Advanced strategies in improving outcomes during mechanical ventilation

Ph.D. Thesis Booklet

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1. INTRODUCTION

1.1. Overview of the topics

During general anesthesia, progressive atelectasis develops in dependent areas of the lungs, leading to hypoventilation in these regions. At the same time, due to atelectasis, inspiratory pressures may cause excessive overdistention in the aerated parts of the lung Following a perioperative lung-protective ventilation approach may reduce the incidence of postoperative pulmonary complications (PPCs), which are major contributors to postoperative morbidity and mortality. Given that an optimal PEEP has yet to be clearly defined, individualized ventilation strategies have recently gained attention, focusing on setting PEEP based on patient-specific needs and optimizing parameters like driving pressure to reduce lung injury.

Lung-protective ventilation has been extensively evaluated in patients with ARDS and remains a pivotal component of supportive care. The pathophysiology of ARDS involves hyperactivated or dysregulated host-response of immune pathways, resulting in both systemic and localized inflammation. This provides a rationale for investigating the role of immunomodulatory therapies, such as hemoadsorption, in ARDS.

2. OBJECTIVES

2.1. Study I. – Individualized vs. fixed intraoperative PEEP settings

Conducting a systematic review and meta-analysis we aimed to assess the perioperative effects of two mechanical ventilation strategies in patients undergoing abdominal surgery: using individualized PEEP titration methods versus conventional fixed PEEP settings maintained throughout the surgical procedure. We hypothesized that individualized approach is superior and may reduce the incidence of PPCs.

2.2. Study II. – Hemoadsorption as Adjuvant Therapy in ARDS

Given the current lack of solid evidence in the literature, our aim was to summarize the existing data and currently available evidence regarding hemoadsorption in patients treated for severe ARDS in this systematic review and meta-analysis.

3. METHODS

We conducted two systematic reviews and meta-analyses following the PRISMA 2020 guideline and adhered to the recommendations outlined in the Cochrane Handbook. Additionally, the pre-study protocols were registered in advance in PROSPERO.[17,18]

3.1. Study I. – Individualized vs. fixed intraoperative PEEP settings

3.1.1. Systematic search, eligibility

The study was registered on PROSPERO (CRD42021282228) on October 13, 2021. A systematic search was conducted on October 14, 2021, and updated on April 26, 2024, across four medical databases: MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, and Web of Science, using a predefined search strategy. The research included only randomized controlled trials (RCTs) comparing individually titrated PEEP with fixed PEEP levels or zero PEEP (ZEEP) in adult patients undergoing abdominal surgery under general anesthesia. Both elective and non-elective surgeries, including laparoscopic and open abdominal procedures (major gastrointestinal, gynecological, and urological), were considered. Trials involving pediatric patients (<18 years) or patients ventilated for reasons unrelated to abdominal surgery were excluded.

3.1.2. Selection, data syntesis and statistical analysis

Two authors independently performed the study selection process, first by screening titles and abstracts, and then by reviewing the full texts of studies that met the inclusion criteria. Any disagreements were resolved through consultation with a third author. Data extraction from the selected articles was also carried out independently to ensure accuracy and precision.

Given at least three studies reporting a specific outcome, performing a meta-analysis was feasible. For continuous variables, mean differences were calculated based on the reported mean ± SD. If medians, quartiles, minimums, and maximums were presented in the article, we employed the Luo and Shi methods to estimate the mean ± SD. For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to compare the different PEEP strategies. For pooled results, the exact Mantel–Haenszel method (without continuity correction) was used to address zero cell counts.

The Hartung–Knapp adjustment was applied when more than five studies were available for a given outcome.

Statistical analyses were performed with R (R Core Team 2021, v4.1.2) using the meta (Schwarzer 2022, v6.2-1) and dmetar (Cuijpers, Furukawa, and Ebert 2020, v0.0.9000) packages.

3.1.3. Quality of evidence and risk of bias assessment

Following the Cochrane Collaboration's recommendations, investigators independently evaluated the quality of the studies using the "Revised Tool for Assessing the Risk of Bias in Randomised Trials." Any disagreements were resolved by involving a fourth author. The quality assessment of the included studies was conducted using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, following Cochrane guidelines, and implemented through the GRADEPro Guideline Development Tool.

