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Original Article

Effect of Atorvastatin on clinical symptoms and laboratory markers of patients with cholecystitis: A double-blind randomized controlled trial

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Abstract

Introduction: Adopting a suitable strategy to reduce the complications of cholecystectomy plays a significant role in the well-being of patients. We investigated the effects of atorvastatin on clinical symptoms, and inflammatory markers of patients undergoing cholecystectomy.

Methods: This double-blind randomized controlled trial was conducted in Imam Reza Hospital, Birjand in 2021. In this study, 47 patients received 40 mg atorvastatin (intervention group) and 47 patients received placebo both daily for 4 weeks (placebo group). Then, the frequency of fever, abdominal pain, and nausea before and after cholecystectomy, as well as peri-operative data (duration of operation, and intraoperative bleeding) and laboratory data [White Blood Count (WBC), C-Reactive Protein (CRP), Aspartate AminoTransferase (AST), and Alkaline Phosphatase (ALT)] was collected. The data was analyzed using (SPSS Version 22) based on chi-squared, and independent t-tests at the significance level of ($P \leq 0.05$).

Results: The duration of hospitalization was not significantly different in both groups ($P=0.26$), however, the duration of operation was significantly longer in the intervention group ($P<0.001$). The frequency of fever, abdominal pain, and nausea after cholecystectomy was not statistically different ($P>0.05$). The volume of intraoperative bleeding in the placebo group was more than the intervention group ($P=0.05$). The decrease of WBC, CRP, and the ALT levels after cholecystectomy was not statistically different ($P>0.05$); however, AST level after cholecystectomy was higher in the intervention group ($P=0.05$).

Conclusions: The use of atorvastatin effectively reduced the volume of intraoperative bleeding. However, this intervention with this dose and duration could not have a significant role in reducing the duration of patients' hospitalization, duration of operation, and levels of WBC, CRP, ALT, and AST.

Keywords: Cholecystitis, Acute, Cholecystectomy, Atorvastatin, C-Reactive Protein, Leukocyte Count, Aspartate Aminotransferases, Alanine Transaminase

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Introduction

Gallstones and the use of cholesterol-lowering statins are very common in Iran which accompany with important economic effects (1). Gallstones are one of the most important causes of hospitalization of patients in the general surgery department (2). The prevalence of gallstones is increasing worldwide due to reasons such as obesity, insulin resistance, and aging. In Western countries, most cases of gallstones are composed of cholesterol (3). Cholesterol gallstones make up 80-95% of gallstone cases that undergo cholecystectomy (4, 5).

Acute cholecystitis is an infection of the gallbladder, which in most cases is caused by gallstones or other underlying problems (tumor, inflammation, or edema in the gallbladder wall), which lead to obstruction of the cystic duct. In 5-10% of cases, the inflammatory process of the gallbladder leads to ischemia and necrosis of the gallbladder wall. Also, secondary bacterial infection occurs in 15-30% of patients, which leads to gangrene, abscess, and perforation of the gallbladder due to the severe gallbladder infection, which is accompanied by peritonitis or emphysematous cholecystitis (6-8). Patients with acute cholecystitis should receive intravenous fluids and broad-spectrum antibiotics effective against gram-negative, and anaerobic bacteria along with painkillers (9, 10).

Acute cholecystitis manifests with biliary colic in the epigastrium and right upper quadrant of the abdomen. The patient often mentions fever, anorexia, nausea, and vomiting. In the physical examination, there is tenderness and guarding in the right upper quadrant of the abdomen, and there is also a pause in breathing when this area is touched, which is called Murphy's sign (11).

Normally, there is a mild to moderate leukocytosis of 12,000 to 15,000 cells, and values of more than 20,000 leukocytes indicate gangrenous cholecystitis, perforation, and cholangitis. Liver tests are usually normal, but slight increases in serum levels of bilirubin, alkaline phosphatase, amylase, and transaminases may be reported (11). Ultrasound, with a diagnostic sensitivity of 70-90%, is diagnostic for acute cholecystitis, especially if it is accompanied by tenderness (sonographic Murphy's sign). Computed tomography scan is more sensitive for diagnosing acute cholecystitis. Also, nuclear scan has 90% diagnostic sensitivity if the gallbladder is not filled with radionuclide material after 4 hours (11,12). Definitive treatment of acute cholecystitis is laparoscopic cholecystectom, which can be performed within 72 hours from the onset of symptoms or in 6-10 weeks after medical treatment and resuscitation of the patient (10,13).

