

# Effects of propofol and inhalational anesthetics on the optic nerve sheath diameter in patients undergoing surgery in the steep Trendelenburg position: a systematic review and meta-analysis

# Jinkun Yang, Xueping Yang, Xijuan Li, Shan Ou

Department of Anesthesiology, Chengdu First People's Hospital, Chengdu, China

*Contributions:* (I) Conception and design: J Yang; (II) Administrative support: S Ou; (III) Provision of study materials or patients: J Yang; (IV) Collection and assembly of data: J Yang, X Yang; (V) Data analysis and interpretation: J Yang, X Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Shan Ou. Department of Anesthesiology, Chengdu First People's Hospital, 18 Wanxiang North Road, Chengdu, China. Email: composer163@163.com.

**Background:** Optic nerve sheath diameter (ONSD) is recognized as a surrogate indicator of intracranial pressure (ICP) during surgery. Due to the requirements of surgery, the adjustment to the steep Trendelenburg position and the establishment of  $CO_2$  pneumoperitoneum can lead to an increase in ICP, resulting in an increase in the ONSD. Anesthetic agents have different impacts on cerebral blood volume and ICP. The aim of this study was to evaluate the effects of propofol and inhalational anesthetics on the ONSD based on data from randomized controlled trials (RCTs).

**Methods:** The electronic databases of PubMed, EMBASE, Ovid MEDLINE, the Cochrane Library, and other databases were searched systematically using specified keywords from their inception to June 2021. The Chi-square test and I<sup>2</sup> test were used to evaluate the heterogeneity across the studies. The weighted mean difference (WMD) with 95% confidence interval (CI) were adopted to analyze continuous data.

**Results:** A total of 379 patients from 7 studies were involved in this meta-analysis. There were borderline significant differences in the ONSD atT2 between propofol and the control group: T2 (WMD =-0.15, 95% CI: -0.31, -0.00, P=0.005). There were significant differences at T3 (WMD =-0.23,95% CI: -0.42, -0.05, P=0.013) and T4 (WMD =-0.18, 95% CI: -0.29, -0.07, P=0.001). After statistical verification, there was no significant difference in the ONSD at T1 between the 2 groups: T1 (WMD =-0.08, 95% CI: -0.26, 0.10, P=0.368). There were also no significant differences in mean arterial pressure (MAP) (P=0.654, 0.445, 0.698, and 0.562, respectively) and end tidal CO<sub>2</sub> (ETCO<sub>2</sub>) (P=0.081, 0.506, 0.126, and 0.983, respectively) at T1, T2, T3 and T4 between propofol and inhalational anesthetics.

**Discussion:** The findings in the present study indicated that the ONSD during propofol anesthesia was significantly lower than that during inhalational anesthesia after adopting the Trendelenburg position and  $CO_2$  pneumoperitoneum. These analysis results suggest that propofol anesthesia may help to minimize changes in ICP compared to inhalational anesthetics.

**Keywords:** Propofol; inhalational anesthetics; optic nerve sheath diameter (ONSD); Trendelenburg position; CO<sub>2</sub> pneumoperitoneum

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# Introduction

During robot-assisted laparoscopic radical prostatectomy (RLRP) and laparoscopic gynecological surgery, it is necessary to adjust to a steep Trendelenburg position and establish a  $CO_2$  pneumoperitoneum to facilitate the exposure of the surgical area, but this may cause the intracranial pressure (ICP) to be 10 mmHg higher than the baseline (1,2). The increase in ICP leads to a decrease in cerebral perfusion pressure, which is related to postoperative neurological complications, including cerebral ischemia and cerebrovascular diseases (3).

Anesthetic agents can have an impact on ICP during surgery. Dose-related reductions in cerebral blood flow (CBF), ICP, and cerebral metabolic rate have been reported during propofol anesthesia (4,5), while all volatile anesthetics (such as desflurane and sevoflurane, among others) have a direct, dose-dependent vasodilator effect on the cerebral vessels, resulting in an increase in cerebral blood volume and ICP (4,5). It is unclear whether different anesthetics have different influences on ICP due to postural position and CO<sub>2</sub> pneumoperitoneum during surgery.

