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The effect of chamomile on nausea and vomiting after laparoscopic cholecystectomy: A triple-blind randomized clinical trial

Soheila BAKHTIARI[1], Gholamreza KHALILI[2], Razieh Salimi ZADAK[3*]

[1]Department of Operating Room, School of Nursing and Midwifery, Isfahan University of Medical Science, Isfahan, Iran
[2]Department of Anesthesia, Isfahan University of Medical Science, Isfahan, Iran
[3]Student Research Committee, Faculty of Nursing and Midwifery, Isfahan University of Medical Science, Isfahan, Iran

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Abstract
The present study aimed to evaluate the effect of Chamomilla Recutita on nausea and vomiting after laparoscopic cholecystectomy. Chamomilla Recutita (L.) fell into either chamomile or placebo groups randomly. The intervention was performed one hour before the operation. The severity of nausea and the frequency of vomiting was measured using a visual analog scale. Both groups were studied in three stages before the operation, after the operation in recovery, and 2 hours after the operation. Data were analyzed using descriptive and analytical statistics (SPSS). The mean severity of nausea increased significantly over time in both groups; however, this increase was significantly slighter in the chamomile group than that in the placebo group. The frequency of preoperative nausea in the chamomile and placebo groups was 6.2% and 25%, respectively, before being discharged from the recovery. Two hours later, in the surgical ward, this frequency was estimated to be 31.2% in the chamomile group and 75% in the placebo group ($P < 0.05$). The frequency of vomiting in the surgical ward was 15.6% and 56.2% in the chamomile and placebo groups, respectively. Thus, this frequency in the chamomile group was significantly lower than in the placebo group ($P<0.001$). It seems that in laparoscopic surgeries, the use of chamomile drops as a preventive drug reduces postoperative nausea and vomiting.

Keywords: Chamomilla Recutita, nausea, vomiting, laparoscopy, cholecystectomy

1. Introduction

Postoperative nausea and vomiting (PONV) is a common complication found in 20 -30% of cases (1, 2), and its prevalence in laparoscopic surgery (up to 80%) is caused by carbon dioxide gas used for pneumoperitoneum (1, 3, 4). Therefore, laparoscopic surgery is the only risk factor for PONV (5). One of these surgeries is laparoscopic cholecystectomy which is a standard surgical procedure for patients with symptomatic gallstones(6). The treatment of complications following laparoscopic cholecystectomy is complex and significantly affects the patient's quality of life (7). Inadequately controlled pain can cause PONV as well (4). Nausea and vomiting can cause spasms, pulmonary aspiration, electrolyte imbalance, bleeding, and abdominal pain. If continued, it reduces blood pressure, increases intracranial pressure (ICP) and intraocular pressure (IOP), and delays discharge from the recovery ward. Furthermore, it burdens costs, so it is necessary to eliminate it (1, 3-5, 8, 9).

Several drugs (such as Metoclopramide and Ondansetron) commonly used to treat PONV can lead to headaches, gastrointestinal disorders, hypotension, and extrapyramidal complications (2, 10). These complications may continue even with the widespread use of chemical drugs such as serotonin and neurokinin receptor antagonists.

To date, no single strategy has conclusively demonstrated to prevent PONV (4, 11). For this reason, further studies for novel treatments are required due to the ineffectiveness of chemical drugs and their side effects, the public's tendency to use herbal medicines, the variety of herbal medicines in Iran, and their minor side effects (8, 12, 13).

The global trend towards complementary medicine entices researchers to study the sources of traditional medicine (13) . The World Health Organization has considered developing traditional medicine to fulfill the slogan of "Health for All" (14).

One of the most prominent medicinal plants is Chamomilla Recutita, which stands out in traditional Iranian medicine and is used to treat disorders related to the nervous, gastrointestinal, and respiratory systems (15). Chamomile, an anti-inflammatory, anti-spasm, anti-flatulence drug, is used to treat stomach ulcers, eliminate digestive disorders, and relieve pain and fever (16-21).

Chamomile has minor side effects and occasionally leads to minor allergic reactions (12, 17). There is no adequate information on the toxicity of chamomile Recutita (species: *M. chamomilla*) (17).

