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THALIS HENRIQUE DA SILVA

Lidocaína em aerossol não confere benefícios como terapia complementar para reduzir a dor associada à fisioterapia respiratória após cirurgia cardíaca congênita pediátrica: um estudo randomizado, duplo-cego controlado por placebo

RIBEIRÃO PRETO

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Área de concentração: Saúde da Criança e do Adolescente.

Orientador: Prof. Dr. Fabio Carmona

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Dedico este trabalho a todos os integrantes da unidade de terapia intensiva pediátrica e grupo de cardiopatias congênitas do HC-FMRP-USP, pelo crescimento do serviço, pela dedicação dos profissionais e pela constante busca pelo aperfeiçoamento.

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RESUMO

Silva, TH. **Lidocaína em aerossol não confere benefícios como terapia complementar para reduzir a dor associada à fisioterapia respiratória após cirurgia cardíaca congênita pediátrica: um estudo randomizado, duplo-cego controlado por placebo**. 2021. 30 fl. Tese (Doutorado) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2021.

Objetivo: Investigar se a fisioterapia respiratória aumenta a dor, se a lidocaína inalada pode atenuar o aumento da do rem bebês e crianças submetidos à cirurgia para cardiopatia congênita.

Métodos: trata-se de um estudo duplo-cego, randomizado e controlado por placebo. Local: Unidade de terapia intensiva pediátrica de um hospital universitário brasileiro de atenção terciária. Pacientes: foram inclusos 119 pacientes <18 anos de idade submetidos à cirurgia cardíaca aberta para correção de cardiopatia. Intervenções: Lidocaína em aerosol (1 mg/kg) antes das manobras de fisioterapia respiratória e aspiração traqueal, em comparação com o placebo.

Resultados: A dor foi avaliada pela escala de face, pernas, atividade, choro, consolabilidade da dor-revisada (FLACC-R), juntamente com os parâmetros hemodinâmicos e ventilatórios, antes e após a fisioterapia e aspiração, nos 1º, 3º e 7º dia pós operatórios. Lidocaína ou placebo foram administrados imediatamente antes da fisioterapia. A fisioterapia induziu pequenas alterações na dor, que não foram atenuadas pela lidocaína (confirmadas na análise multivariada) e também induziu efeitos menores e não clinicamente relevantes nos parâmetros hemodinâmicos e ventilatórios, que também não foram modificados pela lidocaína.

Conclusões: A fisioterapia respiratória não aumentou a dor no pós operatório em paciente que realizado cirurgia para correção de cardiopatia congênita pediátrica até o 7º dia, a lidocaína em aerosol não apresentou qualquer efeito clinicamente significativo sobre a dor ou outros parâmetros hemodinâmicos ou ventilatórios. Portanto a administração traqueal de lidocaína não reduz a dor após a fisioterapia respiratória em crianças submetidas à cirurgia cardíaca.

Palavras-chave: dor pós operatória, cardiopatia congênita, fisioterapia respiratória, cirurgia cardíaca, droga anestésica.

ABSTRACT

Silva, TH. **Aerosolized lidocaine does not confer benefit as an add-on therapy to reduce respiratory therapy-associated pain after pediatric congenital heart surgery: a randomized, double-blind, placebo-controlled trial.** 2021. 30 p. Thesis (Doctorate) – Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, 2021.

Objective: To investigate whether respiratory therapy (RT) increases pain if inhaled lidocaine can attenuate pain increase in infants and children undergoing surgery for congenital heart disease (CHD).
Design: Double-blind, randomized, placebo-controlled trial.
Setting: Pediatric intensive care unit in a Brazilian tertiary-care, university hospital.
Patients: 119 patients < 18 years submitted to open-heart surgery for CHD.
Interventions: Aerosolized lidocaine (1 mg/kg) before RT maneuvers and tracheal suction, compared to placebo.
Measurements and main results: Pain was assessed by the face, legs, activity, cry, consolability pain scale – revised (FLACC-R), along with hemodynamic and ventilatory parameters, before and after RT and tracheal suction on postoperative days 1, 3, and 7. Lidocaine or placebo were administered right before RT. RT induced minor changes in pain, which were not attenuated by lidocaine (confirmed in multivariate analysis). RT also induced minor, not clinically relevant effects in hemodynamic and ventilatory parameters, which were also not modified by lidocaine.
Conclusions: Respiratory therapy did not increase postoperative pain in patients after pediatric congenital heart surgery up to the 7th day, nor aerosolized lidocaine exhibited any clinically significant effect on pain or other hemodynamic or ventilatory parameters.

