Original Article

Intraoperative lung protective ventilation in peritonitis patients undergoing emergency laparotomy: A randomised controlled trial

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Submitted: 21-Jun-2021
Revised: 26-Aug-2021
Accepted: 06-Nov-2021
Published: 23-Nov-2021

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ija.ija_573_21
Quick response code

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ABSTRACT

Background and Aims: Lung protective ventilation (LPV) is recommended in acute respiratory distress syndrome. However, role of intraoperative LPV in elective laparotomy is controversial and it has not been evaluated in emergency laparotomy (EL). The aim of the study was to identify whether use of intraoperative LPV in EL in peritonitis patients reduces postoperative pulmonary complications (POPC). **Methods:** After institutional ethics committee approval and informed written consent, 98 adult patients undergoing EL for peritonitis were randomised into two groups. Patients in group 1 received LPV (tidal volume 6–8 ml/kg, positive end expiratory pressure (PEEP) 6–8 cm H_2O and recruitment manoeuvre every 30 min) and patients in group 2 received conventional ventilation (tidal volume 10-12 ml/kg, without PEEP/recruitment). Primary outcome was incidence of POPC on day 7. **Results:** Data of 94 patients (n = 45 in group 1 & n = 49 in group 2) were available. Baseline demographic & laboratory parameters were comparable. Incidence of POPC was similar in both the groups [42.9% in group 1 vs. 53.3% in group 2; risk difference -10.4% (-30.6%, 9.6%); *P* = 0.31]. Mortality during hospital stay was 26.7% patients in group 1 and 26.5% patients in group 2 [risk difference (95% CI) 0.14%, (-17.7, 18.0); *P* = 0.98]. Length of hospital stay [median interquartile range (IQR) 13 (9–18) days in group 1 vs. 13 (8–21) days in group 2; *P* = 0.82] and length of intensive care unit stay [median (IQR) 7 (4–10) days vs. 6 (3–12) days; *P* = 0.88] were also similar in both groups. **Conclusion:** LPV during EL in peritonitis patients does not reduce the incidence of POPC compared to conventional ventilation.

Key words: Laparotomy, mechanical ventilation, peritonitis

INTRODUCTION

Postoperative pulmonary complications (POPC) can adversely affect clinical outcomes in patients undergoing major abdominal surgery.[1] Lung protective ventilation (LPV) with low tidal volume (Vt) and positive end expiratory pressure (PEEP) has been shown to reduce mortality in mechanically ventilated patients with acute respiratory distress syndrome (ARDS).[2]

Use of high Vt (10–15 ml/kg predicted body weight) and no PEEP is still common in operating room. However, the benefit of LPV has been demonstrated in a number of clinical settings in patients without ARDS.[3-5] LPV has been associated with reduced levels of inflammatory cytokines in plasma and broncho-alveolar lavage fluid[3] and lower risk of prolonged mechanical ventilation, intensive care

How to cite this article: Chowdhury AR, Subramanian R, Maitra S, Bhattacharjee S, Lakshmy R, Baidya DK. Intraoperative lung protective ventilation in peritonitis patients undergoing emergency laparotomy: A randomised controlled trial. Indian J Anaesth 2021;65:798-805.

unit (ICU) stay and haemodynamic instability. The IMPROVE trial demonstrated fewer postoperative complications with LPV (6–8 ml/kg Vt, 6–8 cm H_2O PEEP and recruitment manoeuvres every 30 min) in elective major abdominal surgery.[4] On the contrary, another randomised trial found that intraoperative low Vt ventilation does not prevent POPC after elective abdominal surgery.[6]

However, these trials of intraoperative ventilation strategy were conducted in patients scheduled for elective surgery.[3,6] Patients presenting with complicated intra-abdominal infection and sepsis undergo laparotomy and may subsequently develop POPC including lung injury or ARDS and often require mechanical ventilation.[7-9] Any beneficial role of intraoperative LPV in such patients should be of more interest. However, effect of LPV has not been studied in patients with perforation peritonitis undergoing emergency laparotomy (EL) and specific recommendation about mechanical ventilation strategy is lacking in patients with sepsis without ARDS.[10]

We therefore planned to conduct this study to determine the effect of LPV in reducing POPC in patients with perforation peritonitis undergoing EL.

