The relationship between post-operative complications and children's quality of life: a mediation analysis to explore the role of family factors

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Conflicts of interest

None

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Tweet: family psychological support is crucial when children experience severe morbidities after pediatric cardiac surgery.

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Abstract

Objective

To explore whether post-operative morbidities after pediatric cardiac surgery affected children's health related quality of life (HRQOL) at six months, through potentially modifiable parental psychological factors.

Design

We undertook a mediation analysis, to explore the causal pathway, based on data from a prospective, case-matched cohort study of children undergoing cardiac surgery.

Setting

Five centers in the U.K.

Interventions

No intervention.

Measurements

Cases of morbidity were identified early after pediatric cardiac surgery and matched controls with no morbidities were identified at discharge. Four mediators were assessed at six weeks after surgery, using the PedsQL Family Impact Module (Parent HRQOL and Family Function) and the PHQ-4 (Anxiety and Depression). The study outcome of child HRQOL was assessed at six months with the PedsQL.

Results

Of 666 children, 408 (65% of those surviving) contributed to the primary outcome. Children who had extracorporeal life support (ECLS) (n=11) ($P<0.05$) and multiple morbidities (n=62) ($P<0.01$) had worse six-month HRQOL than those with a single morbidity (n=125) or no morbidity (n=209). After adjustment for case mix complexity and sociodemographic variables, there were significant indirect effects of parent HRQOL at six weeks, on the PedsQL Total Score (ECLS: -5.1 (-8.4,-1.8), p=0.003; multiple morbidities: -2.1 (-3.7,-0.5), p=0.01), PedsQL Physical Score (ECLS: -5.1 (-8.7,-1.4), p=0.007; multiple morbidities: -2.1 (-3.8,-0.4), p=0.016) and PedsQL Psychosocial Score (ECLS: -5.3 (-8.7,-1.8), p=0.003; multiple morbidities: -2.2 (-3.9,-0.5), p=0.01) . The proportion of the total effect of ECLS and multiple morbidity on the study outcomes mediated through parent HRQOL, ranges between

18%-61%. There was no evidence that the other three mediators had indirect effects on the study outcome.

Conclusions

Parental HRQOL at six weeks after surgery contributes to child HRQOL at six months, amongst those with the severest types of morbidity, and as such should be a target for future interventions.

Research in Context

- Children may experience complications after pediatric cardiac surgery.
- Clinical teams wish to improve patient outcomes, including their recovery from complications.
- We previously found that children who experience the most severe types of complications, which can be referred to as 'morbidities', also had poorer quality of life 6 months after surgery.

At the Bedside

- The poorest quality of life at six months after surgery is experienced by children who have post-operative ECLS or multiple morbidities.
- A causal mediation analysis found that parental health related quality of life at six weeks after surgery, significantly contributed to child quality of life at six months after surgery for children in these severe morbidity groups.
- Psychological interventions should be evaluated focused on parents of children who experience severer post-operative morbidities.

Introduction

Early survival after pediatric cardiac surgery is excellent, with 97-98% of children discharged home.(1, 2) Hence there is international interest from stakeholders in studying additional more complex outcome measures, such as specific post-operative adverse events, because these may have consequences for survivors' health related quality of life (HRQOL). (3) Our qualitative research found that clinicians and parents may have differing views about which specific adverse events are important after cardiac surgery. (4, 5) Therefore, we used the term *morbidity*, a state of health generally viewed as bad for you, to label the range of adverse early outcomes, including complications, that were prioritized by clinicians and lay people.(5) We previously published the selection (5) and definition (6) of nine key surgical morbidities that were considered the most important: acute neurological event, renal failure, necrotizing enterocolitis (NEC), major adverse events (e.g. cardiac arrest), extracorporeal life support (ECLS), post-surgical infection, prolonged pleural effusion or chylothorax, unplanned re-intervention, and feeding problems. In order to explore the relevance and significance of these morbidities to patients, families and the National Health Service, we measured their incidence,(7) and we assessed HRQOL and parent psychological outcomes for a nested cohort of children with morbidities and matched children with no morbidities, over 6 months.(8) Amongst 3090 procedures in five of the ten UK children's heart centers, 22.8% children had at least one of the morbidities.(7) Following up the nested cohort of 666 children in depth for six months, we found that after adjustment for case mix and family factors, morbidities were linked to poorer HRQOL at six weeks after surgery, with improvement in HRQOL over six months (8) In the current study, *we aimed to explore whether the outcome of HRQOL at six months after surgery was mediated by modifiable family and parental factors as measured at the six-week time point, by analyzing the study data using a mediation analysis approach.* We wished to explore this issue since it could inform efforts to improve post-operative care for patients.

