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Comparative Study between General Anesthesia versus General Anesthesia Combined with Thoracic Epidural Analgesia on Cytokine Response in Laparoscopic Cholecystectomy Patients

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Abstract

Background and Objectives: The main benefits of laparoscopic surgery in comparison to open surgery involve the rapid discharge from recovery room, decreased postoperative hospital stays, reduced postoperative discomfort, easier getting back to work and faster return to ordinary daily life as well as cosmetic surgical wounds. The anesthesia type has an essential role in attenuation of the surgical stress and achievement of these advantages. We aimed to determine the outcome of giving general anesthesia in conjunction with thoracic epidural analgesia (TEA) compared to general anesthesia alone on stress response to surgery and anesthesia by investigating cytokine reaction (interleukin 6 and 8 levels), hemodynamic changes (BP, HR, RR, SPO2), and Visual Analogue Scale (VAS) scores postoperatively in patients subjected for laparoscopic cholecystectomy. **Methods:** This study included 40 patients aged 20 - 60 years old with American Society of Anesthesiologists physical status (ASA) I and II. They were planned for laparoscopic cholecystectomy at Aswan University Hospital from April 2017 to March 2018. They were randomly allocated into two groups. Group A (n. 20) received general anesthesia only and Group B (n. 20) received general anesthesia in conjunction with thoracic epidural analgesia using fentanyl and bupivacaine in the epidural catheter. Chi-square was applied to differentiate categorical variables, whereas comparison between continuous variables was done by using t-test. Two-tailed p

< 0.05 was estimated as statistically significant. **Results:** As regards IL-6 and IL-8 post-operative there is significant difference ($p < 0.05$) between two groups during 2nd and 4th hr and 24th hr postoperative, with significantly increased postoperative levels of IL-6 and IL-8 in comparison to their preoperative baseline values. The largest increase in IL6 & IL8 levels was in group A (GA group). VAS score showed significant lower values in TEA group in comparison to GA group. No significant difference between groups as regard intraoperative and postoperative hemodynamic changes. **Conclusion:** Regional techniques including TEA attenuate and decrease cytokine reaction secondary to surgery which decreases inflammatory process and improves patient outcome and reduces pain score postoperatively.

Keywords

General Anesthesia, Thoracic Epidural Analgesia, Cytokine, Laparoscopic Cholecystectomy

1. Introduction

Laparoscopic cholecystectomy has now considered as the typical operation for treatment of patients having cholecystitis indicated for surgical removal of gall bladder. This type of surgery has certain benefits including small incision, decreased loss of blood, less postoperative analgesic requirements, and decreased recovery time and hospitalization. Nonetheless, pneumoperitoneum induces hemodynamic alterations due to sympathetic stimulation causing elevated mean blood pressure (MAP) and increased heart rate (HR) [1].

A 10 - 15 mmHg intra-Abdominal pressure (IAP) is used. Carbon dioxide (CO_2) is widely used as it is an inert gas, with faster absorption due to high solubility in blood which may cause respiratory acidosis due to hypercapnia [2].

Previous studies have identified different reasons of postoperative discomfort after laparoscopic surgery as rapid peritoneal distension, nerve injury due to neural traction, liberation of inflammatory mediators, or as a sequalae of gall bladder removal, high abdominal pressure, and CO_2 residue under the diaphragm (causing irritation of phrenic nerve or tension on the coronary and triangular ligaments caused by sagging of the liver) [3].

Stress response to surgical injury involves stimulation of hypothalamic pituitary adrenal axis and production of inflammatory cytokines. In this response inflammatory cytokines, especially interleukin-6 (IL-6) and interleukin-8 (IL-8) play a very important role [4]. They can cause a long-lasting hyperalgesia [5].

After operation, cytokine levels are highest at almost 24 hours and continue to stay high postoperatively throughout 48 - 72 hours [4]. It does not induce hemodynamic disruptions, but it is a strong neutrophils activator. Inflammatory cytokines; IL-6, IL-8, and granulocyte-colony stimulating factor have been documented to be up-regulated during and after major surgical procedures [4].

Factors such as anesthesia, surgery, hypoxia, hemorrhage, fluid-electrolyte changes, and pain cause different responses in the neuroimmuno-endocrine systems. This response is influenced by anesthetic agents, anesthesia type, and duration [6].

Our research aimed to establish the impact of general anesthesia (GA) with or without thoracic epidural analgesia (TEA) on cytokine reaction and on the surgical and anesthetic stress response by investigating interleukin 6 and 8 levels and observing hemodynamic changes both intra and postoperatively, and observing visual analogue scale score (VAS) postoperatively.

