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Attenuation of increased intraocular pressure with propofol anesthesia: A systematic review with meta-analysis and trial sequential analysis

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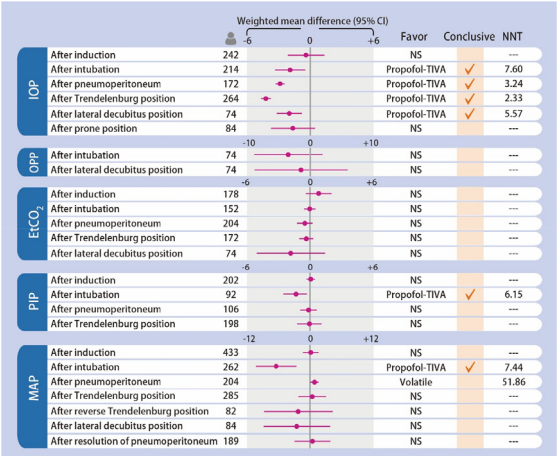
GRAPHICAL ABSTRACT

This study provides an overview of intraocular pressure (IOP) changes due to surgery and anesthesia. Intubation and pneumoperitoneum with CO_2 are associated with increased IOP. Trendelenburg, prone, and lateral decubitus positions are associated with increased IOP. Propofol-based total intravenous anesthesia (TIVA) attenuates elevated IOP, and may reduce postoperative visual loss.



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ABSTRACT

Attenuation of an increase in intraocular pressure (IOP) is crucial to preventing devastating postoperative visual loss following surgery. IOP is affected by several factors, including the physiologic alteration due to pneumoperitoneum and patient positioning and differences in anesthetic regimens. This study aimed to investigate the effects of propofol-based total intravenous anesthesia (TIVA) and volatile anesthesia on IOP. We searched multiple databases for relevant studies published before October 2019. Randomized controlled trials comparing the effects of propofol-based TIVA and volatile anesthesia on IOP during surgery were considered eligible for inclusion. Twenty studies comprising 980 patients were included. The mean IOP was significantly lower in the propofol-based TIVA group after intubation, pneumoperitoneum, Trendelenburg positioning, and lateral decubitus positioning. Moreover, mean arterial pressure and peak

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Propofol
Trial sequential analysis

inspiratory pressure were also lower after intubation in the propofol-based TIVA group. Trial sequential analyses for these outcomes were conclusive. Propofol-based TIVA is more effective than volatile anesthesia during surgery at attenuating the elevation of IOP and should be considered, especially in at-risk patients.

Introduction

Intraocular pressure (IOP) is a crucial parameter in determining the ocular perfusion pressure (OPP) during surgery. IOP is affected by several factors, including aqueous humor and choroidal blood volumes, mean arterial pressure (MAP) [1], extraocular muscle (EOM) tone controlled by central diencephalic centers [2], hypercapnia [3], coughing, straining, and vomiting [4]. In addition, with the advent of laparoscopic and robotic surgery, the physiologic change after carbon dioxide (CO_2) pneumoperitoneum and Trendelenburg positioning also affect IOP [5,6]. An increase in IOP blocks the retrograde transport of neutrophilic factors from the brain [7], reduces ocular blood flow [8], leads to optic nerve edema and ischemia [6,9], and may result in rare but catastrophic postoperative visual loss (POVL) [10].

Anesthetic techniques can help attenuate the increase in IOP in several ways. Most intravenous and volatile anesthetics decrease IOP to some extent. The mechanisms underlying such a phenomenon include decreased choroidal blood volume due to decreased blood pressure [11], decreased ocular wall tension due to relaxation of the EOM via depression of the central diencephalic centers [2], decreased formation of aqueous humor, and the facilitation of aqueous outflow [12,13]. Depolarizing neuromuscular blocking agents (NMBAs) has been known to cause an IOP increase due to fasciculation of the EOM [14], whereas non-depolarizing NMBAs demonstrated a comparatively lower IOP [15]. Short-acting opioids, such as fentanyl, alfentanil [16], sufentanil [17], and remifentanil [18], decrease IOP at induction. Previous studies investigated the effects of propofol-based total intravenous anesthesia (TIVA) and volatile anesthesia (VA) on IOP during surgery, but the results are inconclusive. Thus, we conducted this meta-analysis to evaluate the most recent studies and determine whether different anesthetic techniques for maintenance influence IOP.

Material and methods

Study design

This meta-analysis of randomized controlled trials (RCTs) aimed to evaluate the effects of propofol-based TIVA versus VA on IOP in patients undergoing surgery. This study complies with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [19]. Ethical committee approval was not required for this meta-analysis.

Eligibility criteria

Patients aged $\geq$18 years scheduled for elective surgery were considered eligible for this study. We excluded patients who underwent previous eye surgery or had a medical history of glaucoma, uncontrolled hypertension, chronic obstructive lung disease, a known allergy to anesthetics, or a history taking medications known to alter IOP.

Search strategy

PubMed, EMBASE, Cochrane Library, and Scopus databases were searched through October 2019. MeSH terms including "Intraocular Pressure"[Mesh], "Anesthesia, Intravenous"[Mesh], "propofol" [Mesh], "Anesthesia, Inhalation"[Mesh], "desflurane"[Mesh], "sevoflurane"[Mesh], "isoflurane"[Mesh], "enflurane"[Mesh], "halothane"[Mesh] and "Balanced Anesthesia"[Mesh] were used in combination with plain text to search PubMed. Similar strategies were applied to search the other databases. A detailed description of the search strategies is provided in Supplement 1. The reference lists of the included studies were manually searched to identify additional studies.

Study selection

All studies were selected by two independent reviewers (C.Y. Chang and Y.J. Chien) according to the following criteria, with all conditions being met: (a) study of RCTs involving adult patients undergoing elective surgery; (b) study including clinical outcomes of interest, i.e., IOP. We did not exclude studies by date, region, or language. A third reviewer (M.Y. Wu) provided consensus or discussion in cases of disagreement.

Risk of bias assessment

The methodological quality of the RCTs was assessed using RoB 2, a revised tool for assessing risk of bias in randomized trials [20]. Two reviewers (C.Y. Chang and Y.J. Chien) independently evaluated the methodological quality of the included studies. Disagreements were resolved through consensus or discussion with a third reviewer (M.Y. Wu).

Data collection

Data sets were extracted by two independent reviewers (C.Y. Chang and Y.J. Chien) from each eligible study. The required information included the first author's name, publication year, surgery type, age, sex, regimen for anesthesia induction and maintenance, outcomes of interest, and the protocol for measuring IOP. In circumstances in which the data were insufficient for meta-analysis, efforts were made to contact the authors of the original articles for additional information.

Statistics

The efficacy was estimated for each study by the mean difference and its 95% confidence interval (CI). The weighted mean difference (WMD) and 95% CI were calculated using the inverse variance method with a random-effects model (DerSimonian-Laird estimator [21]). Statistical heterogeneity was assessed by the Cochran Q statistic and quantified by the I^2 statistic. A subgroup analysis was conducted to examine whether different intravenous anesthetics used for induction in the volatile anesthesia group could have confounded the IOP or MAP after induction and intubation. A sensitivity analysis using influence analysis (leave-one-out method) and replacing one outcome measurement with another after the same event but for a different duration (e.g., outcome of interest measured at 5 and 60 min after lateral decubitus positioning [LDP]) was conducted to test the robustness of the results. Trial sequential analysis (TSA) was conducted to estimate the information size required for a conclusive meta-analysis and

evaluate whether the results were subject to type I error due to an insufficient number of included studies [22]. In the TSA, type I error was set at 5%, power was set at 80%, and a heterogeneity adjustment factor was incorporated into the estimation of the required information size (RIS). Cohen's d was calculated in the outcomes with significant intergroup differences yielded from the meta-analysis. Number-needed-to-treat (NNT) was obtained from Cohen's d using Furukawa's method with the control event rate set at 20% [23]. The data synthesis and subgroup analysis were performed using Review Manager software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The sensitivity analysis was performed using R version 3.6.1 with the "meta" package. The TSA was conducted using TSA software (version 0.9.5.10 Beta). P values <0.05 were considered statistically significant.

Results

Study selection

A total of 348 studies were identified from four major databases, including PubMed (n = 49), EMBASE (n = 134), Cochrane (n = 52), and Scopus (n = 113). One additional record was identified through a Google search. After the removal of 179 duplicates, the remaining studies were screened for eligibility. One hundred and forty-one studies were excluded due to being irrelevant, animal studies, conference abstracts, or other reasons listed in Fig. 1. As a result, 29 studies were subjected to full-text review. However, one article was excluded because it did not compare propofol-based TIVA with VA, while another 8 articles were excluded because the full text could not be retrieved. Finally, 20 studies comprising 980 patients were included in the qualitative synthesis. Four studies [24–27] were not included in the further quantitative analysis due to insufficient information despite direct contact of the authors, leaving 16 studies included in the meta-analysis. The detailed PRISMA flow diagram is shown in Fig. 1.

