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Premedication with Intravenous Ibuprofen Improves Recovery Characteristics and Stress Response in Adults Undergoing Laparoscopic Cholecystectomy: A Randomized Controlled Trial

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Abstract

Objective(s). Examine the effect of preoperative dose of IV ibuprofen on stress response and postoperative recovery in laparoscopic cholecystectomy patients.

Design. Prospective, randomized, controlled, double-blind, multicenter trial.

Setting. Three university-based, tertiary care hospitals.

Subjects. Fifty-five adults, ASA 1, 2, or 3 scheduled for laparoscopic cholecystectomy were given a single preoperative dose of placebo or IV ibuprofen 800 mg.

Methods. Neurobehavioral assessments were evaluated preoperatively, in PACU, POD 1, and POD 3, using the 40-item Quality of Recovery questionnaire (QoR40), 9-item Modified Fatigue Severity Scale (MFSS), and 15-item Geriatric Depression scale (GDS). Blood samples were taken for cytokines (TNF-alpha, IL-1β, IL-2, IL-6, IL-10, IFNγ), cortisol, CRP, epinephrine, and norepinephrine prior to the administration of study drug/placebo, intraoperatively, and after surgery.

Results. Global QoR40 scores remained at baseline for ibuprofen patients but significantly decreased in the placebo group. Severity of fatigue increased in patients receiving placebo but had no change with ibuprofen. The placebo group had lower GDS scores on POD 3. Epinephrine and norepinephrine were significantly lower intraoperatively for the ibuprofen group. Cortisol decreased postoperatively in the ibuprofen group. There was an impact of drug treatment on the immune response, as seen by an increase in TNFα and an increase in IL-10 when compared with placebo.

Conclusions. Our results suggest the addition of NSAIDs may improve the overall quality of recovery, postsurgical fatigue, and early postoperative outcomes. Preoperative administration of IV ibuprofen modulates the stress and inflammatory response, as demonstrated by a decrease in the level of catecholamines, cortisol, and cytokines.

Trial registration: Clinicaltrials.gov identifier: 01938040.

Key Words. Analgesic; Anesthesiology; Anti-Inflammatory; Cognitive Function; Fatigue; NSAIDs; Outcome Assessment; Quality of Life; Surgery; Treatment Outcome; Postoperative Quality of recovery; Stress Response; Inflammatory Response; Postsurgical Fatigue

Introduction

Surgical injury to tissue causes a variety of physiological reactions that are essential for the restoration of an organism's homeostasis. The stress response involves a surge of hormones (i.e., ACTH, cortisol, catecholamines), activation of the complement system, migration of leukocytes to the site of injury, and the release of cytokines (i.e., interleukins, tumor necrosis factor), as well as other cellular products (i.e., superoxide radicals, proteases, growth factors) [1–3]. An appropriate inflammatory cascade is essential for tissue reconstitution and infection control. The associated impairment of multiple organ function is generally mild because of the physiological reserve of the biological systems. However, a systemic stress/inflammatory response may also lead to postoperative complications in the elderly, neonates, and patients with significant comorbidity [4,5]. In addition, mediators of inflammation may induce fatigue and prolong convalescence in healthy patients [4,5,7]. Conversely, dysregulation or suppression of the inflammatory process may lead to improper wound healing, infection, and, as demonstrated recently, even an increase in cancer recurrence due to reduced natural killer cell activity [6,7].

Anesthetic management may affect both immunostimulatory and immunosuppressive mechanisms either directly by modulating function of immune cells or indirectly by attenuating the stress response. Therefore the choice of anesthetic technique may alter the balance between pro- and anti-inflammatory responses, thus affecting clinical outcomes. An optimized anesthetic regimen would enhance or have a neutral effect on cellular immunity while minimizing contribution to the systemic inflammatory response.

COX inhibitors decrease the production of inflammatory mediators [8,9] and attenuate increases in corticosterone and eicosanoid levels after endotoxin injection [10,11]. These results suggest that IV ibuprofen may shorten postsurgical convalescence by preventing untoward inflammatory responses. Singla et al. revealed that the perioperative administration of IV ibuprofen for orthopedic surgery significantly decreased pain scores and postoperative opioid requirements [12]. However, no previous studies have evaluated the biochemical basis for this benefit, including the relationship between the administration of IV ibuprofen, ensuing immunomodulation, and long-term outcomes.

The aim of the reported study was to examine the effect of IV ibuprofen on stress response. We hypothesized that the addition of IV ibuprofen would reduce the levels of stress mediators, thus improving the quality of recovery.