2. Patients and Methods

Following approval of departmental ethics and research committee (120/4/17) and upon getting documented and signed informed consent, forty male and female patients (Figure 1), aged 20 - 60 years old, with American Society of Anesthesiologists (ASA) physical state I and II were involved in our study. They were prepared and planned for laparoscopic cholecystectomy. This study was conducted at Aswan University Hospital for one year from April 2017 to March 2018.

Patients with ASA status III-IV, on chronic steroid therapy, or with any contraindications to regional anesthesia as coagulopathy, hepatic or renal decompensation, uncooperative patients or patients refused to sign the consent were

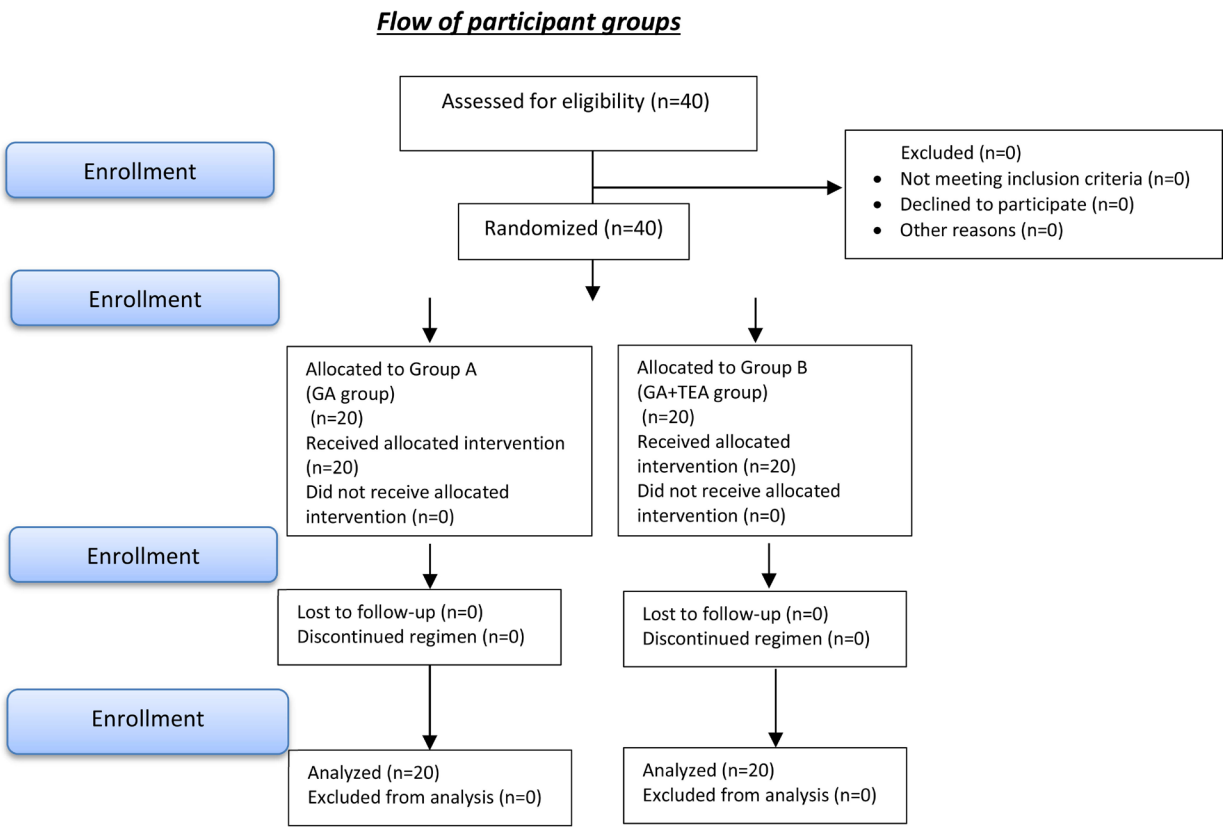

Figure 1. Flow of participant groups.

eliminated from the research study. Also, patients with history of allergic reaction to any of the used medications, with coronary artery disease or thoracic vertebral anomalies were omitted from the research study.

Patients were randomly allocated into two groups.

Group A: GA group) (n. 20) received general anesthesia only.

Group B: (GA + TEA group) (n. 20) received general anesthesia combined with thoracic epidural analgesia (TEA).

Patients of both groups were submitted to the study after proper preoperative assessment including previous history of general or regional anesthesia problems or any medical problems, clinical examination, and routine investigations including CBC, Coagulation profile, renal functions and liver functions were done. In pre-anesthetic room, an intravenous cannula was inserted, then patients were sedated with midazolam 2 mg iv. then patients were transferred to operating room. Complete monitoring as non-invasive blood pressure (NIBP), heart rate (HR), oxygen saturation (SPO2), electrocardiogram (ECG), and end-tidal carbon dioxide ($ETco_2$) were connected to patients then baseline readings of blood pressure, heart rate and oxygen saturation were recorded. Blood samples for IL-6 and IL-8 assessment were withdrawn before induction of GA.

