JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v13i4.44956
JKD (DMJ), Volume 13, Number 4, July 2024 : 182-190

COMPARISON OF INTRAVENOUS INDOCYANINE-GREEN AND INFLATION-DEFLATION METHOD IN LUNG SEGMENTECTOMY: A META-ANALYSIS

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ABSTRACT

Background: Inflation-deflation technique had been a conventional method for delineating the intersegmental plane during lung segmentectomy. Over the last decade, the use of icg has shown a significant increase as an alternative method. According to the European Society of Thoracic Surgeons' (ESTS) newly released expert consensus recommendations, Systemic ICG is the preferred method for performing ISP delineation. **Objective:** This study aimed to determine the safety of intravenous ICG in lung segmentectomy compared to inflation-deflation method. **Methods:** PubMed, Science direct, and Scilit were systematically reviewed. Studies comparing ICG with inflation-deflation method in lung segmentectomy were included. The main outcome included operation time while blood loss, length of hospital stay, and air leakage event became secondary. Odd Ratio (OR) and Mean Difference (MD) with 95% of Confidence Interval (CI) were applied for dicotomous and continous variable, respectively. Heterogeneity was assessed using Cochrane Q and I statistics, as reviewers also manually tested for heterogeneity with sensitivity analysis. **Results:** Six studies with a total of 839 patients were retrieved. All of them were retrospective comparative studies, mainly with a diagnosis of pulmonary nodules. Most studies utilized peripheral vein injections of 2.5 mg/mL ICG solution, which had a dosage range of 3–10 mL. Intravenous ICG administration was associated with a noticable operation time [MD = -19.30, 95% CI -28.29 to -10.31, $p < 0.00001$], length of hospital stay [MD = -0.61; 95% CI -1.16 to -0.06, $p = 0.03$], as well as a significant OR observed in the number air leakage [OR = 0.39; 95% CI 0.20 to 0.75, $p = 0.005$]. Meanwhile, there was no significant difference in the amount of bleeding between the inflation-deflation group and the ICG group [MD = -5.18, 95% CI -12.08 to 1.72, $p = 0.14$]. **Conclusion:** This meta-analysis has demonstrated statistically that the duration of surgery, length of hospital stay, and the probability of postoperative air leak are significantly lower with the application of ICG in lung segmentectomy.
Keywords: *Indocyanine-green, Inflation-deflation, Lung, Segmentectomy, Surgery*

INTRODUCTION

The second most frequent cancer and the main cause of cancer-related deaths in the US is lung cancer. Following the Lung Cancer Study Group's randomized controlled trial, the standard of care for the treatment of early-stage non-small cell lung cancer (NSCLC) has been anatomic lobectomy combined with mediastinal lymph node biopsy[1]. Compared to lobectomy, anatomical segmentectomy is thought to provide superior pulmonary function preservation[2]. The rapid rise of computed tomography (CT) screening for lung cancer, which enables early detection, has led to a surge in the practice of segmentectomy. This procedure is motivated by the belief that decreasing resected lung volume may increase the likelihood of subsequent resections in case of second primary lung cancer[3].

On the other hand, precise segmentectomy presents more challenges than lobectomy due to anatomical differences in lung segments' bronchi and blood arteries and intersegmental boundary lines[4]. Techniques for locating these lines include inflation-deflation and near-infrared or infrared fluorescence imaging with intravenous indocyanine green (ICG). Nevertheless, the inflation-deflation technique can be technically unstable and challenging, especially in video-assisted thoracic surgery (VATS) as the lung may fail to deflate enough, potentially affecting operative vision[5]. Moreover, the advanced collateral respiratory structures in the lung parenchyma making VATS using the inflation-deflation method cannot be done with blunt dissection and fingers, especially in patients with emphysema[6-7].

For over 50 years, ICG fluorescent dye has been utilized in clinical settings. After intravenous administration, it binds firmly to serum proteins and absorbs near-infrared light. Previous study suggests that the variations in blood flow inside the lung can be seen by combining an ICG injection with an infrared (IR) thoracoscopy[8]. It was shown that either IR or near-infrared (NIR) thoracoscopy and ICG may be used to find the intersegmental line without inflating the lung[9].