Methods

This was a randomized, double-blind, placebo-controlled, multicenter study. Ethical approval was obtained from the Institutional Review Boards at New York University School of Medicine (NYU) [NYU IRB #11-01108, Director Elan Czeisler on August 24, 2011], Methodist Hospital (MH) [MH IRB #217594, Director Pearlia Fullard on April 15, 2012], and Rutgers-New Jersey Medical School (NJMS) [NJMS IRB #2012001793, Director Judith Neubauer on August 8, 2012]. All patients were 18 years or older, nonlactating, ASA physical class 1, 2, or 3, and scheduled for laparoscopic cholecystectomy. Patients were excluded if they were cognitively impaired; required additional surgery within 90 days; had chronic use of steroids or opioids; received COX inhibitors within 3 days of surgery; or had any contraindications to COX inhibitors, opiates, or benzodiazepines. In addition, patients were automatically excluded if they were non–English-speaking because the questionnaires were copyrighted and validated in English only. Patients were randomly assigned to one of two groups based on computer-generated random-block codes maintained in sequentially numbered envelopes. Pharmacy-prepared 250-mL bags of IV ibuprofen 800 mg or placebo were given to the responsible anesthesiologist on the day of the surgery. An investigator who was not aware of the treatment group and not involved in the intraoperative care conducted the interviews and administered the questionnaires.

Surgery and Anesthesia

Upon arrival into the operating room for surgery and within 10 minutes of induction of anesthesia, patients were administered either 800 mg of IV ibuprofen or placebo. After pre-oxygenation, general anesthesia was induced using lidocaine (1 mg/kg), propofol (2 mg/kg), fentanyl (up to 5 μg/kg), and rocuronium (0.6 mg/kg) to facilitate endotracheal intubation. Anesthesia was maintained with a mixture of air/oxygen (FiO2 = 0.4) and sevoflurane. Additional doses of fentanyl were given at the discretion of the anesthesiologist. All patients received ondansetron 4 mg before the completion of surgery. Patients were awakened and extubated in the operating room and transferred to the postanesthesia care unit (PACU) upon following simple commands. In the PACU, rescue opioids were given to all patients who indicated that their pain score was >2 on a Numeric Pain Rating Scale or upon request.

Data Collection and Analysis of Blood Samples

Blood samples for the analysis of cortisol, C-reactive protein (CRP), cytokines (TNF-alpha, IL-1β, IL-2, IL-6, IL-10, IFNγ), epinephrine, and norepinephrine were collected at three different time points: at baseline before administration of any medications, including IV ibuprofen or placebo; at the end of surgery in the operating room; and 2 to 3 hours after the surgery in the PACU. Samples were centrifuged within 30 minutes of collection and plasma was stored at –80°C until analysis.

Neurobehavioral Assessments

Quality of recovery, level of fatigue, and mood were assessed at four time points: preoperatively in the PACU, postoperative day (POD) 1, and POD 3. The 40-item Quality of Recovery questionnaire (QoR40) consists of five domains scored on a 5-point Likert scale: comfort (12 questions), emotion (9 questions), physical independence (5 questions), patient support (7 questions), and pain (7 questions) [13]. We used the Modified Fatigue Severity Scale (MFSS) to measure the severity of fatigue [14,15]. The MFSS is composed of nine statements concerning the respondent's level of fatigue, e.g., how fatigue affects motivation, exercise, physical functions, carrying out of duties, work, family, or social life [14]. A low MFSS score indicates a strong disagreement with the statement, while a high MFSS score indicates a strong agreement. Mood is reliably assessed using the 15-item Geriatric Depression Scale (GDS), which also reflects functional ability and quality of life [16]. Pain intensity was measured using a 10-point numeral rating scale, and patients were asked to participate in the neurobehavioral tests only if their pain score was < 2.

Statistical Analysis

The primary endpoints were the global QoR40 scores. Individual QoR40 domains were analyzed using two-way repeated measure ANOVA with drug group as the between-subjects factor and period of testing as the within-subjects factor. In addition, our major conclusions were tested using bootstrap resampling techniques, as previously described by Leslie et al. [17] and Bekker et al. [15].

We previously performed a very similar study with population sizes nearly equal to those in this study. In the previous study, we compared dexmedetomidine (n = 26) with propofol (n = 28), using the same QoR40 instrument. The analysis of the total composite score showed significant effects for both time ($P < 0.001$) and drug ($P = 0.042$), with pairwise differences between the lowest values (POD1, POD2) versus baseline being significant ($P < 0.001$). The time point with the most significant pairwise difference in mean QoR40 by drug group was POD 3. The mean difference there in total score was –13.74 comparing the dexmedetomidine and propofol arms (standard deviation [STD] = 13; $P = 0.005$; effect size > 1). This is larger than the threshold for a clinically meaningful value for the QoR40 of 10.

Using reverse power calculations, the minimum effect size for this comparison, which we could have detected in this population, was 0.77, and the power was greater than 80%, with alpha value = 0.05. Taken together and assuming a similar effect size, these data and calculations support a total of ~54 patients as a suitable sample size with which to compare IV ibuprofen to placebo for the augmentation of postsurgical recovery.

The secondary endpoints were MFSS, GDS, and the perioperative values in the blood biomarkers. Analysis in this case is similar to that for the primary endpoint global QoR40, with several exceptions. QoR40 had three time points, so there were three values for the within-subject factor: pre-op, POD1, and POD3. MFSS had four time points: pre-op, PACU, POD1, and POD3. The stress response (Cortisol, CRP) and the sympathetic response (epinephrine, norepinephrine) all had three time points: pre-op, intra-op, and PACU. For all of these cases, the repeat measure ANOVA used drug group as the between-subject factor. The cytokines, due to their potential for non-normal distribution and undetectable low values, were analyzed, where possible, using repeat measures ANOVA, but were also tested pairwise using the Tukey test by drug group for particular combinations of pre, intra, and PACU time points.