METHODS

After obtaining permission from institutional ethics committee (IEC/NP-221/03-07-2014) and written informed consent from the participants, 100 patients were assessed for eligibility and 98 patients were recruited in this randomised controlled trial between January 2015 and December 2017. The study was registered in the Clinical TrialsRegistry- India (CTRI/2014/12/005256; www.ctri.nic.in).

Inclusion criteria were age 18–70 years, EL with expected duration >2 hour and <5 hour, peritonitis (suspected or identified abdominal source of infection) of less than 5 days' duration, preoperative risk index[11] for pulmonary complications >2.

Exclusion criteria were mechanical ventilation within 2 weeks preceding surgery, body mass index (BMI) ≥35, <18 kg/m^2, history of respiratory failure or sepsis within the 2 weeks preceding surgery, requirement for intrathoracic surgery, history of lung surgery, history of chronic obstructive pulmonary disease (COPD) with non-invasive ventilation and/or oxygen therapy at home and/or repeated systemic corticosteroid therapy for acute exacerbations of COPD, progressive neuromuscular illness, ARDS, persistent haemodynamic instability or intractable shock.

The patients were randomised into two groups with a computer-generated random number table and allocation concealment was performed with sealed envelope technique. Intra-operative blinding was not done. Anaesthesiologists were aware of the group assigned. However, post-operative care-providers and outcome assessor were blinded to the group assigned.

Group 1 received LPV with Vt 6-8 ml/kg of predicted body weight and PEEP 6–8 cm H_2O, along with recruitment manoeuvres (30 cm H_2O for 30 s) every 30 min from the time of intubation.

Group 2 received conventional mechanical ventilation (CV) with Vt 10–12 ml/kg, no PEEP and no recruitment manoeuvres.

A plateau pressure of not more than 30 cm H_2O was targeted in each group. Respiratory rate was adjusted to keep a normal end-tidal CO_2. Fractional concentration of oxygen (FiO_2) was kept at 0.5 in the beginning and adjusted to maintain peripheral oxygen saturation (SpO_2) >93%. The predicted body weight was calculated based on previously defined formula.[2] In the event of desaturation, use of FiO_2 1.0, use of higher Vt, recruitment manoeuvre and PEEP were allowed.

Use of anaesthetic agents, intraoperative and postoperative pain management, peri-operative fluid management were done according to the standard clinical practice and protocol of our institution. Anaesthesia was induced in all the patients with fentanyl 2 μg/kg, propofol 2 mg/kg. Atracurium 0.5 mg/kg was used for muscle relaxation. In the event of pre-existing hypotension [mean arterial pressure ((MAP) <70 mmHg] before induction, etomidate 0.3 mg/kg was used instead of propofol. Anaesthesia was maintained with oxygen, air (FiO_2 0.5) and isoflurane. Intravenous infusion of fentanyl at 1–2 μg/kg/hour and atracurium 0.2 mg/kg/hour were used to maintain analgesia and muscle relaxation, respectively.

At the end of surgery, patients who were haemodynamically stable and able to maintain

normoxia and normocarbia on spontaneous breathing were extubated and transferred to the post anaesthesia care unit (PACU) and received oxygen by facemask at 5 L/min. Patients who required postoperative ventilatory support or vasopressor support were managed in the ICU or high dependency unit as per standard protocol of the institute. Balanced salt solution was used for fluid resuscitation and noradrenaline was the vasopressor of choice whenever required in the preoperative, intraoperative and postoperative period. Fluid and vasopressor management were guided by invasive arterial, central venous pressure, blood gas with lactate and point of care ultrasound monitoring as and when required with target MAP >65 mmHg, urine output >0.5 ml/kg/h as per sepsis guideline.[10] Broad-spectrum antibiotics were initiated at presentation as per institute protocol and appropriate cultures (blood, urine, abdominal fluid and tracheal aspirate whenever suitable) were sent. In patients requiring postoperative mechanical ventilation, LPV with moderate PEEP and low Vt targeting plateau pressure <30 cm H_2O was used.

