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Prognostic Value of Blood Lactate and Base Deficit in Refractory Cardiac Arrest Cases Undergoing Extracorporeal Life Support

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Abstract

Objective: Cardiac arrest (CA) resuscitation is associated with an 'ischaemia-reperfusion' syndrome characterised by lactic acidosis as assessed by lactate and base deficit (BD). Both biomarkers are usually measured in patients suffering from refractory CA (RCA) subjected to extracorporeal life support (ECLS) to evaluate tissue reperfusion. However, their prognostic value has never been compared. The aim of the present study was to compare the prognostic value of both biomarkers measured at 0 and 3 h after the initiation of ECLS in patients with RCA on mortality.

Methods: Patients who were admitted to the intensive care unit with RCA were consecutively included in the study.

Results: Sixty-six patients were included. Lactate correlated with BD ($R2=0.44$, $p<0.001$). An area under the curve of 0.72 (95% confidence interval (CI) 0.59-0.84) was found for lactate and of 0.60 (95% CI 0.46-0.73) for BD. Using multivariable logistic regression, lactate (odds ratio (OR) 1.22, 95% CI 1.03-1.48) remained associated with mortality on day 28, but not BD (OR 0.99, 95% CI 0.86-1.14).

Conclusion: We report a difference in the prognostic value of lactate and BD on mortality. Three hours from the initiation of ECLS in patients with RCA, lactate should be preferred to BD to predict the efficiency of ECLS.

Keywords: Base deficit, blood lactate, extracorporeal life support, prognosis, refractory cardiac arrest

Introduction

Death caused by cardiac arrest (CA) reaches approximately 0.5-1 per 1000 individuals annually (1, 2), with a survival rate of 12% at hospital discharge in the United States (3). Refractory CA (RCA) is defined as the failure of advanced life support (ALS) (4). The exact moment when resuscitation measures are considered inefficient remains controversial between countries (4, 5). In France, CA is considered refractory upon 30 min of ALS measures (5). In this case, the prehospital medical team must decide between the termination of ALS, organ donation after eligibility and the implementation of extracorporeal life support (ECLS) in- or out-of-hospital. In RCA, ECLS used to maintain an efficient peripheral circulation is shown to improve survival (6-8). However, the exact indication of ECLS in RCA has not yet been clearly established. Nevertheless, patients eligible for ECLS resuscitation are currently highly selected to avoid failure and the maintenance of a circulation when resuscitation is hopeless (9, 10).

During resuscitation, an 'ischaemia-reperfusion injury' occurs, leading to multiorgan failure (11, 12). Multiorgan failure results from a flow-demand mismatch, inducing vasoconstriction and other dysfunctional responses responsible for tissue hypoperfusion. On the biological level, blood lactate increases, and base deficit (BD) decreases, resulting in lactic acidosis. Therefore, blood lactate and BD are useful biomarkers reflecting the intensity of the ischaemia-reperfusion syndrome occurring in CA (13). Treatment of CA aims at restoring an efficient circulation to restore adequate tissue perfusion. Interestingly, blood lactate and BD were associated with increased mortality in pa-

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tients treated by ECLS in the context of RCA (13). Additionally, blood lactate concentration ≥2.1 mmol L^{-1} was shown to predict premature ECLS discontinuation (14). Le Guen et al. (7) reported a significant difference in blood lactate clearance during the first hour of ECLS between patients who survived less versus more than 24 h.

However, the two biomarkers, blood lactate and BD, are not completely equivalent. BD reflects the acid-base status and can be influenced by fluid loading, i.e. isotonic sodium chloride that can induce chloride acidosis (15). Blood lactate mainly reflects lactic acidosis as influenced by other factors, such as decreased hepatic clearance or toxic insults (16). The prognostic value of both biomarkers was previously evaluated (13). However, both parameters have not yet been compared to evaluate the early efficiency of ECLS in the prognosis of patients with RCA under ECLS (13, 14, 17, 18).

The aim of this observational cohort study was to assess the impact of blood lactate and BD at 3 h (H3) from the initiation of ECLS on mortality on day 28 in patients with RCA.

Methods

Study population

All consecutive patients who were admitted to the intensive care unit (ICU) of Necker University Hospital for RCA from January 2011 to January 2016 were included in the study. All causes of out-of-hospital CA were enrolled in the study excluding traumatic injuries. ECLS was initiated upon 30 min of ALS measures in the prehospital setting or at ICU admission.