Results

A study participant flow diagram is provided in Figure 1. Patient characteristics were similar between the two groups, as seen in Table 1.

Quality of Recovery

The global QoR40 scores are presented in Figure 4. A repeated measure two-way ANOVA revealed a significant effect of time ($F_{2,106} = 14.6$, $P < 0.001$), drug group ($F_{1,106} = 9.9$, $P = 0.003$), and time and drug group together ($F_{2,106} = 9.4$, $P < 0.001$). *Post hoc* analysis indicated that there was no difference in preoperative scores between placebo and ibuprofen groups. However, QoR40 scores were higher for patients in the ibuprofen group than in the placebo group ($P < 0.001$) on POD 1. Although there was no difference in the three testing period scores for the ibuprofen group, QoR40 scores were significantly decreased (lower quality of recovery) in the placebo group on POD 1 as compared with the preoperative score ($P < 0.001$). The score then recovered to preoperative levels on POD 3 ($P = 0.9$).

Global QoR40 scores are composed of scores from five individual domains, which we also analyzed separately using two-way repeated measure ANOVA. We found that there was a statistically significant interaction between time and study drug in three of the domains, "comfort" ($F_{2,106} = 11.5$, $P < 0.001$), "emotion" ($F_{2,106} = 8.0$, $P < 0.001$), and "pain" ($F_{2,106} = 11.9$, $P < 0.001$) between placebo and ibuprofen treatment groups. Examining the treatment using pairwise comparisons (placebo vs ibuprofen), there was a significant decline in the scores for "comfort" (51.2 ± 1.6 vs 57.8 ± 0.6, $P < 0.001$), "emotion" (40.2 ± 0.8 vs 44.3 ± 0.3, $P < 0.001$), and "pain" (26.9 ± 1.4 vs 33.5 ± 0.4, $P < 0.001$) on POD 1 for patients in the placebo group. Furthermore, all domains had a significant response to time ($F_{2,106} > 3.3$ $P < 0.05$). In the placebo group, all domains except for "patient support" displayed a change between pre-op and POD 1: "comfort" ($P < 0.001$), "emotion" ($P < 0.01$), "physical independence" ($P < 0.05$), and "pain" ($P < 0.001$). However,

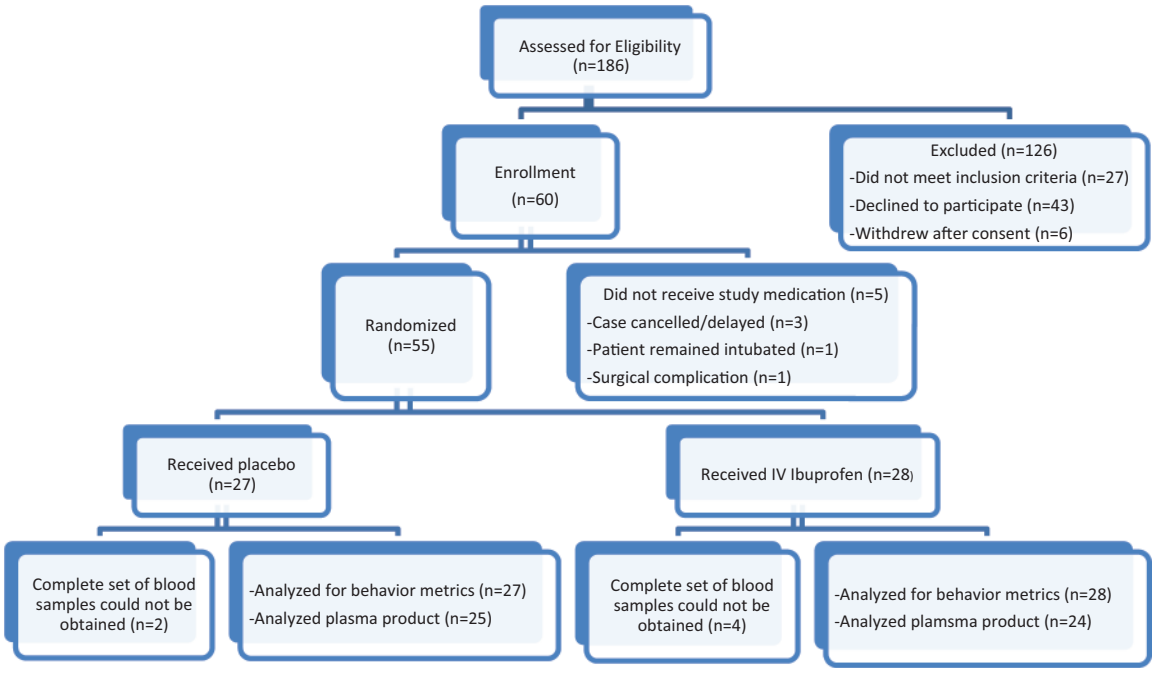

Figure 1 Patient population.

