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Neonatal surgery: Towards evidence-based practice and management

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ABSTRACT

Like all modern medical therapy, neonatal surgery is founded on clinical research, well-tried clinical practice and basic scientific research. Likewise, modern neonatal surgery strives increasingly for evidence-based management and practice. The very nature of neonatal and pediatric surgery renders associated research challenging because of the rarity and small numbers of surgical disorders and varying resources in different countries and institutions and consequently only a few well-designed trials on truly important issues in neonatal surgical treatment have been performed. This article highlights the research methods by which valid evidence-based research data is obtained in observational studies, randomized controlled trials, and meta-analyses. The problem of small numbers of patients may be overcome by multi-center trials, meta-analyses, and networking. Consideration is also given on the quality and the validity of the study data as well as ethical issues in neonatal surgical research.

Introduction

Active clinical research forms basis for evidence-based practice and management of neonatal surgical conditions. The main goal of clinical research is to improve patient outcomes by acquiring information on pathophysiological mechanisms of the diseases and their management. However, the very nature of neonatal and pediatric surgery renders associated research challenging in many ways. These challenges include rarity and small numbers of most surgical disorders and patients resulting in limited experience among individual surgeons and centers. Varying financial and professional resources as well as health care systems may considerably modify treatment and follow-up protocols between different institutions and countries. Interventions in fragile newborns must be planned with special scrutiny not to mention unborn fetuses and their mothers. Many of the congenital surgical disorders occur in conjunction with other associated anomalies and diseases complicating their reliable individual assessment. Physiology of different organ systems such as pulmonary or bowel function continues to mature during growth, and the final stage of functional outcome cannot be assessed before adulthood after completion of growth. Some disorders and their surgical treatment produce profound pathophysiological alterations, leading to entirely new extent of health problems and diseases such as esophageal atresia-associated gastroesophgaeal reflux and risk of cancer and parenteral nutrition-associated liver injury in intestinal failure. Clearly, assessment and treatment of surgical neonatal disorders should be as evidence based as possible, which is not possible without ongoing pediatric surgical research. In clinical research, better evidence means larger number of patients and improved quality of study designs. Small number of patients may be overcome by combining experience in multi-center studies, research networks, or patient registries. Every study should be designed individually depending on the nature of the problem at hand and characteristics of outcome measures. Larger numbers also enables better quality in terms of randomized controlled trials. They are at their best in comparing two different treatment modalities, which are not eminently dependent on a single surgeon's personal technical expertise. Prospective follow-up studies provide reliable information on long-term outcomes and are especially useful in describing “natural history” of different surgical disorders. However, an important prerequisite for all successful clinical research in neonatal and pediatric surgery lies in well-recorded standardized treatment protocols and close patient follow-up enabling continuous quality control and generation of relevant research hypotheses by identifying improvement points in patient management.

Neonatal surgical research—what is the evidence?

The majority of research on neonatal surgery is based on case series and has mostly been retrospective and observational. A major reason for this is the fact that most neonatal surgical

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conditions are uncommon with incidences typically ranging from 1:1000 to 1:20,000 live births. Most case series are institutional and collected during a relatively long period of time. Retrospective neonatal surgical case series typically describe early outcomes of neonatal surgical conditions. Typical outcome measures include incidence, mortality, complications, and today also health economical issues. However, large institutional case series have had a significant impact on the overall knowledge of incidence, classification, and pathophysiology of neonatal surgical conditions.[1] Case series have also been elemental in the development of pediatric surgery, as case series have defined the field of pediatric surgical practice.

Institutional neonatal surgical case series have definitive value if certain prerequisites are fulfilled. The case series need to be all inclusive and all cases, also those who were not offered treatment or died without treatment need to be included in the series. Ideally, case note series are also population based. Unfortunately, truly comprehensive case series studies are rare although in pediatric surgery, case series compose the great majority of clinical evidence.

In neonatal surgical research, retrospective cohort studies are used to compare outcomes of two (or more) groups of patients that have undergone different treatments, typically an operation for a certain condition. A typical example is retrospective institutional studies comparing different surgical methods to treat Hirschsprung's disease.[2] Retrospective cohort studies have usually used historical controls, i.e., patients operated during a certain time period with a certain technique are compared with another cohort that has previously undergone a different operation. Studies using concurrent controls are much more uncommon in neonatal surgical literature.[3]

In this kind of study setting, there are many obvious limitations. In cohort studies using concurrent controls there is no guarantee that the patients in the respective cohorts would be similar or have a completely matching clinical characteristics. With historical controls, there are many more confounding factors and possibilities for a bias between cohorts. The surgeons in different time periods may have been different, the timing of surgery may have been different, and the overall care of the patients including intensive care facilities and spectrum of antibiotics available may have been different just to record some factors.

