

Evidence based neonatal medicine: dilemmas remain

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Abstract. Evidence-based medicine has become increasingly important over the years. Getting research evidence into practice is a necessity in current practice. It has to be kept in mind that every patient population has its own special characteristics and this may make the best available research evidence sometimes not the best option for that particular population. Some examples of how the characteristics of a population may influence important evidence-based treatment decisions are discussed.

Key words: Evidence-based medicine, beractant, poractant, palivizumab, umbilical artery catheterisations

1. Introduction

In this era, all doctors are encouraged to practice evidence based medicine. Data from high quality research are summarised in systematic reviews and often these reviews manage to show that one or the other intervention is effective, does not make a difference or is harmful. Examples of interventions that are proven to be effective and that should be practiced on an as close as possible to 100% basis include the usage of antenatal steroids for women at high risk of delivering the baby preterm,

Equally often however the conclusion of reviews is that there is a need for further research and that recommendations for practice cannot be made based on currently available evidence. Even if the review authors conclude that there is enough evidence to recommend a practice, it is still the duty of each and every practitioner to evaluate the evidence presented, compare the populations in whom the evidence was generated with their own patient population and to look at their own facilities and skills whether or not the treatment supported most by research is suitable to be practiced in their setting.

As shown in figure 1 evidence based practice is only true evidence based practice where patients'

background, doctor's background and research evidence meet.

The discussion below deals with examples of practices in the neonatal ward where extra caution is desired in the interpretation of available evidence and dilemmas continue to exist.

2. Issues regarding the patient population

2.1 Porcine or bovine surfactants

Animal-derived surfactants have been shown to be superior to synthetic surfactant without proteins (1). Synthetic surfactants with proteins are still in the experimental stage but are perhaps promising (2). When bovine and porcine derived surfactant preparations were compared, data were favouring the porcine derived surfactant in 5 randomised controlled trials (3-7) and two retrospective studies.

In predominantly Muslim populations however there is a high level of aversion towards anything porcine. Even though the religion allows the consumption of porcine products if it would be lifesaving in the absence of alternatives, it could be considered a lack of respect for cultural and religious values if one was to use a porcine derived substance with only marginal benefits over a similar bovine product.

Potential consequences of the use of porcine products in a predominantly Muslim population include an increased use of services from traditional healers, an increase in home deliveries or a patient overload in other hospitals, each of which could affect patient's outcome adversely. In the practice of EBM consideration of the

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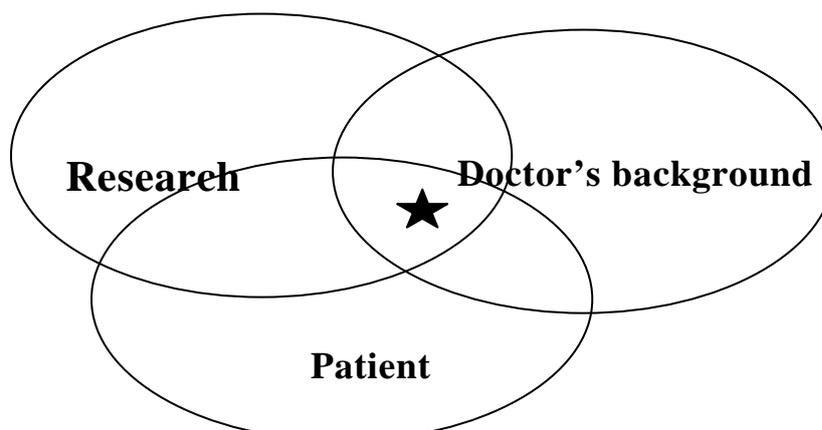


Fig. 1. Only when research evidence meet patient needs and background and the doctor's skills and background, true evidence based medicine is practiced (★)

patient's background is essential. However, evidence in favour of the porcine derivative is getting stronger. A meta-analysis of randomised controlled trials (8) showed a significantly lower mortality in the babies receiving the porcine derivative (RR 0.57 (0.34-0.96)). This is mainly due to the largest trial reporting 3% mortality with 200mg/kg of poractant versus 11% mortality with 100mg/kg of beractant. In the era of antenatal steroids and availability of natural surfactants, a reduction in mortality from 11 to 3 percent is unlikely to be solely the result of a higher dose of a different type of surfactant. Anyhow if large differences in survival are proven by larger high quality trials, it may become increasingly difficult to defend ethically the use of the bovine preparations based on cultural preferences of the patients.