Study characteristics

Eight studies enrolled patients undergoing laparoscopic surgery, including lower abdominal surgery [28], colorectal surgery [29], radical prostatectomy [30], cholecystectomy [31,32], pelvic surgery [32], and gynecological surgery [25,33,34]. Six studies enrolled patients undergoing ophthalmic surgery, including cataract surgery [24,35,36], anterior segment surgery [37], a variety of ophthalmic surgeries [38], and unspecified ophthalmic surgery [39]. Two studies enrolled patients undergoing spine surgery in the prone position [40,41]. Two studies enrolled patients undergoing orthopedic surgery, thoracic surgery, and nephrectomy requiring LDP [42,43]. One study enrolled patients undergoing open gynecological or urological surgery [27]. One study enrolled patients undergoing unspecified non-ophthalmic surgery [26]. Overall, the mean patient age ranged from 30.9 [25] to 74.5 [36] years. In studies in which the patients underwent ophthalmic surgery, the mean age ranged from 56.5 [24] to 74.5 [36] years, while in studies in which the patients underwent laparoscopic surgery, the mean age ranged from 30.9 [25] to 64.9 [30] years. IOP was measured with/without topical anesthetics. In ophthalmic surgery, IOP was measured only in the non-operated eye in five studies [24,35–37,39] and was measured in both eyes before the surgical procedures and in the non-operated eye at the end of surgery in one study [38]. In non-ophthalmic surgery, IOP was measured in both eyes in seven studies [28,29,31,32,40,42,43], while the rest did not specify which eye was measured. All studies used an endotracheal tube for intubation except for one that used a laryngeal mask airway [36] and one that did not specify [26]. Sevoflurane was used for maintenance in the VA group in seven studies [27,28,30,34,35,41,43], desflurane in six studies [26,29,31–33,42], isoflurane in seven studies [24–26,36,37,39,40], and enflurane in one study [38]. Depolarizing NMBA was only used in two studies to facilitate endotracheal intubation [34,39], while non-depolarizing NMBA was used in the rest of the studies. The Hwang et al. study [32] enrolled patients undergoing surgery involving

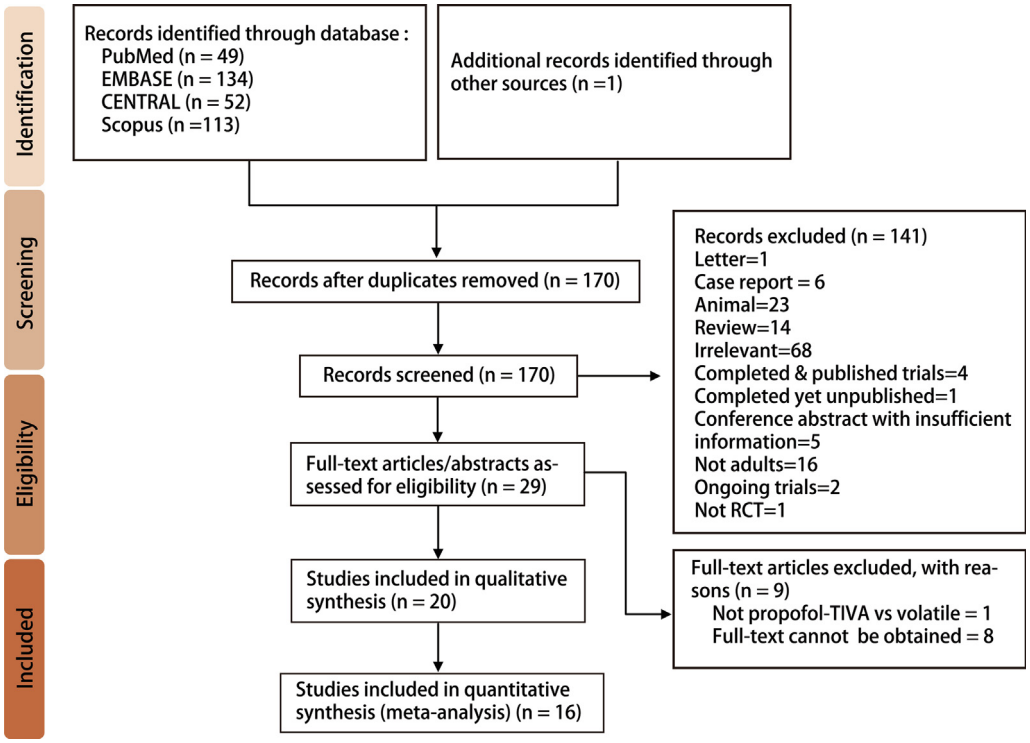

Fig. 1. PRISMA flow diagram.

two different intraoperative positions, Trendelenburg and reverse Trendelenburg, which may have distinct effects on IOP. Accordingly, the Hwang et al. study was considered two individual studies for the further analysis and discussion (denoted as Hwang 2013-T and Hwang 2013-RT, respectively). A brief summary of the study characteristics is shown in Table 1.

Risk of bias

Six studies were considered as having a low risk of bias. Some concerns for bias were raised in 13 studies due to insufficient information for judgment regarding the blinding of the outcome assessors, which could possibly (although unlikely) influence the intergroup outcome assessment. The Mirkheshti [40] study was considered as having a high risk of bias in that the baseline demographics showed significant intergroup differences in IOP (16 ± 3 in the isoflurane group versus 18 ± 5 in the propofol-based TIVA group, P = 0.02) and sex (66.7% male in the isoflurane group versus 26.7% male in the propofol-based TIVA group, P = 0.002), suggesting a problem with the randomization process. The risk of bias graph and summary are shown in Fig. 2.

Intraocular pressure

IOP values were reported in six studies (n = 242) after induction, six studies (n = 214) after intubation, three studies (n = 172) after CO_2 pneumoperitoneum, five studies (n = 264) after Trendelenburg positioning, two studies (n = 74) after LDP, and two studies (n = 84) after prone positioning. The pooled effect estimate showed a significantly lower IOP in the propofol-based TIVA group versus the volatile group after intubation (WMD, −1.87; 95% CI, −3.32 to −0.42; P = 0.01), after CO_2 pneumoperitoneum (WMD, −2.83; 95% CI, −3.27 to −2.38; P < 0.01), after Trendelenburg positioning (WMD, −4.23; 95% CI, −4.70 to −3.75; P < 0.01), and after LDP (WMD, −1.95; 95% CI, −3.15 to −0.75; P < 0.01). In the induction and prone positions, the pooled effect estimate showed no significant difference in IOP (Fig. 3). A sensitivity analysis was also performed with exclusion of the Mirkheshti et al. study [40] because the baseline IOP in the propofol-based TIVA group was significantly higher than that in the volatile-based anesthesia group. The pooled effect estimate after induction remained non-significant after the exclusion of this study (WMD, −0.98; 95% CI, −2.65 to 0.68; P = 0.25).

In the TSA of induction, the cumulative Z-curve surpassed the traditional boundary for statistical significance after the Schafer et al. study [35] and the Sugata et al. study [41] but fell within the traditional boundaries thereafter. The adjusted boundary for the significance threshold was ignored due to too little information use (1.95%). In the TSA of intubation, the cumulative Z-curve surpassed the upper sequential monitoring boundary for the adjusted statistical significance threshold (TSA-adjusted CI, −3.55 to −0.19; calculated Cohen's d, −0.406; NNT, 7.60). In the TSA of LDP, the cumulative Z-curve reached the RIS and surpassed the traditional significance boundary (TSA-adjusted CI, −3.80 to −0.10; calculated Cohen's d, −0.535; NNT, 5.57). In the TSA of CO_2 pneumoperitoneum and Trendelenburg positioning, the estimated RIS was exceeded by the first information; thus, the sequential monitoring boundaries were not renderable. The cumulative Z-curve surpassed the traditional significance boundary (calculated Cohen's d, −0.862; and NNT, 3.24 in CO_2 pneumoperitoneum; calculated Cohen's d, −1.168; and NNT, 2.33 in Trendelenburg positioning). In the TSA of the prone position, the estimated RIS was not reached by the cumulative Z-curve and the cumulative Z-curve did not surpass the traditional boundary (TSA-adjusted CI was −6.04 to 2.81) (Suppl. Fig. S2).

In the propofol-TIVA group, propofol was used for induction in all studies. However, in the VA group, etomidate was used in two studies [36,37], thiopental in three [29,38,42], and propofol in one [43] for induction. The subgroup analysis showed that IOP after intubation in the propofol-TIVA group was significantly lower than that in the VA group with thiopental as the induction agent (WMD, −2.94; 95% CI, −4.42 to −1.46; P < 0.01). However, IOP was not significantly different in the propofol-TIVA group versus the VA group with etomidate (WMD, −0.39; 95% CI, −3.62 to 2.85; P = 0.82) and propofol (WMD, −2.00; 95% CI, −5.31 to 1.31; P = 0.24) as the induction agent (Suppl. Fig. S3).