Anesthesia Techniques:

Group A (GA group): The induction of GA was carried out with 2 μg/kg fentanyl, 1 - 2 mg/kg of propofol followed by 0.5 mg/kg of atracurium. After full muscle relaxation, patients were intubated, confirmed by capnography which was immediately connected. Anesthesia was maintained using 1% - 1.5% isoflurane in 50% oxygen and 50% air, mechanical ventilation with fentanyl, 1 μg/kg and atracurium 0.1 mg/kg as needed. Intraabdominal CO_2 pressure was kept between 12 and 15 mmHg. At the end of operation, isoflurane was stopped and neuromuscular blockade was reversed using atropine 0.02 mg/kg plus neostigmine 0.04 mg/kg iv. Then patients were shifted to postanesthetic care unit (PACU) after being fully conscious and obeying command. Pethidine 50 mg diluted in 10 ml normal saline was given slowly iv 12 hours postoperative and paracetamol 1 gm iv infusion every 6 hours were given to all patients in both groups as a fixed dose.

Group B (GA combined with TEA group): The same anesthesia technique like group A, except that thoracic epidural catheter was inserted and T6-level sensory block was confirmed before administration of GA as follows: With the patients in the sitting position, under complete aseptic technique, the skin over 8^{th} - 9^{th} thoracic interspace was infiltrated with 1% lidocaine. The extradural space was determined by using a 18-gauge Touhy needle using paramedian approach with loss of resistance to air injection. A 20-gauge epidural catheter was advanced and fixed 3 - 5 cm in the epidural space. After negative aspiration for CSF and blood, 3 ml test dose of lidocaine 2% with epinephrine 1:200,000 was administered and then the catheter was flushed with saline 2 ml to exclude subarachnoid or intravascular injection. The patient was then turned supine, five

minutes after the test dose and in the absence of any adverse sequelae, a bolus dose of 6 - 8 ml of 0.25% bupivacaine with 50 μg fentanyl was administered through epidural catheter. The extent of sensory blockade was evaluated by pin prick test bilaterally along the midclavicular line by assessing changes in pin-prick sensation using a 25-gauge needle. After confirming upper sensory blockade up to T6 level, patients received general anesthesia the same like Group A. Continuous epidural infusion began after induction of general anesthesia as 0.125% bupivacaine with fentanyl 1.5 μg/ml at 0.1 ml/kg/h via syringe pump. The epidural infusion continued throughout the surgical procedure and stopped with the termination of surgery.

In both groups; mean arterial pressure (MAP), heart rate (HR), and oxygen saturation (SpO2) values were recorded intra and postoperatively.

2.1. Primary Outcome

Blood Samples were withdrawn prior to any intervention (baseline), then at 2nd, 4th, and 24th hours after the operation to measure and record plasma concentrations of IL-6 & IL-8.

2.2. Secondary Outcome

Included post-operative pain assessment recorded after extubation, at 30, 60 min and 2, 4, 6, 8, 12 and 24 hours postoperatively for visual analogue scale score (VAS) to record pain intensity ranged from 0 = no pain, to 10 = the worst imaginable pain. Vital signs as mean arterial pressure, heart rate, and arterial oxygen saturation were recorded intraoperatively before and after epidural insertion, immediately after intubation, immediately after skin incision, 15 min, 30 min and 1 h from the start of the operation, and also recorded immediately after extubation, at 30, 60 min and 2, 4, 6, 8, 12 and 24 hours postoperatively.

2.3. Power of Study

Using the Rao soft sample size calculator Setting alpha errors at 5%, power at 80% and results from previous study (Ozcan, S., *et al.*, 2016) [7] who also studied the effects of combined general anesthesia with thoracic epidural analgesia on cytokine reaction in laparoscopic cholecystectomy patients, therefore 20 patients are required in every group to conduct this study.

2.4. Statistical Analysis

Before additional statistical analysis, the results were reviewed for normality using the Anderson-Darling method and for variances in homogeneity. Categorical variables were represented by number and percentage (N, %), whereas continuous variables were represented by mean and standard deviation (Mean ± SD). Chi-square was applied to differentiate categorical variables, whereas comparison between continuous variables was done by using t-test. Two-tailed $p < 0.05$ was estimated as statistically significant. The IBM SPSS 20.0 program was

used to carry out all tests.