Primary outcome was POPC. POPC included mild respiratory failure with PaO_2/FiO_2 <300 requiring supplemental oxygen or severe respiratory failure due to pneumonia, ARDS and pneumothorax requiring invasive or noninvasive mechanical ventilation. ARDS was defined as per the revised Berlin criteria[12] and pneumonia was defined as the presence of new and/or progressive pulmonary infiltrates on chest radiograph plus two or more of the following: a) fever ≥38.5°C or hypothermia <36°C, b) leucocytosis ≥12000 white blood cells (WBC)/mm^3 or leucopenia <4000 WBC/mm^3) purulent sputum and/or new onset or worsening cough or dyspnoea.[4]

Secondary outcomes were noted during the follow-up period till patient discharge. Secondary outcomes were median POPC grade in four-point grade from 0–4, with grade 0 representing the absence of any pulmonary complication and grades 1 through 4 representing successively the worse forms of complications[13] Other outcomes were in-hospital mortality, requirement of inotropes/vasopressors, length of ICU stay and length of hospital stay and pre and postoperative change in serum interleukin (IL)-6, IL-8, and tumour necrosis factor (TNF) α. First serum sample was obtained at the beginning of surgery and second sample obtained at 24 hour.

There was no previous study investigating LPV in patients with abdominal sepsis undergoing EL. From the previous database of our institute, we observed that the incidence of POPC following EL was around 40%. To detect a 25% point reduction in POPC with 80% power and alpha of 0.05, n = 96 patients was required to reject the null hypothesis.

Data analysis was carried out by using statistical software Stata 13.0 (StataCorp. 2011. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). Normally distributed data were presented as mean and standard deviation and skewed data as median [interquartile range (IQR)]. For comparison of unrelated samples, the unpaired *t* test was used for normally distributed data and the Mann–Whitney *U* test for skewed data. Differences in proportions were evaluated using the Fisher's exact test, and absolute risk reduction with associated 95% confidence interval (CI) was reported. Probability of death during hospital stay was evaluated by Kaplan–Meir survival analysis and hazard ratio with 95% CI was reported.

RESULTS

One hundred patients were assessed for eligibility and 98 patients were recruited in this randomised controlled trial and all of them received allocated treatment. However, four patients were lost to follow-up (either left hospital against medical advice or transferred to another medical facility as per their wish in the postoperative period). So, data from 94 patients (45 patients in group 1 and 49 patients in group 2) were analysed in this study [Figure 1].

Baseline demographic and laboratory parameters were comparable in the two groups [Table 1]. Two patients in group 1 and three patients in group 2 required FiO_2 above 0.5 to maintain SpO_2 >93% but none of the patients required higher Vt in group 1 or PEEP and recruitment manoeuvre in group 2. Details of intraoperative ventilation and other data are provided in Table 2. Incidence of POPC were similar in both the groups [42.9% in group 1 vs. 53.3% in group 2; risk difference (95% CI) -10.5% (-30.6%, 9.6%); P = 0.31, Chi-square test)]. About 8.9% patients in group 1 and 6.1% patients in group 2 developed ARDS in the postoperative period [risk difference (95% CI) 2.8% (-7.9%, 13.5%); P = 0.90, Fisher's exact test]. Severity of POPC was similar [median (95% CI) of POPC grade in

group 1 was 2 (1–4) vs. 3 (1–4) in group 2; $P = 0.45$] between the groups. None of the recruited patients developed pneumothorax in the postoperative period [Table 3].

