Relation between Postoperative Fatigue and Serum Calcium

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Zusammenfassung

Das Ziel dieser Arbeit ist die Untersuchung der Korrelation zwischen postoperativer Müdigkeit und den Veränderungen in totalem und ultrafiltrierbarem Calciumgehalt im Blut. Für diese Studie wurden 60 freiwillige Patienten (36 Frauen und 24 Männer), die für Bauchoperationen vorgesehen waren, untersucht. Diese Studie wurde in vier Stadien ausgeführt, dem präoperativen (PRE) Stadium, am 9. (9-POS), am 27. (27-POS) und am 45. (45-POS) Tag des postoperativen Stadiums. Der Müdigkeitsfaktor (F) wurde vermittels einer subjektiven Skala, die von 0 bis 10 eingeteilt war, ermittelt. Die Serumproteine (TP) und das menschliche Serum-Albumin wurden vermittels Kolorimetern (Biuret-Methode) bestimmt. Der Calciumgehalt im Serum, total (CaT) und ultrafiltrierbar (CaU), wurden durch Spektrophotometrie mit atomarer Absorption gemessen. Unsere Ergebnisse zeigten eine Verringerung des (CaU) am 9. postoperativen Tag (9-POS), es erhöhte sich an den folgenden Tagen bis zu den Werten der präoperativen Phase. Eine negative Korrelation zwischen dem Calciumgehalt im Serum, dem CaT, dem CaU und dem Grad der Müdigkeit wurde ebenfalls beobachtet.

Summary

The aim of this work is to investigate the correlation between postoperative fatigue and changes in total and ultrafiltrable serum calcium. To carry out the research, 60 volunteer patients (36 women and 24 men) programmed for elective abdominal surgery were studied. The study was carried out in four states, preoperative (PRE), on the 9th (9-POS), 27th (27-POS) and 45th (45-POS) day of the postoperative period. The measurement of fatigue (F) was carried out by means of a subjective scale graduated from zero to ten. In serum total protein (TP) and albumin were determined by colorimetric method (Biuret) in an automatic autoanalyser. Total calcium (CaT) and ultrafiltrable calcium (CaU) in serum were calculated by atomic absorption spectrophotometry and the CaU were obtained by ultrafiltration. Our results, show a decrease in the CaT concentration in the early postoperative period (9-POS), followed by a recovery in days running (the levels in 27-POS and 45-POS are similar or higher than the PRE levels). This decrease in the CaT coincides with a similar changes in serum ultrafiltrable calcium (CaU). A significant positive correlation ($p < 0.05$) being observed between CaU and CaT in all stages studied, and correlated negatively with subjective fatigue.

Résumé

Le but de ce travail est etudier les correlations entre le calcium serique, total et ultrafiltrable, et le degré d'asthénie (fatigue). Nous avons inclus soixante volontairs devant subir une intervention abdominale élective (36 femmes et 24 hommes). On a fait l'étude dans le preopératoire (PRE) et dans le postopératoire (9, 27 et 45 jours). Le degré d'asthénie a été determiné à l'aide d'une échelle subjective spécialement conçue. Les proteins seriques (TP) et l'albumin serique humaine (HSA) ont été determinées par cholorometrie (méthode biuret). Le calcium serique, total (CaT) et ultrafiltrable (CaU) ont été measurés par spectrophotometrie d'absorption atomique. Le calcium serique dans l'ultrafiltrat (CaU) diminué dans le 9ème jour postopératoire (9-POS), àpres pendant les suinats periodes augment j'usquà les niveaux du preopertoire. On a observé aussi une correlation negative entre le calcium serique, CaT et CaU, et le degré d'asthénie.

Introduction

Calcium (Ca) is divised in serum approximately 45% associated with proteins (mainly albumin 80% and globulins 20%), 50% in free state (unbound, ionized, ionic, etc.), and 5% is bound to substances not associated with proteins [1]. The ionized calcium, an important physiological regulator is contained in the ultrafiltrable fraction.

