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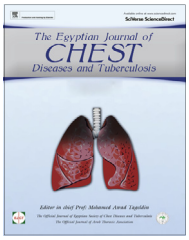

ORIGINAL ARTICLE

Immunomodulatory effect of propofol versus sevoflurane in patients undergoing thoracic surgery using one lung ventilation technique

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KEYWORDS

OLV;
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Abstract *Introduction:* One lung ventilation (OLV) has become a standard procedure for many interventions in thoracic surgery with a need for deflation of the lung to facilitate the surgical procedure. Mechanical ventilation can induce a proinflammatory reaction in the non-deflated ventilated lung. However only limited data exist on inflammatory alterations in the temporarily deflated, non-ventilated lung in patients undergoing thoracic surgery.

Aim of the work: The aim of this work is to compare between the effects of propofol and sevoflurane as regards: the systemic inflammatory response, the pulmonary inflammatory response, C-reactive protein, leucocyte count, and recovery status, in patients undergoing thoracic surgery using OLV technique.

Patients and methods: This study include 40 adult patients, who were randomly classified into two groups: group (I) 20 patients received total intravenous anesthesia with propofol. Group (II) 20 patients received inhalational anesthesia with sevoflurane. Every patient was subjected to a careful pre-anaesthetic assessment, anaesthesia, bronchoalveolar lavage (BAL) analysis for human inflammatory mediators (IL-6 and TNF-α), serum analysis for systemic inflammatory mediators (IL-6 and TNF-α) (Both were measured before OLV and 15 min after OLV ended and resumption of two lung ventilation (TLV) at the end of surgery, and C-reactive protein and leukocyte count in blood (before OLV, 15 min after OLV ended and resumption of (TLV) at the end of surgery and on the 2nd postoperative day).

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Results: According to IL-6 and TNF-α, there was no statistically significant difference between the two groups before OLV, however they were significantly increased in both groups in serum and BAL after OLV in relation to before OLV with significant increase in group I relative to group II. A significant correlation was present between increased level of IL-6 and TNF-α in BAL and their levels in serum after OLV in the group II but this correlation was not present in the group I. Also no significant correlation between duration of OLV and inflammatory mediators (IL-6 and TNF-α) in serum and BAL in both groups. As regarding to CRP, there was no statistically significant difference between the two groups before OLV. After OLV and on the 2nd postoperative day the level of CRP increased significantly in both groups with significant increase in group I relative group II. According to WBC count there was no statistically significant difference between the two groups as regards the level of WBC before OLV. After OLV the level of WBC increased significantly in group I only. On the 2nd postoperative day the level of WBC increased significantly in both groups with significant increase in group I relative to group II. Also no significant correlation between duration of OLV with the increased levels of CRP and WBC count in both groups.

Conclusion: Propofol increased pulmonary and systemic cytokine release more than sevoflurane during OLV. Propofol has increased CRP level and WBC count more than sevoflurane during OLV.

Introduction

One lung ventilation is a technique that allows isolation of the individual lungs under anesthesia. Safe implementation of this technique requires an understanding of specialized airway equipment's, and of the physiological changes that occur during the procedure [1].

Selective intubation was described for the first time in 1932 by Gale and Waters, who used a single-light tube that was inserted into the right or left main stem bronchus. Since then, alternative methods have been proposed in order to make this technique safer and facilitate its practice [2].

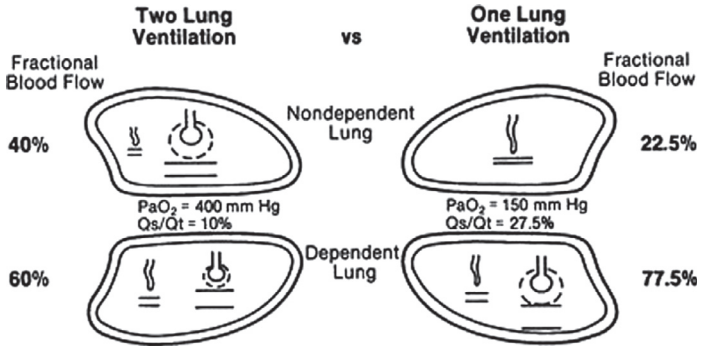
The main indications for OLV include, isolation of the lungs, improve surgical access, greater control over ventilation as in unilateral bronchopleural fistula, unilateral BAL, and differential lung ventilation in ICU. OLV could be established by double lumen endotracheal tubes, bronchial blockers, and endo bronchial intubation.

During TLV in the lateral position, the mean blood flow to the nondependent lung is assumed to be 40% of cardiac output (COP), whereas 60% of COP goes to the dependent lung. Normally, venous admixture (shunt) in the lateral position is 10% of COP and is equally divided as 5% in each lung. Therefore, the average percentage of COP participating in gas exchange is 35% in the nondependent lung and 55% in the dependent lung [3].

One lung ventilation creates an obligatory right-to-left trans pulmonary shunt through the nonventilated, nondependent lung because the V/Q ratio of that lung is zero. In theory, an additional 35% should be added to the total shunt during OLV. However, assuming active hypoxic pulmonary vasoconstriction (HPV), blood flow to the nondependent hypoxic lung will be decreased by 50% and therefore is (35/2) = 17.5%. To this, 5% must be added, which is the obligatory shunt through the nondependent lung. The shunt through the nondependent lung is therefore 22.5%. Together with the 5% shunt in the dependent lung, total shunt during OLV is 22.5% + 5% = 27.5%. Because 72.5% of the perfusion is directed to the dependent lung during OLV, the matching of ventilation in this lung is important for adequate gas exchange. The dependent lung is no longer on the steep (compliant) portion of the volume-pressure curve [3].

Mechanical TLV produces homogeneously distributed alveolar damage itself and generates an inflammatory response in the alveoli even in healthy lungs. The resulting ventilation-induced lung injury is characterized by dysfunction of the surfactant system, alveolar and interstitial edema, leukocyte recruitment, cytokine production and neutrophil-dependent tissue destruction [4].

One lung ventilation as an established procedure during thoracic surgery may be injurious in terms of increased



Two-lung ventilation versus one-lung ventilation (OLV).[3]

mechanical stresses characterized by alveolar cell stretch, over distension, increased cyclic recruitment of alveolar units, compression of alveolar vessels and increased pulmonary alveolar resistance. This may result in ventilator induced lung injury with pro inflammatory cytokine production [5].

After acute injury or during infections, TNF-α is among the earliest and most potent mediators of subsequent host responses. The primary sources of TNF-α synthesis include monocytes, macrophages and T cells [6].

TNF-α is also a major inducer of muscle catabolism and cachexia during stress by shunting available amino acids to the hepatic circulation as fuel substrates. Other functions of TNF-α include activation of coagulation, promoting the expression or release of adhesion molecules, prostaglandin E2, PAF, glucocorticoids and eicosanoids [7].