Data were retrieved from prehospital and hospital medical records.

The study was approved by the local ethics committee in accordance with the French legislation (Comité de Protection des Personnes, Est 3, Nancy, France). Patient consent was waived for participation in this observational study (no. 17.12.05).

Blood lactate and BD measurements

Blood samples including blood lactate and BD levels were obtained from arterial access at baseline when ECLS was initiated (H0) in the ICU or in the prehospital setting and at 3 h after the initiation of ECLS (H3) in the ICU. Blood sample analyses were immediately performed using an arterial blood gas analyser (ABL 800 FLEX, Radiometer©; Copenhagen, Denmark) according to the manufacturer's instructions including daily calibration and quality control checks.

As, considering the Henderson-Hasselbalch theory, arterial pH is influenced by carbon dioxide arterial partial pressure ($PaCO_2$) and bicarbonate (HCO_3^-) levels, we decided to focus our attention on lactate and BD to assess metabolic disturbance.

The normal level of lactate was defined as ≤2.2 mmol L^{-1} (19). Stratification of lactate levels was performed as follows: ≤2.2, 2.3-5.0, 5.1-9.9 and ≥10 mmol L^{-1}. These strata were reported to be associated with different mortality levels in traumas (19).

Base deficit was calculated using the following equation: Base deficit=125.58−(13.77×arterial pH)−(0.02786×carbon dioxide partial pressure×$10^{(pH-6.1)}$) [19]. The normal level of BD was defined as ≤2.2 mmol L^{-1}. Stratification of BD levels was defined as previously reported in traumas as follows (20): ≤2.2, 2.3-6.0, 6.1-9.9 and ≥10 mmol L^{-1}.

Therapeutic management of patients

As previously described, all patients were treated by the same medical team of critical care physicians (13). Protocols for the management of critically ill patients did not change over the study period, thus ensuring no major discrepancies between patients with respect to organ supports and therapies.

Haemodynamic support was achieved by ECLS (Cardiohelp System®; Maquet, Rastatt, Germany), which was set up via venous-arterial femoral cannulation by two experienced ICU physicians. Mean blood pressure target was 50-60 mmHg. To prevent coagulation of the ECLS membrane oxygenator, unfractionated heparin was intravenously administered at low dose during ECLS, with repeated controls to maintain the activated clotting time ratio >2.0.

Sedation was started as soon as possible. All patients were sedated with midazolam 0.1 mg kg^{-1} h^{-1} plus sufentanil 0.2 μg^{-1} h^{-1} and paralysed with atracurium 0.1 mg kg^{-1} h^{-1} (dose was adjusted to obtain a neuromuscular response ≤2 at the 'train of four' monitoring). Sedation status was monitored using bispectral index (BIS monitor®; Covidien, Boulder, CO, USA). Ventilation was adjusted to obtain a $PaCO_2$ of 40 mmHg and an oxygen arterial partial pressure (PaO_2) of between 100 and 200 mmHg. Minimum lung ventilation was maintained to avoid pulmonary collapse with a tidal volume of 5 mL kg^{-1}, a respiratory rate of 8 min^{-1} and a positive end-expiratory pressure of 5 cm H_2O. Central venous oxygen saturation ($ScVO_2$) was continuously monitored with the aim of achieving an $ScVO_2$ >70%. Fluid expansion (fluid administration 30 mL kg^{-1} day^{-1} of isotonic sodium chlorine) and catecholamines (dobutamine 5 µg kg^{-1} min^{-1} and norepinephrine) were adjusted to obtain a mean blood pressure between 50 and 60 mmHg and to prevent pulmonary oede-

ma. Blood transfusion was performed to achieve a target of haemoglobin 10 g dL^{-1}, platelets 100,000 mm^{-3}, fibrinogen >1.5 g L^{-1} and prothrombin rate >50%.

If return of spontaneous circulation occurred, the haemodynamic status was monitored by echocardiography and continuous cardiac output monitoring devices (Vigileo®; Edwards Lifesciences, Irvine, CA, USA) to decide the proper time to remove ECLS.

