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European Journal of Cardio-thoracic Surgery 30 (2006) 700—705

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Review

Low birth weight or diagnosis, which is a higher risk? — a meta-analysis of observational studies

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Received 12 July 2006; received in revised form 11 August 2006; accepted 24 August 2006; Available online 27 September 2006

Summary

Published experience with surgical treatment of newborns with low birth weight and congenital heart disease is circumscribed to isolated single case reports and a limited number of case-series. To better assess the risks of early surgical treatment and its relationship to weight and diagnosis we performed a meta-analysis of observational studies, limited to those from which data on individual patients could be extrapolated. A search on the subject in peer-reviewed journals published between 1993 and 2004 limited the number of studies, according to our restrictive criteria, to six articles. Our own series of 37 patients was added to the body of data collected in the meta-analyses. Data on 356 individually identified patients was extracted from the articles. Median weight was 2.05 kg (range 1.1—2.5) and median gestational age was 34.2 weeks (range 26—42). Overall surgical survival was 83.9% but survival was higher when a full repair was done (86.1%). According to our analysis, diagnosis was the most significant predictor of mortality ($p = 0.001$). Other important predictors were the presence of a surgical complication ($p = 0.01$), palliative surgery ($p = 0.03$) and the need for reoperation during the same admission ($p = 0.03$). We concluded that similarly to larger newborns, diagnosis in this group of patients is the most important predictor of mortality. Independently of patient's weight a full anatomic and physiologic repair is justified in most cases.

Keywords: Congenital; Low birth weight; Surgery; Heart

1. Introduction

Upon analyzing our own series of patients operated for congenital heart disease (CHD) at a weight of 2.5 kg or less, we realized that the prevailing wisdom regarding early surgical treatment on newborns with low birth weight (LBW) and CHD was based solely on single case reports and a small number of published case-series.

While our mortality was comparable to published data, our risk estimation was limited due to our sample size and the numerous diagnoses. Furthermore, risk estimation in the published series was limited for the same reasons, nevertheless the conclusions of those publications encouraged early repair.

In order to better understand the risks of early surgical repair in this difficult population and to base our decisions on solid epidemiological data, we conducted a meta-analysis (MA) of individual patients in the published literature.

2. Background

Early surgical repair of CHD during the newborn period generated great enthusiasm during the second half of the 1980s. Yet, it would seem that insufficient attention has been paid to a step halfway between fetal life and a full term newborn. Surgical repair of congenital heart defects in patients before they reach a weight of 2.5 kg presents a unique challenge to the surgical team.

The relatively small number of patients included in each published case series compounded by the multitude of diagnoses and surgical approaches make specific risk assessments of mortality inaccurate if not impossible.

The published literature on the subject of surgical repair of CHD in LBW patients considers overall mortality to be acceptable despite published rates as widely variable as 9—21% [1—6]. A sub-categorical classification of the different CHD diagnoses may demonstrate that although the overall mortality may be acceptable, some sub-groups may have a more acceptable mortality than others.

We hypothesize that independently from the low weight, specific diagnoses and other variables play a major role on surgical mortality. Those risks must be identified and carefully considered before parents can be appropriately counseled.

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doi:10.1016/j.ejcts.2006.08.021

The primary goal of this MA is to produce an estimated odds ratio for mortality based on initial diagnosis. Our secondary goal is to investigate the effect of a number of variables, other than diagnosis, on early mortality.

3. Methods

3.1. Bibliographic search and inclusion criteria

An electronic database search (Pub-Med) was performed on articles published in peer-reviewed journals between January 1990 and October 2004. The senior author and two data abstractors (Kanhai, Zwets) conducted a bibliographic search independently from each other. The following Index terms were entered in the query: Low birth weight, congenital heart disease and surgery. The results of the queries were identical, retrieving a total of 65 publications under the constrained headings.

Following a pre-established exclusion criteria a total of six case-series from which data on individual patients could be reliably collected were selected for the MA. In addition to those articles, data from our 37 patients was also included. Once individual patients were identified from each publication, a unique identifier was assigned and available values for demographic, preoperative, surgical and postoperative variables were extracted for each one of them. A complete summary of the included population can be seen in Table 1.

3.2. Exclusion criteria

Publications were excluded following a very specific and pre-established criteria set by the authors (Fig. 1). Publications in languages other than English, single case reports and reports for which only an abstract was available were not included. Multiple reports from the same institution or author were also excluded. Case-series dealing with a single malformation at a single institution as well as those related to the surgical treatment of isolated closure of patent ductus arteriosus in preterm newborns were also excluded.