Hypercholesterolemia is an important risk factor for atherosclerosis, which is considered as one of the most common causes of death in developing countries. Statins are used to treat dyslipidemia, so these medications can prevent cardiovascular and cerebrovascular events. Statins are one of the most commonly used medications in Western countries (14-16). For example, in Finland, the use of statins has increased about 11 times between 1995 and 2005 (17).

Atorvastatin is a medication that limits the production of cholesterol which belongs to the HMG-CoA reductase inhibitor group. The bioavailability of atorvastatin has been reported 14%. The effects of this medication initiate 3-5 days after the use of atorvastatin and last for 2-3 days. Myopathy and rise in hepatic enzymes are reported as side effects of atorvastatin (18).

Inflammatory complications after cholecystectomy are one of the most common complications of this procedure (19). Therefore, adopting a suitable strategy to reduce these complications plays a significant role in the well-being of patients and in reducing problems after the operation. Due to the fact that several studies have shown the anti-inflammatory effects of atorvastatin (18, 20).

We investigated the effects of atorvastatin on clinical symptoms, duration of hospitalization, and patients' inflammatory markers in a comparative way in two intervention and control groups.

Methods

In this double-blind randomized controlled trial, all patients who were candidates for gallbladder

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removal surgery who were referred to the general surgery department of Imam Reza Hospital, Birjand, Iran from April to December 2021 were selected as the study population. Then, people who met the inclusion and exclusion criteria were recruited. The inclusion criteria included signing the informed consent form and eligibility for the cholecystectomy. The exclusion criteria included the presence of any underlying diseases such as cardiovascular disease, respiratory disease, atherosclerosis, dyslipidemia, etc. (for whom cholecystectomy was not possible and they were candidates for cholecystostomy), history of taking atorvastatin, cases with contraindications for the use of atorvastatin such as drug allergy, pregnancy, active liver disease, hepatitis, unjustified increase of liver enzymes, and lactating women. Also, cases with the possibility of a negative effect of the intervention such as the occurrence of hepatotoxicity symptoms, icteric sclera, jaundice, abdominal pain, dark urine, anorexia, weakness, and unusual fatigue were excluded.

Eligible people were selected from the general surgery department of Imam Reza Hospital, Birjand, Iran from April to December 2021 with convenience sampling method. To calculate the sample size, the study of Pulkkinen et al. was used (21). In this way, considering the duration of operation for the intervention and placebo groups equal to 81 ± 21minutes and 70 ± 20 minutes, respectively, and the power of 80% and the confidence interval of 95%, the sample size in each group was estimated to be 45 people. Considering the lack of follow-up in each group, 47 people were included, who were selected among the eligible subjects. The patients were randomly divided into two groups using block randomization with a random sequence of 4 block sizes.

Before the intervention and 10 days after the intervention, the frequency of cases of fever, abdominal pain, and nausea, duration of hospitalization, duration of operation, frequency of intraoperative bleeding, intraoperative bleeding volume, and inflammatory markers of (WBC, CRP, ALT and AST) in both intervention and control groups were investigated. For the intervention group, atorvastatin 40 mg daily was used for 4 weeks. For the control group, a placebo with characteristics and appearance similar to the intervention medication but without the effective substance with anti-inflammatory effects was used. The main outcome of the current study was the effect of atorvastatin in accelerating the recovery and ease of treatment of cholecystitis (including improvement of clinical and laboratory symptoms of patients).

Before starting the study, all subjects were given complete explanations about the study, and subjects completed the informed consent form. In addition, people were allowed to leave the study during the study course. The present study has been approved by the Research Ethics Committee of Birjand University of Medical Sciences (IR.BUMS.REC.1399.460), and the Iranian Registry of Clinical Trials (IRCT20210119050084N1). The collected data were entered into SPSS (Version 22) to compare the two groups in terms of different variables, Independent t-test and Chi-Squared test were used at a significance level of ($P \leq 0.05$).

