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Effect of the Prolonged Inspiratory to Expiratory Ratio on Oxygenation and Respiratory Mechanics During Surgical Procedures

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Abstract: Prolonged inspiratory to expiratory (I:E) ratio ventilation has been researched to reduce lung injury and improve oxygenation in surgical patients with one-lung ventilation (OLV) or carbon dioxide (CO_2) pneumoperitoneum.

We aimed to confirm the efficacy of the 1:1 equal ratio ventilation (ERV) compared with the 1:2 conventional ratio ventilation (CRV) during surgical procedures.

Electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar were searched.

Prospective interventional trials that assessed the effects of prolonged I:E ratio of 1:1 during surgical procedures.

Adult patients undergoing OLV or CO_2 pneumoperitoneum as specific interventions depending on surgical procedures.

The included studies were examined with the Cochrane Collaboration's tool. The data regarding intraoperative oxygenation and respiratory mechanics were extracted, and then pooled with standardized mean difference (SMD) using the method of Hedges.

Seven trials (498 total patients, 274 with ERV) were included. From overall analysis, ERV did not improve oxygenation at 20 or 30 minutes after specific interventions (SMD 0.193, 95% confidence interval (CI): −0.094 to 0.481, $P = 0.188$). From subgroup analyses, ERV provided significantly improved oxygenation only with laparoscopy (SMD 0.425, 95% CI: 0.167–0.682, $P = 0.001$). At 60 minutes after the specific interventions, ERV improved oxygenation significantly in the overall analysis (SMD 0.447, 95% CI: 0.209–0.685, $P < 0.001$) as well as in the subgroup analyses with OLV (SMD 0.328, 95% CI: 0.011–0.644, $P = 0.042$) and laparoscopy (SMD 0.668, 95% CI: 0.052–1.285, $P = 0.034$). ERV provided lower peak airway pressure (P_{peak}) and plateau airway pressure (P_{plat}) than CRV, regardless of the type of intervention.

The relatively small number of the included articles and their heterogeneity could be the main limitations.

ERV improved oxygenation at all of the assessment points during laparoscopy. In OLV, oxygenation improvement with ERV was observed 1 hour after application. ERV could be beneficial to reduce the P_{peak} and P_{plat}.

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Abbreviations: A-aDO_2 = alveolar-arterial oxygen tension difference, ARDS = acute respiratory distress syndrome, CI = confidence interval, CO_2 = carbon dioxide, CRV = 1:2 conventional ratio ventilation, D-L = DerSimonian–Laird, ERV = 1:1 equal ratio ventilation, HR = heart rate, I:E = inspiratory to expiratory, IRV = inverse ratio ventilation, IV = inverse variance, MBP = mean arterial blood pressure, OLV = one-lung ventilation, PaO_2 = arterial oxygen tension, PaO_2/FiO_2 = arterial oxygen tension/fraction of inspired oxygen, PEEP = positive end-expiratory pressure, P_{mean} = mean airway pressure, P_{peak} = peak airway pressure, P_{plat} = plateau airway pressure, SMD = standardized mean difference, TLV = two-lung ventilation, V/Q = ventilation to perfusion, Vd/Vt = physiological dead space.

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INTRODUCTION

Various interventions such as one-lung ventilation (OLV) and carbon dioxide (CO_2) pneumoperitoneum are necessarily applied to optimize the surgical space depending on the type of surgery.[1,2] However, these procedures can result in adverse physiologic effects on multiple organs, including those in the respiratory system.[2,3]

Significant hypoxemia can occur in 5% to 10% of patients undergoing OLV due to increased ventilation to perfusion (V/Q) mismatching and intrapulmonary shunt.[2,4,5] Compared with two-lung ventilation (TLV), an approximately 55% increase in the peak airway pressure occurs during OLV.[6] The increased airway pressure during OLV may contribute to the development of acute lung injury.[7]

In laparoscopic surgery, increased intraabdominal pressure derived from CO_2 pneumoperitoneum can be associated with potential problems, including oxygenation deterioration and an increase in airway pressure.[8] Reduction in lung volume/compliance and the consequent increase in atelectasis can lead to impairment of oxygenation, hypercapnia, and acidosis.[3,9] The higher airway pressure has also been related to serious events including pneumothorax, emphysema, and a decrease in preload and cardiac output.[10,11]

Prolonged inspiratory to expiratory ratio (I:E ratio) ventilation has been originally suggested to improve lung function in patients with acute respiratory distress syndrome (ARDS).[12,13] The main mechanism of prolonged I:E ratio ventilation has been subdivided into preventing alveolar collapse by elevating the mean airway pressure and reducing airway pressure by increasing the inspiratory time in the respiratory cycle.[14]

Recently, prolonged I:E ratio ventilation has been vigorously researched to resolve the growing concerns about the adverse effects of specific interventions such as OLV and CO_2 pneumoperitoneum.[5,7,13,15,16] Thus, we performed a systematic review and meta-analysis to confirm the clinical efficacy of the prolonged I:E ratio of 1:1 for intraoperative oxygenation and respiratory mechanics compared with the conventional I:E ratio of 1:2.

METHODS

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[17] The protocol of this study was registered with PROSPERO (registration number: CRD42015026825; www.crd.york.ac.uk/PROSPERO).

Our data were obtained from published studies and therefore, an ethical approval was not necessary.

Study Eligibility Criteria and Search Strategy

We included prospective interventional trials that assessed the effects of prolonged I:E ratio ventilation in adult patients undergoing elective surgical procedures under general anesthesia. In October 2015, 2 members (JHP and MSK) independently searched electric databases including PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, and Google Scholar for eligible prospective interventional trials using the following search terms: ''equal ratio ventilation,'' ''inverse ratio ventilation,'' ''inversed ratio ventilation,'' ''prolonged inspiratory time,'' ''inspiratory to expiratory ratio,'' ''surgery,'' ''one-lung ventilation,'' ''surgical patients,'' ''laparoscopic,'' and ''laparoscopy.'' Search builder using these terms in PubMed was (((((((equal ratio ventilation) OR inverse ratio ventilation) OR inversed ratio ventilation) OR prolonged inspiratory time) OR inspiratory to expiratory ratio)) AND (((((surgery) OR one-lung ventilation) OR surgical patients) OR laparoscopic) OR laparoscopy)). Language restrictions or limitations were not imposed during the electronic searches. After the 2 members chose the eligible trials independently, disagreements over trial choice were resolved by discussion with a third member (JSL). References in the finally chosen articles were also reviewed to confirm the presence of potentially eligible trials.

