

Digestive and renal complications in premature infants with patent ductus arteriosus treated with indomethacin and ibuprofen

Complicaciones digestivas y renales por indometacina e ibuprofeno en prematuros extremos con ductus arterioso permeable

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Abstract

The symptomatic patent ductus arteriosus (sPDA) is common in extremely premature infants (EPI). In order to decrease the hemodynamic repercussion and avoid complications it is necessary to close it. Indomethacin or ibuprofen are used for this purpose with its associated risks. **Objective:** Characterize digestive and renal complications in EPI who received indomethacin or ibuprofen as sPDA treatment. **Patients and Method:** Retrospective study on EPI between January-2004 and December-2013. Three groups were compared: treated with indomethacin or ibuprofen and a non-treated group. EPI with other serious complications were excluded. The primary outcomes on each group were digestive and/or renal complications. Statistical significance was $p < 0.05$. **Results:** 599 EPI were included, 33.1% with PDA received treatment and 66.9% did not need it. A statistical association was found between sPDA and lower gestational ages, neonatal depression and respiratory distress. In the non-treated group, 5% presented enterocolitis and 0.25% renal failure; on the treated group, 2.5% presented enterocolitis and 1.0% renal failure. No significant differences were found between the treated and non-treated groups in relation to complications considering enterocolitis ($p = 0.11$) or renal failure ($p = 0.33$) alone, or combined ($p = 0.17$). No difference were detected either between those treated with indomethacin or ibuprofen. **Conclusions:** The results show that in absence of other clinical complication, medical treatment of sPDA with indomethacin or ibuprofen, do not increase the risk of serious digestive or renal disorders. There were no advantages of using indomethacin or ibuprofen over the other.

Keywords:

Patent ductus arteriosus; premature infants; indomethacin; ibuprofen; enterocolitis

Introduction

Patent ductus arteriosus (PAD) corresponds approximately to 7% of all congenital heart defects, with a predominant incidence in premature newborns^{1,2} and correlate with lower gestational age (GA) and lower birth weight (BW). In Chile, 26% of premature infants younger than 32 weeks of gestational age (GE) are diagnosed of PAD, increasing to 36% in premature infants GE 24 to 27 weeks³. International data show that 55% of premature infants under 1,000 g have PAD requiring medical treatment⁴. The closure of the ductus is late in the extreme premature patients (EP), generally beyond the first week of life, due to a smaller number of muscle fibers and sub-endothelial tissue, also delaying the closure or reopening in situations of systemic inflammation⁵.

The clinical repercussion of the ductus depends on the magnitude of the left-right short circuit and the redistribution of blood flow to the tissues. It becomes symptomatic when signs of heart failure (blow, tachycardia, cardiomegaly), diastolic hypotension or increase of the differential, bulging pulses, respiratory distress, etc. Clinical research may be delayed or confused with other heart diseases⁶. The echocardiography confirms the PAD, verifies the cardiac structures, allows to measure the ductal size, the severity of the short circuit and the hemodynamic repercussion, being very suggestive when the ductal diameter is ≥ 1.5 -2.0 mm, left atrial diameter ratio/Aortic diameter > 1.5 ; Low flow in the superior vena cava, retrograde holosystolic flow in the descending aorta, pulmonary flow/systolic flow > 2 to 1, ratio duct size/diameter of the descending aorta > 0.5 ; among others⁷.

It has the advantage that it detects a symptomatic or hemodynamically significant PAD (PADs) before symptoms or clinical complications, associated to intracranial hemorrhage, heart failure, pulmonary hemorrhage, acute renal failure, necrotizing enterocolitis (NEC), Chronic lung disease, periventricular leukomalacia and finally death⁸.

The need to treat PADs is due to the attempt to avoid or reduce the hemodynamic impact on the organs and to associate morbidity and mortality, the magnitude of which is directly related to the degree of immaturity⁹. Indomethacin and ibuprofen, non-steroidal anti-inflammatory drugs (NSAIDs) with the same mechanism of action but with different pharmacokinetic and pharmacological properties are used for this purpose¹⁰. Indomethacin, used since 1976, has been shown to be effective in producing closure of the ductus between 60 to 80% of patients, decreasing its effectiveness at younger gestational age^{11,12}. In the last decade, similar results have been observed with the use of ibuprofen IV; both drugs have been shown to be

equally effective in ductal closure and to reduce surgical ligation rates of PAD¹³⁻¹⁵. If closure of the PAD is not achieved with one or two cycles of NSAID therapy, surgical closure is indicated¹⁶. More recently, paracetamol has been used, however clinical experience is still under development^{17,18}.