Ocular perfusion pressure

Only two studies reported ocular perfusion pressure (OPP) measured after intubation and LDP. The pooled effect estimate showed no significant difference after intubation (WMD, −3.39; 95% CI, −8.85 to 2.07; P = 0.22) and LDP (WMD, −1.36; 95% CI, −8.79 to 6.07; P = 0.72) (Fig. 4). In the TSA of intubation, the cumulative Z-curve did not reach the estimated RIS and did not surpass the traditional boundary for statistical significance or the sequential monitoring boundary for the adjusted significance threshold (TSA-adjusted CI, −17.23 to 10.44). In the TSA of LDP, the cumulative Z-curve did not surpass the traditional boundary for statistical significance. The sequential monitoring boundary for the adjusted significance threshold was ignored due to too little information used (1.64%) (Suppl. Fig. S4). In the sensitivity analysis, we replaced the OPP measured at 5 min after the adoption of LDP with that measured at 1 h after LDP reported in the Yamada et al. [43] study to evaluate if the effect of the propofol-based TIVA and the volatile-based anesthesia on OPP was influenced by the duration of the positional change. The intergroup difference in the pooled effect estimate remained non-significant (WMD, 2.56; 95% CI, −2.64 to 7.75; P = 0.33).

End-tidal CO_2

End-tidal CO_2 was investigated in four studies (n = 178) after induction, four (n = 152) after intubation, four (n = 204) after pneumoperitoneum, three (n = 172) after Trendelenburg positioning, and two (n = 74) after LDP. The pooled effect estimate showed no significant difference in IOP after induction (WMD, 0.83; 95% CI, −0.39 to 2.05; P = 0.18), after intubation (WMD, −0.02; 95% CI, −0.55 to 0.52; P = 0.96), after pneumoperitoneum (WMD, −0.48; 95% CI, −1.22 to 0.25; P = 0.20), after Trendelenburg positioning (WMD, −0.34; 95% CI, −1.00 to 0.32; P = 0.32), and after LDP (WMD, −1.82; 95% CI, −5.07 to 1.43; P = 0.27) (Fig. 5).

In the TSA, the cumulative Z-curve did not reach the estimated RIS and did not surpass the sequential monitoring boundary for the adjusted significance threshold after induction (TSA-adjusted CI, −1.92 to 3.58), after pneumoperitoneum (TSA-adjusted CI, −2.29 to 1.32), after Trendelenburg positioning (TSA-adjusted CI, −3.03 to 2.36), and after LDP (TSA-adjusted CI, −15.09 to 11.44). In the TSA of intubation, the cumulative Z-curve did not surpass the traditional significance boundary, and the sequential monitoring boundary for adjusted significance threshold was ignored due to too little information used (0.07%) (Suppl. Fig. S5).

Peak inspiratory pressure

Peak inspiratory pressure (PIP) was analyzed in four studies (n = 202) after induction, two (n = 92) after intubation, two (n = 106) after pneumoperitoneum, and four (n = 198) after Trendelenburg positioning. The pooled effect estimate showed no significant intergroup difference in IOP after induction (WMD, 0.07; 95% CI, −0.33 to 0.47; P = 0.74), after pneumoperitoneum (WMD,

Table 1
Study characteristics.

Study	Surgery	Position	Number		VA	Age		Sex		Regimen		Airway	Tonometer
			P-TIVA (n)	VA (n)		P-TIVA	VA	M (n)	F (n)	P-TIVA	VA		
Kim 2019	Arthroscopic shoulder surgery	Lateral decubitus	23	23	Desflurane	59.22(7.70)	59.17(8.50)	21	25	Induction: propofol 1.5–2.5 mg/kg, remifentanil continuous infusion and rocuronium 1 mg/kg. Maintenance: continuous infusion of 2% propofol and remifentanil. Propofol was administered via a TCI system with Cet 2.5–5 mg/ml.	Induction: thiopental 5–6 mg/kg, remifentanil continuous infusion and rocuronium 1 mg/kg. Maintenance: Desflurane 5–8 vol% and continuous infusion of remifentanil using a TCI system with Cet 3–6 ng/ml.	ETT	Tono-Pen® AVIA, Reichert Technologies, Depew, NY, USA
Kaur 2018	Lower abdominal laparoscopic surgery	25°–30° Trendelenburg position	30	30	Sevoflurane	30.53(11.05)	31.87(11.81)	29	31	Induction: propofol 1.5 mg/kg, fentanyl 2 μg, midazolam 1 mg, atracurium 0.5 mg/kg. Maintenance: propofol infusion 5–10 mg/kg/h	Induction: propofol 1.5 mg/kg, fentanyl 2 μg, midazolam 1 mg, atracurium 0.5 mg/kg. Maintenance: sevoflurane 1–4 vol%	ETT	Schiotz tonometer
Seo 2018	Laparoscopic anterior resection of the sigmoid colon; laparoscopic low anterior resection of the rectum	Supine-Trendelenburg (30°) with right tilt (10°–15°)-reverse Trendelenburg (20°–25°) with right tilt-Trendelenburg with right tilt	23	23	Desflurane	58.43(7.39)	59.61(9.67)	30	16	Induction: propofol 1.5–2.5 mg/kg, rocuronium 1 mg/kg. Maintenance: propofol TCI (Cet: 2.5–5 μg/mL), remifentanil TCI (Cet:3–6 ng/mL).	Induction: thiopental 5–6 mg/kg, rocuronium 1 mg/kg. Maintenance: desflurane 5–8 vol%, remifentanil TCI (Cet:3–6 ng/mL).	ETT	Tono Pen® AVIA, Reichert Technologies, Depew, NY, USA
Mirkheshti 2017	Lumbar disc herniation surgery	Prone	30	30	Isoflurane	46.5(12)	47.3(9)	28	32	Induction: thiopental 5 mg/kg, fentanyl 2 μg/kg, midazolam 0.02 mg/kg, atracurium 0.5 mg/kg. Maintenance: propofol 100–200 μg/kg/min	Induction: thiopental 5 mg/kg, fentanyl 2 μg/kg, midazolam 0.02 mg/kg, atracurium 0.5 mg/kg. Maintenance: isoflurane 1%.	ETT	Tono-Pen AVIA, Reichert, USA
Yamada 2016	Sevoflurane group: lung operation, hip replacement, femoral plate removal Propofol group: lung operation, nephrectomy	Lateral decubitus	14	14	Sevoflurane	66.1(7.5)	63.5(16)	13	15	Induction: propofol TCI (Cet: 3.0–5.0 μg/ml), remifentanil 0.2–0.5 μg/kg/min, vecuronium (0.12–0.15 mg/kg) or rocuronium (0.65–0.9 mg/kg). Maintenance: propofol TCI (Cet: 2.8–4 μg/ml), fentanyl 50–100 μg bolus and/or remifentanil 0.1–0.3 μg/kg/min infusion as needed.	Induction: 1.8–2.5 mg/kg propofol bolus, remifentanil 0.2–0.5 μg/kg/min, vecuronium (0.12–0.15 mg/kg) or rocuronium (0.65–0.9 mg/kg). Maintenance: sevoflurane 1.5–2.0 vol%, fentanyl 50–100 μg bolus and/or	ETT	Tono-Pen® XL Applanation tonometer (Reichert, Depew, NY, USA)

(*continued on next page*)

Table 1 (*continued*)

