

Scientific letters

Ductus Arteriosus Closure With Paracetamol: a Pilot Study**Cierre de conducto arterioso con paracetamol: estudio piloto****To the Editor,**

Patent ductus arteriosus is frequent in premature babies. With an incidence of 1:2500–5000, it accounts for 9% to 12% of congenital heart disease.¹ Several different drugs have been tried for closure of hemodynamically significant patent ductus arteriosus. The first to be used was indomethacin, with a success rate of 70% and a reopening rate of 35%; however, the high cost of this drug has driven the search for other options such as ibuprofen.² But such drugs are not harmless and are associated with decreased renal, mesenteric, and cerebral perfusion, and ibuprofen is associated with hyperbilirubinemia.³ Recently, paracetamol has been demonstrated to be effective in this indication, with no reports of toxicity to date.

In this study, we report the use of oral paracetamol in premature babies. The drug was safe and effective at closing the hemodynamically significant patent ductus arteriosus. Premature patients in their first 10 days of life with a gestational age of 30 to 36 weeks and hemodynamically significant patent ductus arteriosus were included in this study. The defect was considered hemodynamically significant when the Qp/Qs ratio was greater than 1.5/1 and the left atrium/aortic root ratio was greater than 1.8 in echocardiography and the patient needed ventilatory support.² Patients with heart disease resulting from the defect, intraventricular hemorrhage, thrombocytopenia, renal failure, hyperbilirubinemia, and necrotizing enterocolitis were excluded. Patients were divided into 2 groups according to weight: group 1 weighing less than 1 kg and group 2 weighing more than 1 kg. Both groups were treated with oral paracetamol at 15 mg/kg/dose every 6 hours (total cumulative dose 60 mg/kg). Echocardiographic follow-up was done at 48 hours after the first dose. A second cycle of the drug was administered if the ductus arteriosus had not closed. If the ductus arteriosus still had not closed after this second cycle, the patient was referred for surgical closure. All patients received fluid therapy on the first day at 70 mL/kg/d, with a daily increase of 10 to 20 mL/kg/d up to a maximum of 160 mL/kg/d at the end of the first week of life.

Ten patients were included for pharmacological treatment. Of these, closure was obtained in 6 with the first cycle of treatment. Four patients entered a second cycle, with 1 additional closure reported. The remaining 3 patients underwent surgery, with a final success rate of 70%. The success rate was greater in patients weighing more than 1 kg (6 patients). There ratio of girls to boys was 3/1 (75%). As shown in Table, the size of the ductus arteriosus ranged from 1 mm to 5 mm in diameter. The echocardiographic parameters were as follows: mean cardiac load in systole 292.5 mmHg (range, 143–440 mmHg), mean Qp/Qs ratio 2 (range, 1.1–3.5), mean left atrium/aortic root ratio 1.23 (range, 1–1.8). Liver function and platelet count were monitored during treatment, with no significant changes observed.

Two patients died: patient 4 due to septic shock, with death occurring 48 hours after completing the treatment cycle and patient 8 due to hypovolemic shock after surgery (Table). These deaths were not considered related to drug administration.

The success rate for closure of the ductus arteriosus with paracetamol is similar to that of nonsteroidal antiinflammatory drugs, which also have a success rate of 70%. As in this study, other authors have found that paracetamol has similar success rates to other drugs. For example, the Cochrane Plus review in 2008 found a success rate for indomethacin of approximately 70%.² In another study by Jones et al,⁴ indomethacin was compared to ibuprofen in the treatment of hemodynamically significant patent ductus arteriosus in premature patients. The authors found that indomethacin was effective in up to 70% of cases in the first cycle and in 60% when a second cycle was required. With ibuprofen, the closure rate was 75% in the first cycle and 55% in the second cycle. In the study conducted by Ozmer et al,⁵ a success rate of 71.4% was reported with the use of paracetamol. These success rates are similar to those found in the present series. It is important to highlight paracetamol is apparently innocuous: no short- or medium-term complications were reported. This is presumably because the drug works through nonselective inhibition of cyclooxygenase, the enzyme responsible for prostaglandin synthesis, without any vasoconstriction or reduction in renal, mesenteric, or cerebral blood flow.⁶ Paracetamol is readily available and innocuous in neonates. Its ability to induce closure of hemodynamically significant patent ductus arteriosus may therefore shorten intrahospital stays and reduce associated morbidity.

Table
Characteristics of Patients Included in the Study

Patient	Weight, kg	PDA, mm	SCO	Qp/Qs	LA/AoR	Cycle 1	Cycle 2	Qx	Death
1	1.15	1	258	1.9	1.07	Successful			
2	1.35	5	320	3.6	1.20	Successful			
3	1.20	2	270	2.0	1.00	Successful			
4	0.84	1	440	1.1	1.01	Successful			Yes
5	1.20	2	355	1.4	1.26	Successful			
6	1.60	2	281	1.9	1.20		Successful		
7	0.98	2	143	3.0	1.30			Yes	
8	0.97	3	273	1.2	1.80			Yes	Yes
9	1.20	3	168	1.5	1.90	Successful			
10	1.30	2.5	210	1.9	2.10			Yes	

AoR, aortic root; LA, left atrium; PDA, patent ductus arteriosus; SCO, systolic cardiac output.

