ORIGINAL ARTICLE

Comparative study of systemic early postoperative inflammatory response among elderly and non-elderly patients undergoing laparoscopic cholecystectomy.

Estudo comparativo da resposta inflamatória sistêmica no pós-operatório precoce entre pacientes idosos e não idosos submetidos à colecistectomia vídeo-laparoscópic

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ABSTRACT

Objective: to evaluate and compare the early postoperative period systemic inflammatory response between elderly and non-elderly patients submitted to laparoscopic cholecystectomy, mainly performing a quantitative analysis of interleukin-6 (IL-6), a marker of inflammatory activity systemic. **Methods:** we compared a series of cases over a period of six months at the Gaffrée and Guinle University Hospital of the Federal University of the State of Rio de Janeiro, involving 60 patients submitted to elective laparoscopic cholecystectomy. We used non-probabilistic sampling for convenience, selecting, from the inclusion criteria, the first 30 patients aged 18-60 years, who comprised group I, and 30 patients with age equal to or greater than 60 years, who formed group II. **Results:** the 60 patients involved were followed for at least 30 days after surgery and there were no complications. There was no conversion to open surgery. The values of the medians found in the IL-6 dosages for the preoperative period, three hours after the procedure and 24 hours after surgery were, respectively, 3.1 vs. 4.7 pg/ml, 7.3 vs. 14.1 pg/ml and 4.4 vs 13.3 pg/ml. **Conclusion:** Elderly patients were more responsive to surgical trauma and had elevated IL-6 levels for a longer period than the non-elderly group.

INTRODUCTION

Brazil has been presenting a process of rapid and intense population aging. In the USA, the population aged 65 or over was 8.1% in 2000 and reached 12.4% in 2015. The estimate for 2020 is that about 88.5 million (20.2%) of Americans are 65 or older[1]. In Brazil, it is estimated that the elderly population reaches the order of 30 million in 2020[2]. Consequently, the number of elderly patients who undergo surgical procedures has increased considerably[3,4]. Cholelithiasis is the most common abdominal surgical disease in these individuals[5] and several studies describe the increase of cholecystectomies in octagenarians[6-8]. The high prevalence of cholelithiasis makes cholecystectomy one of the most performed surgical procedures in the world[9,10].

With the advent of minimally invasive surgery, laparoscopic cholecystectomy has become the gold standard treatment for biliary lithiasis, and the laparoscopic procedure has been proven to be associated with a faster recovery and lower systemic inflammatory response[11,12]. Several population studies have shown that the incidence of cholelithiasis and acute cholecystitis increases with age. The prevalence of cholelithiasis is 9.3% for the general population, 21.4% for individuals between 60 and 69 years of age, and 27.5% for individuals aged 70 years or older[5]. Some studies have shown that biliary lithiasis behaves particularly in the elderly population, since there is an approximation of incidence between the genders, a higher incidence of choledocholithiasis and other complicated forms of the disease (cholecystitis, pancreatitis, biliary fistulas), a higher incidence of gallbladder cancer and higher mortality associated with emergency surgery[6,13-15].

Other studies demonstrate a higher morbidity in the postoperative evolution of laparoscopic cholecystectomy in the elderly population (especially above 80 years). These individuals present higher complication rates, higher rates of conversion to open surgery and longer hospital stays[7,16,17]. There is no single reason to explain the greater surgical morbidity found in the elderly population. Probably this cause is multifactorial. Some series have shown that the large number of comorbidities present in this population, associated with low cardiopulmonary reserve, negatively influence postoperative recovery[7,18]. Moreover, other authors have already demonstrated differences in the systemic inflammatory response between young and old individuals in certain situations[19,20].

The objective of this study was to evaluate and compare the systemic inflammatory response between elderly and non-elderly patients submitted to elective laparoscopic

cholecystectomy.

METHODS

This is a case series study, conducted over a six-month period, at the Gaffrée and Guinle University Hospital (HUGG), involving 60 patients submitted to elective laparoscopic cholecystectomy. The criteria used for surgical indication were the clinical history (biliary lithiasis or symptomatic polyp) and ultrasonographic findings, such as microcalculi, a calculus greater than or equal to 3cm, a polyp associated with biliary calculus and a polyp greater than or equal to 1cm in asymptomatic patients.