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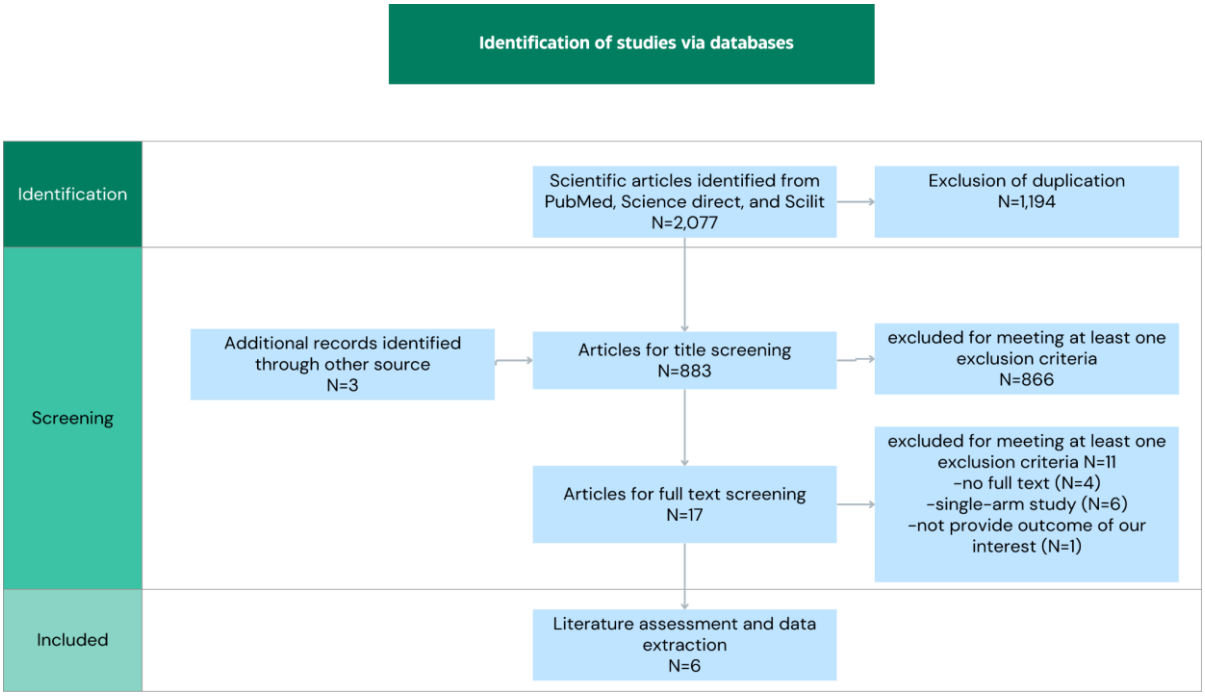

Figure 1 PRISMA flow diagram

The objective of the present study was to perform a systematic review and meta-analysis of the available literature to determine the safety of intravenous ICG in lung segmentectomy compared to inflation-deflation method.

METHODS

Search Strategy

The study results were reported in compliance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines [10]. The datasets used and/or analyzed in the current study are available from the corresponding author upon reasonable request. PubMed, Science direct, and Scilit were systematically searched from inception to May, 18 2024. The structured search strategies using a combination of the keywords "lung segmentectomy," "efficacy," "safety," "time," "complication," and the MeSH terms "indocyanine green" and "Lung Segmentectomy.". The search was restricted to human subjects, but there was no restriction in terms of language. After the relevant studies had been identified, the duplicate reports were removed, and the abstracts of the remaining studies were independently reviewed.

Data Extraction

Two independent researchers evaluated the eligibility of all of the identified publications and extracted the data using a standardized Excel file. The following information was extracted: author, publication year, type of study, country, sample size, patients' age, dose of regiment, and the outcome data (operation time (OT), blood loss (BL), hospital stay (HS), and complications). If the studies did not provide the direct available data, we contacted the corresponding author for this information.

Quality Assessment

We assessed the probability of bias of the included studies using the Newcastle-Ottawa Scale (NOS). The NOS criteria were used to evaluate the likelihood of bias in non-randomized research and consist of three main components: selection, comparability and outcome. The highest possible score is 9 with the higher score indicating better quality studies[11]. All articles were scored by two reviewers.