From the chosen articles, 2 members (SS and NHM) independently extracted the following data: primary author's name, publication year, study design, type of surgery, patient number and characteristics, specific interventions such as carbon dioxide (CO_2) pneumoperitoneum, OLV, or specific positioning according to surgical procedures, anesthesia protocol, airway device, ventilation mode, the presence of positive end-expiratory pressure (PEEP), intraoperative oxygenation indices such as arterial oxygen tension (PaO_2) and arterial oxygen tension/fraction of inspired oxygen (PaO_2/FiO_2), physiological dead space (Vd/Vt), alveolar-arterial oxygen tension difference (A-aDO_2), peak airway pressure (P_{peak}), plateau airway pressure (P_{plat}), mean airway pressure (P_{mean}), dynamic compliance, static compliance, mean arterial blood pressure (MBP), and heart rate (HR). When there were the missing values, we contacted the corresponding authors via email. The primary outcomes in this meta-analysis were intraoperative oxygenation indices. If the data collection in the trials with parallel-group design was performed at more than 2 time points during specific intervention and positioning, the results at the first time points were used for pooled analyses with those obtained from crossover trials. Data at the second time point in parallel-group trials were analyzed separately. When the outcomes were provided as the median, range, or interquartile range, we estimated the mean and standard deviation using previously described formulas, that were proposed by Hozo et al.[18] The mean was calculated from the formula using the median and the high and low ends of the range in studies with a sample size less than 25. The median itself was used as the mean value in studies with a sample size more than 25. The standard deviation was calculated from the formula using the median and high and low ends of the range in studies with a sample size less than 15, the range/4 in studies with a sample size from 15 to 70, and the range/6 in studies with a sample size greater than 70.

Risk of Bias Assessment

Two members (JHP and JHL) independently examined the quality of the studies using the Cochrane Collaboration's tool to assess the risk of bias in several domains, including selection, performance, detection, attrition, and reporting bias.[19] Each domain was graded as ''high risk,'' ''low risk,'' or ''unclear risk.'' Discrepancies in grading were resolved through discussion between the members or by the referral of another member (MSK).

Statistical Analysis

Stata software (Version 14.0; Stata Corporation, College Station, TX) and Comprehensive Meta-Analysis software (version 2.0; Biostat, Englewood, NJ) was used to conduct meta-analyses. Crossover trials were considered and analyzed as parallel-group trials. For continuous variables, the standardized mean difference (SMD) at each study level and pooled SMD using the method of Hedges were calculated using the inverse variance (IV) method in a fixed-effects model or DerSimonian–Laird (D-L) method in a random-effects model.[20,21] Assessment of heterogeneity was established using Q-test and Chi-squared test. If the I^2 value greater than 50% or the P-value < 0.10 on Chi-squared test was observed, significant heterogeneity of the effect sizes was considered to be present, and a random-effects model was used instead of a fixed-effect model. Subgroup analyses based on specific interventions such as OLV and laparoscopy according to the surgical procedures were conducted to identify the potential causes of heterogeneity. Publication bias was assessed by visual inspection of funnel plots and the Egger linear regression test.[22] Possible publication bias was indicated with the presence funnel plot asymmetry and a P-value < 0.10 on the Egger test.

RESULTS

Study Search and Characteristics

We conducted electronic database searches and identified seven full-text articles for inclusion in this review (Figure 1).[5,9,15,16,23–25] The included articles consisted of 4 randomized parallel-group trials,[5,9,15,25] 2 randomized crossover trials,[16,24] and 1 nonrandomized single-group trial.[23] The characteristics of the included trials are presented in Table 1. All of the included articles compared 1:1 equal ratio ventilation (ERV) and 1:2 conventional ratio ventilation (CRV). In crossover trials and a nonrandomized single-group trial, the time period of the application of each ratio was 20[23] or 30[16,24] minutes, and data collection for each ratio was thus established only once. In all of the included parallel-group trials,[5,9,15,25]

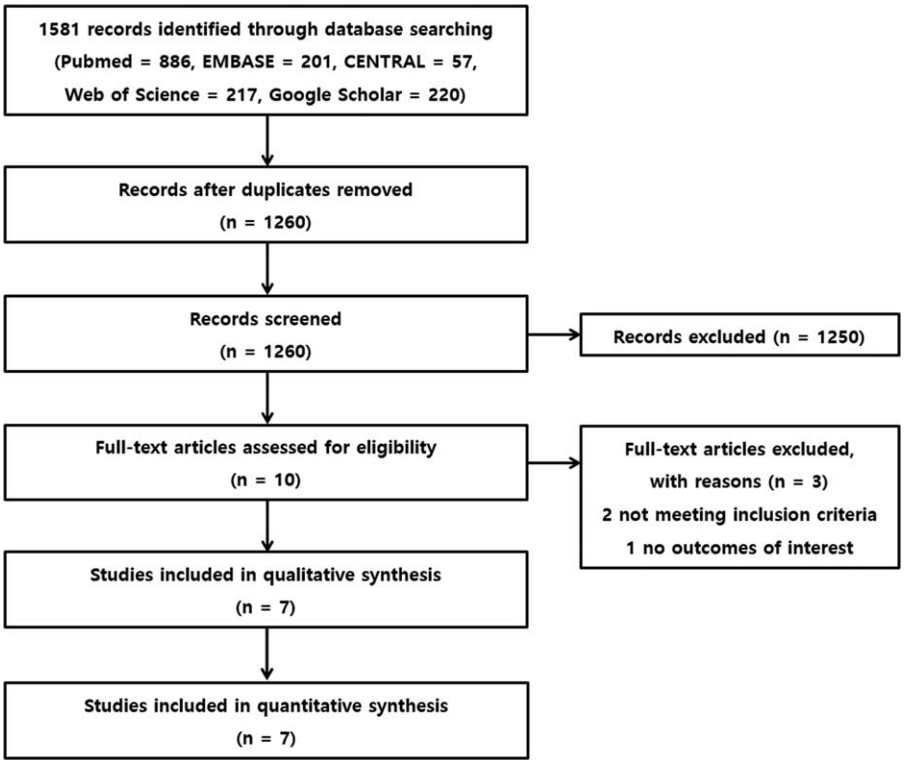

FIGURE 1. Flow diagram of the article selection process.