Inclusion criteria were: age equal to or greater than 18 years, any gender, uncomplicated cholelithiasis, patients without comorbidities (ASA-I) or with clinically compensated comorbidities (ASA-II). Exclusion criteria were: need for conversion to open surgery, intraoperative finding of complicated biliary lithiasis (acute cholecystitis, choledocholithiasis and acute pancreatitis), use of immunosuppressive drugs (corticosteroids and immunomodulators), acquired immunodeficiency syndrome, malignant disease in activity, and those who did not sign the informed consent form.

We used non-probabilistic sampling for convenience, selecting, according to the inclusion criteria, the first 30 patients aged 18-60 years, who comprised group I, and the first 30 patients with age 60 years or greater, who formed group II.

In all the patients studied, we collected blood samples for the quantitative analysis of interleukin-6 (IL-6), a marker of systemic inflammatory activity. This collection occurred in three different moments: in the anesthetic induction, three hours and 24 hours after the end of the procedure. Other parameters studied were plasma leukometry (measured before and after surgery), surgical time (started at the time of the first incision and finished after the last cutaneous suture), presence of comorbidities, body mass index (BMI), variation in pre and post-operative platelet counts and C-reactive protein (CRP) measured 24 hours after the surgical procedure.

All patients underwent general anesthesia, without epidural block and without the use of corticoids or opioids.

We constructed tables to describe the measures of central tendency (mean and median) and dispersion (minimum and maximum values, amplitude, percentiles and standard deviation) of the continuous quantitative variables. We evaluated the difference between means with the Student's t-test for independent samples, the One-way ANOVA test for comparison of variances for paired samples, the Wilcoxon test for comparison between medians of paired samples, and the Mann-Whitney test to compare medians of

unpaired samples. We used the Excel 2016 software and the statistical package SPSS 21.0 (Statistical Package for Social Science - Chicago, IL, 2008) for the analysis. Statistical significance was considered at p<0.05.

This work was approved by the HUGG Ethics Committee, protocol number 03297312800005258, and all the patients involved in the present study signed the informed consent form.

RESULTS

We followed all 60 patients for at least 30 days after the end of surgery. There were no complications or death in this period. No case required conversion to open surgery or insertion of an extra trocar.

Regarding gender, six individuals from group I were male (20%), and in group II, five (16.7%). The majority of the participants, therefore, were female, 80 and 83.3%, respectively (Table 1).

Table 1. Patients undergoing cholecystectomy by gender and age group.

Gender/Group	I		II		p-value*
	n	%	n	%	
Male	6	20.0%	5	16.7%	0.74
Female	24	80.0%	25	83.3%	
Total	30	100%	30	100%	

* Chi-square test.

Regarding surgical risk (Table 2), 66.7% of the individuals in group I were ASA 1, and in group II, 80% of the individuals were classified as ASA 2. Thus, we verified that the greater the age, the greater the number of comorbidities.

Table 2. Patients undergoing cholecystectomy by ASA and age group.

ASA/Group	I		II		P-value*
	n	%	N	%	
ASA 1	20	66.7%	6	20.0%	< 0.001
ASA 2	10	33.3%	24	80.0%	
Total	30	100%	30	100%	

* Chi-square test.

Comparison of body mass index (BMI) revealed a similar mean between groups, 23.1kg/m^2 in group I and 23.2kg/m^2 in group II. The mean duration of the cholecystectomies was approximately one hour for both groups, thus confirming that the surgical time was very close between the two groups, with a mean of 68.3 minutes for group I and 68.1 for group II.

The mean values of C-reactive protein (CRP) measured 24 hours after the surgical procedure were 6.3 for group I and 1.4 for group II, but the standard deviation showed a high variability between observations (Table 3). Regarding preoperative and postoperative leukometry, the mean had similar results. Group I had 6,581.9/mm³ versus 6,678.1/mm³ in group II; and in the postoperative period, 11,246.1/mm³ versus 10,864.3/mm³ for groups I and II, respectively. The mean platelet analysis present the same similarity. In the preoperative period, the values were 266.9 thousand/mm³ in group I versus 260.5 thousand/mm³ in group II, and in the postoperative period they were 255.9 thousand/mm³ versus 241.3 thousand / mm³ for groups I and II, respectively (Table 3).