Study	Surgery	Position	Number		VA	Age		Sex		Regimen		Airway	Tonometer
			P-TIVA (n)	VA (n)		P-TIVA	VA	M (n)	F (n)	P-TIVA	VA		
											remifentanil 0.1–0.3 μg/kg/min infusion as needed.		
Montazeri 2015	Cataract surgery	–	67	67	Isoflurane	With remifentanil: 58.7(13.4) With normal saline: 62.7 (7.1)	With remifentanil: 54.2(12.3) With normal saline: 60.6 (13.9)	50	84	Induction: thiopental 5 mg/kg, remifentanil 1 μg/kg, atracurium 0.5 mg/kg. Maintenance: propofol 100 μg/kg/min with either remifentanil 0.1 μg/kg/min or normal saline.	Induction: thiopental 5 mg/kg, remifentanil 1 μg/kg, atracurium 0.5 mg/kg. Maintenance: isoflurane with either remifentanil 0.1 μg/kg/min or normal saline.	ETT	Handheld applanation tonometer
Yoo 2014	Robot-assisted laparoscopic radical prostatectomy	30° Trendelenburg position	33	33	Sevoflurane	64.7(8.3)	65.1(6.7)	–	–	Propofol TCI (Cet: 2–5 μg/ml) and remifentanil TCI (Cet: 2–5 ng/ml) for induction and maintenance. Rocuronium 0.6 mg/kg for intubation, rocuronium 0.15 mg/kg during maintenance as needed.	Induction: propofol 1.5 mg/kg bolus, remifentanil, rocuronium 0.6 mg/kg. Maintenance: sevoflurane 1.5–2.5 vol%, remifentanil TCI (Cet: 2–5 ng/ml), rocuronium 0.15 mg/kg as needed.	ETT	Tono-Pen® XL, Medtronic, Jacksonville, FL, USA
Asuman 2013	Laparoscopic cholecystectomy	15° reverse Trendelenburg	14	18	Desflurane	49.57(9.93)	46.33(11.32)	11	21	Induction: propofol 2 mg/kg, rocuronium 0.6 mg/kg. Maintenance: propofol infusion 5–10 mg/kg/h, fentanyl 0.5–1 μg/kg as needed	Induction: thiopental 5 mg/kg, rocuronium 0.6 mg/kg. Maintenance: desflurane 3–6 vol%, fentanyl 0.5–1 μg/kg as needed	ETT	Shioetz tonometer
Hwang 2013-RT	Laparoscopic cholecystectomy	20° reverse Trendelenburg position	25	25	Desflurane	51(14)	54(15)	–	–	Induction: propofol TCI (Cet: 4 mg/mL), alfentanil 6 mg/kg, rocuronium 0.6 mg/kg. Maintenance: propofol TCI (Cet: 2–4 mg/mL).	Induction: thiopental 5 mg/kg, alfentanil 6 mg/kg, rocuronium 0.6 mg/kg. Maintenance: desflurane 4–8 vol%.	ETT	Tono-penXL (Medtronicsolan, Jacksonville, FL)
Hwang 2013-T	Pelvic laparoscopy	20° Trendelenburg position	25	25	Desflurane	42(11)	41(8)	–	–	Induction: propofol TCI (Cet: 4 mg/mL), alfentanil 6 mg/kg, rocuronium 0.6 mg/kg. Maintenance: propofol TCI (Cet: 2–4 mg/mL).	Induction: thiopental 5 mg/kg, alfentanil 6 mg/kg, rocuronium 0.6 mg/kg. Maintenance: desflurane 4–8 vol%.	ETT	Tono-penXL (Medtronicsolan, Jacksonville, FL)
Sugata 2012	Prone spine surgery	Prone	12	12	Sevoflurane	68(12)	69(10)	14	10	Induction: TCI doses of propofol and remifentanil 0.2–0.3 mg/kg/min, vecuronium or rocuronium to facilitate intubation. Maintenance: TCI of propofol, fentanyl, and remifentanil 0.15–0.2 mg/kg/min.	Induction: propofol 1.5–2.5 mg/kg, remifentanil 0.2–0.3 mg/kg/min, vecuronium or rocuronium to facilitate intubation. Maintenance:	ETT	Tonopen XL hand-held tonometer (Medtronic SOLAN, Jacksonville, FL)

Table 1 (*continued*)

Study	Surgery	Position	Number		VA	Age		Sex		Regimen		Airway	Tonometer
			P-TIVA (n)	VA (n)		P-TIVA	VA	M (n)	F (n)	P-TIVA	VA		
											sevoflurane (concentration no specified), fentanyl, and remifentanil 0.15–0.2 mg/kg/min		
Park 2006	Laparoscopic gynecological surgery	10° Trendelenburg position	21	21	Desflurane	42.0(11.1)	40.6(8.3)	0	42	Induction: propofol TCI (Cet: 4 μg/ml), alfentanil 6 μg/kg, rocuronium 0.6 mg/kg. Maintenance: propofol TCI (Cet: 2.5–4 μg/ml)	Induction: thiopental 5 mg/kg, alfentanil 6 μg/kg, rocuronium 0.6 mg/kg. Maintenance: desflurane 4–8 vol%.	ETT	Tono-penRXL, Medtronicsolan, Jacksonville, FL, USA).
Son 2005	Laparoscopic hysterectomy	15°–20° Trendelenburg	15	16	Sevoflurane	42.7(6.1)	44.3(7.6)	–	–	Induction: propofol TCI (Cet: 5 μg/ml), fentanyl 1.5 μg/kg, succinylcholine 1 mg/kg. Maintenance: propofol TCI (Cet: 3–4.5 μg/ml), vecuronium	Induction: thiopental 5 mg/kg, fentanyl 1.5 mg/kg, succinylcholine 1 mg/kg. Maintenance: sevoflurane (1.5–3 vol%), vecuronium	ETT	Tono-pen tonometer (Tono-pen XLR, Mentor O & O inc, USA) after one dose of 0.5% proparacaine hydrochloride
Mowafi 2003	Gynecologic laparoscopy	15°–20° Trendelenburg position	20	20	Isoflurane	30(7.1)	31.8(6.0)	–	–	Induction: propofol 2.5 mg/kg, fentanyl 2 μg/kg, atracurium 0.5 mg/kg. Maintenance: propofol infusion 5–10 mg/kg/hr, atracurium 0.15 mg/kg as needed.	Induction: thiopental 5 mg/kg, fentanyl 2 μg/kg, atracurium 0.5 mg/kg. Maintenance: isoflurane 1–2 vol%, atracurium 0.15 mg/kg as needed.	ETT	Schioetz tonometer
Sator-Katzenschlager 2002	Elective gynaecological or urological procedures	–	16	17	Sevoflurane	–	–	–	–	Induction: propofol 2 mg/kg, fentanyl 2 μg/kg, vecuronium 0.1 mg/kg. Maintenance: propofol infusion 6–8 mg/kg/hr.	Induction: propofol 2 mg/kg, fentanyl 2 μg/kg, vecuronium 0.1 mg/kg. Maintenance: sevoflurane 1.5–2.5 vol%.	ETT	Hand-held Perkins applanation tonometer.
Schafer 2002	Cataract surgery	–	20	20	Sevoflurane	71(14)	75(11)	9	31	Induction: propofol 1.5–2.0 mg/kg bolus, remifentanil 10 mg/kg/h over 2 mins, mivacurium 0.12 mg/kg. Maintenance: propofol 3.0–7.0 mg/kg/h, remifentanil 10 mg/kg/hr.	Induction: propofol 1.5–2.0 mg/kg bolus, remifentanil 10 mg/kg/h over 2 mins, mivacurium 0.12 mg/kg. Maintenance: sevoflurane 0.7–1.2 vol%, remifentanil 10 mg/kg/hr.	ETT	Draeger handheld applanation tonometer, Moeller-Wedel Inc., 22,668 Wedel, Germany

(*continued on next page*)

Table 1 (*continued*)

Study	Surgery	Position	Number		VA	Age		Sex		Regimen		Airway	Tonometer
			P-TIVA (n)	VA (n)		P-TIVA	VA	M (n)	F (n)	P-TIVA	VA		
Sator 1998	Elective non-ophthalmic surgery	–	16	Isoflurane: 16 Desflurane: 16	Isoflurane, desflurane	–	–	–	–	Induction: thiopental 3–5 mg/kg, vecuronium 0.1 mg/kg, fentanyl 2–4 μg/kg. Maintenance: propofol 4–8 mg/kg/hr	Induction: thiopental 3–5 mg/kg, vecuronium 0.1 mg/kg, fentanyl 2–4 μg/kg. Maintenance: 1 MAC of isoflurane or desflurane	Unspecified	Hand-held applanation tonometer (Perkins)
Moffat 1995	Cataract surgery	–	20	20	Isoflurane	72(range 60–86)	77(range 64–88)	–	–	Anesthesia was induced and maintained with propofol using a computer-controlled infusion device (target plasma concentration 6 μg/ml –> 4 μg/ml).	Induction: etomidate 0.25 mg/kg, vecuronium 0.075 mg/kg. Maintenance: isoflurane 0.5–1 vol%	LMA	Perkins tonometer
Polarz 1995	Ophthalmic surgery	–	20	20	Isoflurane	73.3(7.2)	74.2(8.1)	13	27	Induction: propofol 1.5 mg/kg bolus, alfentanil 15 μg/kg bolus, succinylcholine 1 mg/kg. Maintenance: propofol 6 mg/kg/h, alfentanil 15 μg/kg/h, vecuronium 0.07 mg/kg.	Induction: thiopental 4 mg/kg, alfentanil 15 pg/kg, succinylcholine 1 mg/kg. Maintenance: isoflurane 0.5–0.8 vol %, vecuronium 0.07 mg/kg.	ETT	Möller-Wedel applanation tonometer on health eyes
Mets 1992	Anterior segment surgery	–	20	20	Isoflurane	67.6(8)	70.1(7.1)	18	22	Induction: propofol (2.05 ± 1.07 mg/kg), vecuronium 0.1 mg/kg. Maintenance: propofol 90 μg/kg/min, vecuronium 0.1 mg/kg.	Induction: etomidate (0.23 ± 0.09 mg/kg), alfentanil 15 μg/kg, vecuronium 0.1 mg/kg. Maintenance: isoflurane 0.5%, vecuronium 0.1 mg/kg.	ETT	Schiotz tonometer
Guedes 1988	Cataract extraction, strabismus, dacryocystectomy, secondary implantation, detachment of the retina, vitrectomy, trabeculectomy	–	15	15	Enflurane	73.6(21)	71.6(0.2)	16	14	Induction: propofol (1.8 ± 0.39 mg/kg) bolus, vecuronium (unspecified dose). Maintenance: propofol continuous infusion (5.2 ± 1.55 mg/kg/hr)	Induction: thiopental 6.8 ± 1.16 mg/kg, vecuronium (unspecified dose). Maintenance: enflurane 1.1 ± 0.39 vol%	ETT	Perkins tonometer