Methods

Dataset

The study received ethical approval from London City Road Research Ethics Committee (14-LO-1442) and all participants provided written consent. This study is a secondary analysis of a prospective, multi-center case matched cohort study of 666 children.(9) Patients were eligible to participate if they were <17 years of age and had pediatric cardiac surgery in one of five centers in the UK, were UK residents, and their family were able to speak and understand English to a reasonable standard without requirement for an interpreter, as judged by the clinical team. From the eligible pediatric cardiac surgery patients meeting criteria, all patients with at least one of the selected morbidities were approached for participation as a morbidity case. A subset of patients with none of the selected morbidities were approached for participation as morbidity-free controls prior to hospital discharge. These controls were matched to cases within center, based on age and the number of functional ventricles. Follow up data were collected with families at six weeks and six months after surgery excepting when the child had died. If a child was still in hospital at follow-up, data were collected wherever possible. Data were collected either face-to-face, by telephone or electronically, depending on parental preference, by researchers qualified to use the measures.

The components

The primary research study purchased and held licenses for the measures used in the study (National Institute for Health Research Health Services and Delivery Research *P*rogramme (Project No: 12/5005/06).

Primary outcome

The primary outcome, ascertained at six months after surgery, was the PedsQL4.0 Total Score, plus the Physical Score and Psychosocial Scores shown separately. We used the PedsQL™ Generic and Infant scales,(10-12) which include parent-proxy assessment for children aged 1 month-18 years, with each scale reported between 1-100.

Exposure of interest

The exposure of interest was the post-operative morbidity type. We had small numbers of patients within certain single morbidity categories, hence we collapsed the data into three broad groups

based on clinical views about severity of: 'single morbidity' (occurrence of any one of the selected morbidities other than ECLS), 'multiple morbidity' (more than one selected morbidity other than ECLS) 'ECLS morbidity' and a fourth group 'no morbidity'.

Mediators

The mediators considered were all evaluated at six weeks after surgery. These were Parent HRQOL, family functioning, parental anxiety, and parental depression. The Family Impact Module (FIM) was used to measure parent HRQOL and family function. The FIM is applicable for use with parents of children aged 1 month-18 years, with each scale reported between 1-100.(13) The PHQ-4 was used to assess parental anxiety and depression.(14) This ultra-short screening measure comprises four questions, two each for anxiety and depression. Parent PHQ-4 scores were dichotomized to indicate the potential presence or absence of anxiety and depression.

Risk factor variables

We adjusted the mediation analysis for important baseline variables, previously linked to early mortality and/or HRQOL after pediatric cardiac surgery (variables are presented in Supplementary Materials Table A).(15, 16) The adjusting variables included in the analyses were study site, patient age, weight, cardiac procedure category, cardiac diagnosis category, bypass time, presence of single ventricle disease, history of comorbidities either congenital or acquired, additional cardiac risk factors, high severity of illness prior to surgery, ethnic group, family income and parent educational level.(8)

The mediation analysis

Causal mediation analysis is a technique by which the effect of an exposure variable on an outcome variable is decomposed into two parts.(17) The first route is the direct effect of the exposure on the outcome and the second route accounts for the fact that the exposure can affect an intermediary factor known as a mediator, and the intermediary factor then affects the outcome. The results of a mediation analysis is presented in terms of several parameters:

i. Total effect is the effect of exposure on outcome either direct or mediated through other factors.

ii. Direct effect is the effect of exposure on the outcome excluding the part mediated through the specified mediators.

iii. Indirect effect is the effect of exposure on outcome mediated through intermediary factors. i.e.: the mediators.

iv. The proportion mediated is the proportion of indirect effect among the total effect. For a single mediator the range is usually 0 to 1, and this is calculated dividing the indirect effect by total effect. The value can be greater than 1 if multiple mediators are considered in the analysis when the mediators may be related to one another. The proportion also can be greater than 1 when a single mediator is considered and it is possible for the direction of direct effect and indirect effect to be in opposite directions.(18) When the proportion mediated goes beyond 1 the result cannot be interpreted. We used the STATA package 'g-formula', which allows multiple categories in exposure variable to consider a single mediator at a time and then multiple mediators. The multiple mediators included in the model provide the cumulative proportion of indirect effect through all four exposure categories. After running the mediation analysis with all morbidity groups, we then dropped the single morbidity category from the mediation analysis, because given the small differences between this category and the reference category of no morbidity for the primary outcome, the results of the mediation analysis including this group was non interpretable. We present a complete case analysis, and all missing data are listed in results. All analyses were performed in Stata v16.

