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Is the creatine kinase isoenzyme MB level a marker of myocardial ischemia in ventilated premature infants?

O nível sérico de creatinofosfoquinase fração MB serve como marcador de isquemia miocárdica em recém-nascidos prematuros ventilados?

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ABSTRACT

Introduction: It is not clear whether the levels of troponin I (TI) and creatine kinase isoenzyme MB (CK-MB) are changed in premature infants (PI) without evidence of myocardial ischemia (MI). **Objectives:** To investigate whether TI and CK-MB change their levels in newborns without MI while on mechanical ventilation (MV). **Methods:** We conducted a prospective cohort study in which 165 PI were divided into control group ([CG]; $n = 68$), mechanical ventilated group ([VG]; $n = 21$) and a surfactant therapy group ([SG]; $n = 76$), and had their TI, creatine kinase (CK) and CK-MB levels were determined. After the division, within the first four hours after the introduction of the mechanical ventilation (MV) and one hour after the withdrawal of it, we performed a new measurement of TI, CK and CK-MB to all PI from VG and VS. We used the chi-square test to evaluate the association among qualitative variables and the Kruskall-Wallis test to compare the serum levels of TI, and CK-MB among the groups, before, during and after MV using the statistical package SPSS 16.0 software. **Results:** TI, CK, and CK-MB serum values before the groups were divided were considered normal. The TI concentration among the groups before and after MV ($p > 0.05$) did not changed; however, the CK-MB levels were higher in VG when compared to the CG ($p = 0.009$). **Conclusion:** The increase of CK-MB serum levels in VG and SG seems to indicate an increased work of thoracic skeletal muscle and do not represent a MI signal, which invalidate its use as a marker.

Key words: premature infant; newborn; troponin I; creatine kinase MB form; mechanical ventilation.

INTRODUCTION

The detection of silent myocardial ischemia (SMI) in premature infants (PI) with hyaline membrane disease (HMD) receiving mechanical ventilation (MV) remains a challenge[1-3]. SMI markers used for diagnoses in adults, such as troponin I (TI) and creatine kinase isoenzyme MB (CK-MB), are still the gold standard due to their effectiveness and low cost[4-13]. Therefore, we have decided to investigate whether TI and CK-MB change their levels in newborns without SMI.

METHODS

We carried out a prospective study between November 2010 and February 2013 at the Neonatal Intensive Care Unit in the Hospital Universitário Antônio Pedro of the Universidade Federal Fluminense (UFF) in Niterói (RJ), Brazil. One hundred and sixty-five PI were selected for convenience, among them 68 PI had no disease (control group [CG]). Ninety-seven PI had HMD confirmed by clinical and radiological examinations; they were divided into two groups: the mechanical ventilated group ([VG]; $n = 21$) and the surfactant therapy group ([SG]; $n = 76$); the latter group included treatment with exogenous surfactant in the PI. The gestational age of the newborn was calculated based on the obstetric ultrasound examination and by New Ballard score. Premature infants with congenital heart disease and detectable genetic disease revealed by physical examination or newborns who needed to be resuscitated at birth or required more than one cycle of MV were not included in the study. The newborn that was selected for the VG and then required use of surfactant was included in the SG. The TI, creatine kinase (CK) and CK-MB dosages were determined

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in all PI before the newborns were divided into groups. TI, CK and CK-MB dosages were dispensed to all PI within the first four hours after the initiation of MV and only in the first MV cycle and also in the first dose of surfactant, and after the withdrawal of MV. In the CG the same laboratorial examinations were also performed in the first four hours of life. The TI dosage was determined by the ELFA® method. The CK and CK-MB dosages were determined by the enzymatic method (Dimension®). Electrocardiogram (ECG), echocardiography (ECHO), transfontanel ultrasonographic (TFUS) and ophthalmoscopy (OE) examinations were performed on all newborns eligible to participate in the study, at the initiation and at the withdrawal of MV. We used chi-square test (χ^2) to assess the association with the nonparametric variables, and we used the Kruskall-Wallis test to compare the TI and CK-MB average levels of the three groups (CG, VG and SG) before their division, during and after MV. We applied Dunn post-test at $p < 0.05$. The data were analyzed by SPSS 16.0 software. The 5% probability of error was considered acceptable.

The study was approved by the institutional ethics committee.

RESULTS

We did not record any changes in TI, CK and CK-MB concentrations in patients before the groups were divided. No changes were found in TI concentration among the groups before and after MV and/or before and after the use of exogenous surfactant ($p > 0.05$). When the PI of the three groups were compared in terms of TI, CK and CK-MB levels, pH and pO_2, the CK-MB values showed a significant difference compared to the CG levels ($p = 0.009$). However, there were no records on differences between VG and SG. There were no significant differences among the groups regarding the use of vasoactive amines, and the changes found in the ECG and ECHO were not related to myocardial dysfunction (**Table**).

DISCUSSION

The results of ECG and ECHO and TI concentrations before, during and after MV showed no variation, suggesting the absence of possible myocardial ischemic injury in the newborns analyzed. However, serum levels of CK-MB were increased in both VG and SG compared to CG and the concentration before MV. During MV, the mean values of CK-MB in VG infants were higher than in SG infants, which may be a clue/an indication that these children have a greater need to use their thoracic and diaphragmatic accessory muscles.