Age is presented as mean (SD).
P-TIVA: propofol-based total intravenous anesthesia; VA: volatile anesthesia; M: male; F: female; TCI: target-controlled infusion; Cet: target effect-site concentration; IOP: intraocular pressure; ETT: endotracheal tube; LMA: laryngeal mask airway.

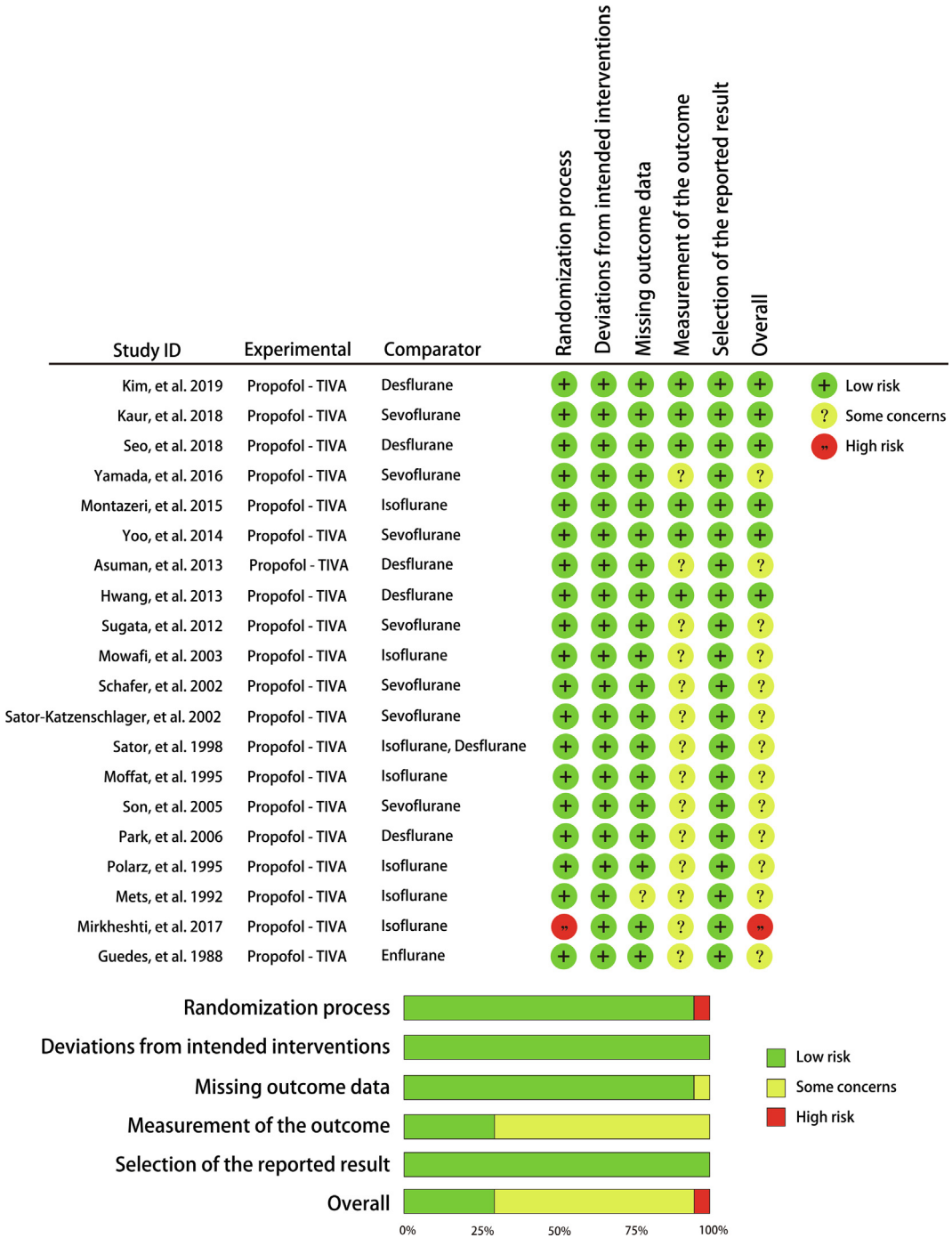

Fig. 2. Risk of bias graph and summary.

−0.13; 95% CI, −0.92 to 0.65; P = 0.74), and after Trendelenburg positioning (WMD, −0.05; 95% CI, −1.22 to 1.11; P = 0.93). However, after intubation, PIP was significantly lower in the propofol-based TIVA group (WMD, −1.32; 95% CI, −2.53 to −0.29; P = 0.01) (Fig. 6).

In the TSA, the estimated RIS was not reached by the cumulative Z-curve and the cumulative Z-curve did not surpass the traditional boundary for statistical significance after induction, after pneumoperitoneum, and after Trendelenburg positioning. In these three situations, the sequential monitoring boundary for the adjusted significance threshold was ignored due to too little information used (1.49%, 1.35%, and 0.09%). After intubation, the estimated RIS was 115 and was not reached by the cumulative Z-curve (92). Nonetheless, the cumulative Z-curve surpassed the upper sequential monitoring boundary for the adjusted significance threshold after inclusion of the Kim et al. study [42] (TSA-adjusted CI, −2.51 to −0.14; calculated Cohen's d, −0.490; and NNT, 6.15) (Suppl. Fig. S6).

Mean arterial pressure

MAP was analyzed in 10 studies (n = 433) after induction, seven (n = 262) after intubation, four (n = 204) after pneumoperitoneum, six (n = 285) after Trendelenburg positioning, two (n = 82) after