3.3. Type of study design

Included studies dealt exclusively with preterm newborns or neonates small for gestational age who underwent surgical intervention for their CDH at a weight of or under 2.5 kg. Once a paper was accepted for inclusion in the MA, data on a number of variables was tracked and recorded for each individually identified patient. A Cochran—Mantel—Haenszel statistic analysis was applied to analyze the relationship between death and each one of the variables collected. Due to inconsistencies of the distribution of data (missing data for some patients or some variables) a multivariable analysis for predictors of mortality could not be carried out.

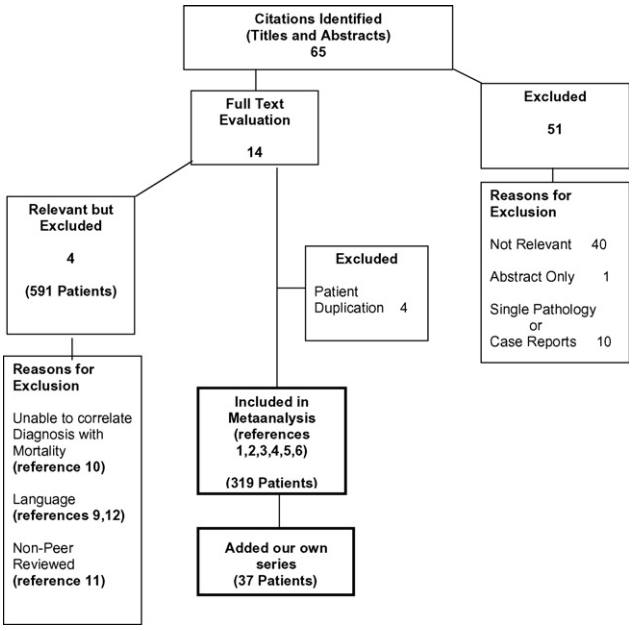

Fig. 1. Results of bibliographic search and criteria for exclusion from the meta-analysis.

3.4. Rationale for selection and coding of data

Due to persistent variations in the nomenclature and classification of congenital heart malformations a total of 46 different diagnoses were reported among all the included publications. To facilitate the analysis patients were distributed according to their diagnoses in several groups. As a reference we used groups (group 1—7) representing the anatomical classificatory categories of the Society of Thoracic Surgeons database for CHD. An extra category

Table 1
Summary of the patients in the included series, dates of data collection, number of patients, demographic characteristics, hospital survival and length of stay

	Pawade/Mee	Chang/Castañeda	Beyens/Deuvaert	Reddy/Hanley	Rossi/Griepp	Cardarelli	Bove/Van Nooten
Data collection	1979—1990	1987—1991	1990—1997	1990—1997	1992—1997	1993—2002	1995—2003
Number of patients	60	56	23	102	30	37	49
Weight at surgery (kg)	2.1 (mean)	2.2 (median)	2.2 (mean)	2.1 (median)	1.8 (median)	1.9 (median)	2.1 (mean)
Age at surgery (days)	17.9 (mean)	9 (median)	24 (mean)	16 (median)	19.5 (median)	10 (median)	15.2 (mean)
Gender	40 Males 20 females	N/A	12 Males 12 females	N/A	N/A	23 Males 14 females	N/A
Race	N/A	N/A	N/A	N/A	N/A	15 Caucasian 20 Afr. Amer. 2 Hispanic	N/A
Full repair (patients)	60	39	21	102	15	26	31
Overall hospital survival (%)	83.5	78.6	78	90	83	81.1	82
Length of stay	N/A	26 (median)	N/A	19 (median)	39 (median)	37.8 (median)	13.5 (median)

Patients with lack of correlation between diagnosis and outcome in the original publications were excluded from final meta-analyses.