3. Results

Demographic data for both study groups of patients revealed no statistical significant difference ($p > 0.05$) in age (years), height (m), weight (kg), gender, BMI and time of the surgical procedure (in hours) (Table 1).

IL-6 and IL-8 levels were evaluated before surgery (baseline), then 2 hrs, 4 hrs and 24 hrs after the start of surgery. Table 2 & Table 3 with Figure 2 & Figure 3 showed significantly increased postoperative (at 2nd, 4th and 24th postoperatively)

Table 1. Comparison between groups as regard demographic data.

	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
Gender			
Male [No. (%)]	12 (60%)	8 (40%)	0.206
Female [No. (%)]	8 (40%)	12 (60%)	
Age (years)	30.6 ± 8.6	34.7 ± 8.18	0.131
Weight (kg)	76.6 ± 6.82	74.2 ± 6.52	0.263
Height (m)	1.68 ± 0.08	1.69 ± 0.08	0.659
BMI (kg/m^2)	27.13 ± 2.09	25.98 ± 2.32	0.105
Duration of the surgery(min)	74 ± 11.88	68.0 ± 9.89	0.091

Data are presented as means ± SD or numbers and percentages; No statistical significant differences among study groups (p value > 0.05).

Table 2. Baseline and postoperative IL-6 level in both groups.

IL-6 (pg/ml) post-operative	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
0 min. (Baseline, before intervention)	3.4 ± 2.4	3.2 ± 2.3	0.707
2nd hr	23.8 ± 3.2	21.4 ± 3.2	0.023*
4th hr	22.3 ± 3.3	19.7 ± 3.6	0.021*
24th hr	19.4 ± 3.6	17.0 ± 2.9	0.025*

Data presented as mean ± SD, * significant differences among study groups (p value < 0.05).

Table 3. Baseline and postoperative IL-8 level in both groups.

IL-8 (pg/ml) post-operative	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
0 min. (Baseline, before intervention)	3.5 ± 0.95	3.3 ± 1.03	0.527
2nd hr	17.6 ± 1.64	16.15 ± 1.59	0.031*
4th hr	17.45 ± 1.47	16.05 ± 1.67	0.045*
24th hr	17.3 ± 1.59	15.9 ± 1.6	0.042*

Data presented as mean ± SD, * significant differences among study groups (p value < 0.05).

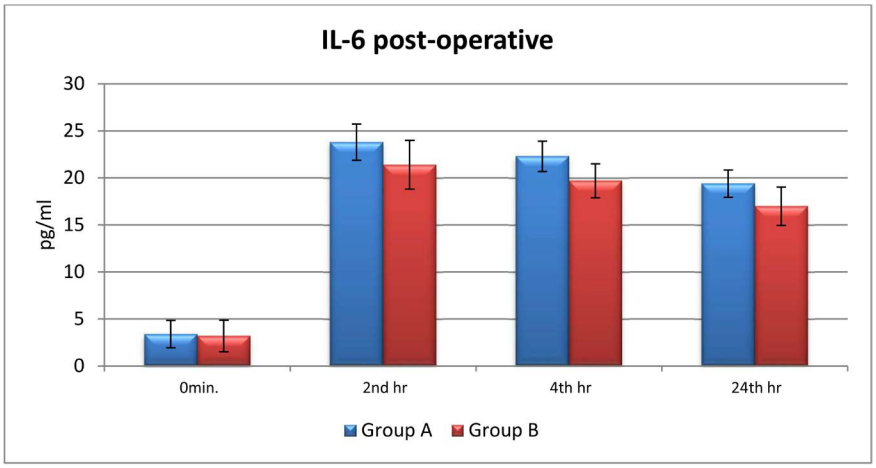

Figure 2. Clustered column chart showing (Mean ± SD) of IL-6 post-operative distribution between two groups.

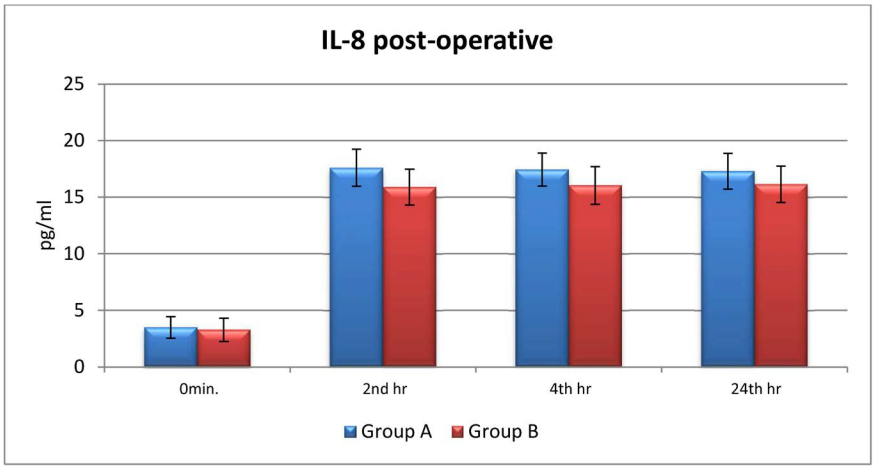

Figure 3. Clustered column chart showing (Mean ± SD) of IL-8 post-operative distribution between two groups.

