



STUDY OF C-REACTIVE PROTEIN AS A PROGNOSTIC AND DIAGNOSTIC FACTOR IN COLORECTAL CANCER

Morate A¹, Rabadán J², De Andrés B², Pérez V³, Bustamante R⁴, Catalina M²

¹Emergency Castilla y León, ²Department of General Surgery "B", ³Department of Néphrologie, ⁴Department of Central Laboratory, Clinical University Hospital of Valladolid, Spain

KEYWORDS:

C-reactive protein, colorectal cancer, surgery.

Correspondence:

ARANCHA MORATE BENITO
C/ Constitución nº 17
Villamarciel, Valladolid, España.
Tel: 34 983 770560
E-mail: raularan@teleline.es

SUMMARY

BACKGROUND: We studied the behaviour of C-reactive protein in patients with colorectal cancer.

METHODS: In the current study serum was sampled from 40 patients: 20 with colorectal cancer and 20 with groin hernia, who were treated with surgery. All these patients formed the control group. Paediatric ages (under 15) were excluded. Pre-operative, immediate post-operative (between 3 and 6 hours after surgery) and late post-operative (at least 1 month after surgery) blood samples were collected for quantitative serum C-reactive protein measurement.

RESULTS: We observed that C-reactive protein concentrations were higher in the group with neoplastic pathology than in the control group in the three measurements, being these differences significant ($p < 0,050$) and very significant ($p < 0,001$). In the immediate (30,58 mg/l) and late post-operative periods (44,88 mg/l), the patients with colorectal cancer showed a concentration of C-reactive protein higher than in the pre-operative period (16,64 mg/l), being their statistical value significant and very significant, respectively.

CONCLUSION: The above explained suggests that C-reactive protein behaves as a sensitive prognostic marker for colorectal cancer.

INTRODUCTION

It is common knowledge that early detection is highly important with regard to the adequate choice of treatment to any pathology. This is very relevant when the pathology to be treated is a malignant tumour disease such as colorectal cancer. This neoplasia appears as the second mortality cause after lung cancer¹ in USA. Its incidence remains in the last few years, being favoured, among other factors, by the lifestyle of developed countries and their diet habits. However, the mortality rate has dropped by nearly 17% between 1973 and 1992² due to early detection and more advanced treatment strategies like surgical treatment. This one is mostly preferable for colorectal neoplasia and its aggressiveness must be taken into account even if it is malignant. Any resection is regarded as an acute traumatism in view of the elevation in non-specific inflammatory markers observed after surgery.³

It is well known that there are some plasmatic proteins whose concentration changes in the inflammatory focus that

are considered as acute-phase reactants, either positive (if their concentration increases) or negative (if it declines). C-reactive protein (CRP) is found among positive reactants. CRP increases its concentration more than 100 times in the inflammatory focus, peaks in 4-6 hours of the tissue injury and can remain at high levels for a long time. CRP is a sensitive marker for inflammation and tissue injury and, for some authors⁴, a prognostic indicator of further complications in acute appendicitis.

CRP concentrations have been associated not only with infections but also with the accuracy of an anti-microbial therapy, being an objective index of the response to treatment⁵. Elevated CRP levels together with interleukin-6 have been regarded as prognostic and inflammatory nutritional index⁶. It is thought that the measurement of CRP can be useful in the pre-operative period. Pre-operative CRP was a prognostic marker in patients with colorectal cancer⁷ as well as a factor predicting an early tumour recurrence in patients who were apparently cured⁸. In contrast, Chung y Chang⁹ observed that the

increased pre-operative serum CRP concentration was not a factor predicting survival.