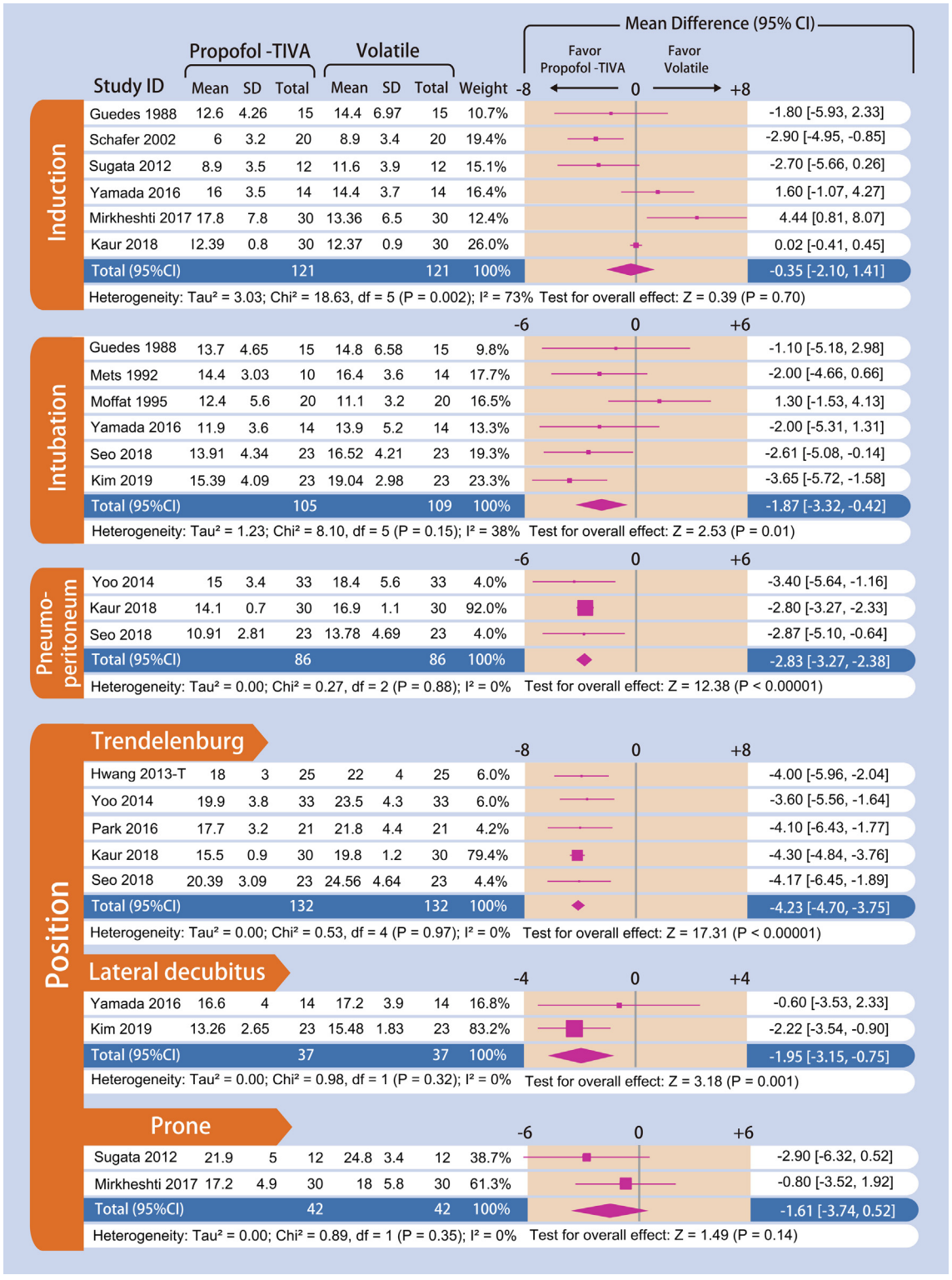

Fig. 3. Forest plot of intraocular pressure at different timings.

reverse Trendelenburg positioning, two (n = 74) after LDP, and four (n = 189) after the resolution of pneumoperitoneum. After intubation, MAP in the propofol-based TIVA group was significantly lower than that in the VA group (WMD, −6.61; 95% CI, −10.56 to −2.66; P < 0.01). However, after pneumoperitoneum, MAP was significantly higher in the propofol-based TIVA group (WMD, 0.81; 95% CI, 0.01 to 1.60; P = 0.05). There was no significant heterogeneity across studies after intubation and pneumoperitoneum (Chi^2 = 4.92, P = 0.55, I^2 = 0%; Chi^2 = 0.75, P = 0.86, I^2 = 0%). The pooled effect estimate showed no significant intergroup difference in IOP after induction (WMD, 0.08; 95% CI, −1.42 to 1.59; P = 0.91), after Trendelenburg positioning (WMD, 0.37; 95% CI, −2.30 to 3.03; P = 0.79), after reverse Trendelenburg positioning (WMD, −2.34; 95% CI, −9.00 to 4.32; P = 0.49), after LDP (WMD, −2.62;

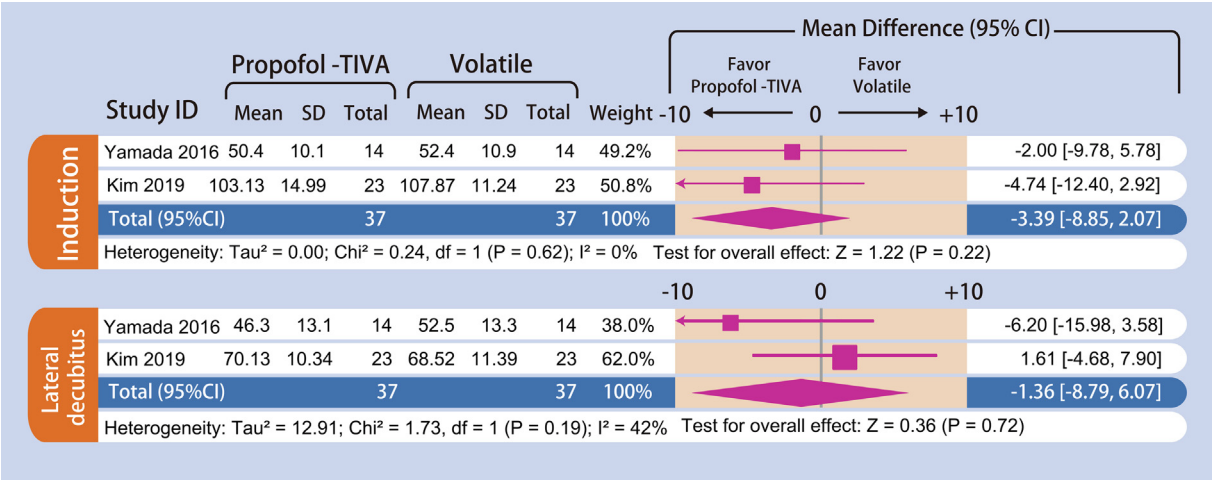

Fig. 4. Forest plot of ocular perfusion pressure at different timings.

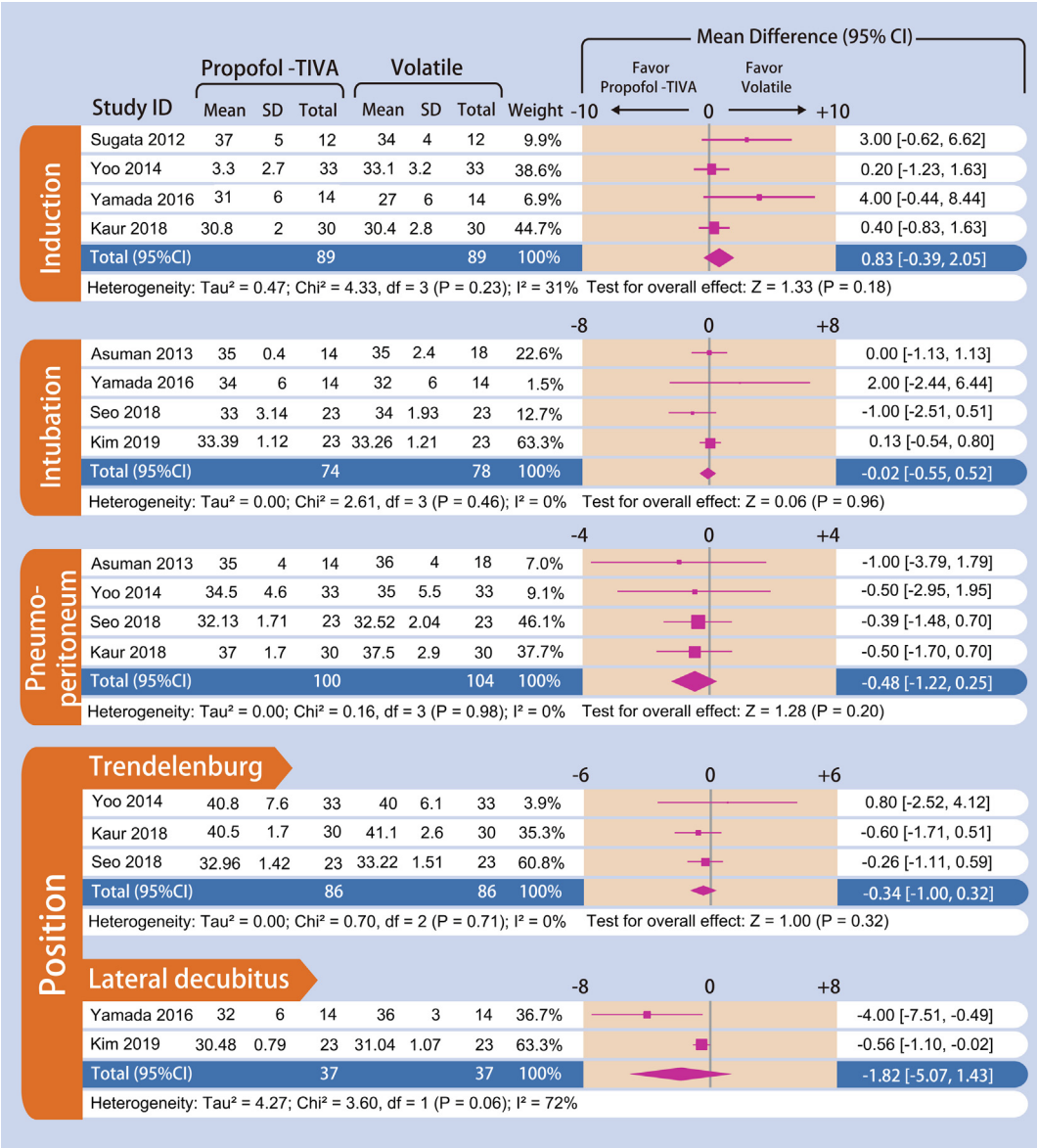

Fig. 5. Forest plot of end-tidal CO_2 at different timings.

