

PRO-CALCITONIN AND INFLAMMATION IN CHRONIC HEMODIALYSIS

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Abstract Procalcitonin (PCT) has emerged as a marker of infection, a frequent complication in hemodialysis (HD). We analyzed PCT levels in chronic non-acutely infected HD subjects, assessed its correlation with inflammatory and nutritional markers and propose a PCT reference value for non-infected HD patients. In an observational cross-sectional study, 48 chronic HD patients and 36 controls were analyzed. Variables: age, gender, time on HD; diabetes; vascular access, PCT, C-reactive protein (CRP), albumin, malnutrition inflammatory score (MIS), hematocrit, leukocyte count, and body mass index (BMI). Subsequently, control (G1, n = 36, 43%) vs. non-infected patients (G2, n = 48, 57%) groups were compared. In control subjects (G1), age: 54.3 ± 13.7 years, range (r): 30-81; males: 19 (53%); median PCT 0.034 ng/ml (r: 0.02-0.08); median CRP 0.80 mg/dl (r: 0.36-3.9); p95 PCT level: 0.063 ng/ml. In G2, age: 60.2 ± 15.2 years; males 32 (67%), time on HD: 27.0 ± 24.4; diabetics: 19 (32%); median PCT: 0.26 ng/ml (r: 0.09-0.82); CRP: 1.1 mg/dl (r: 0.5-6.2); p95 PCT level: 0.8 ng/ml. In control subjects, PCT and CRP were significantly lower than in G2: PCT: 0.034 vs. 0.26 ng/ml, p = 0.0001; CRP: 0.8 vs. 1.1 mg/dl, p = 0.0004. PCT-CRP correlation in G2: $\rho = 0.287$, p = 0.048. PCT and CRP concentrations are elevated in chronic non-acutely infected HD subjects, independently of infection, diabetes and vascular access. A p95 PCT level of 0.8 ng/ml may be considered as the upper normal reference value in non-acutely infected HD subjects. The PCT cut-off level in HD is yet to be determined in HD.

Key words: procalcitonin, hemodialysis, inflammation, C-reactive protein

Resumen *Pro-calcitonina e inflamación en hemodiálisis crónica.* La procalcitonina (PCT) puede ser un marcador de infección en la hemodiálisis (HD). Analizamos los niveles de PCT en sujetos sin infección aguda en HD crónica, su correlación con marcadores inflamatorios y nutricionales y, de acuerdo a ello, proponemos niveles de referencia de PCT. En un estudio observacional transversal se estudiaron 48 pacientes en HD y 36 controles. Variables: edad; sexo, tiempo en HD; diabetes; acceso vascular, PCT, proteína C-reactiva (PCR), albúmina, *score* de malnutrición-inflamación, hematocrito, recuento leucocitario, e índice de masa muscular (IMC). En los controles se determinaron PCT y PCR. Se comparó grupo control (G1, n = 36, 43%) vs. pacientes (G2, n = 48, 57%). G1: edad, 54.3 ± 13.7, rango (r): 30-81 años; hombres: 19 (53%); PCT mediana: 0.034 ng/ml (r: 0.020-0.080); PCR mediana: 0.8 mg/dl (r: 0.36-3.9); el nivel p95 de PCT: 0.063 ng/ml. En el G2, edad media 60.2 ± 15.2 años, hombres: 32 (66%), tiempo en HD: 27.0 ± 24.4; diabéticos: 19 (32%); PCT: 0.26 ng/ml (r: 0.09-0.82); PCR: 1.1 mg/dl (r: 0.5-6.2); p95 PCT: 0.8 ng/ml. En G1 los niveles de PCT y PCR fueron significativamente más bajos que en G2: PCT: 0.034 vs. 0.26 ng/ml, p = 0.0001; PCR: 0.8 vs 1.1 mg/dl, p = 0.0004. Correlación PCT-PCR en G2: $\rho = 0.287$, p = 0.048. La PCT y la PCR están elevadas en HD crónica independientemente de infección, diabetes y acceso vascular. Se propone p95 de PCT de 0.8 ng/ml como límite superior del intervalo de referencia en sujetos sin infección aguda en HD. El valor de PCT en HD está por determinarse.