Keywords: postoperative pain; respiratory therapy; congenital heart disease; open-heart surgery; anesthetic drugs.

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SUMÁRIO

Title page

Aerosolized lidocaine does not confer benefit as an add-on therapy to reduce respiratory therapy-associated pain after pediatric congenital heart surgery: a randomized, double-blind, placebo-controlled trial.

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Keywords: postoperative pain; respiratory therapy; congenital heart disease; open-heart surgery; anesthetic drugs.

Ribeirão Preto, 2021.

1 Introduction

Congenital heart disease (CHD) is still an important cause of mortality in Brazil (1). About 20% of cases will resolve spontaneously, but many will require corrective or palliative surgery (2). These patients are at risk of postoperative pain, which has short- and long-term consequences to the patients, both physical and emotional (3). Andrade et al found that 86.7% of patients after surgery for CHD experience pain at least once in the hospital stay (4).

Postoperative pain is associated with changes in the respiratory system, such as decreased lung compliance and atelectasis (5, 6). Respiratory therapy (RT) plays a significant role in preventing and minimizing pulmonary complications. RT can restore the respiratory function through manual techniques and tracheal suction (5, 6). However, RT itself can be a cause of pain and stress, especially when associated with tracheal suction, leading hemodynamic and respiratory manifestations, such as: tachycardia, hyper- or hypotension, tachypnea, increased work-of-breathing, patient-ventilator asynchrony, among others (7, 8). This is often attenuated by the administration of boluses of sedative and/or analgesic agents right before RT, but the ideal drug and dose are still a matter of debate (9).

There are reports on the use of lidocaine (instilled into the tracheal tube) to minimize pain associated with tracheal suction after pediatric heart surgery (10). Tracheal administration of lidocaine can potentially reduce pain, cough reflex, bronchospasm, vagal reflex, and hypertension (11). However, the efficacy of this intervention has not been investigated after congenital heart surgery, to the best of our knowledge.

Therefore, this study was designed to test the hypotheses that: (a) RT increases pain, despite the preventive use of opioid boluses, and (b) inhaled

lidocaine, as compared to placebo, can attenuate this pain increase in infants and children undergoing open heart surgery for CHD. Secondarily, we planned to assess the effects of RT and lidocaine on hemodynamic and ventilatory parameters.

2 Patients and Methods

This was a double-blind, randomized, placebo-controlled, parallel clinical trial conducted Clinics Hospital, Ribeirão Preto Medical School, University of São Paulo. This is a tertiary-care, university hospital that holds between 100 and 200 pediatric open-heart surgeries annually. The study was approved by the local institutional review board (ethics committee). All parents or legal guardians signed an informed consent before inclusion. This trial was registered in the Brazilian Registry of Clinical Trials (http://www.ensaiosclinicos.gov.br).

The inclusion criteria were age < 18 years and being submitted to open-heart surgery for CHD. Exclusion criteria were parental request, intraoperative death, or a hemodynamic instability that precluded RT, defined as one of the following: (a) refractory shock, defined as signs of poor perfusion, hypotension and/or increasing lactate values despite optimum inotropic/vasoactive therapy; (b) tachy- or bradyarrhythmia with hemodynamic impairment (poor perfusion and/or hypotension); (c) significant postoperative bleeding; or (d) crises of pulmonary hypertension.

