Reviewer’s report

Title: Left ventricular dysfunction postsurgical patent ductus arteriosus ligation in children: predictor factors analysis

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Reviewer: Vibeke Hjortdal

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Left ventricular dysfunction post surgical patent ductus arteriosus ligation in children: predictor factors analysis

The left to right shunting through hemodynamically significant patent ductus arteriosus (PDA) causes pulmonary overcirculation with resultant left ventricle (LV) volume overload and remodeling. The left ventricle compensates by increasing stroke volume, but in patients with greater shunts, it causes symptoms of congestive heart failure.

Closure of a PDA by ligation or surgery does in a subset of patients (up to 50% in very preterm neonates) lead to cardio-respiratory instability which could potentially affect the long-term outcome. There is evidence of impaired left ventricular (LV) systolic performance but also vascular tone dysregulation. A "postligation cardiac syndrome" is described in the literature as ventilation/oxygenation failure, hypotension, and the need for increased inotropic support usually occurring 6-12 hours after ligation.

Dr. Mohamed Abdel Bary et al perform a study including 50 children with an average age of well over one year that had their patent ductus arteriosus closed surgically. Echocardiography was performed pre-operatively and postoperatively within the first 24 other, after 1 month and 6 months in order to describe LV systolic function. The further evaluated the association of preoperative findings with the development of LV systolic dysfunction.

Several studies have investigated the physiologic mechanisms contributing to cardiorespiratory instability after PDA ligation and demonstrated a decrease in shortening fraction and ejection fraction associated with an increase in systemic vascular resistance (SVR) and a sudden reduction in preload. Information on preoperative factors that can predict postligation cardiovascular compromise, however, is scarce. Most studies of post ligation problems have been performed in preterm neonates. However, there are major differences in myocardial structure and function between neonates and older children or adults. The search for noninvasive preoperative predictors of postligation syndrome is needed.
In the following our comments are listed.

Title:

Page 1 Line 3 We suggest you follow the STROBE guideline for observational studies (cohort study) also when writing the title. This guideline is very good guidance also in the other sections of the manuscript.

P1 L3 Postsurgical. We think that is one and not two word. Please make sure that it is spelled correctly.

Abstract:

P 2 L 9 We do not understand what you mean by "viewed as a standout".

P 2 L 22 Methods: We suggest that all results - also on PDA diameter - are put in the results section and not in methods. Also later you describe data not only preoperatively but also postoperatively and 1 and 6 months later. This should be included also in the abstract.

Background:

P4 L 2 Possible rewrite the first sentence "is a fetal circulation shunt" to "is a shunt in the fetal circulation".

P4 L 6 Would authors please explain "happens by unexpected contraction of the PDA wall"?

P4 L11 Authors give numbers on the prevalence of PDA in very low birth weight neonates. It however, it is important to remember that PDA is most prevalent in preterm neonates, and that a large percentage of preterm neonates are born with a low gestational weight (for gestational age). Sometimes weight is used as a proxy for gestational age, if it is not known for certain.

PDA in the very preterm neonate is associated with adverse outcome. The discussion on the management of PDA in preterm neonates is however rather controversial. A very high percentage will close spontaneously. And there is a lack of evidence to demonstrate any benefits from PDA closure.

This figure is from Semberova et al. Pediatrics, 2016:140: e20164258

P4 The "background" would benefit from a re-write in order to be more clear. Present the PDA, why should it be closed, what is the problems in the closure (the postligation cardiac syndrome) and then that it is important to identify preoperative factors that could help to children
that are likely to develop postligation cardiac syndrome. Also emphasize that you have studied children and not preterm neonates.

P4 L 37 Authors state that "This study aims to anticipate the predictor factors of LV dysfunction following PDA surgical ligation". We do however find that identifying associations between pre-operative findings and post-operative LV functions is only a rather small part of this study. We suggest authors including the changes in echocardiographic measures as their primary aim and that a secondary aim is to identify predictor factors of LV dysfunction following PDA surgical ligation.

P4 L 38 "anticipate the predictor factors" We suggest authors consider if they want to "identify predictive factors" or possibly "preoperative factors associated with factors of LV dysfunction following surgical ligation of a PDA".

Methods:

Study population

P4 L45 Could authors add information on how the children were selected for this study. Did the cohort include all children operated in the given period of time? Also what is the indication for closure of PDA at this center?

P4 L45 Did you exclude children operated for other cardiovascular malformations - you state that they had to be hemodynamically significant? Did you exclude preterm neonates? You may include a flowchart, please look at the STROBE guideline.

P4 L47 Was you follow up complete - Did all the children complete all examinations?

P5 L55 How did you define "echocardiographic proof of hemodynamically critical PDA"

Does authors have clinical data including blood pressure, need for mechanical ventilation.