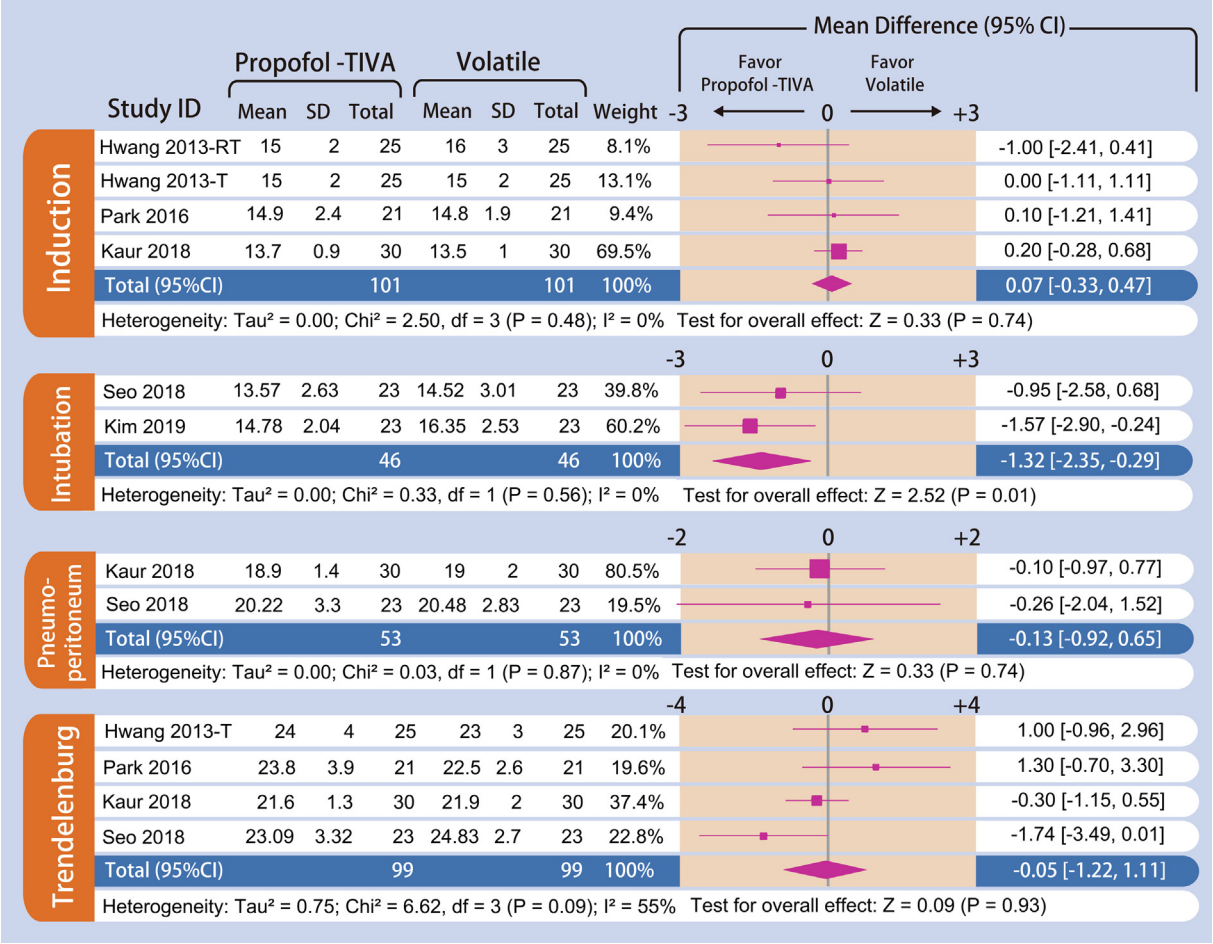

Fig. 6. Forest plot of peak inspiratory pressure at different timings.

95% CI, −9.07 to 3.83; P = 0.43), and after resolution of pneumoperitoneum (WMD, 0.41; 95% CI, −3.03 to 3.86; P = 0.82) (Fig. 7).

In the TSA of intubation, the cumulative Z-curve reached the estimated RIS and surpassed the traditional boundary for statistical significance (TSA-adjusted CI, −10.99 to −2.12; calculated Cohen's d, −0.414; and NNT, 7.44). In the TSA of pneumoperitoneum, the cumulative Z-curve surpassed the traditional boundary for statistical significance but did not reach the estimated RIS and did not surpass the lower sequential monitoring boundary for the adjusted significance threshold (TSA-adjusted CI, −0.39 to 2.01; calculated Cohen's d, 0.067; and NNT, 51.86). In the TSA of LDP and reverse Trendelenburg positioning, the cumulative Z-curve did not reach the estimated RIS and did not surpass the sequential monitoring boundary for the adjusted significance threshold. In the TSA of induction, Trendelenburg positioning and pneumoperitoneum resolution, the sequential monitoring boundary for the adjusted significance threshold was ignored due to too little information used (0.26%, 0.94%, and 1.53%) (Suppl. Fig. S7).

In the outcome of MAP after induction, propofol was used for induction in the propofol-TIVA group in all studies, while thiopental was used in five studies [32–34,38,39] and propofol in four [28,30,35,41] for induction in the VA group. In the subgroup analysis, MAP after induction was not significantly different between the propofol-TIVA group and the VA group with thiopental (WMD, −1.02; 95% CI, −4.19 to 2.15; P = 0.53) or propofol (WMD, 0.55; 95% CI, −1.49 to 2.60; P = 0.60) as the induction agent (Suppl. Fig. S8). In the outcome of MAP after intubation, propofol was used for induction in the propofol-TIVA group in all studies, whereas thiopental was used in five studies [29,31,38,39,42] and propofol in two [35,43] for induction in the VA group. The subgroup analysis showed that MAP after intubation in the propofol-TIVA group was significantly lower than that in the VA group with thiopental as the induction agent (WMD, −7.90; 95% CI, −12.77 to −3.02; P < 0.01). However, MAP was not significantly different between the propofol-TIVA group and the VA group with propofol as the induction agent (WMD, −4.08; 95% CI, −10.87 to 2.72; P = 0.24) (Suppl. Fig. S9).

Influence analysis

An influence analysis was conducted for each outcome except those including only two studies. The results of the influence analysis for all outcomes showed that the re-calculated pooled estimates after the omission of one study at a time were within the 95% CI of the pooled estimate of all studies, indicating the robustness of the results (Suppl. Figs. S10-14).

Discussion

Endotracheal intubation is associated with a marked increase in IOP, likely attributable to the increase in MAP and subsequent increase in the choroidal blood flow [44]. Propofol-based TIVA has been shown to result in lower heart rate and MAP after induction and intubation than sevoflurane and isoflurane in a previous study [45], thereby leading to a lower IOP. Different induction agents may also play an important role in IOP after intubation.