Interleukin 6 is also a primary effector in the production of other acute-phase proteins, including antiproteinases and fibrinogen, which are involved in nonspecific and specific immunity as inflammatory mediators, scavengers and protease inhibitors. Accordingly, increased levels of IL-6 in surgical trauma are associated with marked elevations of levels of C-reactive proteins and neutrophil elastase [8].

IL-6 may influence polymorphonuclear leukocyte (PMNL) mediated inflammation via its role in stimulating the proliferation of PMNL progenitors in the bone marrow [9]. Other cytokines may have less important roles in postoperative immune dysfunction.

CRP is a phylogenetically highly conserved plasma protein, with homologs in vertebrates and many invertebrates, that participates in the systemic response to inflammation. Its plasma concentration increases during inflammatory states, a characteristic that has long been employed for clinical purposes the measurement of cytokines in BAL fluid are indicators of inflammatory activity in the distal airways [10]. Cytokines can be quantified using immunoassays such as the enzyme-linked immunosorbent assay (ELISA), which measure total antigenic material, or using bioassays as a measure of function. Immunoassays, give an indication of the total cytokine burden, while bioassays indicate whether the cytokine retains activity and whether natural cytokine inhibitors are present [11].

Aim of the work

The aim of this work was to compare between the effects of propofol and sevoflurane regarding:

(1) The systemic inflammatory response (IL-6 and TNF-α) through serum analysis.
(2) The pulmonary inflammatory response (IL-6 and TNF-α) through BAL analysis.
(3) C-reactive protein and leukocyte count in serum.
(4) Recovery status.

All of these parameters were measured in patients scheduled for open thoracic surgeries using OLV.

Patients

This study was carried out on 40 adult patients, of both sexes, admitted to Alexandria Main University Hospital, Department of Cardiothoracic Surgery. Patients were scheduled for elective lung resection surgery through thoracotomy. Patients were randomly classified into two equal groups twenty patients each;

- Group I: Patients received total intravenous anaesthesia with propofol as maintenance.
- Group II: Patients received inhalational anaesthesia with sevoflurane as maintenance.

Exclusion criteria

(1) Acute pulmonary or extra pulmonary infections.
(2) Severe chronic obstructive pulmonary diseases, and history of recurrent pneumothoraces.
(3) Pneumonectomy and lung volume reduction surgery.
(4) Contraindications for epidural catheter insertion.
(5) Patients on chemotherapy, radiotherapy, immunosuppressant drugs or corticosteroids.
(6) History of allergy to local anaesthetic drugs.
(7) Trauma patients.

Methods and measurements

After approval of the Ethical Committee of the Faculty of Medicine and an informed written consent was obtained from each patient, a prospective randomized blind study was performed.

Every patient was subjected to a careful pre-anesthetics assessment including

(1) History taking as regards current medical illnesses and drug therapy.
(2) Thorough clinical examination and routine laboratory investigations.
(3) Pulmonary function tests.

Anaesthesia

Premedication: midazolam (7.5 mg) was given orally 60 min before induction of anaesthesia.

Before intubation a thoracic epidural catheter was inserted at T4–T5 to T7–T8 for intraoperative and postoperative analgesia.The position of the catheter tip was verified by a test dose of 3 ml lignocaine 2% with adrenaline (5 μg ml).

Induction of anaesthesia was initiated with fentanyl (2 μg/kg) and propofol till loss of verbal contact; tracheal intubation was facilitated with cisatracurium (0.15 mg/kg) in both groups.

According to the studied group, maintenance of anaesthesia was performed by

(1) Propofol infusion technique (50–200 μg/kg/minute) in Group I. Started with 150–200 μg/kg/minute, after 30 min 100-150 μg/kg/minute and after 2 h 50–100 μg/kg/minute.
(2) Sevoflurane (1-2 MAC) in Group II.

Intraoperative pain was managed with continuous epidural infusion of 0.125% bupivacaine (5–8 ml/h) and fentanyl (1 μg/ml of 0.125% bupivacaine) through epidural catheter using syringe pump.

In both groups, a double-lumen endobronchial tube was inserted and the correct position was confirmed by auscultation and flexible fibroptic bronchoscopy (FOB). Volume-controlled ventilation was used for both TLV and OLV. For TLV, tidal volumes of (8–10 ml/kg) and a respiratory frequency of 10–12/minute were chosen to maintain arterial carbon dioxide normocapnic. For OLV, tidal volumes of 6–7 ml/kg with a respiratory frequency of 12–16/min were used with FiO_2 of 1.0.

After completion of surgery, reventilation of the previously non ventilated lung was performed, and after discontinuation of anaesthetic agents,, neuromuscular blockade was reversed using neostigmine and atropine sulphate, patients were extubated and taken to the intensive care unit for postanaesthetic care.

Postoperative pain was managed as intraoperatively. Analgesia was maintained for 2–4 days until the chest tubes were removed.

In all patients, BAL was performed by FOB under sterile conditions. The tip of the bronchoscope was wedged into a subsegmental bronchus of the nondependant lung. Different segments were randomly chosen for repetition of BAL. Lavage was performed by sequential instillation and gentle aspiration of isotonic sodium chloride solution (10-ml portions, with a total of 50 ml) then the lavaged fluid was aspirated. The first BAL was performed before OLV on the operated side (T1), and the second BAL was performed 15 min after reexpansion and reventilation of the same lung at the end of surgery (T2). At the same time points, T1 and T2, 10 ml peripheral blood were collected for laboratory investigations.

Both BAL and blood samples were centrifuged. Cell pellets from centrifuged BAL and blood samples were assessed for human inflammatory mediators (interleukin 6 [IL-6] and tumor necrosis factor α [TNF-α].

Monitoring

A Using multichannel monitor, patients were continuously monitored for:
  (1) Non invasive arterial blood pressure.
  (2) Lead II electrocardiography.
  (3) Heart rate.
  (4) Arterial oxygen saturation.
  (5) End tidal carbon dioxide tension.

B Ventilatory monitoring (mean airway pressure and peak airway pressure).

Measurements

The following parameters were measured for all patients in both groups:

(1) Demographic data, age (yrs), sex, height (cm) and weight (kgs).
(2) Type of surgery (lobectomy, segmentectomy and lung biopsy).
(3) Haemodynamic parameters including:
A Heart rate (beats/minute).
B Mean arterial blood pressure (mmHg).

(4) Parameters were recorded at the following times; base line value (before induction), just after intubation, with skin incision, every 15 min during surgery, before OLV and 15 min after OLV ended and resumption of TLV.
(5) Arterial blood gases analysis (before OLV and 15 min after OLV ended and resumption of TLV.
(6) BAL analysis for human inflammatory mediators (IL-6 and TNF-α) and serum analysis for systemic inflammatory mediators (IL-6 and TNF-α). Both were measured before OLV and 15 min after OLV ended and resumption of TLV at the end of surgery.
(7) C-reactive protein and leukocyte count in blood (before OLV, 15 min after OLV ended and resumption of TLV at the end of surgery and on the 2nd postoperative day).
(8) Duration of anesthesia, surgery and OLV (minutes).
(9) Recovery status (modified Steward Score) [12]. A score for consciousness, airway and motor activity. The score was recorded on admission to the recovery room and 15 min after that.