Table 1 Baseline characteristics and perioperative parameters

	Placebo (n = 27)	Ibuprofen (n = 28)	*P* value
Age	39.5 (15.1)	45.4 (15.0)	0.53#
Sex (F/M)	22/5	18/10	0.172 [–0.0638, 0.3835]; $p = 0.1524$**
BMI	29.8 (7.3)	29.1 (6.1)	0.8#
ASA status (1/2/3)	8/17/2	7/19/2	chi sq = 0.16, df = 2, $p = 0.9231$
HTN	5	2	0.1138 [–0.0726, 0.3027]*
DM	2	2	0.0026 [–0.1614, 0.174]*
Asthma	1	1	0.0013 [–0.1433, 0.1501]*
Obesity (BMI $\geq$ 30)	11	11	0.0146 [–0.2301, 0.2576]; $p = 0.9124$**
GERD	1	2	0.0344 [–0.1203, 0.1924]*
Thyroid disease	0	2	0.0714 [–0.0634, 0.2265]*
Duration of surgery (minutes)	86.0 (30.7)	99.0 (44.5)	0.65#
Anesthetics Fentanyl (micrograms)	266.3 (87.7)	234.3 (115.8)	0.75#
Ondansetron given	25	27	0.0385 [–0.1128, 0.2007]*
Postoperative nausea	3	0	0.1111 [–0.0297, 0.2806]*
Use of postoperative rescue opioids	6	1	0.1865 [0.0035, 0.3742]*

Values are mean ± SD.
**Male/Female: 0.172 is the difference in the proportions of male versus total for the two arms: 0.1852 (placebo) and 0.3571 (ibup). *For the indicated parameters (*HTN, DM, Asthma, GERD, Thyroid disease, Ondansetron given, Postoperative nausea), the difference in proportions was calculated where the number of subjects with the condition was divided by the total population for either placebo versus ibuprofen. # Continuous parameters were analyzed based on a t-test, with no significant differences between groups.
ASA, American Society of Anesthesiologists; BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; GERD, gastroesophageal reflux disease.

there was no significant difference in the three testing periods across all domains for the ibuprofen group.

Assessment of Fatigue

Analysis of MFSS total score revealed a significant effect of time ($F_{3,159} = 6.7$, $P < 0.001$), drug group ($F_{1,159} = 7.8$, $P = 0.006$), and time × drug ($F_{3,159} = 3.3$, $P = 0.02$). Patients in the ibuprofen group had significantly lower MFSS scores at every postsurgical evaluation time than patients in the placebo group, indicating less fatigue. This was confirmed by *post hoc* pairwise comparison (placebo-ibup) in the PACU ($P = 0.01$), POD 1 ($P < 0.001$), and POD 3 ($P = 0.03$). *Post hoc* pairwise comparison also indicated a significant effect of time in the placebo group, with significantly higher MFSS scores in the PACU and POD 1 than preoperatively. There was no difference in MFSS scores between the four testing periods in the ibuprofen group, remaining essentially unchanged throughout the evaluation period (Figure 5).

Assessment of Cognitive Recovery

Analysis of the GDS indicated a significant main effect of time ($F_{3,159} = 9.7$, $P < 0.001$), with no effect of drug treatment and interaction between time and group. *Post hoc* comparison showed that patients in the placebo group, but not the ibuprofen group, had a significant drop in GDS scores on POD 3 compared with preoperative scores ($P < 0.05$). There was no difference in GDS scores between the two study groups in any testing period.

Stress Response

Cortisol and CRP serum concentrations are shown in Figure 2. *Post hoc* analysis indicated that cortisol serum concentrations significantly increased intraoperatively and in the PACU in both placebo and ibuprofen groups. There was no difference in cortisol concentrations intraoperatively between both groups. However, cortisol levels were significantly lower in the PACU for the ibuprofen group as compared with the placebo cohort (173.6 ± 29.5 pg/mL vs 289.5 ± 25.9, $P = 0.001$). Comparison of cortisol serum concentrations showed that there was a significant main effect of drug treatment ($F_{2,96} = 5.39$, $P = 0.024$), testing time ($F_{1,96} = 85.46$, $P < 0.001$), and interaction between time and group ($F_{2,96} = 3.16$, $P = 0.048$). There were no significant differences in CRP serum levels.

Sympathetic Response

A repeated measure two-way ANOVA revealed a significant effect of time ($F_{2,98} = 11.7$, $P < 0.001$) and drug group ($F_{1,98} = 4.9$, $P = 0.03$), but no interaction between time and drug treatment ($F_{2,98} = 2.0$, $P = 0.13$). *Post hoc* analysis indicated that epinephrine plasma concentrations significantly increased intraoperatively in the placebo patients, then returned to preoperative levels in the PACU (Figure 3). However, no difference was revealed in epinephrine concentrations in the ibuprofen patients among the three testing periods. More importantly, epinephrine levels were significantly lower intraoperatively for the ibuprofen group than the placebo group (placebo 0.23 ± 0.05 pg/mL vs ibup 0.11 ± 0.03 pg/mL, $P = 0.004$). Although epinephrine levels were still low in the ibuprofen group in the PACU, there was no significant difference between the placebo and ibuprofen groups in the PACU.

