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Review

Comparison of recovery parameters for xenon versus other inhalation anesthetics: systematic review and meta-analysis☆

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Abstract

Study objective: To summarize and evaluate the available data describing the recovery parameters of xenon anesthesia.

Design: Systematic review and meta-analysis.

Setting: Anesthesia for elective surgeries.

Patients: Systematic review of randomized controlled trials (RCTs) from databases including Medline (1964-2013), the Cochrane Central Register of Controlled Trials (CENTRAL, 1990-2012), and Google Scholar (1966-2013).

Interventions: Inhalation of xenon or other anesthetics was administered in elective surgery.

Measurements: Recovery parameters (time to recovery, alertness/sedation scale scores at "eye opening," bispectral index at "reaction on demand," time to extubation, and time to orientation).

Main results: Eleven RCTs (N = 661 patients) met the inclusion criteria. Recovery from xenon anesthesia was significantly faster in terms of the time to eye opening (mean difference [MD], −4.18 minutes; 95% confidence interval [CI], −5.03 to −3.32 minutes; $P < .00001$), the time to reaction on demand (MD, −5.35 minutes; 95% CI, −6.59 to −4.11 minutes; $P < .00001$), the time to extubation (MD, −4.49 minutes; 95% CI, −5.40 to −3.58 minutes; $P < .00001$), and the time to orientation (MD, −4.99 minutes; 95% CI, −6.45 to −3.52 minutes; $P < .00001$).

Conclusions: This meta-analysis confirmed that recovery from xenon anesthesia is faster than other inhalation anesthesia.

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1. Introduction

An ideal anesthetic agent provides a rapid onset of effect with a short time to recovery [1]. Xenon, an inert gas, has attracted renewed interest because it possesses many of the properties of an ideal inhaled anesthetic [1–3]. It is odorless, nonpungent, nontoxic, nonexplosive, and nonflammable.

The blood-gas partition coefficient of an inhaled anesthetic indicates its onset time and recovery speed. In the late 1990s, Goto et al [4] confirmed that the blood-gas coefficient of xenon may be lower than 0.14 and closer to 0.115, the lowest of all known anesthetics. On the basis of xenon's pharmacokinetic characteristics, it may have a profile that favors rapid recovery from anesthesia. This offers a number of advantages. Results from preclinical studies indicate the inhalational anesthetics like xenon may increase neuronal apoptosis and reduce neurogenesis and therefore affect neuron development in neonatal animals. This may be of particular importance in elderly patients. Elderly patients who undergo surgery have a higher risk of experiencing postsurgery cognitive decline. The mechanism is unclear, but nonclinical models suggest that interactions between inhalational anesthetics and neurodegenerative mechanisms, similar to observed in Alzheimer disease, may be responsible for postoperative cognitive dysfunction [5]. Thus, inhalational anesthetics that have a rapid onset of action and short recovery time may be preferable in certain patient populations because these agents minimize the amount time of patients under anesthesia.

To demonstrate the recovery advantages of xenon, we performed a systematic review to quantitatively evaluate the available evidence for the recovery parameters of xenon versus other inhaled anesthetic agents.

2. Methods

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6]. We conducted a comprehensive literature search of MEDLINE