Results

In this study, 94 people in two groups of 47 people were included. Figure 1 shows the enrollment, randomization, and intervention assignment of the patients. There was no significant difference in the mean age of patients between the two groups (P=0.37). In the intervention and placebo groups, 23.4% and 14.9%of the study subjects were male, respectively, based on which the gender distribution was not significantly different (P=0.30). In the intervention and placebo groups, 57.5% and 44.7% of the subjects mentioned the history of any underlying disease, respectively, which was not significantly different (P=0.22, Table 1).

Duration of hospitalization after cholecystectomy was 3.91 ± 4.54 and 3.13 ± 1.88 days in the intervention and placebo groups, respectively, which did not show a significant difference (P=0.26). Also, the duration of operation was 101.81 ± 35.85 and 75.40 ± 33.74 minutes for

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the intervention and placebo groups, respectively. However, this difference is statistically significant (P<0.001, Table 1).

The frequency of abdominal pain and nausea before cholecystectomy did not show any significant difference between the two groups (P>0.05), but in the placebo group, the cases of fever before cholecystectomy were significantly higher compared to the intervention group (42 (89.4%) vs. 30 (63.8%) of cases, P=0.003). Also, there was no significant difference between the two groups in terms of the mentioned variables after the operation (P>0.05, Table 2).

The cases of intraoperative bleeding in the intervention and placebo groups were equal (1 vs. 1 case, P=1). Although the volume of intraoperative bleeding in the placebo group was significantly higher than the intervention group (21.30 ± 44.60 cc vs. 8.32 ± 22.77 cc, P=0.05, Table 3).

In terms of laboratory markers, no statistically significant difference was observed between the two groups in terms of changes in WBC and CRP levels (P>0.05), although the decrease in WBC and CRP was higher in the intervention group. Regarding the level of AST, no significant difference was observed between the two groups before the operation (P=0.16), but the level of AST was significantly higher in the intervention group compared to placebo group after the operation (P=0.05). Also, the difference in AST levels before and after the operation was not significantly different between the two groups (P=0.59). In terms of ALT levels, there was no significant difference between the two groups before and after the operation (P>0.05). Also, the difference in ALT level before and after the operation was not significant (P>0.05, Table 4).

After removing the gallbladder, the sample was sent to the laboratory and the relevant pathology was examined. The most common reported pathology in both groups was chronic calculous cholecystitis (68.1% and 87.2% of cases in the intervention and placebo groups, respectively). There was no significant difference in the frequency of different types of reported gallbladder pathologies between the two groups (P=0.15, Table 5).

Table 1. Demographic information of the study population

Variable	Subgroup	Intervention group	Placebo group	P-value
Age (Years, Mean ± SD)		16±68 48±74	45.70 ± 15.73	0.37
				0.30
Sex, N (%)	Male	11 (23.4)	7 (14.9)	
	Female	36 (76.6)	40 (85.1)	
Underlying disease, N (%)				0.22
	No	20 (42.6)	26 (55.3)	
	Yes	27 (57.4)	21 (44.7)	
Duration of hospitalization (Days, Mean ± SD)		3.91 ± 4.54	3.13 ± 1.88	0.26
Duration of operation (Minutes, Mean ± SD)		101.81 ± 35.85	75.40 ± 33.74	<0.001
Total		47 (50.0)	47 (50.0)	

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Table 2. Comparison of frequency of fever, abdominal pain, and nausea before and after the operation

Variable	Subgroup	Intervention group	Placebo group	P-value
Fever, before the operation, N (%)	No	30 (63.8)	42 (89.4)	0.003
	Yes	17 (36.2)	5 (10.6)	
Fever, after the operation, N (%)	No	41 (87.2)	43 (91.5)	0.50
	Yes	6 (12.8)	4 (8.5)	
Abdominal pain, before the operation, N (%)	No	23 (48.9)	23 (48.9)	1
	Yes	24 (51.1)	24 (51.1)	
Abdominal pain, after the operation, N (%)	No	5 (10.6)	2 (4.3)	0.22
	Yes	42 (89.4)	45 (95.7)	
Nausea, before the operation, N (%)	No	37 (78.7)	35 (74.5)	0.63
	Yes	10 (21.3)	12 (25.5)	
Nausea, after the operation, N (%)	No	26 (55.3)	24 (51.1)	0.68
	Yes	21 (44.7)	23 (48.9)	