In retrospective cohort studies, the patients' data are retrieved from case notes. It is common knowledge that these data are inaccurate and commonly incomplete. The data in case notes has been created solely for clinical needs and may lack important information in the context of clinical research. On the other hand, when compared with case series, cohort studies are potentially more powerful in relieving differences in outcomes and typical patterns of adverse events associated with compared treatment modalities.

Observational longitudinal cohort studies can be made also prospectively although these are uncommon in neonatal surgical research. Typically, two groups of patients with a similar underlying condition are compared after different types of surgical procedures, for example, open or endoscopic repair of a diaphragmatic hernia.[4] Prospective studies should be designed to include preset inclusion and exclusion criteria before patient enrollment. Also, outcome variables and end points should be pre-specified and recorded.

The limitation in prospective neonatal surgical research is again the rarity of index conditions. In a single institution, the numbers are most likely too small to reveal significant differences in a reasonable time frame. Also, many of these conditions have a heterogeneous presentation that may require variable surgical decisions that may be affected by the experience of the operating surgeon. A main limitation is that prospective studies do not have randomization. To be successful, prospective studies in neonatal surgery require multi-institutional involvement that may be difficult to organize and may be expensive. Potentially, prospective studies in neonatal surgery can be very valuable. In many cases, randomized studies are not feasible in neonatal surgical conditions. Prospective cohort studies may still provide information on complications and outcomes after surgical procedures. Moreover, the data may be useful for designing randomized controlled trials.

Cross-sectional studies are commonly used to study outcomes of neonatal surgical conditions, typically long-term outcomes. Typical outcome variables are a function of an organ system, for example, bowel function, quality of life and occurrence of other symptoms related to the condition, for example, asthma after repair of esophageal atresia.[5,6] Cross-sectional studies as such are not very valuable; however, significant value is added if controls are used. Cross-sectional case–control studies that use healthy controls that are matched by age, gender, and municipality can give valuable information about the morbidity burden that is associated with a population of patients with a neonatal surgical condition.[6–8] Cross-sectional case–control studies are difficult to design and also not very expensive to perform. These studies can utilize many different outcome variables. Therefore, logistic regression models can be used to assess the effect of a variable to outcomes.

Cross-sectional case–control study design is amenable to some important bias especially in the long-term outcomes setting. It may be difficult to recruit all the affected patients to the study, and the responders may have a different outcome than non-responders, despite similar clinical and demographic background. Typically females respond more willingly than males[9] to questionnaire-based cross-sectional studies. There is also recall bias that means that patients affected by the condition are more aware of potential symptoms and risk factors than healthy controls.

Randomized controlled trials (RCT) are the gold standard when outcomes following treatment modalities are compared. In RCTs, the condition that is studied and the study population are clearly defined. The sample sizes in well-designed RCTs should be calculated to be appropriately powered. Unfortunately, sample size calculations are not always reported. In neonatal surgical literature, there are only a few well-designed and executed randomized controlled trials. Again the main problem is the rarity of neonatal surgical conditions. Neonatal surgical conditions that have been appropriately studied with RCTs include necrotizing enterocolitis (NEC) and hypertrophic pyloric stenosis.

There are two recent well-designed RCT studies for NEC, Net trial[10] and NECSTEPS,[11] that compared laparotomy and peritoneal drainage as an initial surgical therapy for perforated NEC. The primary end points in these studies were survival of the patients. Both studies found that rates of survival rates for peritoneal drainage and laparotomy were not statistically different. A Cochrane review combined the results of these studies and concluded that there is no benefit or harm of peritoneal drainage over laparotomy.[12] Both these well-designed and executed studies failed to achieve full accrual of the patients that were calculated in the power analysis.[13] This reflects the complexity of RCTs in a neonatal surgical setting. The major problem was patient enrollment that was influenced by the willingness of surgeons and neonatologists and difficulties in the consent process.

Operative treatment of hypertrophic pyloric stenosis is an issue that has been studied recently by blinded RCTs. Classic open technique has been compared with laparoscopic approach.[14,15] The outcomes have been very similar after both approaches and only minor differences have been detected. There have been only slight differences in the overall incidence of complications between study groups. The length of hospital stay has somewhat favored laparoscopic operation. A recent meta-analysis[16] found no