levels of IL-6 and IL-8 in comparison to their preoperative baseline values. The preoperative cytokine levels were comparable, then increased at 2 hrs and at 4 hrs, then started to decrease again 24 hrs after the operation in both groups. Regarding IL-6 and IL-8, these results showed significant statistical difference between the two groups at 2 hrs, 4 hrs and 24 hrs postoperative. The largest increase in IL6 & IL8 levels was in group A (GA group).

VAS pain score showed highly significant lower values after extubation, at 30 minutes, 1 hr and 2 hrs after operation in group B (GA+TEA) in comparison to group A (GA) ($p < 0.01$, Table 4). Also, VAS pain scores at 4 hrs and 6 hrs after operation were statistically significant lower in group B (GA+TEA) in comparison to group A (GA) ($p < 0.05$, Table 4). With no statistical significant difference between the two groups at 8 hrs, 12 hrs and 24 hrs as shown in Table 4.

There were no significant statistical differences as regard intraoperative and postoperative noninvasive mean arterial blood pressure (NMBP), heart rate (HR) and arterial oxygen saturation (SPO2) as shown in Tables 5-7.

Table 4. Postoperative VAS score in both groups.

VAS post-operative	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
After extubation	6.7 ± 1.13	0.4 ± 0.68	0.001*
30 min	6.6 ± 1.39	0.5 ± 0.69	0.001*
1 hr	5.8 ± 1.99	0.9 ± 0.85	0.001*
2 hr	4.7 ± 2.05	1.3 ± 0.66	0.001*
4 hr	3.3 ± 1.66	2.4 ± 0.94	0.041#
6 hr	2.8 ± 1.51	1.8 ± 1.01	0.018#
8 hr	2.4 ± 1.23	2 ± 1.03	0.271
12 hr	2.2 ± 1.36	1.8 ± 0.92	0.283
24 hr	2.4 ± 1.23	1.7 ± 1.23	0.080

Data presented as mean ± SD, *highly significant differences among study groups (p value < 0.01). #significant differences among study groups (p value < 0.05).

Table 5. Comparison of noninvasive mean arterial pressure (NIMBP) in both groups intra and postoperatively.

NIMBP (mmhg)	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
Intraoperative:			
Before epidural insertion	97.9 ± 7.7	97.5 ± 8.21	0.875
After epidural insertion	89.1 ± 5.02	88.8 ± 8.98	0.914
After intubation	92.4 ± 4.55	84.5 ± 20.11	0.095
After skin incision	90.9 ± 10.13	84.1 ± 12.79	0.070
15min	82.7 ± 9.56	77.6 ± 9.44	0.098
30min	85.4 ± 11.8	79.6 ± 9.09	0.089
1 hr	84.6 ± 13.69	77.3 ± 11.03	0.071
After extubation	92.7 ± 10.06	88.6 ± 11.21	0.231
Postoperative:			
30 min	84.7 ± 12.01	82.8 ± 7.73	0.555
1 hr	87.2 ± 10.98	84.8 ± 5.76	0.394
2hr	84.1 ± 6.45	83.5 ± 5.38	0.751
4hr	86.5 ± 5.81	84.2 ± 5.27	0.197
6hr	85.4 ± 6.56	85.1 ± 5.48	0.876
8hr	86.1 ± 4.8	84.7 ± 4.5	0.347
12hr	84.3 ± 4.31	85.6 ± 5.55	0.413
24hr	89.6 ± 4.31	90.8 ± 1.88	0.261

Data presented as mean ± SD, No statistical significant differences among study groups (p value > 0.05).

Table 6. Comparison of heart rate (HR) in both groups intra and postoperatively.