Table 3. Frequency and volume of intraoperative bleeding in the two study groups

Variable	Subgroup	Intervention group	Placebo group	P-value
Intraoperative bleeding, N (%)	No	46 (97.9)	46 (97.9)	1
	Yes	1 (2.1)	1 (2.1)	
Intraoperative bleeding (cc, Mean ± SD)		8.32 ± 22.77	21.30 ± 44.60	0.05

Table 4. Mean levels of WBC, CRP, AST, and ALT in the two studied groups

Variable	Subgroup	Intervention group	Placebo group	P-value
WBC (10*9 cells, Mean ± SD)	Before the operation (B)	9.71 ± 2.63	9.47 ± 2.48	0.64
	After the operation (A)	8.42 ± 4.28	8.51 ± 3.85	0.92
	A-B	-1.28 ± 3.77	-0.93 ± 4.01	0.66
CRP (mg/dL, Mean ± SD)	Before the operation (B)	0.32 ± 0.59	0.59 ± 0.99	0.11
	After the operation (A)	0.70 ± 1.69	0.98 ± 2.32	0.54
	A-B	0.38 ± 1.89	0.36 ± 2.73	0.96
AST (U/L, Mean ± SD)	Before the operation (B)	45.57 ± 70.01	30.87 ± 14.46	0.16
	After the operation (A)	34.17 ± 33.78	23.93 ± 11.05	0.05
	A-B	-11.40 ± 55.41	-6.93 ± 13.86	0.59
ALT (U/L, Mean ± SD)	Before the operation (B)	52.46 ± 97.80	35.38 ± 19.49	0.24
	After the operation (A)	29.31 ± 27.65	28.87 ± 19.72	0.92
	A-B	-23.14 ± 81.96	-6.51 ± 18.68	0.18

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Table 5. The reported pathology of gallbladder in the two studied groups

Gallbladder pathology	Intervention group	Placebo group	P-value
Chronic calculous cholecystitis, N (%)	32 (68.1)	41 (87.2)	0.15
Acute on chronic cholecystitis with cholelithiasis, N (%)	4 (8.5)	0 (0.0)	
Chronic cholecystitis, N (%)	5 (10.6)	4 (8.5)	
Acute on chronic gangrenous cholecystitis, N (%)	1 (2.1)	0 (0.0)	
Acute on chronic calculous cholecystitis, N (%)	3 (6.4)	1 (2.1)	
Acute on chronic gangrenous calculous cholecystitis, N (%)	2 (4.3)	1 (2.1)	