Several studies have shown that the measurement of optic nerve sheath diameter (ONSD) by ultrasound is a noninvasive and repeatable technique for the evaluation of ICP elevation (6,7). Hence, ONSD can be used as a surrogate for the direct measurement of ICP (8) in real time which is simple, accurate, and rapid (9).

To better understand the effects of propofol and inhalational anesthetics on ICP and to provide clinicians with more distinct guidance, we conducted this systematic review to explore the relationship between anesthetic agents and the ONSD. We present the following article in accordance with the PRISMA reporting checklist (10) (available at https://dx.doi.org/10.21037/apm-21-2363).

# Methods

This review was registered in PROSPERO (CRD42021264559).

# Search strategy

Two researchers (YJK and YXP) performed a systematic search in the electronic databases of PubMed, the Cochrane Library, EMBASE, Ovid MEDLINE, and other databases updated to June 2021. The search keywords were "propofol", "sevoflurane", "desflurane", "inhalational anesthetics", "optic nerve sheath diameter", "trendelenburg position", and " $CO_2$ pneumoperitoneum". The search terms of each database were modified. When there was any conflict between the search results of the 2 researchers (YJK and YXP), it was resolved through discussion and an agreement was reached. Appropriate combinations of keywords related to anesthetic agents and ONSD were selected. The following is an example of a search strategy applied to PubMed:

(((((((((((((((((propofol) OR (propofol[MeSH Terms])) AND (sevoflurane)) OR (sevoflurane[MeSH Terms])) OR (desflurane)) OR (desflurane[MeSH Terms])) OR (inhalational anesthetics)) OR (inhalation anesthetics)) OR (inhalation anesthetics[MeSH Terms])) AND (optic nerve sheath diameter)) OR (trendelenburg)) OR (trendelenburg position)) OR (Head-Down Tilt[MeSH Terms])) OR (Trendelenburg Position[MeSH Terms])) OR (Pneumoperitoneum)) OR (Pneumoperitoneum[MeSH Terms])) OR (Artificial Pneumoperitoneum)) OR (Artificial Pneumoperitoneum]MeSH Terms]).

# Eligibility criteria

Before the systematic review and meta-analysis, all authors had predetermined the inclusion criteria. The inclusion criteria were as follows: (I) the study was a randomized controlled trial (RCT), regardless of the states and language; (II) included patients undergoing surgery in the Trendelenburg position with  $CO_2$  pneumoperitoneum under general anesthesia; (III) the effect of propofol on the ONSD was compared to the effect of inhalational anesthetics on ONSD in the study; (IV) ONSD measured by ultrasound at various time points was depicted in the trial. The exclusion criteria were as follows: (I) non-RCTs; (II) ongoing studies; (III) the full texts of studies were not available; (IV) unable to extract the outcome data for analysis.

#### Data collection and quality assessment

Data extraction was independently performed by 2 researchers (YJK and YXP) according to a standardized Population Intervention Comparison Outcome (PICO) scheme. The extracted information consisted of the year of publication, the first author, study design, type of surgery, intervention, sample size, measure time, and outcome variables. The Cochrane Bias Risk Scale, which covers 7 specific items, was used to assess the methodological quality of these studies (11). The risk of bias for each item

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Figure 1 PRISMA flowchart of the included studies. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

was classified as unclear, low, or high. The methodological quality assessments were conducted independently by 2 researchers, and if there was any conflict, it would be properly resolved by a third researcher (LXJ) based on the original report.

