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The Heart of the Matter of Opinion and Evidence: The Value of Evidence-Based Medicine

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ABSTRACT

Evidence-based medicine is an important aspect of continuing medical education. This article reviews previous and current examples of conflicting topics that evidence-based medicine has clarified to allow us to provide the best possible patient care.

INTRODUCTION

Current medical training emphasizes the importance of using and implementing evidence-based medicine (EBM), but is EBM really the best source for developing guidelines and protocols to provide the best possible patient care? This article reviews the arguments and provides evidence demonstrating the true value of EBM.

Tonelli[1] defined EBM as having two parts: ''First, EBM deals with the issue of knowledge in medicine, defining optimal ways to develop knowledge and describing hierarchies of medical evidence,'' and second, ''it [EBM] attempts to describe a clinical practice centered on evidence derived from clinical studies.''

One of Tonelli's phrases needs more attention: ''hierarchies of medical evidence.'' This hierarchy in relation to evaluating therapies is described by Devereaux and Yusuf,[2] who conclude that the various types of randomized controlled trials (RCTs) are among the top 4 of 11 forms of evidence, above cohort studies, case-control studies, and case series. Straus and McAlister[3] describe RCTs as the gold standard of the hierarchy of evidence for instituting types of intervention but not the gold standard for other aspects of medicine. In other words, a more descriptive definition of EBM would include, as Straus and McAlister[3] comment, evidence derived from not just clinical studies but also from the best available evidence. A good example of this concept of using the best available evidence, and not exclusively RCTs, is the initial association of smoking tobacco and lung cancer.

OPINION

Expert opinions cannot be considered evidence based because they only represent opinions. Yet, as Alton Ochsner[4] described in 1973, the parallel rise of cigarette sales and the appearance of a ''new disease'' (lung cancer) since the first World War, a time frame he considered long enough for the possible carcinogenic effect of tobacco to become evident, was the only evidence he had for describing the relationship we all understand as fact today. However, Ochsner's opinion was not enough to convince the medical community. Wynder and Graham[5] studied 684 cases of bronchiogenic carcinoma, and through interviews and surveys they concluded, using the best evidence available at the time, that excessive and prolonged use of tobacco was an important factor in the cause of bronchiogenic carcinoma.

Although the association between smoking tobacco and lung cancer may seem straightforward today, considerable effort and EBM were required to prove the relationship. Although one might question why an RCT was not performed, we know that because of the strong association between smoking and lung cancer,

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subjecting cohorts to smoking to prove what was already a clinically apparent fact would have been unethical. Straus and McAlister[3] therefore appear correct in their assertion that RCTs may not be the gold standard in the hierarchy of evidence, especially in relation to diagnosis, prognosis, and, in this case, harm.

EVIDENCE

When are RCTs the gold standard? Over the past 2-3 decades, various observational data and analyses of therapeutic interventions have been questioned via RCTs. The best evidence is the evidence that is available,[2] so from a systematic review of several cohort and case-control studies, a curious clinician might design an RCT to prove the evidence already available and considered true. However, many RCTs have contradicted what clinicians believed to be true based on previous observational studies as shown in the following examples. Note that when one RCT trial contradicts a clinical ''fact,'' other RCTs are created to support the findings and identify the best possible practices in patient care—in other words, to allow clinicians to use EBM.

Vitamin E

The relationship between the consumption of vitamin E and the risk of coronary heart disease (CHD) was studied in the early to mid-1990s in men, middle-aged women, and elderly populations. All three studies suggested a protective effect of vitamin E supplements and a lower risk of CHD,[6-8] but the researchers pointed out that further research and clinical trials were warranted before any guidelines could be promulgated regarding the use of vitamin E.

In the Heart Outcomes Prevention Evaluation (HOPE) study of high-risk patients, vitamin E supplementation for a mean of 4.5 years showed no apparent effect on cardiovascular diseases (CVD).[9] According to the Devereaux and Yusuf hierarchy of medical evidence, the only type of research ranked above a clinical trial is a meta-analysis of clinical trials; Miller et al[10] published a meta-analysis of vitamin E consumption in 2005. They analyzed 19 clinical trials and did not find the beneficial effect the observational studies did, but rather discovered that high doses of vitamin E correlated with an increase in all-cause mortality.[10] Additional evidence and a more detailed comparison of the observational studies versus the RCTs had already been outlined in Morris and Carson's 2003 article.[11] These outcomes allowed the medical community to shift from the original idea that vitamin E was beneficial to CVD while researchers continued to investigate and plan further RCTs of longer duration for a more thorough conclusion.

Homocysteine and Folic Acid

A meta-analysis of homocysteine and the risk of CHD and stroke published in 2002 concluded that a 25% reduction in serum homocysteine was associated with an 11% reduction of the risk of major CHD and CVD.[12] A year earlier, another meta-analysis demonstrated a causal association between homocysteine and CVD and found that lowering homocysteine concentrations by 3 μmol/L would reduce the risk of CHD by 16%.[13]

Based on the knowledge from such observational studies and the understanding that folic acid and vitamins B_6 and B_{12} lower homocysteine levels, clinicians developed RCTs to assess whether such supplements would reduce the risk of CVD. In HOPE, investigators instead found that a combination of these supplements versus placebo did not reduce the risk of major CVD events, although participants' mean plasma homocysteine levels decreased.[14] Another RCT studied the value of folic acid in secondary prevention; although researchers noted a decrease of 18% in the plasma homocysteine, all-cause mortality and a composite of CVD events did not decrease in 2 years of treatment with folic acid compared with placebo.[15] Loscalzo[16] reported further RCTs on this topic in a major editorial and concluded unequivocally that no benefit from the use of folic acid and vitamin B_{12} in patients with CVD exists.