The main therapeutic effects and many of the adverse reactions of NSAIDs can be explained by their inhibitory effect on cyclooxygenase activity, reducing the synthesis of endogenous prostaglandins that exert a vasodilatory effect on the ductus and other organs. With the inhibition of prostaglandin synthesis, ductal closure is achieved, but gastrointestinal, renal and cerebral perfusion can be compromised, explaining the appearance of complications, often of a serious nature¹⁹⁻²¹. Also, complications caused by NSAIDs may be influenced by other factors, such as hemodynamic instability, dehydration, sepsis, asphyxia, use of other drugs, among others.

In the Neonatal Service of the Barros Luco Care Center (CABL by its acronyms in Spanish), about 120 premature infants (PI) are born every year, defined as younger than 32 weeks and/or less than 1500 g. The rate of PADs among those who survive at least 7 days is about 20%, and among those under 1,000 g is around 30%. EP patients undergo echocardiography by cardiologist to confirm the presence of PAD, and if this is hemodynamically significant, pharmacological treatment according to national guides, indomethacin or ibuprofen, is started²². In case of therapeutic failure, the outline can be repeated if the patient's clinical condition allows it, if the symptomatic PAD persists, surgical closure is indicated. Indomethacin systemic (iv) was used from 2001 to 2008, switching to ibuprofen iv because reports of a lower rate of digestive and renal complications. The neonatal team's impression of switching from Indomethacin to Ibuprofen for medical treatment of PAD was controversial in relation to the associated severe complication rates.

The objective of this research was to perform a comparison of digestive and renal complications associated to the use of Indomethacin and/or intravenous Ibuprofen in extreme premature infants with symptomatic ductus.

Patients and Methods

A retrospective, longitudinal study in extreme premature infants born between January 1, 2004 and December 31, 2013 in the Neonatal Service of the Barros Luco Care Center, evaluated for the presence of PAD using clinical and/or echocardiographic methods. If the PAD is closed or small, without hemodynamic repercussion, it was not treated and spontaneous closure

was expected; In contrast, when PAD was symptomatic or hemodynamically significant, pharmacological treatment with indomethacin until July 2008 and subsequently ibuprofen was indicated. Inclusion criteria were Premature infants 24 to 31 weeks of GA; BW 500 to 1500 g, and survival > 7 days. All the data was recorded in the database of the Program of Prematurity Monitoring at our Service. Exclusion criteria were Apgar at 5 minutes less than or equal to 3; genetic syndromes and malformations; symptomatic PAD unable to receive NSAIDs due to platelet count < 60,000, BUN \geq 30 mg/dl, creatinine \geq 1.8 mg/dl, diuresis \leq 0.5 ml/kg/h in the last 8 hours; active bleeding; persistence of PADs after drug therapy with NSAIDs, requiring a second cure with indomethacin or Ibuprofen and/or need for surgical closure; PAD closed with only one dose of NSAID; renal or digestive disease prior to treatment with NSAIDs; severe neonatal asphyxia; connatal infection; ;death of the patient due to extradigestive or extrarenal causes before 14 days after the start of pharmacological treatment; infection associated with health care before 7 days post-treatment of non-digestive cause; shock before 14 days post treatment.

The total number of premature infants who met the above criteria was included, and no sample size calculation was calculated. The EPs were distributed in 3 groups according to treatment received: premature newborns without PADs that did not require NSAIDs, those who presented PADs treated with indomethacin, and those with PADs treated with Ibuprofen. The study was not randomized, according current service regulations.

Serious gastrointestinal complications were considered a necrotizing enterocolitis, gastric or intestinal perforation not associated with enterocolitis, and massive digestive hemorrhage. In addition, severe renal complication was considered any event of transient or permanent renal failure defined as oliguria < 1 cc/kg/h for 24 hours or more, and/or a creatinine above 1.8 mg/dl.