During hospital stay, 26.7% patients died in group 1 and 26.5% patients died in group 2 [risk difference (95% CI) 0.14% (-17.7, 18.0); $P = 0.98$, Chi-square test). A Kaplan–Meier survival analysis

Table 1: Baseline demographic, clinical & laboratory variables

Parameters	Group 1 (*n*=45)	Group 2 (*n*=49)	Significance
Age	35 [24-62]	39 [26-61]	*P*=0.06
Body weight (kg)	56 [48-65]	58 [50-68]	*P*=0.57
Sex (Male/Female)	29/16	35/14	*P*=0.47
Diagnosis (small bowel perforation/large bowel perforation)	26/19	28/21	*P*=0.95
Pre-existing co-morbid illness (Yes/No)	11/34	13/36	*P*=0.82
Duration of surgery (minutes)	135 [115-165]	120 [110-150]	*P*=0.67
Haemoglobin (g/dl)	10.5 [8.8-11.7]	10.7 [8.6-13.2]	*P*=0.32
Total leucocyte count	9400 [5010-14000]	11300 [5920-17400]	*P*=0.20
Serum Creatinine (mg/dl)	0.9 [0.5-1.3]	0.72 [0.45-1.05]	*P*=0.37
Serum Albumin (mg/dl)	2.6 [2-3.9]	2.4 [2-2.7]	*P*=0.21
PaO_2 (mmHg)	95 [78-108]	91 [76-112]	*P*=0.62
$PaCO_2$ (mmHg)	33 [30-37]	36.5 [31-41]	*P*=0.44
pH	7.25 [7.15-7.44]	7.23 [7.15-7.42]	*P*=0.67
Base deficit	6 [8-3]	7 [8-3]	*P*=0.71

Data represented in Median [IQR]; LPV=Lung protective ventilation; CV=conventional ventilation; PaO_2=Partial pressure of oxygen; $PaCO_2$=Partial pressure of carbon-di-oxide

Table 2: Intraoperative details

Parameters	Group 1 (*n*=45)	Group 2 (*n*=49)	Significance
Tidal volume (ml)	400 [340-450]	500 [490-570]	*P*<0.0001
PEEP (cmH_2O)	6 [6-6]	0 [0-0]	*P*<0.0001
Peak Pressure (cmH_2O)	26 [23-28]	28 [27-31]	*P*<0.0001
Plateau Pressure (cmH_2O)	25 [21-26]	27 [25-29]	*P*<0.0001
Blood loss (ml)	300 [200-500]	300 [250-500]	*P*=0.74
Compliance (ml/cmH_2O)	23.9 [17.6-26.7]	20 [17.5-21.7]	*P*=0.004
Intraoperative fluid (ml)	2400 [1800-2600]	2200 [1800-2500]	*P*=0.52

PEEP=Positive end expiratory pressure

Table 3: Outcome parameters

Parameters	Group 1 (n=45)	Group 2 (n=49)	Significance
POPC (%)	42.9	53.3	Risk difference (95% CI) -10.4% (-30.6%, 9.6%); *P*=0.31
POPC grade	2 (1-4)	3 (1-4)	*P*=0.45
ARDS (*n*/%)	4/8.9	3/6.1	Risk difference (95% CI) 2.8% (-7.9%, 13.5%); *P*=0.90
Pneumonia (*n*/%)	11/24.4	14/28.6	Risk difference (95% CI) -4.1% (-21.9%, 13.7%); *P*=0.65
Septic shock (*n*/%)	13/28.9	15/30.6	Risk difference (95% CI) -1.7% (-20.2%, 13.7%); *P*=0.86
Acute Kidney Injury (*n*/%)	14/31.1	16/32.7	Risk difference (95% CI) -1.5% (-20.4%, 16.8%); *P*=0.87
Vasopressor (*n*/%)	8/17.8	6/12.2	Risk difference (95% CI) 5.5% (-8.9%, 20%); *P*=0.64
Mortality (*n*/%)	12/26.7	13/26.5	Risk difference (95% CI) 0.14% (-17.7, 18.0); *P*=0.98
LOS-ICU Median (IQR) days	7 (4-10)	6 (3-12)	*P*=0.88
LOS-Hospital Median (IQR) days	13 (9-18)	13 (8-21)	*P*=0.82
Cumulative fluid balance at the end of surgery Median (IQR) ml	950 (750-1450)	900 (700-1500)	*P*=0.72
Cumulative fluid balance at day 7 Median (IQR) ml	2250 (1050-3100)	2000 (1200-3450)	*P*=0.65
PRBC transfusion till day 7 Median (IQR) units	2 (1-2)	2 (1-2)	*P*=0.76