HR (Beat per min.)	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
Introperative			
Before epidural insertion	87.8 ± 10.49	89 ± 14.65	0.767
After epidural insertion	88.7 ± 8.5	85.9 ± 13.06	0.436
After intubation	88.4 ± 7.94	87.8 ± 9.07	0.825
After skin incision	89.5 ± 10.82	85.6 ± 6.6	0.179
15 min	84.5 ± 14.86	80.2 ± 13.06	0.337
30 min	85.1 ± 13.21	77.6 ± 16.1	0.116
1 hr	82.6 ± 13.24	78.4 ± 12.18	0.303
After extubation	86.2 ± 10.85	86.3 ± 10.37	0.976
Postoperative			
30 min	81.5 ± 11.58	80.5 ± 9.32	0.765
1 hr	85.5 ± 6.57	82 ± 8.61	0.156
2 hr	80.4 ± 7.1	81.3 ± 6.68	0.682
4 hr	82.5 ± 5.05	81 ± 6.62	0.425
6 hr	78 ± 7.08	78.7 ± 6.31	0.743
8 hr	78.8 ± 5.02	77.6 ± 4.5	0.431
12 hr	81.7 ± 7.14	80.4 ± 3.5	0.471
24 hr	78.5 ± 5.05	81.4 ± 5.75	0.098

Data presented as mean ± SD, No statistical significant differences among study groups (p value > 0.05).

Table 7. Comparison of arterial oxygen saturation (SPO2) in both groups intra and postoperatively.

SPO2 (%)	Group A (n = 20)	Group B (n = 20)	p value
	Mean ± SD	Mean ± SD	
Intraoperative:			
Before epidural insertion	99 ± 0.95	98 ± 0.92	0.336
After epidural insertion	97.5 ± 0.89	97.8 ± 1.11	0.276
After intubation	99.3 ± 0.47	98.6 ± 1.94	0.125
After skin incision	99.5 ± 0.51	98.7 ± 2.05	0.098
15 min	99.3 ± 0.66	99.1 ± 0.31	0.228
30 min	99.5 ± 0.51	99 ± 1.6	0.191
1 hr	99.1 ± 0.55	98.7 ± 1.66	0.313
After extubation	99.3 ± 0.47	98.8 ± 1.41	0.141
Postoperative:			
30 min	99 ± 1.65	98.3 ± 1.03	0.116
1 hr	99 ± 0.46	98.5 ± 1.51	0.165

Continued

2 hr	98.7 ± 0.47	98.7 ± 0.66	1.000
4 hr	98.9 ± 0.31	98 ± 2.46	0.113
6 hr	98.9 ± 0.55	98.2 ± 1.77	0.099
8 hr	98.7 ± 1.47	98.1 ± 1.07	0.148
12 hr	98.9 ± 1.31	98.2 ± 0.89	0.055
24 hr	98.9 ± 1.31	98 ± 1.92	0.091

Data presented as mean ± SD, No statistical significant differences among study groups (p value > 0.05).

4. Discussion

The goal of this work was to compare between GA alone and GA combined with TEA on cytokine release (IL-6 & IL-8) at different times; before any intervention then at 2nd, 4th, and 24th hours after the operation, and to observe and document postoperative VAS scores in both groups. Also, to compare intraoperative and postoperative hemodynamic changes (BP, HR, SPO2) in cases submitted for laparoscopic cholecystectomy.

Our current study was carried out on patients planned for laparoscopic cholecystectomy. This surgical procedure has many benefits like small surgical incision, decreased or minimal intraoperative blood loss, decreased postoperative pain and short postoperative stay in the hospital [8]. Epidural analgesia inhibits the stimulation of the neuro-endocrine axis [9], leading to hemodynamic changes depending on the level of sympathetic block, age and cardiovascular status of the patient [10].

In our study IL.6 and IL.8 levels increased at 2h postoperative and started to decrease to basal level at 24 h postoperative in both groups which was not coincide with Ozcan *et al.* [7] study who reported that cytokine levels increased at 2 hrs, peaked at 4 hrs, and then returned to preoperative levels 24 hrs after surgery in all groups which might be due to reduced cytokine production. We observed that, IL-6 and IL8 showed statistical significant difference ($p < 0.05$) between the two groups in the 2nd, 4th hr and 24th hr postoperative. The largest increase in IL6 & IL8 levels was in group A (GA group). This is because that anesthetic agents and anesthesia type can influence the neuro-immuno-endocrine reaction to surgery and pain [11], as regional anesthesia lead to reduced monocyte stimulator factor level which lead to decreased plasma cytokine response [12].

In comparison with Vicente *et al.* [13] study, systemic biomarker analysis of patients undergoing elective hepatic resection for metastatic disease in a randomized controlled study to compare TEA with IV-PCA, they demonstrated that the patients had epidural analgesia showed a favorable postoperative biomarker profile for oncologic surgery with dampened response to surgery in fold changes of IL-6 & IL-8. The TEA patients on POD1 (postoperative day 1) had relatively lower mean fold changes from baseline compared to IV-PCA patients in IL-6 which agreed with our current study.