Current national guides on treatment of PADs were used. Indomethacin and ibuprofen, expressed in mg/kg/dose, with infusion in 30-60 minutes are detailed in table 1, where 3 doses correspond to a complete cure:

	Indomethacin (mg/kg/dose, every 12 hours, iv route)			Ibuprofeno (mg/kg/dose, every 24 hours, iv route)	
Start Age	< 48	2-7	> 7		
Treatment	hours	days	days		
1st dose	0.20	0.20	0.20	1st dose	10
2nd dose	0.10	0.20	0.25	2nd dose	5
3rd dose	0.10	0.20	0.25	3rd dose	5

A descriptive analysis of all variables is presented; tables of frequency summaries according to the categories of cases (indomethacin, ibuprofen and untreated). Measurements, summaries, averages with standard deviations for numerical variables (discrete or continuous) and proportions with confidence intervals for dichotomous variables or differences of probabilities are presented. For tables with low frequencies in some boxes the Fischer Exact Test will be used. Multivariate analysis, including logistic regression are used when pertinent. The probability of relevant randomness will be calculated for each studied association and the standard alpha error values of $p \leq 0.05$ and a Beta error of 0.20 will be used to define statistical significance.

Results

During the study period 777 EPs were born in the CABL that met the inclusion criteria. 178 children were excluded, most of them due to death, followed by persistence of PADs after drug treatment and the need for a second cure or surgical closure, infections, asphyxia and other causes. Finally 599 EP were enrolled in the study, of which 198 had PADs and therefore received treatment with NSAIDs (33.1%); Subdivided in 102 children treated with indomethacin (51.5%) and 96 with ibuprofen (48.5%). In turn the 401 who did not have PADs make up the control or untreated group (66.9%). The diagnostic method of PAD was mainly echographic (71.8%). In the EP with PADs, and therefore treated, there was echographic confirmation in 166 of 198 (83.5%), whereas in those who did not present PADs, only echocardiography was performed in 264 of 401 children (65.8%).

Among the demographic characteristics of the groups compared, there were no statistically significant differences in relation to gender, BW distribution, gestational age, weight adequacy for gestational age, Apgar test at 5 minutes and proportion of cases treated with Indomethacin or Ibuprofen. Regarding BW, EPs of 500 to 1,000 g presented PADs in 36.4% of the cases (74/203), and in those of 1,001 to 1,500 g the PADs were present in 31.3% of the cases (124/396). The risk of presenting PADs is slightly higher in those of 500 to 1,000 g, but does not represent a statistically significant difference between the groups (OR = 0.79, 95% CI 0.56-1.13 and $p = 0.12$); Therefore, in this study, BW of preterm infants did not significantly influence the need for treatment for ductal closure.

Children with adequate BW for gestational age represent 78.3% of the total enrolled EPs and 35.6% of them had DAPs. The small ones for GA (21.7% of the total) presented PADs only in 23.9%. There were no cases of large preterm infants for GA. These diffe-

Table 1. Apgar at 5 minutes in groups according to treatment received

APGAR 5 min	Treatment									
	Ibuprofen		Indomethacin		Trated		No treated		Total	
	n	%	n	%	n	%	n	%	n	%
4 to 6	10	19.6	13	25.5	23	45.1	28	54.9	51	100
7 to 10	85	15.6	89	16.4	174	32.0	370	68.0	544	100
Total	95	16.0	102	17.1	197	33.1	398	66.9	595	100

Fisher's Exact Test $p = 0.04236$

rences are statistically significant (OR = 0.5663 95% CI 0.3627-0.8841, $p = 0.0069$). However, "small" patients favor a higher average GA than the "adequate" ones (29.2 vs 28.2 weeks), this would help to explain the lower incidence of PADs in them, since it is difficult to conclude that being "Small" would have a protective effect of PADs. The diagnosis of PADs and the treatment used were not biased by GA. PAD were diagnosed in 45.6% of the children with the lowest GA (24-27 weeks) and only 27.9% in those with the highest GA (28-31 weeks), with GA being a variable that showed statistical differences Significant with respect to the presence of PADs (OR = 0.4612 IC 95% 0.3197-0.6654, $p = 0.000027$); Which confirms the lower GA (or greater immaturity) as a risk factor for the presence of PADs. In children treated with PADs there were slight differences in the proportion of indomethacin or ibuprofen use between 24 and 27; and 28-31 weeks but no significant differences (OR = 0.7563 95% CI = 0.4272 - 1.3390 $P = 0.20$).