All patients were on sedation/analgesia during the study: patients on mechanical ventilation received continuous infusions of midazolam (0.1-0.2 mg/kg/h) or dexmedetomidine (0.2 µg/kg/h), plus fentanyl (1-2 µg/kg/h), while those spontaneously breathing were on intermittent dipyrone (15 mg/kg/dose) and/or tramadol (1.25 mg/kg/dose).

The patients were initially randomly allocated (1:1) to one of two groups, receiving either inhaled/aerosolized lidocaine (1 mg/kg) or placebo (normal saline) right before RT. The randomization was in blocks of random size (4 or 6), and the list was generated in https://www.sealedenvelope.com by a statistician. The allocation was concealed by a computerized system. The interventions were identical in appearance: both were prepared at the hospital's pharmacy, which was the only staff aware of patient allocation. The lidocaine solution (1%) contained 10 mg/mL, so a volume of 0.1 mL/kg yielded the desired dose of 1 mg/kg. The same volume was used for placebo.

All patients were assessed six times: before and after RT on days 1, 3, and 7 after surgery, according to the following protocol: (a) a "before" assessment, 10 minutes before RT, (b) administration of intravenous opioids (fentanyl 1–2 μg/kg in bolus), (c) administration of aerosolized intervention (lidocaine or placebo), (d) RT maneuvers and tracheal suction (for those on mechanical ventilation), and (e) an "after" assessment, 10 minutes after RT. The protocol was repeated on days 3 and 7. Demographic and clinical data were collected from the medical charts, as well as the main clinical outcomes (death, hospital length-of-stay). Surgical complexity and risk of death were assessed with the Risk Adjustment for Congenital Heart Surgery 1 (RACHS-1) and the Society of Thoracic Surgeons and European Association for Cardiothoracic Surgery (STS-EACTS) scores (12, 13). All data were entered in a Research Electronic Data Capture (REDCap) password-protected database (14).

The primary outcome was pain intensity, prospectively assessed with the face, legs, activity, cry, consolability pain scale – revised (FLACC-R), which is validated in Portuguese for patients between 2 and 18 years of age (15). Each domain is scored 0 to 2 points, yielding a maximum of 10 points. To minimize assessment bias,

FLACC-R was applied by two independent staff members, and any disagreement was resolved by a third assessor. In addition, all RT maneuvers were conducted by the same professional (THS).

Secondary outcomes were assessed in the same timepoints, and included vital signs [heart rate (HR), spontaneous respiratory rate (RR), mean arterial pressure (MAP), and peripheral oxygen saturation (SpO_2)] and ventilatory support [peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP), mandatory respiratory rate (mRR), volume tidal (VT), and inspired fraction of oxygen (FiO_2)].

2.1 Statistical analysis

Since there was no prior data on the effect of aerosolized lidocaine on FLACC-R in children, we planned to include all patients operated on for two years as our sample size.

All variables were described by their mean plus standard deviation, median plus total range, or counts plus percentages, as appropriate. Exploratory comparisons between and within groups were initially made with Student's *t* test or Fisher's exact test (univariate).

After description of the variables, Bayesian linear regression models were adjusted, with the dependent variable being a ratio of after/before measurements of the variables of interest (outcomes) on each assessment day, and the independent variables being the day of assessment, treatment group, and a random effect to accommodate the within-subjects repeated measures. Mean differences with credible intervals of 95% (95%CrI) were estimated. The interpretation of these intervals is that the true mean difference has a 95% likelihood of lying within the limits of the interval. The result is considered significant at 5% alpha when the 95%CrI does not contain zero. Statistical packages StataSE 14.0, JAGS and R 3.5.1 were used.

3 Results

A total of 126 open-heart surgeries occurred between January 2018 and January 2020 at our hospital. We stopped recruiting after two years, as planned. Of the 126 patients, 119 patients (94.4%) were included (**Figure 1**), whose baseline characteristics are depicted in **Table 1**. The frequency of types of CHD are listed in **Supplementary table 1**. The two groups of patients were fairly similar at baseline regarding sex, age, surgical complexity (RACHS-1 and STS-EACTS scores), and duration of cardiopulmonary bypass (CPB), aortic cross-clamping (XAo), and deep hypothermic circulatory arrest (DHCA). The reasons some patients were not included were hemodynamic instability, precluding RT, intraoperative death, or data loss.