A *Consciousness:* awake (2), responding to stimuli (1) and not responding (0).
B *Airway:* coughing on command or crying (2), maintaining good airway (1), and airway requires maintenance (0).
C *Motor activity:* moving limb purposefully (2), non purposeful movements (1) and not moving (0).

A total score of six for a fully recovered patient. A score of zero would be assigned to an unresponsive, immobile patient whose airway requires maintenance.

Statistical analysis of the data

Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data was expressed using Range, mean and standard deviation while Qualitative data was expressed in frequency and percent. Qualitative data was analyzed using Chi-square test also exact tests such Fisher exact and Monte Carlo was applied to compare the two groups. While, McNemar–Bowker was used to analyze the significance between the different stages. Quantitative data was analyzed using Mann Whitney test to compare between two groups. Wilcoxon Signed Rank test was used to compare between the different periods.

Results

Patients were randomly classified into; Group I: 20 Patients received total intravenous anaesthesia with propofol as maintenance.Group II: 20 Patients received inhalational anaesthesia with sevoflurane as maintenance.

Demographic data

The age of patients of group I ranged from 34 to 69 with a mean of 52.9 ± 9.8 years and ranged from 29 to 71 with a mean of 54.5 ± 12.4 years in group II with no significant difference between both groups. ($P = 0.643$). 30 Patients (65%) of group I were males and 7 (35%) were females. In group II, there were 12 males (60%) and 8 females (40%) with no

Table 1 Demographic data of the two studied groups.

Ser	Age (yrs)		Sex		Height (cm)		Weight (kg)	
	Group I	Group II	Group I	Group II	Group I	Group II	Group I	Group II
1	45	54	Male	Male	160	187	70	74
2	56	48	Female	Male	165	167	71	90
3	44	62	Male	Female	188	170	75	78
4	55	58	Female	Male	172	180	56	105
5	66	55	Female	Male	168	179	82	91
6	62	60	Male	Female	185	169	69	71
7	35	65	Male	Male	177	168	101	93
8	44	29	Female	Male	172	176	67	75
9	49	68	Male	Male	166	186	110	97
10	58	35	Male	Female	188	163	79	57
11	49	58	Male	Male	191	184	88	86
12	55	66	Female	Female	181	171	65	72
13	65	61	Female	Male	166	185	54	71
14	69	71	Male	Male	179	193	85	109
15	53	41	Male	Female	182	170	73	73
16	60	30	Male	Female	169	162	82	57
17	34	60	Female	Male	168	189	59	108
18	51	48	Female	Female	170	174	66	76
19	62	66	Male	Female	172	166	86	61
20	45	55	Female	Male	161	177	54	98
Min	34.0	29.0	M 13 (65%)	M 12 (60%)	160.0	162.0	54.0	57.0
Max	69.0	71.0	F 7 (35%)	F 8 (40%)	191.0	193.0	110.0	109.0
Mean	52.9	54.5	X^2	0.10	174.0	175.8	74.6	82.1
±SD	9.8	12.4			9.3	9.2	14.9	16.2
P	0.643		0.749		0.542		0.136	

p is significant if $\leqslant 0.05$.

significant difference between both groups. ($P = 0.749$).The height of patients of group I ranged from 160 to 191 cm with a mean of 174 ± 9.3 cm, and ranged from 162 to 193 cm with a mean of 175.8 ± 9.2 cm in group II with no significant difference between both groups. ($P = 0.542$).The weight of patients of group I ranged from 54 to 110 kg with a mean of 76.6 ± 14.9 kg and ranged from 57 to 109 kg with a mean of 82.1 ± 16.2 kg in group II with no significant difference between both groups ($P = 0.136$) Table 1.

Type of operation

Fig. 1; In Group I: Lobectomy was done in 10 patients (50%), segmentectomy in 5 patients (25%), and lung biopsy in 5 patients (25%). While in Group II: lobectomy was done in 11 patients (55%), segmentectomy 5 patients (25%), and lung biopsy in 4 patients (20%), with no significant difference between both groups. ($P = 0.924$).

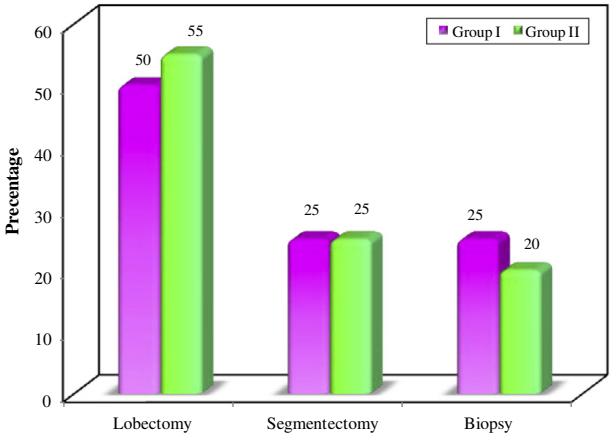


Figure 1 Comparison between both groups as regards type of operation.

Hemodynamic data

(A) Heart rate; Fig. 2; The mean value of the level of the heart rate in Group I was 73.5 ± 6.5 beats/min, and74.1 ± 6.4 beats/min in Group II, with no significant difference between both groups as regards the heart rate at the base level or at any interval of measurements intraoperatively.

(B) Mean arterial blood pressure (MAP) mmHg: Fig. 3. The mean value of the base level of the MAP in group I was 91.8 ± 9.6 mmHg, with no statistically significant difference in the MAP in relation to the preoperative base level during the whole intraoperative intervals of measurements. The mean value of the base level of the MAP in group II was 93.8 ± 9.6 mmHg, with no statistically significant difference in the MAP in relation to the preoperative base level during the whole intraoperative interval of measurements. There was no significant difference between both groups as regards the MAP at the base level or at any interval of measurements intraoperative.

