Inflammation, High-sensitivity C-reactive Protein, and Persistent Patent Ductus Arteriosus in Preterm Infants

Inflamación, proteína C reactiva ultrasensible y persistencia del conducto arterioso permeable en pacientes prematuros

To the Editor,

Patent ductus arteriosus (PDA) affects 70% of preterm infants and is often associated with severe complications. Postnatal ductal closure is normally regulated by increased oxygen pressure and decreased prostaglandin E₂ level, which remains elevated in preterm infants. Cyclooxygenase is a key enzyme in prostaglandin synthesis and therefore cyclooxygenase inhibitors are used to treat PDA. However, many patients with PDA do not respond to treatment. Some studies have associated treatment failure with chorioamnionitis and sepsis, which are risk factors related to a systemic inflammatory response. Inflammation may increase cyclooxygenase-1 activity and prostaglandin E₂ production, implying that it is an important factor in persistent PDA. The ultrasensitive C-reactive protein test (us-CRP) can be used to

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### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Without AD (n = 631)</th>
<th>With AD (n = 228)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>65.8 ± 12.9</td>
<td>61.1 ± 11.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Women, %</strong></td>
<td>148 (23.5)</td>
<td>61 (26.8)</td>
<td>.320</td>
</tr>
<tr>
<td><strong>HTN, %</strong></td>
<td>372 (59.0)</td>
<td>135 (59.2)</td>
<td>.946</td>
</tr>
<tr>
<td><strong>Smoking, %</strong></td>
<td>227 (36.0)</td>
<td>100 (43.9)</td>
<td>.036</td>
</tr>
<tr>
<td><strong>Diabetes, %</strong></td>
<td>160 (25.4)</td>
<td>91 (39.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>GRACE</strong></td>
<td>150.3 ± 34.3</td>
<td>139.2 ± 35.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>TC</strong></td>
<td>158 [133 to 190]</td>
<td>172 [149 to 203]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td>96.8 [74.7 to 121.1]</td>
<td>95.3 [73.5 to 119.9]</td>
<td>.683</td>
</tr>
<tr>
<td><strong>TC/HDL-C</strong></td>
<td>4 [3.4 to 4.8]</td>
<td>5.5 [4.8 to 6.5]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>LDL-C/HDL-C</strong></td>
<td>2.4 [1.9 to 3.1]</td>
<td>3 [2.5 to 3.8]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>High-intensity statins on discharge, %</strong></td>
<td>420 (66.6)</td>
<td>143 (62.7)</td>
<td>.295</td>
</tr>
<tr>
<td><strong>Fibrates on discharge, %</strong></td>
<td>5 (0.8)</td>
<td>16 (7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>LDL-C &lt; 70 mg/dL at follow-up, %</strong></td>
<td>271 (42.9)</td>
<td>100 (43.9)</td>
<td>.829</td>
</tr>
<tr>
<td><strong>HDLC at follow-up, %</strong></td>
<td>61 (9.7)</td>
<td>107 (46.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Stroke/myocardial infarction at follow-up, %</strong></td>
<td>32 (5.1)</td>
<td>19 (8.3)</td>
<td>.074</td>
</tr>
</tbody>
</table>

AD, atherogenic dyslipidemia; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol. * Median [25th percentile to 75th percentile].

Our study highlights the lack of compliance with therapeutic goals and current recommendations on prescription of high-intensity statins in patients with ACS. The percentage reduction in LDL-C was much smaller than theoretically expected. This could have been affected by poor compliance with treatment and lifestyle modifications.

Statin therapy does not alter high-density lipoprotein cholesterol or triglyceride levels. The only drugs that have shown efficacy in increasing high-density lipoprotein cholesterol and reducing triglycerides are fibrates. However, there is little evidence on their benefits in patients with ACS and therefore recommendations on their use are not well established.