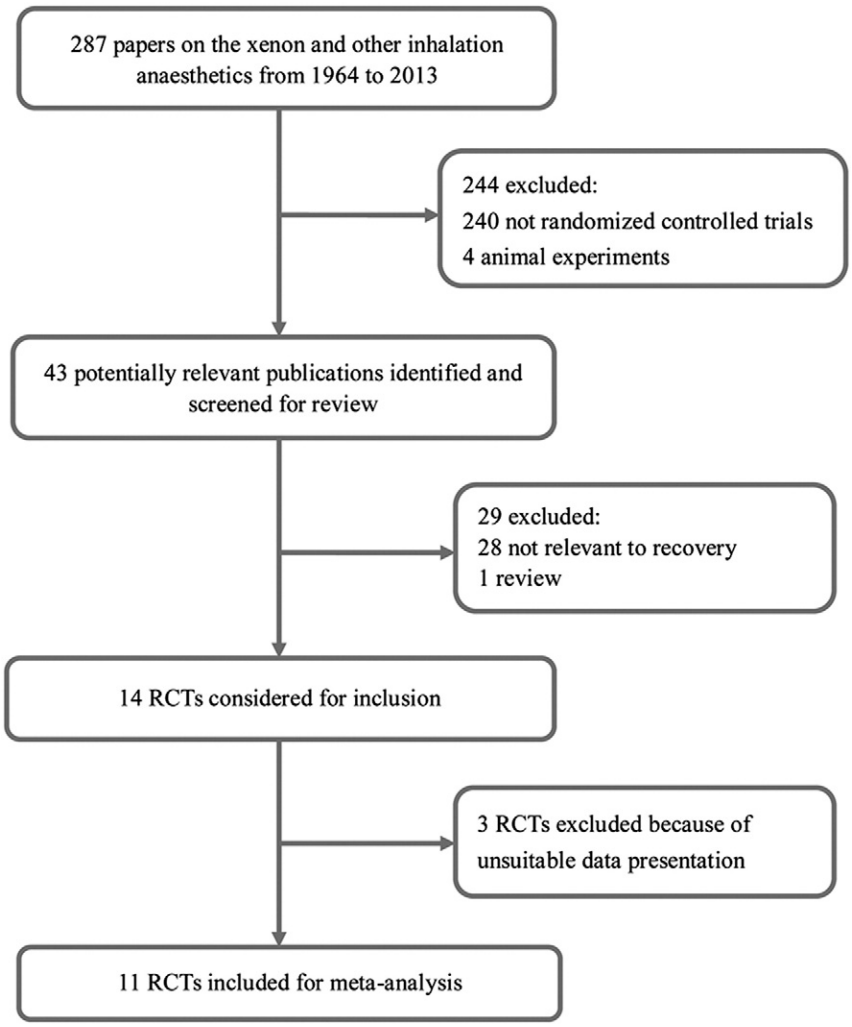

Fig. 1 Flow diagram of screening process for studies eligible for analysis.

Table 1 Characteristics of the randomized trials included in the meta-analysis.

Study	Age, y	Sex (male/female)	BMI	ASA	Type of anesthesia	Anethesia time, min	No.	Type of surgery
Stoppe et al [18]	20-80	6/34	25 ± 6	I-III	Xenon (53-56 vol% MAC)	126 ± 46	20	Gynecology
	20-80				Sevoflurane (1-1.4 vol% MAC)	126 ± 46	20	Urology
Cremer et al [17]	65-75	24/15	–	I-III	Xenon (1.1-1.4 vol% MAC in 30% oxygen)	121-181	18	Trauma Orthopedics
	65-75				Sevoflurane (60 ± 3 vol% MAC in 30% oxygen)	121-206	20	ENT Gynecology Urology Neurosurgery Abdominal surgery
Fahlenkamp et al [15]	22-74	27/30	–	I-II	Xenon (60 ± 5 vol% MAC in 30% oxygen)	123 ± 9.6	29	Abdominal surgery
	22-71				Sevoflurane (2 ± 0.2 vol% MAC in 30% oxygen)	157 ± 13.7	28	
Fahlenkamp et al [14]	69 ± 1	23/16	–	I-III	Xenon (53.2 ± 0.8 vol% MAC in 30% oxygen)	162 ± 19	19	Elective noncardiac surgery
	70 ± 1				Sevoflurane (1.6 ± 0.1 vol% MAC in 30% oxygen)	148 ± 14	20	
Bronco et al [13]	59 ± 13	21/38	26 ± 4	I-II	Xenon (60 vol% MAC)	133 ± 65	29	General surgery
	58 ± 16		24 ± 5		Sevoflurane (1.4 vol% MAC)	162 ± 76	30	Ear nose and throat surgery Gynecological surgery Orthopedic surgery and urological surgery
Abranmo et al [12]	23-49	14/6	42-83	I-III	Xenon (60-65 vol% MAC)	–	10	Roux-en-Y laparoscopic
	19-57		39-71		Sevoflurane (1 vol% MAC)	–	10	gastric bypass
Stuttmann et al [16]	41.5	14/47	–	I-II	Xenon (63 vol% MAC in 30% oxygen)	–	31	Visceral strumectomy Knee arthroscopy
	38.9		–		Isoflurane (0.6 vol% MAC in 30% oxygen)	–	30	Liposuction Mammaplasty
Coburn et al [11]	65-75	24/14	–	I-III	Xenon (60 vol% MAC in 30% oxygen)	98-138	18	Trauma Head, neck, and ear
	65-75		–		Desflurane (5.2-5.5 vol% MAC in 30% oxygen)	102-150	20	Gynecology Urology
Rossaint et al [3]	52.3 ± 16.7	113/111	–	I-III	Xenon (60 ± 5 vol% MAC in oxygen)	175.3 ± 94.0	112	Elective surgery
	52.5 ± 15.5		–		Isoflurane-N_2O (0.5 vol% MAC isoflurane with 60 ± 5% N_2O in oxygen)	180.1 ± 84.4	112	
Goto et al [9]	33-58	7/47	–	I-II	Xenon (60 vol% MAC)	58-380	18	Elective lower
	32-64		–		N_2O-sevoflurane (0.7 vol% MAC sevoflurane with 60% N_2O)	58-303	18	abdominal surgery
	34-56		–		N_2O-isoflurane (0.5 vol% MAC isoflurane with 60% N_2O)	61-296	18	
Goto et al [2]	44 ± 3	–/–	–	I-II	Xenon (60 vol% MAC)	122 ± 39	10	Elective total
	44 ± 7		–		N_2O-sevoflurane (0.7 vol% MAC sevoflurane with 60% N_2O)	119 ± 41	10	abdominal hysterectomy
	43 ± 4		–		N_2O-isoflurane (0.5 vol% MAC isoflurane with 60% N_2O)	121 ± 26	10	

