOP fell outside of the target pressures, it was considered to be an "event." From a subanalysis of the TVT Study, the event ratio of the subgroup with a history of cataract surgery was determined. The event ratio in the subgroup with trabeculectomy was 59% (control event rate 59%). The event ratio in the tube surgery group was 26% (experimental event rate 26%). If tube surgery is performed, rather than trabeculectomy, then the absolute risk reduction (ARR) decreases from 59% to 26% = 33%. The ARR is the difference in the outcome rate between the control treatment (trabeculectomy) and the experimental treatment (tube surgery).

The inverse of ARR is referred to as the number needed to treat (NNT) to prevent a bad outcome. In the present case, the NNT would be 1/0.33 = 3, which indicates that it is necessary to treat three people with tube surgery rather than trabeculectomy to prevent one additional person from suffering from IOP problems. When the NNT is large, then a large number of people must be treated to prevent one additional bad event. This indicates that the treatment effect is small. In this case, the NNT is 3, which suggests that the effect of tube surgery on IOP control is more effective than trabeculectomy.

One must consider not only IOP reduction, but also any potential adverse events. The TVT Study reported that the incident rate of adverse events in the early phase after trabeculectomy was higher than that of tube surgery. Overfiltration and low IOP are common adverse events after both glaucoma surgeries. Most of the cases show a normal condition during observation. For cases of overfiltration, atropine eye drops, aqueous humor suppression, and anti-inflammatory agents are used as standard therapies. When a flat anterior chamber is observed, viscoelastic materials are injected into the anterior chamber. Ligation of the tube after tube

Table 1
Level of evidence of therapy studies.

Level of evidence	Study
1a	Systematic review of RCTs
1b	Individual RCT
2a	Systematic review of cohort studies
2b	Individual cohort studies
3a	Systematic review of case–control studies
3b	Individual cohort case–control study
4	Case series
5	Expert opinion

RCT = randomized control trial.

Table 2
Terminology for evidence-based medicine.

Definition	Abbreviation	Description
Control event rate	CER	Event ratio in control group
Experimental event rate	EER	Event ratio in experimental group
Relative risk reduction	RRR	Proportional reduction in event rate
Absolute risk reduction	ARR	Difference in outcome rate between control & experimental treatment
Number needed to treat	NNT	Number of patients we need to treat to prevent 1 additional bad outcome
Relative risk increase	RRI	Proportional increase in event rate
Absolute risk increase	ARI	Difference in bad event rate between control & experimental treatment
Number needed to harm 1 more patient	NNH	Number needed to harm 1 more patient
Likelihood of being helped & harmed	LHH	Indicator of the possible benefit & harms

Event = surgical failure; risk = adverse event.

surgery and scleral suturing over the conjunctiva after trabeculectomy are also effective to recover from overfiltration. The most frequent additive surgical procedure for trabeculectomy is bleb revision, whereas tube surgery requires corneal transplantation and patch procedures for eroded tube materials. The procedure of bleb revision is similar to trabeculectomy. Thus, it is a familiar procedure for glaucoma surgeons. However, corneal transplantation and patch graft surgery are not common maneuvers for glaucoma surgeons and require assistance by corneal specialists (Figures 2 and 3) The outcomes of corneal transplantation after tube surgery are poor.[20]

Nine eyes (8.4%) in the tube surgery group underwent corneal transplantation. One eye (1%) underwent corneal transplantation after trabeculectomy. EBM calculated the incidence rate of adverse events to be the same as the effect on IOP. The absolute risk (adverse event) increase (ARI) ratio required for corneal transplantation after tube surgery was 7.4%. The number needed to harm one more patient (NNH = 1/ARI) was 13.5 patients. This number indicates that if 14 patients undergo tube surgery, then one would require corneal transplantation. When diplopia was considered, tube erosion and corneal transplantation would not be tolerable, and thus the ARI would be 15.8% and the NNH would be 6.3 patients.

When making clinical decisions, EBM recommends calculating the likelihood of being helped and harmed (LHH).

One can obtain the LHH using the following formula:

$$\mathrm{LHH} = (1/\mathrm{NNT})/(1/\mathrm{NNH}) \tag{1}$$

Regarding the LHH for this glaucoma patient, corneal transplantation was considered to be the only adverse event that must be avoided. Therefore, the NNH of the tube group was 13.5. The NNT was 3 as described previously.

$$\mathrm{LHH} = (1/\mathrm{NNT})/(1/\mathrm{NNH}) = (1/3)/(1/13.5) = 4.5 \tag{2}$$

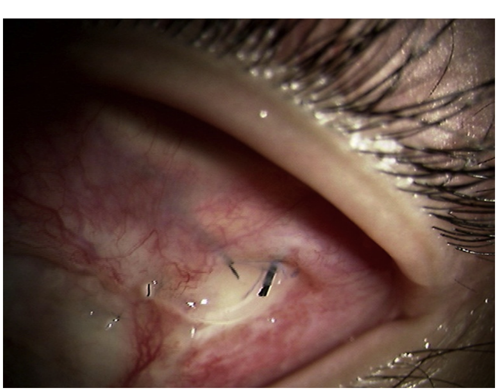

Figure 2. Tube erosion.