Table 2
Patients included in the meta-analyses according to classification taken from the society of thoracic surgeons database (groups 1–7) plus group 8 for mixed diagnoses

Diagnostic category	# Cases	Early deaths	%
1. Septal defects ASD, VSD, CAVC, AP window, truncus, hemitruncus	56	3	5.3
2. Pulmonary vein anomalies TAPVR, PAPVR, core tri-atriatum, pulmonary vein stenosis	15	1	6.6
3. Right heart lesions ToF, pulmonary atresia, tricuspid atresia or stenosis, ebstein	71	15	21.1
4. Left heart lessions aortic stenosis, aortic atresia, mitral stenosis, mitral atresia, HLHS	26	8	30.7
5. Single ventricle	13	1	7.6
6. Transposition of the great arteries (DORV)	48	9	18.3
7. Aortic malformations, CoA, ALCAPA, vascular ring and sling, IAA.	44	4	9.1
8. Any two or more of the above	41	10	24.3
Total	314	51	16.2

Also shown early mortality and percentage.

was added (group 8) to include patients with multiple diagnoses (i.e.: ventricular septal defect *plus* coarctation of the aorta). The diagnosis included in each group, the number of patients in each category, the early mortality with its percentage are showed in Table 2.

The following were collected as dichotomous variables: genetic syndromes, associated pathologies, postoperative complications, preterm birth, preoperative mechanical ventilation, prostaglandins, full repair, delayed chest closure, use of deep hypothermia circulatory arrest (DHCA), need for further surgery during the same admission and early mortality.

Meanwhile, the following were entered as continuous values: gestational age, age at surgery, birth weight, weight at surgery, procedure, cardio-pulmonary bypass (CPBT) time, cross-clamp (X-Clamp) time, length of DHCA, length of delayed chest closure and length of hospital stay.

Gender, race, type of reintervention and cause of death were recorded for each individual, but not used in the MA analysis due to lack of information in a large number of patients.

4. Results

A total of 356 patients were individually identified as having had surgical repair of their congenital heart defect at a weight of 2.5 kg or below. The five most common diagnoses were: ventricular septal defect, tetralogy of fallot, transposition of the great arteries, coarctation of the aorta and total anomalous pulmonary venous return. A full repair was accomplished in 78.9% of the patients and palliative repair was performed in the rest. Overall surgical survival was 83.9% with better survival when a full repair was done (86.1%).

The most commonly reported postoperative complication was sepsis (6.1%) followed by pneumonia (5.6%).

A particular problem arose when Stage I type procedures (i.e.: Norwood, Damus-Kay-Stanzel) had to be coded as a variable. Three of the included series [1,2,6] classified a Stage I repair as a palliative surgery. Meanwhile, two other articles [4,5] classified it as a full repair. Our experience involved only one such case and the remaining included series did not have any Stage I surgery. Since unification of the classification criteria is fundamental to the ability to run a MA, we had to consolidate all Stage I surgeries under one variable. Arbitrarily we choose to collect them under the full repair heading. Had we chosen to classify a Stage I procedure as a palliative surgery, survival for full repair surgeries would have increased to 87.4%. The reader should take this under consideration when analyzing the results of the MA.

4.1. Univariable analysis

Due to difficulty in correlating diagnosis and death in some of the some original articles, only 314 patients were included in the univariable analysis.

The most significant univariable predictors for mortality were: Diagnostic group ($p = 0.001$), the presence of any surgical complication ($p = 0.01$), performing a palliative surgery ($p = 0.03$) and the need for a surgical reintervention during the same hospitalization ($p = 0.03$) (Table 3). In reviewing the results it is evident that of all variables studied (demographic, preoperative, surgical and postoperative) the high-risk variables for mortality are concentrated on the last three. Meanwhile the demographic variables (Gestation age, age at surgery, gender, race and weight at time of surgery) did not seem to have a major influence on outcome.

By using the Society of Thoracic Surgeons categorical classification of CHD plus our added category for mixed diagnosis we calculated the odds ratio for mortality of each group related to the group with the lowest mortality (group 1). Diagnostic groups 3,4, 6, and 8 had increased odds ratios for mortality while groups 2, 5, and 7 did not reach statistical significance to differentiate themselves from group 1 (Table 4). Our analysis cannot prove whether groups 2, 5, and 7 had a truly low risk or, more likely, the result is an

Table 3
Variables studied

Demographic	Preoperative	Surgical	Postoperative
Gestational Age	Ventilatory support	CPB time	**Any complication ($p = 0.01$)**
Age	Preoperative catheterization	X-clamp time	Chest left open
Weight	Use of PGE1	DHCA	Length of stay
Gender	Genetic syndrome	CPB technique	**Need for reoperation ($p = 0.03$)**
Race	Other congenital malformation	**Palliative repair ($p = 0.03$)**	
	Diagnosis group ($p = 0.001$)		

Bold variables are the ones with statistical significance for mortality. Notice than none of the variables in the demographics group were significant.
CPB: cardiopulmonary bypass; X-clamp: aortic cross-clamp; DHCA: deep hypothermia circulatory arrest.