*Correspondence: soha.rad412@outlook.com

Sanaati et al. (2016) performed studies on the effect of chamomile and ginger on nausea and vomiting in patients undergoing chemotherapy and showed that both plants affected patients' vomiting but had no effect on nausea (19). Conversely, Borhan et al.'s study (2017) on patients undergoing chemotherapy showed that the consumption of chamomile extract reduces nausea caused by chemotherapy; but does not mitigate vomiting (21). Pakniat et al.'s (2018) study on the effect of chamomile, ginger, and vitamin B6 on the treatment of nausea and vomiting during pregnancy showed that the use of all three drugs effectively reduces nausea and vomiting during pregnancy (22). A study performed by Zargaran et al. (2018) on patients with migraines showed that pain, nausea, and vomiting were significantly reduced by topical application of chamomile Oleogel (23). Johnson et al. (1988) investigated the effect of chamomile oil extract in the treatment of migraines. Patients receiving placebo had severe headaches, nausea, and vomiting (24). The study of Putri et al. (2019) on 30 patients with cervical cancer undergoing chemotherapy showed that chamomile aromatherapy effectively reduces nausea after chemotherapy (25).

Since the technician plays a vital role in providing patient care during, before, and after surgery (26), it is essential to eliminate postoperative complications and ensure patients' convenience. As nausea and vomiting are the most common complications after the surgery and general anesthesias and drugs used to prevent these complications can cause side effects, the present study aimed to determine the effect of chamomile on nausea and vomiting after laparoscopic cholecystectomy surgery. The hypothesis of the study focuses on the mean score of severity of nausea, frequency of vomiting, and nausea in the control group and the intervention group when coming to the operation room, before discharge from recovery, and 2 hours later in the ward.

2. Materials and Methods

The study population comprises all patients referred to the operating room of selected training hospitals affiliated with Isfahan University of Medical Sciences for cholecystectomy in June, July, and August 2020. In the study, the following formula with 95% confidence interval and 80% test power, the number of samples for each group (n=32) was used:

$$n = \frac{(Z1 + Z2)2(2S)2}{d\,2}$$

The patients were selected by the convenience sampling method and divided into chamomile (n= 32) and placebo groups (n= 32) randomly.

Inclusion criteria included being on the list of laparoscopic cholecystectomy surgery, insensitivity to herbal medicine, the age range of 18 to 65 years, BMI range of 18 to 28, consciousness or the lack of psychotic symptoms, not being pregnant, not having vestibular symptoms, gastrointestinal diseases, lack of addiction to drugs and benzodiazepines and willingness to participate in the study.

Exclusion criteria included the inability to continue cooperation for any reason, a transformation of the anesthesia method, transfusion of blood during the operation, and receiving any anti-nausea drug as prophylaxis.

After obtaining permission from the educational supervisor and the head nurse of the operating room and explaining the study's aims to the patients, the researcher obtained their written consent. One hour before the surgery and on arrival in the operating room, the intervention group received two dosages of 20 drops each of a standardized chamomile water extract containing 17% Chamazulenein and 45% Bizabolol solution in 20 cc water (DER=80kg/0.4kg=200) with a glass of distilled water and the placebo group received only distilled water. The study population was randomly divided into control and intervention groups using a table of random numbers. All patients were unaware of the type of substance and its effects. We did not need to show both drugs (water and chamomile) to the patient at the same time to notice their color differences. Patients' demographic information and clinical and therapeutic conditions were obtained through clinical histories and interviews.

At first, the severity of nausea and vomiting was determined and measured by the VAS scale before the intervention (According to the duration of patient evaluation, the VAS scale was the best choice). This tool consists of a 10 cm line (0-10). Zero shows no nausea, and the number 10 is equal to severe nausea. The score 1 to 3 in this tool indicates the severity of mild nausea, the score 4 to 7 indicates the severity of moderate nausea, and score 8 to 10 indicates the severity of severe nausea. The researcher instructed all patients to rate their severe nausea based on the visual scale criteria. The frequency of vomiting was recorded based on the researcher's observation and patients' self-declaration.

To prevent the psychological effect of the type of intervention on the results, patients undergoing laparoscopic cholecystectomy were asked to drink a harmless substance to ensure they were safe. However, the type of substance and its effect on the patient were not described (single-blind). The severity of nausea and vomiting was recorded in 3 stages: before the intervention, before being discharged from the recovery ward, and two hours after the surgery based on the patient's self-declaration. The researcher recorded all preoperative information. On the other hand, he provided all postoperative information (severity and frequency of nausea, frequency of vomiting) in questionnaires handed out in the recovery room and two hours after the operation (Double_blind).

