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Leukocytosis After Intraperitoneal Hydrocortisone Instillation

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Background: Laparoscopic surgery provides tremendous benefits to patients, including faster recovery, shorter hospital stay, and earlier return to normal activities and less immunologic impairments.

Objectives: In this study we aimed to study the effect of different intraperitoneal instillations on leukocyte count to evaluate patients' immunologic response.

Patients and Methods: We studied 125 patients in a double-blind, randomized clinical trial. The patients received either instillation of 250 mL of normal saline (n = 31) or 100 mg bupivacaine diluted in 250 mL of normal saline (n = 31) or 100 mg hydrocortisone diluted in 250 mL of normal saline (n = 31) or 100 mg hydrocortisone plus 100 mg bupivacaine diluted in 250 mL normal saline (n = 32) before insufflation of Carbon Dioxide into the peritoneum randomly. Leukocyte counts were recorded before and after the operation. We recorded abdominal pain using visual analogue scale (VAS), postoperative analgesics needed and recovery variables in the recovery room and 6, 12 and 24 hours after the operation.

Results: The study was completed by 120 patients. Patients who received intraperitoneal hydrocortisone and hydrocortisone plus bupivacaine had higher white blood cell (WBC) count ($P < 0.0001$). The patients were similar with respect to demographic information, operational characteristics and recovery variables. The abdominal pain scores were significantly lower in patients receiving instilled intraperitoneal hydrocortisone plus bupivacaine and less analgesic was require by them ($P < 0.0001$).

Conclusions: We conclude that intraperitoneal hydrocortisone instillation caused leukocytosis and is thus suggested not to be used in immune-compromised patients.

Keywords: Hydrocortisone; Injections, Intraperitoneal; Leukocytosis

1. Background

Laparoscopic surgery provides tremendous benefits to patients, including faster recovery, shorter hospital stay, and earlier return to normal activities. Additionally, laparoscopic procedures provide better cosmetic results and greater patient's satisfaction that result in greater interest of patients for this new procedure and greater demand for new procedures. These beneficial effects result in reduced surgical trauma and lower immunologic stress response subsequently (1, 2). To minimize the surgical-related stress, improvements in anesthetic and operative techniques have been suggested. Considering the significantly lesser trauma to the upper abdominal wall, laparoscopic surgery seems to provide less stress compared to traditional laparotomy (3-5). But, postoperative pain is still a common complaint after laparoscopic operations and different methods have been proposed to relieve postoperative pain following laparoscopic cholecystectomy (6) like pre-incisional infiltration, plus intraperitoneal instillation of levobupivacaine 0.25% (7); intraperitoneal ropivacaine plus a gas drain (8); intraperitoneal levobupivacaine with epinephrine (9); intraperitoneal application of bupivacaine plus morphine (10); preincisional injection of bupivacaine (11) and intraperitoneal lidocaine combined with intravenous or intraperitoneal tenoxicam (12) and intraperitoneal hydrocortisone (13). As the authors know, no studies have evaluated the effect of these intraperitoneal injections on the immune response of immune-compromised patients.

2. Objectives

We aimed to study the effect of different intraperitoneal instillations on leukocyte count to evaluate patients' immunologic response.

3. Patients and Methods

After approval of the Zahedan University of Medical Sciences Ethics committee and obtaining informed consent from patients, patients (n = 125) with American Society of Anesthesiologists (ASA) physical status I-II scheduled for elective laparoscopic cholecystectomy in Imam-Ali educational hospital of Zahedan from March 2010 to October 2011 were randomly divided in 4 groups of 30 cases. The study was a double-blind prospective randomized clini-

cal trial with stratified random sampling and parallel block randomization. This study does not have RCT code.

Our exclusion criteria consisted of other chronic pain diseases beside gallstone disease (chronic or current), use of opioids, tranquilizers, steroids, non stroiod anti-inflammatory drugs (NSAIDs), and alcohol, acute cholecystitis, allergy to corticosteroids or local anesthetics, neuromuscular diseases, and bleeding disorders. A standard anesthesia was given: After receiving 5 mL/kg crystalloids, pre-oxygenation with 100% O_2 for 3 minutes, 2 g/kg of fentanyl and 0.05 mg/kg of midazolam, anesthesia was induced with 5 mg/kg thiopenthal followed by 0.15 mg/kg of cisatracurium to facilitate endotracheal intubation. Anesthesia was maintained with 60% N_2O in oxygen and 4-6 mg/kg/hr propofol (to keep cerebral state index at 40-60) and 0.05-0.5 g/kg/min remifentanyl (to maintain mean arterial blood pressure and pulse rates within 20% of the baseline values). All patients received 1 g/kg of fentanyl 5 minutes before the termination of operation to reduce postoperative pain. Nasogastric tube was inserted for all patients after induction and was removed at the end of the surgery.