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The ionized Ca is involved on important mechanisms as: neuronal excitability, membrane permeability, hormonal liberation, enzymes activity, bone mineralization, skeletal muscle contraction, etc. In skeletal muscle contraction, the activation of the contractile proteins is triggered by the rise of intracellular ionized concentration, due to the movement of calcium from the storage site in the sarcoplasmic reticulum to the myoplasm. With repeated contraction there is a progressive loss of force producing capacity, termed muscle fatigue.

The fatigue that is defined as originated from: continuous high-frequency stimulation, repeated tetanic stimulation [2, 3], long-duration rhythmic activity [4], continuated convalescent period, etc. The convalescent period is characterized by increased fatigue, which is correlated with a deterioration in nutritional status [5, 6]. The fatigue appears in a progressive form due to various factors such: impairment of Ca^{2+} release form the sarcoplasmic reticulum [7], reduced myofibrillar Ca^{2+} sensitivity and reduced maximum Ca^{2+}-activated tension [3].

Measures of muscle functions have shown a deterioration in the immediate post operative period that was not restored until several weeks after surgery [5, 6].

In previous works we have investigated the relation between magnesium levels and fatigue in patients programmed for elective abdominal surgery [5] and changes in serum trace elements Cu and Zn after surgery in predictive postoperative fatigue [8]. Changes on serum concentrations of Na^+, K^+ and of inorganic phosphate have been seen [9] and, *Brookes* et al. [10] have been reported that total concentration of calcium and ionic calcium were slightly reduced after 24 hours in patients undergoing cardiopulmonary bypass. For that we believe that alterations in serum concentration of inorganic electrolytes are one part of the complex events leading to the development of fatigue.

The aim of this work is to investigate the correlation between postoperative fatigue and changes in total and ultrafiltrable serum calcium.

Material and Methods

To carry out the research, 60 volunteer patients (36 women and 24 men) were studied, all of them belong to the middle class. They were admitted to hospital for a variety of elective surgical abdominal procedures. The study was carried out in four states, preoperative (PRE), on the 9th (9-POS), 27th (27-POS) and 45th (45-POS) day of the postoperative period. The requisites for inclusion in the study were as follows: they were not to be suffering any kind of illness other than the one for which they were undergoing surgery; they were not to have been undergoing any pharmacological treatment in the previous three months; they were not to have lost more than 10% of their normal weight in the previous six months nor more than 5% in the previous month; they were not to be suffering any complications in the first 27 postoperative days, they had an axila temperature below 38 °C during the first 72 postoperative hours.

The physical characteristics of the patients were: mean ± SD, age, 53 ± 15.5 years; weight 63.5 ± 9.3 Kg and height 156 ± 0.22 cm.

The measurement of fatigue (F) was carried out by means of a subjective scale graduated from zero to ten [11]. The grade was obtained after confronting the patient with a series of graphs which displayed typical day to day situations of effort, such as housework, walking, etc., and the need for asleep. At each examination the fatigue scale was thoroughly explained to the patients and each score was made without reference to previous score results. Blood samples were taken after a period of three hours without food by venopunction (Venojet), obtained preoperatively and 9, 27 and 45 days postoperatively. In serum total protein (TP) and albumin were determined by colorimetric method (Biuret) in an automatic autoanalyser.

Total calcium (CaT) and ultrafiltrable calcium (CaU) in serum were calculated by atomic absorption spectrophotometry (Perkin Elmer 272). The CaU were obtained by ultrafiltration by a method described in a previous work [12].

Data were expressed as means ± SEM. The analysis of variance was applied, and only when this was significant ($p < 0.05$) was a comparison of paired-samples averages taken by Student's t-test. Later, lineal regression was used between variables.

Results

Tab. 1 reflect the average values obtained for serum total proteins (TP) and serum albumin (HSA) that decreased significantly on the 9th day of postoperative period (9-POS) and were completely recovered on 27th and 45th days of postoperative period.

Fig. 1 showed the evolution of serum total calcium (CaT), serum ultrafil-

Tab. 1: Evolution of total proteins (TP) and human serum albumin (HSA). Statistics significances: 9-POS, 27-POS and 45-POS vs PRE [a] $p < 0,01$.