3.2. Study II. – Hemoadsorption as Adjuvant Therapy in ARDS

3.2.1. Systematic search, eligibility

After registering our study protocol on PROSPERO (CRD42022292176), we conducted a systematic search in the same five databases—MEDLINE via PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science—on December 17, 2021, using a predefined search query. The search was repeated on February 25, 2023. The target population for this research comprised patients with ARDS, and we aimed to compare those who received hemoadsorption therapy with patients who received only standard medical treatment. Prospective and retrospective studies, as well as case reports and case series, were eligible for inclusion in our systematic review.

3.2.2. Selection, data syntesis and statistical analysis

As in the previous study, the selection and data extraction were conducted independently by two authors following the selection criteria. Any disagreements were resolved by involving a third author.

For case reports or case series with very few eligible patients, data were pooled and visualized using boxplots. A Wilcoxon test was performed to determine whether there was a significant difference in the before- and after-treatment values.

For each continuous outcome, we analyzed the before- and after-treatment means as well as mean differences. In one outcome, at least one study also provided the difference between before- and after-treatment means for a control group (CG). In such cases, we also analyzed the difference in these mean differences. The Hartung-Knapp adjustment was applied, and we used the classical inverse variance method with the restricted maximum likelihood estimator.

Heterogeneity was assessed using the I^2 statistic with confidence intervals and the Cochrane Q test. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.

In some instances, only the median and interquartile range of a continuous outcome were available. In these cases, we used methods outlined by Luo et al., and Wan et al., similar to the first study. While standard deviations for before- and after-treatment outcomes were available or estimable, the standard deviation of the change was missing. Following the Cochrane Handbook guidelines, we tested correlations ranging from −0.5 to 0.9. All tested correlations yielded similar results, and the published results were based on a correlation of 0.8.

3.2.3. Quality of evidence and risk of bias assessment

We followed the Cochrane Collaboration's recommendations for evaluating the quality of studies and used the GRADE approach for assessment. The methodological quality of the case series was recommended to be assessed using the Joanna Briggs Institute Critical Appraisal Tool. The evaluations were conducted independently by two authors, with a third author consulted to resolve any disagreements. For the risk of bias assessment, we employed study-type-appropriate tools: the Joanna Briggs Institute Critical Appraisal Tool for case reports and case series; the ROBINS-I tool for cohort studies; and the RoB-2 tool for randomized controlled trials.

4. RESULTS

4.1. Study I. – Individualized vs. fixed intraoperative PEEP settings

4.1.1. Systematic search and selection

Our systematic search identified 1,541 articles, which underwent the selection process. Eventually, 30 studies were deemed eligible for inclusion in our data synthesis.

4.1.2. Baseline characteristics

We analyzed data from 30 studies encompassing a total of 2,602 patients. Seven trials focused on PEEP titration in obese patients, while the remaining studies involved non-obese patients undergoing either laparoscopic or open surgeries. Some studies included mixed populations or surgery types; these were categorized into the miscellaneous group.

4.1.3. Outcomes

The primary outcome was the incidence of postoperative pulmonary complications (PPCs). Data on atelectasis, pneumonia, ARDS, and pulmonary aspiration—either individually or in combination—were pooled from 12 studies involving 1,466 patients. Among these, 444 patients experienced PPCs. Our analysis indicated that patients receiving personalized PEEP settings were 30% less likely to develop PPCs than those receiving fixed PEEP settings (24.8% vs. 35.7%; RR = 0.70, CI: 0.58–0.84, $I^2 = 7\%$, p = 0.002).

PaO_2/FiO_2 at the End of Surgery

Based on the results of 20 trials (1,843 patients), patients receiving optimal PEEP had a nearly 56 mmHg higher PaO2/FiO2 ratio at the end of the surgery, then those receiving a fixed level of PEEP (MD = 55.99 mmHg, 95% CI: 31.78–80.21, I2 = 91%, $p < 0.001$).

[DRZ1] megjegyzést írt: You used this method (1843 patients) to present data in this first study, but you used another one in the second study (n = …). Maybe you should unify. What is your opinion?

Titrated PEEP Values in the SGs

We analyzed and compared the PEEP levels in each group. Based on data from 20 studies (1,471 patients), the PEEP level was approximately 6 cm H_2O higher in the individually titrated PEEP group compared to the group receiving a predefined PEEP setting (MD = 6.27 cm H_2O, CI: 4.30–8.23, $I^2 = 98.0\%$, $p \leq 0.001$).