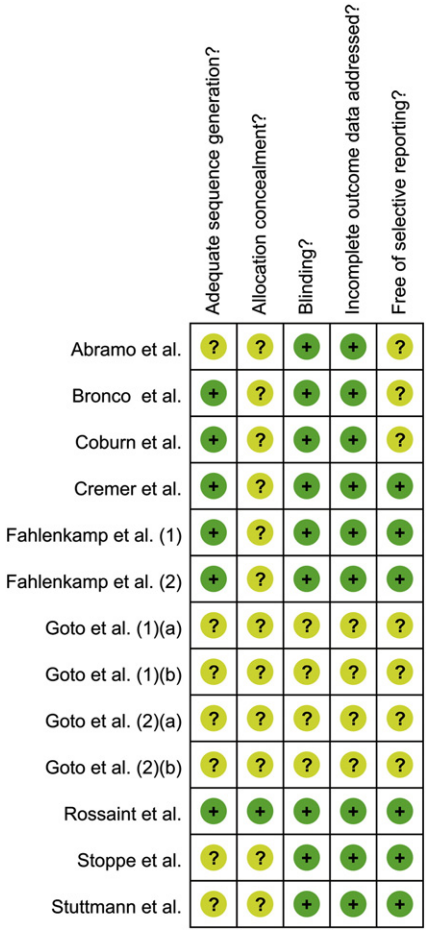

Fig. 2 Methodological qualities of the included studies were determined using the Cochrane Risk of Bias Assessment Tool. There are 5 domains: sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.

(1964-2013), Cochrane Central Register of Controlled Trials (CENTRAL, 1990-2012), and Google Scholar (1966-2013) databases using the following search terms: *xenon*, *methyl ethers*, *sevoflurane*, *isoflurane*, *desflurane*, *enflurane*, *halothane*, *nitric oxide*, *mononitrogen monoxide*, *nitrogen monoxide*, *endogenous nitrate vasodilator*, and combinations of these keywords. The search was limited to clinical trials and randomized controlled trials (RCTs) in humans, without any language restrictions. This initial search yielded 287 randomized clinical trials. We excluded children or infant studies, case reports, and reviews by reading abstracts. All RCTs included in the review had 10 or more patients; studies with less patients were excluded [7]. Bibliographies were checked for retrieved articles. When the full text for an article could not be found, authors were contacted to obtain a copy of the original.