#### Statistical analysis

Stata (version 16, Stata Corporation) software was used for statistical analysis. The bilateral test level of significance for the pooled data was set at  $\alpha$ =0.05. The weighted mean difference (WMD) was used as the analysis statistic for continuous variables, and its 95% confidence interval (CI) was provided. For heterogeneity analyses, data that were significantly homogeneous (P>0.05 and I<sup>2</sup><50.0%) were carefully analyzed with a fixed-effect model. If there was heterogeneity among the study results, the random-effects model was adopted after excluding significant clinical heterogeneity. Sensitivity analysis evaluated the impact of an individual study with a high risk of bias on the stability of the pooled data by excluding one trial at a time (12). Egger's test was performed to assess publication bias, and P<0.05

#### **Results**

#### Literature search

The initial search in PubMed, EMBASE, Ovid MEDLINE, the Cochrane Library, and other databases updated to June 2021 identified 798 reports. Duplication removal reduced the number of reports to 404. After reviewing titles and abstracts, 388 studies were further excluded. After reading the full texts of the remaining 16 reports, 9 of them were excluded for one or more of the following reasons: the article was a review (n=7), or the research data could not be extracted or used for analysis (n=2). The list of included studies was then reviewed and no new eligible studies were found. Finally, a total of 7 RCTs were included in the meta-analysis (13-19). The flow diagram in *Figure 1* illustrates the literature search and trials screening process.

#### Characteristics of the included studies

As shown in *Table 1*, a total number of 798 patients involved in the seven RCTs were enrolled in this metaanalysis (13-19). Among these seven RCTs, six studies used sevoflurane as the inhalational anesthetic for anesthesia

Deferences	Design	The type of surgery	The characteristics of surgery	Intervention		Maaanina tinaa Outaania	
References				Trial	Control	- Measure time	Outcome
Geng <i>et al.,</i> 2021	RCT	Laparoscopic gynecological surgery	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=58	Sevoflurane N=58	[1] [2] [3]	(a) (b)
Yang <i>et al.</i> , 2020	RCT	Laparoscopic gynecological surgery	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=20	Sevoflurane N=20	[1] [2] [3]	(a) (b) (c)
Kim <i>et al.</i> , 2019	RCT	RLRP	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=16	Sevoflurane N=16	[2] [3] [4]	(a) (c)
Lee <i>et al.,</i> 2019	RCT	Robotic or laparoscopic gynecological surgery	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=25	Sevoflurane N=25	[1] [2] [4]	(a) (b) (c)
Sujata <i>et al.</i> , 2019	RCT	Robot-assisted pelvic surgery	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=25	Sevoflurane N=24	[2] [3] [4]	(a)
Yu <i>et al.</i> , 2018	RCT	RALP	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=18	Sevoflurane N=18	[1] [2] [3] [4]	(a)(c)
Choi <i>et al.</i> , 2018	RCT	RALP	Steep Trendelenburg position, $CO_2$ pneumoperitoneum	Propofol N=28	Desflurane N=28	[1] [3] [4]	(a) (b) (c)

Table 1	Characteristics	of the	included	studies
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(a) = ONSD; (b) = MAP; (c) = PETCO2. [1] T1: 0–10 min after changing to the steep Trendelenburg position and introducing a pneumoperitoneum; [2] T2: 30 min after changing to the steep Trendelenburg position and introducing a pneumoperitoneum; [3] T3: 60 min after changing to the steep Trendelenburg position and introducing a pneumoperitoneum; [4] T4: 0–10 min after returning the patient's position to supine. RCT, randomized controlled trial; RLRP, robot-assisted laparoscopic radical prostatectomy; RALP, robot-assisted laparoscopic prostatectomy; ONSD, optic nerve sheath diameter; MAP, mean arterial pressure; ETCO<sub>2</sub>, end-tidal carbon dioxide.

maintenance (13-18) and 1 study used desflurane as the inhalational anesthetic (19). Three out of the 7 trials included patients who underwent laparoscopic gynecological surgery (13,14,16) or robotic or laparoscopic gynecological surgery, three studies included patients who underwent robot-assisted laparoscopic prostatectomy (RALP) or RLRP surgery (15,18,19), and 1 study (robot-assisted pelvic surgery) was not clear (17). The risk of bias in the studies was assessed as described in *Figure 2*. One study had a high level of risk due to a lack of methods for allocation concealment (14). Three studies (15-17) had an unclear risk of bias because of the unclear random sequence generation or allocation concealment (selection bias), or unclear participant and researcher blindness (performance bias). The remaining three studies all had a low risk of bias.