Palabras clave: procalcitonina, hemodiálisis, inflamación, proteína C reactiva

Infections account for a vast morbidity and mortality in HD^{1, 2}. Not infrequently, inflammatory laboratory parameters may be misleading and add confusion to an appropriate interpretation of these results due to uremia itself. In HD patients, inflammation is stimulated by

acute-phase responses triggered by exposure to bacteria, immunologic phenomena related to the HD procedure, metabolic and immunological disorders due to uremia *per se*³. Therefore, not infrequently, inflammation and infection biomarkers tend to overlap. Since the determination of PCT molecular structure in 1981 and its association with bacterial infection in 1993, PCT has been proposed not only as a rapid, specific and accurate marker or mediator of systemic inflammatory response syndrome (SIRS) and sepsis in the general population, but also as an indicator of severity according to the levels encountered: a PCT level

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> 2 ng/ml tends to correlate with severe sepsis⁴⁻⁷. Finally, it has been stated that PCT-guided antibiotic therapy for respiratory tract infections can significantly reduce antibiotic exposure⁸.

PCT is a polypeptide of 116 aminoacids (MW 13 kDa), and one of the precursors of calcitonin. PCT half life is 30-48 hours, and no plasma enzymes can break down circulating PCT^{5, 9}. Circulating levels of PCT in healthy subjects are below the detection limit and are only enhanced in medullar thyroid carcinoma or in small cell carcinoma⁵. As calcitonin synthesis is increased in HD patients, it has been proposed by Mori et al. that this phenomenon could explain the higher PCT levels in HD patients^{10, 11}. PCT of non-thyroid origin cannot be converted to calcitonin because conversion can be performed only by thyroid C cells. Therefore, PCT that cannot be converted to calcitonin peripherally could also be another cause of PCT increase, triggered during bacterial infections¹¹. However, PCT has been found to be elevated even in thyroidectomized septic patients, suggesting a non-thyroid PCT origin. PCT is synthesized in the small intestine, lungs and liver in septic patients^{12, 13}. It is now accepted that circulating macrophages appear to be the main source of plasma PCT, which play critical roles both in inflammatory and in infectious processes¹⁰.

To our knowledge, only 13 studies have analyzed possible roles PCT may play in HD^{11, 14-25}. Half of the studies are mainly related to PCT and inflammatory states, while the rest is aimed to assess PCT as a marker of infection. Studies on peritoneal dialysis (PD) are similar in number and in findings²⁶⁻²⁸. This shortage of publications contrasts with the vast number of studies and reviews performed in non-uremic patients about PCT and sepsis, that have uninterruptedly been published since 1993 until today^{6-8, 29, 30}. In HD, PCT has been reported to be elevated in both inflammatory and infectious situations, to be a marker of infection, and also to be high in non-infected PD patients^{11, 15, 23, 25}. Despite the firm association between PCT and bacterial infections in the general population, in dialysis subjects these considerations may be misleading and contradictory, and consequently the proposed PCT cut-off values may be mistaken. Publications here considered included those appearing in Medline/Pubmed, in English, referred to clinical studies in adult patients, and that assessed PCT in the chronic dialysis setting. Thirteen manuscripts were related to HD and nine to PD up to the time of this study.

We decided to measure PCT levels in non-infected stable chronic HD patients, correlate them with CRP levels and with other inflammatory and nutritional parameters and the type of vascular access. Finally, we suggest a PCT reference value in non-infected HD individuals and a possible pathophysiologic mechanism by which PCT is elevated without active infection in uremia.

Materials and Methods

In a cross-sectional observational comparative study, a total of 48 chronic HD patients gave their informed consent to participate in the study. The Institutional Review Board of the *Hospital Británico de Buenos Aires* was notified about the collection of data. In order to obtain our own local normal PCT values, PCT levels were measured in 36 subjects randomly chosen (no history of cancer, signs of active infection or renal disease), and included in the control group. Chronic HD patients over 18 years of age were enrolled when time on HD was ≥ 3 months. One patient was HIV positive and another one HBV positive. Patients with cancer or active infection were excluded. Infection was defined as an overt clinical picture and/or presence of positive blood cultures. Vascular accesses: arteriovenous fistulae: 30 (63%); polytetrafluoroethylene grafts (Gore-tex[®], W.L. Gore & Associates Inc., Newark, DE, USA): 13 (27%); tunnelized catheters (Tesio[®], med-comp Pennsylvania USA or Quinton Permcath, Covidien AG, MA, USA): 5 (10%).