After the patients entered the recovery room and the surgical ward, the severity of nausea was measured using the VAS scale. According to the anesthesiologist's instructions, medication would be routinely started for them if patients gave

severe nausea with a score of 4 or higher. Data were obtained by a statistical consultant who did not know the groups. (triple_blind; analytical statistics).

Mean, standard deviation, and frequency indices were used to report the descriptive statistical part of the results. The necessary statistical tests include a t-test (to compare age, BMI, and surgical indicators), analysis of variance with repeated measurement (to compare the severity of nausea), Fisher's exact test, and Chi-square (to compare the frequency of nausea and vomiting) were used.

The article was prepared based on the consort checklist.

The research flowchart is shown in Fig. 1.

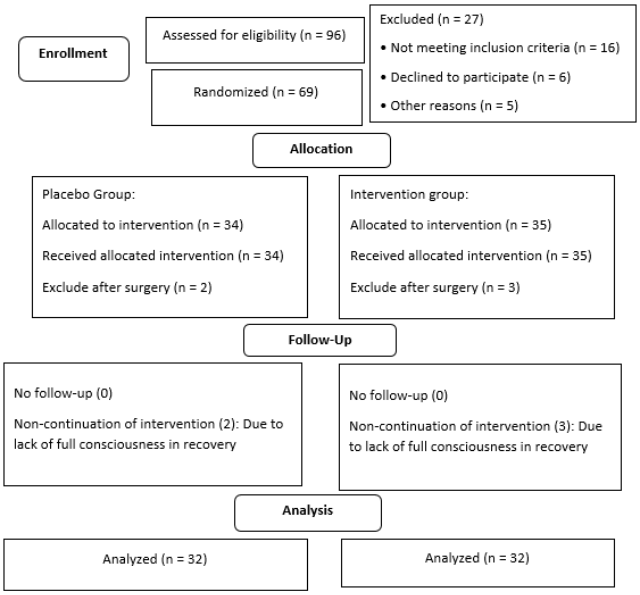

Fig. 1. Consort statement

3. Results

Five of the total 69 samples in this study were excluded from the study due to the lack of full unconsciousness in the Recovery Unit. Thus, 32 cases aged 23 to 65 years in the chamomile group and 32 cases aged 19 to 65 years in the placebo group (with a BMI range of 18 to 28) were studied. The results of the independent t-test showed that the mean age and body mass index were not significantly different between the chamomile and placebo groups (25.05 ± 2.28 vs. 25.55 ± 2.22) (P> 0.05) (Table 1).

Moreover, there was no significant difference between both groups regarding the frequency distribution of sex (X^2=1/04 and P> 0.05). In the chamomile group, 53.1% of patients were male, and 46.9% were female; and in the placebo group, 65.6% were male, and 34.4% were female. The results of the Mann-Whitney test showed no significant difference between both groups in terms of the level of education (P> 0.05).

Analysis of variance with repeated observations of the significant effect of time on nausea severity score (P <0.001). Therefore, the mean severity of nausea increased significantly over time in both groups. However, this increase in the chamomile group was significantly slighter than that in the placebo group (Table 2).

Table 1. Mean age, weight, height, and body mass index in the intervention and placebo groups

Variable	Chamomile group		Placebo group		independent t-test		
	Mean	SD	Mean	SD	t	df	P
Age (year)	43.66	13.70	44.37	12.43	0.22	62	0.83
Weight (kg)	69.89	11.79	70.56	10.47	0.24	62	0.81
Height (cm)	166.37	9.42	165.81	8.27	0.25	62	0.80
Body Mass Index (BMI)	25.05	2.28	25.55	2.22	0.89	62	0.38

Table 2. The mean of nausea severity in different periods in the intervention and placebo groups

Time	Chamomile group		Placebo group		P^1(effect of time)	P^2 (effect of group)
	Mean	SD	Mean	SD		
Before surgery	0.66	0.15	0.66	0.14	<0.001	<0.001
Before leaving recovery	0.37	0.14	1.47	0.22		
At ward	1.19	0.32	5.28	0.68		

Fisher's exact test showed that the frequency of nausea before the operation and on arrival in the recovery room was not significantly different between the two groups (P> 0.05). The Chi-square test showed that the frequency of nausea before leaving the recovery room and in the ward in the chamomile group was significantly less than that in the placebo group (P <0.05) (Table 3).