The assessment of the risk of bias in the included studies. (I) Summary of the risk of bias illustrating the authors' judgments on each item of bias risk for each involved study; (II) graph of the risk of bias illustrating the assessment of bias risk for all included studies expressed as a percentage.

# Effects of propofol and inhalational anesthetics on the ONSD

After collecting and analyzing the data of the 7 studies using propofol or inhalational anesthetics in the maintenance of anesthesia (n=379, propofol =190, inhalational anesthetics =189), a random-effects model was used for meta-analysis, and the results suggested that there were borderline significant differences in the ONSD at T2 between propofol and the control group: T2 (WMD =-0.15, 95% CI: -0.31, -0.00, P=0.005). There were significant differences at T3 (WMD =-0.23, 95% CI: -0.42, -0.05, P=0.013) and T4 (WMD =-0.18, 95% CI: -0.29, -0.07, P=0.001) (*Figure 3*). At T1, no significant differences in the ONSD were identified between the two groups after statistical correction: T1 (WMD =-0.08, 95% CI: -0.26, 0.10, P=0.368) (*Figure 3*). Egger's test demonstrated that there was no publication bias in the included studies (*Table 2*).

## Sensitivity analysis

We conducted sensitivity analyses to evaluate the influence



Figure 2 The risk of bias of all the included trials. (A) Risk of bias summary: review authors' judgements about each risk of bias item for each included study. (B) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

of each study on the overall effect estimated by omitting one study at a time from the analysis. The sensitivity analysis to estimate the effects of propofol and inhalational anaesthetics on the ONSD is shown in *Figure 4A,4B*. The results of the sensitivity analysis on the ONSD indicated that no significant effect was observed after excluding any single study and calculating the aggregate outcomes, suggesting that the results were relatively robust.

# Comparison of mean arterial pressure (MAP) and end tidal $CO_2$ (ETCO<sub>2</sub>) between the two groups

The comparison of the MAP and  $ETCO_2$  at each point in time between the two groups is illustrated in *Figures 5* and *6*. There were no significant differences in MAP (P=0.654,

0.445, 0.698, and 0.562, respectively) and ETCO<sub>2</sub> (P=0.081, 0.506, 0.126, and 0.983, respectively) at T1, T2, T3 and T4 between propofol and inhalational anesthetics.

# Discussion

In the current systematic review and meta-analysis of data from 379 patients in 7 RCTs, we found that the ONSD was significantly lower during propofol anesthesia than during inhalation anesthesia at 30 and 60 minutes after changing to the Trendelenburg position and introducing a pneumoperitoneum.

In comparison of conventional measured method for ICP, such as invasive intracranial monitoring which is associated with risk of complications-in particular