Analysis of norepinephrine plasma concentrations (Figure 3) indicated a significant main effect of drug treatment ($F_{1,98} = 4.6$, $P = 0.036$), with no effect of time ($F_{2,98} = 2.4$, $P = 0.11$) and no interaction between time and group ($F_{2,98} = 1.7$, $P = 0.18$). *Post hoc* analysis indicated that norepinephrine levels were significantly lower in the intraoperative testing period for the ibuprofen group than the placebo group (placebo 1.06 ± 0.12 pg/mL vs ibup 0.52 ± 0.09 pg/mL, $P = 0.004$). No difference was seen in the norepinephrine plasma concentrations between the placebo and ibuprofen groups in the PACU.

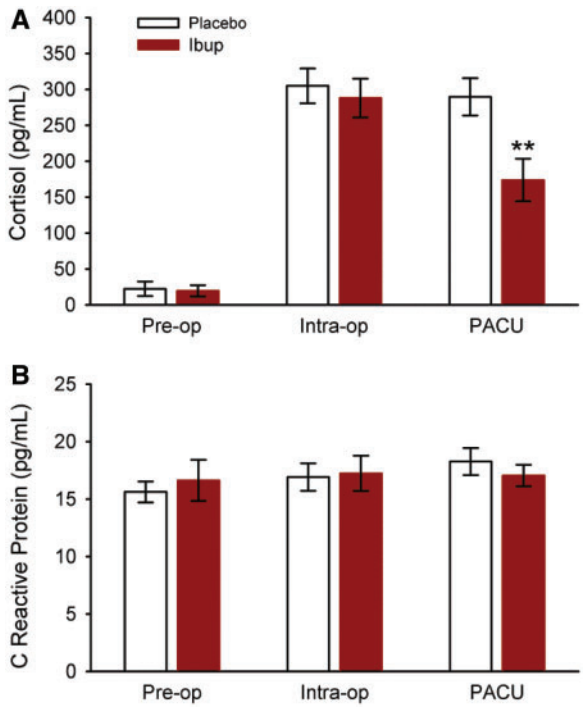

Figure 2 Serum concentrations of cortisol (A) and C-reactive protein (CRP) (B) preoperatively (pre-op), intraoperatively (intra-op), and after surgery (postanesthesia care unit [PACU]). Cortisol levels were significantly higher in the PACU for the placebo group than in the ibup group ($P = 0.001$). There was no significant difference in CRP values between groups.

Table 2 Cytokine concentrations

	Placebo (pg/mL)			Ibup (pg/mL)		
Variables	pre, N	intra, N	PACU, N	pre, N	intra, N	PACU, N
TNFα	11.3 (2.9–28.1), 24	8.9 (2.8–21.0), 25	10.6 (3.6–23.0), 24	12.1 (2.9–31.2), 23	14 (4.5–76.7), 22*	11.8 (3.6–43.1), 23
IL-10	1.3 (0.23–24.2), 21	2.5 (0.6–26.0), 23	21.8 (0.1–113.0)###, 24	2.1 (0.0–11.2), 22	3.3 (0.3–76.3), 23	8.3 (0.1–32.2)***, 24
IL-6	1.2 (0.4–14.5),16	1.1 (0.3–22.7),17	7.7 (0.5–59.1)#, 23	1.4 (0.3–22.2),16	1.9 (0.4–56.4),15	8.3 (0.9–80.4), 22
IFN	6.5 (2.7–139), 9	3.4 (0.8–21.2), 9	6.4 (2.0–64.9), 7	5.0 (0.8–58.3), 11	4.9 (1.7–52.7), 9	6.2 (2.3–48.6),9
IL-1β	L (L–7.1), 3	L (L–L), 0	L (L–L), 0	L (L–5.53), 4	L (L–41.4), 1	L(L–27.0), 1
IL-2	L (L–12.8), 6	L (L–10.9), 6	L (L–8.8), 7	L (L–7.0), 5	L (L–33.8), 7	L(L–23.0), 6

***$P < 0.001$: there is a significant difference between placebo and ibuprofen group at the PACU; *$P < 0.05$: there is a significant difference between placebo and ibuprofen group at the Intra; #$P < 0.05$, ###$P < 0.001$: there is a significant difference between Pre and PACU in the same group. L refers to concentration of the cytokine in a sample, which is below a limit of detection; N is the number of samples with a measurable level of cytokine.

Immune Response

Cytokine concentrations (IFNγ, IL-1β, and IL-2) in many serum samples were below the limit of detection and no assessments could be made (Table 2). However, IL-10 showed a detectable response in 78.5–100% of subjects across the three testing time points. A two-way repeated measure ANOVA showed that there was a statistically significant interaction between time and placebo/ibuprofen groups ($P < 0.001$, two-way repeated measure ANOVA). *Post hoc* analysis indicated that IL-10 levels increased after surgery (pre vs PACU, $P < 0.001$) in the placebo group, but there was no change during the three testing times in the ibuprofen group. Furthermore, IL-10 values for the ibuprofen group were significantly lower than those of the placebo group in the PACU (placebo vs ibup, $P < 0.001$).