3.1 Primary outcome

Regarding the primary outcome, as shown in **Table 2**, RT induced minor changes in pain (measured by FLACC-R), and there were no differences between the treatment groups (**Figure 2**). These findings were confirmed in multivariate analysis (**Table 3**).

3.2 Secondary outcomes

RT induced minor increases in HR, RR, and SpO_2 that, although statistically significant, are of minor clinical relevance (**Table 4**). RT also induced slight, clinically irrelevant changes in ventilatory support (**Table 5**). In short, decreases in PIP, PEEP, mRR, and FiO_2, besides increases in VT. No differences were detected between the two groups. In multivariate analyses, the effects of time (1st, 3rd, or 7th day) and treatment were not statistically significant on any of the secondary outcomes (data not shown).

No adverse events related to the intervention were recorded.

4 Discussion

In the present study, we did not find a beneficial effect of aerosolized lidocaine in preventing pain associated with RT and tracheal suction, as compared to placebo. In addition, RT itself produced only minor changes in hemodynamic and ventilatory parameters.

Pollak et al have recently discussed the aspects related to intra- and postoperative pain management after congenital heart surgery. In their excellent review, they comment on how these patients respond to stressful perioperative stimuli with altered hemodynamic status and stress hormones levels, besides respiratory compromise and pulmonary hypertension, that can be fatal (7). They emphasize the need of using appropriate pain scales and individually tailoring sedation and analgesia. This individualized approach could incorporate the use of tracheal anesthesia before suction, as described by Mills et al (10). Indeed, the results obtained by Paltura et al in adults undergoing suspension laryngoscopy for benign laryngeal diseases support this strategy (11). Samantaray et al, in their interesting study, randomized children undergoing open-heart surgery to receive either caudal anesthesia or intravenous analgesia in addition to general anesthesia. They showed that the association of caudal anesthesia was superior to intravenous analgesia in achieving better hemodynamic control and reducing postoperative pain 24 hours after surgery (16).

The explanations to why, in our study, RT did not induce any discomfort include the universal, individualized use of continuous infusion of sedatives and analgesics, plus the prophylactic opioid boluses given before RT in our hospital, which seemed to have been effective, associated with the fact that, in our patients, all

RT maneuvers were conducted by a single, very experienced respiratory therapist. This is contrary to what was found by Araújo et al, that compared the frequency of pain and hemodynamic and respiratory compromise after RT in children submitted to open-heart surgery for CHD at our hospital a couple of years before (8). In this study, pain was assessed by FLACC-R, the same scale we used. They found that RT was associated with an increase in pain and with a transient elevation of systolic blood pressure and heart rate. Our results cannot be generalized to units where the therapist is less experienced, or at which prophylactic opioid infusion is not universal. Therefore, we speculate that the sedation/analgesia scheme our patients were on were effective in preventing any potential deleterious effects of RT. Therefore, tracheal lidocaine administration does not appear to confer any benefit to children already in use of other sedative or analgesic drugs.

We also found that RT induced minor improvements in ventilatory support that, although statistically significant, are of modest clinical relevance. This was also reported by Moreira et al that studied adult patients under mechanical ventilation and showed that respiratory therapy improved lung compliance and resistance, VT, and SpO_2 (17).

An important fact about out study is that we assessed pain using FLACC-R, which is widely used in almost all ages, validated in Portuguese (15), and that all measurements were done by two observers. The limitations of this study include: (a) heterogeneity of our patients regarding the types of heart defects; (b) wide range of patients' age at surgery; and (c) other factors that could cause pain, such as chest tubes and surgical incision, were not controlled. Regarding sample size, the number of patients we studied would have had 80% power to detect a significant difference in pain only if the effect size of lidocaine was at least 0.52 (medium) (18). Therefore,

although we cannot rule out a type-2 error, we consider it unlikely given the very small differences we found between the groups.