Data represented in number (percentage) or median (IQR) as appropriate; POPC=postoperative pulmonary complications; ARDS=Acute respiratory distress syndrome; ICU=Intensive care unit; LOS=length of stay; PRBC=Packed red blood cell; CI=Confidence interval; IQR=Interquartile range

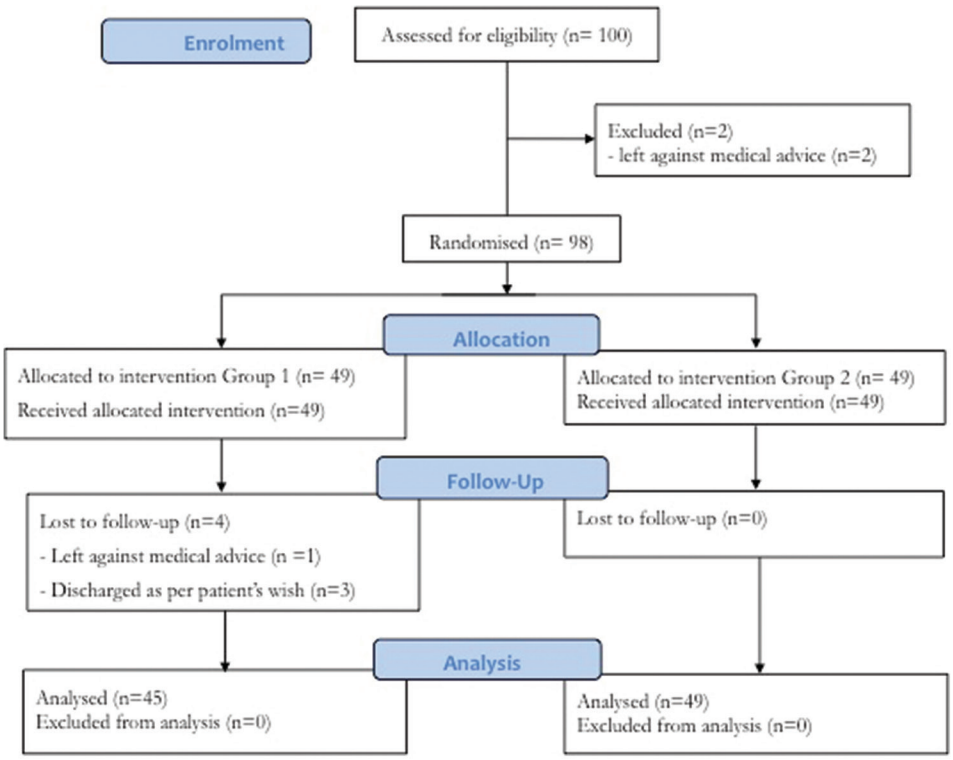

Figure 1: CONSORT diagram

confirmed that the risk of death during hospital stay was similar in the two groups [p = 0.79, log-rank test; Figure 2]. Length of hospital stay [median (IQR) 13 (9–18) days in group 1 vs. 13 (8–21) days in group 2; $P = 0.82$] and length of ICU stay [median (IQR) 7 (4–10) days vs. 6 (3–12) days; $P = 0.88$] were similar in the two groups. Cumulative positive fluid balance at the end of surgery, at day 7 and packed red cell transfusion by day 7 were similar in both the groups [Table 3].

Comparisons of preoperative and postoperative IL-6, IL-8 and TNFα were similar between the groups [Mann–Whitney U test, Table 4].