In the previous study of Vicente *et al.* [13] epidural analgesia was related with an initial dampened proinflammatory response in IL6 and IL8 with persistently lower levels of immunosuppressive signaling throughout the postoperative period in patients with epidural analgesia, which might confirm the suggestion that epidural analgesia is associated with early benefits of patient satisfaction and pain control.

Kun, L., *et al.* [14] studied seventy-one patients with gastric cancer who received radical resection, assigned randomly under combined general/epidural anesthesia (study group) and general anesthesia alone (control group). Natural killer (NK) cell activity and serum concentrations of protumorigenic cytokines IL-1β and IL-6, and antitumorigenic cytokines IL-2 and IL-10 were evaluated in both groups before anesthesia (T1), 4 hours after skin incision (T2), and 24 hours after skin incision (T3). They found that the concentrations of IL-6, and IL-10 elevated at T2 and T3 relative to T1, whereas IL-2 concentration and NK cell activity decreased at T2 and T3. Furthermore, the study group exhibited less suppression of NK cell activity, upper levels of IL-2 and IL-10, and lower levels of IL-1β and IL-6 in the early stage after the operation compared with the control group, which coincided with our current study as regards IL-6 levels at 2nd, 4th and 24th hr postoperative.

Moselli *et al.* [15] reported that IL-6 incremented its basal value of more than 7-fold at 24 h from the incision time but level of increase was lower in epidural analgesia (EA) group than intravenous analgesia (IA) group which coincide with our study as we have detected that IL-6 and IL-8 levels remained high 24 h after the surgery.

In Moselli *et al.* [15] study, the baseline IL-6/IL-10 ratio was almost the same across the two groups the EA group and the IA group. In the IA group it significantly increased at T3h and T24 h compared with the EA group (p-value < 0.05) which agreed with our study.

Cheng-Yong *et al.* [16] studied the impact of epidural anesthesia and postoperative epidural analgesia on the immune function in esophageal carcinoma patients scheduled for thoracic surgery via four groups, groups I and II given total intravenous anesthesia (TIVA), while groups III and IV given TIVA combined with TEA. Postoperatively, groups I and III received postoperative patient-controlled intravenous analgesia (PCIA), while groups II and IV given PCEA. They found that GA with TEA reduced the serum levels of IL-6 more effectively than GA alone. Compared to group IV, the IL-6 levels in group I were higher at T1 (2 h after incision), T2 (4 h postoperatively) and T4 (48 h postoperatively) ($p < 0.05$) which coincide with our study at 2nd and 4th hr but our study limited to 24th hr. The levels of IL-6 in group II were higher compared to those in group IV at both T1 and T2 ($p < 0.05$) which also coincide with our study

Kuo *et al.* [17] observed that, administration of lidocaine before the beginning of surgery through epidural or i.v. route can diminish IL-6, IL-8 and IL-1RA production in patients undergoing colonic surgery. The least rise in cytokine

level was noticed in TEA group, then by iv group and control group. This finding was compatible with our current study as TEA group (group B) showed significant reduction in IL-6 & IL-8 at 2nd, 4th and 24th hr in comparison with general anesthesia group (group A) (p-value < 0.05).

Fant *et al.* [9] studied that TEA could reduce the stress response in early postoperative period but could not reduce the acute inflammatory reaction after radical prostatectomy. They found that TNF-α and IL-6 plasma levels did not differ between both iv-based analgesia and epidural-based analgesia groups at any time point so, concluded that epidural-based analgesia did not significantly suppress the concentration of the proinflammatory plasma cytokines TNF-α and IL-6, which disagreed with our study, as we found considerable difference among both groups as regard IL-6 (p-value < 0.05). Fant *et al.* [9] did not study a larger number of patients due to financial constraints and they advised future studies to assess other methods to further obtund the inflammatory response to surgery.

In our current study, we gave fentanyl-bupivacaine epidural bolus dose preoperatively, then epidural infusion started intraoperatively after induction of general anesthesia to be stopped at the end of the surgical procedure which provided postoperative analgesia in TEA group. VAS showed a significant lower score after extubation, at 30 minutes, 1 hour, 2nd hr, 4th hr and 6th hr postoperative in patients of TEA group (Group B) who received preoperative bolus dose and intraoperative infusion of bupivacaine and fentanyl compared to group A who received general anesthesia alone ($p < 0.05$), but no noticeable difference was detected between both groups from 8th hr till 24th hr postoperative. Erol *et al.* [18] found that epidural analgesia using bupivacaine/fentanyl mixture demonstrated improved results of statistical and clinical significance in the management of postoperative pain relative to IV analgesia during the first 24 hours following laparoscopic surgery but in our study pain score improved postoperatively in TEA group till only 6 hr postoperative but remaining time from 8th hr till 24th hr no difference in VAS score among both groups of our study as epidural infusion was stopped at the end of operation and analgesic effect of epidural infusion started to decrease at almost 6th hr postoperative.