Two authors (FJL and SPZ) independently screened all articles and abstracts and assessed their methodological validity using the Cochrane Risk of Bias Assessment Tool [8]. Criteria that used for assessing the risk of bias included the following: adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and free of selective reporting. The decision on the suitability of a study of our analysis was determined by 2 authors (SSO and LKY). Disagreements on inclusion of the articles were resolved by discussion among the evaluators. If an agreement could not be reached between the 2 investigators, the decision was made by a third investigator (SPZ).

The data were extracted independently by at least 2 individuals on a standardized data collection sheet. Meanwhile, data were extrapolated from available figures if the data were not in the tables or the authors did not respond. Dichotomous data on the presence or absence of adverse effects were extracted and converted to incidence while continuous data were recorded using mean and SD. Data presented only as median and range were converted to mean and SD using previously described methodology [9]. When data were presented with 95% confidence intervals (CIs), the SD was calculated from a standard formula for a normal distribution (SD = 95% CI/1.96 × $\sqrt{n}$). Time data presented in seconds were converted to total minutes by dividing the time reported by 60. Collected data included baseline characteristics of studies and recovery parameters (time to "open eyes," "reaction on demand," "extubation," and "orientation"). These end points were chosen because of their clinical importance and frequency of reporting. Two studies [2,3] recorded the time point at which the patient could count backward or count down from 10 to 1 instead of the time point when the patient could react on demand.

2.1. Meta-analysis

All data extracted from the relevant studies were transcribed to RevMan 5.0 (Review Manager, Cochrane Collaboration, UK) for analysis. Studies with the same first author were numbered [author et al (number)]. Studies of the same first author with more than one intervention group were numbered [author et al (number) (alphabet)]. The weighted mean difference (MD) was calculated for numerical data, and the odds ratio was calculated for dichotomous data, both with 95% CI. Statistical heterogeneity was assessed using the I^2 index. Data were analyzed using a random effects model due to clinical or methodological heterogeneity [10]. A statistical significance was assumed if 95% CIs did not include the value 1.0 for relative risk and 0 for MD.

3. Results

A total of 287 papers on the xenon and other inhalation anesthetics (1964-2013) were identified using the search strategy. After carefully screening the titles and abstracts, 276 were excluded: 240 were not RCTs, 4 were animal experiments, 28 were unrelated studies, 1 was a review article, and 3 RCTs included unsuitable data presentations. Eleven studies that included 661 patients were deemed eligible for inclusion in this systematic review [2,3,11–19]. Three research groups were responsible for most of the studies included in this