data collection was conducted at 30 and 60 minutes after applying specific interventions such as OLV or laparoscopy according to the surgical procedures. The results at the first assessment point, that is, at 30 minutes, were used for primary analyses of crossover trials. Data at the second assessment point, that is, at 60 minutes in parallel-group trials, were analyzed separately. One enrolled trial comparing ERV and CRV measured cardiac output noninvasively, and no significant difference was observed between ERV and CRV.[15] Intraoperative oxygen indices, the primary outcomes in this meta-analysis, were provided as PaO_2 in most of the included articles,[9,15,16,23–25] except one article that presented PaO_2/FiO_2.[5]

Quality Assessment

The risks of bias for each domain are provided in Table 2. Most of the trials were graded as unclear or high risk in domains regarding the blinding of participants or personnel, and outcome assessment. One nonrandomized single group trial was considered to have a high risk of bias in random sequence generation, allocation concealment and blinding.[23]

ERV Versus CRV at the First Assessment Point

All of the included articles contained comparisons of intraoperative oxygenation indices, including PaO_2[9,15,16,23–25] or PaO_2/FiO_2[5] between the ratios. The overall analysis did not show any differences in intraoperative oxygenation (SMD 0.193, 95% confidence interval (CI) −0.094 to 0.481, $P = 0.188$, $I^2 = 56.6\%$, D-L random), and publication bias was not suspected in Egger test ($P = 0.370$). The subgroup analyses of 4 trials with laparoscopy provided significantly improved oxygenation in ERV (SMD 0.425, 95% CI: 0.167–0.682, $P = 0.001$, $I^2 = 48.1\%$, IV fixed).[9,15,23,24] However, the subgroup analyses of 3 trials with OLV did not show improved results in ERV (SMD −0.113, 95% CI: −0.385 to 0.159, $P = 0.416$, $I^2 = 0\%$, IV fixed).[5,16,25] Figure 2 shows a forest plot of the analyses of intraoperative oxygenation at this time point between ERV and CRV.

Table 3 shows results of pooled analyses from other respiratory and hemodynamic data. Vd/Vt in ERV was significantly smaller in the overall analysis, but with considerable heterogeneity. From the subgroup analyses, this improved result was observed only in trials with OLV, and heterogeneity was not relieved. Significantly lower P_{peak} and P_{plat}, and a higher P_{mean} were observed in ERV from the overall analysis. Subgroup analyses showed similar results, except P_{plat} in the OLV group that did not reach statistical significance (SMD −0.495, 95% CI: −1.012 to 0.022, $P = 0.060$, $I^2 = 58.4\%$, D-L random). A forest plot of P_{peak} is presented in Figure 3. From analyses regarding compliance, dynamic compliance in ERV was significantly improved in the overall and OLV subgroup analyses. Regarding static compliance, a meaningful improvement was not observed in ERV. There were no differences in the MBP and HR between the ratios.

ERV Versus CRV at the Second Assessment Point

Four parallel-group trials provided data collected at 60 minutes after applying the specific interventions as the second assessment point.[5,9,15,25] From the overall analysis, intraoperative oxygenation assessed was significantly improved in ERV (SMD 0.447, 95% CI: 0.209–0.685, $P < 0.001$, $I^2 = 30.4\%$, IV fixed), and no possibility of publication bias was observed in Egger test ($P = 0.422$). The subgroup analyses according to OLV and laparoscopy also showed significantly improved results in each

TABLE 1. Characteristics of Prospective Interventional Trials Selected in This Meta-Analysis

Trials	Study Design	Surgery	Interventions	Group	N	Age (y)	BMI (kg/m^2)	Airway Device	Mode	PEEP (cmH_2O)
Lee et al[16]	Randomized	Thoracoscopic lung lobectomy	One-lung ventilation	1:1 ratio	26	60.8 (13.4)	23.1 (2.8)	Left-sided double lumen tube	PCV	5
	Crossover			1:2 ratio	26					
Kim et al[15]	Randomized	Robot-assisted laparoscopic prostatectomy	Trendelenburg position and	1:1 ratio	39	65.1 (7.2)	23.5 (2.7)	Conventional endotracheal tube	VCV	0
	Parallel-group		CO_2 pneumoperitoneum	1:2 ratio	40	64.1 (8.5)	24.3 (2.4)			
Jo et al[23]	Nonrandomized single-group	Laparoscopic sleeve gastrectomy	Reverse Trendelenburg position and	2:1 ratio	28	34 (8)	35.2 (3.8)	Conventional endotracheal tube	PCV	5
			CO_2 pneumoperitoneum	1:1 ratio	28					
				1:2 ratio	28					
Mousa[24]	Randomized	Laparoscopic gastric band ligation	Reverse Trendelenburg position and	1:1 ratio	30	35.40 (5.72)*	48.93 (2.43)*	Conventional endotracheal tube	PCV	5
	Crossover		CO_2 pneumoperitoneum	1:2 ratio	30	34.73 (5.27)*	49.27 (1.91)*			
Lee et al[5]	Randomized	Lung lobectomy	One-lung ventilation	1:1 ratio	50	60 (12)	23.5 (2.7)	Double lumen tube	VCV	5
	Parallel-group			1:2 ratio	50	58 (12)	23.5 (3.3)			
Kim et al[9]	Randomized	Laparoscopic gynecologic surgery	Trendelenburg position and	2:1 ratio	22	43 (12)	22.3 (2.1)	Conventional endotracheal tube	VCV	0
	Parallel-group		CO_2 pneumoperitoneum	1:1 ratio	23	39 (11)	22.3 (2.6)			
				1:2 ratio	22	37 (9)	21.6 (2.1)			
Kim et al[25]	Randomized	Thoracoscopic lung lobectomy	One-lung ventilation	1:1 ratio	28	60.3 (10)	23.5 (3.0)	Left-sided double lumen tube	VCV	0
	Parallel-group			1:2 ratio	28	61.7 (11)	23.6 (2.6)			

Values are presented as number or mean (standard deviation).
BMI = body mass index; CO_2 = carbon dioxide; PCV = pressure controlled ventilation; PEEP = positive end expiratory pressure; VCV = volume controlled ventilation.
*Groups according to the first applied I:E ratio.