Table 4
Odds ratio for mortality (with 95% CI) for groups 2–8 when compared to group 1

Diagnostic group	# Patients	Odds ratio	95% CI
Group 2	15	1.2	0.12–12
Group 3	71	4.6	1.43–17
Group 4	26	7.6	1.94–31
Group 5	13	1.4	0.13–14
Group 6	48	3.9	1.07–15
Group 7	44	1.7	0.37–7.8
Group 8	41	5.5	1.47–21

artifact due to the small number of patients in those particular diagnostic groups. Further research on those particular groups seems warranted.

The mean or median values (as presented in the original publications) for age (days) and weight (kg) at the time of the surgery can be found in Table 1.

Gender distribution was available for only 120 patients and within that group the male:female ratio distribution was 1.6:1.

Of the included series, the presence of a concomitant genetic syndrome was diagnosed in 51 patients (15%). The most frequent syndrome were CATCH 22 (n = 12), Trisomy 21 (n = 12) and VACTER Syndrome (n = 12).

Preoperatively mechanical ventilation was needed in 37% of the 271 patients for whom such information was available. Prostaglandin E_1 was used preoperatively in 52% of a cohort of the 190 patients for whom the information was accessible. These two variables had a weak degree of statistical association with mortality (p = 0.07 and 0.06, respectively).

Cardiopulmonary bypass was used to accomplish the repair in 262 of the total 356 patients (73.6%). Mean CPB time was 131 minutes (range 49–285) in the 156 patients for whom the data was available. Cross-clamp time was available for 70 patients with a mean duration of 49 min (range 12–94). Deep hypothermia and circulatory arrest time had a mean duration of 28 min (range 2–74) in the 39 patients for whom data was collectable. The use of cardiopulmonary bypass had no statistical impact on mortality.

Length of hospital stay for survivors was available as a median value from five of the authors, representing a total of 225 hospital survivors; details can be seen on Table 5.

Long term follow up varied among the authors. Four groups ([3,4,6] and ours) totaling 109 hospital survivors report a mean follow up of 27 months (range 2–100 months) with a late mortality rate of 12.8% while Reddy et al. [5] reported a median follow up of 30 months (range 9–59 months) for 88 of their 90 survivors with a late mortality of 9.1%.

Table 5
Median length of hospital stay for survivors in five groups (total of 225 survivors for whom the data was available)

Author	Median LOS (days)	Range (days)	# Patients
Rossi	39	6–122	25
Bove	13.5	5–86	30
Chang	26	7–101	50
Reddy	19	5–105	90
Cardarelli	27.5	5–177	30

5. Statistical discussion

Meta-analyses are traditionally performed to summarize the results of multiple clinical trials. Meta-analyses of observational studies usually provoke a certain degree of skepticism in the minds of those familiar with its particular challenges. Inherent biases and differences in designs of the analyzed studies limit the external validity of such studies [7] including this one, yet the number of MA of observational studies in healthcare continues to increase [7].

A meta-analyses of observational studies, when properly conducted, has the potential to answer questions that single small case-series reports are not designed to address [8]. The reader of such analysis must bear in mind that meta-analyses are subjected to publication bias. Such bias is the fact that for the most part only papers with positive results get published, therefore when selecting publications for inclusion in a MA the case series with poor or negative results (poor surgical outcomes in our case) are unlikely to be available for inclusion in the analysis.

The current medical literature has seen a literal explosion of meta-analysis of pooled data [8], in other words meta-analyses that combine the final results of each study. Pooled data meta-analyses, while useful in estimating how a treatment works within a population, lends itself to ecological confounding. Epidemiologically speaking, we are in the presence of ecological confounding when data from the group does not represent the individual patient [8]. Prevention of ecological fallacy rests upon the analysis of the data from each individual, as in our work, rather than the analysis of the summary of data [8,13].