Mild therapeutic hypothermia was performed during the first 12-24 h following ICU admission. Central body temperature was maintained between 32°C and 34°C using external cooling (ice packs placed on femoral and humeral vessels) and ECLS thermoregulatory device.

Statistical analysis

The primary endpoint was mortality on day 28 in the ICU.

Analyses were performed according to the guidelines for reporting the risk marker (21-23). Unpaired Student's t-test was used for comparison of two means. Mann-Whitney U test was used for comparison of two medians, and Fisher's exact test was used for comparison of proportions. Correlation between two variables was assessed using logistic regression analysis.

The predictive performance of lactate and BD for mortality on day 28 was evaluated using unadjusted averaged receiver operating characteristic curves obtained by averaging 1000 populations bootstrapped (sampling with replacement) from the original study population. All p-values were two sided. A p-value <0.05 was considered significant.

We first performed a univariate analysis between all covariates, followed by a multivariable logistic regression. The multivariable logistic regression model included age, no-flow, low-flow and ECLS implementation in the prehospital setting or at ICU admission to assess the association of blood lactate and BD with mortality on day 28. The effect of no-flow time duration on lactate and BD was analysed in the model.

Liver biological parameters were not included in the model considering that the time was too short to enable significant changes.

Data are expressed as mean±SD for quantitative variables or absolute value (percentage) for qualitative variables.

All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

Study characteristics

A total of 66 patients with RCA treated by ECLS were included in the study. The main characteristics of the studied population are reported in Table 1. Of the 66 patients, 51 (77%) were male. Mean no-flow time was 2±3 min, and low-flow time reached 94±29 min. Acute coronary syndrome was the major cause of CA, which occurred in two-thirds of the cases (Table 2). Owing to persistent haemodynamic instability despite ECLS, coronary angiogram was not performed to all patients to identify the cause of CA. For those patients without coronary angiogram, acute coronary syndrome was suspected by clinical history and electrocardiogram. ECLS was set in the prehospital setting for 26 (39%) patients and at ICU admission for 40 (61%) patients. Arterial blood lactate and BD were measured for all patients at H0 and H3 from ECLS initiation (no missing data for both parameters). No patient had previous comorbidities that could affect lactate metabolism.

Table 1. Characteristics of patients with RCA 3 h after starting ECLS

	Mean±SD
Age (years)	51±14
Weight (kg)	89±23
Height (cm)	175±14
No-flow (min)	2±3
Low-flow (min)	94±29
Length of stay in the ICU (days)	13±18
pH	7.32±0.17
$PaCO_2$ (mmHg)	34±11
PaO_2 (mmHg)	178±98
BD (mmol L^{-1})	8.6±6.4
Lactate (mmol L^{-1})	10.5±5.4
Serum creatinine (mmol L^{-1})	112±43
Troponin (ng mL^{-1})	81,006±178,589
Haemoglobin (g L^{-1})	11±3

RCA: refractory cardiac arrest; ECLS: extracorporeal life support; SD: standard deviation; ICU: intensive care unit; $PaCO_2$: carbon dioxide arterial partial pressure; PaO_2: oxygen arterial partial pressure; BD: base deficit

Table 2. Suspected aetiologies of RCA

Aetiology	n (%)
Acute coronary syndrome	44 (67)
Drugs intoxication	5 (8)
Hypertrophic cardiomyopathy	4 (7)
Hypothermia	4 (7)
Pulmonary embolism	1 (2)
Undefined	6 (9)

RCA: refractory cardiac arrest

Lactate and BD

Both baseline lactate and BD levels were elevated in all patients, with mean values of 10.6±5.4 mmol L^{-1} and 8.6±6.4 mmol L^{-1}, respectively (Table 1).