TABLE 2. Risk of Bias Assessment

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participant and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Bias
Lee et al[16]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Low risk
Kim et al[15]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Jo et al[23]	High risk	High risk	High risk	High risk	Low risk	Low risk	Low risk
Mousa[24]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Lee et al[5]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk
Kim et al[9]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Kim et al[25]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear

subgroup (SMD 0.328, 95% CI: 0.011–0.644, $P = 0.042$, $I^2 = 0\%$, IV fixed; SMD 0.668, 95% CI: 0.052–1.285, $P = 0.034$, $I^2 = 61.8\%$, D-L random, respectively) (Figure 4).

Table 4 summarizes the results of pooled analyses from other respiratory and hemodynamic data at the second assessment time. From the overall analysis, Vd/Vt was significantly reduced in ERV, but with significant heterogeneity. From the subgroup analyses, the better result was found only in the group with OLV; however, substantial heterogeneity was not reduced. Significantly lower P_{peak} and P_{plat}, and a higher P_{mean} were observed in ERV from the overall analysis. Subgroup analyses provided similar results, except P_{peak} in the laparoscopic group (SMD −0.705, 95% CI: −1.438 to 0.029, $P = 0.060$, $I^2 = 73.6\%$, D-L random) and P_{mean} in the OLV group (SMD 0.741, 95% CI: −0.024 to 1.506, $P = 0.058$, $I^2 = 79.6\%$, D-L random), neither of which reached statistical significance. A forest plot of P_{peak} is presented in Figure 5. There were no differences in the dynamic and static compliance between the ratios from the overall analyses. Only dynamic compliance in the OLV subgroup was significantly improved in ERV. We did not find any differences in the MBP and HR between the ratios.

Postoperative Complications

Four studies stated information about complications during the postoperative period.[5,9,15,16] Three studies reported no postoperative complications in all of the enrolled patients.[9,15,16] In one study comparing ERV and CRV under OLV, 6 of 50 patients (12%) in each ratio group demonstrated respiratory complications, and the intensive care unit or hospital stay was similar between the groups.[5]

DISCUSSION

This systematic review and meta-analysis showed that a prolonged I:E ratio of 1:1 provided oxygenation improvement at all of the assessment points after CO_2 pneumoperitoneum and only at the second assessment point (ie, 60 minutes) after OLV, compared with a conventional I:E ratio of 1:2. From the overall analyses, P_{peak} and P_{plat} with the I:E ratio of 1:1 were

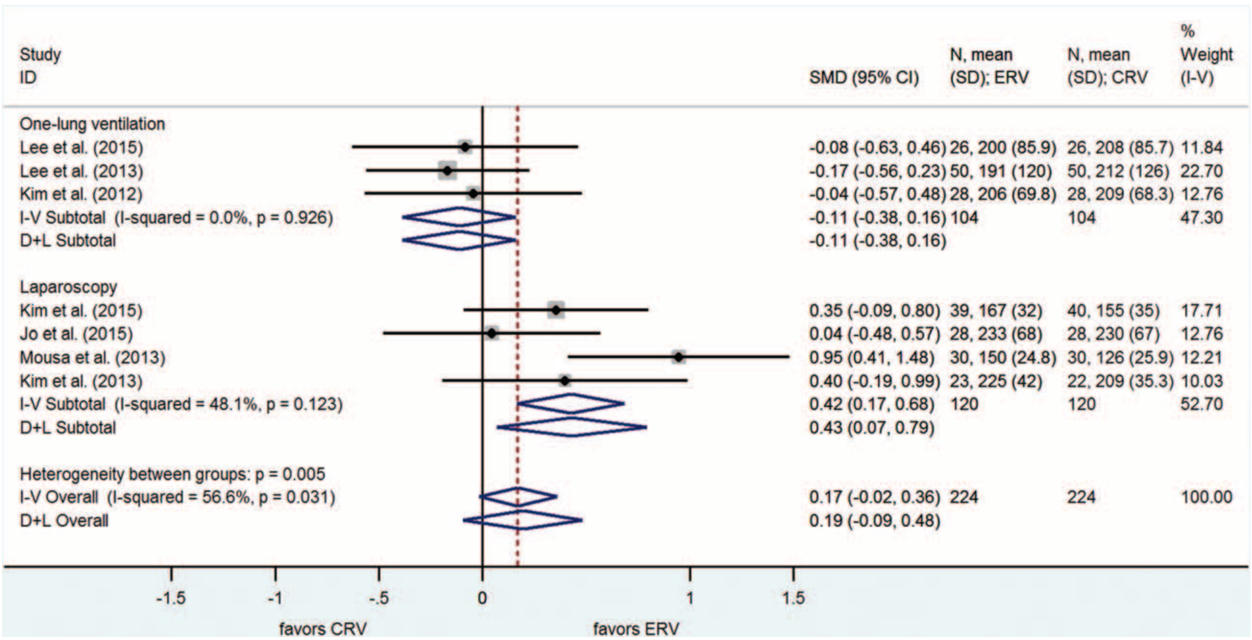

FIGURE 2. A forest plot of intraoperative oxygenation presented as PaO_2 or PaO_2/FiO_2 between equal and conventional ratio ventilations at 20 or 30 minutes after initiating one-lung ventilation or laparoscopy as the first assessment point.