Table 3. Patients' epidemiological and laboratory profile.

	18-59 years (n=30) Mean (SD)	≥60 years (n=30) Mean (SD)	p value*
Age	44.3 (12.6)	67.8 (7.6)	< 0.001
BMK	23.1 (3.3)	23.2 (2.1)	0.96
WBC			
Preoperative	6,581.9 (1540.5)	6,678.1 (1739.5)	0.82
Postoperative	11,246.1 (3756.7)	10,864.3 (2285.1)	0.63
Platelets			
Preoperative	266.9 (61.3)	260.5 (64.4)	0.69
Postoperative	255.9 (78.5)	241.3 (66.8)	0.44
C-Reactive Protein	6.3 (18.1)	1.4 (1.8)	0.81
Surgery time	68.3 (27.3)	68.1 (23.4)	0.97

SD: Standard Deviation; * Student t Test comparison of means (independent samples).

As for Interleukin 6 (IL-6), the comparison within each group showed that, in the three moments analyzed (preoperative, three hours after surgery and 24 hours after surgery), its median values in group I were, 3.1, 7.3 and 4.4 pg/ml, respectively, and in group II, 4.7, 14.1 and 13.3 pg/ml, respectively, both with statistically significant differences (Table 4).

Table 4. IL-6 levels at the preoperative time and at three and 24 hours after the procedure.

	Group I				Group II			
	Preop	3 hours	24 hours	p value	Preop	3 hours	24 hours	p value
Mean (SD)	7.3 (10.4)	19.4 (34.6)	26.6 (67.1)	0.24 *	17.7 (32.3)	54.5 (124.3)	24.3 (44.1)	0.15 *
25 Percentile	2	2.5	1.8	X	2	8.2	5.8	x
Median	3.1	7.3	4.4	<0.01**	4.7	14.1	13.3	<0.001**
75 Percentile	9.5	13.1	11.9	X	16.4	43.1	19.2	x
Minimum-Maximum	-50.0 2.0	2.5 -174.0	1.8 -332.7	X	-138.0 41.5	2.7 -684.4	2.1 -223.8	x
Amplitude	48	171.5	330.9	X	136.5	681.7	221.7	x

Preop: preoperative time; SD: Standard deviation; * One-way ANOVA comparison of variances (paired samples). ** Wilcoxon test comparison between medians (samples paired by posts).

Regarding comparison between groups, the median values of IL-6 were 3.1 x 4.7 pg/ml in the preoperative period, 7.3 x 14.1 pg/ml three hours after the procedure, and 4.4 x 13.3 pg/ml at the 24th postoperative hour. Only the medians of three and 24 hours showed statistically significant differences (Table 5).

Table 5. Comparison between the IL6 dosage times, preoperative, three hours and 24 hours.

	Preoperative		p value	3 hours		p value	24 hours		p value
	Group I	Group II		Group I	Group II		Group I	Group II	
Average [SD*]	7.3 [10.4]	17.7 [32.3]	0.10**	19.4 [34.6]	54.5 [124.3]	0.14**	26.6 [67.1]	24.3 [44.1]	0.87**
Median	3.1	4.7	0.67***	7.3	14.1	<0.01***	4.4	13.3	<0.001***

* SD: Standard deviation; ** Student's t-Test comparison of means (independent samples); *** Mann-Whitney test comparison of medians (paired samples).

DISCUSSION

Tissue injury triggers a systemic inflammatory response[21], which is influenced by several factors, such as tissue injury volume and trauma intensity. This has already been described when comparing open cholecystectomy with laparoscopic one, the latter with an attenuated inflammatory response, probably due to less associated tissue damage[11,22,23]. Tissue injury from surgical trauma activates different cellular elements responsible for the immune response, like macrophages, neutrophils and natural killer (NK). Once activated, these cells initiate the production of cytokines, such as interleukin-6, which directly participates in the systemic inflammatory response[24]. Riese et al. demonstrated that during abdominal surgeries the peritoneum reacts rapidly, increasing the production of interleukin-6[25]. It has been clearly demonstrated in several studies[12,24,25] that IL-6 can be used as an inflammatory marker, since its levels are elevated early in the face of tissue damage. Therefore, the dosages of interleukin-6 and C-reactive protein have been used by several authors as a method of choice for the evaluation and comparison of the systemic inflammatory response in different groups[26,27]. Like IL-6, C-reactive protein can also be used as a marker of inflammation[2].