Table 3. the frequency distribution of nausea in different periods in the intervention and placebo groups

Time	Chamomile group		Placebo group		Chi-square test		
	No.	%	No.	%	χ^2	df	P
Before the operation	3	9.4	4	12.5	-	-	0.50
Before leaving recovery	2	6.2	8	25	4.27	1	0.040
At ward	10	31.2	24	75	12.30	1	<0.001

Vomiting was not observed in either group before the operation and on arrival in the recovery room. Fisher's exact test showed that the frequency of vomiting before leaving the recovery room was not significantly different between the two groups (P> 0.05). The Chi-square test showed that the frequency of vomiting in the surgical ward was 15.6% and 56.2% in the chamomile and placebo groups, respectively. These results indicate that the frequency of vomiting in the ward in the chamomile group was significantly lower than that in the placebo group (P<0.001) (Table 4).

Table 4. The frequency distribution of vomiting in different periods in the intervention and placebo groups

Time	Chamomile group		Placebo group		Chi-square test		
	No.	%	No.	%	χ^2	df	P
Before the operation	0	0	0	0	-	-	1
Before leaving recovery	0	0	2	6.2	-	-	0.25
At ward	5	15.6	18	56.2	11.47	1	0.001

The Chi-square test showed that the frequency of ondansetron use was 0% (in the chamomile group) and 15.6% (in the placebo group) in the recovery room, 25% in the surgical ward (in the chamomile group), and 62.5% (in the placebo group). On the other hand, the frequency of ondansetron use in the recovery room and the ward in the chamomile group was significantly less than that in the placebo group ($P < 0.05$). The independent t-test showed that the mean amount of Morphine administered, gas volume, and gas pressure was not significantly different between both groups. Also, the duration of operation was not significantly different between both groups. To control this confounding variable, random allocation of samples was used between the intervention and control groups. Different surgical operations in terms of operation duration were randomly assigned to each of the two intervention and control groups, and in this way, the confounding effect of the duration of the operation was removed. ($p > 0.05$). These results show that anesthesia and surgery were the same in both groups (Table 5). Complications such as gallbladder perforation, intra-peitoneal drain and etc. were not observed in any of both groups. Nasogastric tube was not placed in any of both groups because all patients were NPO.

Table 5. A dose of anesthesia drugs, duration of operation, gas volume, and gas pressure in the intervention and placebo groups

Variable	Chamomile group		Placebo group		Independent t-test		
	Mean	SD	Mean	SD	t	df	P
The dose of received fentanyl	119.37	15.76	132.81	18.54	1.03	62	0.31
The dose of received Morphine	9.50	1.83	9.84	1.55	0.81	62	0.42
Operation period (min)	82/8	0.49	81	0.45	0.25	62	0.80
Gas volume	97.59	10.75	93.83	8.70	0.27	62	0.79
Gas pressure	14.12	1.07	14.47	0.88	1.40	62	0.16

4. Discussion

The results of the present study showed that the scores of severe nausea and frequency of vomiting before the intervention in both groups were not statistically significant; however, the mean severity of nausea increased significantly over time in both groups, but the severity of increase in chamomile group was significantly lower than that in the placebo group. Furthermore, the frequency of vomiting in the surgical ward, before leaving the recovery room, and two hours after the operation were significantly lower in the chamomile group than that in the placebo group.

Factors playing a role in the development of PONV included patient-related factors (old age, female gender, history of movement disease), factors related to anesthesia and operation techniques (anesthesia drugs, general anesthesia, longer duration of operation, intra-abdominal surgery including gynecological and laparoscopic surgery), and postoperative factors (use of opioid drugs to control pain) were noted (9, 27, 28) in the present study. The study groups were homogeneous for the prevention of the effect of the above factors.

In a study on 105 pregnant women comparing the effects of ginger and chamomile on reducing nausea and vomiting during pregnancy, Modarres et al. (2011) showed that oral chamomile capsules reduce nausea and vomiting symptoms during pregnancy (12). These results are consistent with those of the present study and emphasize the effect of chamomile in reducing nausea. Although the samples differ in terms of gender in both studies, the results are consistent.