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Statistical Analysis

The mean difference with 95% CI was used to measure the absolute difference between the mean value in both groups (OT, BL, and HS), and odd ratios (OR) with 95% CI were used to estimate the dichotomous variables (complication). Heterogeneity among the included studies was assessed using Cochrane Q and I statistics[12]. $p < 0.1$ or I 2 > 50% indicated evidence of heterogeneity[12]. Pooled estimates were calculated using a fixed-effects model[13] or a randomized-effects model[14], depending on the heterogeneity among the included studies. For clinical heterogeneity, we conducted a sensitivity analysis by excluding each study one by one to explore the influence of each individual study on the overall estimate. The assessment of publication bias was performed using Begg[15] and Egger[16] tests. $p < 0.05$ was regarded statistically significant, except where a certain p value had been specified. All analyses were performed using Review Manager version 5.4.1[17].

RESULTS

Identification of Eligible Studies

Our search yielded 2,077 relevant studies, 1,194 of which were excluded because they were duplicate publications. We also added 3 manually looked-for studies that did not appear in previous search engine results. After screening the title and abstract, 866 studies were removed because they were reviews, case reports, and/not meeting the PICO criteria in this study, leaving 17 studies for the full-text review. Among the potential studies, 4 were excluded because they do not provide full text, 6 studies were a single-arm study, and 1 studies did not present outcomes of our interest. Finally, 6 studies[4,18-22] with a total number of 839 patients were included in this systematic review and meta-analysis (Fig. 1).

Characteristics of the Included Studies

The main characteristics of the included studies are presented in Table 1. The sample size among the included studies ranged from 60 to 200. Among the included studies, 5 were conducted in China[4,19-22], and 1 in South Korea[18]. All of them were retrospective comparative studies with a diagnosis of pulmonary nodules mainly, confirmed to be lung cancer after surgery[4,18-19,22], another study with chronic lung disease (CLD)[21], and a group of Congenital Pulmonary Airway Malformation (CPAM) in children[20]. This study does not limit the age of the patient as segmentectomy or other thoracic surgery is required in various cases in all age ranges. However, the mean age of the youngest in the included studies in this review was 4.9 months and the oldest was 70.9 years. The majority of studies used 2.5 mg/mL ICG solution with a dose range of 3-10 mL which were injected via a peripheral vein [16-19]. Another study showed the use of a 0.25 mg/kgBW dosage as well as pure doses of 5 to 25 mg ICG[19-20,22]. The NOS score for the non-randomized studies ranged from 8 to 9 points. These demonstrated that these studies were of high quality.

Operation time

The main outcome of this meta-analysis is to compare the duration of segmentectomy using indocyanine-green fluorescence with the inflation-deflation technique. All included studies, presented by the mean and standard deviation of the operation time (in minutes), suggested that the use of ICG in surgery shortens the duration of surgery [MD = -19.30, 95% CI -28.29 to -10.31, $p < 0.00001$] as shown in Fig. 2 (A). A sensitivity analysis was carried out to explore the potential heterogeneity, starting off by excluding a study by Huang et al[20] involving pediatric patients. The results showed a slight change [MD = -17.26, 95% CI -29.96 to -4.57, $p = 0.008$] with the heterogeneity that was still present [$I^2 = 90\%$, $p < 0.00001$]. Thus, we tried to exclude the study by Bae et al from the analysis on the grounds that their study was the only one involving the role of robotics in surgical procedures with estimated points and line of widths that were seemingly different from the other five studies. The overall estimate changed substantially [MD = -26.18, 95% CI -29.45 to -22.91, $p < 0.00001$] and the heterogeneity was reduced [$I^2 = 20\%$, $p = 0.29$].

Blood loss during surgery

Four of the 6 included studies (n = 520) showed the amount of blood loss (mL), either reported "intraoperatively"[19,21] or outcomes derived from perioperative data[20,22]. Figure 2 (B) presented the pooled estimation using a random-effect model showing the use of ICG-based infrared during segmentectomy procedures might minimize bleeding although it was not statistically significant [MD = -5.18, 95% CI -12.08 to 1.72, $p = 0.14$]. In terms of heterogeneity, we tried to

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exclude the study of Huang et al[20] for the reasons also mentioned previously. Apparently, the heterogeneity disappeared [I^2 = 0%, p = 0.61] and the overall effect became significant [MD = -9.92; 95% CI -17.40 to -2.43, p = 0.009]. Much the same when the study by Liu et al was excluded [MD = -1.03; 95% CI -1.90 to -0.15, p = 0.02; I^2 = 0%, p = 0.44]. This may have happened due to the ambiguity in reporting mean or median data in their research .