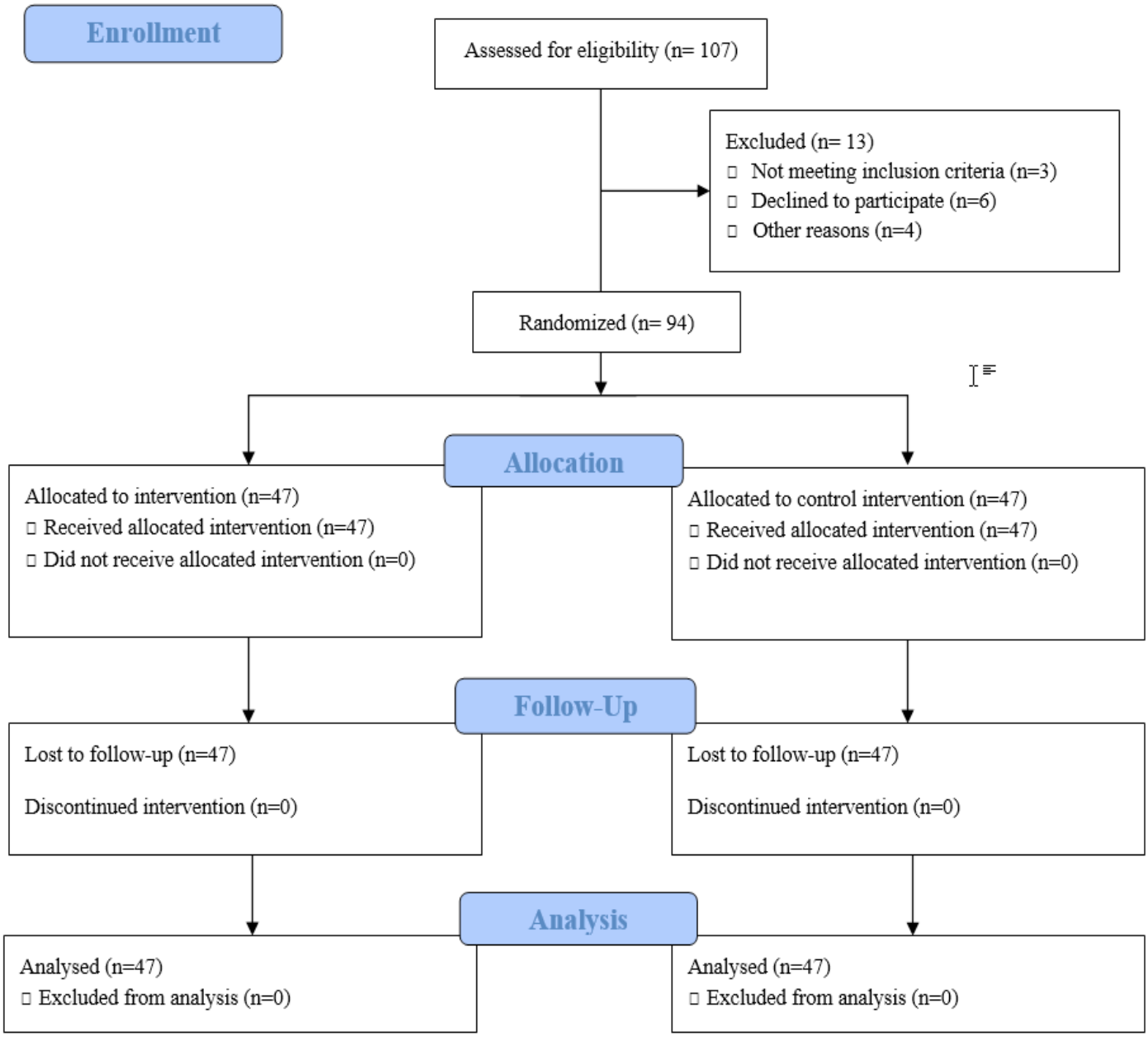

Figure 1. Enrollment, randomization, and the intervention assignment of the patients

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Discussion

The current study is a randomized double-blind controlled trial, which aimed to investigate the effects of atorvastatin on clinical symptoms, duration of hospitalization, and inflammatory markers of patients undergoing cholecystectomy in a comparative manner in two intervention and control groups.

In this study, the patients who entered the intervention and placebo groups were similar in terms of age, gender distribution, and history of underlying diseases. Among the patients included in the study, 76 (80.9%) were female (76.6% and 85.1% of cases in the intervention and placebo groups, respectively). Also, the mean age of the patients was 48.74 ± 16.68 and 45.70 ± 15.73 years in the intervention and placebo groups, respectively. According to a study by Fabienne et al. in 2016 in Switzerland, 59.2% of people who underwent cholecystectomy were female. Also, 89.9% of people in the mentioned study were over 40 years old, which is consistent with the findings of current study and the fact that most of the candidates for cholecystectomy are female and over 40 years old (22-24). Also, in another study conducted by Merzon et al. in 2010, the results were consistent with the current study (25).

In the current study, the duration of hospitalization in the intervention group was slightly longer compared to the placebo group, although this difference was not statistically significant. Similar to the current study, in another study conducted by Pulkkinen et al. in 2014, the length of hospital stay was longer in people who did not take statins compared to people who took different types of statins, although this difference was not statistically significant (21). One of the reasons for lack of the effect of statin use on the duration of hospitalization in various studies can be the fact that according to the standards in different hospitals around the world, after each operation, the patient needs to stay in the hospital for a certain period of time. This is true even when the patient has not shown any specific complications. For this reason, although the duration of hospitalization in the intervention group was longer than the placebo group, this difference was not statistically significant.

In this study, the duration of cholecystectomy operation was significantly longer in the group receiving atorvastatin compared to the placebo group. Contrary to this study, in another study conducted by Pulkkinen et al. in 2014, the duration of operation was significantly shorter in the group receiving atorvastatin compared to the control group (21). One of the reasons for the difference in the findings of these two studies could be the type of statin use. In the current study, atorvastatin 40 mg daily was used for the intervention group for 4 weeks, but the subjects included in the case-control study of Pulkkinen et al. (21).