Of the group of patients studied, we observed a predominance of the female gender, remembering that gallstones are more prevalent in females[5,9]. Regarding surgical risk, we found a predominance of individuals with comorbidities in group II. However, we included only patients with controlled comorbidities in this study, to minimize their effects on the behavior of inflammatory markers. We also analyzed the two groups regarding body mass index (BMI) and operative time, since the higher BMI could represent greater technical difficulty and longer surgical time. Therefore, we verified that the means of BMI

and operative times were very close between the two groups, emphasizing the homogeneity of the sample. Several studies[26,27] used IL-6 as the main marker of inflammatory response after surgical trauma.

In the results shown in tables 4 and 5, it is possible to note that both groups responded to surgical trauma with elevation of IL-6. In the younger population this initial variation was lower than in the elderly. When comparing the median values of IL-6 dosages of the young and elderly groups in three and 24 hours after surgery, we observed statistically significant differences ($p<0.01$ and $p<0.001$, respectively). By analyzing the results, we can suggest that there is an initial major inflammatory response in the elderly group, since there was a more exacerbated IL-6 release in this group, with a statistically significant difference between the medians. And we also observed that the inflammatory response is more sustained in this same group II.

In summary, it is possible to suggest that the elderly patients have a more exacerbated response to surgical trauma and had this inflammation maintained for a longer period, unlike the younger ones, who responded to the surgical trauma with a lower release of IL-6 and a faster normalization of its levels.

Although CRP was widely used to track inflammatory response in clinical practice, this marker was not sensitive to detect differences in the inflammatory response between the groups (young and old) undergoing a minimally invasive procedure, unlike IL-6, which is a more sensitive marker. Leukometry also behaved similarly between groups I and II. Its initial dosage did not present a significant statistical difference, neither a significant variation between the groups in the postoperative period.

In view of our results, the elderly patient has a more exacerbated response to the surgical trauma of laparoscopic cholecystectomy, an inflammatory response that is maintained for a longer period.

RESUMO

Objetivo: avaliar e comparar a resposta inflamatória sistêmica no pós-operatório precoce de pacientes idosos e não idosos submetidos à colecistectomia vídeo-laparoscópica, realizando, sobretudo, análise quantitativa de interleucina-6 (IL-6), que representa um marcador de atividade inflamatória sistêmica. **Métodos:** estudo de série de casos, comparativo, realizado num período de seis meses, no Hospital Universitário Gaffrée e Guinle da Universidade Federal do Estado do Rio de Janeiro, envolvendo 60 pacientes com indicação de colecistectomia laparoscópica eletiva. Amostragem não probabilística por conveniência foi utilizada, selecionando, a partir dos critérios de inclusão, os primeiros

30 pacientes com idades entre 18 e 60 anos, que compuseram o grupo I e os 30 pacientes com idade igual ou maior que 60 anos, que formaram o grupo II. **R**esultados: os 60 pacientes envolvidos foram acompanhados por no mínimo 30 dias após o término da cirurgia e não houve complicações. Não houve conversão para cirurgia aberta. Os valores das medianas encontrados nas dosagens da IL-6, nos grupos I e II, para cada momento analisado (pré-operatório, três horas após e 24 horas após) foram, respectivamente: 3,1 x 4,7 pg/ml no pré-operatório, 7,3 x 14,1 pg/ml após três horas do procedimento e 4,4 x 13,3 pg/ml na 24ª hora do pós-operatório. **C**onclusão: pacientes idosos responderam de forma mais exacerbada ao trauma cirúrgico e apresentaram elevação dos níveis de IL-6 por um período maior do que o grupo de não idosos.

Descritores: Colecistectomia Laparoscópica. Síndrome de Resposta Inflamatória Sistêmica. Interleucina-6.

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