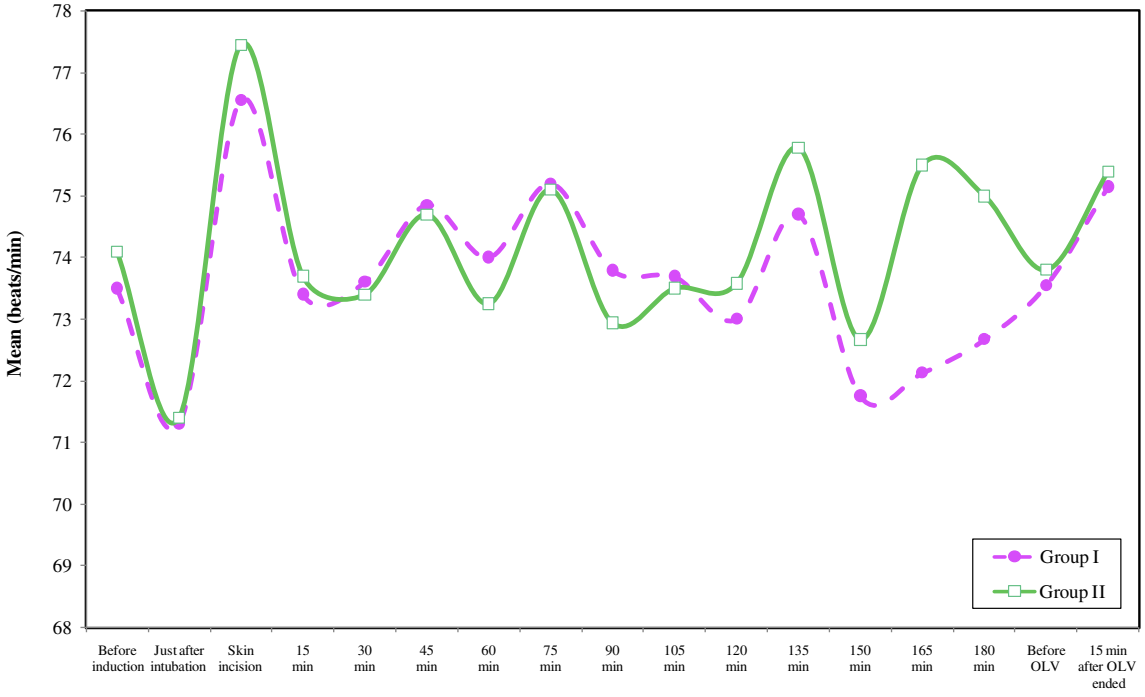


Figure 2 Comparison between the two studied groups regarding changes in heart rate (beats/min).

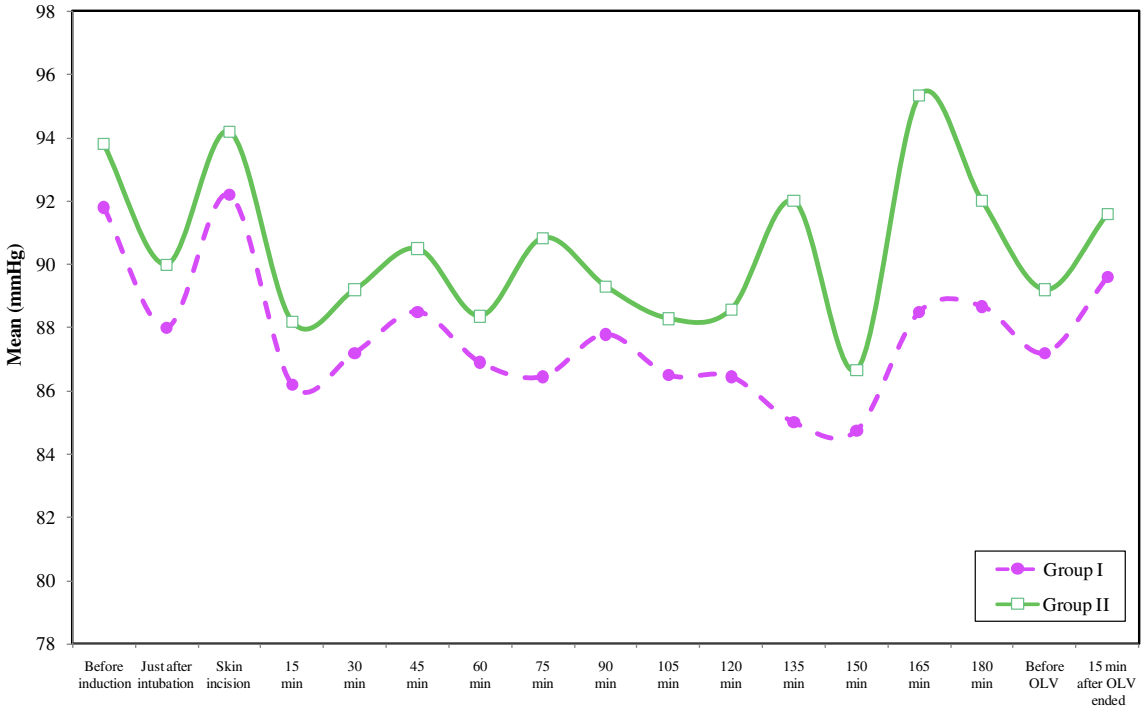


Figure 3 Comparison between the two studied groups regarding changes in MAP (mmHg).

Arterial blood gases (ABG) analysis

pH: There was no statistically significant difference between the two groups before and after OLV with a *P* value of (0.780 and 0.739) respectively Table 2.

PaO_2 (mmHg): There was no statistically significant difference between the two groups before and after OLV ($P = 0.235$ and 0.086 respectively)

$PaCO_2$ (mmHg): There was no statistically significant difference between the two groups as regards mean $PaCO_2$ level before and after OLV. ($P = 0.057$ and 0.067 respectively).

Table 2 Comparison between the two studied groups regarding arterial blood gases (ABG) analysis.

	pH before OLV	pH 15 min after OLV	PaO_2 before OLV	PaO_2 15 min after OLV	$PaCo_2$ Before OLV	$PaCo_2$ 15 min after OLV	HCO_3 Before OLV	HCO_3 15 min after OLV
Group I								
Min	7.35	7.36	193.0	132.0	35.0	33.0	25.20	25.30
Max	7.47	7.47	387.0	234.0	45.0	45.0	29.30	29.40
Mean	7.41	7.40	271.90	184.0	38.7	38.0	26.85	27.01
±SD	0.03	0.03	56.11	28.64	2.6	2.8	1.27	1.27
Group II								
Min	7.33	7.35	179.0	100.0	33.2	33.0	24.60	24.60
Max	7.47	7.45	327.0	225.0	43.0	43.0	29.10	29.10
Mean	7.41	7.40	252.25	164.20	36.8	36.3	26.74	26.53
±SD	0.04	0.03	50.82	42.57	2.6	2.6	1.35	1.36
P	0.780	0.739	0.253	0.086	0.057	0.067	0.792	0.252

P is significant if ⩽0.05.

Table 3 BAL and Serum analysis for IL-6 (Pg/dl) and TNF-α (Pg/dl) in group I.