5 Conclusions

Respiratory therapy did not increase postoperative pain in patients after pediatric congenital heart surgery up to the 7th day, nor aerosolized lidocaine exhibited any clinically significant effect on pain or other hemodynamic or ventilatory parameters.

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Tables

Table 1. Baseline demographic and surgical data of all participants, by group.

Variable	**All patients (n=119)**	**Lidocaine (n=60)**	**Placebo (n=59)**
Gender (male)	62 (52%)	39 (65%)	31 (52,5%)
Age (months)	33.6 ± 46.3	29.9 ± 39.9	37.5 ± 52.0
RACHS-1	2.2 ± 0.9	2.2 ± 0.9	2.2 ± 0.9
STS-EACTS	1.9 ± 1.1	1.9 ± 1.1	1.9 ± 1.0
CPB duration (min)	77.6 ± 45.5	73.7 ± 41.0	81.7 ± 49.8
XAo duration (min)	50.0 ± 31.8	43.5 ± 27.3	56.2 ± 34.7
DHCA duration (min)	11.4 ± 6.8	11.6 ± 7.6	11.0 ± 8.4

Legend: RACHS-1, risk adjustment for congenital heart surgery 1; STS-EACTS, Society of Thoracic Surgeons (STS) and European Association for Cardiothoracic Surgery (EACTS) score; CPB, cardiopulmonary bypass (minutes); XAo, aortic cross clamping (minutes); DHCA, deep hypothermic circulatory arrest (minutes). Data are expressed as mean ± standard deviation.

Table 2. Pain assessment at all three timepoints, before and after respiratory therapy, by group.

Variable	Lidocaine (n=151)	Placebo (n=151)	Between group p-value*
FLACC-R before RT	2.95 ± 1.90	2.85 ± 1.90	0.895
FLACC-R after RT	2.68 ± 1.70	2.62 ± 1.80	0.495
Within group p-value*	**0.025**	0.054	

Legend: FLACC-R, face, legs, activity, cry, consolability pain scale – revised; RT, respiratory therapy; *, adjusted for repeated measures. Data are expressed as mean ± standard deviation.

Table 3. Adjusted (multivariate) comparison of pain intensity between groups, assesses with face, legs, activity, cry, consolability pain scale – revised (FLACC-R), by timepoint.

Timepoint	Mean difference (placebo – lidocaine)	95%CrI lower limit	95%CrI upper limit
Day 1	0.02	-0.02	0.07
Day 3	-0.01	-0.05	0.03
Day 7	-0.02	-0.07	0.03

Legend: 95%CrI, credible interval of 95%. None of the comparisons were statistically significant.

Table 4. Hemodynamic data at all three timepoints, before and after respiratory therapy, by group.

Variable	Lidocaine (n=151)	Placebo (n=151)	Between group p-value*
MAP before RT	65.5 ± 12.7	67.4 ± 11.7	0.588
MAP after RT	66.1 ± 11.3	67.3 ± 10.5	0.611
Within group p-value*	0.280	0.912	
HR before RT	128 ± 22	127 ± 22	0.809
HR after RT	130 ± 18	131 ± 20	0.317
Within group p-value*	**0.007**	**0.028**	
RR before RT	31 ± 8	30 ± 9	0.652
RR after RT	31 ± 6	31 ± 7	0.944
Within group p-value*	0.725	**0.019**	
SpO_2 before RT	95.6 ± 6.1	96.1 ± 5.3	0.058
SpO_2 after RT	95.9 ± 6.1	96.4 ± 5.1	**0.013**
Within group p-value*	**0.029**	0.347	

Legend: MAP, mean arterial pressure (mm Hg); HR, heart rate (beats per minute); RR, respiratory rate (incursions per minute); SpO_2, peripheral oxygen saturation (%); RT, respiratory therapy; *, adjusted for repeated measures.