Hospital stay length

From 5 inspected studies (n = 639), the overall hospital stay (days) was found to be significantly shorter in the ICG-based infrared segmentectomy group [MD = -0.61; 95% CI -1.16 to -0.06, p = 0.03], shown in Fig. 2 (C). The sensitivity analysis remains to be carried out to determine possible transformation in heterogeneity. Although this change was not significant, it has been proposed that the trial by Liu et al[21] may be a factor in the variability of the heterogenity [MD = -0.39; 95% CI -0.79 to -0.01, p = 0.05; I^2 = 0%, p = 0.52].

Complication occurred

Among included studies, the most frequently reported complication was a postoperative air leakage. The air leak specifically occurs when it has appeared more than 2 days in the study by Huang et al[20] or extends for more than 5 days as in the study by Liu et al[21] and 7 days in Sun et al[22]. The odds ratio from four studies (n = 579), as appeared in Fig. 2 (D), illustrated that the probability of air leakage in the ICG-based infrared segmentectomy group was significantly minimal compared to the inflation-deflation procedure [OR = 0.39; 95% CI 0.20 to 0.75, p = 0.005]. Further analysis to evaluate heterogeneity was not performed since the results of four studies had indicated a low and insignificant heterogeneity [I^2 = 19%, p = 0.30].

DISCUSSION

The aim of current meta-analysis is to evaluate intravenous ICG efficacy over the inflation-deflation method in lung segmentectomy. Out of all the different kinds of study evaluating ICG-based infrared in segmentectomy, We chose comparative analytical research. Samples from the population of lung cancer patients were used in most studies. It is also known that egmentectomy was also utilized for other diseases like CLD or CPAM, either with ICG or with the inflation-deflation approach[20-21]. The inflation and deflation (ID) method was commonly used for assessing intraoperative margins during segmentectomy [18]. Moreover, Wang et al reported[24] a modified inflation-deflation method which depends on the reabsorption of oxygen by pulmonary arteries to disclose the inter segmental plane (ISP).

Nevertheless, the inflation-deflation approach is difficult to apply in the restricted space of a single lung segment and it is not optimal in chronic obstructive pulmonary disease[25]. A novel method was presented to visualize nearby segments using a near-infrared camera[26]. A fluorescence demarcation between the targeted (nonfluorescent) and preserved (fluorescent) segments is created by an intravenous injection of ICG following segmental pulmonary artery occlusion or division[26-27]. Since it is often difficult to stain and cut the proper intersegmental line in the brief period of time before the ICG dye is removed, an application of a temporary clamp at the pulmonary vein throughout the lobe was then suggested to extend ICG visualization[28].

Weight-based dosages of ICG ranging from 0.15[29], 0.25[5,20,30], 0.5[31-32], and 5 mg/kgBW [22] were used in the majority of clinical trials. Other studies also shot straight to the universal dose of 25mg intravenously[8,19]. Toxicity studies indicate that a 5.0 mg/kg of ICG injection is safe and well-tolerated[33]. Tokuno et al[34] added since ICG was easily visible intraoperatively, even if it was disseminated at a certain depth from the lung's surface, injection of the extremely periphery bronchi was unnecessary. These traits may have contributed to a lower risk of complication namely pneumothorax[34]. In fact, the ICG administration via peripheral vein has been linked to fewer side effects as well as intraoperative problems, compared to other methods such as CT-guided, without compromising patient safety[35-36].

A recent systematic review found that up to 94% of intravenous ICG instances showed clear ISP visualization for segmental lung resections [37]. Fan et al.[4] also mentioned that because ISP was precisely identified, ICG-navigated segmentectomy resulted in acceptable surgical margins, no postoperative complications, and time savings. Studies found that while inflation-deflation method required a deeper

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incision into the hilum, which may increase the likelihood of protracted air leaks, however, the overall complication rate was similar between the 2 groups[18,20-22]. A number of additional complications, such the prevalence of atelectasis or lung infections like pneumonia, which were not recorded in all included trials, did not demonstrate a major difference between the two[18-19,21]. The amount of blood loss from the two groups was likewise observed to differ insignificantly in the current analysis as well. Additionally, neither group experienced any significant postoperative problems or deaths following surgery[20-21].