Case No.	BAL analysis				Serum analysis			
	IL-6 (Pg/dl)		TNF-α (Pg/dl)		IL-6 (Pg/dl)		TNF-α (Pg/dl)	
	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended
1	6	17	5.2	22.8	6	15.8	10	80.5
2	8	78	6	22.1	7	16.3	12.9	66.7
3	15	80	5.1	23.6	10	26.7	12.5	60
4	10	55	6.1	25.1	6.5	25.8	16.1	77.2
5	15	16	5.3	28.7	7.9	22.4	14.1	70.3
6	12	22	6.7	31	8.2	16.6	15.1	66.9
7	31	55	6	30.1	8.9	18.4	18.9	80.6
8	28	60	6.5	27.2	9.1	36.7	19.2	88.9
9	14	20	4	20.2	9.3	17.2	11.3	66.3
10	34	84	4.5	26.8	7.2	18.9	10.1	70.4
11	35	100	6.4	25.7	8.9	28.5	10.2	80.5
12	7	10	4.9	22.7	8.5	32.4	15.3	84.6
13	30	70	7	35	9.1	30.8	14.3	77.3
14	25	57	4	23.4	10	33.9	12.5	78.3
15	22	50.6	7	34	9.9	40	20	100
16	32	60.4	7	30	8.4	40	19.9	99.5
17	6	15	5	20	7.6	20.7	14.2	85.2
18	11	60.5	6	25	7.1	38	14.3	74.6
19	18	27	4	22	9.2	16.8	12.3	66.8
20	9.3	35	5.2	23	8.6	15.2	13.7	70.7
Min	6.0	10.0	4.0	20.0	6.0	15.2	10.0	60.0
Max	35.0	100.0	7.0	35.0	10.0	40.0	20.0	100.0
Mean	18.4	48.6	5.6	25.9	8.4	25.6	14.3	77.3
±SD	10.2	26.8	1.0	4.3	1.2	8.9	3.2	10.7
P	0.0001*		0.0002*		0.0001*		0.0003*	

* P is significant if ⩽0.05.

HCO_3 (mEq/L): There was no statistically significant difference between the two groups as regards mean HCO_3 level before and after OLV (P = 0.792 and 0.252, respectively).

The pulmonary inflammatory response (TNF-α and IL-6) through BAL analysis

(A) Interleukin 6 [IL-6]: Tables 3–6.

- In Group I; Table 3 The level of IL-6 before OLV ranged from 6 to 35 pg/ml with a mean value of 18.4 ± 10.2 pg/ml and after OLV ranged from 10 to 100 pg/ml with a mean value of 48.6 ± 26.8 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.0001).
- In Group II :Table 4, The level of IL-6 before OLV ranged from 4 to 40 pg/ml with a mean value of 20.6 ± 11.7 pg/ml

Table 4 BAL and Serum analysis for IL-6 (Pg/dl) and TNF-α (Pg/dl) in group II.

Case No.	BAL analysis				Serum analysis			
	IL-6 (Pg/dl)		TNF-α (Pg/dl)		IL-6 (Pg/dl)		TNF-α (Pg/dl)	
	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended
1	4	28.2	4.9	11.1	6	17.5	10.5	39.8
2	17.2	6.9	6	10	9	18.2	7	44.3
3	18.6	6	5.3	10.8	9.2	17	11.7	50.7
4	8.5	25.4	4.6	11.3	7.1	19.9	12.2	35
5	28.4	19.5	6.2	12.1	7.9	18.7	14.3	47.8
6	31.4	15.8	5.4	15.8	10.1	20.1	20.1	45.3
7	38.1	39.7	7.7	16.4	9	22.7	14.3	40.9
8	25.7	40.7	7.5	18.3	10.2	23.5	8.9	58.3
9	22	55.8	5.1	14.6	8	20.5	18.6	70
10	19.2	60.4	4.8	18.4	7.2	19.2	15.1	62.4
11	18.7	23.3	5.4	22.6	8.1	17.3	11.5	65.8
12	10.6	17.8	6.7	20.8	9.8	19.6	9.7	55.4
13	30.4	22.5	3.8	21.8	9.1	18.8	8.9	41.3
14	20.5	15.6	4.2	20.3	10	20.1	15.4	37.8
15	40	70	8	25	10	25	22	70
16	39.8	65.8	7.4	24.7	8.2	22.5	20.4	69.6
17	4.8	18.4	3.8	12.5	8.4	18.2	14.2	40.1
18	22.5	48.9	4.7	11.6	8.9	17.9	10.1	39.5
19	5	15.8	3.5	18.5	10.1	18.6	8.9	47.5
20	6.4	20.5	5.1	22.1	10	21.2	14.2	60.4
Min	4.0	6.0	3.5	10.0	6.0	17.0	7.0	35.0
Max	40.0	70.0	8.0	25.0	10.2	25.0	22.0	70.0
Mean	20.6	30.9	5.5	16.9	8.8	19.8	13.4	51.1
±SD	11.7	19.7	1.4	5.0	1.2	2.2	4.3	11.9
P	0.024*		0.021*		0.001*		0.002*	

* *P* is significant if ⩽0.05.

Table 5 Comparison between the two studied groups regarding changes in IL-6 (Pg/dl) and TNF-α (Pg/dl) in BAL and serum.

Groups	BAL analysis				Serum analysis			
	IL-6 (Pg/dl)				TNF-α (Pg/dl)			
	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended	Before OLV	15 min after OLV ended
Group I								
Min	6.0	10.0	4.0	20.0	6.0	15.2	10.0	60.0
Max	35.0	100.0	7.0	35.0	10.0	40.0	20.0	100.0
Mean	18.4	48.6	5.6	25.9	8.4	25.6	14.3	77.3
±SD	10.2	26.8	1.0	4.3	1.2	8.9	3.2	10.7
Group II								
Min	4.0	6.0	3.5	10.0	6.0	17.0	7.0	35.0
Max	40.0	70.0	8.0	25.0	10.2	25.0	22.0	70.0
Mean	20.6	30.9	5.5	16.9	8.8	19.8	13.4	51.1
±SD	11.7	19.7	1.4	5.0	1.2	2.2	4.3	11.9
P	0.665	0.002*	0.617	0.048*	0.208	0.038*	0.357	0.001*

* *P* is significant if ⩽0.05.

and after OLV ranged from 6 to 70 pg/ml with a mean value of 30.9 ± 19.7 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.024).

Comparing the two groups: Table 5, There was no statistically significant difference between the two groups before OLV ($P = 0.665$). After OLV the level of interleukin-6 increased significantly in Group I in relation to Group II ($P = 0.002$).

B-Tumor necrosis factor α [TNF-α]: Tables 3–6.

- In Group I: Table 3; The level of TNF-α before OLV ranged from 4 to 7 pg/ml with a mean value of 5.6 ± 1.0 pg/ml

Table 6 Correlation between BAL and serum levels of IL-6 and TNF-α after OLV.

Group	Item	IL6		TNF-α	
		Serum level (pg/ml)		Serum level (pg/ml)	
		r	*P*	*r*	*P*
Group I	BAL 15 min after OLV ended (pg/ml)	0.28	0.231	0.31	0.184
Group II	BAL 15 min after OLV ended (pg/ml)	0.45	0.041*	0.54	0.014*

r: Spearman correlation co efficient.
* *P* is significant if ⩽0.05.

and after OLV ranged from 20 to 35 pg/ml with a mean value of 25.9 ± 4.3 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.0002).