Vasopressor Requirement

Data from 14 studies (1,261 patients) indicated a higher prevalence of vasopressor use when individually titrated PEEP was applied compared to the CG receiving any vasopressor agent (58.9% vs. 54.7%). This was further supported by analysis, which showed a tendency toward a higher risk of requiring vasopressors with individually titrated PEEP. However, this finding did not reach statistical significance (RR = 1.07, 95% CI: 1.00–1.14, $I^2 = 0\%$, p = 0.062).

Our analysis found no significant differences between groups regarding the maximum norepinephrine doses, or the amount of vasopressors (ephedrine, phenylephrine) used (MD = −0.19 mcg/min/kg 95% CI: −2.40–2.01; MD = 0.22 mg 95% CI: −1.23–1.68; MD = 0.00 mcg 95% CI: −0.00–0.00).

Respiratory Mechanics

Data on dynamic and static compliance (Cdyn, Cstat) from 20 studies (1,573 patients) at the end of surgery suggested an increase in dynamic compliance, though it did not reach statistical significance (Cdyn: MD = 3.26 mL/cm H_2O, 95% CI: −0.08 to 6.61, $I^2 = 96\%$, p = 0.055). However, the increase in static compliance was statistically significant (Cstat: MD = 11.92 mL/cm H_2O, 95% CI: 6.40 to 17.45, $I^2 = 85\%$, p < 0.001).

Driving pressure (dP) at the end of surgery, based on 15 studies including 1,530 patients, was significantly lower with titrated PEEP settings compared to a fixed PEEP strategy (MD = −2.75 cm H_2O, 95% CI: −3.95 to −1.55, $I^2 = 89\%$, p < 0.001).

Plateau pressure (Pplat) (18 studies, 1,762 patients), was approximately 2.5 cm H_2O higher in patients receiving individually titrated PEEP, a statistically significant difference compared to the CG (MD = 2.49 cm H_2O, 95% CI: 1.08 to 3.90, $I^2 = 92\%$, p = 0.002).

Duration of Anaesthesia and Surgery

According to our analysis, both the duration of anesthesia (19 studies, 1,822 patients) and the duration of surgery (24 studies, 2,096 patients) were longer among patients receiving individualized PEEP. However, statistical significance was observed only for the latter outcome, with neither reaching a mean difference of 5 minutes (MD = +0.49 minutes, 95% CI: −6.08 to 7.06; MD = +4.82 minutes, 95% CI: −2.84 to 6.81, respectively).

Length of Hospital Stay, Length of ICU Stay, and Mortality

Our data on the length of hospital stay (14 studies, 1,699 patients) and the length of ICU stay (4 studies, 626 patients), showed no significant differences between the study groups (SGs) (MD = −0.06 days, 95% CI: −0.71 to 0.59, I^2 = 71.0%, p = 0.855, and MD = −0.10 days, 95% CI: −2.70 to 2.51, I^2 = 77%, p = 0.914, respectively).

The 28-day mortality rates were reported in 5 studies (850 patients), and the overall risk ratio (RR) showed no significant differences between the groups (RR = 1.0, 95% CI: 0.41–2.46, I^2 = 0%, p = 0.991).

Finally, there were outcomes for which data were insufficient to conduct a meta-analysis, such as oxygen saturation, postoperative IL-6, C-reactive protein (CRP), and procalcitonin (PCT).

4.1.4. Risk of bias and quality of evidence assessment

According to the recommendations, the authors assessed the risk of bias in the included studies using the Cochrane Collaboration Risk of Bias tool. They suggested "some risk" for the majority of the studies and a ’low risk’ of bias for some. During the GRADE quality assessment, the level of evidence was ’high’ regarding the duration of anesthesia and ’moderate’ for PPCs, the PaO2/FiO2 ratio, the need for vasopressors, the duration of surgery, and the doses of ephedrine. It was ’low’ for outcomes such as the PEEP value used, the maximum dose of norepinephrine (NE), Cdyn, Cstat, dP, Pplat, LOH, LO ICU, and phenylephrine used, and ’very low’ level of evidence for 28-day mortality. Any disagreements were resolved by a third author during both processes.