Table 5. Ventilatory data at all three timepoints, before and after respiratory therapy, by group.

Variable	Lidocaine (n=151)	Placebo (n=151)	Between group p-value*
PIP before RT	15.4 ± 4.4	15.1 ± 4.2	0.562
PIP after RT	15.0 ± 4.4	14.7 ± 4.4	0.830
Within group p-value*	**0.000**	**0.000**	
PEEP before RT	5.7 ± 0.8	5.7 ± 0.7	0.638
PEEP after RT	5.6 ± 0.7	5.5 ± 0.6	0.380
Within group p-value*	0.132	**0.031**	
mRR before RT	23 ± 11	25 ± 7	0.001
mRR after RT	18 ± 13	21 ± 10	0.003
Within group p-value*	**0.000**	**0.000**	
VT before RT	6.7 ± 1.0	6.9 ± 1.0	0.722
VT after RT	7.1 ± 1.0	7.3 ± 1.0	0.852
Within group p-value*	**0.000**	**0.003**	
FiO_2 before RT	37 ± 23	34 ± 20	0.205
FiO_2 after RT	33 ± 21	30 ± 17	0.042
Within group p-value*	**0.000**	**0.000**	

Legend: PIP, peak inspiratory pressure (cm H_2O); PEEP, positive end-expiratory pressure (cm H_2O); mRR, mandatory respiratory rate (cycles per minute); VT, volume

tidal (mL/kg); FiO_2, inspired fraction of oxygen (%); *, adjusted for repeated measures.

Figure legends

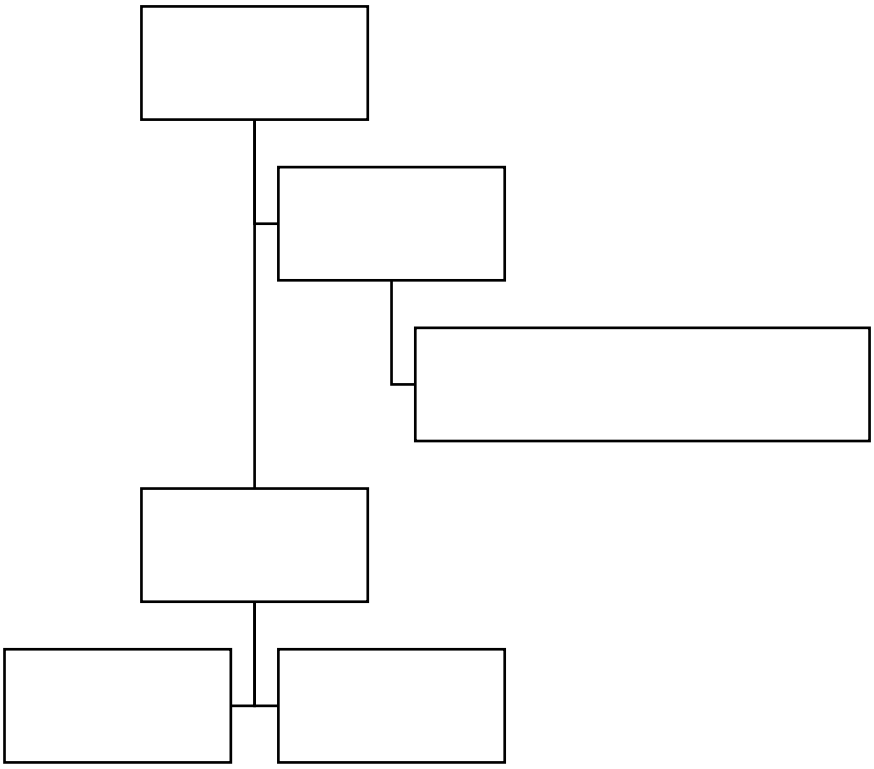

Figure 1. Flowchart of patient recruitment.