Dialysis treatment consisted on 3 x 4-5 hours weekly. HD was performed with low-flux membranes (Polyamide Polyflux 21 L, Gambro[®], Sweden, or Sureflux 190, Nipro[®] Japan). Standard bicarbonate was mixed in ultrapure water (Ozone water treatment, FG Ingeniería, Mar del Plata, Argentina). Regular microbiological tests showed no bacterial growth. Average water tank ozone concentration: 0.25 ppm; return steal pipe ozone concentration: 0 ppm. Dialysate flow rate: 500 ml/min; mean blood flow: 400 ml/min. Mean KT/V: 1.3 ± 0.1 (range 1.0-1.5). Automatic dialysis machines were employed (Surdial 190, Nipro[®], Matsubara, Japan). Blood samples were drawn in fasting conditions from the arterial site of the vascular access before starting dialysis, in the midweek session after a 48-hour interval.

Serum PCT was determined by an electrochemiluminescence immunoassay (Cobas e411 Brahms PCT, Cobas[®] Roche Diagnostics, Mannheim, Germany), with a lower detection limit of quantification of 0.06 ng/ml. According to the manufacture brochure, the p95 PCT for the general population is 0.05 ng/ml, up to this level there is a low risk of severe sepsis and/or septic shock, while a concentration > 2 ng/ml is associated with high risk of severe sepsis and/or septic shock. Inter- and intra-assay variation coefficients: for a PCT concentration of 0.06 ng/ml, the intra-assay variation coefficient was 9.3% and the inter-assay variation coefficient was 12.3%. For a PCT concentration of 0.5 ng/ml, the intra-assay variation coefficient was 1.3% and the inter-assay 1.6%.

High sensitivity CRP (normal value: < 0.3 mg/dl) was calculated by immunoturbidimetry (VITROS 5600[®], Johnson & Johnson, New Jersey, USA).

Other standard biochemical and hematological laboratory tests were routinely measured.

Nutritional assessment was performed employing the MIS (Malnutrition Inflammatory Score), updated every three months, while the anthropometric measurements were obtained at the end of a dialysis session, performed at the end of the respective quarter.

Results are expressed as the mean ± SD for variables with normal distribution, and as the median plus ranges for variables with non-normal distribution. Normality was assessed with Shapiro-Wilk test. Comparisons between groups were performed using Student t test for variables with normal distribution, and Mann-Whitney and Kruskal-Wallis tests for variables with non-normal distribution. Relationships between parameters were studied by Spearman correlation test. Significance was considered when $p < 0.05$. Statistical program employed: Stata 9.2, Statacorp, Texas, USA.

Results

G1: Mean age: 54.3 ± 13.7 (r: 30-81 years), gender: males 19 (53%), mean creatinine value: 0.88 ± 0.18 mg/dl; p 5 and p95 PCT levels: 0.02 and 0.063 ng/ml, respectively. Median PCT 0.034 ng/ml (r: 0.02-0.08); median CRP 0.80 mg/dl (r: 0.36-3.9). Correlation between PCT and PCR: $\rho = 0.4938$; $p = 0.0022$. Results for G2 are outlined in Table 1. Briefly, mean age 60.2 ± 15.2 years; gender males 32 (67%), time on HD 27.0 ± 24.4 months; diabetics comprised 40% of the population (n = 19). Mean creatinine: 7.09 ± 3 mg/dl. Median BMI: 25.22 (r: 17-48.3); MIS: 4.17 (r: 0-19). PCT: 0.26 ng/ml (r: 0.071-1.14); CRP: 1.1 (r: 0.5-6.2). Vascular access distribution: arteriovenous fistulae 30 (63%); grafts 13 (27%); tunnelized catheters 5 (10%). Subjects with catheters showed significantly lower albumin levels 3.5 g/dl (r: 2.8-3.9), $p = 0.0219$. The non-infected p5 and p95 PCT levels were 0.09 and 0.824 ng/ml, respectively. G2 PCT showed a weak significant correlation with CRP: $\rho = 0.287$, $p = 0.048$. Other significant correlations are depicted in Table 2.