	TP (g/dl)	HSA (g/dl)
PRE	7.2 ± 0.6	3.8 ± 0.4
9-POS	6.7 ± 0.6[a]	3.3 ± 0.5[a]
27-POS	7.5 ± 0.5	3.8 ± 0.5
45-POS	7.5 ± 0.4	3.8 ± 0.4

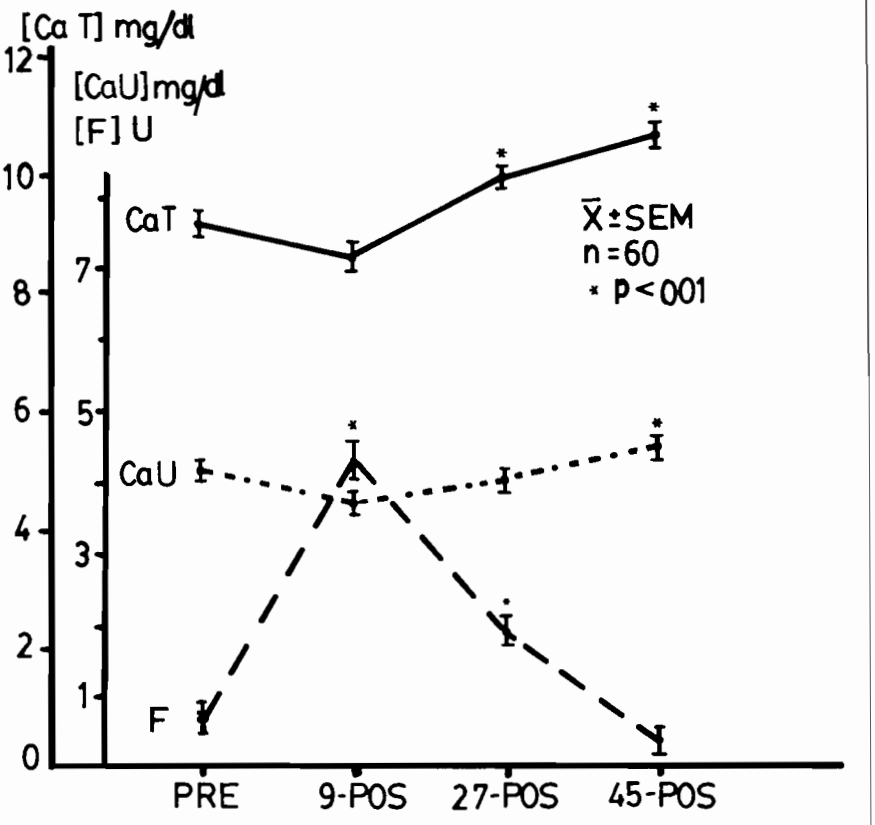

Fig. 1: Evolution of fatigue (F), total calcium (CaT) and ultrafiltrable calcium (CaU) in all stages studied. Significant differences with respect to preoperatory state, * $p < 0.01$.

Tab. 2: Lineal regression analysis of postoperative fatigue on the 9th (9-POS), 27th (27-POS) and 45th (45-POS) day vs preoperative fatigue (FP).

Etapa	Ecuación de regresión	r	p
9-POS	F9 = 0.58 FP + 3,95	0,379	0,003
27-POS	F27 = 0,71 FP + 1,42	0,425	0,001
45-POS	F45 = 0,52 FP + 0,03	0,590	0,000

trable calcium (CaU) and subjective fatigue (F) (X ± SEM) in the four phases of study. The level of fatigue (F) in the 9th postoperative day (9-POS) and in the 27th postoperative day was much higher ($p < 0.001$) than that found in the preoperative period (PRE), and recovered on 45th day the PRE levels. The total calcium (CaT) were higher ($p < 0.01$) on 27th and 45th days of convalescene than PRE levels. The ultrafiltrable calcium (CaU) were not completely recovered until 45th day of convalescence ($p < 0.01$).
In tab. 2, a significant correlation was observed between preoperative fatigue (FP) and postoperative fatigue on 9-POS (F9) ($p < 0.01$); and postoperative fatigue on 27-POS (F27); ($p < 0.01$) and postoperative fatigue on 45-POS (F45) ($p < 0.01$).