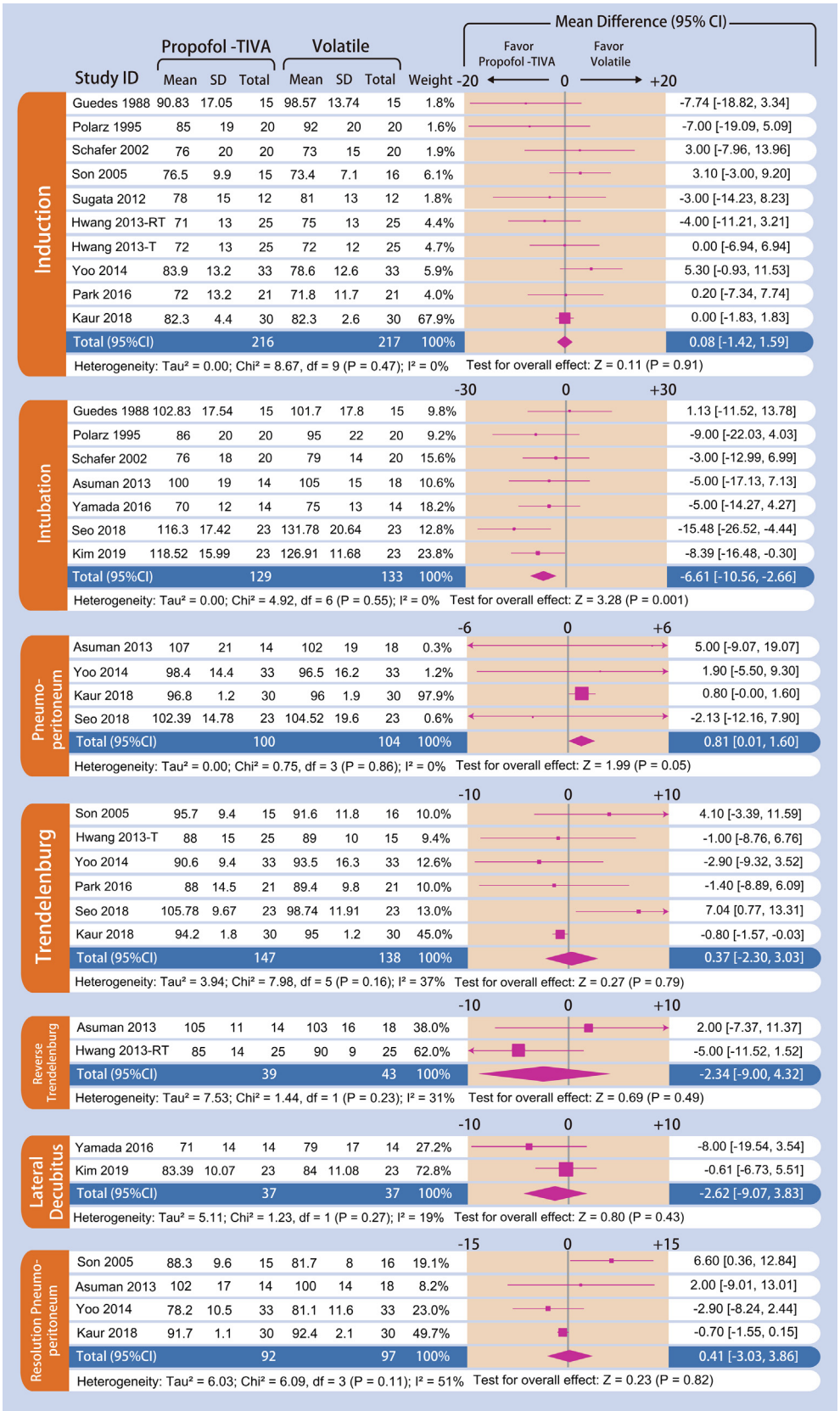

Fig. 7. Forest plot of mean arterial pressure at different timings.

For example, induction by thiopental was associated with higher IOP and blood pressure after induction and intubation than were propofol and etomidate [46–48]. This was compatible with our subgroup analysis in which we found that IOP and MAP after intubation in the propofol-based TIVA group were significantly lower than that in the VA group with thiopental as the induction agent.

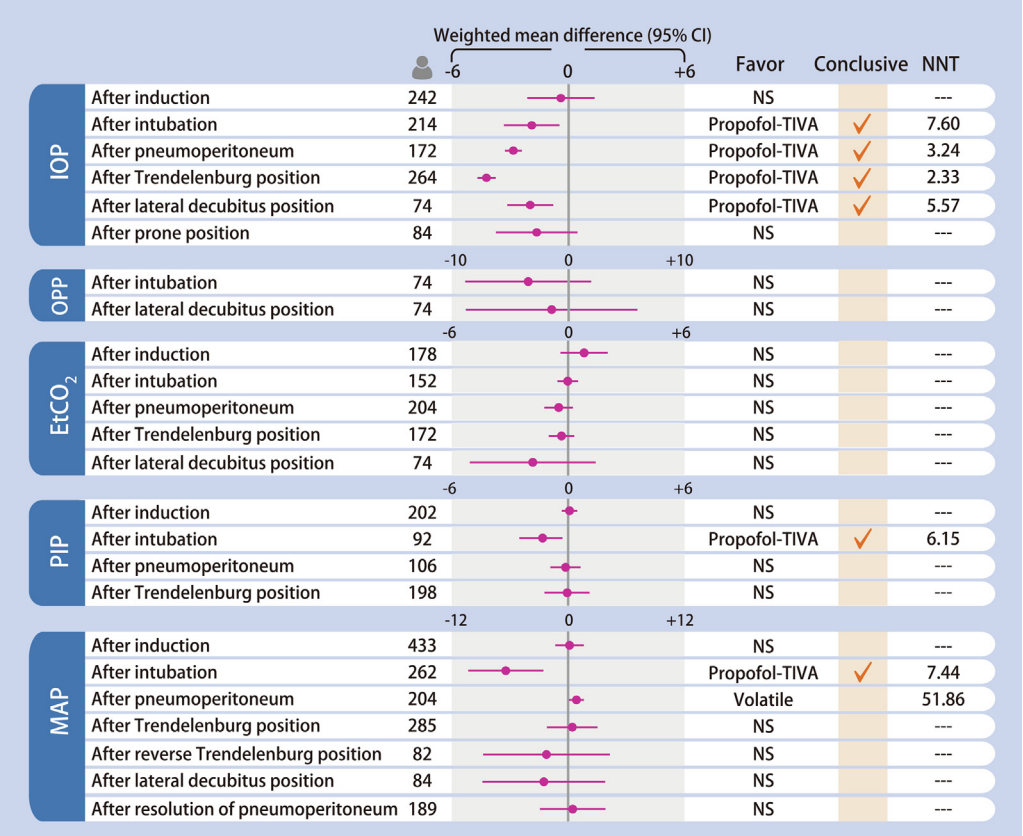

Fig. 8. Forest plot of all brief conclusions.

PIP has been shown to increase IOP [49]. The proposed mechanism for the positive correlation between PIP and IOP is that the increased intrathoracic pressure increases the central venous pressure, which in turn increases the episcleral venous pressure and blocks the aqueous humor outflow [9,50], leading to an increased IOP. Propofol and most of the volatile anesthetics are well documented for their bronchodilation property via inhibiting intracellular calcium mobilization [11]. Clinical studies evaluating the effects of propofol and sevoflurane on respiratory mechanics during surgery found no significant difference in PIP [51,52]. However, a recent study demonstrated that the total inspiratory resistance of desflurane is significantly higher than that of sevoflurane and isoflurane at a 1.5 minimum alveolar concentration (MAC) [53]. Therefore, we postulated that the significantly lower PIP after intubation observed in the present study was due to desflurane use in the studies by Seo et al. and Kim et al. [29,42]. Further investigations are required to confirm our theory.

IOP after pneumoperitoneum and Trendelenburg positioning in the propofol-based TIVA group was significantly lower than that in the VA group. The mechanism underlying such a difference was proposed to be the inhibitory effect of propofol on arginine vasopressin (AVP), which increased during laparoscopic surgery [54,55] and Trendelenburg positioning [56]. AVP and its synthetic derivative desmopressin has been shown to increase IOP [57,58]. Propofol inhibits magnocellular neuron excitability in the paraventricular nucleus [59] and supraoptic nucleus [60] via gamma-aminobutyric acid(A)-mediated inhibitory currents; therefore, it may attenuate the increase in IOP during pneumoperitoneum and Trendelenburg positioning. On the contrary, the plasma concentration of AVP was not altered by volatile anesthetics [61].

LDP has been shown to increase the IOP of the dependent eye in both anaesthetized patients and healthy subjects [62,63]. The increased IOP in LDP is likely due to the increased episcleral venous pressure and choroidal volume resulting from gravity or a shift of body fluid and jugular vein compression [63]. In the present study, we found that IOP after LDP in the propofol-based TIVA groups was significantly lower than that in the VA group. The mechanism remains unclear. It was postulated that the reducing effect of propofol on IOP was greater than the increasing effect of LDP, but not volatile anesthetics [43]. Further investigations are necessary to explore this finding.

Our study has some limitations. First, the time elapsed between the IOP measurement and intubation was mentioned in some studies [29,31,35–37,39,42] but unclear in others. Moreover, information was unavailable regarding the exhaled concentration of the VA or the MAC after intubation at which the IOP was measured. As a result, it was unclear to what extent the volatile anesthetics affected the IOP and may underestimate the effects of VA after intubation. Second, some of the included studies were not included in the meta-analysis due to insufficient information. As a result, the pooled effect may have been shifted in either direction if these studies had been included in the meta-analysis. Third, our search strategy was based on the primary outcome, i.e., IOP. Although the literature was searched comprehensively, it remains possible that some studies reporting our secondary outcomes were not included. Consequently, the results of the secondary outcomes in this study may be subject to type one or type two errors. Finally, despite attempts to explore possible modulating factors by meta-regression to account for the intergroup heterogeneity, we were unable to perform it due to insufficient data.

Conclusions

To the best of our knowledge, this is the first meta-analysis of RCTs to evaluate the effects of propofol-based TIVA and VA on

IOP in patients undergoing surgery. We found that IOP, MAP, and PIP after intubation in the propofol-based TIVA group were significantly lower than that in the VA group. Moreover, the IOP was also significantly lower in the propofol-TIVA group after pneumoperitoneum, Trendelenburg positioning, and LDP (Fig. 8.). Thus, propofol-based TIVA should be the regimen of choice during anesthesia maintenance, especially in at-risk patients.

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Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2020.02.008.

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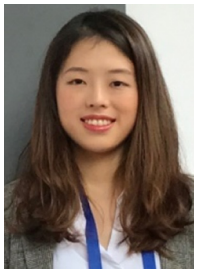

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