ORIGINAL ARTICLE

Impact of Medication and Surgical Treatment on Cytokine Concentrations in Patients with Acute and Chronic Cholecystitis

Taalaibek Bekov[1], Arystanbek Atykanov[2], Tugolbai Tagaev[3], Yethindra Vityala[3]

[1]Department of Surgery, Osh City Clinical Hospital, Osh, Kyrgyzstan, [2]Department of Research and Analytics, International Higher School of Medicine, Bishkek, Kyrgyzstan, [3]Department of Research, Honorary International Faculty, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India

Abstract

Background: Cholecystitis is defined as the sudden inflammation of the gallbladder. Surgical intervention is usually necessary to treat this condition because of the difficulty in achieving non-surgical resolution and frequent recurrence without surgery. **Objective:** We aimed to assess the effect of medication and surgical treatment on cytokine concentrations in patients with acute and chronic cholecystitis who showed disease progression. **Methods:** A total of 133 patients with cholecystitis admitted to our hospital were categorized into two distinct groups. The acute cholecystitis group included 79 patients with acute cholecystitis, whereas the chronic cholecystitis group included 54 patients with chronic cholecystitis. An automatic immunoassay analyzer was used to assess the levels of cytokines interleukin 1 (IL-1), IL-4, IL-6, and tumor necrosis factor-alpha in the blood plasma. **Results:** IL-6 concentrations dramatically increased by a five-fold amount compared to those in the control group. IL-6 concentrations were considerably higher in patients with chronic cholecystitis ($P < 0.01$), but the concentrations of other cytokines were not significantly different ($P > 0.05$). The Evaluation of cytokines demonstrated that IL-6 levels increased by 88% in the acute cholecystitis group and 81% in the chronic cholecystitis group, with regard to sensitivity and specificity. In the chronic cholecystitis group, the level of serum IL-1β remained significantly elevated ($P < 0.05$) during discharge relative to its pre-treatment level; in contrast, other cytokines did not show significant changes ($P > 0.05$). **Conclusion:** IL-6 levels increase during inflammation, but treatment reduces cytokine concentrations and elevates IL-4 levels.

Key words: Acute cholecystitis, chronic cholecystitis, cytokines, gallbladder, interleukin

INTRODUCTION

Inflammatory and degenerative illnesses of the gallbladder affect approximately 15% of individuals in affluent countries.[1] Cholecystitis is the primary sign of gallstone formation.[2] Gallstones are solid masses made up predominantly of calcium ions, bilirubin, and lipids, along with small amounts of proteins and additional compounds, present in the gallbladder.[3,4] Surgery is usually required in cases of sudden gallbladder infections leading to cholecystitis. Achieving remission without surgery is challenging and there is a high likelihood of recurrence.[5] About 80–85% of individuals with acute cholecystitis have gallstone disease as the primary cause. The most common purulent symptoms are perivesical infiltration and suppurative cholecystitis. Subhepatic abscess, hydrocholecystis, localized peritonitis, and extensive peritonitis were observed in 3.6%, 7.5%, 1.3%, and 2.3% of patients, respectively.[6,7]

Interleukin 1 (IL-1a), IL-6, and tumor necrosis factor-alpha (TNF-α) are stronger cytokines generated mainly by monocytes and macrophages. They have pro-inflammatory effects on immune responses and inflammation.[8,9] TNF-α stimulates the production of IL-6, affecting gallbladder functions, such as absorption, secretion, and smooth muscle contractions,

Address for correspondence:
Yethindra Vityala, AJ Institute of Medical Sciences and Research Centre, Mangalore, Karnataka, India.
Phone: +91-9121925658.
E-mail: yethindravityala10@gmail.com

Received: 12-02-2024
Revised: 22-03-2024
Accepted: 29-03-2024

which play a key role in initiating inflammation.[10-12] IL-6 trans-signaling is essential for transitioning from acute to chronic inflammation, hence sustaining disease states.[13]

We aimed to assess the effect of medication and surgical treatment on cytokine concentrations in patients with acute and chronic cholecystitis who showed disease progression.