Limitations of this study include the small number of patients, which means that precise conclusions cannot be drawn. Nevertheless, so far paracetamol has been shown to be effective with few side effects. Larger studies with longer follow-up would be needed to more clearly demonstrate the pharmacological effect and provide a more rigorous analysis of potential complications.

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Endovascular Carotid Revascularization Performed by a Multidisciplinary Team: First Experience in Spain



**Revascularización endovascular carotídea realizada por un
equipo multidisciplinar: primera experiencia en España**

To the Editor,

Cerebrovascular diseases are the second leading cause of death in Spain, and extracranial carotid disease is responsible for one-third of ischemic strokes. The indication for revascularization of a carotid lesion will be determined by the patient's symptomatic status and the severity of obstruction. Endovascular intervention with a stent is an optimal form of carotid revascularization, and the medium- and long-term results are similar to those of endarterectomy.¹

Interventional cardiologists have proved to be professionals with optimal skills for safely deploying the stent in the carotid artery.² However, in contrast to the situation outside Spain, interventional cardiologists do not participate in this type of procedure in this country.³

The Endovascular Unit of the *Hospital Virgen Macarena* in Seville, Spain, combines endovascular care with care of cardiovascular diseases. The unit is a multidisciplinary group for the treatment of carotid disease and is composed of interventional cardiologists and neurologists. The integrative approach represents an innovation in Spain.

The role of the neurologist consists of indicating the procedure, performing the clinical monitoring during the intervention, and conducting the follow-up. Interventional cardiologists have participated in a dedicated training program for carotid revascularization with stents, under the initial tutelage of an interventional radiologist. In addition, the cardiologists were trained by an interventional neuroradiologist in the handling of the devices to enable resolution of intracranial thromboembolic complications.

This letter presents our experience of stent revascularization of extracranial carotid lesions, and assesses whether the skills of interventional cardiologists can be readily transferred to this procedure to reduce the steepness of the learning curve.

From May 2008 through April 2014, 300 patients with carotid lesions were revascularized. These patients, with a mean (standard deviation [SD]) age of 68.9 (8.6) years, were mainly symptomatic (81.3%). Overall, 53% of the patients were diagnosed with a lesion

in another vascular territory, mainly in the lower limbs (31%) and coronary arteries (23.7%).

Access was mainly transfemoral (91%), although in the last 2 years, right transradial access has started to be used for ipsilateral carotid interventions. The rate of aortic arches not readily amenable to carotid catheterization was 26%. Significant disease (< 50%) of the contralateral carotid artery was found in 48% of the patients.

In all interventions, the use of brain protection devices was considered, although this was not feasible in 11 (4%). Distal protection was used in two-thirds of the patients. In most cases, a filter-type device was used (56%), although distal balloon occlusion was also used (11%). Proximal protection was used in 75 procedures (29%). In general, in the case of hypoechogenic or anechogenic plaques with a high degree of obstruction, proximal protection and, more recently, an occluding balloon was chosen as distal protection (Figure).

The overall success rate, taken as revascularization with residual stenosis < 50% and absence of major events (death, stroke, or infarction) in the first 24 hours, was 98%. A major clinical event occurred in 6 patients (1 major stroke, 4 minor strokes, and 1 non-ST-elevation myocardial infarction).

Once the periprocedural phase had passed and during the first 30 days, 4 patients died (3 due to intracranial hemorrhage probably caused by hyperperfusion syndrome, and 1 due to thrombosis probably arising from the stent), and 4 had a stroke. Thus, overall, the composite rate of neurological events (death or stroke) at 30 days was 4.3%. These clinical outcomes were similar to those obtained in other Spanish studies⁴ (Table).

To assess the impact of our learning curve, we compared the clinical outcomes obtained in the first third of our experience (100 initial procedures) with the remaining 200 interventions. The success rate was very high from the start of the program (96%), although there was a tendency toward a higher success rate during the period with greatest cumulative experience (99%; $P = .08$). No significant differences were found between periods in the composite events in the first 30 days, but the outcomes were better in the final phase of our experience (3.5% vs 6.0% initially; $P = .37$) due to a lower mortality rate (0.5% vs 3% initially; $P = .11$). These outcomes indicate that, although a learning curve for the intervention does exist, the interventional cardiologists showed an appropriate skills transfer right from the outset (Table).

In conclusion, our multidisciplinary model for the endovascular treatment of carotid disease showed optimal clinical outcomes,