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Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: a double-blind, randomized placebo-controlled study

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Abstract
Objective Better patient-reported outcomes (PROs) of laparoscopic cholecystectomy (LC) are premised upon PROs such as postoperative pain and fatigue. These PROs are indices of convalescence and return to normal activity. Curcumin (turmeric) is used in India for traumatic pain and fatigue for its anti-inflammatory/antioxidant and tissue modulation/healing properties. We studied the effect of curcumin on pain and postoperative fatigue in patients of LC.
Methods and procedures From July to September 2009, 50 consecutive day-care LC candidates were enrolled for a prospective, double-blind randomized placebo-controlled study. A uniform general anesthesia and analgesia protocol was followed. Curcumin/placebo and rescue analgesic were prescribed at discharge. Patients were told to maintain pain/fatigue/adverse event diaries based upon 100-point visual analog pain scale (VAS) and 10-point interval rating fatigue scale (IRS). Patients were followed up at third day (D3), first week (W1), second week (W2), and third week (W3). The blind labels were opened at the end of study.
Results Demographic characteristics, comorbidity, and gallbladder pathology profiles were comparable in the study ($n = 25$) and control groups ($n = 25$). There was no adverse surgical outcome, adverse PRO or withdrawal. Pain and fatigue scores at D3 were similar in the two groups. At W1 and W2, the study group showed significantly lower (p value 0.000) mean pain scores, i.e., 15 ± 5.204 versus 30 ± 13 in controls. Fatigue scores at W1, W2, and W3 were significantly lower (p value 0.000) in the study group, i.e., 2.16 ± 1.748, 1, and 0, respectively, versus 5.16 ± 1.375, 4.20 ± 1.633, and 1 in controls. All patients were pain free at W3. Analgesic tablet usage was significantly lower (p value 0.000) in the study group, i.e., 6.96 ± 1.837 versus 39.32 ± 16.509 in controls.
Conclusions Turmeric (curcumin) improves postoperative pain- and fatigue-related PROs following LC.

Keywords Laparoscopic cholecystectomy · Postoperative pain · Postoperative fatigue · Turmeric · Curcumin · Patient-reported outcomes

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Popularity of laparoscopic surgery amongst patients as well as surgeons is attributable to better patient-reported outcome (PRO) as indicated by smoother and speedier convalescence. Laparoscopic cholecystectomy (LC) is a commonly performed surgical procedure [1]. It is also an index procedure for innovations towards improving

patient-reported outcomes (PROs) in laparoscopic surgery [1, 2]. Convalescence after LC is an important outcome measure indicative of patient discomfort and its socioeconomic impact [3]. The duration of convalescence depends upon surgical stress response and pain [4]. Pain after uncomplicated LC continues to evade perfect solution despite a multimodal analgesic regime [5]. The median or mean post-LC convalescence is surprisingly long, extending up to 5 weeks [3]. Turmeric (curry powder) has been traditionally used in India for centuries as an acceptable remedy for traumatic pain and fatigue [6]. Curcumin (diferuloylmethane) is the active ingredient of turmeric [6]. It has been shown to possess anti-inflammatory and prohealing properties at molecular level through various pathways [6, 7]. Turmeric-containing Indian spices have also been shown to have benefits in PROs of minimally invasive surgical procedures [8]. This study was undertaken to evaluate the effect of curcumin on postoperative PROs, i.e., pain and fatigue, following LC.

Patients and methods

This was an open-ended, double-blind, randomized, label-blinded placebo-controlled study, conducted with adherence to ethics committee guidelines and informed consent protocol. Consecutive candidates for day-care LC were enrolled for the study with the following criteria:

Inclusion criteria

- Laparoscopic cholecystectomy candidates of more than 18 years of age
- They should be able to understand and sign an informed consent
- They should be literate enough to understand the maintenance of a diary recording pain scores, fatigue scores, and any adverse event
- They should be willing to meticulously maintain PRO diary.

Exclusion criteria

- Age less than 18 years
- Presence of comorbidity precluding the patient's fitness for general anesthesia
- Females who are pregnant, lactating or desirous of bearing children
- Patients with any peripheral or central neuropathic pain
- Patients used to taking over-the-counter painkiller pills
- Patients with history of alcohol intake/drug dependence
- Patients with history of psychosis
- Patients with chronic inflammatory diseases who cannot be taken off nonsteroidal anti-inflammatory drugs (NSAIDs)/painkillers
- Patients on immunosuppressive/cytotoxic/steroid therapy.