- In Group II: Table 4; The level of TNF-α before OLV ranged from 3.5 to 8 pg/ml with a mean value of 5.5 ± 1.4 pg/ml and after OLV ranged from 10 to 25 pg/ml with a mean value of 19.6 ± 5.0 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.021).

Comparing the two groups: Table 5; There was no statistically significant difference between the two groups before OLV (*P* = 0.617). After OLV level of TNF-α increased significantly in Group I in relation to Group II (*P* = 0.048).

The systemic inflammatory response (TNF-α and IL-6) through serum analysis

A- Interleukin 6 [IL-6]; Tables 3–6.

- In Group I: Table 3: The level of IL-6 before OLV ranged from 6 to 10 pg/ml with a mean value of 8.4 ± 1.2 pg/ml and after OLV ranged from 15.2 to 40 pg/ml with a mean value of 25.6 ± 9.8 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.0001).
- In Group II: Table 4: The level of IL-6 before OLV ranged from 6 to 10.2 pg/ml with a mean value of 8.8 ± 1.2 pg/ml and after OLV ranged from 17 to 25 pg/ml with a mean value of 19.8 ± 2.2 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.001).

Comparing the two groups: Table 5; There was no statistically significant difference between the two groups before OLV (*P* = 0.208). After OLV level of interleukin-6 increased significantly in Group I in relation to Group II (*P* = 0.038).

B-Tumor necrosis factor α [TNF-α], Tables 3–6.

- *In Group I:* Table 3; The level of TNF-α before OLV ranged from 10 to 20 pg/ml with a mean value of 14.3 ± 3.2 pg/ml and after OLV ranged from 60 to 100 pg/ml with a mean value of 77.3 ± 10.7 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.0003).
- *In Group II:* Table 4; The level of TNF-α before OLV ranged from 7 to 22 pg/ml with a mean value of 13.4 ± 4.3 pg/ml and after OLV ranged from 35 to 70 pg/ml with a mean value of 51.1 ± 11.9 pg/ml with statistically significant increase in relation to before OLV and a *P* value of (0.002)

Comparing the two groups: Table 5; There was no statistically significant difference between the two groups before OLV (*P* = 0.375). After OLV level of TNF-α increased significantly in Group I in relation to Group II (*P* = 0.001). A significant correlation (Table 6) was present between increased level of IL-6 and TNF-α in serum and their increase in BAL after OLV in group II but this correlation was not present in group I.

C-reactive protein (CRP) in serum: Fig. 4.

- *In Group I:* Fig. 5; The level of CRP before OLV ranged from 2.5 to 6.5 pg/ml with a mean value of 4.1 ± 1.1 pg/ml, after OLV it ranged from 6.9 to 27 pg/ml with a mean value of 15.8 ± 5.4 pg/ml and on the 2nd postoperative day it ranged from 9.6 to 41 pg/ml with a mean value of 23.8 ± 7.7 pg/ml. There was significant increase in the level of CRP after OLV and on the 2nd postoperative day relative to level before OLV with a *P* value of (0.0001 and 0.0002) respectively.
- *In Group II:* Fig. 6; The level of CRP before OLV ranged from 2.5 to 5.8 pg/ml with a mean value of 4.1 ± 1.1 pg/ml, after OLV it ranged from 5.6 to 25.9.

Pg/ml with a mean value of 12.5 ± 5.8 pg/ml and on the 2nd postoperative day it ranged from 8.6 to 39.9 pg/ml with a mean value of 19.4 ± 7.8 pg/ml. There was significant increase in the level of CRP after OLV and on the 2nd postoperative day relative to the level before OLV with a *P* value of (0.002 and 0.003) respectively.

Comparing the two groups: Fig. 6; There was no statistically significant difference between the two groups before OLV (*P* = 0.184).After OLV and on the 2nd postoperative day the level of CRP increased significantly in Group I relative to Group II (*P* = 0.040 and 0.036) respectively.

Leukocyte count (WBC) ($\times 10^3$): Fig. 5.

- In Group I: Fig. 5; The level of WBC before OLV ranged from 4.5to 8.9 with a mean value of 6.6 ± 1.3, after OLV it ranged from 5.5 to 9.3 with a mean value of 7.49 ± 0.90 and on the 2nd postoperative day it ranged from 7.5 to 12 with a mean value of 9.78 ± 1.19. There was significant increase in the level of WBC after OLV and on the 2nd postoperative day relative to the level before OLV with a *P* value of (0.012 and 0.001), respectively.
- In Group II: Fig. 5; The level of WBC before OLV ranged from 5 to 9.5 with a mean value of 6.8 ± 1.3, after OLV it ranged from 5.2 to 11 with a mean value of 7.5 ± 1.4 and on the 2nd postoperative day it ranged from 6.8 to 11.8 with a mean value of 8.8 ± 1.5. There was no significant increase in the level of WBC after OLV and a significant increase in

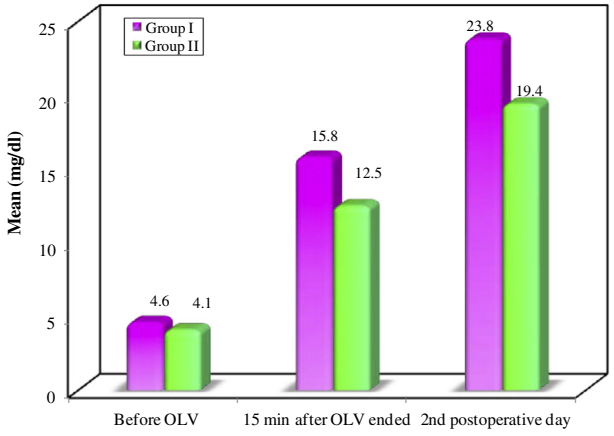


Figure 4 Comparison between the two studied groups regarding changes in CRP (mg/dl) in serum.

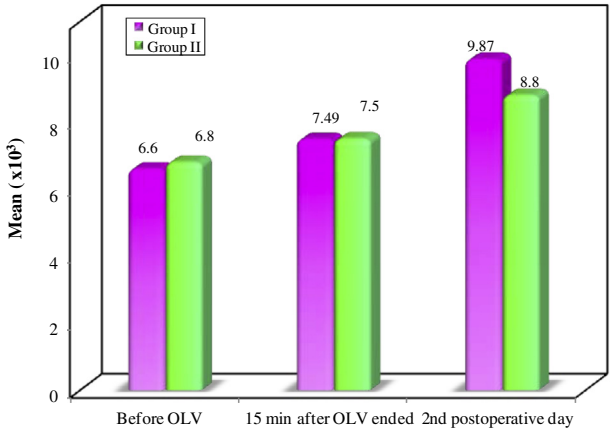


Figure 5 Comparison between the two studied groups regarding changes in WBC count ($\times 10^3$) in serum.

the level of WBC on the 2nd postoperative day relative to the level before OLV with a *P* value of (0.089 and 0.002) respectively.