TNFα also showed a detectable response in 78.6–100% of subjects in the three time periods. Two-way repeated measure ANOVA showed that there was an impact of drug treatment ($F_{1,89} = 4.8$ $P < 0.05$). Interestingly, *post hoc* analysis revealed that TNFα values in the ibuprofen group were significantly higher than that of the placebo group at the intraoperative period (placebo vs ibup, $P < 0.05$).

IL-6 showed a detectable response in 53.6–69.2% of subjects preoperatively and intraoperatively and was measurable in greater than 91.6% of subjects in the PACU. However, there was no distinction between the placebo and ibuprofen treatment groups at any sampling time.

Discussion

Stress response associated with surgery may lead to increased morbidity secondary to depressed immune function, higher risk of postoperative infection, poor wound healing, and organ failure [4,5,7]. Although the laparoscopic approach is less stressful than open procedures, the exaggerated response is still an important concern due to the size of the surgical (trocar) incision, abdominal distension, and carbon dioxide absorption [17,18]. In this study, we attempted to determine the effects of preoperative administration of IV ibuprofen on the quality of recovery in patients undergoing laparoscopic cholecystectomy. As a secondary outcome, we evaluated the perioperative stress response and immune response. There was a meaningful difference in patients who received ibuprofen, as demonstrated by changes in the release of systemic catecholamines, inflammatory cytokines, and stress hormones. Patients treated with IV ibuprofen had an improved recovery profile and reported less fatigue early after surgery.

Studies examining cognitive dysfunction after surgery have suggested a correlation between elevated inflammatory biomarkers and a delayed return to baseline function [19]. QoR40 has been widely used to assess postoperative recovery from anesthesia where higher scores correlate with improved recovery and well-being [13,21,22]. Myles et al. found that early postoperative poor recovery was predictive of decreased quality of life 3 months after surgery [22]. There was a noticeable decrease in QoR40 scores in the placebo group on POD 1 that then returned to baseline on POD 3. The addition of IV ibuprofen maintained QoR40 scores at baseline through all testing periods. The individual components of the QoR40 score include comfort, emotion, pain, physical independence, and patient support. All of these factors except for patient support are primarily dependent on the patient's clinical and emotional status. Patient support is a variable that may hinge on the patient's social situation. The decline of the QoR40 score on POD 1 in the placebo group was seen in all categories except patient support, also suggesting that subjects had improved early emotional and physical recovery with IV ibuprofen.

The total QoR40 scores on POD1 were 174.8 + 4.1 for placebo (n = 27) and 193.2 + 2.2 for ibuprofen (n = 28; mean + SE). This was the point of greatest difference between study groups. Similar to the QoR40 results, the MFSS showed that the placebo cohort had increased

Table 3 Inflammatory markers and their characteristic systemic effects

TNF-α	• Earliest and most potent pro-inflammatory cytokine after tissue injury • Peak effect at 1 hour; half-life is 20 minutes • Activates the cytokine cascade downstream, including IL-6 • Activates coagulation
IL1-β	• Pro-inflammatory cytokine that works synergistically with TNF-α • Half-life is 6 minutes • Generates the febrile response to injury
IL-2	• Induces T-lymphocyte and immunoglobulin production • Half-life is 10 minutes
IL-6	• Major cytokine with pro-inflammatory and anti-inflammatory effects • Detectable after 60 minutes with peak effect at 4–6 hours • IL-6 levels correspond to the extent of tissue injury • Anti-inflammatory effect of weakening TNF-α and IL-1 activity • Stimulates CRP production
IL-10	• Anti-inflammatory cytokine • Modulates TNF-α activity • Peak effect at 3 hours
IFN-γ	• Pro-inflammatory cytokine that induces IL-2, IL-12, and IL-18 production • Activates circulating and tissue macrophages • Detectable at 6 hours and persists for up to 8 days

Measured cytokines and their roles within the inflammatory cascade.

levels of fatigue in the PACU and POD 1, while patients in the ibuprofen group had no change at all testing times. These results suggest that the addition of IV ibuprofen decreased the intensity of fatigue sustained by surgery and anesthesia in the immediate postoperative testing period.

To evaluate the stress response to surgery, we measured cortisol, CRP, and catecholamines epinephrine and norepinephrine, which were found to correspond most consistently with surgical trauma [23,24]. Six cytokines, TNF-α, IL-1β, IL-2, IL-6, IL-10, and IFN-γ, were chosen as immune biomarkers (Table 3). TNF-α is a potent pro-inflammatory modulator of the cytokine inflammatory cascade that works synergistically with IL-1β. Together, they produce the systemic febrile response and function to decrease tissue damage. IL-2 primarily stimulates the production of T-lymphocytes and