The results of Zargaran et al.'s study (2018) on 100 patients with migraines without aura support the effectiveness of chamomile Oleogel as a pain reliever and reduce nausea and vomiting in this type of migraine. The results of this study are consistent with those of the present study (23). Johnson et al. (1988) investigated the effect of chamomile oil extract in treating migraines. Based on their results, patients receiving a placebo had significantly higher frequency and severity of headache, nausea, and vomiting (24). The results of this study are consistent with those of the present study. In this study, patients were evaluated shortly after the intervention (30 minutes), which is consistent with the present study and emphasizes the immediate effect of chamomile. In addition to these studies, Pakniat et al. (2018) investigated the effect of three drugs, including chamomile, ginger, and vitamin B on the treatment of nausea and vomiting in 105 pregnant women with nausea and vomiting. The results showed that all three drugs reduce nausea and vomiting during pregnancy, although there were no significant therapeutic benefits from these three drugs (22). This study's results are consistent with those of the present study and emphasize the effect of chamomile on reducing nausea and vomiting.

In the present study, the mean score of nausea in patients in the surgical ward was 1.19 (in the chamomile group) and 5.28 (in the placebo group); the score difference of the nausea severity between both groups was 4.09. In a study on 30 patients with cervical cancer undergoing chemotherapy, Putri et al. (2019) showed that chamomile aromatherapy can reduce nausea after chemotherapy. According to this study, the mean

score of nausea was 7.33 and 2.87 in the control and intervention groups, respectively. On the other hand, the score difference for nausea intensity was 4.46 in both groups (25). Although chamomile was used by inhalation in this study, overall results confirm those of the present study.

Matthews et al. (2015) conducted a review study of various interventions on nausea and vomiting in the early stages of pregnancy. In this study, 37 clinical trials were performed on 5049 women in the early stages of pregnancy. These studies concluded that ginger and vitamin B6 could reduce nausea effectively and mentioned chamomile as one of these interventions; However, due to the lack of objective evidence, they could not recommend any of these interventions (29). The results of this study are consistent with those of the present study, although the present study concluded significant results from the use of chamomile.

Sanaati et al. (2016) showed that ginger and chamomile had no effect on the severity of nausea in cancer patients undergoing chemotherapy and were effective only in the frequency of vomiting (19). These results differ from those of the present study regarding the efficiency of chamomile on the severity of nausea, which may be due to the research methods or differences in sex and type of disease. Of course, the role of gender in this study may not be considered a reason for differences in the results because, in the study of mentioned researchers (Modares et al. (2011), Matthews et al. (29) and Pakniat et al.) (22), the gender (all were female) was different from those of the present study. However, the results are consistent with those of the present study and emphasize the effect of chamomile on reducing the severity of nausea.

Conversely, in a study on 60 patients undergoing chemotherapy, Borhan et al. (2017) showed that consumption of chamomile extract reduced nausea caused by chemotherapy; but did not reduce vomiting (21). This study differs from the present study as chamomile was administered orally and once. However, the results of this study are different from those of the present study regarding the effectiveness of chamomile on the frequency of vomiting in patients. This difference results from differences in the subjects or dosage of chamomile. Another reason for the difference is that samples were evaluated two hours after the operation in the present study but 12 hours in Borhan's study.

Research limitations include:

Prolonged sampling, the reduced number of hospitalized patients due to the prevalence of coronary heart disease,

Short-term evaluation of patients only up to two hours after surgery,

Lack of cooperation of some anesthesiologists to give chamomile drops to patients before surgery,

Making a mistake in diagnosing the severity of nausea as it was self-declaration,

Due to the importance of controlling nausea and vomiting in patients following laparoscopic surgery, the present study seems to be the first study done in this field after laparoscopic surgery. It seems that chamomile drops, as a preventive drug, effectively reduce postoperative nausea and vomiting in laparoscopic surgeries. However, further studies with a longer-term evaluation to investigate the effectiveness of chamomile in reducing nausea and vomiting will be done.

Ethical statement

This triple_blind randomized clinical trial study was registered in the Iranian clinical trial database with the code IRCT20200612047737N1 and in the ethics committee of Isfahan University of Medical Sciences (IR.MUI.RESEARCH.REC.1398.745).

Conflict of interest

The authors declared no conflict of interest.

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Acknowledgments

The study complies with the guidelines for human studies and is performed ethically based on the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent. The Ethics Committee of Isfahan University of Medical Sciences approved the study (IR.MUI.RESEARCH.REC.1398.745).

This triple-blind randomized clinical trial was registered in the Iranian clinical trial database with the code IRCT20200612047737N1.

Authors' contributions

Concept: S.B., R.S.Z. Design:S.B.,R.S.Z. Data Collection or Processing: R.S.Z., S.K.,G.K. Analysis or Interpretation: R.S.Z.,S.B.,G.K. Literature Search: R.S.Z.,S.B.,G.K., Writing: R.S.Z.,S.B.,G.K.

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