Controls vs. non-infected patients were different according to age: G1 vs. G2, 54.3 ± 13.7 vs. 60.2 ± 15.2 years, $p = 0.03$; to creatinine, 0.88 ± 0.18 vs. 7.09 ± 3 mg/dl, $p = 0.0001$; to PCT: 0.034 vs. 0.26 ng/ml, $p = 0.0001$ (Fig. 1); and CRP concentrations: 0.8 vs 1.1 mg/dl, $p = 0.0004$, respectively. Gender was not different between groups: G1 males 19 (53%) vs. G2 males 32 (67%).

Discussion

Our study shows that in chronic non-acutely infected HD patients, PCT levels are significantly higher than in normal individuals, suggesting that in HD PCT concentrations

TABLE 1.– Variables in chronic non-acutely infected HD patients

		NON INFECTED (G2)		
		Vascular access		
		Arteriovenous fistulae	Grafts	Catheters
	n	30	13	5
PCT	Median	0.24	0.25	0.37
ng/ml	Range	0.071-0.824	0.091-1.14	0.14-0.82
CRP	Median	0.95	1.3	0.9
mg/dl	Range	0.5-6.2	0.5-3.3	0.7-2.0
ALB*	Median	4.0	3.9	3.5
g/dl	Range	3.5-4.6	3.4-4.7	2.8-3.9
MIS	Median	3.50	4.0	5.0
	Range	1.0-15.0	0.0-14.0	3.0-19.0
WBC	Median	6.95	7.90	7.6
mm3	Range	4.1-10.0	5.7-12.0	4.5-10.3
HCT%	Median	34.5	33.0	31.0
BMI	Range	27.0-44.0	28.0-41.0	27.0-35.0
	Median	26.95	26.6	22.1
	Range	17.0-35.2	21.8-48.3	18.7-29.1

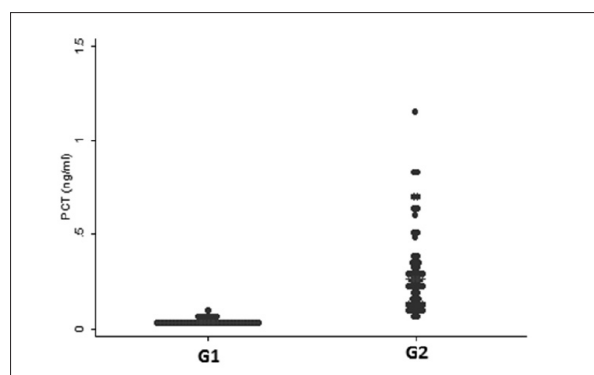
Abbreviations: HD, hemodialysis; PCT, procalcitonin; CRP, C-Reactive Protein; ALB, albumin; MIS, Malnutrition Inflammatory Score; WBC, white blood cell count; HCT, hematocrit; BMI, body mass index. Symbols: * $p = 0.02$

TABLE 2.– Significant correlations in group 2 (G2)*

		G2			
		MIS	BMI	WBC	CRP
PCT					0.287c
CRP			0.299b	0.314b	
ALB	-0.543a				
MIS			-0.285c		
BMI				0.299b	

PCT, procalcitonin; CRP, C-Reactive Protein; ALB, albumin; MIS, Malnutrition Inflammatory Score; WBC, white blood cell count; BMI, body mass index.

*Correlations as expressed with ρ coefficient; a $p = 0.0001$; b $p = 0.03$; c $p = 0.04$.



PCT Controls (G1) vs. G2 (non-infected), $p = 0.0001$

Fig. 1.– PCT levels in controls and non-infected patients

are usually elevated²². CRP levels in HD patients were also higher than in our control population. These results underscore the uremic inflammatory condition that PCT may indicate. PCT and CRP profiles were independent of the infectious condition, of diabetes and of the vascular access. Despite both groups were different according to age, no reports indicate any association between PCT and aging. At these low levels, PCT may be a poor marker of infection in HD. Based on our PCT p95 result, we propose an upper limit reference value of PCT ≤ 0.8 ng/ml in HD to discriminate between inflammation and a possible infection, instead of the commonly employed value of 0.5 ng/ml. Moreover, our control median PCT level of 0.034 ng/ml is averagely in agreement with that of other authors²¹, but contrasts with the normal PCT concentration of 0.5 ng/ml quoted by other HD studies^{15, 22, 23, 25}. As it has recently been reviewed, PCT cut-off levels vary considerably, and could have spread some conflicting information and erroneous interpretations about PCT as a marker of inflammation and/or infection⁷. We believe this may be due to the fact that, particularly in HD, (micro) inflammation is to be distinguished from infection.