TABLE 3. Meta-Analysis of Additional Data Comparing 1:1 Equal Ratio Ventilation and 1:2 Conventional Ratio Ventilation at the First Assessment Point

Variables	No. of Studies	SMD (95% CI)	I^2	*P*	*P* in Egger Test
Physiological dead space					
Overall analysis[5,9,15,16,23,25]	6	−0.982 (−1.694 to −0.270)*	90.5%	0.007	0.107
One-lung ventilation[5,16,25]	3	−1.493 (−2.618 to −0.368)*	91.5%	0.009	0.226
Laparoscopy[9,15,23]	3	−0.486 (−1.385 to 0.412)*	88.0%	0.288	0.510
Alveolar-arterial oxygen tension difference					
Overall analysis[5,9,23,25]	4	−0.011 (−0.256 to 0.235)	0%	0.933	0.263
One-lung ventilation[5,25]	2	0.127 (−0.188 to 0.441)	0%	0.429	—
Laparoscopy[9,23]	2	−0.225 (−0.617 to 0.168)	2.7%	0.262	—
Peak airway pressure					
Overall analysis[5,9,15,16,23–25]	7	−1.642 (−2.547 to −0.737)*	94.2%	<0.001	0.045
One-lung ventilation[5,16,25]	3	−1.069 (−1.703 to −0.435)*	77.4%	0.001	0.658
Laparoscopy[9,15,23,24]	4	−2.433 (−4.213 to −0.653)*	96.8%	0.007	0.087
Plateau airway pressure					
Overall analysis[5,15,25]	3	−0.516 (−0.777 to −0.255)	32.2%	<0.001	0.245
One-lung ventilation[5,25]	2	−0.495 (−1.012 to 0.022)*	58.4%	0.060	—
Laparoscopy[15]	1	−0.656 (−1.109 to −0.202)	—	0.005	—
Mean airway pressure					
Overall analysis[5,9,15,16,23–25]	7	0.772 (0.578 to 0.965)	37.4%	<0.001	0.999
One-lung ventilation[5,16,25]	3	0.773 (0.301 to 1.244)*	61.6%	0.001	0.963
Laparoscopy[9,15,23,24]	4	0.774 (0.509 to 1.038)	31.4%	<0.001	0.907
Dynamic compliance					
Overall analysis[5,9,16,23–25]	6	0.520 (0.141 to 0.900)*	68.5%	0.007	0.094
One-lung ventilation[5,16,25]	3	0.892 (0.605 to 1.178)	0%	<0.001	0.262
Laparoscopy[9,23,24]	3	0.189 (−0.123 to 0.501)	49.2%	0.234	0.018
Static compliance					
Overall analysis[5,9,15]	3	0.635 (−0.179 to 1.448)*	88.1%	0.126	0.496
One-lung ventilation[5]	1	1.413 (0.973 to 1.853)	—	<0.001	—
Laparoscopy[9,15]	2	0.281 (−0.074 to 0.636)	29.1%	0.120	—
Mean arterial blood pressure					
Overall analysis[5,9,15,23–25]	6	0.146 (−0.052 to 0.344)	0%	0.147	0.241
One-lung ventilation[5,25]	2	0.125 (−0.190 to 0.440)	13.3%	0.437	—
Laparoscopy[9,15,23,24]	4	0.160 (−0.094 to 0.414)	0%	0.217	0.637
Heart rate					
Overall analysis[5,9,15,16,23–25]	7	0.003 (−0.183 to 0.189)	3.6%	0.977	0.017
One-lung ventilation[5,16,25]	3	0.112 (−0.161 to 0.384)	0.0%	0.421	0.329
Laparoscopy[9,15,23,24]	4	−0.092 (−0.347 to 0.162)	15.2%	0.476	0.131

CI = confidence interval; no = number, SMD = standardized mean difference.
*Random effects analysis.

reduced significantly, compared to that with an I:E ratio of 1:2.

The potential mechanisms of ventilation with a prolonged I:E ratio to improve oxygenation is the elevation of P_{mean}, improvement in the intrapulmonary distribution of the inspired gas due to slower inspiratory flow, and intrinsic PEEP derived from the short expiratory time.[13,26] P_{mean} typically refers to the average pressure exerted on the airway and lungs during the ventilatory cylcle.[26,27] In patients undergoing positive pressure ventilation, P_{mean} corresponds to the mean alveolar pressure, which is the average pressure to enable the alveoli to open and inflate against the elastic recoil of the lung. Thus, alveolar recruitment and shunt reduction arising from an increased P_{mean} may ameliorate blood oxygenation.[13,28]

This meta-analysis demonstrated that the P_{mean} with ERV was significantly higher than that with CRV at all of the assessment points. From the overall analyses, intraoperative oxygenation at 60 minutes after initiating ventilation was improved significantly with ERV, but the improved oxygenation in ERV was not observed at 20 or 30 minutes. More effective recruitment of lung units may be established under sustained elevation of airway pressure because sustained traction is necessary to open nonaerated alveoli.[29] Thus, the ultimate benefit of the prolonged I:E ratio ventilation may be time dependent, and oxygenation improvement may be earned over a period of time after its application.[12] The differences in results according to subgroups could also affect the results of the overall analyses. From the subgroup analyses, ERV at 20 or 30 minutes in the OLV group did not provide the improved oxygenation although ERV in the laparoscopy group showed significantly favorable changes in oxygenation ($P = 0.001$). Previous studies have provided several possible reasons for no meaningful change in the oxygenation in the OLV group.[16,25] Unlike TLV, oxygenation during OLV is dependent