DISCUSSION

In this study, we observed that intraoperative LPV strategy did not reduce POPC, in-hospital mortality and duration of hospital and ICU stay in peritonitis patients undergoing EL.

In a previous study, it was observed that use of LPV strategy with Vt 6 ml/kg and PEEP 6 cm H_2O with intermittent recruitment manoeuvre reduced the incidence of POPC (5% vs. 17%, relative risk 0.29; 95% CI, 0.14 to 0.61; $P = 0.001$) and length of hospital stay (mean difference, -2.45 days; 95% CI, -4.17 to -0.72; $P = 0.006$) significantly compared to non-protective ventilation in patients undergoing elective abdominal surgery.[4] We used similar ventilation strategy in our intervention group and found 10.4% absolute reduction of POPC with the use of LPV. However, this reduction was not statistically significant. We think that the duration of surgery in our study population was too short for LPV to make any significant beneficial impact on the reduction of POPC. In a previous study, significant elevation of lung injury biomarkers could be demonstrated only after 5 hours of mechanical ventilation with large tidal volumes.[5] Moreover, use of recruitment manoeuvre in the LPV group could have caused some lung injury and thereby minimised any benefit of LPV in this group.[14] Therefore, further research with use of LPV may be done without recruitment manoeuvre. In addition, role of LPV may be explored in a larger sample of patients undergoing surgeries—where risk of lung injury is high—like cardio-thoracic surgery, emergency abdominal surgery in septic patients, laparoscopic surgery leading to high airway pressures and long duration surgery. This may provide more insight into the role of intraoperative LPV.[15,16]

PROVE network investigators performed a multicentre randomised controlled trial (PROVHILO)

Table 4: Preoperative & postoperative inflammatory markers in both the groups

Parameters (pg/ml)	Group 1 (*n*=45)	Group 2 (*n*=49)	Significance
Preoperative IL-6	269 [9.8-547]	74.8 [27-194]	*P*=0.69
Postoperative IL-6	236 [50-439]	210 [46-520]	*P*=0.61
Preoperative IL-8	46.2 [31.3-168.4]	39.3 [33.8-78]	*P*=0.83
Postoperative IL-8	67.2 [34.3-302.6]	56.3 [34.9-151.9]	*P*=0.86
Preoperative TNFα	24.2 [18.3-34.2]	22.4 [19.2-26.7]	*P*=0.58
Postoperative TNFα	21.2 [19.2-24.5]	19.5 [18.2-23.4]	*P*=0.38