Results

The study cohort and risk factors

The study cohort of 666 children involved 340 with at least one morbidity and 326 with none of the selected morbidities (controls), of whom 558 were case-matched. We present a flow chart to show patients in the study at the stages of baseline (surgery, n=666), follow up at 6-weeks (mediator data collection n= 485) and follow up at 6-months (outcome, n=408), in supplementary material Figure A, and we show details of the various risk factors in the study population in Supplementary Materials Table A. At baseline, 410 (76.6%) were under a year old; 121 (18.2%) had non-Down congenital comorbidities and 8.4% had Down syndrome, and 135 (20.3%) had functionally univentricular hearts.

In terms of family factors, 361 (63.3%) had an annual income of >£25,000 per annum (median for UK), and 501 (83%) were of White ethnicity. Patients in the three morbidity categories were more complex, based on CHD types and underlying health conditions, than those in the no morbidity category, as we have reported elsewhere.(7)

Follow up data: mediators

At the six-week time point, when the mediator variables were collected, 19 (2.9%) patients had died and 485 (74.9%) of the remaining 647 participated completed at least one measure. We present the proportion of patients with each risk variable at the timepoints of baseline, 6 weeks, and 6 months in Supplementary Table B. At the 6 weeks timepoint the participating patients were less likely to have had critical illness at the time of surgery or additional cardiac risk factors, and there was slight variation in participation by site. We show the mediator variables of parent HRQOL, family function, parent anxiety and parent depression in Tables 1 and 2, unadjusted for case mix. FIM scores were lower in the morbidity categories, particularly ECLS followed by multiple morbidities and the proportions with anxiety and depression were higher for the morbidity categories of ECLS and multiple morbidities.

Follow up data: primary outcome

By the follow up time point of six months, 39 (5.9%) had died and 408 of 627 (65.1% of those alive) participated in follow up, providing at least one measure of the primary outcome data as shown in Table 3. These patients included 209 with no morbidities, 125 with a single morbidity, 62 with multiple morbidities and 11 with ECLS. As shown in Supplementary Table B, at the 6-month timepoint, participating patients were less likely to have been low weight at surgery and again there was slight variation in participation by hospital site.

As we have reported elsewhere,(8) and show for information purposes in Supplementary Materials Table C, patients with multiple morbidities and ECLS had significantly poorer HRQOL at six months, whilst this outcome was similar between the single morbidity and no morbidity group. We report unadjusted differences in HRQOL at six months by morbidity group in Table 3, where we show a mean reduction in PedsQL Total score of 9.3, $p<0.05$ for ECLS and 5.5 $p<0.01$ for multiple morbidity

(compared to no morbidity). This was predominantly a consequence of lower Physical Scores (mean reduction of 15.4, p<0.01 for ECLS and 9.3 p<0.001 for multiple morbidity (compared to no morbidity). Although PedsQL Psychosocial Scores were highest in the no morbidity group, the differences with the scores in the three morbidity groups were all non-significant. The patients with single morbidities had slightly lower PedsQL scores across all three domains than the no morbidity group, but none of these differences were statistically significant.

The mediation analysis

We present the medication analysis in Table 4, adjusted for the stated baseline clinical and sociodemographic risk factors, firstly by the four mediating factors combined, and then by each mediator as a standalone factor, for the primary outcome of Peds QL total score and each of the two Peds QL subscales separately.

Indirect effects

For both ECLS and multiple morbidities, the most important indirect mediator was parent HRQOL, which had strongly significant effects that were of a consistent magnitude on child HRQOL at 6 months. This was shown by the PedsQL Total scores for ECLS: -5.1 (-8.4,-1.8), p=0.003; and multiple morbidities: -2.1 (-3.7,-0.5), p=0.01), for PedsQL Physical Score (ECLS: -5.1 (-8.7,-1.4), p=0.007; and multiple morbidities: -2.1 (-3.8,-0.4), p=0.016) and for PedsQL Psychosocial Score (ECLS: -5.3 (-8.7,-1.8), p=0.003; and multiple morbidities: -2.2 (-3.9,-0.5), p=0.01.

The mediator parent HRQOL, accounted for 31% of the total effect on the PedsQL Total score for ECLS and 59% for multiple morbidity. The same mediator accounted for 18% and 30% of the total effect on the PedsQL Physical score for ECLS and for multiple morbidity respectively. 61% of the total effect of ECLS morbidity on the PedsQL Psychosocial score was mediated through the parent HQROL, but since the percentage of the total effect of multiple morbidities on the PedsQL Psychosocial score, mediated through parent HRQOL, goes beyond 100% due to the opposite direction of direct and indirect effect, we cannot interpret this parameter.

There was no clear evidence that the other three mediators had indirect effects on the study outcomes.