Association with death occurrence

Death occurred in 40 (61%) patients. An area under the curve (AUC) of 0.72 (95% confidence interval (CI) 0.59-0.84; p=0.008) was found for blood lactate and of 0.60 (95% CI 0.46-0.73; p=0.16) for BD for mortality on day 28. No difference was found between the AUC of blood lactate and BD (p=0.24) for mortality on day 28 (Figure 1). When considering the predefined class of both biomarkers, a visual subjective analysis suggested that the relationship between blood lactate categories and mortality on day 28 was linear, whereas that of BD was not (Figure 2). At H3, univariate analysis revealed significant differences between alive and deceased patients for the length of stay in the ICU (p<0.001), pH (p=0.04), PaO_2

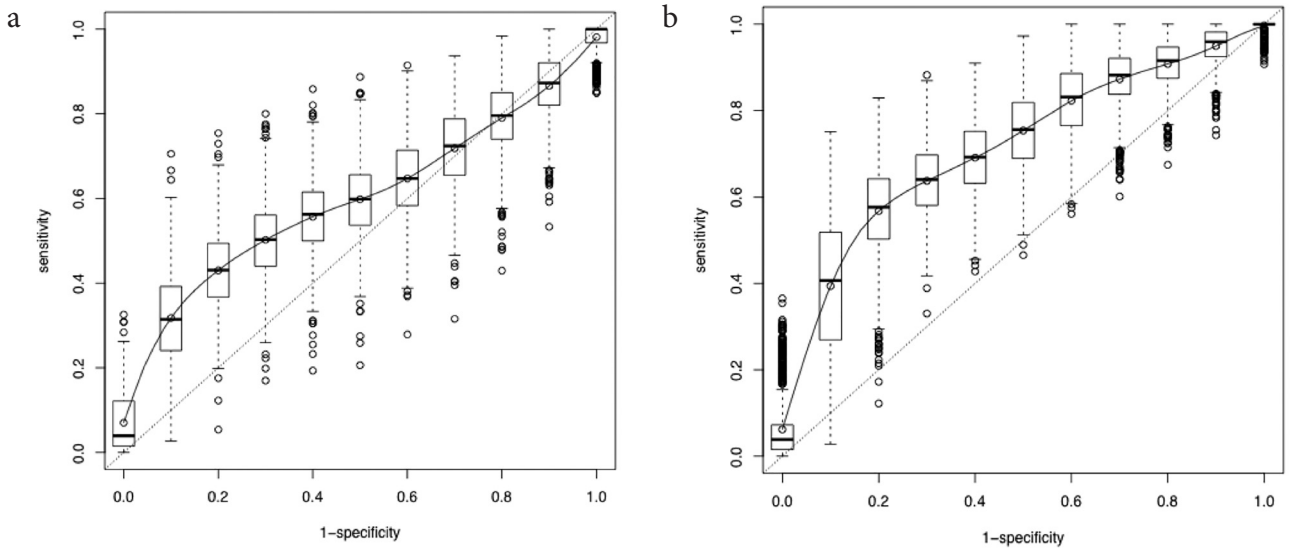

Figure 1. a, b. Average receiver operating characteristic (ROC) curves of base deficit and blood lactate at 3 h of the initiation of ECLS to predict mortality on day 28 of patients with refractory cardiac arrest treated by ECLS. ROC curves evaluating the prognosis value of base deficit (a) and lactate (b) at H3 to predict mortality on day 28 are represented by the solid line. The dotted line corresponds to the non-discrimination curve

