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Early mobilization in children with pneumonia in mechanical ventilation: randomized clinical trial

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ABSTRACT. Immobility in the bed of pediatric patients in intensive care units increases the risk of morbidities such as pneumonia, with consequences for autonomic function. Physiotherapy based on physical exercise is part of the rehabilitation process and can modify autonomic function. To compare the effects of two physical therapy protocols, one conventional and the other based on physical exercise, on heart rate variability, length of stay and invasive mechanical ventilation in children with ventilator-associated pneumonia. This is a randomized clinical trial, the volunteers were divided into a control group (submitted to a physiotherapy protocol with only breathing exercises and passive mobilization) and an experimental group (submitted to a physiotherapy protocol based on physical exercise). Patients aged 1 to 8 years, on invasive mechanical ventilation, with pneumonia were included. The rehabilitation protocol took place for 4 consecutive days. The collection of heart rate variability occurred in the pre-protocol period, on the 2nd day, 1 day after the end of the protocol. 25 patients completed the study. There was a reduction in the time of invasive mechanical ventilation in the experimental group ($p = 0.01$). There was an improvement in the heart rate variability of the experimental group in all indices ($p < 0.01$). The post-protocol analysis of the groups showed significant values in all variables ($p < 0.05$). Exercise-based physical therapy protocol improved autonomic heart rate modulation and reduced IMV time in children with ventilator-associated pneumonia.

Keywords: ventilator-associated pneumonia; physical therapy; exercise; autonomic nervous system; heart rate.

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Introduction

The management of critical pediatric patients in the Pediatric Intensive Care Unit (PICU) aims to maintain maximum hemodynamic and ventilatory stability in patients who are usually sedated and confined to bed for prolonged periods (Piva, Ferrari, & Schaan, 2019), which is associated with other risk factors, which can result in significant losses of muscle mass due to the effects of systemic inflammation and interventions imposed during severe illness (Zheng et al., 2018).

Immobility in bed increases the risk of secondary morbidities such as weakness acquired in the PICU, delirium and Ventilator-Associated Pneumonia (VAP) (Joyce et al., 2018), the latter being the most common nosocomial infection in patients using Invasive Mechanical Ventilation (IMV), occurring in up to 32% of patients using IMV for more than 24 hours and is associated with up to 3 times higher child mortality (Mourani & Sontag, 2017).

Immobility also reduces the autonomic modulation of heart rate (Ferretti et al., 2009) in healthy individuals, it is the oscillations in the duration of the intervals between consecutive heartbeats and indicates the efficiency of the heart in responding to multiple physiological and external stimuli (Bento, Fonseca-Pinto, & Póvoa, 2017). Thus, the greater the variability of heart rate (HRV) the better the adaptation of the heart and indicates efficient adaptive physiological mechanisms. The opposite, in turn, infers insufficiency of the Autonomic Nervous System (ANS) and is associated with poor prognosis, higher morbidity and mortality in a variety of clinical conditions (Karmali, Sciusco, May, & Ackland, 2017; Grandemange et al., 2019).

Thus, interventions such as physiotherapeutic conducts based on physical exercise, also commonly called early mobilization of the patient in the PICU, should be considered in the rehabilitation process, as it is

associated with positive outcomes such as reduced hospital stay, sedation, delirium, duration of mechanical ventilation, and improvement in muscle strength (Cameron et al., 2015). Current data indicate that exercise-based physical therapy in critically ill pediatric patients is safe, feasible and may have several short and long-term benefits (Choong et al., 2018; Walker & Kudchadkar, 2018).

Therefore, this study seeks to investigate the effects of a physical therapy rehabilitation protocol based on physical exercise, on HRV, length of stay and IMV in children with VAP in the PICU.

Material and methods

Study design and registration

The study was a randomized, longitudinal, double-blind, prospective and quantitative clinical trial, in which the changes produced by the proposed intervention in the experimental group (EG) were evaluated. This trial was carried out at the PICU of Fundação Santa Casa Misericórdia do Pará (FSCMP) from August 2018 to September 2019, registered at <http://clinicaltrials.gov> with registration NCT03343717.