In conclusion, we found underuse of high-intensity statins in patients discharged with a diagnosis of ACS, which was not in line with current recommendations. High-intensity statins were associated with a greater LDL-C reduction and with achieving therapeutic goals, whereas lower-intensity statins were associated with a higher incidence of cardiovascular events. The prevalence of AD is high in patients admitted with a diagnosis of ACS. Treatment with moderate-intensity or lower-intensity statins is not sufficient to control the residual lipid risk in these patients. Fibrate therapy, which is underused in this population, could achieve greater control of AD and reduce the ongoing risk in these patients.

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accurately quantitate low concentrations of C-reactive protein (CRP), which are currently regarded as accurate markers of low-grade inflammation. Therefore, we hypothesized that at the time of diagnosis hs-CRP levels would be higher in patients with PDA than in those without PDA.

We conducted a retrospective study of all preterm infants who weighed ≤ 1500 grams, had a gestational age of ≤ 30 weeks, and were born between January 1, 2009 and December 31, 2014 in the Hospital Privado Universitario de Córdoba (Argentina). Exclusion criteria consisted of congenital, chromosomal, or genetic abnormalities, premature death, twins, sepsis, necrotizing enterocolitis, and intraventricular and intestinal hemorrhage. During the study period, all preterm infants underwent echocardiography on the third day of life. Significant PDA was defined as a ductal diameter > 1.5 mm and the presence of at least 2 of the following criteria: left atrium/aorta ratio > 1.5, pulsatile flow in the arterial duct, retrograde or absent diastolic flow in the anterior cerebral artery or descending aorta, or fractional shortening < 40%. Data were collected on weight, gestational age, gender, chorioamnionitis, respiratory distress syndrome, and the use of prenatal corticosteroids. High-sensitivity C-reactive protein was measured with a detection limit of 0.06 mg/dL.

Variables are expressed as 95% confidence intervals (95%CI), means (standard deviation), or medians (95%CI) according to the formula \( M = \left[ \frac{n-t_{0.05} \sqrt{n+1}}{2} \right] \) and \( M = \left[ \frac{n + t_{0.05} \sqrt{n-1}}{2} \right] \). Differences were determined using the Student t-test, Mann-Whitney U test, and Fisher exact test as needed. A P value of \( f < .05 \) was used as a cutoff for statistical significance.

The study was approved by the Institutional Ethics Committee and the confidentiality of patient data was maintained.

Of 138 eligible patients, 4 were excluded due to death and 2 due to incomplete data; thus, the final sample comprised 132 patients. Eight of the 74 patients with PDA died (10.8%; 95%CI, 3.1 to 18.6) and 4 of the 58 patients without PDA died (6.9%; 95%CI, 1.9 to 16.7) (\( P = .637 \)). The Table shows the baseline clinical characteristics of the 2 groups and their differences. Patients with PDA had significantly lower weight and gestational age, and a significantly higher rate of chorioamnionitis.

On the third day, the median hs-CRP level was 0.47 mg/dL (95%CI, 0.36 to 0.58) in patients with PDA vs 0.18 mg/dL (95%CI, 0.05 to 0.31) in those without PDA (\( P < .001 \)). On the seventh day, the median hs-CRP level was 0.42 mg/dL (95%CI, 0.31 to 0.53) in patients with PDA vs 0.35 mg/dL (95%CI, 0.22 to 0.48) and in those without PDA (\( P = .230 \)).

To our knowledge, this is the first study to investigate the relationship between hs-CRP and PDA. We found that PDA patients have significantly higher levels of hs-CRP. This finding would support the hypothesis that patients with PDA exhibit an inflammatory response, which increases cyclooxygenase-1 activity and prostaglandin E2 production, and maintains PDA. Patients with sepsis were not included, which excludes bacterial infection as a cause of inflammation. The intense oxidative stress observed in patients with PDA could be caused by inflammation or by any remaining prenatal inflammation. In this study, chorioamnionitis was a significant factor in the persistence of PDA. This finding has been reported elsewhere.

This study is limited by its retrospective nature and the relatively small sample size. We attempted to minimize selection and information bias by the use of strict definitions and statistical cutoffs. We calculated that 44 patients per group would be needed for a sample size with sufficient power to detect a difference of 0.30 mg/dL of hs-CRP. Although the sample had sufficient power, the results should be confirmed by larger prospective studies.

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