PATIENTS AND METHODS

This study yielded 40 patients, 9 women and 31 men (aged between 15 and 88), who were divided into two groups. First, 20 patients with neoplastic pathology who had colorectal cancer and were treated with surgery. Second, 20 patients (control group) who underwent abdominal surgery of a pathology, which was neither neoplastic nor inflammatory like, groin hernia. 19 men and 1 woman, who ranged in age from 19 to 82 years, formed the control group. Of these, 15 suffered from right groin hernia and the remaining 5 patients from left groin hernia. There were 12 men and 8 women in the group with neoplastic pathology. They ranged from 56 to 88 years. Of these, 4 patients had rectum neoplasia, 8 patients right colon neoplasia and 2 other patients showed double (rectum and left colon) neoplasia.

We measured serum CRP concentration in the pre-operative, immediate post-operative (between 3 and 6 hours after surgery) and late post-operative (at least 1 month after surgery) periods by using the nephelometer. SPSS statistical program was used for statistical analysis. We calculated indexes that define data distribution: sample size, arithmetic mean, standard deviation and variance. Non-parametric tests were used for the comparison of means and variances in order to avoid normal distribution. Spearman Rank Correlation was used to calculate statistical values. Finally, p-value of <0,001 was considered very significant, <0,050 significant and <0,100 hardly significant, respectively.

RESULTS

Now, we evaluate the different results from the two groups studied and classify them individually. No significant anthropometric differences were reported.

Control group: Table I shows CRP mean in the three measurements performed. Immediate post-operative and pre-operative CRP levels showed no significant change. In contrast, it increased with significant elevated values in the late post-operative period with respect to preoperative concentration.

Table I.

DETAILS OF CRP STATISTICAL VALUES IN THE CONTROL GROUP

	PRE-OPERATIVE	IMMEDIATE POST-OPERATIVE	LATE POST-OPERATIVE
X	9,35	8,05	9,16
S.D	5,22	5,27	12,63
N	20	20	20

(X= arithmetic mean, S.D= standard deviation, N= sample size)

Group with neoplastic pathology: These patients in comparison to patients in the control group had a different median age (68, 15 for the cancer group and 60,10 for the control group), with a p- value of <0,100, hardly significant.

Table II.

DETAILS OF CRP STATISTICAL VALUES IN THE GROUP WITH NEOPLASIC PATHOLOGY

	PRE-OPERATIVE	IMMEDIATE POST-OPERATIVE	LATE POST-OPERATIVE
X	16,64	30,58	44,88
S.D	26,46	52,16	44,38
N	20	20	19

(X= arithmetic mean, S.D= standard deviation, N= sample size)

Different statistical values obtained from the group with neoplastic pathology are detailed in Table II.

CRP rise was statistically significant, both in the immediate and late post-operative periods with respect to the pre-operative value. A difference of p <0,050 was found between the pre-operative and immediate post-operative measurements and p <0,001 between the pre-operative and late post-operative measurements. Besides, a p-value of <0,050 was obtained between the immediate and late post-operative periods.

DISCUSSION

We tried to analyse not only the role that C-reactive protein (acute-phase protein) plays against aggression, but also how it behaves in malignant neoformative processes like colorectal cancer and elucidate if it is relevant both for the diagnosis and the post-operative progress of the patient. Even though we set other analytical parameters, they were only a reference to discuss the results, not the object of the current study.

CRP has been regarded as one of the best laboratory indicators to assess the disease development, being its secretion higher during the acute phase¹⁰. Bourguignat and his colleagues¹¹ prefer CRP to ESR (Erythrocyte Sedimentation Rate) since this one can be influenced by several factors and shows slower measurements and less sensitivity.

Nowadays, CRP is found to be a sensitive marker for inflammation and any tissue injury, being its use unavoidable for Okamura¹². Its kinetics presents remarkable differences with the other acute-phase reactants, with a highest serum elevation within 4 and 6 hours of the tissue destruction, remaining elevated for a long period of time¹³.