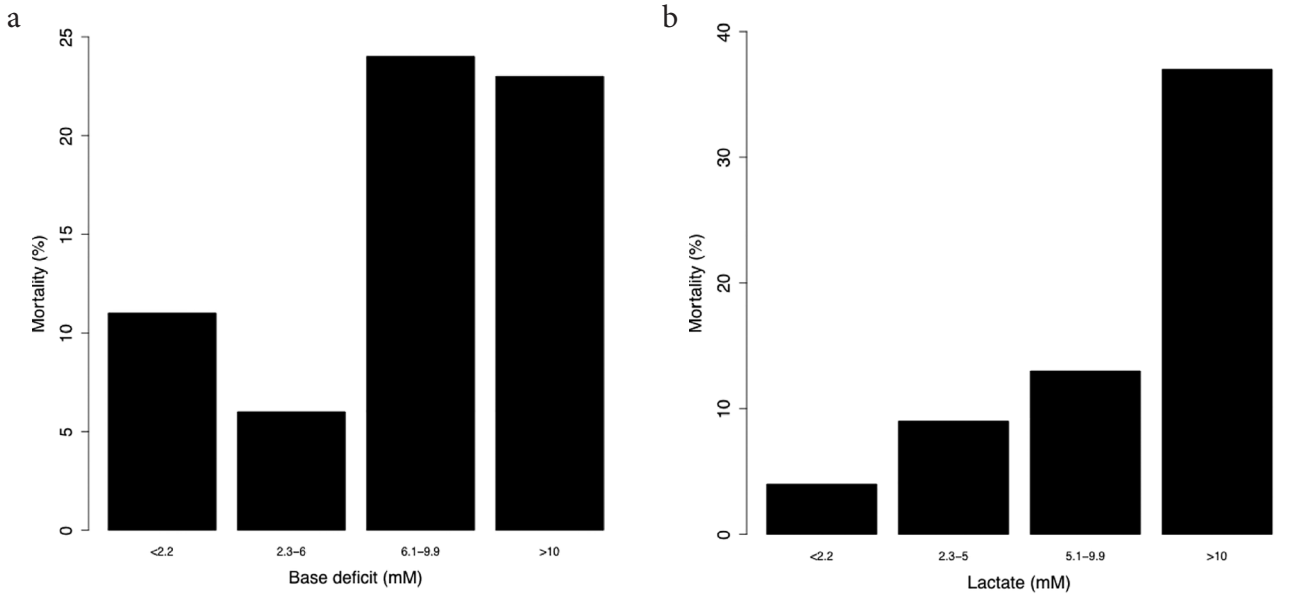

Figure 2. a, b. Mortality on day 28 in the predefined categories of blood lactate and base deficit 3 h after starting ECLS. Base deficit (a) and lactate (b) range levels are given according to mortality rate

Table 3. Results of univariate analysis

	Alive (n=21) Mean±SD	Deceased (n=40) Mean±SD	p
Age (years)	49±15	52±14	0.522
Weight (kg)	87±26	89±22	0.734
Height (cm)	173±20	176±9	0.364
No-flow (min)	2±3	3±3	0.373
Low-flow (min)	88±22	97±32	0.21
Length of stay in the ICU (days)	28±21	4±7	<0.001*
pH	7.37±0.11	7.28±0.20	0.04*
$PaCO_2$ (mmHg)	32±5	36±14	0.156
PaO_2 (mmHg)	148±98	198±93	0.049*
BD (mmol L^{-1})	7.0 (4.2-8.6)	8.5 (5.3-14.7)	0.162
Lactate (mmol L^{-1})	8.6 (4.2-11.2)	12.9 (8.6-15.0)	0.008*
Serum creatinine (mmol L^{-1})	98±41	122±43	0.042*
Troponin (ng mL^{-1})	505 (30-4.5×10^3)	1107 (33-1.2×10^3)	0.324
Haemoglobin (g L^{-1})	11.4±2.9	10.6±3.0	0.31

*p<0.05. Data are expressed as mean with SD and as median with interquartile range (25^{th}-75^{th} percentile) for troponin, BD and lactate. A p value <0.05 is considered significant. SD: standard deviation; ICU: intensive care unit; $PaCO_2$: carbon dioxide arterial partial pressure; PaO_2: oxygen arterial partial pressure; BD: base deficit

Table 4. Results of multivariable logistic regression analysis

	OR (95% CI)	p
Lactate H3	1.22 (1.03-1.48)	0.03*
Base deficit H3	0.99 (0.86-1.14)	0.89
No-flow	1.18 (0.74-1.89)	0.48
Low-flow	1.00 (0.97-1.03)	0.96
Age	1.02 (0.98-1.08)	0.33
In-/out-of-hospital ECLS	2.75 (0.71-12.02)	0.15
No-flow×lactate H3	0.99 (0.94-1.04)	0.59
No-flow×base deficit H3	1.01 (0.97-1.04)	0.76

*p<0.05. Results are expressed in OR with 95% CI. A p value <0.05 is considered significant. In-/out-of-hospital ECLS corresponds to ECLS implementation in the prehospital setting or at ICU admission
OR: odds ratio; CI: confidence interval; H3: 3 h after the initiation of ECLS; ECLS: extracorporeal life support

(p=0.049), blood lactate (p=0.008) and serum creatinine (p=0.042) (Table 3). No difference was found between mortality on day 28 and age, weight, height, no-flow, low-flow, $PaCO_2$, BD, troponin and haemoglobin (Table 3). In the multivariable logistic regression model, including age, no-flow, low-flow and ECLS implementation in the prehospital setting or at ICU admission, only blood lactate remained significantly associated with mortality on day 28 (odds ratio (OR) 1.22, 95% CI 1.03-1.48; p=0.03). No association was found for BD (OR 0.99, 95% CI 0.86-1.14; p=0.89) (Table 4). No-flow and low-flow times were not significantly associated with mortality on day 28 (Table 4).