Comparing the two groups: Fig. 5; There was no statistically significant difference between the two groups before OLV and after OLV with a *P* value of (0.578 and 0.893) respectively. On the 2nd postoperative day the level of WBC increased significantly in Group I relative to Group II ($P = 0.015$).

Duration of anesthesia, surgery and OLV (mins): Duration of anaesthesia In group I it ranged from 97 to 202 min with a mean of 150.95 ± 36.76 min and ranged from 97 to 207 min with a mean of 146 ± 35.94 min in group II with no significant difference between both groups ($P = 0.669$).

Duration of surgery; In group I it ranged from 75 to 180 min with a mean of 131.25 ± 36.05 min and ranged from 75 to 180 min with a mean of 123.75 ± 35.72 min in group II with no significant difference between both groups ($P = 0.513$).

Duration of OLV; In group I it ranged from 38 to 135 min with a mean of 88.9 ± 32.16 min and ranged from 44 to 130 min with a mean of 83.2 ± 30.61 min in group II with no significant difference between both groups ($P = 0.569$).

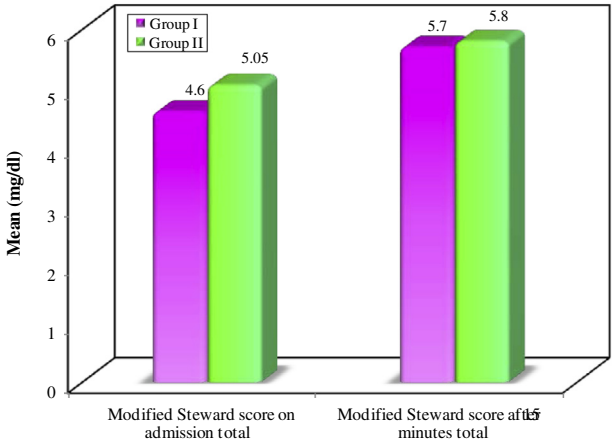


Figure 6 Comparison between both groups as regards recovery status (modified Steward Score).

There was no significant correlation between duration of OLV with inflammatory mediators (IL-6 and TNF-α) in serum and BAL Table 7. Also no significant correlation between duration of OLV with the increased levels of CRP and WBC count in both groups (Table 8).

Recovery status (modified Steward Score); Fig. 6

On Admission to the recovery room

Consciousness; There was no statistically significant difference between the two groups with a *P* value of (0.530).

Airway patency; There was no statistically significant difference between the two groups with a *P* value of (0.317).

Motor activity; There was no statistically significant difference between the two groups with a *P* value of (0.202).

Fifteen minutes thereafter

Consciousness; There was no statistically significant difference between the two groups with a *P* value of (0.965).

Airway patency; There was no statistically significant difference between the two groups with a *P* value (0298).

Motor activity; There was no statistically significant difference between the two groups with a *P* value of (0.987).

Comparing the two groups on admission to recovery room and 15 min thereafter: Fig. 6, there was significant increase in total score 15 min after admission to recovery room relative to time of admission in both group I and group II with a *P* value of (0.001 and 0.003) respectively.

Discussion

The present study was carried out on 40 adult patients of both sex admitted to the cardiothoracic surgery department of the Alexandria Main University Hospital, scheduled for elective lung resection surgery through thoracotomy under general anesthesia. Patients were randomly classified using closed envelope technique into two equal groups. In group I patients received total intravenous anesthesia with propofol and in group II patients received inhalational anesthesia with sevoflurane.

Table 7 Correlation between BAL and serum levels of IL-6 and TNF-α after OLV with OLV duration.

Group	Item	BAL		Serum	
		OLV duration		OLV duration	
		r	*P*	*r*	*P*
Group I	TNF-α after OLV (pg/ml)	−0.05	0.838	0.21	0.367
	IL6 after OLV (pg/ml)	−0.34	0.138	0.05	0.843
Group II	TNF-α after OLV (pg/ml)	0.09	0.719	0.35	0.128
	IL6 after OLV (pg/ml)	0.21	0.364	0.01	0.990

r: Spearman correlation co efficient.
P is significant if ⩽0.05.

Table 8 Correlation between CRP level and WBC count on 2nd postoperative day with duration of OLV.

Group	Item	OLV duration	
		r	*P*
Group I	WBCs 2nd postoperative day	0.09	0.707
	CRP 2nd postoperative day	−0.05	0.835
Group II	WBCs 2nd postoperative day	−0.04	0.858
	CRP 2nd postoperative day	−0.35	0.136

r: Spearman correlation coefficient.
P is significant if ⩽0.05.

As regards the demographic data there was no statistically significant difference between the two studied groups as regards age, sex, and height and body weight.

As regards type of operation there was no statistically significant difference between the two studied groups.

In the present study, the basal readings of heart rate and MAP were within normal physiological ranges with no significant difference between both groups during all times of measurements.

In the current study there was no significant difference in ABG analysis between both groups. Also in each group there was no significant difference in ABG analysis after OLV relative to before OLV except for PaO_2 where it was significantly decreased after OLV in both groups.

In agreement with the present study Pruszkowski et al. [13] found that no significant difference between sevoflurane and propofol on Pao2 before and during OLV, the choice between these anesthetic agents could be independent of their effects on oxygenation. Also there was significant decrease in PaO_2 in both groups during OLV.

In a study done by Karzai et al. [14] they compared the effects of desflurane with those of propofol on oxygenation during TLV and OLV.They found that when changing from TLV to OLV, PaO2 decreased more during desflurane than during propofol. Changing between desflurane and propofol during OLV resulted in small but significant increases in PaO2 during propofol.

In the present study, there was no statistically significant difference between both groups regarding the base level (before OLV) of interleukin-6 and TNF-α in BAL and serum with statistically significant increase in both groups after OLV but more increase in group I relative to group II. No significant correlation between the duration of OLV and increased levels of IL-6 and TNF-α in BAL and serum was present in both groups. A significant correlation was present between increased level of IL-6 and TNF-α in serum and their levels in BAL after OLV in the group II but this correlation was not present in groupI.

In agreement with the present study De Conno et al. [15] compared the effect of propofol versus sevoflurane on both pulmonary and systemic inflammatory response in thoracic surgery through BAL and serum analysis for inflammatory mediators. Inflammatory mediators (tumor necrosis factor – α, interleukin 1B, interleukin 6, interleukin 8, monocyte chemoattractant protein 1) were analyzed in BAL and serum. They found that OLV resulted in an increase in the measured inflammatory mediators in both groups. However, the increase of inflammatory mediators upon OLV in porpofol group was significantly higher for all parameters except IL-1B compared with sevoflurane group.