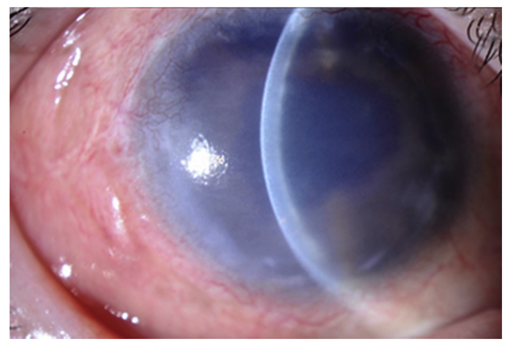

Figure 3. Corneal decompensation after tube implant.

The LHH was 4.5, indicating that tube surgery was nearly 4.5 times more likely to help this patient than trabeculectomy.

When the doctor cannot cope with corneal transplantation, diplopia, and tube erosion, then the ARI is 7.4% + 3.7% + 4.7% = 15.8%; the NNH is 1/0.158 = 6.3, and the:

$$\mathrm{LHH} = (1/\mathrm{NNT})/(1/\mathrm{NNH}) = (1/3)/(1/6.3) = 2.1. \tag{3}$$

In this case, the advantage of tube surgery over trabeculectomy would be nearly two times greater.

One must remember that there are several reasons as to why the TVT Study findings may not change clinical practice. Many glaucoma specialists have proposed some reasons as to why the findings of this study were unlikely to change clinical practice[21]: (1) tube implantation is not superior to trabeculectomy, especially when lower IOPs are desired; (2) the relatively high rate of complications after trabeculectomy in the TVT Study is not a universal experience; (3) motility problems after tube implantation are frequent and serious; and (4) the success rate of individual trabeculectomy experiences is much better than the trabeculectomy group in the TVT Study.

However, these biases can be adjusted using coefficients of the usefulness (f_t) and risk of adverse events (f_h).

For example, if we believe that a patient is at half the risk of the outcome of control patients (trabeculectomy group), then the f_t would be 0.5. By contrast, we may believe that a patient has three times the risk of adverse events from therapy (tube surgery group). In this case, the f_h would be 3. Using previous clinical experience and expertise, the f_t and f_h values can be determined.

Using an adjusted formula for the LHH,

$$\text{the adjusted LHH} = [(1/\mathrm{NNT}) \times f_t]/[(1/\mathrm{NNH}) \times f_h] = [(1/3) \times 0.5]/[(1/6.3) \times 3] = 0.35, \tag{4}$$

which indicates that this patient is more likely to be harmed than helped by tube surgery.

7.1. Cost effectiveness

Many countries are suffering from increases in health-care payments and societies must allocate finite resources for cost-effective medical care. Kaplan et al[22] assessed the cost effectiveness of trabeculectomy with MMC and Baerveldt implant and compared them with the maximal medical treatment according to the results of the TVT Study. The mean costs for medical treatment, trabeculectomy, and Baerveldt implantation were US $6172, US $7872, and US $10,075, respectively. The quality-adjusted life years (QALYs) are now a common indicator for cost-effectiveness modeling. QALYs regard death (blindness) as 0, and complete health is rated as 1. The quality of life is multiplied with the year of life and the (quality of life $\times$ life years) is summed up until the patient dies. For instance, if a man lived at 0.5 quality for 10 years, then his QALYs would be $0.5 \times 10 = 5$. If a second man lived at a quality of 1.0 for 5 years and then lived at 5 years with 0.5 quality, then his QALYs would be $1.0 \times 5 + 0.5 \times 5 = 7.5$. Both men survived for the same 10 years. However, the second man lived with a better quality of life than the first man. A survival curve analysis cannot distinguish this difference. When the mean 5-year probability of blindness was 4% for both surgical procedures and 15% for the medical treatment, the QALYs for medical treatment, trabeculectomy, and tube surgery were 3.10, 3.30, and 3.38, respectively. The additional cost required to gain one QALY from changing trabeculectomy to tube surgery [incremental cost-effectiveness ratio (ICER)] was estimated to be US $29,055. The willingness-to-pay (WTP) represents the amount of additional cost that the society is willing to pay for one additional QALY. The WTP threshold is generally set at US $50,000 for each QALY. In this example, the ICER is lower than the WTP.

Previous studies have shown not only the usefulness (e.g., 86%), but also the 95% confidence interval of the estimated value (e.g., 80–92%). This indicates that the true usefulness lies between 80% and 92% with a 95% probability. The usefulness of 86% is uncertain. In such cases, the changes in cost effectiveness can be simulated using a probabilistic sensitivity analysis. In the study by Kaplan et al,[22] the authors concluded that trabeculectomy was more likely to be preferred at lower WTP values.

All of these issues must be considered when making a final decision. EBM requires clinical expertise for producing and interpreting evidence, performing clinical skills, and integrating the optimal research evidence with the patient values and circumstances.

In this study, EBM was applied to a patient according to the results of one randomized control study. The final decision must be made with the results of additional studies. A new TVT Study on surgical history naïve patients is currently underway and its results are greatly anticipated.

8. Step 5. The last step is to evaluate the decision made during Steps 1–4.

There are several ways to perform EBM. EBM for the prognosis, diagnosis, and screening requires different methods and techniques, which must be learned step-by-step.

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