Total effects

The findings presented for total effects of the exposures on the study outcome are in line with the unadjusted findings presented in Table 3. If we consider the total effect of ECLS on the six-month PedsQL Physical Score, there was a consistent adjusted reduction in excess of 20 points, based on the mediators combined, and each of the mediators considered in isolation. Similarly, there was evidence for a total effect of multiple morbidity on the six-month PedsQL Physical Score for the total mediators combined and for each of the mediators considered individually, although the magnitude was smaller with an adjusted reduction in score between 6 and 7.

Discussion

We explored the role of potentially modifiable parent and family factors, measured at six weeks after surgery, in mediating children's HRQOL at six months after surgery in the presence of morbidities. Given that the primary outcome of HRQOL was significantly reduced at six months post-surgery, for children who had ECLS and multiple morbidities (compared to those with no morbidities), but not for children with single morbidities, we focussed our mediation analyses on the children with these more significant morbidities. Of the variables considered, we found that parent HRQOL based on the FIM, was the clearest mediator of child HRQOL six months after surgery, for children with ECLS and multiple morbidities.

HRQOL based on FIM

HRQOL based on the FIM explores parental perception of their physical function, (headaches, tiredness) emotional function, (sadness, anxiety), social support (feelings of isolation), cognitive function, (inability to think straight), problems with communication (difficulty sharing) and worries (fears about their child's condition).(13) If the parent experiences severe difficulties in coping with the stress of their child's illness, they may be less able to effectively support their child during recovery, thus indirectly contributing to the child's subsequent HRQOL. Then considering the complexity of this area and the potential for the experiences of the parent and the child to be inter-related, it is also possible that parents of children who were the sickest, and more severely affected by their morbidities, may have scored higher in these areas, whilst these children also were slower

to recover thus had worse HRQOL at six months, thus representing the total effect linking the morbidities to child HRQOL at 6 months.

Psychological support

Parental mental health problems that are associated with a child's critical illness and paediatric intensive care unit (PICU) admission are common. (19) Such difficulties are more likely for children who experience morbidity: our wider study found that a higher proportion of parents whose children had morbidity had anxiety or depression at six weeks post-surgery, in comparison to those without morbidity.(8) We previously reported that depression scores of parents of children in the ECLS and multi-morbidity groups increased between six weeks and six months, likely related to the residual effects of these morbidities. (8) Similar findings are shown from different PICU diagnostic groups, for example, a recent study of children admitted to PICU with sepsis found that an important subset of families experienced protracted stress over the months after their child's illness and recommended screening parents to help access to targeted psychological support.(20)

A recent systematic review and best practice guideline concluded that there have been very few trials of psychosocial interventions for parents of children with CHD during intensive care admission.(21) Although all centers in the UK offer psychological support, it is unlikely that the needs of all parents are recognised and met. The use of screening tools such as the PHQ-4 might facilitate early, targeted referral. Further studies of psychological interventions are needed in this area, and our data suggest that such interventions (if proven therapeutic to parents) have the potential to lead to improvements in child HRQOL.

Rehabilitation after heart surgery

Early rehabilitation has been noted to be extremely variable in content and in the degree to which is undertaken across centers both in Europe(22) and North America.(23) Our study found that in the paediatric cardiac patients, Physical HRQOL was most impacted, and this may relate to the physical demands and effects of living with a complex heart defect and is consistent with other studies.(24, 25) As might be expected, children's physical HRQOL improved over time as they recovered after surgery. Our data support the potential importance of early rehabilitation for children with the

severest post-operative morbidities given their lower PedsQL Physical Scores. Moreover, our data suggest that the support and promotion of parental mental being could be an important component of PICU rehabilitation, given the mediating effect of this on the child's HRQOL.

Study limitations

Our findings may have been influenced by various aspects of the study design including measure selection and by the number of patients in each category, given that smaller effects require a larger sample to be measurable. The multiple morbidity category consists of a range of differing complications, which could have differing impacts. Whilst we successfully recruited 60% of eligible patients to our original study cohort at baseline, and we had a high completion of follow up measures, some children were lost to follow up and thus did not contribute. The measures required at least one parent to speak English, which might have contributed to the relatively high proportion of White British families and introduces a further source of bias. For our primary outcome we used a generic measure (PedsQL), which is less able to discriminate between severity levels of a condition than a disease-specific measure. The primary outcome data were provided by parents because most children (92.4%) were under 5 years of age: hence there may be shared method variance at play in our findings.

Conclusions

An important number of children who undergo cardiac surgery experience significant post-operative morbidities, and these children are at risk of impairments to their HRQOL six months after surgery. We found that parental HRQOL, measured earlier in their child's recovery phase at six weeks, to be an important mediator in their child's recovery. Psychological interventions to support parents of children who experience morbidities may contribute to improvements in child HRQOL six months after heart surgery.

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