Study medication: dosage and mode of administration

Curcumin was given at dosage of one 500 mg cap once every 6 h per orally.

Label-blind comparator: dosage and mode of administration

The comparator was a placebo, with matching capsule and dosage.

A total of 50 boxes containing 100 capsules each of either curcumin or placebo were supplied by Indsaff, Inc., India [9, 10]. The placebo was an identical gelatin capsule with 250 mg dextrose powder. Curcumin and comparator capsules were gifted by Indsaff Inc. following the same quality process as for other studies reported in literature [9, 10].

Methodology

All included patients had routine hematological, biochemical, and other diagnostic investigations. They were assessed for suitability for general anesthesia by an independent senior anesthesiologist. Patients were allocated to the study (curcumin) group and control (placebo) group according to label breaking at the end of study. Surgeon, patient, and investigator were thus blinded to the randomization process.

Patient demographic data, clinical profile, and investigations were entered in a standard sheet. All patients underwent LC under general anesthesia, performed by a single surgeon following similar surgical technique with standard laparoscopic equipment in a single operating theater. All patients had standard preoperative medication, peroperative anesthetic medication, prophylactic antibiotic, and perioperative analgesia protocol. All surgeries were done on day-care ambulatory basis. Postoperative advice incorporated either curcumin or the identical comparator to be taken as soon as the patient was discharged. Paracetamol 650 mg was prescribed to all as rescue pain medication. Patients were instructed to take this rescue medication in case of significant pain or as desired by them. Patients were told to maintain a pain, fatigue, and adverse event diary. Pain was assessed on a 100-point visual analog scale (VAS). Postoperative fatigue was assessed on a 10-point interval rating scale [IRS (1 = fit and 10 = fatigued)] [11].

Patients were clinically followed subsequently on day 3 (D3), first week (W1), second week (W2) and third week (W3) for the following:

Study end points

1. *Pain*: VAS score either in the morning on getting up from bed or in the evening on retiring to bed, whichever was higher
2. *Postoperative fatigue*: IRS score either in the morning on getting up from bed or in the evening on retiring to bed, whichever was higher
3. *Analgesia usage*: total number of paracetamol tablets consumed until W3 follow-up
4. Any adverse event or side-effect

Withdrawal from the study analysis

Patients requiring hospitalization for more than 24 h, re-intervention, developing postoperative complications, and requiring rehospitalization were to be withdrawn from the data analysis, as were those who failed to maintain the end points diary. The random code assigned labels were opened at the end of study and entered for the corresponding patients by the medical secretary for further analysis. Appropriate statistical analysis was done. Continuous variables are expressed as mean (standard deviation, SD) or median (interquartile range, IQR) as applicable, and categorical variables are expressed as percentages. Comparison of continuous variables was done using Student's t test or Mann–Whitney U test. Categorical data were analyzed using chi-square test. SPSS version 17.0 was used for statistical analysis. p-Value < 0.05 was considered significant.

Results

A total of 50 candidates were enrolled from July to September 2009, as shown in the flowchart in Fig. 1. Those who received curcumin were the study group, and those who received placebo were the control group. Patients in the study ($n = 25$) and control groups ($n = 25$) were comparable in terms of demographics, comorbidity, and gallbladder inflammation parameters (Tables 1, 2). All patients were discharged as day-care patients without any complication or adverse outcome. There was no withdrawal from the study or failure to maintain diary. None of the patients from either group reported any adverse PRO. There was no adverse surgical outcome, adverse PRO or withdrawal. Pain and fatigue scores at D3 were similar in the two groups. At W1 and W2, the study group showed