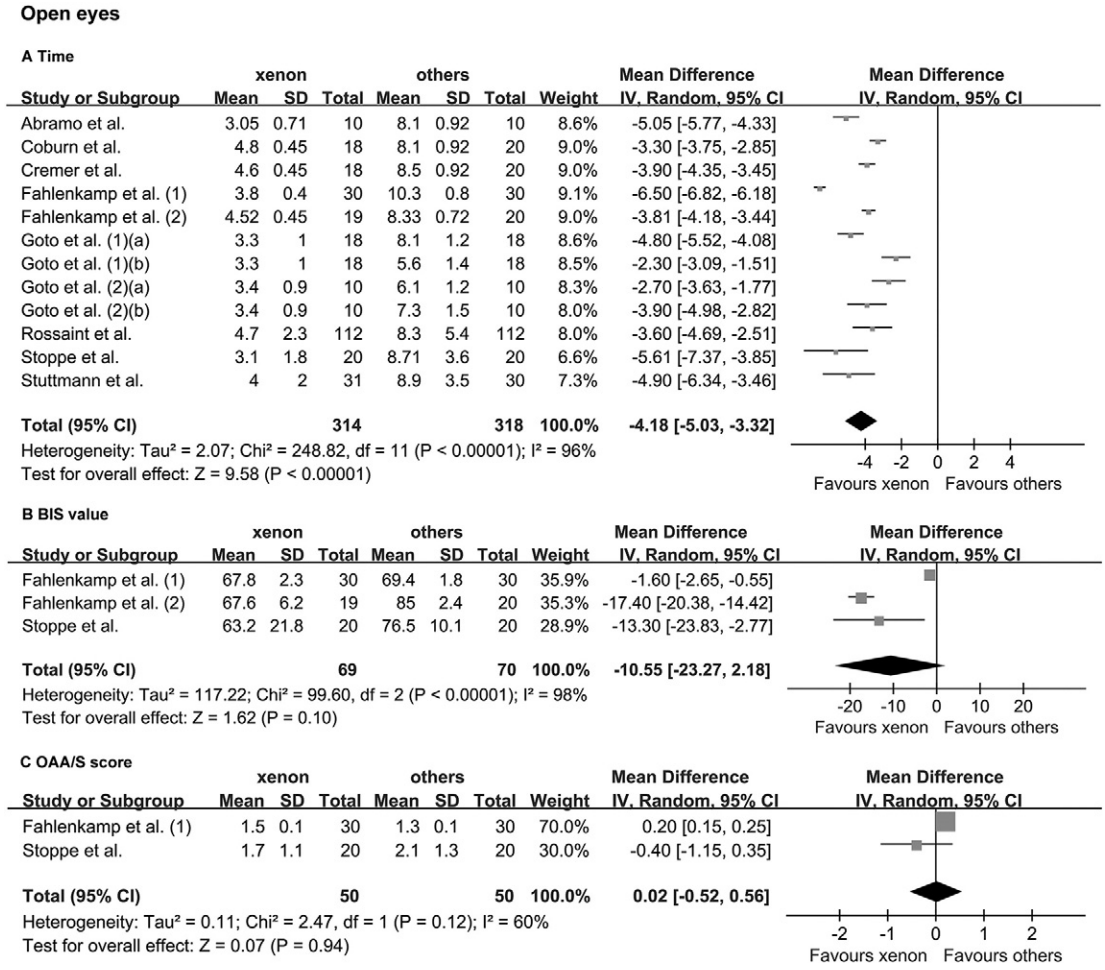

Fig. 3 Forest plot of meta-analysis of trials comparing xenon anesthesia with other inhalation anesthesia on the time to recovery (open eyes) and anesthetic parameters at the time points. (**A**) Time to open eyes. (**B**) BIS values at the time point eye opening. (**C**) OAA/S scores at the time point eye opening. Studies with the same first author were numbered [author et al (number)]. Studies from the same first author with more than one intervention group were numbered [author et al (number) (alphabet)]. Xenon, xenon anesthesia; others, other inhalation anesthesia.

review. The analysis included 2 studies from the Morita group [2,3], 2 studies from the Rossaint group [12,13], and 3 studies from the Coburn group [15–17]. A flow chart that illustrates how we located relevant studies is presented in Fig. 1. The characteristics of the randomized trials are described in Table 1. There was no important imbalance at baseline in each study. The studies in this review included comparisons of xenon versus other inhalation anesthetics. Inhalation anesthetics included methyl ethers, such as sevoflurane (6 studies) [13–17,19], isoflurane (1 study) [18], and desflurane (1 study) [12]. The remaining studies [2,3,11] included xenon alone or comparisons to nitrous oxides in combination with either sevoflurane or isoflurane.

3.1. Quality assessment

The methodological quality scores of the included studies are summarized in Fig. 2. Six [3,12,14–17] of the 11 studies had an adequate sequence generation for randomization. Only 1 study [3] had allocation concealment, the remaining studies were unclear. With the exception of 2 studies [2,3] in which the blinding protocol was unclear, participants, personnel, and outcome assessors were blinded to randomized groups [11–19]. Six [3,13,15–18] of the 11 studies were free of selective reporting.

3.2. Open eyes

Ten studies reported time to open eyes as mean and SD (Fig. 3*A*) [2,3,11–13,15–19]. Patients in the xenon group showed significantly faster recovery with respect to time to open eyes than other inhalational anesthetics (MD, −4.18 minutes; 95% CI, −5.03 to −3.32 minutes; $P < .00001$; $I^2 = 96\%$).

Three studies recorded bispectral index (BIS) values at the time of "eye opening" (Fig. 3*B*) [13,15,16]. There was no difference in BIS values between the xenon group and other inhalational anesthetics (MD, −10.55 minutes; 95% CI, −23.27 to −2.18 minutes; $P < .00001$; $I^2 = 98\%$).