4.2. Study II. – Hemoadsorption as Adjuvant Therapy in ARDS

4.2.1. Systematic search and selection

The initial and un updated systematic literature search identified a total of 1,653 records. Following a two-stage screening process conducted independently by two reviewers—initially based on titles and abstracts, followed by full-text assessment—26 studies met the eligibility criteria and were included in the final analysis.

4.2.2. Baseline characteristics

The included studies primarily comprised case reports, case series, and retrospective analyses, along with two randomized controlled trials. Collectively, these studies encompassed data from 243 patients.

4.2.3. Outcomes

Data from eight studies (162 patients) evaluating the primary outcome demonstrated a statistically significant enhancement in the PaO_2/FiO_2 ratio following HA therapy, with a mean difference (MD) of 68.93 mmHg (95% CI: 28.79 to 109.06; $I^2 = 96\%$; $p = 0.005$). Additionally, aggregated results from seven individual case reports (n = 7) indicated a

[DRZ2] megjegyzést írt: please see my earlier comment

Inflammarory Biomarkers

Seven studies involving COVID-19 patients (132 patients) demonstrated a significant reduction in serum CRP levels following treatment, with an MD of −45.02 mg/dL (95% CI: −82.64 to −7.39; $I^2 = 95\%$; $p = 0.026$). Serum interleukin-6 (IL-6) levels were assessed in seven studies (124 patients), revealing a non-significant trend toward reduction after HA therapy (MD = −241.17 pg/mL; 95% CI: −570.38 to 88.05; $I^2 = 77\%$; $p = 0.123$). These results on CRP and IL-6 levels were further supported by the analysis of pooled individual case data ($p = 0.008$ and $p = 0.016$ respectively).

Effects on vasopressor requirement and lactate

Data from seven studies (160 patients) assessing norepinephrine (NE) requirements before and after HA therapy demonstrated a significant reduction following treatment, with a MD of −0.23 µg/kg/min (95% CI: −0.43 to −0.04; $I^2 = 99\%$; $p = 0.028$) Additionally, analysis of four studies (126 patients) that included a CG indicated a non-significant trend toward lower vasopressor requirements in patients treated with HA compared to those receiving standard medical care (MD = −0.12 µg/kg/min; 95% CI: −0.29 to 0.05; $I^2 = 74\%$; $p = 0.108$). In this comparison, the certainty of evidence was rated as low. Serum lactate levels based on eight studies were also significantly reduced after HA therapy, with a mean difference of −1.63 mg/L (95% CI: −3.05 to −0.21; $I^2 = 96\%$; $p = 0.030$).

Length of Stay and Mortality

Based on data from three studies (92 patients) comparing HA therapy to standard medical treatment, no significant difference was observed in ICU length of stay (MD = 1.17 days; 95% CI: −18.61 to 20.96; $I^2 = 64\%$; p = 0.82), with the certainty of evidence rated as low. Mortality data were reported in five studies, though the follow-up periods ranged from 28 to 90 days. A non-significant reduction in mortality was noted in the HA group (RR = 0.64; 95% CI: 0.11 to 3.65; $I^2 = 80\%$; p = 0.52), with the certainty of evidence rated as very low.

Safety Outcomes, and Subgroup Analysis

No device-related adverse events were reported, irrespective of the platform used. We conducted a subgroup analysis on COVID-19 patients, and after excluding non-COVID cases, only the PaO_2/FiO_2 ratio improvement remained significantly better.

4.2.4. Risk of bias and quality of evidence assessment

The risk of bias evaluations was assessed with the Rob-2 tool (randomized controlled trials), with the Robins I tool (retrospective studies).

The JBI critical appraisal tools for case reports and case series. The GRADE summary of findings for the included studies are shown on

5. CONCLUSIONS

5.1. Study I. – Individualized vs. fixed intraoperative PEEP settings

Our findings indicate that individualized PEEP titration significantly lowers the risk of PPCs and improves oxygenation compared to a conventional fixed PEEP strategy. It may also enhance lung mechanics. Based on these results, further research is needed in a more homogeneous population, with standardized titration methods, consistent definitions, uniform outcome measurement timepoints, and comparisons across various preset PEEP levels.

5.2. Study II. – Hemoadsorption as Adjuvant Therapy in ARDS

Based on our findings, hemoadsorption therapy in patients with ARDS appears to be safe and is associated with improved oxygenation and a reduction in inflammatory mediators. However, these conclusions are supported by a low level of evidence.

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