METHODS

One hundred and thirty-three patients admitted to the department of surgery at our hospital with cholecystitis were categorized into two distinct groups. Acute cholecystitis group has 79 patients with acute cholecystitis, whereas the chronic cholecystitis group consisted of 54 patients with chronic cholecystitis. The control group has 38 patients with biliary tracts who tested negative for hypokinesis or hyperkinesis. Each clinical diagnosis was validated based on the clinical symptoms and ultrasound examination.

Within the research sample, the control group consisted of 64% females, the acute cholecystitis group had 82% females, and the chronic cholecystitis group had 79% females. The mean patient age was 45 years. The percentage of patients older than the average age was 56% in the control group, 71.4% in acute cholecystitis group, and 65.7% in chronic cholecystitis group. The majority of patients in the acute cholecystitis group were hospitalized within 24 hours of the onset of sickness symptoms (79.3%). About 81% of the surgical procedures in both clinical groups included laparoscopic surgery.

An automatic immunoassay analyzer (Lepu Medical Technology, Beijing, China) was used to assess the levels of cytokines IL-1, IL-4, IL-6, and TNF-α in blood plasma.

Statistical analyses were performed using Statistica v8.0 software developed by StatSoft, Inc., Tulsa, USA. The data are presented as the mean ± standard deviation. Student's t-test was utilized to assess disparities across groups. A margin of error was used to evaluate the change encompassing the highest and lowest limits of variation in each group at various significance levels ($P < 0.05$ [95%]; $P < 0.01$ [99%]; $P < 0.001$ [99.9%]). The sensitivity and specificity of the cytokine parameters were assessed using traditional methods.[11] Data obtained from patients who provided informed consent were kept confidential. This study was approved by the Bioethics Committee of the International Higher School of Medicine in Kyrgyzstan (protocol No. 93, dated October 21, 2022) and was conducted in accordance with the guidelines of the Declaration of Helsinki.

RESULTS

The concentrations of IL-1β ($P < 0.001$), IL-4 ($P < 0.05$), and IL-6 ($P < 0.001$) were notably higher in the patients in the acute cholecystitis group [Table 1]. The concentration of TNF-α was not substantially different from that in the control group ($P > 0.05$). IL-6 concentrations were dramatically increased by a five-fold amount compared with those in the control group. IL-6 concentrations were considerably higher in patients with chronic cholecystitis ($P < 0.01$), but the concentrations of other cytokines were not significantly different ($P > 0.05$). The concentrations of IL-1, IL-4, and IL-6 were significantly lower in the chronic cholecystitis group than those in the acute cholecystitis group ($P < 0.05$–$P < 0.01$). There was no significant difference in TNF-α concentration between the acute and chronic cholecystitis groups.

In patients with acute cholecystitis, IL-6 concentrations were significantly greater compared to in the control group ($P < 0.001$). TNF-α levels showed a substantial increase ($P < 0.05$), but IL-1 and IL-4 concentrations did not show a significant difference ($P > 0.05$) [Figure 1]. At the time of discharge from the hospital, the levels of IL-1β, IL-6, and TNF-α in the chronic cholecystitis group were substantially reduced compared with those before surgery [Figure 2]. However, IL-4 and IL-6 levels were substantially higher than those in the control group.

In the chronic cholecystitis group, the level of serum IL-1β remained significantly elevated ($P < 0.05$) during discharge relative to its pretreatment level [Figure 3]; in contrast, other cytokines did not show significant changes ($P > 0.05$). Relative to the levels in the control group, IL-1β and IL-6 levels were significantly increased ($P < 0.05$).

We examined the variations in cytokine concentrations over time in both groups on patient discharge [Figure 4]. The acute cholecystitis group had higher levels of IL-1β and TNF-α than the chronic cholecystitis group ($P > 0.05$), while IL-4 concentrations were lower ($P > 0.05$).