Ethical aspects

The study complied with the standards for research involving human beings established by Resolutions number 466/12 and number 580/18 of the National Health Council. It was approved by the Ethics and Research Committee of the FSCMP, under approval 2.695.309. All participants involved had authorization to participate in the study provided by their legal guardians by signing the Free and Informed Consent Form.

Sample Calculation

The sample size calculation for the study was performed using the GraphPad StatMate application, version 1.01, with a significance of 5% and a test power of 99%, based on the number of hospitalizations for the collection period and the participation of 20 volunteers in the study. study, with 10 volunteers in each group.

Randomization

After the initial evaluation, the volunteers were randomized by a blind researcher on the website <http://www.random.org>, being allocated to the Control Group (CG) and EG.

Participants

Patients aged between 1 year and 8 years, on IMV between 72 and 96 hours, with VAP confirmed by imaging and blood count, certified by the physician, with hemodynamic stability that allowed the performance of the physical therapy protocol (Blood Pressure (BP) and Heart Rate (HR) with a variation of up to 20% of the expected for age) were included (Martins, 1988; Brasil, 2012). Patients with decompensated heart failure, congenital heart disease, severe respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 100$), active bleeding, acute brain disorder ($\text{ICP} > 10$ mmHg in infants and $\text{ICP} > 15$ mmHg in children), presence of orthopedic contraindications (fractures, dislocations, postoperative period, unstable spine), neurological impairment without minimal functionality (PEDI scale < 1), neuromuscular disease and presence of menarche were excluded from the study.

Monitoring and security

To monitor the safety of the technique, the volunteers' vital signs were constantly evaluated during the study. HR, BP and Peripheral Oxygen Saturation (SPO₂) were collected by monitoring the patient in the PICU using the OMNI 600® multiparameter monitor (OMNIMED LTDA, Belo Horizonte, Brazil). The security level for the experimental protocol was based on the algorithm proposed by Mendez-Tellez, Nusr, Feldman, & Needham, 2012) and adapted for pediatrics.

Intervention

The Control Group (CG) was submitted to the hospital's rehabilitation protocol, which consisted of breathing exercises that include bronchial hygiene maneuvers (postural drainage, percussion, vibration, chest compression, mechanically assisted cough) (Gosselink et al., 2008). With the objective of clearing the airways, aspiration of the airways, lung expansion techniques (hyperinflation with a ventilator or manual, PEEP)

(França et al., 2012) for reversing atelectasis, passive mobilization techniques in the Upper Limbs (ULM) and Lower Limbs (LL) with objective of reducing deformities and preserving joint mobility.

The second group, called EG, in addition to performing the same rehabilitation protocol of the hospital, was submitted to an experimental protocol proposed by the authors of the research with the performance of exercises divided into 4 phases according to the activity levels presented by the patients, evaluated by the Glasgow Coma Scale (ECG) in addition to the levels of muscle strength by the Medical Research Council (MRC) Scale. The protocol applied to the experimental group was divided into 4 phases:

- Phase 1: Aimed at unconscious patients, in which passive mobilization was performed with 3 sets of 10 repetitions in each joint movement and muscle stretching with 2 repetitions of 20 seconds for the upper limbs (shoulder: flexion, adduction-abduction; elbow: flexion-extension, prone-supination; wrist: flexion-extension) and for lower limbs (hip: flexion, adduction-abduction; knee: flexion-extension; ankle: plantar dorsiflexion).

- Phase 2: Performed in collaborative patients with the ability to respond to 3 of 5 simple verbal commands, according to chronological age. Starting with passive exercises and phase 1 stretching, followed by active-assisted or active exercises with 5 repetitions in each joint movement in the upper and lower limbs. Then, sitting on the bedside for 5 minutes.

- Phase 3: Performed on collaborative patients who had biceps muscle strength with grade 3 to 5 on the MRC. Starting with active-assisted or active exercises with 5 repetitions in each joint movement in the upper and lower limbs. Then, the patient was placed in a sitting position at the bedside for 5 minutes. Afterwards, he remained in orthostatism/stimulation of standing with the help of the physical therapist for 5 minutes.

- Phase 4: With collaborative patients who presented quadriceps muscle strength grade 3 to 5. Starting with active-assisted or active exercises with 5 repetitions in each joint movement in the upper and lower limbs. Followed by bedside sitting or possible postural transfers performed for 5 minutes. Ambulation/stimulation to ambulation, according to the chronological age of the patients. The progression of the phases occurred according to the clinical evolution and level of consciousness of the patients.