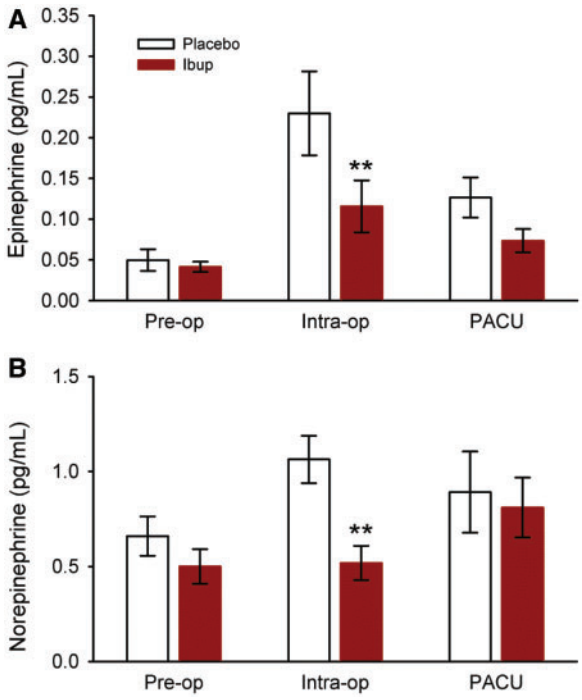

Figure 3 Plasma concentrations of epinephrine (A) and norepinephrine (B) preoperatively (pre-op), intra-operative (intra-op) and immediately after surgery (postanesthesia care unit [PACU]). Both epinephrine and norepinephrine levels were significantly lower in the intraoperative testing period for the ibuprofen group than the placebo group ($P = 0.004$). There was no significant difference in the PACU between groups..

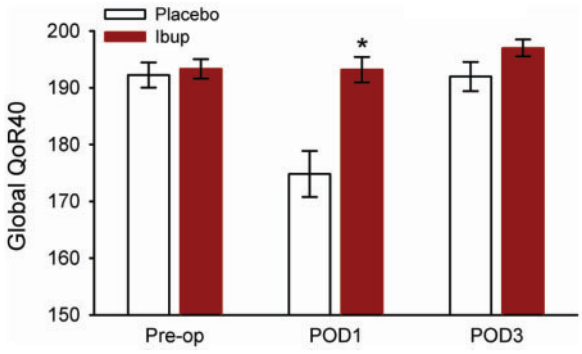

Figure 4 Changes in global 40-item quality of recovery questionnaire (QoR40) scores over time. The global QoR40 scores were analyzed using two-way repeated measure ANOVA with drug group as the between-subjects factor and period of testing as the within-subjects factor. The main effects of time ($P < 0.001$) and drug ($P = 0.003$) were significant. Scores were significantly higher in the ibuprofen treatment group than in the placebo treatment group on postoperative day (POD) 1 ($P < 0.001$). Data are expressed as mean ± S.M.E. n = 27 for placebo group, n = 28 for ibuprofen group.

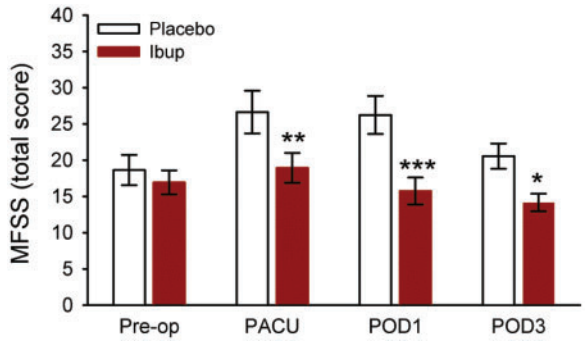

Figure 5 Changes in MFSS over time. The MFSS total scores were analyzed by two-way repeated measure ANOVA with drug group as the between-subjects factor and period of testing as the within-subjects factor. The main effects of time ($P < 0.001$) and drug ($P = 0.006$) were significant. Scores were significantly lower in the ibuprofen treatment group vs placebo treatment group in the PACU ($P = 0.01$), postoperative day (POD) 1 ($P < 0.001$) and POD 3 ($P = 0.03$). Data are expressed as mean ± S.M.E. n = 27 for placebo group, n = 28 for ibuprofen group.

immunoglobulins. However, due to its short half-life of minutes, it is not commonly demonstrable after acute injury. IL-6 is a potent pro-inflammatory and anti-inflammatory marker that has multiple functions, including synthesis of hepatic acute phase reactants and neutrophil activation. IL-6 levels correspond to the extent of tissue injury rather than the duration of surgery and can be detectable after 60 minutes.

Plasma cortisol significantly increased in the intraoperative and postoperative periods for both cohorts. The observed increase may be due to the activation of the hypothalamic-pituitary-adrenal (HPA) axis via the vagus nerve caused by the iatrogenic pneumoperitoneum produced in laparoscopic surgery [25]. Consistent with the other studies, there were no differences between the cortisol levels for the ibuprofen group and the placebo group intraoperatively [25,26]. Activation of the HPA axis does not seem to be attenuated by the administration of ibuprofen [23]. However, cortisol was significantly lower in the ibuprofen group as compared with the placebo group in the PACU. This suggests that after the effect of abdominal distension is removed, there may be an influence of ibuprofen on neuroendocrine response to surgical stress. There were no changes in CRP plasma levels throughout all three testing periods for both the ibuprofen and placebo groups. CRP synthesis is mediated by IL-6 production and does not rise until 20–30 hours after hepatocyte stimulation by IL-6 [25]. Therefore, no change would be expected during the immediate intraoperative and postoperative periods for our study because we did not perform plasma analyses after discharge from the PACU [23,25].