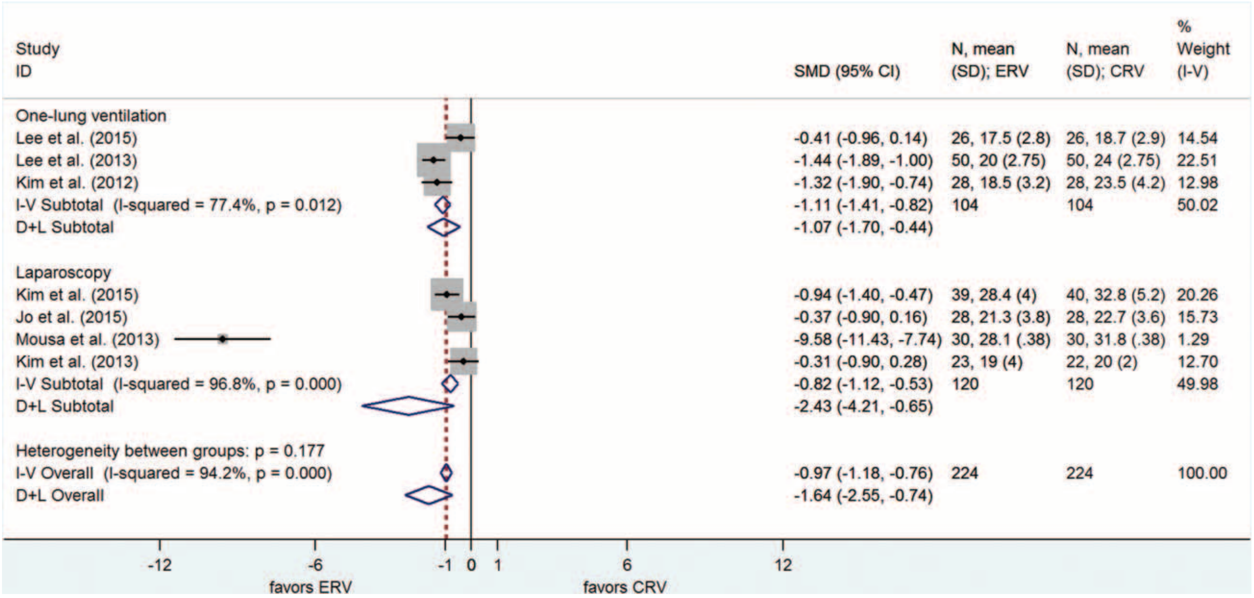

FIGURE 3. A forest plot of the peak airway pressure between equal and conventional ratio ventilations at 20 or 30 minutes after initiating one-lung ventilation or laparoscopy as the first assessment point.

on various factors including V/Q mismatch in the ventilated lung, intrapulmonary shunt in the nonventilated lung, venous saturation, cardiac output, and the hemoglobin level.[2,16]

The major issue when applying prolonged I:E ratios are adverse hemodynamic effects, including the decrease in cardiac output due to an increase in the P_{mean}.[12] Kim et al[25] reported the significantly reduced central venous oxygen during OLV with ERV, indicating the decreased cardiac output. Lack of improved oxygenation during OLV with ERV might be derived from the decreased cardiac output and inadequate tissue oxygenation. The extent or clinical implication concerning the change in cardiac output during ventilation with ERV still remains uncertain. In one included trial with robot-assisted laparoscopic prostatectomy, no difference was observed in the noninvasively measured cardiac output between ERV and CRV.[15] In a previous study comparing PEEP and inverse ratio ventilation (IRV) in patients with ARDS, the cardiac output was not influenced by the type of ventilatory modalitiy.[13] In this meta-analysis, the MBP and HR during ERV were comparable to those with CRV. In addition, oxygenation at 60 minutes after initiating ERV showed significantly improved results with no significant heterogeneity in the both OLV and laparoscopy subgroups. In OLV, adverse effects of the decreased cardiac output on oxygenation might be overcome by ongoing recruitment of nonaerated alveoli.[25] The controversy about the change in cardiac output during ERV should be resolved with additional information.

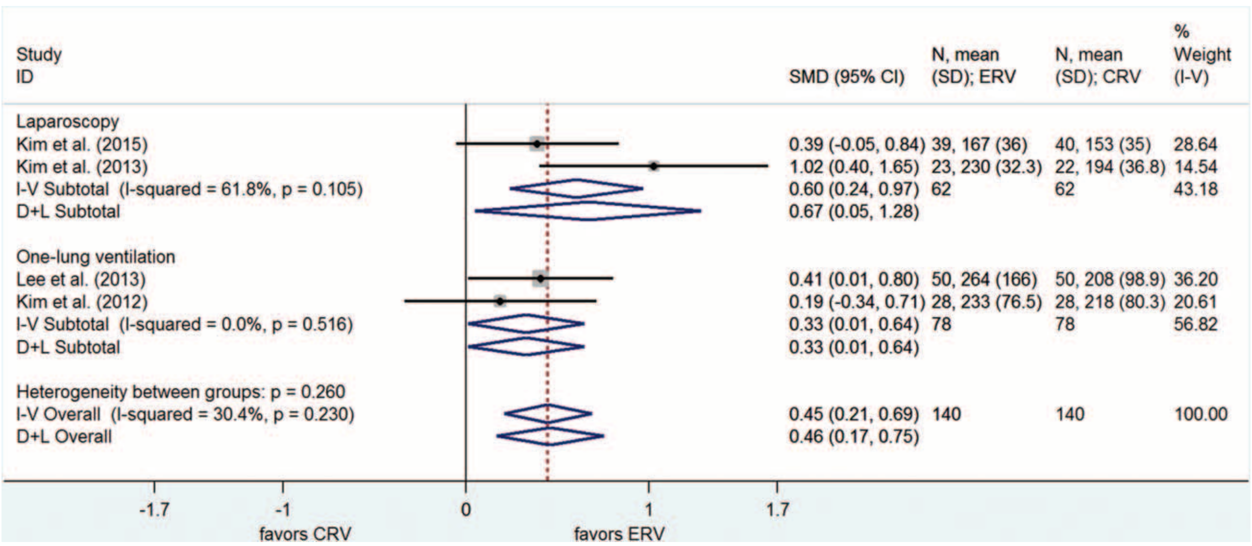

FIGURE 4. A forest plot of intraoperative oxygenation presented as PaO_2 or PaO_2/FiO_2 between equal and conventional ratio ventilations at 60 minutes after initiating one-lung ventilation or laparoscopy as the second assessment point.