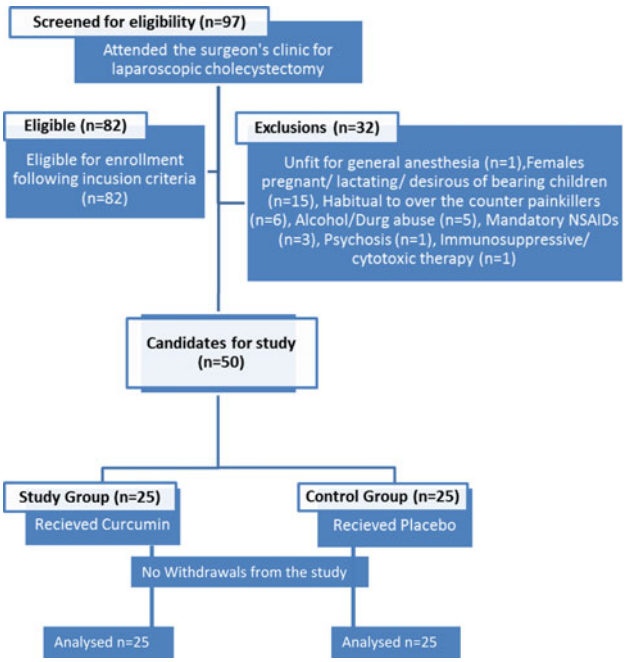

Fig. 1 Study flow chart

significantly lower (p value 0.000) mean pain scores, i.e., 15 ± 5.204 versus 30 ± 13 in controls. Fatigue scores at W1, W2, and W3 were significantly lower (p value 0.000) in the study group, i.e., 2.16 ± 1.748, 1, and 0, respectively, versus 5.16 ± 1.375, 4.20 ± 1.633, and 1 in controls. All patients were pain free at W3. Analgesic tablet usage was significantly lower (p value 0.000) in the study group, i.e., 6.96 ± 1.837 versus 39.32 ± 16.509 in controls. The results are presented in Table 3.

Discussion

Improving patient-reported outcome is a well-stated objective for assessing any therapeutic intervention in surgical patients [12]. Laparoscopic surgery has become popular primarily due to better patient-reported outcomes. Laparoscopic cholecystectomy (LC) is an index laparoscopic surgery for evaluation of various outcome measures [13]. Findings have shown that decreased pain is the primary benefit of LC, but it is still not a pain-free procedure [14]. Pain and attendant prolonged convalescence are still substantial and constitute the two main clinical problems after LC [4]. Pain is the most common complaint after LC. Apart from prolonged convalescence, it increases length of hospital stay and may necessitate resort to rescue opioids [4]. Laparoscopic cholecystectomy has evolved to being a day-care ambulatory surgical procedure [15]. To facilitate this, a variety of analgesic interventions have been studied. None of these have addressed the issue in totality [4, 14],

Table 1 Demography and comorbidity spectrum ($n = 50$)

	Control ($n = 25$)	Study ($n = 25$)	p-value
Age, mean (SD), years	37.16 (12.7)	38.44 (12.8)	0.778
Gender			
Males	4 (16 %)	5 (20%)	1.000
Females	21 (84%)	20 (80%)	
Hypertension (HT)	5 (20%)	7 (28%)	0.741
Diabetes mellitus (DM)	7 (28%)	9 (36%)	0.762
HT + DM	10 (40%)	12 (48%)	0.776
Chronic obstructive airway disease	3 (12%)	2 (8%)	0.999
Hemolytic anemia	1 (4%)	0	1.000
Hypothyroidism	3 (12%)	3 (12%)	1.000

Table 2 Spectrum of disease ($n = 50$)

Disease	Control ($n = 25$), *N* (%)	Study ($n = 25$), *N* (%)	p-value
Previous abdominal surgery	3 (12)	4 (16)	
Upper abdominal surgery	0	0	
Lower abdominal surgery	3 (12)	4 (16)	0.999
Stones			
Single	9 (36)	8 (32)	1.000
Multiple	16 (64)	17 (68)	
Grade of inflammation			
Acute cholecystitis	8 (32)	9 (36)	1.000
Chronic cholecystitis	5 (20)	4 (16)	1.000
Empyema GB	3 (12)	3 (12)	1.000
Mucocele of GB	9 (36)	8 (32)	1.000
Perforated/gangrenous GB	0	1 (4)	
Adhesions	23 (92)	21 (84)	0.667
Omental	22 (88)	16 (64)	0.095
Duodenal	2 (8)	3 (12)	0.999
Omental + duodenal	22 (88)	17 (68)	0.170
Colonic/others	6 (24)	4 (16)	0.725
Post-ERCP status	2 (8)	3 (12)	0.999