Since those born with severe or asphyxiated depression were not enrolled, the distribution of the Apgar Test values at 5 min did not have cases with values lower than 4. There were 4 cases of out-of-hospital births remaining outside this part of the analysis; (51.6%) with moderate neonatal depression (values in the range of 4-6) and 544 EP (91.4%) were classified as having EP, without neonatal depression (values between 7-10). From the subjects who did not present PADs (untreated), 7.04% (28 of 398 cases) presented Apgar

at 5 min in moderate depression range, and in those with PADs (treated) 11.68% (23 cases of 197), (table 1). Although the difference between the groups is only 4.64%, there is a slight statistically significant difference ($p = 0.0423$), therefore, the antecedent of moderate respiratory depression A slightly greater risk of presenting PADs in this cohort.

As a result of this study, as a characterization of the study population, 526 children out of 599 (87.8%) presented respiratory distress after childbirth, distributed in 441 (73.6%) patients with disease Of Hyaline Membrane (DHM), 86 (14.4%) with Transient Distress and 9 (1.5%) classified as "Other". Among the EPDs with PADs there was distress in 190 of 198 (96.0%), of which 177 (89.4%) were by DHM. Among the 401 PE that did not present PADs, 336 (83.8%) had some type of respiratory distress, of which 261 were by DHM (65.1%). From the children diagnosed with respiratory distress at birth, 36.1% of them had PADs and were treated; In contrast, among those who did not have respiratory distress, only 11.0% had PADs; This difference is highly statistically significant [OR = 4.585 (95% CI = 2.2776-10.4428); $P = 0.0000332$].

Regarding the objectives presented the results show that the number of serious complications, both digestive and renal, was very low; 28 cases out of 599 children studied (4.7%), shown otherwise, 95.3% of the total were free of complications of this type (Table 2). There were no cases of patients with both complications, digestive and renal.

The group without PADs provided 21 cases of complications, either digestive or renal, out of a total of 401 (5.2%), and among those receiving NSAID treatment only 7 subjects presented complications from a total of 198 (3.5%), Table 3.

This distribution is not statistically significant ($p = 0.174$), with no association in this cohort between the drug treatment of PADs and the presence of severe digestive and renal complications.

In the digestive tract, of the total of 599 EP there were 25 cases of enterocolitis (4.2%), and none with gastric or intestinal perforation, nor massive digestive

Table 2. Number and percentage of complications according to their type

Type of complication	n	%	% accumulated	95% confidence intervals
Enterocolitis	25	4.2%	4.2%	2.8%-6.2%
High creatinine	3	0.5%	4.7%	0.1%-1.6%
Without complications	571	95.3%	100%	93.2%-96.8%
Total	599	100%	100%	

Table 3. Serious complications associated to NSAID treatment in PADs

NSAID treatment	Complications presence							Total
	With complications				Without complications			
	Enterocolitis		Renal failure					
No	20	5.0%	1	0.2%	380	94.8%	401	100%
Yes	5	2.5%	2	1.0%	191	96.5%	198	100%
Total	25	4.2%	3	0.5%	571	95.3%	599	100%

Chi Square Test. $p = 0.174$.

Table 4. Enterocolitis presence according treatment types

Enterocolitis presence	Treatment types						Total	
	With NSAID			Without NSAID				
	Indomethacin		Ibuprofen					
No	100	98.0%	93	96.9%	381	95.0%	574	95.8%
Yes	2	2.0%	3	3.1%	20	5.0%	25	4.2%
Total	102	100%	96	100%	401	100%	599	100%

Chi Square Test. $p = 0.3367$.

hemorrhage attributable to NSAIDs. Of the 401 children without NSAID treatment, 20 subjects had enterocolitis (5.0%); And of the 198 who received NSAIDs, 5 EP were diagnosed as enterocolitis (2.5%). Table 3 shows a slight difference in favor of children treated with NSAID to present less enterocolitis; The analysis of the presence of enterocolitis in the groups according to the treatment received clearly shows that there was no statistically significant association between NSAID treatment and enterocolitis (OR = 0.4935 95% CI 0.1824 - 1.3351; $p = 0.1124$).

