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PURPOSE: *In this study, we compared the endocrine and cytokine reaction of the patients which laparoscopic and conventional appendectomy was done for acute appendicitis.*

MATERIALS AND METHOD: *50 patients who were operated for acute appendicitis in Ankara Atatürk Research and Training Hospital between the dates December 2013 and February 2014 were enrolled and grouped as either laparoscopic or conventional. Serum ACTH, IL-6 and CRP levels were obtained at induction of anesthesia and postoperative 6th hour.*

RESULTS: *There was no significant difference between the groups in terms of gender, co-morbidities, and perforation rate. Preoperative ACTH levels were similar for both groups while it is significantly lower in postoperative period for laparoscopy group. Moreover, IL-6 levels were also higher in postoperative period for conventional period compared to laparoscopy group. Despite preoperative CRP value of the laparoscopic group was significantly higher than the conventional group, postop values showed no statistical difference. The mean operation time of the laparoscopic appendectomy group was significantly higher than the conventional group.*

CONCLUSION: *Laparoscopic appendectomy causes less metabolic and cytokine response than conventional surgery. ACTH and IL-6 levels could be assessed to evaluate metabolic outcome of surgical intervention.*

KEY WORDS: ACTH, Appendectomy, Conventional appendectomy, IL-6, CRP, Laparoscopic appendectomy, Perforation

Introduction

Acute appendicitis is one of the most common causes of acute abdomen in surgical practice. The conventional appendectomy technique which was first described by McBurney, has been regarded as the gold standard for surgical management of acute appendicitis. While conventional appendectomy is a safe technique to apply ;

laparoscopic appendectomy has recently become popular due to its advantages including less postoperative pain, more rapid recovery, shorter hospital stay, and better visualization of lower abdominal quadrants ¹⁻³.

A surgical intervention causes a kind of trauma followed by an inflammatory and neuro-endocrinological response. In this study we expected to observe less endocrinological and cytokine responses to trauma in laparoscopic surgery compared to conventional surgery.

Materials and Method

This study included 50 patients who applied to Ankara Atatürk Research and Training Hospital with acute abdominal pain between December 2013 and February

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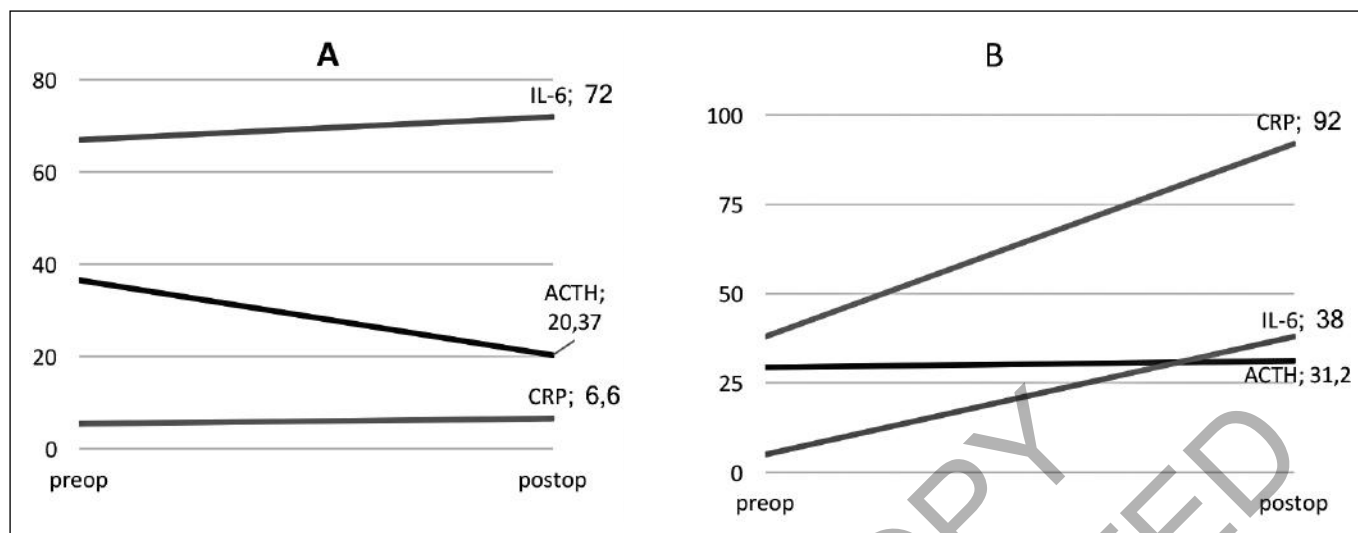


Fig. 1: Changes in levels of inflammatory markers between preoperative(preop) and postoperative (postop) periods in laparoscopy group (A) and conventional surgery group (B). We observe an obvious drop in ACTH level in laparoscopy group but not in conventional group.

2014. All patients were treated with appendectomy after appendicitis was proved by radiological imaging. All patients were informed about the technique, advantages and disadvantages for surgical procedure.