Patients were submitted to the rehabilitation protocol once a day for 4 consecutive days with children from the 3rd or 4th day after the installation of IMV.

Data collection

The HRV collection took place in the pre-protocol period, on the 2nd day of application and 1 day after the end, in the morning. Capture was performed using a POLAR® HR monitor, model RS800CX (Polar Electro TM, Kempele, Finland), and the HR signal was captured by a strap adapted to the signal receiver, placed on the child's chest height of the xiphoid process of the sternum. Then, the data captured by the frequency meter were transferred to the Polar ProTrainer Software (Polar Electro OY, Kempele, Finland), where they were stored and exported to .txt format so that, later, a blind researcher who did not know the collection period analyzed by a mathematical routine in the Kubios HRV 2.2 program (MATLAB, Kuopio, Finland) according to the guidelines presented in the task force of the European Society of Cardiology and the North American Society of Electrophysiology (Heart Rate Variability, 1996). Five minutes with greater signal stability, discarding the initial 30 seconds and the final 30 seconds of the collection.

Data analysis

The collection data were tabulated in a Microsoft Excel spreadsheet for a comparison of pre- and post-treatment data found in the evaluations. Data analysis was performed using the Bioestat® 5.2 program (Instituto Miramauá, Tefé, Brazil), for data normality the Shapiro-Wilk test was used and the data variance by the two-way Anova test with Tukey's post hoc. The analysis of demographic data by the chi-square test.

In addition to the aforementioned tests, the possible influence of treatments was tested using an effect measure (Effect size) to compare the two groups. For this, the Cohen's d pooled method was used. This analysis was performed using the "Effect Size Generator" application, version 2.3 (Swinburne University of Technology, Center for Neuropsychology, Melbourne, Australia). The results were interpreted as proposed by Cohen (1988), considering a value below 0.49 as a small effect, between 0.5 and 0.79 as a medium effect, and between 0.8 and 1.29 as a large effect, considering insignificant values below 0.19.

Values of $p < 0.05$ were considered statistically significant.

Results

Figure 1 shows the flowchart of patients participating in the study. Included patients were randomized and allocated into two groups. Some patients developed complications and were excluded from the study. Totaling an $n = 25$ for analysis of results, 12 in the CG and 13 in the EG.

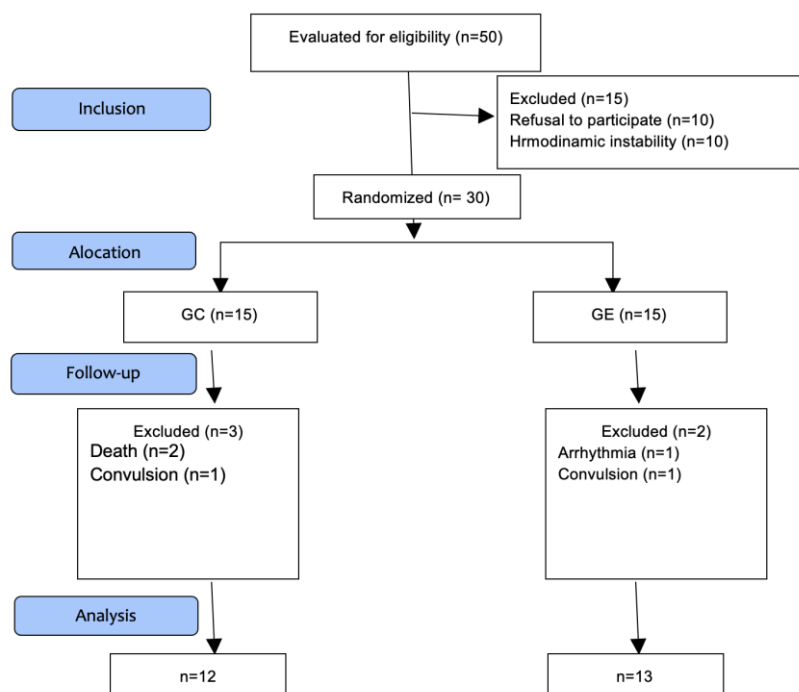


Figure 1. Flowchart of patients involved in the study. CG: Control group; EG: Experimental group.