Perioperative events will ultimately impact the length of hospital stay. In fact, our meta-analysis shows that ICG-based segmentectomy has led to significantly lower odds ratios and mean differences for duration of stay and incidence of air leaks, respectively. The incidence of air leakage defined chest-tube indwelling where the patient may only be discharged one day after the tube is withdrawn and no additional issues arise[20-21], offering another possible cost-saving alternative [37]. In laparoscopic cholecystectomy, Reeves et al[38] showed that shorter operational durations and a reduced conversion rate to open procedures might result in long-term cost savings.

Notewithstanding, one of the significant cost-related issues in ICG operations is the availability of instruments like infrared technology. The consensus-based recommendation from the ESTS in 2023 suggested utilizing near-infrared imaging (NIRI) to define the ISP following systemic injection of ICG[39]. It requires the availability of an infrared camera, which might result in a significant increase in cost[37]. This method also seems to require experts as occasionally the excitation light of the ICG might rouse the illusion that light seems to weaken via the monitor to the surgeon's eyes due to similarities in the nature of anthracosis[40]. At long last, the expert panel agrees that treating pulmonary lesions still calls for routine thoracoscopic surgery performed under fluorescence guidance[25].

We acknowledge that there are limitations in our meta-analysis, such as variations in the two studies' population groups with respect to disease; variations in one study's age groups; and variations in the ICG dosages used in several trials. The limited sample size, variation in outcomes, and discussion, especially on cost-effectiveness or cost-benefit in our meta-analysis suggest the need for larger, more robust studies to assess the feasibility of intravenous ICG-fluorescence segmentectomy.

Table 1. Characteristic of included studies

Study, year of publication	Country	Treatment Regimen	Patient,n	Age (yr/mo), mean ± SD	ICG Dosage	NOS
Feng et al, 2019	China	ICG-based VATS	20	60.55 ± 13.28 yr	25 mg	9
		ID-based VATS	40	60.68 ± 8.29 yr		
Fan et al, 2022	China	ICG-based VATS	100	54 ± 11.25 yr	4–5 mL of 2.5 mg/ml solution	9
		ID-based VATS	100			
Liu et al, 2022	China	ICG-based VATS	92	69.8 ± 52 yr	6–10 mL of 2.5 mg/ml solution	9
		ID-based VATS	92	70.9 ± 3.5 yr		
Sun et al, 2021	China	ICG-based VATS	100	59.8 ± 10.5 yr	5 mg/kgBW	8
		Modified ID-based VATS	92	60.6 ± 7.9 yr		
Huang et al, 2024	China	ICG-based VATS	28	4.99 ± 1.51 mo	0.25 mg/ kgBW	9
		Modified ID-based VATS	56	4.94 ± 1.53 mo		
Bae et al, 2024	South Korea	ICG-based VATS/RATS	58	65.1 ± 8.6 yr	3–5 mL of 2.5 mg/ml solution	8
		ID-based surgery	61	67.9 ± 7.6 yr		

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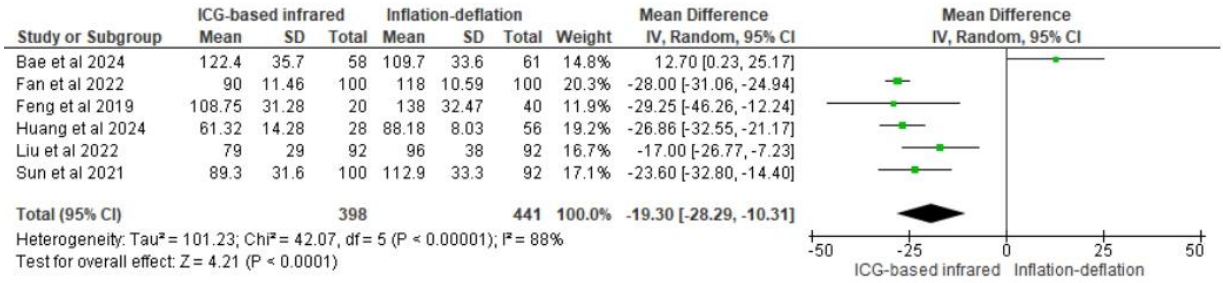
A)