Estrogen

Given the amount of observational evidence that strongly supported the protective effects of estrogen on the risk of CHD, Stampfer and Colditz[17] quantitatively assessed all the epidemiologic evidence available and agreed in 1991 that postmenopausal estrogen therapy could substantially reduce the risk of CHD. In 2002, Mikkola and Clarkson[18] evaluated 2 RCTs as well as observational studies, and although they agreed that the trials demonstrated disappointing outcomes, they believed that enough evidence existed to support the beneficial effects of estrogens in the early stages of atherogenesis.

However, different opinions about the benefits of estrogen on CHD were circulating. In a major RCT of 309 women with established disease that was published in 2000, researchers concluded that neither estrogen alone nor estrogen with medroxyprogesterone acetate had any effect on the progression of coronary atherosclerosis.[19] In a much larger RCT of 16,608 postmenopausal women, the Women's Health Initiative in 2002 showed that after 5 years of follow-up, the overall health risks exceeded the benefits from the use of combined estrogen plus progestin.[20] The Heart and Estrogen/progestin Replacement Study (HERS) Research Group had clearly identified one of

those risks in 1998, finding that after a mean follow-up of 4.1 years in 2,763 women, oral estrogen plus progestin did not reduce the overall rate of CHD but rather demonstrated an increase in thromboembolic events as well as a pattern of early increase in the risk of CHD events.[21]

Antiarrhythmic Therapy for Ventricular Ectopy

Premature ventricular contractions (PVCs) have been shown to be a risk factor for cardiac death after myocardial infarctions (MIs),[22] and a rate of >10 PVCs per hour is associated with a fourfold increase in mortality.[23] With this in mind, physicians set out to decrease the mortality rate with antiarrhythmic (AA) medications. An early (1982) retrospective analysis of AA drug action demonstrated a worsening of arrhythmia in 80 of 772 AA drug tests, suggesting the possibility that instead of suppressing ventricular arrhythmias, these drugs may augment them instead.[24]

It was not until 1991, however, that a multicenter RCT, the Cardiac Arrhythmia Suppression Trial, revealed that the use of AA medications in patients with left ventricular dysfunction after MI carried a risk of increased mortality.[25] The initial hypothesis of the study was that the suppression of ventricular arrhythmias with AA medications after MI would reduce the rate of death attributed to arrhythmia. The study was stopped early, however, because of an excess mortality associated with AA therapy. This study provided yet another example of the importance of placebo-controlled trials and the significance of EBM in providing the best possible patient care.

Therapy for High-Density Lipoprotein Cholesterol

The epidemiological evidence from the Framingham Heart Study in the 1980s demonstrated that low levels of high-density lipoprotein cholesterol (HDL-C) were associated with increased mortality.[26] A meta-analysis by Gordon et al[27] (1989) demonstrated an inverse relationship between HDL-C levels and CHD event rates, later affirmed in a cohort study by deGoma et al[28] (2008) showing that a 10 mg/dL decrease in HDL-C was associated with a 10% increase in either myocardial injury or CHD.

With the 1980s evidence at hand, Brousseau et al[29] attempted to find a medication that would increase HDL-C and therefore theoretically decrease CHD event rates. They demonstrated that torcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor, could increase HDL-C by up to 106%. This evidence led Nissen et al[30] to investigate the effects of torcetrapib on the progression of coronary atherosclerosis, but they were only able to reaffirm the ability of this CETP inhibitor to substantially increase HDL-C.[30] Additionally, the study by Nissen and colleagues found treatment with torcetrapib to be associated with an increase in blood pressure, and the progression of coronary atherosclerosis did not significantly decrease, as would have been expected. Furthermore, the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events study involving 15,000 patients was stopped prematurely secondary to excess deaths, MIs, and angina among other potentially fatal outcomes in patients receiving torcetrapib plus atorvastatin compared to atorvastatin alone.[31]

More recently, the safety of another CETP inhibitor, anacetrapib, was studied in a randomized, double-blind, placebo-controlled trial. The study, published in 2010, did not show the adverse CVD effects seen with torcetrapib, although anacetrapib did have the same positive effect on HDL-C levels.[32]

These results highlight the importance of EBM, discussed in detail in a 2008 editorial by Lavie and Milani[33] who called for more HDL-C–elevating therapies to undergo the vigors of large-scale RCTs assessing CHD events, so absolute proof of benefit and safety may be determined. Considerable evidence demonstrates that niacin therapy increases HDL-C, reduces the progression of atherosclerosis-promoted regression via reverse cholesterol transport, and reduces major CHD events in small studies. Yet the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health (AIM-HIGH) study, which examined extended-release niacin, was stopped because treatment showed no clinical benefit and a slightly higher stroke rate after 32 months.[34] Further RCTs are needed to establish the safety and efficacy of various HDL-C therapies in primary and secondary CHD prevention.

CONCLUSION

As the examples demonstrate, many observations from cohort and case-control studies cannot be deemed fact until they are put to the vigors of major RCTs. Yet this notion of testing what we believe we already know to find the best treatments and interventions is what exemplifies the true value of EBM. The decisions we make as physicians should always be based on the best available evidence, whether that evidence is opinion from experienced colleagues, observational studies, or RCTs. A number of examples demonstrate the value of retrospective and observational studies, and years later, many of these observations are confirmed in RCTs. We should continue to use and explore the strongest EBM to truly provide the best patient care possible.

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