The immunological processes in acute cholecystitis are affected by cytokine activity, which is influenced by the interactions between antigen-presenting cells and T-cells, leading to structural alterations. Cytokines mediate interactions between immune system cells and the epithelium. TNF-α is usually triggered by viruses, endotoxins, lipids, and various bacterial components when cholecystitis progresses and bile crystals obstruct the bile ducts.

The evaluation of cytokines demonstrated that IL-6 levels increased by 88% in the acute cholecystitis group and 81% in the chronic cholecystitis group with regard to sensitivity and specificity. IL-1β levels reached 66% in the acute cholecystitis group and 71% in the chronic cholecystitis group. The percentages of IL-4 were 63% and 57% in the acute and chronic cholecystitis groups, respectively, whereas the percentages of TNF-α were 65% and 60% in the same groups. Cytokines can act as sensitive indicators of disease progression and severity of cholecystitis as well as for assessing the effectiveness of acute therapy.

Table 1: Blood plasma cytokine concentrations and statistical parameters in each group

Groups	Cytokines (pg/mL)			
	IL-1β	IL-4	IL-6	TNF-α
Control group (38 patients)	5.24±0.47	3.32±0.31	11.51±0.92	8.4±0.65
Acute cholecystitis group (79 patients)	15.8±52.21***	7.94±0.86*	66.6±7.54***	9.1±1.21
Chronic cholecystitis group (54 patients)	6.45±0.72**	4.39±0.66*	26.7±4.31***	7.65±1.09*

M ± m = mean ± standard deviation. *P<0.05; **P<0.01, ***P<0.001. IL-1β: Interleukin 1β, IL-4: Interleukin-4, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-α

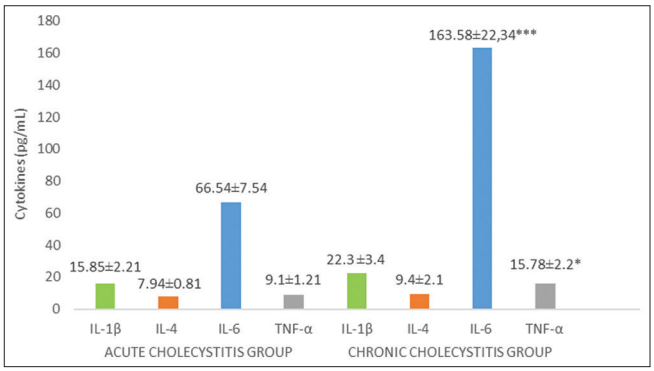

Figure 1: Differences in cytokine concentrations in the blood plasma of individuals with acute cholecystitis (Group 1) and chronic cholecystitis (Group 2)

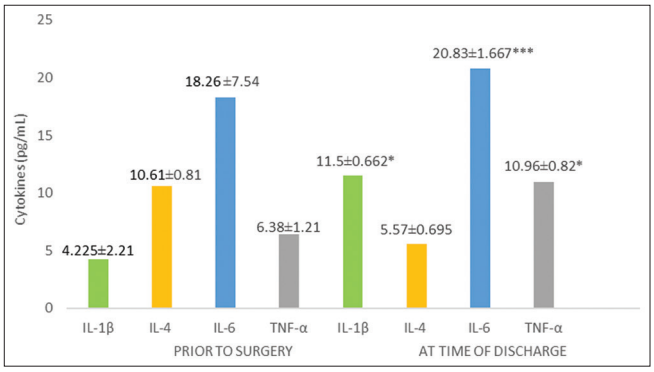

Figure 2: Blood plasma cytokine concentrations in the acute cholecystitis group before surgery and at discharge