Used statins for a longer period of time. Also, in the current study, only atorvastatin was used for intervention, but in Pulkkinen et al.'s study, the most common type of statin used was simvastatin. Therefore, it can be said that with long-term use of statin, the size of cholesterol particles and gallstones has been significantly reduced, which has led to a shorter duration of operation. However, in the current study, the duration of intervention (4 weeks) may not be enough to reduce the size of cholesterol particles and gallstones, and thus, the duration of operation in the intervention group was longer compared to the control group.

The investigated clinical symptoms included fever, abdominal pain, and nausea. The only significant difference between the intervention and placebo groups before cholecystectomy was the frequency of fever cases, which was higher in the placebo group. However, after cholecystectomy, there was no significant difference between the two groups in terms of the mentioned clinical signs and symptoms. Therefore, atorvastatin has not been able to reduce the frequency of fever, abdominal pain, and nausea after cholecystectomy. According to the review conducted by researchers, there has been no study that has investigated the effect of statins on the frequency of fever, abdominal pain, and nausea after cholecystectomy.

In this study, the frequency of intraoperative bleeding cases after the operation was equal in both

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intervention and placebo groups, but the volume of intraoperative bleeding was significantly higher in the placebo group compared to the control group. Consistent with the results of this study, Pulkkinen et al. in 2014 also reported that the volume of intraoperative bleeding was higher in the group that did not use statins compared to the group that used statins, although this difference was not statistically significant. Also, there was no significant difference between the cases of intraoperative bleeding in the two groups (21). The mechanism of the effects of statins on reducing the amount of intraoperative bleeding is unknown and more studies in this field are needed. One of the possible causes could be the effect of statins on the coagulation cascade.

In this study, the levels of WBC and CRP were investigated before, and after the operation, and no significant difference was observed. Similar to our findings, Pulkkinen et al. in 2014 also reported that CRP levels did not differ between the group of statin users and the group that did not use statins (21). Although atorvastatin has anti-inflammatory properties, these anti-inflammatory effects are probably through parallel pathways, and leukocytosis and CRP markers are not a suitable measure to assess the inflammatory effects of statins (18, 20).

In this study, the effects of atorvastatin on the levels of ALT and AST were also investigated. There was no significant difference in ALT and AST levels before the operation in both study groups. Also, the level of ALT after the operation was not significantly different between the two groups, but the level of AST after the operation was significantly higher in the intervention group compared to the control group. In terms of the differences in ALT and AST levels before and after the operation, there was no significant difference in either of these two groups. One of the reasons for the higher level of AST in the intervention group compared to the placebo group could be that statins can lead to an increase in the levels of liver enzymes such as ALT and AST (26). It should also be noted that AST compared to ALT, is more affected by other conditions such as heart damage, myopathy, pancreas damage, etc. in addition to liver diseases. Therefore, the increase in AST levels in the intervention group may be related to other issues not investigated in this study (27).

In this study, the most common reported pathology of gallbladder in both groups was chronic calculous cholecystitis. This finding is completely consistent with the fact that the most common cause of cholecystectomy is chronic cholecystitis caused by gallstones (28).

It is recommended to carry out further studies in this field, taking into account different doses and intervention periods of the medication along with the other clinical, laboratory, and inflammatory factors, as well as a larger sample size for a more detailed investigation of this issue.

However, this study had some limitations. The COVID-19 pandemic and its effect on the trend of the referral of patients to the healthcare facilities, and the subsequent lower number of patients involved in this study was one of the limitations of the present study. Moreover, the data were collected from the medical files of the operating room, in which the data are not recorded for the research purposes.

Conclusion

In conclusion, the use of atorvastatin for 4 weeks with a daily dose of 40 mg was effective in reducing the volume of intraoperative bleeding. Although this intervention with this dose and duration could not have a significant role in reducing the duration of hospitalization, duration of operation, levels of WBC and CRP, as well as the levels of ALT and AST. Therefore, the use of atorvastatin 40 mg daily for 4 weeks before cholecystectomy can reduce the complication of intraoperative bleeding.

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Conflicts of interest

The authors have no conflicts of interest.The Authors also indicate that they did not have a financial relationship with the organization that sponsored the research and had full control of all primary data and agree to allow the journal to review their data if requested.

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