It is also fundamental for the validity of this type of study to demonstrate that the subjects included in a MA are homogeneous and truly representative of the rest of the population with similar characteristics but not included in the MA. Hospital mortality for 591 patients not included in

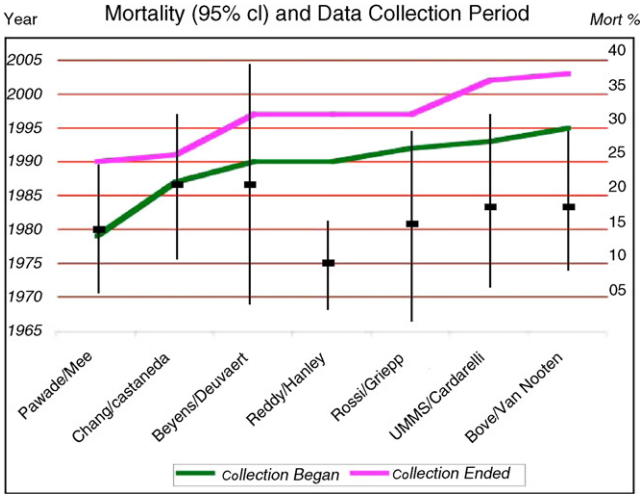

Fig. 2. Left column: Green line represents the beginning and the pink line represents the end of the data collection period for each included series and our own study. Left column: Year of data collection. Right column: Surgical mortality with the corresponding 95% CI for each included series (shown by vertical black lines). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the MA [9—12] ranged between 6 and 18.1% with a mean mortality of 12.65% (95% CI 2.68), which is similar to the mortality for the included series.

Similarly, the variation in mortality for the studies included in the MA (as low as 9.8% and as high as 21.7%) and the wide time span during which the data for these observational studies was accumulated (1979—2003) might lend itself to biases.

When the 95% confidence intervals (CI) for the mortalities observed by each author are plotted against the timeline of the studies (Fig. 2) we can observe that despite the 24-year span in patient-data collected from all the included publications, there is overlapping of mortality between the series. This would suggest a homogeneous population having similar interventions and with overall comparable results.

6. Clinical discussion

The maturation process in the newborn continues beyond the uterus, especially in children born preterm. This process involves all organs, some of particular importance during the postoperative period, yet an ideal maturational level at which the morbidity and mortality risks of these type of patients are minimized is difficult to define and unlikely to be quantifiable.

The common parameter among the patients included in this MA is that all of them were operated upon before reaching a weight of 2.5 kg. The degree of their internal organ maturation though was variable, depending on their gestational and chronological age at the time of surgery. Since those elements are unknown in the majority of patients entered in this MA, it would be imprudent for us to reach overstretching conclusions on how gestational age alone (or chronological age for that matter) affects the results of surgery in this special group of newborns. Similarly, it would also be erroneous to conclude that all LBW patients would react similarly to surgical insult.

Justification for early intervention in the majority of the published material on the subject [1,3—6] rests on the results of two earlier publications [2,14]. Due to the serious limitations of those studies and lack of epidemiological data, it would be erroneous to conclude solely based on them that an aggressive early surgical approach is best for every child born under those circumstances. For medical and ethical reasons it would be equally flawed to believe that a prospective, randomized study on early versus late surgical repair would be a workable option. Perhaps it would be more sensible to admit that like in many other areas of medicine in general and surgery in particular, we do choose a determined course of action (in this case, early intervention) because the patient has a clinical need and we have the technology and the base knowledge necessary to achieve what we judge to be acceptable results.

The combination of LBW and CHD presents a double challenge to the health services of any society. The severity of medical conditions and the patient's low birth weight, combined with the professional resources needed, and perhaps more importantly the economic ones, prevents the achievement of successful survival of such patients in most of the developing world. The experiences included in this work represent a sample of the population and practices from western countries with developed healthcare systems, including USA ([2,4,5,6] and our own), Belgium [3] and Australia [1]. It is very likely that our conclusions may not easily translate to populations and/or healthcare systems elsewhere.

7. Conclusions

Early surgical mortality of congenital heart disease in low birth weight patients is closely related, as it is the case in full-term neonates, to diagnosis and surgical approach. Our results seem to agree with earlier published data indicating that patient's weight or gestational age should play a lesser role in the decision process.

This work, provides those managing LBW newborns with CHD with solid epidemiologically data in order to help parents through the intricacies of achieving an informed decision.

In their precedent setting paper, Castañeda and co-workers reasoned: 'primary repair of CHD offers the opportunity to make an impact on both the mortality of the underlying defect and the secondary effects of the CHD on the development of other organ systems' [15]. We believe this paradigm to be as applicable today for patients born with a combination of low birth weight and congenital heart disease, as it was 20 years ago for those born full-term with similar conditions.

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