2. 2. Palivizumab: yes or no

Another dilemma in modern neonatology is the use of palivizumab, a monoclonal antibody against RSV. Evidence from one large trial shows that Palivizumab can reduce the need for hospitalisation in ex-preterm babies (9). This trial was a very well conducted randomised multicentre double blind placebo controlled trial performed in the USA, Canada and the United Kingdom. There was no reduction in the need for intensive care and it did not reduce the mortality among the preterm babies. Subsequent studies have shown that in countries where the costs of hospitalisation are very high, that the use of Palivizumab could be cost effective if applied to high risk infants only (10). Cost calculations based on available evidence in middle income countries like Malaysia were showing that the use of Palivizumab would be not cost effective (11). But then again what is the emotional cost of rehospitalisation of preterm babies having spent

the first three months of their lives in neonatal wards? At least based on the above, the use of palivizumab is a controversial very high cost intervention.

If population characteristics are taken into consideration, the picture may be quite different for some middle or low income countries. These countries can least afford to buy palivizumab, but evidence from developed nations may require a more thorough interpretation than just focusing in on costs. Evidence is available that RSV is endemic during the raining season parts of Malaysia (12). This is the season when floods are happening as well. Floods may prohibit parents to bring children requiring hospitalisation to the hospital. Besides this, a large distance and difficult accessibility of hospitals and local beliefs in traditional healers may give a completely different picture from what is happening in developed nations (where the large study was done). Preterm babies after discharge, having RSV infection who require hospitalisation may not reach the hospital in time and die before they reach the hospital. Of course, the above requires proper research to be done, but it is not unlikely that if palivizumab reduces the need for hospitalisation, it could well reduce mortality in preterm babies post discharge in these countries.

Another factor rendering decision making a bit more difficult is the huge push of the pharmaceutical industry. There is definitely the danger that a bias in favour of palivizumab occurs due to that, but even in the presence of extensive sponsorships, it is still the duty of each of us to make our decisions as objective as possible. Opponents of the use of palivizumab have grown sometimes so worried about this company induced bias that they introduced their own opinion based bias against the product. Cost effectiveness calculations as such have been

based on the epidemiology of bronchiolitis alone (13). These practitioners clearly overlooked that RSV causes pneumonia in a high number of cases as well (12) and ignored the long term consequences of RSV infection (14).

3. When evidence appears to be convincing

High versus low umbilical arterial catheter

In a Cochrane review (15) on the position of the umbilical artery catheter (UAC) there were 6 randomised controlled trials (16-21) included. Most of the trials showed a much higher incidence of local complications with the low position and each of the trials showed a very slight increase in incidence of NEC with the high position. Meta analysis was performed and the local ischaemic complications were significantly more with the low position but the difference in NEC was not significant. The authors recommended based on this review the high position of the umbilical arterial catheter.

Most of the studies were done in developed nations more than 15 years ago. Most of the studies were done in the time where antenatal steroids and surfactant use was not a routine for preterm babies. In that time the need for mechanical ventilation of preterm babies was much higher and duration of ventilation tended to be much longer. A longer duration of ventilation meant also that the arterial line was kept for a longer duration. The studies reported incidences of local ischaemic complications as high as fifty percent. With the use of antenatal steroids and surfactant, ventilation is shortened and so is the use of the arterial lines. This may result in a lower incidence of local complications.

On the other hand, NEC tends to occur or be at least initiated during the most critical phase of the disease where perfusion of the bowel is reduced. A further reduction in bowel perfusion by a catheter passing by at the orifice of the mesenteric artery may be responsible for the trend toward higher NEC with the high position of the UAC.

In developing nations the percentage of babies with small birth weight for gestational age (SGA) tends to be higher and as such the risk for NEC may be higher. Furthermore if NEC occurs, it is a potentially lethal complication whereas most of the local complications are readily treated by removal of the arterial line, provided there is a good monitoring of the baby available. So, even when the systematic review seems to strongly support the high position, just noticing that all included studies were very old and the potential

differences in population between developed and developing nations may make the evidence a bit less robust. A higher risk for NEC may outweigh the risk for short term complications if studies were repeated in this era and in developing nations.

4. Conclusions

Evidence based medicine has definitely helped many clinicians in making the right decisions for their patients. The Cochrane library is still a very valuable resource to make evidence based decisions. However, the three examples given above highlight that it remains important to consider in each case the characteristics of one's own patient population and one's own settings before blindly applying the available evidence of research.

As such there may be reasons to deviate from recommendation made by experts and apply the evidence that suits best the patients that are actually treated. The above discussion underlines also the need for more and specific research into areas important to developing nations.

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