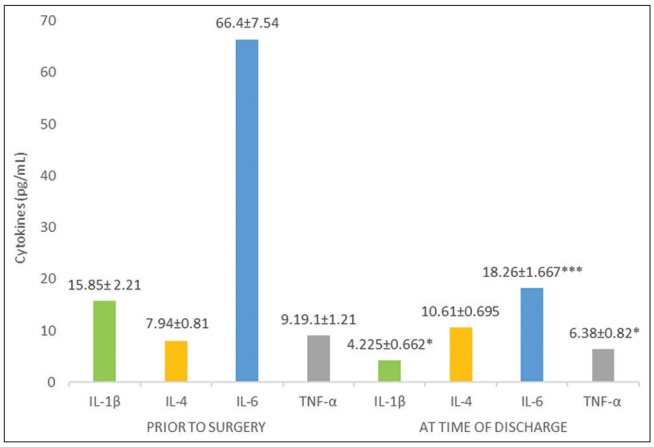

Figure 3: Blood plasma cytokine concentrations in the chronic cholecystitis group before surgery and at discharge

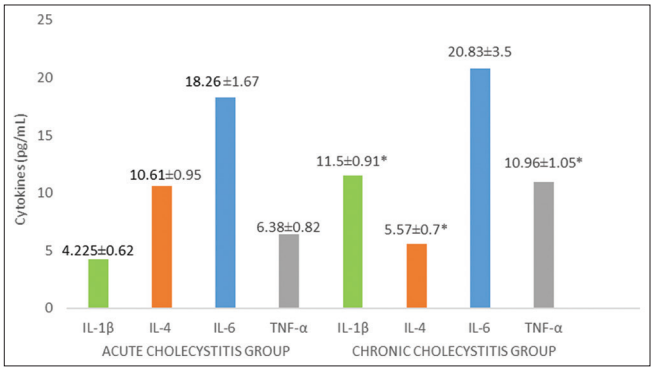

Figure 4: Blood plasma cytokine concentrations in the acute and chronic cholecystitis groups at the time of discharge

DISCUSSION

The rise in IL-4 in the acute cholecystitis group in the early stages is a protective compensatory response to elevate the cytokines IL-1β and IL-6.[14,15] Increasing IL-4 levels promotes the generation of immunoglobulin G and components related to antibody-mediated immunity, while also decreasing the number of cytotoxic T-cells and lowering the concentrations of prostaglandin and gamma-interferon.[16,17] After a scheduled surgical procedure resolved an acute condition in the liver, gallbladder, and bile ducts, the concentrations of IL-1β, IL-6, and TNF-α decreased, while the level of IL-4 increased compared with those in the chronic cholecystitis group.

Cytokines sometimes have systemic effects on inflammation. Pro-inflammatory cytokines help to accumulate neutrocytes and macrophages at infection sites, boost their phagocytic and bactericidal functions, and stimulate the adaptive immune reaction, contributing to worsening inflammation.[18] The mechanisms by which these activities harm the liver, gallbladder, and bile ducts are not well known.

Cytokines play significant roles in initiating and advancing inflammation by aiding in antigen recognition, enabling the production of major histocompatibility complexes and adhesion molecules, and stimulating, enhancing, and distinguishing immune cells to generate effector cells, thereby shaping the characteristics of the immune response.[14] TNF-α plays a role in gallstone formation in patients with chronic cholecystitis.[17] In patients with chronic cholecystitis, there was no correlation between TNF-α and IL-4 levels. TNF-α

protein expression was higher than IL-4, suggesting that patients with gallstones may have a predisposition to form gallstones. Iranian research has shown that IL-4 suppresses the development of gallstones, and even TNF-α promotes inflammation in the gallbladder and accelerates the production of gallstones.[19] Patients with gallstones have a significant decrease in IL-4 levels compared to those with IL-6, IL-1, and TNF-α.[17] Pro-inflammatory cytokines in the blood become more abundant through inflammatory processes occurring in the gallbladder. Because IL-6 levels increase in direct proportion with inflammation levels, IL-6 levels are commonly used as an indicator of inflammation.[17]

Studying inflammatory mediators can help understand the malfunction of the liver, gallbladder, and bile ducts. Elevated concentrations of pro-inflammatory cytokines in the bloodstream are linked to inflammatory, congestive, and calculi-forming conditions in the gallbladder. Inflammation in the form of cholecystitis and gallstone development occurs when cytokine concentrations increase.