Study	WMD (95% CI)	Weight%
T1 Geng et al. 2021 Yang et al. 2020 Lee et al. 2019 Yu et al. 2018 Choi et al. 2018 Total (I-squared = 68.6%, p = 0.013)	0.18 (0.02, 0.34) -0.30 (-0.64, 0.04) -0.11 (-0.48, 0.26) -0.13 (-0.38, 0.12) -0.16 (-0.29, -0.03) -0.08 (-0.26, 0.10)	25.17 14.75 13.47 19.54 27.07 100.00
T2 Geng et al. 2021 Yang et al. 2020 Kim et al. 2019Right Lee et al. 2019Left Lee et al. 2019 Yu et al. 2018 Sujata et al.2018 Total (I-squared = 73.4%, p = 0.001)	$\begin{array}{c} 0.15 \ (0.01, \ 0.29) \\ -0.40 \ (-0.74, \ -0.06) \\ -0.28 \ (-0.44, \ -0.11) \\ -0.24 \ (-0.43, \ -0.05) \\ -0.04 \ (-0.39, \ 0.31) \\ -0.20 \ (-0.43, \ 0.03) \\ -0.16 \ (-0.36, \ 0.04) \\ -0.15 \ (-0.31, \ -0.00) \end{array}$	17.66 10.26 16.79 15.69 10.08 14.22 15.29 100.00
T3 Geng et al. 2021   Yang et al. 2020 Image: Constraint of the second se	$\begin{array}{c} 0.17 \ (0.03, \ 0.31) \\ -0.50 \ (-0.81, \ -0.19) \\ -0.21 \ (-0.40, \ -0.02) \\ -0.28 \ (-0.49, \ -0.06) \\ -0.30 \ (-0.51, \ -0.09) \\ -0.22 \ (-0.45, \ 0.01) \\ -0.37 \ (-0.51, \ -0.23) \\ -0.23 \ (-0.42, \ -0.05) \end{array}$	15.88 11.62 14.67 13.99 14.24 13.78 15.82 100.00
T4 Kim et al. 2019Right Kim et al. 2019Left Lee et al. 2019 Yu et al. 2018 Sujata et al. 2018 Choi et al. 2018 Total (I-squared = 37.1%, p = 0.159) NOTE: Weights are from random effects analysis	-0.30 (-0.51, -0.09) -0.32 (-0.51, -0.13) -0.09 (-0.41, 0.23) -0.11 (-0.37, 0.15) -0.01 (-0.18, 0.16) -0.21 (-0.38, -0.04) -0.18 (-0.29, -0.07)	16.87 18.31 9.07 12.63 21.41 21.71 100.00
l 0.81 0	I 0.81	

Figure 3 Forest plot for effects of propofol and inhalational anaesthetic on ONSD. ONSD, optic nerve sheath diameter.

Table 2 Egger's test

	T1	T2	Т3	T4
Egger's test (WMD)	0.701	0.293	0.261	0.962

hemorrhage or infection, the measurement of ONSD has the advantages of being low cost, with short investigation times, good reproducibility, and bedside availability, and most importantly of being non-invasive and simple (6,20).

Chin *et al.* (8) confirmed the relationship between the ONSD and  $CO_2$  pneumoperitoneum in the Trendelenburg position and found that  $CO_2$  intraperitoneal infusion increased CBF and eventually led to the increase of ICP, and the Trendelenburg position resulted in a higher intrathoracic pressure leading to increased ICP. Kim *et al.* claimed that the ONSD increased immediately after establishing a  $CO_2$  pneumoperitoneum and adjusting

to the steep Trendelenburg position, but then remained unchanged (21).

Sevoflurane has a dose-dependent effect on the relaxation of vascular smooth muscles and vasodilation of intrinsic cerebral vascular, so the CBF increases significantly during sevoflurane anesthesia, leading to increased ICP (22). In addition, it is well known that desflurane causes greater increases in CBF than sevoflurane. However, doserelated decreases in brain metabolic rate, ICP, and CBF have been reported during propofol anesthesia (23,24). In our review, some studies (14,15,17-19) suggested that propofol anesthesia might help to minimize ICP changes after changing to the Trendelenburg position and introducing a pneumoperitoneum, while others (13,16) suggested that the ONSD was slightly larger with propofol anesthesia compared to inhalational anesthesia, or there was no difference in the ONSD between the two general anesthesia maintenance methods. The depth of anesthesia

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Figure 4 Sensitivity analysis of ONSD. (A) Sensitivity analysis of ONSD on T1 and T2. (B) Sensitivity analysis of ONSD on T3 and T4. ONSD, optic nerve sheath diameter.

and the average age of patients may be the cause of the inconsistent results (13,16). According to a previous study, the changes in the ONSD were related to age during RALP. The ONSD variation was greater in older patients than in patients aged less than 63 years (25), which may suggest that self-regulation of ICP is better in younger patients. The depth of anesthesia may affect the changes in CBF, and thus the changes in ICP and ONSD. However, a study by Lee *et al.* (16) only maintained the bispectral index (BIS) in the range of 40–60 during the whole procedure, but did not statistically compare the BIS values between the 2 groups. In our review, sensitivity analysis was conducted by excluding studies one by one, but there was no difference in the analysis outcome.