Echocardiography

P5 L 23 Would authors please add information on who performed the echocardiography? Also did you validate the measurements? Did you do any blinding in term of clinical sign/symptoms indication postoperative PDA ligation syndrome?

P5 L32 Authors write "and listed for the body surface", not sure "listed" is the correct word to use.
Did you perform more than one cardiac cycle - often three consecutive cardiac cycles were acquired and digitally stored for an offline analysis.

Could authors please add further information on how the PDA diameter was measured. Was it with or without color Doppler. Was it measured at the most narrow point?

Statistics

In order to evaluate the relationship between PDA size and changes in echocardiographic parameters authors used using the Pearson linear correlation and linear regression analysis. We are concerned that this is not sufficient in this case as you have both repeated measurements and multiple comparisons.

Authors write that "we classified our patients into two gatherings as indicated by FS % based on a definition of LV systolic dysfunction; group I with FS ≤ 29% and group II with FS > 29%.”

So was this the preoperative FS or one of the postoperative measurements? We presume it is postoperatively. This information needs to be included in the section on the study population.

In order to be able to work further on this, You need to present descriptive data on the two groups in order to establish if they differed in other ways (that is essentially what you do in Table 4). Here you find several variables that are different between the two groups including PDA diameter. Authors then argue that the differences you find are predictors - that PDA diameter is a predictor of FS postoperatively. However, you need to do further analysis and possible adjust for confounders.

Results:

"The respiratory tract infection and the postoperative hospital stay were recorded" are these the data used in table 4?

Replace "non-significant changes" with "was unchanged" or "did not change".

As explained under Table 1 and 2, Make this into one. Please see below.

If authors want to identify "predictive factors" these factors must happen before the outcome of interest.

"Our clarification for this perception is that the….." the first part of this sentence is not very clear. It could possibly be removed.
P7 L3  The reason for the cardiovascular instability after PDA ligation is rather complex and remains to be clarified.

Table 1 and 2 both contain data on comparison between the post ligation LV systolic function, dimensions & LA/AO ratio in children after PDA closure. In general should one be able to understand tables and figure from the legends and explanations. So I suggest authors add information on number of children, where the examination took place etc.

However, at both tables contains the same data only in table 1 you compare to preoperative values and in table 2 to first day post ligation. The authors should put the data in one table, as most of the data are listed twice. As already mentioned should authors reconsider the statistics used.

Table 3 except from data on EF table 3 contains the same data as figure 1 and 2. Possibly the R and p-values could be added to the Figure.

Table 4 Please add information on abbreviations and definitions (how was hospital days and Recurrent chest infections).

Discussion

P6 L 41  Would remove the first three lines. And rather start the discussion with a short overview of our findings.

P7 L 5  Authors write that Galal et al. (your reference number 14) demonstrated that children with PDA had significant deterioration in FS immediately after PDA closure, which was followed by normalization within six months. They did compare children with PDA > 3.1 mm to children with a PDA < 3.1 mm and found that PDA diameter was associated with left ventricular performance after PDA closure (percutaneous or surgical). The children in that study were older compared to your study. Children with small and large PDA have the same SF preoperative but a decline is found in children with a large PDA postoperatively.

P 7 L 28  Mechanisms behind the postligation cardiac syndrome are complex and probably not fully understood. Speculations on PDA ligation being followed by altered coronary artery perfusion have been made.

P 8  Would authors please point out strengths and limitations of their study. One limitation is the lack of a control group. Therefore, although echocardiograms were performed before and after PDA ligation and each patient served as his or her own control, you can't control for the effects of anesthesia or the stress of surgery. Also did any of the children receive inotropes during echocardiographic evaluation?
Discuss your choice of SF for evaluation of LV function. SF is a load dependent measure of contractility used to evaluate systolic LV function. Could that be a problem, assuming both pre- and afterload changes after PDA closure?

Also, significantly preoperative low values of LVEDd were detected in those with postoperative FS ≤ 29% (group I). Compared to? Is that group 2?

"Additionally, we found a significantly lower ratio of pre ligation FS in group I and we think that this finding is a reasonable reflection of higher LVEDd in this group according to FS calculation equation." We do not understand this sentence.

We suggest authors consider the work by Noori et al The Journal of Pediatrics, June 2007 Noori et all investigated preterm neonates. When adjusted they found that preligation PDA size correlated significantly with changes in LV output at 2 hours postligation. Indicating that the larger the PDA, the greater the reduction in LV output after ligation.

Also Afif F. EL-Khuffash and Patrick McNamara have some interesting points on PDA ligation.

STROBE checklist can be found at https://www.strobe-statement.org/

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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