CONCLUSION

Serum IL-6 concentrations increased significantly during the purulent inflammatory processes. After receiving medication and surgical therapy, acute cholecystitis is resolved, leading to a notable reduction in pro-inflammatory cytokine concentrations and an elevation in anti-inflammatory IL-4 concentrations. No changes were observed after surgical treatment of chronic cholecystitis. Therapeutic interventions have improved the clinical and functional outcomes of patients with chronic cholecystitis. However, the cytokine profile did not revert to the levels seen in the control group, suggesting that the normalization of cytokine balance occurs gradually after successful treatment of chronic cholecystitis.

REFERENCES

1. Jansen S, Stodolski M, Zirngibl H, Gödde D, Ambe PC. Advanced gallbladder inflammation is a risk factor for gallbladder perforation in patients with acute cholecystitis. World J Emerg Surg 2018;13:9.
2. Rege RV. Inflammatory cytokines alter human gallbladder epithelial cell absorption/secretion. J Gastrointest Surg 2000;4:185-92.
3. Tanaja J, Lopez RA, Meer JM. Cholelithiasis. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
4. Njeze GE. Gallstones. Niger J Surg 2013;19:49-55.
5. Kirkendoll SD, Kelly E, Kramer K, Alouidor R, Winston E, Putnam T, *et al.* Optimal timing of cholecystectomy for acute cholecystitis: A retrospective cohort study. Cureus 2022;14:e28548.
6. Musbahi A, Abdulhannan P, Bhatti J, Dhar R, Rao M, Gopinath B. Outcomes and risk factors of cholecystectomy in high risk patients: A case series. Ann Med Surg (Lond) 2020;50:35-40.
7. Yamashita Y, Takada T, Kawarada Y, Nimura Y, Hirota M, Miura F, *et al.* Surgical treatment of patients with acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg 2007;14:91-7.
8. Dinarello CA. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process. Am J Clin Nutr 2006;83:447S-55.
9. Kishimoto T. The biology of interleukin-6. Blood 1989;74:1-10.
10. Gilloteaux J, Tomasello LM, Elgison DA. Lipid deposits and lipo-mucosomes in human cholecystitis and epithelial metaplasia in chronic cholecystitis. Ultrastruct Pathol 2003;27:313-21.
11. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. Science 1993;259:87-91.
12. Tsai CJ. Steatocholecystitis and fatty gallbladder disease. Dig Dis Sci 2009;54:1857-63.
13. Rose-John S, Scheller J, Elson G, Jones SA.Interleukin-6 biology is coordinated by membrane-bound and soluble receptors: Role in inflammation and cancer. J Leukoc Biol 2006;80:227-36.
14. Deņisova A, Pilmane M, Eņģelis A, Pētersons A. Gallbladder interleukins in children with calculous cholecystitis. Pediatr Rep 2021;13:470-82.
15. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014;6:a016295.
16. Chandramohan V, Sampson JH, Pastan I, Bigner DD. Toxin-based targeted therapy for malignant brain tumors. Clin Dev Immunol 2012;2012:480429.
17. Issa AH, Muthena M. Serum levels of several types of cytokines associated with chronic cholecystitis in Basrah/south of Iraq. Basrah J Sci 2014;32:248-80.
18. Wertz JR, Lopez JM, Olson D, Thompson WM. Comparing the diagnostic accuracy of ultrasound and CT in evaluating acute cholecystitis. AJR Am J Roentgenol 2018;211:W92-7.
19. Ebadi P, Daneshmandi S, Ghasemi A, Karimi MH. Cytokine single nucleotide polymorphisms in patients' with gallstone: Dose TGF-β gene variants affect gallstone formation? Mol Biol Rep 2013;40:6256-60.

Source of Support: Nil. **Conflicts of Interest:** None declared.