Table 1 shows the clinical and demographic characteristics of the research patients, with homogeneity between the groups. After the protocol, the mean time spent on IMV of the patients was analyzed, resulting in a significant p value (0.01). PICU length of stay and hospital stay, despite being shorter in the EG, did not result in significant values.

Table 1. Clinical and demographic characteristics of the research patients.

Characteristic	CG (n=12)	EG(n=13)	P
Age (years)	5.7 ± 3.2	7.8 ± 3.6	0.4
Female (n)	8	9	0.8
Male (n)	4	4	1.0
Underlying Disease			
Kidney failure (n)	3	5	0.8
Postoperative chest drainage (n)	3	3	1.0
Subdural hematoma drainage (n)	1	1	1.0
Septic Shock	5	4	0.8
Drugs (n)*			
Dobutamine	12	13	0.9
Adrenaline	10	10	1.0
Rocuronium bromide	6	6	1.0
Dormonid	9	10	0.9
Midazolam	6	8	0.7
Fluconazole	5	8	0.5
Ciprofloxacin	6	9	0.4
Amikacin	8	6	0.7
Vancomycin	9	8	0.9
Prednisolone	2	2	1.0
Time of ventilation until the beginning of the protocol (hours)	68±22.7	75±17.3	0.3
Time of ventilation after the beginning of the protocol (hours)	53±15.2	29±17.3	0.01
Length of PICU stay (days)	17±15.5	14±10.2	0.1
Length of hospital stay (days)	60±30.2	55±31.2	0.4

CG: control group, EG: experimental group, p : value of significance.

Tables 2 and 3 show the intragroup analyzes of the HRV indices of the CG and EG, respectively. In the analysis of the GC, it is noted that the results of the p value of the variables, iR-R, SDNN, RMSSD, SD1 and SD2, at all times, did not demonstrate statistical significance. In the analysis of the EG, it can be observed that the results of the p value in the same variables resulted in statistically significant values ($p=0.01$; $p=0.01$; $p=0.001$; $p=0.001$ respectively).

Table 2. Heart Rate Variability indices analysis of the CG.

Indices	PRE	DAY 2	POST	p
iR-R (ms)	553.21±301.2	507.21±141.51	525.35±167.12	0.3
SDNN (ms)	21.35±11.21	15.45±12.12	17.2±14.27	0.4
RMSSD (ms)	30.15±20.21	23.42±10.45	25.15±20.19	0.35
SD1 (ms)	15.23±9.80	8.25±8.10	12.30±8.21	0.15
SD2 (ms)	20.2±9.1	15.34±12.05	17.23±15.21	0.15

iR-R: RR intervals; RMSSD: square root of the mean of the squares of the differences between consecutive RR intervals; SDNN: standard deviation of the mean of all normal RR intervals; SD1: dispersion of perpendicular points to the identity line; SD2: Measurement of standard deviations of the dispersion of Poincaré Plot points along RR intervals; Results expressed as mean ± standard deviation. PRE: pre-intervention period; DAY 2: second day of intervention. POST: post-intervention period.

Table 3. Heart Rate Variability indices analysis of the EG.

Índices	PRE	DAY 2	POST	p
iR-R (ms)	457.53±211.5	511.35±230.46	774.45±282.34*	0.01
SDNN (ms)	11.35±10.21	27.45±26.12	57.16±29.67*	0.01
RMSSD (ms)	13.38±6.99	17.9±15.53	55.23±14.56*	0.001
SD1 (ms)	6.90±4.32	15.43±10.12	53.75±17.15*	0.001
SD2 (ms)	16.8±8	28.23±22.45	61.3±19.09*	0.001

iR-R: RR intervals; RMSSD: square root of the mean of the squares of the differences between consecutive RR intervals; SDNN: standard deviation of the mean of all normal RR intervals; SD1: dispersion of perpendicular points to the identity line; SD2: Measurement of standard deviations of the dispersion of Poincaré Plot points along RR intervals; Results expressed as mean ± standard deviation. PRE: pre-intervention period; DAY 2: second day of intervention. POST: post-intervention period.