Discussion

The present study reports that blood lactate level measured 3 h from the initiation of ECLS in patients with RCA who were admitted to the ICU, but not BD, is associated with mortality on day 28. Therefore, we suggest using blood lactate as a tool in scoring systems to assess the prognosis of patients with RCA treated by ECLS.

Blood lactate and BD were already reported as prognostic biomarkers in out-of-hospital patients with RCA due to acute coronary syndrome treated by ECLS (13) and in patients with trauma (15, 19). Both variables were associated with poor outcome during ECLS (13). However, few studies compared their value in the context of RCA prognosis (17, 18). Blood lactate and BD levels might be interesting tools to evaluate the efficiency of tissue perfusion accounting for the quality of resuscitation measures after CA (24-27). However, the concept of lactate clearance, more precisely called 'lactate shift,' was reported to be more relevant as it describes change in lactate concentration over time taking into account both the production and elimination of blood lactate. This concept avoids the use of physiological terminology (28) and is an independent prognostic factor providing additional critical information to blood lactate (29). In our study, despite a significant correlation between lactate and BD, the regression coefficient suggested that lactate and BD were not interchangeable. Actually, blood lactate was a significant predictor of mortality on day 28 with an AUC superior to 0.74, whereas BD was below

significance. Moreover, the prognostic value of blood lactate to assess mortality on day 28 was observed in a univariate analysis and was also supported by the multivariable model.

A possible explanation of the ability of blood lactate, but not BD, to predict mortality could be that fluid loading based on saline serum induces hyperchloremic acidosis, thus reducing the impact of BD (30). Generally, patients with poor outcome require more fluid loading to maintain blood pressure objectives. Additionally, fluid loading leads to haemodilution, modifying protein concentration and thus the acid-base equilibrium (31). Conversely, the effect of carbon dioxide pressure modification on the acid-base equilibrium did not appear to be involved in our study. We cannot strictly rule out that ischaemic effects on liver function affected lactate levels. However, within the short term, this hypothesis is unlikely. Further studies should be performed to test the impact of lactate clearance, ion difference and phosphate or albumin concentration changes and the role of unmeasured anions on mortality in the context of ECLS (32).

The present study has limitations. First, this study is monocentric with a small sample size. Second, our study was performed in a country where the prehospital system includes physicians who are dispatched to the scene to initiate treatments. Therefore, ECLS can be set in the prehospital setting, which is not the case in all countries. In the present study, one-third of the patients received ECLS before their ICU admission. As ECLS was set in the same time range for all patients, meaning as soon as CA was considered refractory, the place where ECLS was set is unlikely to affect our results. To strengthen our results, the multivariate model was adjusted on this parameter. Third, our time points are arguable. We decided to early assess the quality of ECLS. Blood lactate and BD were measured at 3 h from the initiation of ECLS considering this time point as an appropriate time to evaluate ECLS efficiency in restoring tissue perfusion and further improve ECLS settings. Fourth, we cannot totally exclude the role of hyperoxaemia to partly explain the differences between alive and deceased patients. A significant association between hyperoxaemia and poor outcome, such as mortality, has been observed in patients with CA (33-35). Nevertheless, the threshold to define severe hyperoxaemia in patients with CA remains under debate (36).

Conclusion

We report an association between blood lactate and BD values measured 3 h from the initiation of ECLS and mortality on day 28. We suggest using blood lactate level at 3 h from the initiation of ECLS in patients with RCA to early evaluate the efficiency of ECLS and to predict patient's mortality on day 28. This marker could help improve the management of patients with RCA.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Comité pour la Protection des Personnes Est 3, Nancy, France (no. 17.12.05).

Informed Consent: Written informed consent was obtained from patients the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.J.; Design – R.J.; Data Collection and/or Processing – R.J., P.P.; Analysis and/or Interpretation – R.J., A.S.; Writing Manuscript – R.J., A.S.; Critical Review – A.S., P.P., P.C., B.V.

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