Whiteley *et al.* reported that the ONSD was positively correlated with MAP (26). Meanwhile, increases in the

partial pressure of arterial carbon dioxide ( $PaCO_2$ ), which has a strong relationship with  $ETCO_2$ , lead to robust and rapid increases in CBF (27). However, no significant differences in MAP and  $ETCO_2$  were observed between the 2 groups, which might have resulted from vasoactive agents and adjusted ventilator settings in both groups.

#### Limitations

Several limitations of this systematic review and metaanalysis should be acknowledged: (I) the quantity of studies and the general combined sample size were relatively small, and the administration of anesthesia varied substantially; (II) the analysis of this study was based on study-level data, without original data from individual patients (contacting the author of the study to obtain the original data was



Figure 5 Forest plot for effects of propofol and inhalational anaesthetic on MAP. MAP, mean arterial pressure.

unsuccessful); (III) heterogeneity existed in the metaanalysis. An attempt to eliminate heterogeneity was made using sensitivity analysis, however, heterogeneity still existed due to the various surgery types, patients' ages, and the administration of anesthesia in the included studies, which is unlikely to be eliminated. As such, the current data should be carefully interpreted, and further studies are required to validate the findings.

## Conclusions

In conclusion, the findings of our study indicated that the ONSD was significantly lower during propofol anesthesia than during inhalational anesthesia after adopting the Trendelenburg position and  $CO_2$  pneumoperitoneum, suggesting that propofol anesthesia may help to minimize ICP changes compared with inhalational anesthetics.

Study ID		WMD (95% CI)	% Weight
T1			
Yang et al. 2020	-	-1.50 (-2.90, -0.10)	35.93
Lee et al. 2019	•	-0.60 (-2.01, 0.81)	35.38
Choi et al. 2018 -		0.00 (-1.57, 1.57)	28.69
Total (I-squared = 0.8%, p = 0.365)	$\diamond$	-0.75 (-1.60, 0.09)	100.00
Т2			
Yang et al. 2020	•	-1.20 (-2.23, -0.17)	39.59
Kim et al. 2019		0.25 (-1.23, 1.73)	27.33
Lee et al. 2019		0.20 (-1.05, 1.45)	33.08
Total (I-squared = 49.3%, p = 0.139)	$\diamond$	-0.34 (-1.35, 0.66)	100.00
ТЗ	:		
Yang et al. 2020	<b>◆ </b> {	-0.90 (-1.91, 0.11)	58.43
Kim et al. 2019	•	-0.38 (-2.11, 1.35)	19.89
Choi et al. 2018 -		0.00 (-1.66, 1.66)	21.68
Total (I-squared = 0.0%, p = 0.636)	$\Diamond$	-0.60 (-1.37, 0.17)	28.76
Τ4			
Kim et al. 2019 —	•	-0.62 (-2.81, 1.57)	36.87
Lee et al. 2019	<u>.</u>	-0.70 (-2.24, 0.84)	48.71
Choi et al. 2018	· · · · ·	<b>4</b> ,00 (-0.48, 8,48)	14.72
Total (I-squared = $48.5\%$ p = 0.143)	+	0.02 (-1.91, 1.95)	100.00
(	-		
NOTE: Weights are from random effects analysis			
-8.48	0	8.48	

Figure 6 Forest plot for effects of propofol and inhalational anaesthetic on ECTCO<sub>2</sub>.

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#### Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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