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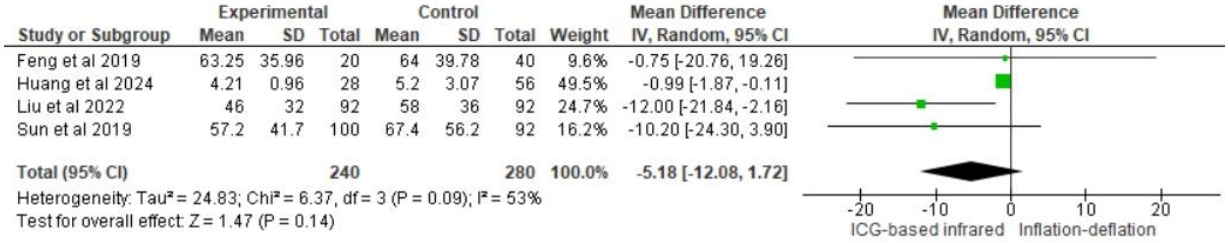

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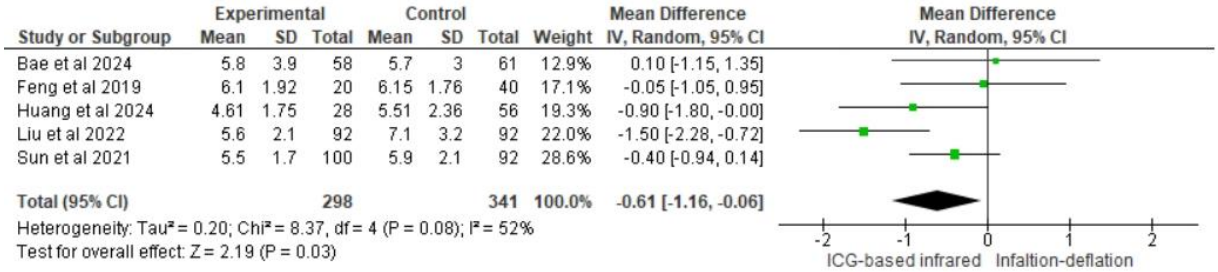

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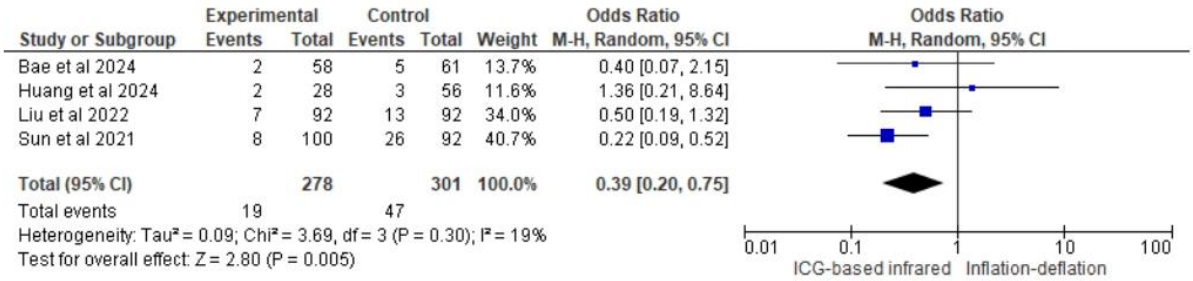

Figure 2. Forest plot presenting the comparison of both groups in the operation time (A); blood loss (B); hospital stay (C), and the complication in form of air leak (D).

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CONCLUSION

The current meta analysis demonstrated that intravenous ICG has an optimal outcome than the inflation-deflation technique when it comes to lung segmentectomy. Surgeons can save operating time by using infrared technology following ICG administration in order to clarify ICP. With less amount of bleeding and odds of perioperative complications, this approach can eventually shorten hospital stays. Large-scale randomized clinical trials in the future are required to confirm our findings.

ETHICAL APPROVAL

This is a meta-analysis, so ethics approval and consent to participate are not needed.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

No specific funding was provided.

AUTHOR CONTRIBUTIONS

H.A.R. and H.A.N.I. contributed to the study design; all of the authors collected the data, performed the data analysis, and prepared this paper.

ACKNOWLEDGMENT

There are no acknowledgments to declare.

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JURNAL KEDOKTERAN DIPONEGORO
(*DIPONEGORO MEDICAL JOURNAL*)
Online : http://ejournal3.undip.ac.id/index.php/medico
E-ISSN : 2540-8844
DOI : 10.14710/dmj.v13i4.44956
JKD (DMJ), Volume 13, Number 4, July 2024 : 182-190

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