Discussion

Uncomplicated major surgery is followed by a pronounced increased of feel fatigue extending throughout the first month in about one-third of patients [6]. During postoperative fatigue a large number of alterations occur [13] and there are many substances that might be involved in contraction fatigue and their roles have not been completely evaluated, for example, the serum calcium ions (Ca^{2+}) that participate in muscle contraction. The Ca^{2+} is the fraction that exert the physiological effects and characteristics signs could be appear when is disturbed. Moderate raising of total calcium (CaT) concentration in extracellular liquid cannot influence on the neuromuscular apparatus. However, the moderate fall of this cation change the time-voltage relation during action potential, in consequence, the exciting threshold decrease notably. *Williams* et al. [14] have shown that extracellular calcium influx may have some influence on skeletal muscle twitches during prolonged repetitive activity.

Our results, show a decrease in the CaT concentration in the early postoperative period (9-POS), followed by a recovery on days running (the levels in 27-POS and 45-POS are similar or higher than the PRE levels). This decrease in the CaT coincides with a similar changes in serum ultrafiltrable calcium (CaU). A significant positive correlation ($p < 0.05$) being observed between CaU and CaT in all stages studied, and correlated negatively with subjective fatigue: Fatigue (F) vs total calcium (CaT) ($r = -0,679, p < 0,01$) and Fatigue (F) vs ultrafiltrable calcium (CaU) ($r = -0,945$, $p < 0,01$) (fig. 1). These results showed the physiological importance of correct serum calcium levels on fatigue, and its direct relation with ionic calcium. A decreased calcium concentration during fatigue has been demonstrated [15], which explains a major part of the reduced force. The present results also suggest that CaT and CaU variations in 9th day after abdominal elective surgery may occur as a consequence of reduction in calcium release.

Various authors [5, 6] have shown that a postoperative decrease in muscle force and endurance is related to subjective postoperative fatigue. Other explanation for the relation between CaU and subjective fatigue could be based in a sequence of mechanisms leading to muscle fatigue. During muscle contraction, Ca^{2+} is released from the sarcoplasmic reticulum and bind to the troponin in the thin, actin-containing muscle filaments.

The failure of Ca^{2+} sequestration by sarcoplasmic reticulum plays a major role in muscle fatigue [16]. The reduced Ca^{2+} concentration in sarcoplasmic reticulum may be due to an excess being bounded to troponin either to a reduction in the amount of ATP necessary to drive Ca^{2+} back [17]. *Appell* et al. [18] based on the assumption that high tensions in muscle cause structural injury, have proposed that sarcolemma damage is accompanied by a net influx of Ca^{2+} from the interstitium into the muscle fibre, where the mitochondria can accumulate the ion, which inhibits cellular respiration.

Different symptoms can be appear if the fall in serum calcium, for example, were originated by hipoproteinemia or by reduction of free calcium. Our results, show a decrease in the total serum proteins and in the serum albumin levels in the early postoperative periode (9-POS). Recently *Sun* et al. [19] concluded that serum albumin and total protein concentrations were significantly reduced by surigcal injury, with significantly greater decreases after abdominal and thoracic surgery. These decreases were caused, in large part, by the volume of intravenous fluid used in resucitation and blood loss.

The total serum proteins returned to PRE- levels on days 27 and 45 of convalescence, however the fraction of CaU remains into small limites (52.2%) in all stages studied. Consequently, the CaT diminution resulted from both calcium bound proteins and free calcium decline. As regards the variation on total serum proteins, serum albumin and subjective fatigue, the results suggested a negative relation in all stages studied. These results are in agreement with those observed by *Makela* et al. [20] who identify the serum albumin levels under 35 g/l as a contributory factor associated with a significantly greater complication in patients operated on for intraabdominal cancer.

In spite of our results are in agreement with those observed by *Schroder* et al. [21] who indicate that the best predictor of postoperative fatigue was preoperative fatigue. Moreover we think that they are a suitable account that allows make use of ultrafiltrable calcium as a predictor of subjective fatigue. We conclude in agreement with *Dart* et al. [22] that measurement of serum ionized/ ultrafiltrable calcium in patients with an acute abdominal crisis is recommended.

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