The variables related to the analysis of intragroup and intergroup HRV are shown in Table 4. In the analyzes before and on the 2nd day of the protocol, the results found did not show statistical significance. However, in the post-protocol analysis of the groups, significant values are evidenced in all variables ($p=0.05$; $p=0.001$; $p=0.01$; $p=0.001$; $p=0.001$ respectively). The comparison between the CG and the EG regarding the sample effect size in all analyzes was classified as having a great effect ($TE=0.8$; $TE=1.2$; $TE=1.0$; $TE=1.2$; $TE=1.2$ respectively).

Table 4. Intragroup and intergroup analysis of variables related to heart rate variability.

Variables	CG pre	EG pre	P1	CG DAY 2	EG DAY 2	P2	CG post	EG post	P3	ES
i-RR (ms)	553.2±301.2	457.5±211.5	0.3	507.2±141.5	511.3±230.4	0.5	525.3±167.1	774.4±282.3	0.05	0.8
SDNN (ms)	21.3±11.2	11.3±10.2	0.1	15.5±12.1	27.4±26.1	0.6	17.2±14.2	57.1±29.6	0.001	1.2
RMSSD (ms)	30.1±20.2	13.3±6.9	0.1	23.4±10.4	17.9±15.5	0.8	25.1±20.1	55.2±14.5	0.01	1.0
SD1 (ms)	15.2±9.8	6.9±4.3	0.1	8.2±8.10	15.4±10.1	0.6	12.3±8.2	53.7±17.1	0.001	1.2
SD2 (ms)	20.2±9.1	16.8±8	0.6	15.3±12.0	28.2±22.4	0.6	17.2±15.2	61.3±19	0.001	1.2

iR-R: RR intervals; RMSSD: square root of the mean of the squares of the differences between consecutive RR intervals; SDNN: standard deviation of the mean of all normal RR intervals; SD1: dispersion of perpendicular points to the identity line; SD2: Measurement of standard deviations of the dispersion of Poincaré Plot points along RR intervals; Results expressed as mean ± standard deviation; CG: control group; EG: experimental group; PRE: pre-intervention period; DAY 2: second day of intervention. POST: post-intervention period; ES: Sample effect size. P1: p-value between pre-protocol CG and EG; P2: p value between CG and EG on the second day of the protocol; P3: p value between CG and EG post protocol. $p < 0,05$.

Discussion

This study investigated the effects of two physiotherapeutic protocols, the experimental protocol, based on physical exercise, which improved autonomic HR modulation and reduced IMV time compared to a conventional physiotherapy protocol in children with VAP.

Recent studies have sought to analyze the effects of physical exercise on the HRV of sedentary and obese children, these have shown benefits in autonomic function (Santos & Borges, 2018; Veijalainen et al., 2019). Such promising repercussions can be compared to the results of the present research, since the proposed protocol is based on exercise physiology, and its effects act directly on the systems, especially the cardiovascular system.

Thus, it is noted that the variables corresponding to the parasympathetic response (RMSSD and SD1) and the variables corresponding to the global variability of HR (SD2 and SDNN), showed a statistically significant difference between the CG and EG groups, with higher values in the EG. In this sense, in a recent study (Rocha, Santos, Oliveira, Avila, & Rocha, 2019) on the effects of an exercise protocol in children with VAP, higher values were observed in the non-linear HRV variables in the intervention group, demonstrating that performing this conduct can improve the autonomic modulation of HR.

However, the measurement of the effects caused by physical exercise is not yet fully established in the current literary collection when it comes to HRV, especially in critically ill pediatric patients. In view of this, it is clear that the outcomes of the present study had a great effect on all the variables studied, suggesting that rehabilitation through physical exercise is essential for the proper functioning of the body.

Children who did not perform the exercise protocol showed a reduction in the global variability of HR, suggesting an inefficient adaptation of the ANS and physiological malfunction (Gardim et al., 2014). In this sense, the immobility associated with the response to critical illnesses can lead to anatomical and physiological changes such as cardiovascular and pulmonary deconditioning and changes in the inflammatory cascade (Piva et al., 2019).

On the other hand, high values of global HR variability are related to greater effectiveness of responses to internal and external stimuli to the body and can be associated with the beneficial influence of the proposed protocol in the regulation of autonomic modulation (Marsillio, Manghi, Carroll, Balmertl, & Wainwright, 2019).