All surgical procedures were performed by a single surgeon. The insufflated Carbon Dioxide was not warmed and humidified. After receiving the standard anesthesia and before insufflations of CO_2, the patients were randomized to receive either instillation of 250 mL of normal saline or 100 mg bupivacaine diluted in 250 mL of normal saline or 100 mg hydrocortisone diluted in 250 mL of normal saline or 100 mg hydrocortisone plus 100 mg bupivacaine diluted in 250 mL normal saline, which were injected into the peritoneum by a surgical scrub nurse who was blind to the study groups. The patients were then rotated into Trendelenburg, anti-Trendelenburg, left and right lateral decubitus, and finally supine positions (each for 2 minutes). Nasogastric tube was inserted for all patients after induction and was removed at the end of the surgery. All surgical procedures were performed by a single surgeon. During laparoscopy, intra-abdominal pressure was maintained at 14 mmHg. Carbon dioxide was carefully evacuated at the end of surgery by manual compression of the abdomen with open trocars. Ten milliliters of 0.25% bupivacaine was injected in laparoscopy entering sites. A blind investigator followed patients for postoperative abdominal and shoulder pain by visual analogue scale (VAS) based on a 0-10 scale (with 0 meaning no pain and 10 meaning the most intense pain experienced ever), presence of nausea and vomiting, time of unassisted ambulation, time of oral intake ability and time of bowel function return in the recovery room and at 6, 12 and 24 hours after the operation. We defined time of return of bowel function as the time from end of anesthesia until presence of intestinal sound or first passage of flatus. Leukocyte count, lymphocyte and polymorphonuclear percentage were recorded for every patient before the operation and 24 hours after operation. We used 0.5 mg/kg intramuscular meperidine hydrochloride and 1 mg/kg as rescue analgesic for VAS 4-7, and 8-10, respectively.

Using SPSS software for Windows, version 15 (SPSS Inc, Chicago, IL, USA), mean and standard deviation values for different variables were calculated and statistical analyses were performed for each group. We used repeated measurement ANOVA test to compare continuous variables exhibiting normal distribution, and Chi-square test for non-continuous variables and Spearman's rho for correlation evaluation. P value less than 0.05 were considered significant.

4. Results

We studied 120 patients undergoing laparoscopic cholecystectomy in 4 groups. Five patients were excluded due to necessary conversion to open cholecystectomy in all five cases because of dense inflammatory adhesions. There were no statistically significant differences among groups in terms of demographic data and duration of surgery (Table 1).

The patients were similar regarding factors w which increase postoperative pain, including bile spillage from punctured gallbladder, difficult dissection due to adhesions from previous surgery, bleeding, need for cholangiography, injury to bowel or other organs, and insertion of drain. The abdominal pain scores were significantly lower in patients who had instilled intraperitoneal hydrocortisone plus bupivacaine in the recovery room and at 6, 12, and 24 hours postoperatively. Patients who received normal saline alone had lowest pain scores (Table 2).

Table 1. Patients Data and Operation Characteristics [a]

	Normal Saline	Hydrocortisone	Bupivacaine	Hydrocortisone Plus Bupivacaine	P Value
Age, y	44.56 ± 3.64	44.60 ± 3.32	44.16 ± 3.39	44.86 ± 2.93	0.59
Gender					0.99
Female	18	19	18	18	
Male	12	11	12	12	
Weight, kg	69.7 ± 8.22	72.2 ± 7.94	70.03 ± 9.60	72.43 ± 9.26	0.503
Height, cm	162 ± 5.75	162 ± 5.45	162.2 ± 5.99	162.3 ± 5.94	0.996
Duration of surgery, min	93 ± 9.65	93.8 ± 10.3	94.16 ± 11.22	95.00 ± 9.46	0.953

[a] Data are presented as mean ± SD.

Table 2. Visual Analogue Abdominal Pain Scores in Groups [a]

	Normal saline	Hydrocortisone	Bupivacaine	Hydrocortisone plus Bupivacaine	P Value
In the recovery room, mg	4.7 ± 0.90	3.73 ± 0.9	2.7 ± 0.77	1.73 ± 0.69	0.00
At 6 hours, mg	4.23 ± 0.77	3.1 ± 0.73	2.2 ± 0.58	1.33 ± 0.47	0.00
At 12 hours, mg	4.33 ± 0.84	3.33 ± 0.84	2.5 ± 0.57	1.53 ± 0.57	0.00
At 24 hours, mg	3.6 ± 0.89	2.6 ± 0.62	1.66 ± 0.60	1.06 ± 0.25	0.00

[a] Data are presented as mean ± SD.