We examined the sympathetic response to surgery by measuring epinephrine and norepinephrine. Consistent with previous reports, epinephrine and norepinephrine levels increased after skin incision, persisted intraoperatively, and gradually declined to baseline postoperatively [24,25]. However, the levels were significantly lower in the ibuprofen group. These results suggest that IV ibuprofen was able to mitigate some of the sympathetic response to surgical stress.

Many of the cytokines, including IFNγ, IL-1β, and IL-2, were below detectable limits. TNF-α levels stayed relatively uniform through all three testing periods for the placebo group, which is consistent with data reported by Chambrier et al. [27]. However, in our study, there was a statistically significant increase in the TNF-α level intraoperatively for the ibuprofen group. Chambrier et al. show a similar rise in TNF-α level for the ibuprofen cohort, but they deemed that the results were too scattered and no significant changes could be determined. Our results are compatible with the concept that NSAIDs directly stimulate mononuclear cells and release TNF-α, thereby causing the subsequent intraoperative upsurge [28–30]. However, the rise quickly diminishes because the half-life of TNF-α is less than 20 minutes.

IL-6 is an important pro-inflammatory cytokine that increases relative to the extent of the trauma. It begins to ascend 1 hour after incision, peaks at 4–6 hours, and will persist well beyond the surgical time. In our study, IL-6 was detectable in 53–69% of the plasma samples, which suggests that laparoscopic cholecystectomies do not produce an acute phase stress response as abundant as more invasive procedures do [25,31]. There were no differences in IL-6 between both ibuprofen and placebo groups at all phases of testing. As expected, there was a slight elevation of IL-6 levels in the PACU for both groups, which correlates with peak plasma levels. IL-10 is a potent anti-inflammatory cytokine and modulates many other circulating cytokines, including IL-6, IL-1, and TNF-α [32,33]. IL-10 is critical in tempering the systemic inflammatory response and decreasing mortality from septicemia [29,33]. High concentrations of IL-10 may signify impending sepsis [8]. Consistent with Kato et al., who examined IL-10 values in upper abdominal surgery, IL-10 values were apparent initially in the PACU period, as it peaks approximately 3–4 hours after incision [29,32]. Our results indicated that not only was there an effect of time on the IL-10 production, but ibuprofen also attenuated IL-10 release. This may indicate that ibuprofen plays a role in the balance between Il-6 and IL-10 by decreasing the pro-inflammatory response and thus requiring less IL-10 modulation.

Because the time points for the neurobehavioral assessments and plasma samples did not coincide in our study (except PACU), it is difficult to establish a correlation between the stress markers and the quality of recovery. We were not able to obtain blood samples on POD 1 and POD 3 because most patients were discharged home following the same-day procedure. Cortisol and ACTH are

immediate acute phase hormonal reactants to surgical stress that are activated by the secretion of IL-6. Although minimally invasive surgery does not cause enough tissue damage to mount substantial IL-6 production, glucocorticoids and catecholamines still increase in laparoscopic surgery because the stimulus is from the abdominal viscera and as well as the abdominal wall. Higher cortisol secretion is associated with the severity of trauma and stress response. Cortisol would be expected to continue to rise many days after surgery, with peak levels approximately 4–6 hours after incision [34,35]. In our study, because cortisol levels were lower in the ibuprofen group than the placebo group, it alludes to an overall reduction in stress response and improved convalescence.

The study has a number of limitations. We were unable to standardize the amount of opioids given during the surgery due to the multiple centers and anesthesia treatment providers. However, no significant differences in opioid use were detected between the groups, allowing us to examine the effect of ibuprofen independent of opioid administration.

Another limitation of the study was the choice of the QoR40 score to assess quality of recovery. This metric was developed in 2000 and has shown both reliability and validity for short-term patient recovery, but cognition is not comprehensively assessed. Moreover, it does not define recovery in an individual patient [36]. New measures such as the Postoperative Quality of Recovery Scale (PQRS) score assess cognitive as well as long- and short-term recovery in multiple domains. It evaluates recovery between groups and at the individual patient level [38]. We began this study in 2011, prior to publication of the PQRS tool.

Our study sought to determine the effect of the preoperative administration of IV ibuprofen on the quality of recovery and stress response. Delayed postoperative convalescence contributes to decreased quality of life and recovery. Other studies [8,23,30,36,38–40] have examined an effect of NSAID or glucocorticoid pretreatment in abdominal surgery on cytokine and neuroendocrine response. However, no studies have specifically examined the effect of a single preoperative dose of IV ibuprofen on quality of recovery measures. Pretreatment with IV ibuprofen seems to be a factor in improving early recovery and may temper the trauma from surgical injury, thereby decreasing the pro-inflammatory processes. An attenuated stress response may also reduce end organ damage, but further studies are required to validate these effects and examine long-term outcomes.

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