GB gallbladder, *ERCP* endoscopic retrograde cholangiopancreatography

Table 3 Postoperative analgesic consumption, pain scores, and fatigue scores

Study point	Control group ($n = 25$) Mean (SD)	Study group ($n = 25$) Mean (SD)	p-value (95% CI)
Pain D3	40.80 (9.3)	45.60 (12.1)	0.056 (–10.953, 1.353)
Pain W1	30.40 (13.1)	15.00 (5.2)	0.000 (9.71, 21.08)
Pain W2	32.36 (13.0)	15.00 (5.2)	0.000 (11.72, 22.99)
Number of tablets used	39.32 (16.5)	6.96 (1.8)	0.000 (25.68, 39.04)
Fatigue D3	6.12 (1.4)	5.96 (1.8)	0.378 (–0.79, 1.11)
Fatigue W1	5.16 (1.3)	2.16 (1.7)	0.000 (2.10, 3.89)
Fatigue W2	4.20 (1.6)	1	0.000
Fatigue W3	1	0	0.000

D3 day 3, *W1* week 1, *W2* week 2, *W3* week 3, *SD* standard deviation, *CI* confidence interval

which remains a concern to surgeons [5, 15]. Pain remains the cardinal index of postoperative inflammatory symptom complex. Post-LC pain is modulated by raised proinflammatory cytokines, C-reactive protein, angiogenic factors, and oxidative stress of surgical trauma [4, 16]. Postoperative pain is thought to be procedure specific, as

should be its analgesic treatment also [5, 17]. Post-LC pain has stimulated a lot of scientific interest, leading to a variety of interventions. These include gasless laparoscopic technique, low-pressure capnosufflation, nitrosufflation, port-site local anesthetic infiltration, intraperitoneal anesthetic instillation, epidural analgesia, and multimodal analgesia, apart from universal use of analgesics including opiod derivatives and/or NSAIDS etc. [4]. Fatigue is also a concern after LC and has impact on convalescence-related quality of life [18]. Some patients even see fatigue as a change in their emotional state [18]. Its association with duration of surgery/type of anesthesia is not as strong as it is with the region of surgery, i.e., abdomen [18]. Though less in laparoscopic surgery, fatigue is still a significant and important indicator of PRO in LC [4, 5]. This is mediated by both hormonal route as well as neuronal route of kinases and proinflammatory cytokines [18]. It can be further accentuated by cytokine-mediated circadian rhythm disturbances in LC [19]. Curcumin, an ingredient of commonly used spice (turmeric), has been shown to possess potent anti-inflammatory properties [20]. Various studies have shown its potential therapeutic value against neoplastic, neurological, cardiovascular, pulmonary, metabolic, and chronic inflammatory diseases [20–23]. Turmeric has been used for centuries as a treatment of inflammatory diseases, pain, and trauma [20]. Its role in postoperative pain has not been reported so far. Testing of a well-founded, potentially beneficial scientific hypothesis with the available tools following scientific methodology is a basic scientific quest [24]. Turmeric (*Curcuma longa*, an Indian spice) has been described in Ayurveda as a treatment for inflammatory diseases. Studies have shown important functions of curcumin binding to a variety of proteins and inhibiting the activity of kinases [6, 7]. By modulating the activation of various transcription factors, curcumin regulates the expression of inflammatory enzymes, cytokines, adhesion molecules, and cell survival proteins. Curcumin down-regulates cyclin D1, cyclin E, and MDM2 and upregulates p21, p27, and p53 [20–23]. Various preclinical cell culture and animal studies suggest that curcumin has potential as a therapeutic agent in wound healing [6]. Clinical trials have shown curcumin to be safe at daily dose >12 g for 3 months [6, 20]. Curcumin-mediated suppression of pain and fatigue pathways has been reported extensively in the literature across a spectrum of experimental models [25–31]. The benefits of curcumin in respect of postoperative pain and fatigue are significant, as shown in our study. These benefits may expedite convalescence after LC. Our study however had small sample size and was conducted in a population where turmeric is routinely used as a spice. There is universal social skepticism about resuming spices in immediate post-operative period. This ensured automatic exclusion of turmeric containing spices by the study population. Hence recommending a spice free diet post-operatively was socially compliant. We advised all patients to continue spice-free diet for 3 weeks after surgery. All patients were well compliant with this, as it concurred with prevalent traditional practice of taking a bland diet after surgery. However, no specific questions were asked of patients, as this might have jeopardized patient blinding from use of curcumin in the study. Hence, the benefits shown in this study need to be evaluated in large multicentric study on multiethnic population. Turmeric is a natural food ingredient, palatable, and harmless. It proves to be beneficial as it may be an ecofriendly alternative to synthesized anti-inflammatory drugs which have a definite carbon footprint due to industrial production [32].

Conclusions

Turmeric (curcumin) potentially improves postoperative pain- and fatigue-related PROs in patients of laparoscopic cholecystectomy.

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