As noted above, only 13 studies have studied PCT in HD. Non-infected chronic kidney failure patients display higher levels when compared to the general population, generally in the range of 0.1-1 ng/ml, probably because PCT may denote an inflammatory state. PCT levels increase as renal function deteriorates, which has been partially ascribed to a decrease in the glomerular filtration rate²⁴. However, Meisner et al. have demonstrated that PCT clearance is independent of renal function as kidneys represent a minor route of PCT elimination³¹. Although uremic inflammation is probably the cause of increased PCT levels, it may be potentiated by renal replacement therapies as HD and PD. Many triggers and sources of plasma PCT levels have been shown: the production of PCT is linked to bacterial endotoxins and to inflammatory cytokines as TNF-alpha, IL-1, IL-2, IL-6, and macrophages are the main sources of circulating PCT, both during infection and in aseptic inflammation in HD^{5, 7, 32, 33}. Besides, increased synthesis of PCT exists in HD patients, as peripheral macrophages secrete more PCT in severely reduced renal function and in renal replacement therapies, possibly contributing to the atherosclerotic burden of uremia²⁴. Pahl et al. state that that mature circulating monocytes from HD patients undergo a slow reversible "uremic programming"³⁴. This enduring uremia effect provoked in macrophages may be consistent with their programmability and extended lifespan. This interesting phenomenon could be due to the fact that uremic macrophages exhibit increased hematopoietic growth factor-inducible neurokinin 1 (HGFIN) gene expression, associated with heightened expression of proinflammatory and a suppressed expression of anti-inflammatory cytokines. The upregulation of HGFIN and

inflammatory cytokines in the uremic monocyte derived macrophages occurs when grown in the presence of either normal or uremic serum, suggesting an enduring effect of the *in vivo* uremic milieu. As noted by Pahl et al. more studies are needed to determine the role of macrophage HGFIN expression in the pathogenesis of HD-associated inflammation and vascular and soft tissue calcification, but it could be a reason why PCT levels remain elevated, and a possible link between PCT, calcitonin, calcium metabolism and atherosclerosis and cardiovascular disease in this population^{24, 34}.

Possible roles of circulating PCT are in the metabolism of calcium, in the cytokine network and in the modulation of nitric oxide synthesis, and also as a pain reliever⁵. Interestingly, it has been found that PCT is not only an inflammatory/infectious marker, but also a molecule with an active role, as inhibition of its action has substantially decreased morbidity and mortality³⁵⁻³⁷, although other authors have found the opposite¹⁶. Undoubtedly, HD discretely elevated PCT levels of 0.8 ng/ml appear to correlate with noninfectious, low-grade inflammation. This phenomenon situates PCT as another clinical relevant marker of cardiovascular function in patients on HD²⁴. Furthermore, the general association between PCT and CRP, a well-established marker for both inflammation and cardiovascular function, underscores this statement³⁸⁻⁴⁰. Finally, this reality should not limit the accuracy of PCT as a marker of severe infection when higher upper reference values are observed, particularly > 2 ng/ml²⁴.

In HD, PCT has been evaluated as a marker of infection or inflammation mainly in 13 publications. The first report was an abstract by Ulrich et al. presented at the ASN 2000 meeting to evaluate PCT as an acute phase parameter. There, in 63 chronic non-infected HD patients moderate elevated PCT levels were found (0.52 ng/ml; *r*: 0.2-8.7), and these levels were higher in subjects dialyzed in a low- vs. high-flux manner. However, PCT did not correlate with CRP levels, but it was significantly associated with β_2 -microglobulin levels. Authors could not explain this phenomenon¹⁴. It was later shown that both PCT and β_2 -microglobulin are cleared only by high-flux HD¹⁷. Moreover, a strong correlation exists between both molecules in chronic HD, suggesting a new pathway by which inflammation and/or infection may play in the development of dialysis-related amyloidosis¹⁹.