Patients were randomly divided into 2 groups as laparoscopic appendectomy (Group 1, n=25) and conventional appendectomy (Group 2, n=25). Standard technique with three ports was used for laparoscopic appendectomy. The operation time was calculated from skin incision to completion of skin suturation. All patients received a prophylactic dose of antibiotic. The antibiotic regimen was continued after surgery in case of perforation. Simple analgesics were used at the postoperative period. The patients started oral fluid intake 4-6 hours after the procedure and were discharged at the next day.

To determine the endocrinological and cytokine responses to trauma venous blood samples were taken during anesthesia induction (first sample) and six hours after the operation. These samples were studied for ACTH, CRP, IL-6 levels. For IL-6 the samples were centrifuged at 4000 rpm for 5 minutes, the uppermost sera were taken into eppendorf tubes and stored at -70 °C. Next, IL-6 level was immunometrically measured with the DIAsource IL-6EASIA Kit using the solid enzyme-tagged

chemiluminescence technique. Plasma ACTH level was measured with the IMMULITE-1 analyser using the chemiluminescence immunometric measurement techniques. CRP plasma level was measured with the BECKMAN COULTER IMMAGE using the nephelometric method. The normal range specified by the kits were 0 - 60 pg/ml for ACTH, 23.3 - 2560 pg/ml for IL-6 and 0 - 0.8 mg/dl for CRP.

Results

The mean age of the study population was 34,28±10,73 (range 18 - 65) years. Sixty percent of cases were male. 10% of patients had comorbidities. Fourteen percent of the cases had perforated appendicitis.

The mean age was greater for laparoscopy group without a statistical significance ($p=0,153$). There were also no significant differences between the groups with respect to gender distribution, comorbidity, and perforation rate ($p>0,05$). The laparoscopic appendectomy group had a significantly longer mean operation time than the conventional appendectomy group ($p=0,002$) (Table I).

There was no significant difference regarding preoperative and postoperative 6th hour ACTH levels for both

TABLE I - Comparison of demographic variables between two groups.

	Laparoscopy Group		Conventional Group		p values
	%		%		
Age (mean)	36.9		32.6		0.15
Gender (Male/ Female)	16/9	64/36	14/11	56/44	0.564
Comorbidities (Yes /No)	5/20	20/80	1/24	4/96	0.189
Perforation	5/20	20/80	2/23	8/92	0.417
Operation time (minute)	41.6		28		0.002

TABLE II - Mean values for inflammatory markers considering perforation presence regardless of surgical technique.

	Perforation present	Perforation absent	P
ACTH (preop)	253.3	29.3	<0.001
ACTH (postop)	40.8	18.3	0.012
CRP (preop)	19.3	2.7	<0.001
CRP (postop)	23	4.7	<0.001
IL-6 (preop)	582	45	<0.001
IL-6 (postop)	435	82	<0.001

groups ($p=0,05$). In laparoscopy group, the postoperative 6th hour ACTH level was significantly lower than the preoperative ACTH level ($p=0,001$). In conventional group, on the other hand, there was no such difference ($p=0,737$) (Graphic I).

Despite preoperative CRP level was significantly higher in the conventional group ($p=0,012$), similar levels for CRP was measured at postoperative 6th hour ($p=0,056$). The CRP level at postoperative 6th hour was significantly greater than the preoperative CRP level in both groups ($p<0,001$) (Fig. 1).

The laparoscopic appendectomy group had a significantly greater preoperative IL-6 level ($p=0,018$) whereas both groups were similar in terms of IL-6 levels at postoperative 6th hour ($p=0,194$). The preoperative and postoperative 6th hour IL-6 levels did not differ significantly in the laparoscopy group. As expected, the conventional appendectomy patients had a significantly greater IL-6 level at postoperative 6th hour compared to preoperative IL-6 level ($p=0,005$) (Fig. 1).

All cases with perforated appendicitis had a significantly greater ACTH, CRP, and IL-6 levels compared to unperforated cases ($p<0,05$) (Table II). The mean operation time of the perforated cases was significantly longer than that of the unperforated cases ($p=0,002$).

Discussion

Surgery poses a stress on an organism and triggers a chain of endocrinological and inflammatory responses as a result of the activation of the hypothalamus-hypophysis-adrenal axis and the sympathetic nervous system³. The neuroendocrine reflexes are stimulated by many factors like pain, fear, anxiety, body temperature, wound itself, infection, fasting, anesthetic agents. In turn, some mediators released as a result of hypothalamic stimulation by these afferent stimulants stimulate hypophysis, making the latter secrete various hormones, predominantly ACTH⁴. The cytokines interleukin IL-1, IL-6, and TNF α are released into systemic circulation following neuroendocrine stimulation. These cytokines further provokes the release of acute phase proteins, especially C-reactive protein (CRP) which is a common indicator for trauma response in clinical practice⁵.

Currently, there is no specific marker for acute appendicitis. Bachmann et al.⁶ performed a literature review and found out that the rate of negative appendectomy has not essentially changed for the twenty years despite the advance of highly accurate diagnostic tests. Türkyılmaz et al. reported that the combination of CRP level elevation and leucocytosis had a sensitivity of 69% for diagnosing acute appendicitis⁶. Our study determined that both groups had significantly higher CRP levels at postoperative 6th hour (crp2) compared to the preoperative CRP levels (crp1). At this point, we should emphasize that elevation was more significant in conventional surgery group ($p<0,001$)^{8,9}.