If we compared the cases of enterocolitis between those treated with indomethacin and ibuprofen (Table 4), it was observed that there were 3 cases in the ibuprofen group (3/96 = 3.13%) and 2 among those receiving indomethacin (2/102 = 1.96%). The numbers of cases are too small to make a robust statistical analysis, the probability of association of these two variables is statistically non-significant ($p = 0.33$). Regarding the complication of renal failure, only 3 cases of the 599 children enrolled (0.5%) were found, with creatinine values higher than 1.8 mg/dL; No cases of oliguria were detected for 24 hours. The distribution was of one case in each group, whose percentages correspond to: no treatment 1/401 = 0.25%, with indomethacin 1/102 = 0.98% and with ibuprofen 1/96 = 1.04%. Considering the small number of children with renal failure, an adequate statistical analysis is not possible, but this shows that there were no significant differences between the

groups that received NSAIDs and those who did not present PADs (OR = 0.2450 95% CI = 0.0221-2.7185, $p = 0.2551$).

Anecdotally, since there is no association between complications and treatments, it can be observed that with ibuprofen there were no complications in 95.8% (92/96), 3.1% (3/96) had enterocolitis and 1.0% renal failure (1/96). At the same time, 97.1% (99/102) of the indomethacin-treated patients had no complications; enterocolitis associated with their use was observed in 2% (2/102) and renal failure in 1.0% (1/102). Although the effectiveness of the ductal closure of each drug is not a matter of the study, we can add that a second cure or ductal surgery was necessary in 14.4% of the patients receiving indomethacin and 12.7% of those treated with ibuprofen; these patients were subsequently excluded because of the study design.

Discussion

The number of severe digestive or renal complications recorded in the total number of enrolled patients was low (4.7%). Statistical analysis definitely did not show significant differences between groups of patients without PADS who did not receive NSAIDs compared to those who presented DAPs and received medication or NSAID treatment, nor were there differences between those receiving indomethacin and ibuprofen.

Although there was no statistically significant difference in the rate of enterocolitis between the group treated by PADs and those without PADs, it was unexpected that the group that received NSAIDs had even a lower percentage of this complication (2.5 vs 5.0%, respectively), Table 3.

It was expected that the EP group of 500 to 1000 g had a higher rate of PADs than those of 1,001 to 1,500 g, but this difference was not significant; In contrast, the relationship between lower GA and higher frequency of PADs was significant, as was expected given the strong association of PADs with immaturity. Apgar in the range of moderate neonatal respiratory depression (score 4 to 6 at 5 minutes) was a variable associated with a higher rate of PADs and need for treatment; There were no significant differences in the presence of complications among depressed-born preterm infants receiving indomethacin or ibuprofen. Previously, severely depressed patients (Apgar 1 to 3) had been excluded, increasing the frequency and severity of all types of complications because this affected the cleanliness of the variables that we wish to study as causes of complications, such as the use of indomethacin or ibuprofen in the treatment of PADs. The Hyaline Membrane Disease was strongly associated with the presence of PADs; both pathologies are closely related to the degree of immaturity²³.

The information provided by this study is that the use of NSAIDs in cases of PADs under the conditions described, i.e. in the absence of clinical situations that increase the risk of digestive and/or renal complications such as infection, asphyxia, hypoperfusion, genotypes, etc. Does not represent an increased risk of complications with respect to the group of premature infants without PADs or who did not receive NSAIDs. Information concordant with international publications in which it is shown that the presence of complications such as enterocolitis is associated with the presence of PADs, has received treatment or not, and that there are no differences if they are treated with NSAIDs. Even in preterm infants receiving prophylactic NSAIDs without PADs, there is no increased risk of enterocolitis^{24,25}. There were also no comparative advantages of one NSAID in relation to the other, so it is consistent with what has been described that they do not present differences in therapeutic effectiveness or associated complications. Several publications show their results in PE with ductus where they are compared according to the different therapeutic strategies that exist: prophylactic, pre-symptomatic, symptomatic and conservative treatment or without medication or surgery²⁶; But no studies were found with the selection criteria that we used to exclude those with concomitant pathologies that increase the incidence of PADs.