Critical pediatric patients on IMV often develop VAP and have worse outcomes in hospital and PICU length of stay. As far as is known, there are no significant findings in the literature, where they report the relationship of autonomic dysfunction in VAP. However, the study by Aliberti et al. (2016) reported an autonomic dysregulation with the occurrence of community pneumonia, which predicts a high risk of morbidity and mortality. Another study (Annane et al., 1999) states that septic shock and sepsis are among the main causes of autonomic dysregulation. Thus, it can be suggested that the time of IMV associated with VAP may be related to abnormal and insufficient adaptation of the ANS.

At the same time, studies (Walker & Kudchadkar, 2018; Smith, Grami, Haseeb, & Ababio, 2019) on the influence and effects of physical exercise in critically ill patients have investigated several factors, such as patient safety, ambulation capacity, muscle strength, duration of IMV, length of stay in the ICU, length of hospital stay and mortality, in addition to functional outcomes such as activities of daily living. Demonstrating that physical therapy can play an essential role in reducing ongoing physical and neuropsychological impairments, both in the short and long term.

Currently, several physiotherapy protocols based on physical exercise in PICU patients have been developed. These include exercises such as: stretching, passive mobilization, functional joint positioning, active-assisted, active-resisted kinesiotherapy, postural transfers, cycle ergometer in upper and lower limbs and orthostasis (Doiron, Hoffmann, & Beller, 2018), which seek to prevent complications and minimize the adverse effects of prolonged immobilization in bed.

It was observed that the IMV time of patients in the PICU after the application of the rehabilitation protocol of the EG compared to the CG was significantly shorter, with a mean difference of 24 hours. This result agrees with the study by Arteaga et al. (2018) who point out the effects of physical exercise in the reduction of some days of IMV (5.1 days to 3.3 days).

In view of this, there are beneficial effects of this conduct, which suggests preventing deleterious complications of immobility, such as: pulmonary edema, atelectasis, blood clots, bone demineralization, loss of muscle mass, contractures, which allows for a shorter IMV time and reduction of morbidity and readmission risks (Drolet et al., 2013). However, the systematic review by Cuello-Garcia, Mai, Simpson, Al-Harbi, and Choong (2018) concludes that the effectiveness of physical exercise-based physical therapy in pediatrics is still undetermined due to the low certainty of the available evidence, despite being feasible and safe in critically ill children.

Although the length of stay in the PICU and hospital was shorter in the EG after the intervention, these results did not show statistical significance. This data agrees with the study by Machado et al. (2017), which did not show significant results in reducing the number of days spent in hospital. However, it contrasts with what was observed in the clinical trial by Morris et al. (2008), which adopted an exercise protocol and this promoted a reduction in time and costs in the intensive care unit and hospital when compared to patients who received usual care.

For a long time, physical therapy in critically ill children was associated with risks, potential complications, hemodynamic instability, accidental tube displacement and/or accidental extubation, falls and anxiety. Despite this, several studies report that physical exercise in the PICU is safe when proper precautions are taken and the mobility levels are adequate for the acuity level. The study Choong et al. (2017) randomized patients into two groups, to perform cycle ergometer in bed and the other to conventional physical therapy, there were no adverse events in any of the patients who performed the protocol.

Abdulsatar, Walker, Timmons, and Choong (2013) did not report adverse events related to the use of Nintendo Wii boxing as an exercise modality. The great initiative by Wieczorek, Burke, Al-Harbi, and Kudchadkar (2015) to implement an early rehabilitation program, entitled "PICU UP!", with 200 patients from a PICU in Baltimore, USA, did not show adverse events or complications that required therapy or additional cost, as in the present study.

Limitations

Finally, it is worth noting that the present study has limitations, such as the non-standardization of drugs and a variety of underlying diseases. In addition, the small number of scientific publications on HRV in pediatric critically ill patients was limiting, which limited the comparison of results with other studies.

Conclusion

It was concluded that the application of the physiotherapeutic rehabilitation protocol, based on physical exercise, in children with VAP in the PICU promoted an increase in HRV indices and a reduction in IMV time. However, there was no significant decrease in the length of hospital stay.

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