Yan *et al.* [19] studied the effect of thoracic epidural anesthesia/analgesia on stress reaction, pain management, duration of hospital stay, and treatment costs of patients undergoing thoracic surgery for treatment of esophageal carcinoma. Pain was assessed using visual analogue scale (VAS) score at 24, 48, and 72 hours postoperative. They observed that VAS pain score at rest and even during coughing were of lower values in PCEA (patient-controlled epidural analgesia) groups than in PCIA (patient-controlled intravenous analgesia) groups ($p < 0.05$) which coincided with our current study concerning postoperative VAS score.

Also, Ozcan *et al.* [7] observed that patients who were given 6 - 8 ml of 0.25% bupivacaine and 0.05 mg fentanyl through the epidural catheter (Group L)

showed decreased postoperative VAS score in comparison with the other groups which agreed with our study at after extubation, at 30 minute, 1 hour, 2nd hr, 4th hr and 6th hr postoperative where VAS showed a significant lower score in group B than group A (p value < 0.05) but disagrees with our study from 8th hr to 24 hour as there is no statistical significant difference between both groups in our study (p value > 0.05) at that times. Ozcan *et al.* [7] proposed that fentanyl and local anesthetics improved postoperative pain score in epidural analgesia group.

Kuo *et al.* [17] observed that, administration of lidocaine before the beginning of surgery through epidural or i.v. route produced noticeable relieve of pain with decreased severity of pain, reduced amount of inhalational anesthetic used and decreased opioid utilization, fast resumption of intestinal movements, and diminished interleukin reaction (decreased production of IL-6 & IL-8). The value of lidocaine was more significant in TEA group which coincides with our study.

In Kuo *et al.* [17] study VAS scores at rest, at 2nd and 4th hr after surgery, and during coughing at 12th h after surgery decreased significantly in IV and TEA groups compared with Group C (normal saline group) (p < 0.05). Resting and coughing VAS pain scores were significantly greater at 4 h and at 12 h after surgery in Group IV compared with Group TEA which coincided with our study at first 6 hrs postoperative where VAS score significantly lowered in group B compared to group A (p < 0.05) but no significant difference from 8th hr till 24th h postoperative.

Intraoperative measurement and recording of mean arterial pressures (MAP), pulse rate (HR), and oxygen saturation (SpO2) values were recorded before intubation, after intubation, after skin incision, 15 min, 30 min, 1h and 2 h from the start of the operation, and after extubation and also recorded at different times 30, 60 min and 2, 4, 6, 8, 12 and 24 hours postoperatively.

As regards hemodynamic changes, it was found that no significant statistical differences as regards intra-operative MAP, HR, arterial O2 saturation (SpO2), or postoperative MAP, HR, arterial O2 saturation between the two studied groups of patients (p-value > 0.05). These findings agreed with Ozcan *et al.* [7] study, but it was against findings of study done by Casati *et al.* [20] on patients subjected to colon resection and found that patients received epidural 0.125% bupivacaine had lower MAP than epidural-saline group and epidural 0.0625% bupivacaine group. They observed that epidural bupivacaine decreased intraoperative isoflurane consumption without changing thiopental dose used during induction. For us we started GA after confirmation of sensory block level, so, there were no significant statistical difference between the two study groups as regard hemodynamics.

There was no significant statistical difference between the study groups as regard intra and postoperative O2 saturation, while Kabon *et al.* [21] suggested that supplementation of GA with TEA improved oxygenation of peripheral tissues during prolonged abdominal surgery.

Therefore, the present study demonstrated that epidural blockage attenuated

the stress-induced rise in cytokine level perioperative and improved VAS score. Combination of TEA with GA contributed to intraoperative hemodynamic stabilization and decreased opioid and anesthetic consumption. This finding may be clarified by the capability of sympathetic nerve blockade enhanced by epidural analgesia to minimize stress response during surgery, involving declines in the levels of plasma catecholamines and cytokine, thereby increasing patient immune response and reducing inflammation.

5. Conclusions

Regional techniques need further study at laparoscopic surgery either to support post-operative pain tools or minimize inflammatory process.

Regional techniques including TEA attenuate and decrease cytokine reaction secondary to surgery which decreases inflammatory process and improves patient outcome and causes postoperative pain score improvement.

Limitations of the Study

In our current study TEA infusion stopped at the end of the operation and pain controlled to 6th hr postoperative due to expected lack of observation and poor recording system in the ward, so we recommended further study to extend TEA infusion or intermittent bolus for 24 hr or more postoperative to maximize benefits and improve pain score.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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