TABLE 4. Meta-Analysis of Additional Data Comparing 1:1 Equal Ratio Ventilation and 1:2 Conventional Ratio Ventilation at the Second Assessment Point

Variables	No. of Studies	SMD (95% CI)	I^2	*P*	*P* in Egger Test
Physiological dead space					
Overall analysis[5,9,15,25]	4	−0.940 (−1.698 to −0.183)*	88.4%	0.015	0.224
One-lung ventilation[5,25]	2	−1.174 (−2.137 to −0.212)*	85.4%	0.017	—
Laparoscopy[9,15]	2	−0.716 (−2.218 to 0.785)*	92.9%	0.350	—
Alveolar-arterial oxygen tension difference					
Overall analysis[5,9,25]	3	−0.402 (−0.956 to 0.152)*	71.8%	0.155	0.430
One-lung ventilation[5,25]	2	−0.126 (−0.440 to 0.188)	0%	0.432	
Laparoscopy[9]	1	−1.082 (−1.711 to −0.452)	—	0.001	
Peak airway pressure					
Overall analysis[5,9,15,25]	4	−0.932 (−1.181 to −0.684)	43%	<0.001	0.309
One-lung ventilation[5,25]	2	−1.073 (−1.409 to −0.736)	0%	<0.001	—
Laparoscopy[9,15]	2	−0.705 (−1.438 to 0.029)*	73.6%	0.060	—
Plateau airway pressure					
Overall analysis[5,15,25]	3	−0.894 (−1.163 to −0.624)	4.9%	<0.001	0.380
One-lung ventilation[5,25]	2	−0.962 (−1.296 to −0.629)	38.8%	<0.001	—
Laparoscopy[15]	1	−0.765 (−1.222 to −0.307)	—	0.001	—
Mean airway pressure					
Overall analysis[5,9,15,25]	4	0.840 (0.459 to 1.220)*	56.1%	<0.001	0.176
One-lung ventilation[5,25]	2	0.741 (−0.024 to 1.506)*	79.6%	0.058	—
Laparoscopy[9,15]	2	0.984 (0.610 to 1.359)	0%	<0.001	—
Dynamic compliance					
Overall analysis[5,9,25]	3	0.535 (−0.547 to 1.617)*	92.2%	0.333	0.247
One-lung ventilation[5,25]	2	1.080 (0.491 to 1.669)*	65.1%	<0.001	—
Laparoscopy[9]	1	−0.554 (−1.151 to 0.043)	—	0.069	—
Static compliance					
Overall analysis[5,9,15]	3	0.929 (−0.573 to 2.430)*	96%	0.225	0.934
One-lung ventilation[5]	1	2.459 (1.935 to 2.983)	—	<0.001	—
Laparoscopy[9,15]	2	0.183 (−0.593 to 0.959)*	77.4%	0.644	—
Mean arterial blood pressure					
Overall analysis[5,9,15,25]	4	0.179 (−0.057 to 0.415)	34.5%	0.136	0.043
One-lung ventilation[5,25]	2	0.199 (−0.404 to 0.802)*	70.1%	0.517	—
Laparoscopy[9,15]	2	0.235 (−0.119 to 0.590)	6.1%	0.193	—
Heart rate					
Overall analysis[5,9,15,25]	4	−0.141 (−0.377 to 0.094)	38.2%	0.240	0.024
One-lung ventilation[5,25]	2	−0.155 (−0.697 to 0.387)*	63.3%	0.575	—
Laparoscopy[9,15]	2	−0.229 (−0.748 to 0.290)*	50.1%	0.388	—

CI = confidence interval; no = number, SMD = standardized mean difference.
*Random effects analysis.

From our meta-analysis, significantly lower P_{peak} and P_{plat} in ERV were observed from the overall analyses at all the assessment points. Similar findings were also confirmed from the subgroup analyses of OLV and laparoscopy. However, there was substantial heterogeneity in the pooled analyses of P_{peak} comparing ERV and CRV at the first assessment point. The heterogeneity may be attributable to patient characteristics, including old age and a high body mass index, type of surgery, specific situations related to the surgical procedure such as Trendelenburg positioning, the use of pressure or volume controlled ventilation, and the presence of PEEP.[6,8,30–32] P_{peak} is the pressure to overcome both the resistance of airflow in the airways and elastic recoil forces of the lungs and chest wall. P_{plat} refers to the pressure in the alveoli and is measured by the inflation-hold maneuver to remove the resistive component of P_{peak}.[33] The prolonged inspiratory time reduces P_{peak} by lowering the inspiratory flow rate under the same tidal volume.[13,34] In the aforementioned study in ARDS,[13] the inspiratory flow rate and, accordingly, P_{peak} were reduced in IRV, compared with those in PEEP. However, there was no difference in P_{plat} between the ventilator modalities. In our meta-analysis, P_{plat} in ERV was also lower than that in CRV, unlike these previous results. The discrepancy in the results between the studies under a prolonged inspiratory time might be derived from differences in the clinical settings (intensive care for ARDS vs general anesthesia for surgery) and I:E ratios (inverse vs equal). A slower inspiratory flow may provide more time to fill the alveoli with slower time constants; consequently, the aeration of these alveoli may contribute to the improvement in lung compliance with lower elastic recoil and oxygenation.[13,33,34] This process might be performed better in surgical patients with transiently increased atelectasis due to laparoscopy or OLV than in patients with ARDS. Thus, the lower P_{plat} in ERV from this meta-analysis may be also associated with the improved lung