EPs are high-risk biomedical patients and therefore any complication can compromise prognosis and quality of life. This creates clinical dilemmas when we want to treat a potentially serious condition such as PADs but we do not want the potential complications arising from treatment to occur. Which forces us to select the best possible to patients candidates for NSAID therapy so that they do not suffer the commented complications. The purpose of the extensive list of exclusion criteria was to clear factors affecting the presentation of PADs and/or the appearance of digestive or renal complications, in order to evaluate the variable complications of ductal treatment with NSAIDs in a more independent way. Among the excluded premature infants, the majority were due to infectious pictures, related to an increased risk of PADs or ductal reopening, and of digestive or renal disorders. The literature mentions that it increases the risk of serious complications after NSAID when were administered in a septic or proinflammatory environment²⁷.

The low number of events with severe digestive and/or renal complications in the untreated groups (without PADs) and those treated with NSAIDs (with PADs) does not allow statistical analysis that is too robust or stable, as well as correlations with multivariate analyzes or logistic regression with other variables such as respiratory distress, neonatal depression, among others. Even so, the statistical tests performed did not show significant differences between the two groups. Due to the scarcity of cases with renal failure, one case in each group, no further statistical analysis is useful, but it is possible to state in this study that indomethacin or ibuprofen have an equal risk of affecting renal function with respect to the control group. This reinforces the local impression that the potential benefits of ibuprofen on indomethacin in relation to renal function and digestive complications are not appreciated in our population, as was shown in some publications^{28,29}.

The ultrasound diagnosis of PADs is currently a very important standard; Although our Service is fortunate to have a cardiologist and exclusive ultrasound equipment, it is impossible to have this support always and at all times; Therefore, when the PAD clinic is suggestive and there is no echocardiography, there is no other possibility than initiating NSAID treatment and attempting further monitoring. In this cohort, 16.5% of the preterm infants treated by PADs did not confirm the diagnosis by ultrasound prior to receiving indomethacin or ibuprofen, and among those who did not present PADs the lack of echocardiography reached 34.2%. This is due to the fact that the procedures to perform the ultrasound were carried out before the treatment of premature infants; On the other hand, in those who did not present PADs, the lack of the test

was more tolerable, because it was not urgent and the clinical evolution until the discharge is available to monitor the presence of a PAD. However, given the study design, it does not substantially change the results.

Patients who presented a small or hemodynamically non-significant PAD, who did not receive NSAID treatment and who progressed to spontaneous closure at a variable time, were tested in the same group of preterm infants without PAD since, from the hemodynamic and with presence of complications observed until discharge in the literature does not describe significant statistical differences in this regard³⁰.

Premature infants who required more than one NSAID cure or required ductal closure surgery were excluded from the analysis because the objectives of the study were to understand the digestive and renal complications in preterm infants who received ibuprofen or indomethacin as part of the treatment of PADs and to compare them with those premature without PADs, each NSAID cure is a risk of complications in itself, so children with two or more NSAID cures are not comparable and because of the severity of the hemodynamic impact of PADs and refractoriness to drug closure, they required Of surgical closure. We were interested in evaluating the complications of a standard NSAID cure and not according to the number of them or the severity of the PADs. However, repeated NSAID cures often are spaced out at intervals of several days, which can be interpreted as individual or independent therapies as risk factors for digestive and/or renal complications, so this may be a weakness of our work.

NSAIDs are nephrotoxic agents that produce oligoanuria due to decreased renal blood flow and glomerular filtration. There is a close relationship between clearance and creatinine concentration with glomerular filtration. However, plasma urea is a poor indicator of the rate of glomerular filtration in preterm infants, as well as the urea/creatinine ratio, and a high plasma concentration of urea is not necessarily associated with renal failure or dehydration³¹, for this reason, the urea nitrogen concentration was not considered as an indicator of renal failure after NSAID therapy.

Conclusion

We can conclude from this study that the enrolled EP who presented PADs and were therefore treated with NSAIDs, either indomethacin or ibuprofen, did not present a statistically significant association with the presence of severe digestive and/or renal complications, in conditions of exclusion from others Clinical situations that affect or cause the complications analyzed. This information is very useful in our clinical practice because considering the great vulnerability of these patients; it allows us a degree of safety in the drug closure of the PADs in terms of not adding more risk of complications compared to those who do not have PADs.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors state that any conflict of interest exists regards the present study.

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