Statistically significant differences between the pre-operative and immediate post-operative (performed 3 hours after surgery) measurements were not reported. However, there was a late post-operative CRP rise with respect to pre-operative and immediate post-operative levels with a hardly significant statistical value. Moreover, we observed that CRP correlated with leukocytes in the three measurements, being statistically significant. For us, this fact backs up the idea that this protein can be considered as a prognostic marker for aggression. In the group of patients with colorectal cancer, they showed elevated CRP levels with regard to the control group, with a clear statistical significance in the three measurements. (Fig. 1)

Nozoe and his group suggested in 1998 that monitoring pre-operative CRP levels was convenient in patients who

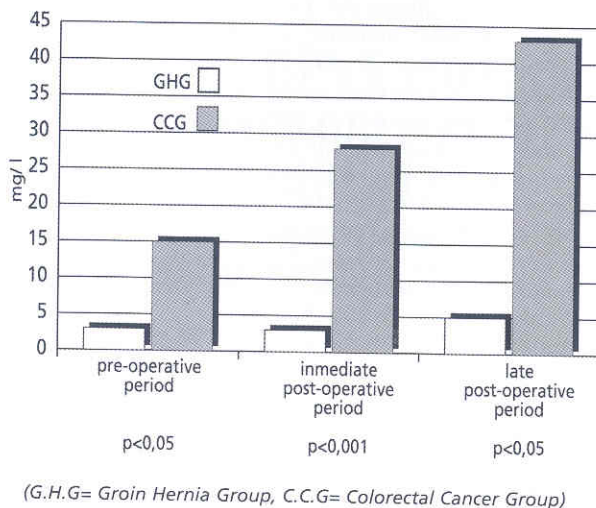


Figura 1.- Diferencias in CRP behaviour between the control group and ythe cancer group.

underwent neoplastic colorectal surgery in order to assess their recovery. Other authors^{14,15} have associated the rise in pre-operative CRP concentration with the risk of developing severe post-operative complications like infections. De Mello and his co-workers¹⁶ suggested the use of CRP as a marker for colorectal cancer since its elevation would be a predictive indicator of the malignant potential of the tumour. Nielsen¹⁷, Durdey¹⁸ and Mahmoud¹⁹ give a great step forward by stating that pre-operative CRP correlates with the tumour extension degree and thus, it provides further information about the likeable resectability. Even, it can be a marker for tumour recurrence, according to Gorasson²⁰ and his group. Later, Nozoe²¹ examined the likeable relationship between the elevation of serum CRP and the decrease in lymphocytes percentages in the peripheral blood, being an indicator of immunity.

Pre-operative CRP was high in our patients with respect to the control group and showed a significance of $p < 0,050$ while the following measurement (performed 3 hours after surgery) reached a great statistical significance of $p < 0,001$, being the difference of $p < 0,050$ in the late post-operative period. These results clearly seem to suggest that CRP can be considered as a reliable indicator of the post-operative progress in these patients since it elevates very significantly between 3 and 6 hours after major surgery and tends to normalise some time after. This is backed up by positive correlations among the three measurements.

However, pre-operative and post-operative percentages of lymphocytes clearly decrease with respect to the control group, being statistically significant in the first and second measurements. The fact that CRP levels are elevated in the three measurements and the lymphocytes percentages decrease can indicate, according to Nozoe, that the patients of this group reflected impaired immunity and this protein can be regarded as a marker for immunity.

In short, elevated CRP levels correlate with colorectal pathology and thus, it can be a sensitive prognostic marker for patients with colorectal cancer.