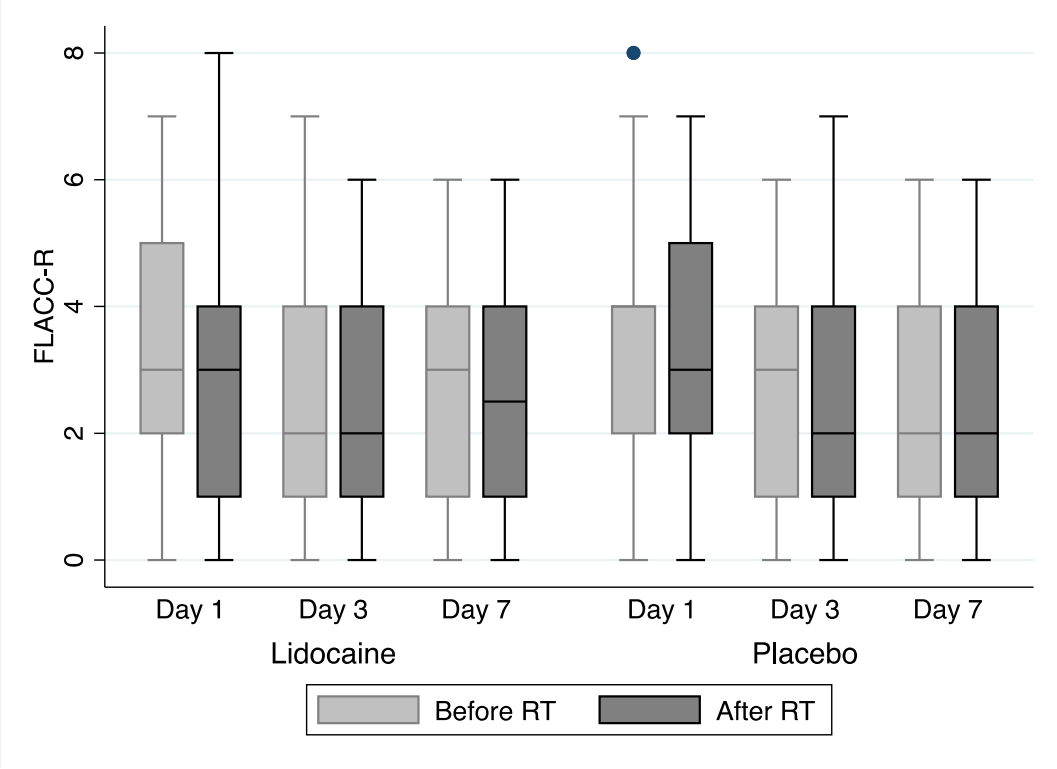

Figure 2. Boxplots of face, legs, activity, cry, consolability pain scale – revised (FLACC-R) scores in both groups, by timepoint, before and after respiratory therapy (RT). There were no significant differences between the two groups.

Supplementary material

Supplementary table 1. Types of congenital heart disease or procedure, by group.

Type of congenital heart disease	Lidocaine (n=60)	Placebo (n=59)
Coarctation/Interrupted aortic arch	6 (10%)	6 (10.1%)
Ventricular septal defect	20 (33.3%)	9 (15.2%)
Transposition of the great arteries		1 (1.6%)
Pulmonary stenosis/atresia (VSD)	14 (23.3%)	7 (11.8%)
Anomalous origin of coronary arteries	1 (1.6%)	1 (1.6%)
Tetralogy of Fallot	1 (1.6%)	8 (13.5%)
Atrial septal defect	9 (15%)	8 (13.5%)
Patent *ductus arteriosus*	2 (3.3%)	4 (6.7%)
Double-outlet right ventricle		2 (3.3%)
Aortic aneurism		1 (1.6%)
Truncus arteriosus communis		1 (1.6%)
Anomalous pulmonary venous connection	1 (1.6%)	1 (1.6%)
Mitral valvoplasty	2 (3.3%)	3 (5%)
Pulmonary atresia (IVS)		1 (1.6%)
Atrioventricular septal defect	4 (6.6%)	6

	(10.1%)

Legend: All values are expressed as count (percentage within group/column).