The ECHO changes in all groups were related to presence of patent ductus arteriosus and were not related to myocardial ischemic injury signs.

The CK-MB concentration in VG newborns is probably due to MV and it may be related to the intensity of how the ventilation parameters were modified due to the needs of each patient; the concentration may not be a marker of myocardial ischemia. This finding may explain the higher mean of CK-MB serum concentration in VG infants, because the use of surfactant contributes to reduce the fluctuations of the parameters that we have studied and to reduce the use of thoracic muscles. Even though the investigation of this circumstance was not our objective, we found that the high concentration of CK-MB has proved to be an indicator of thoracic muscle activity. The probability is that the

TABLE – Group characteristics

Variable	CG ($n = 68$)	VG ($n = 21$)	SG ($n = 76$)	p
Gestational age (week)	32.5 (27-36)	32.6 (27-36)	32.4 (27-36)	0.887*
Birth weight (g)	1318 (790-1,670)	1293.8 (790-1,590)	1249.1 (775-1,750)	0.127*
1-minute Apgar	6 (4-9)	6 (5-9)	6.5 (5-9)	0.319*
5-minute Apgar	8 (4-9)	9 (5-9)	7 (4-10)	0.402*
TI (µg/l)	0.02 (0-0.08)	0.02 (0.01-0.07)	0.02 (0.01-0.22)	0.874*
CK-MB (U/l)	38 (1-479)	303 (1-1058)	120 (6-3462)	0.009*
pH	7.3 (7.2-7.4)	7.3 (7.1-7.4)	7.3 (6.8-7.6)	0.203*
pO_2	74 (36-158)	57.5 (7-121)	78.7 (22-187)	0.374*
pCO_2	34 (19-46)	39 (24-90)	39 (18-244)	0.228*
Blood culture (+)	5 (7.4%)	0 (0%)	1 (1.3%)	0.221**
Abnormal ECG	2 (2.9%)	0 (0%)	3 (3.9%)	0.661**
Abnormal ECHO	20 (29.4%)	11 (52.4%)	36 (47.4%)	0.078**
Abnormal TFUS	28 (41.2%)	8 (38.1%)	22 (28.9%)	0.294**
Abnormal OE	4 (5.8%)	3 (14.3%)	6 (7.9%)	0.531**

*CG: control group; VG: ventilated group; SG: surfactant terapy group; TI: troponin I; CK-MB: creatine kinase isoenzyme MB; ECG: electrocardiogram; ECHO: echocardiogram; TFUS: transfontanel ultrasonography; OE: ophthalmoscopy; *: Kruskal-Wallis test. Dunn's post-test: (CK-MB) CG < VG = SG; **: chi-square test (χ^2).*

event will increase because removing MV allows the CK-MB serum concentration return to the levels observed in the CG newborns and to the values of the period before MV.

An increase in CK-MB concentration was detected in newborns with birth asphyxia who presented myocardial ischemia[16] and in other situations such as in patients who are susceptible to severe asthma[17] and cardiopulmonary post-resuscitation[18]. Therefore, the increase in CK-MB concentration is an ambiguous diagnosis.

The small number of children who only used ventilation ($n = 21$) is a limiting factor of this study and requires follow-up investigations.

CONCLUSION

Increases in CK-MB level in VG and SG infants may be a marker for increased thoracic skeletal muscle work and not a signal for myocardial ischemia.

RESUMO

Introdução: *Não está claro se os níveis séricos de troponina I (TI) e de creatinoquinase fração MB (CK-MB) estão alterados em recém-nascidos prematuros (RNP) sem indícios de isquemia miocárdica (IM).* ***Objetivo:*** *Investigar se os níveis de TI e CK-MB se alteram nos RNP sem IM quando em ventilação mecânica (VM).* ***Métodos:*** *Coorte prospectiva com 165 RNP que, antes de serem divididos em grupo-controle ([CG];* n = *68), ventilado ([VG];* n = *21) e surfactante ([SG];* n = *76), tiveram seus níveis séricos de TI, creatinoquinase (CK) e CK-MB determinados. Após a divisão, dentro das primeiras 4 horas do início da VM e 1 hora após sua retirada, realizamos nova dosagem de TI, CK e CK-MB nos RNP dos VG e VS. Foram utilizados o teste do Qui-quadrado para avaliar a associação entre as variáveis qualitativas e o teste de Kruskall-Wallis para comparar os valores séricos de TI e CK-MB entre os grupos, antes, durante e depois da VM, usando o pacote estatístico SPSS 16.0.* ***Resultados:*** *Os valores séricos de TI, CK e CK-MB antes dos grupos serem divididos foram considerados normais. As concentrações de TI entre os grupos antes e depois da VM não se alteraram (*p > *0,05), entretanto as de CK-MB foram maiores nos ventilados em relação aos do CG (*p = *0,009).* ***Conclusão:*** *A elevação dos níveis séricos de CK-MB nos VG e SG parece indicar aumento do trabalho da musculatura torácica e não um sinal de IM, o que inviabiliza o uso desta como um marcador.*

Unitermos: *prematuro; recém-nascido; troponina I; creatinaquinase forma MB; ventilação pulmonar.*

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