Data expressed as median (IQR); IL=Interleukins; TNF=Tumour necrosis factor

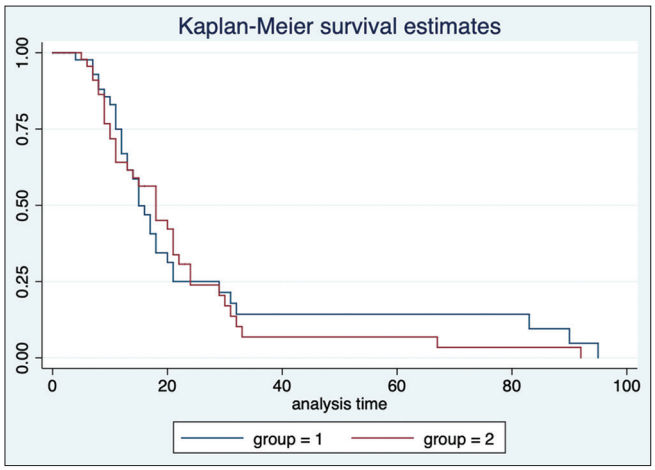

Figure 2: Kaplan–Meier survival estimates in both the groups

in patients undergoing elective surgery, who received either PEEP 12 cm H_2O or 2 cm H_2O, with similar Vt (8 ml/kg), to identify whether the beneficial impact of LPV was attributable to Vt or PEEP. There was no difference observed in POPC but the incidence of hypotension increased significantly in high PEEP group (46% and 36% in high and low PEEP group, respectively).[17] We used moderate PEEP of 6–8 cm H_2O in LPV group and observed much lower 17.8% incidence of hypotension requiring vasopressor therapy. Moreover, underlying sepsis and acidosis could be the reason of hypotension and requirement of vasopressor rather than use of PEEP in the current study. Therefore, use of moderate PEEP of 6–8 cm H_2O as part of intraoperative LPV may be considered acceptable. However, increased age (mean age 65–66 years), presence of co-morbidities (88% American Society of Anesthesiologists physical status grade II and above), longer duration of surgery, blood loss and use of epidural anaesthesia could have contributed to increased incidence of hypotension in the PROVHILO trial.

The actual incidence of POPC in our study was quite high, that is 42%-53%. In the PROVHILO trial conducted in elective surgery in European and American centres, incidence of POPC was as high as 40%. Given the emergency nature of surgery and the fact that perforation peritonitis patients are generally sicker, the high incidence of POPC may be expected. However, majority of the patients had mild respiratory failure requiring oxygen therapy and only 6–9% patients had developed ARDS.

Mortality rate was 26% in the present study. Other studies from India have reported mortality of 15%-17% in peritonitis patients undergoing EL.[18,19] In fact, another subsequent study from our institute reported a mortality rate of 15.04%.[19] In the current study, patients had significant acidosis and hypoalbuminaemia at presentation reflecting perhaps the relatively late presentation to hospital. Moreover, nearly one-fourth patients had co-morbidities as well. In addition, postoperative cumulative positive fluid balance of nearly 1 litre after surgery and approximately 2 litres by day 7 could have been contributory.[20] These factors could have influenced higher mortality in this study. However, as this study was not designed or powered to analyse mortality, it is difficult to comment on the basis of limited observations.

Most of the patients with pre-existing lung diseases were excluded in this study to identify any beneficial effect of LPV on septic peritonitis- induced lung injury model without any confounding factors. Similar criteria were used in previous studies like IMPROVE trial, where the effects of LPV on surgical insult-induced lung injury model were investigated.[4] Moreover, ARISCAT scoring suggests that the study population in the current study was at intermediate risk of POPC due to several risk factors like emergency procedure, upper abdominal surgery and duration of surgery (2–3 hour).[21] PROVHILO trial also used similar criteria and recruited patients with intermediate or high risk of developing POPC.[17]

No significant elevation in serum levels of IL-6, IL-8 and TNFα was observed in CV group compared

to LPV in the current study. Previous studies have demonstrated the LPV attenuated increase in IL-8 and myeloperoxidase in broncho-alveolar lavage (BAL) fluid. However, no change could be demonstrated in BAL TNFα and IL-6 levels and serum IL-6 and IL-8 levels. Moreover, changes in BAL biomarkers were appreciated only in surgeries lasting for more than 5 hours.[5]

The strength of the current study is that this was perhaps the first study where intraoperative LPV was was used in patients for emergency surgery who are at risk of lung injury. Most of the previous studies were performed only in elective surgeries. Moreover, lung injury biomarkers were also assessed in addition to clinical outcomes, and the outcome assessors were blinded to the study group.

There are some limitations in the current study. BAL levels of lung injury biomarkers were not done and only serum levels were performed. This was due to logistic issues of BAL sample collection and preservation at non-routine hours, given the emergency nature of surgery. Another limitation was that the same intraoperative ventilation protocol was not followed in the postoperative period. Patients requiring postoperative mechanical ventilation in both the groups received LPV with Vt 6–8 ml/kg and titrated PEEP. Use of postoperative LPV in patients assigned to CV groups could have confounding effect.

CONCLUSION

To conclude, intraoperative LPV strategy in peritonitis patients undergoing short duration EL does not reduce the incidence of POPC compared to CV.

Financial support and sponsorship

AIIMS, New Delhi provided research grant for the conduct of the study and for presentation in international conference.

Conflicts of interest

There are no conflicts of interest.

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