Arikan et al. (10) found no significant difference between preoperative and postoperative ACTH levels between conventional and laparoscopic appendectomy groups. Our study demonstrated a significantly lower ACTH level at postoperative 6th hour compared to the preoperative period ($p=0,001$) in the laparoscopic appendectomy group. The conventional appendectomy group had no significant difference between preoperative and postoperative 6th hour ACTH levels ($p=0,737$) (Graphic I). There are not much studies in literature about ACTH as inflammatory precursor. Yoshida et al reported same advantage of laparoscopy by proving a significant drop in ACTH in patients whom were operated for cholelithiasis¹¹.

Türkyılmaz et al⁷ reported that cytokine levels (IL-1, IL-6, TNF- α) were also higher at preoperative period in appendicitis cases, and they added that this finding may be predictive for diagnosis. In studies on cellular molecules Braga et al¹² detected that the immun response against surgical stress was more markedly suppressed by laparoscopy. Our study did not find any significant difference between preoperative and postoperative 6th hour IL-6 levels in the laparoscopy group while there was a significant increase in the postoperative 6th hour IL-6 level compared to the preoperative IL-6 level in the conventional surgery group. ($p=0,005$). High preoperative IL-6 levels are expected because of the obvious inflammation. Although IL-6 level measured at postoperative 6th hour was not significantly changed in the laparoscopy group, it was increased significantly in the conventional appendectomy group, suggesting that the conventional surgery caused more stress than the laparoscopic surgery. This finding was also supported by Braga et al.¹².

The length of operation time is considered as one of the disadvantages of laparoscopic surgery¹³. In our study, operation time was significantly higher in laparoscopy group ($p=0,002$). However, this could be misinterpreted if we consider this is not only surgeon dependent also related with additional equipment preparation and need for extra healthcare personel.

Leape et al.¹⁴ reported that laparoscopy significantly reduced unnecessary appendectomy rates, particularly in young women. Also during our study, two patients consulted with us for right lower quadrant pain and suspected to have gynecological problems rather than acute appen-

dicits were laparoscopically explored but were not appendectomized since they had hemorrhagic ovarian cyst rupture; these patients were excluded from the study protocol. Literature data suggest that the perforation rate of acute appendicitis is 25.8% and it usually occurs in small children and elderly patients aged over 65 years of age (%45 and %51, respectively) ⁵. In our study 14% of the acute appendicitis cases had perforation. This may have stemmed from the fact that the mean age of our study population was 34,28±10,73 (range 18-65) years. Five patients undergoing laparoscopic appendectomy and 2 patients undergoing conventional appendectomy had perforated appendicitis. Due to low number of perforated cases, we could not perform an accurate comparison to show whether laparoscopy is a safe technique for perforated cases. Heng-Fu Lin et al. ¹⁵ reported that for perforated appendicitis cases the laparoscopic technique was safe and associated with less postoperative complications, less pain and a shorter hospital stay.

Conclusion

Infection and surgical intervention induce a systemic stress response through global body trauma. As we conclude regarding our findings; the level of stress attained by laparoscopic appendectomy was lower than by conventional appendectomy. More studies are required to compare the hormonal and cytokine responses to trauma created by open and laparoscopic appendectomies in perforated appendicitis.

Riassunto

La finalità di questo studio è stata quella di confrontare la reazione endocrina e della reazione infiammatoria (citochine) nei pazienti sottoposti ad appendicectomia laparoscopica e laparotomica per appendicite acuta su 50 pazienti sottoposti a tali interventi nell'ospedale di Ankara Atatürk Research and Training tra il dicembre 2013 e il febbraio 2014.

I livelli sierici di ACTH, IL-6 e CRP sono stati ottenuti all'induzione dell'anestesia e alla 6^a ora postoperatoria.

Non è risultata alcuna differenza significativa tra i gruppi in termini di genere, co-morbidità e frequenza di perforazione. I livelli preoperatori di ACTH erano simili per entrambi i gruppi mentre è risultato significativamente più basso nel periodo postoperatorio per il gruppo laparoscopico. Inoltre i livelli di IL-6 sono risultati più elevati nel periodo postoperatorio in caso di intervento laparotomico nel periodo convenzionale rispetto al gruppo laparoscopico. Nonostante il valore preoperatorio della PCR del gruppo laparoscopico fosse significativamente più alto rispetto al gruppo convenzionale, i valori postoperatori non hanno mostrato differenze statistiche. La durata dell'intervento in media è risultato maggiore in caso di laparoscopia rispetto

to alla laparotomia. Dunque l'appendicectomia laparoscopica determina una minore risposta metabolica e infiammatoria rispetto alla chirurgia convenzionale. I livelli di ACTH e IL-6 potrebbero essere utilizzati per valutare l'esito metabolico dell'intervento chirurgico.

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