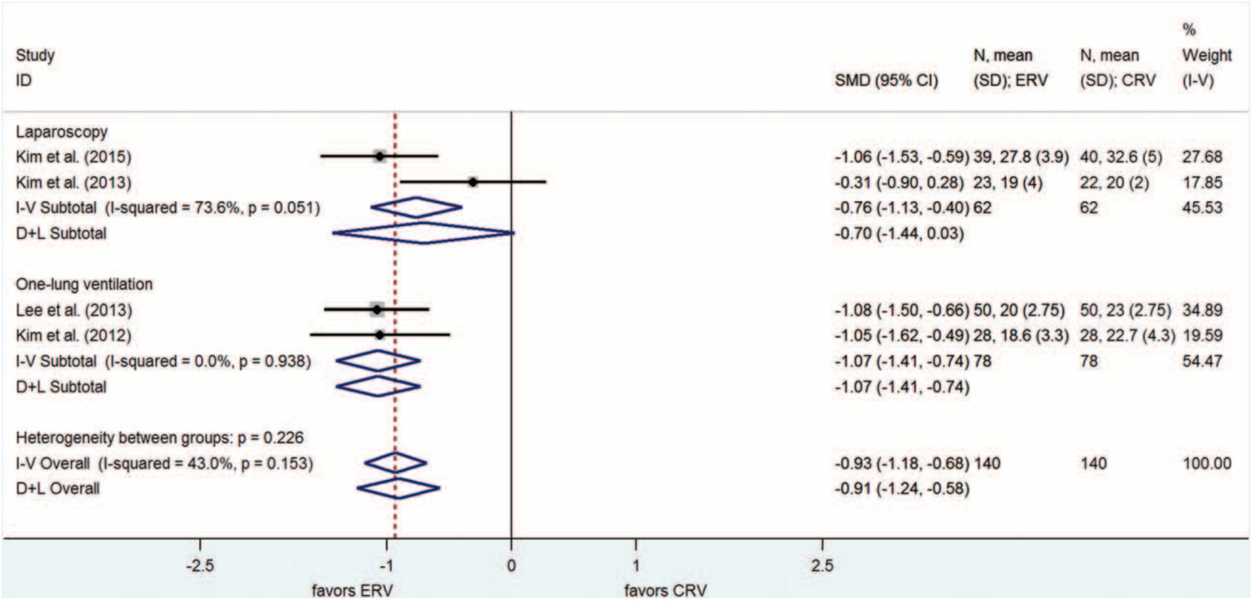

FIGURE 5. A forest plot of the peak airway pressure between equal and conventional ratio ventilations at 60 minutes after initiating one-lung ventilation or laparoscopy as the second assessment point.

compliance elicited by the better intrapulmonary distribution of the inspired gas. However, static compliance did not show any favorable change unlike dynamic compliance. Considering that static compliance is inversely related to P_{plat}, these results might be confusing. A possible explanation for this finding is the limited number of studies that reported on P_{plat} and static pressure. Further researches are required to understand the differences in respiratory dynamics concerning ventilation with prolonged I:E ratios according to clinical situations.

Sustained elevation of the P_{mean} and intrinsic PEEP as the mechanism of improved oxygenation during a prolonged inspiration time may be related to adverse consequences, including barotrauma and air trapping.[12,16,28] The aforementioned report in ARDS stated that the risk of barotrauma was not decreased with IRV because of the increased P_{mean} and P_{plat}.[13] From our meta-analysis, the increase in P_{mean} during ERV was accompanied by a decrease in P_{peak} and P_{plat}. Given that high P_{plat} is considered as a risk factor for acute lung injury and poor postoperative outcomes, the ERV may be beneficial to prevent lung injury in surgical settings.[7,9,16] Incomplete exhalation during ERV could be due to excessive gas trapping or intrinsic PEEP, which could increase the risk of alveolar rupture and volutrauma and decrease cardiac output.[9,35] Thus, the monitoring of intrinsic PEEP should be considered to prevent possible complications during ventilation with prolonged I:E ratios. The level of intrinsic PEEP can be estimated accurately by the end-expiratory occlusion method in some ventilators capable of the end-expiratory hold for the prompt occlusion of the expiratory port precisely at the end of expiration.[36] It is difficult to measure the intrinsic PEEP with most anesthesia machines due to the absence of the end-expiratory hold function and the ventilator manometer open to the atmosphere during the expiration period.[36–38] Thus, several alternative methods such as prolonged expiratory flow on capnography during the apnea test, interrupted expiratory flow in a flow-volume curve, and continuing expiratory flow at the end of expiration in a flow-time curve have been considered to identify the presence of the intrinsic PEEP during anesthesia.[33,36,38] From our review, all of the included studies did not measure the intrinsic PEEP, and some studies monitored the flow-time curve to detect the presence of the intrinsic PEEP.[9,24] Considering the difficulty in quantifying the intrinsic PEEP under surgical settings, the following considerations are needed when applying prolonged I:E ratios. The use of the prolonged inspiratory times should be avoided in patients carrying the risk of alveolar rupture such as chronic obstructive lung disease.[5,9] In addition, anesthesiologists should avoid using an excessively prolonged I:E ratio such as 2:1 or 3:1 unless its use is strongly indicated.[16] The 1:1 I:E ratio may be appropriate to both improve oxygenation and minimize potential complications; however, the use of alternative methods to detect the intrinsic PEEP is strongly recommended during its application.[9,15]

Our systematic review and meta-analysis is limited by the following considerations. First, we could not secure sufficient information to compare from the review of the included articles, and neither benefits nor adverse effects of the prolonged I:E ratio during the postoperative period were confirmed in the meta-analysis. Second, the number of the included articles in this meta-analysis was relatively small and their characteristics were heterogeneous. In addition, ongoing trials may be undetected from our searches. The use of prolonged I:E ratios during general anesthesia for surgery has been issued and researched recently. Thus, the lack of statistical power and possibility of publication bias in our review and analyses may be remedied by the findings updated from additional researches. Finally, the randomized crossover trials[16,24] and nonrandomized single-group trial[23] included in this meta-analysis were regarded and analyzed as parallel-group trials on the assumption that there was no carry-over effect. One crossover trial confirmed the absence of the carry-over effect through comparing variables between 2 groups.[24]

In conclusion, a prolonged I:E ratio of 1:1 could be beneficial to improve oxygenation and lower the P_{peak} and P_{plat} during laparoscopic surgery. In OLV, the use of an I:E ratio of 1:1 also reduced P_{peak} and P_{plat}, but oxygenation improvement was observed 1 hour after its application. Considering the ambivalent effects of the prolonged I:E ratio ventilation on oxygenation and complications, the use of the 1:1 I:E ratio in anesthesia for surgery should be initiated with a detailed consideration of its risks and benefits according to the patients' status and surgical situations.

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