REFERENCES

1. Mayer RJ. Tumores del intestino delgado y grueso. In: Harrison. Principios de Medicina Interna. Madrid: Ed. Interamericana. McGraw-Hill, 1992; Tomo II p.1499-1501.
2. Rennie J, Rusting R. Cerco al cáncer. Investigación y ciencia 1996; Nov: 6-8.
3. Fasching G, Kurz R, Wendler M. The effect of surgical trauma on parameters of inflammation. Z Kinderchir 1988; 43: 3-5.
4. Gatón Gómez J, Farto Nieto N, Fdez de la Gándara F, Lizárraga Febres E, Robina Rosat F y Blanco García S. La determinación de los niveles séricos de Proteína C reactiva puede disminuir la tasa de apendicitis perforadas. Cirugía Española 1991; 50: 267-270
5. Cox ML, Rudd AG, Gallimore R, Hodgkinson HM, Pepys MB. Real-time measurement of serum c-reactive protein in the management of infection in the elderly. Age-Ageing 1986; 15: 257-266.
6. Walsh D, Mahmoud F, Barna B. Assessment of nutritional status and prognosis in advanced cancer: interleukin-6, C-reactive protein, and the prognostic and inflammatory nutritional index. Support Care Cancer 2003; 11 (1): 60-62.
7. Nozoe T, Matsumata T, Kitamura M, Sugimachi K. Significance of preoperative protein as an indicator for prognosis in colorectal cancer. Am J Surg 1998; 176 (4): 335-338.
8. McMillan DC, Wotherspoon HA, Fearon KCh, Sturgeson C, Cooke TG, McArdle CS. A prospective study of tumor recurrence and the acute-phase response after apparently curative colorectal cancer surgery. Am J Surg 1995; 170 (4): 319-322.
9. Chung YC, Chang YF. Serum C-reactive protein correlates with survival in colorectal cancer patients but is not an independent prognostic indicator. Eur J Gastroenterol Hepatol 2003; 15 (4): 369-373.
10. Macynitire SS, Kushner I, Samols D. Secretion of c-reactive protein becomes more efficient during the course of the acute phase response. J Biol Chem 1985; 260: 4169-4173.
11. Bourguignat A, Féraud G, Jenny J-Y, Gaudias J, Kempf I. Diagnostic value of C-reactive protein and transthyretin in bone infections of the lower limb. Clin Chim Acta 1996; 255 (1): 27-38.
12. Okamura JM, Miyagi JM, Tenada K, Hokama. Potential clinical applications of c-reactive protein. J Clin Lab Anal 1990; 4: 231-235.
13. Deodher SD. C-reactive protein: the best laboratory indicator available for monitoring disease activity. Cleve Clin J Med 1989; 56: 126-130.
14. Goransson J, Jonsson S, Lason A. Screening of concentrations of C-reactive protein and various plasma protease inhibitors preoperatively for the prediction postoperative complications. Eur J Surg 1998; 164 (2): 89-101.
15. Franssen EJ, Maessen JG, Elenbaas TW, van Aarnhem EE, van Diei Visser MP. Enhanced preoperative C-reactive protein plasma levels as a risk factor for postoperative

- ve infections after cardiac surgery. *Ann Thorac Surg* 199; 67 (1): 134-138.
16. De Mello Junior JP, Giles GB: Combination of cancer markers in the detection and prognosis of digestive system tumors. *Arq Gastroenterol* 1986; 23 (3): 133-144.
17. Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N. Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. *Ann Surg Oncol* 2000; 7 (8): 617-623.
18. Durdley P, Willians NS, Brown DA. Serum carcinoembryonic antigen and acute phase reactant proteins in the pre-operative detection of fixation of colorectal tumours. *Br J Surg* 1984; 71 (11): 881-884.
19. Mahmoud FA, Rivera NI. The role of C-reactive protein as a prognostic indicator in advanced cancer. *Curr Oncol Rep* 2002; 4 (3): 250-255.
20. Goransson J, Jonsson S, Lasson A. Pre-operative plasma levels of C-reactive protein, albumin and various plasma protease inhibitors for the pre-operative assessment of operability and recurrence in cancer surgery. *Eur J Surg Oncol* 1996; 22 (6): 607-617.
21. Nozoe T, Matsumata T, Sugimachi K. Preoperative elevation of serum c-reactive protein is related to impaired immunity in patients with colorectal cancer. *Am J Clin Oncol* 2000; 23 (3): 263-266.