Table 3. Recovery Variables Among Groups [a]

	Normal saline	Hydrocortisone	Bupivacaine	Hydrocortisone plus Bupivacaine	P value
Time of oral intake, h	13.10 ± 1.70	12.36 ± 1.49	12.70 ± 1.44	12.23 ± 1.47	0.133
Time of unassisted ambulation, h	14.43 ± 1.45	14.60 ± 1.49	14.66 ± 1.47	14.26 ± 1.36	0.711
Time of bowel function, h	20.80 ± 2.31	18.60 ± 1.49	18.96 ± 1.54	17.76 ± 3.49	0.001
Time of hospital stay, h	28.60 ± 1.27	27.56 ± 1.88	27.86 ± 1.87	27.40 ± 1.86	0.04

[a] Data are presented as mean ± SD.

Table 4. WBC Count in Groups [a, b]

Data	Normal Saline	Hydrocortisone	Bupivacaine	Hydrocortisone Plus Bupivacaine	P value
WBC count before operation, $\times 10^3/\mu L$	8.090 ± 1.99	7.310 ± 1.972	7.400 ± 3.234	7.133 ± 1.977	0.420
WBC count after operation, $\times 10^3/\mu L$	11.193 ± 2.006	13.860 ± 2.289	11.110 ± 3.081	13.913 ± 1.886	0.000
WBC count difference, $\times 10^3/\mu L$	3.100 ± 0.737	6.550 ± 1.063	3.810 ± 1.193	6.746 ± 1.333	0.000

[a] Abbreviations: WBC, white blood cell.
[b] Data are presented as mean ± SD.

The patients were similar in frequency of nausea/vomiting, length of hospital stay, time of bowel function return, time of unassisted ambulation, and time of oral intake ability (Table 3).

There was no difference among 4 groups in leukocyte count before the operation, but the patients who received instilled intrapritoneal hydrocortisone or hydrocortisone plus bupivacaine had higher leukocyte count than those who received instilled normal saline or bupivacaine (Table 4). The difference between leukocyte count before and after the operation had similar difference. There were no statistically significant correlations among visual analogue abdominal pain scores and white blood cell count differences before and after the operations in four groups ($P > 0.05$).

5. Discussion

The inflammatory cascade after a surgical trauma causes changes in the activity of a wide variety of chemical substances, including Nitric Oxide, catecholamines, the complement-coagulation cascade, glucocorticoids, cytokines (including tumor necrosis factor, and interleukins), eicosanoids (arachidonic acid and its derivatives; leucotrienes, prostaglandins, and thromboxanes), the kinin-bradykinin system, endothelins, platelet-activating factor, macro radical and heat-shock proteins (3-5). These cascades may interact by stimulating and aggravating various other mechanisms of the inflammatory response, which may lead to circulatory dysfunction and multiple organ failure. This physiological response, influenced mainly by the magnitude of the surgical trauma, is influenced by several factors such as anxiety, operative time, pain, hemorrhage, and infection. The laparoscopic approach to the abdominal cavity has been shown to cause lower peritoneal and systemic immune response activations compared with conventional techniques (14, 15).

While laparoscopy is "minimally invasive," systemic immune responses are still invariably activated. Because alterations are proportional to the extent of injury, the physiologic response to minimally invasive surgery may, intuitively, be different than those of traditional open surgery. Many studies have recently been conducted in both humans and animals. Several mediators evaluated during laparoscopic surgery include interleukin-6 (16), C-reactive proteins (16), tumor necrosis factor (17), interleukin-1 (18), histamine response (19), total leukocyte counts (16, 20), t-lymphocyte populations (21), delayed-type hypersensitivity (5), neutrophil activation and function (22) in peripheral blood and macrophage activation (23), and leukocyte function (24) in peritoneal host defenses. Several studies have indeed demonstrated that the inflammatory response after mini-laparotomy and laparoscopy is also less pronounced than full laparotomy (3, 5, 14). But

no study has evaluated the effect of intraperitoneal instillations on immune response yet.

In our study, we showed white blood cell count and its differences before and after operations increased significantly after intraperitoneal hydrocortisone instillation. Although some studies have demonstrated a significant increase in overall peripheral leukocyte numbers in open procedures (21, 22), there was no significant increase in leukocyte count after intraperitoneal instillation of normal saline or bupivacaine in our study. We controlled factors that might had any effect on leukocyte count, including patient's personal data, operation characteristics and recovery variables and there were no statistical correlation between abdominal pain scores and white blood cell count differences.

Our results do not provide evidence for local immune suppression. Peritoneal macrophages or cytokines and complete peripheral immune profile, including humoral and cellular response, should be assessed in patients who received intraperitoneal instillations or intravenous injection of the same drugs too. Further studies are required to evaluate immune profiles in detail for better understanding of immune response in laparoscopic operations.

In conclusion, leukocytosis caused by intraperitoneal hydrocortisone showed its adverse effect on patient's immunologic status. Although it needs more complete studies but we do not recommend intraperitoneal hydrocortisone for immunosuppressed patients.

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Authors' Contributions

Planning, data collection, analysis and article writing was done by Amene Sabzi Sarvestani and Mehdi Zamiri supervise all process.

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