In another study Sugasawa et al. [16] compared the pulmonary and systemic inflammatory effects of sevoflurane with propofol and investigated whether the pulmonary immunomodulatory effects might differ in the dependent lung and the nondependent lung during thoracic surgery. Epithelial lining fluid (ELF) was obtained from each lung using a bronchoscopic microsampling method. ELF and plasma levels of inflammatory cytokines were measured before and after OLV. They found that ELF levels of interleukin (IL)-1B, IL-6, and IL-8 were significantly increased in the dependent and the nondependent lung after OLV compared with baseline levels in both groups. Moreover, IL-6 ELF level in the dependent lung was significantly higher in the propofol group than in the sevoflurane group after OLV. Serum cytokine concentrations observed in their study were not accompanied by the alveolar proinflammatory response because the plasma cytokine levels of TNF-α, IL-1B, IL-6, IL-8, IL-10, and IL-12p70 were undetectable in both groups.

During thoracic surgery, Mahmoud et al. [17] compared the effects of propofol versus isoflurane on alveolar and plasma concentrations of interleukin-8(IL-8) and tumour necrosis factor-α (TNF-α) malondialdehyde (MDA), superoxide dismutase (SOD), and changes in alveolar albumin concentrations and cell numbers. MDA is an indicator of lipid peroxidation, whereas SOD is an antioxidant enzyme that helps in scavenging free radicals which play a role in tissue injury. Bronchoalveolar lavage of the ventilated dependant lung was done at three time points, after induction of anaesthesia (before OLV), one hour after OLV and one hour after surgery. They found that one hour after OLV and one hour after surgery the alveolar concentration of IL-8 and TNF-α were significantly lower in the isoflurane group, where as alveolar concen-

tration of MDA was significantly lower in the propofol group. Alveolar SOD level increased significantly in the propofol group whereas it showed no significant change in the isoflurane group. Furthermore, the isoflurane group patients developed significantly lower alveolar albumin concentrations and cell numbers. The plasma concentrations of IL-8, TNF-α increased significantly in both groups after OLV, however, they were significantly lower in the isoflurane group.

According to CRP level, it was significantly increased after OLV and on the 2nd postoperative day in both groups and it was significantly increased in group I relative to group II.

The level of WBC was significantly increased in group I after OLV and on the 2nd postoperative day however it was significantly increased in group II on the 2nd postoperative day without significant change after OLV. Comparing the two groups the WBC level was significantly increased in group I relative to group II on the 2nd postoperative day without significant change after OLV.

De Conno et al. [15] assessed C-reactive protein and blood leukocyte count as additional parameters for inflammation preoperatively, on first postoperative day(POD1),third postoperative day (POD3), and fifth postoperative day (POD5) to determine possible differences in the sevoflurane compared with the propofol group. They found that there was no statistically significant difference in CRP and leukocyte count could be detected between the two groups from POD1 to POD5. However there was significant increase in CRP and WBC levels in both groups from POD1 to POD5 with a significant correlation between CRP values and OLV time on POD1 in the propofol group only. A correlation was observed between CRP value on POD1 and increase of plasma IL-6 and MCP-1 concentration in the propofol group, whereas no correlation was observed in the sevoflurane group as a result of the significant difference in OLV time between the two groups (longer duration of OLV in the propofol group (140 ± 76 min) versus the sevoflurane group (98 ± 57 min).

As regarding duration of anaesthesia, surgery and OLV, there was no statistically significant difference between the two studied groups with no significant correlation between duration of OLV and inflammatory mediators in serum and BAL. Also no significant correlation between duration of OLV with the increased levels of CRP and WBC count in both groups.

In agreement with the current study Leite et al. [18] found that the experimental mechanical ventilation in rats with a prolonged surgical time did not produce significant local and systemic inflammatory changes and permit to evaluate other procedures in thoracic surgery.

In contrast with the current study.

In the study of Sugasawa et al. [16] the magnitude of cytokine expression in ELF after OLV showed a progressive increase with prolonged duration of OLV in both groups. There was a correlation between the increase in the level of IL-1b, IL-6, or IL-8 and the duration of OLV in the dependent and the nondependent lung after OLV. Also De Conno et al. [15] found a progressive increase in TNF-α, IL-6, IL-8, MCP-1, and to a lesser degree IL-1B was observed with increasing duration of OLV.

Regarding recovery profile there was no significant difference between both groups regarding to consciousness level, airway patency and motor activity on admission to recovery room and 15 min after that, however there was significant increase in total recovery score 15 min after admission to recovery room in both studied groups without significant difference in between.

Considering the data from other studies in combination with the results of the present study OLV increased the concentration of alveolar macrophages and granulocytes proteins, and inflammatory cytokines [15]. IL-6 is an important chemo-attractant that affects the recruitment of granulocytes and alveolar macrophages [19]. Alveolar macrophages not only act as phagocytes but also secrete biologically active products, thereby playing a significant role in regulating pulmonary inflammatory reactions [20]. Evidence was mounted to suggest that increased levels of these inflammatory cytokines could be clinically relevant to pulmonary complications following thoracic surgery with a potential link between inflammatory mediators in the lung and outcome [15] OLV in patients undergoing lung resection promotes the production and release of proinflammatory substances in the alveoli. Moreover, the administration of sevoflurane significantly suppresses pulmonary proinflammatory response to a greater extent than propofol and so improved outcome for patients in the sevoflurane group. These observations were likely to be related to the more enhanced immunomodulatory effect of sevoflurane. The underlying mechanism for this type of immunomodulation is thought to involve interaction with inducible nitric oxide synthetase by reversible inhibition of voltage-dependent calcium channels and subsequent reductions in intracellular calcium concentration [21].

Conclusion

- The mechanical ventilation and the surgical manipulation induced alveolar and systemic inflammatory responses in patients who had undergone lung resection.
- Pulmonary and systemic inflammatory reactions as reflected by the level of IL-6 and TNF-α are affected by OLV and anesthetic agents.
- After OLV, both propofol and sevoflurane increased the release of pulmonary and systemic inflammatory mediators namely IL-6 and TNF-α.
- Propofol increased pulmonary and systemic cytokine release more than sevoflurane during OLV.
- A significant correlation was present between increased level of IL-6 and TNF-α in BAL and their levels in serum after OLV in the group II but this correlation was not present in the groupI.
- The administration of both propofol and sevoflurane increased release of CRP level and WBC count after OLV and on 2nd postoperative day.
- Propofol has increased CRP level and WBC count more than sevoflurane during OLV.

Recommendations

- Administration of sevoflurane anesthesia is recommended during lung resection in patients undergoing open thoracic surgery using OLV technique.

- Further studies are needed to study other anesthetic techniques that can be used to decrease the inflammatory response during lung resection.
- Further studies are needed to study the immunomodulatory effects of other anaesthetics during OLV in thoracotomy.
- Further studies are needed to study the immunomodulatory effects of propofol and sevoflurane during OLV in other thoracic surgeries as telescopic and esophageal surgeries.

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