Later on, Herget-Rosenthal et al. considered PCT for the acute detection of infection in HD²³. They concluded that PCT could be an accurate marker of infection on intermittent HD. They confirmed the previous reported finding that high-flux membranes decreased substantially PCT levels, compared to low-flux membranes, by 17% in non-infected individuals. Pre HD determinations demonstrated a sensitivity of 89% and a specificity of 81%. However, this prospective study included 68 infected subjects who were indistinctly on chronic or acute HD. The heterogeneity of

this population could explain the wide PCT range encountered in infected patients (median 5.9 ng/ml, r: 2.1-11.5) vs. non-infected (0.8 ng/ml, r: 0.3-1.4), and may have biased the proposed cut-off value of 1.5 ng/ml by Dahaba et al. to discriminate between infected and non-infected patients in 55 HD cases²². In agreement with our study, PCT levels in non-infected subjects were elevated when compared to their normal non-infected population (0.05 ng/ml) and ours (0.063 ng/ml). Interestingly, their non-infected PCT value agrees with our proposed PCT 0.824 reference value. The authors found PCT to be superior to CRP as a marker of infection, although no correlations between both parameters were performed.

Another report by Level et al. assessed PCT as a marker of inflammation and not of infection in 62 chronic HD patients²⁵. Mean PCT before HD were 0.69 ± 0.81 ng/ml, 57% of which were > 0.5 ng/ml. An important issue was that 18% of patients were infected; in this group PCT levels were significantly higher than in the non-infected group (1.15 ± 1.5 vs. 0.58 ± 0.38 ng/ml). Noteworthy, again PCT levels in non-infected subjects were elevated when compared to the normal non-infected population (0.05 ng/ml), and similar to the proposed cut-off to discriminate low-grade infection. They concluded, as in our study, that PCT positively correlated with CRP. However, they also employed both low and flux-membranes, explaining the wide range of PCT values of the population: 1.3-66.4 ng/ml. Moreover, it appears that a non-normal distribution of PCT values may have been present (as in our and other publications), and a median rather than the mean could have better expressed their findings, and the conclusions could have been different.

Sitter et al. assessed both PCT and CRP as tools to discriminate bacterial infections from inflammatory processes in different stages of renal disease, in which 76 were HD patients¹⁵. In coincidence with us, 97% of the mean PCT levels in non-infected chronic HD patients were below the proposed cut-off level of 1.5 ng/ml and higher than in patients with stages 1 to 4 of chronic kidney disease, as shown by others²¹.

Our study presents many drawbacks. The number of patients included may be not representative enough to draw firm, general conclusions, but is similar to all other PCT HD reports. Moreover, the age of both groups shows a mild significant difference, which could have partially influenced on the results. This is due to the fact that the control population was randomly chosen. Finally, the main finding of our study may be that in non-infected subjects PCT levels were elevated, suggesting the relationship between PCT and aseptic inflammation is strong in HD at PCT levels < 0.8 ng/ml, supported by a PCT-CRP significant correlation.

In conclusion, despite the firm association between PCT and bacterial infections in the general population, in dialysis these considerations may be misleading and contradictory in some aspects when the scant available

data is analyzed. In HD patients, PCT appears to be chronically augmented due to many factors. According to data on the general population and in certain reports on severely infected HD patients, PCT levels are substantially increased. In HD, normal PCT reference values may differ from other populations and must be addressed: for non-infected HD patients, our findings suggest levels must not exceed 0.8 g/ml. In this situation, PCT can be a marker of cardiovascular disease, microinflammation and a lower chance of infection. PCT levels between 0.8 and 2 ng/ml can more likely overlap with localized or the initial phase of bacterial infections; PCT levels > 2 ng/ml may be indicating a more serious infectious picture. In HD, PCT cut-off normal values are yet to be properly determined.

Conflicts of interests: PCT kits were donated by Roche.

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La Real Audiencia ha prohibido en la fecha la circulación y lectura de La Estrella del Sur, considerando que es un periódico que propicia ideas abominables y heréticas, difícilmente imaginables. El bando específico que no podrá ser leído ni en público ni en privado, ni retenerla el más corto espacio de tiempo.*

Alberto M. Salas(1915-1995)

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**La Estrella del Sur* o *The Southern Cross*, primer periódico publicado en Montevideo, bilingüe, se publicó entre mayo y julio de 1807, durante los meses que Montevideo estuvo bajo el poder inglés durante la Segunda de las Invasiones Inglesas.