Two studies recorded the observer's assessment of alertness/sedation scale (OAA/S) scores at the time of eye opening (Fig. 3*C*) [13,16]. There was no difference between

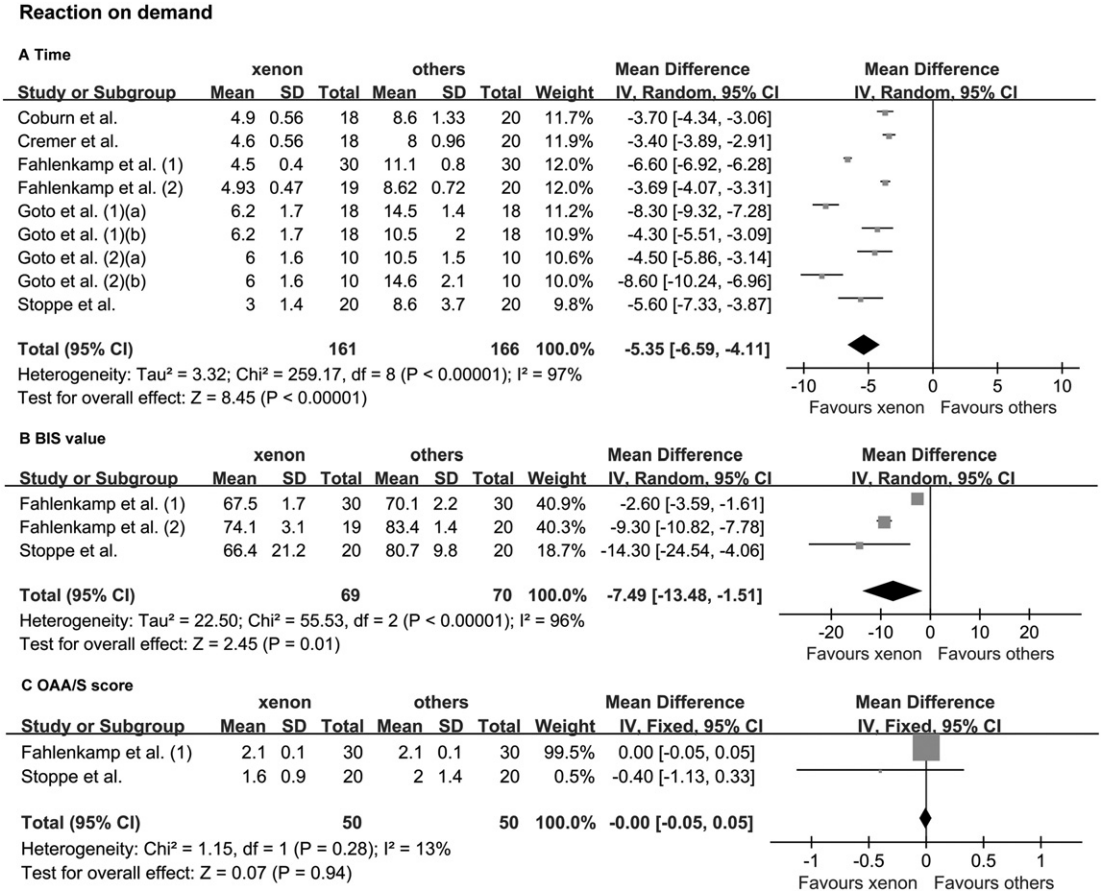

Fig. 4 Forest plot of meta-analysis of trials comparing xenon anesthesia with other inhalation anesthesia on the time to recovery (reaction on demand) and anesthetic parameters at the time points. (**A**) Time to reaction on demand. (**B**) BIS values at the time point reaction on demand. (**C**) OAA/S scores at the time point reaction on demand. Studies with the same first author were numbered [author et al (number)]. Studies of the same first author with more than one intervention group were numbered [author et al (number) (alphabet)]. Xenon, xenon anesthesia; others, other inhalation anesthesia.

the xenon group and other inhalational anesthetics (MD, 0.02 minutes; 95% CI, −0.52 to 0.56 minutes; $P = .12$; $I^2 = 60\%$).

3.3. Reaction on demand

Seven studies reported time to reaction on demand (Fig. 4*A*) [2,3,12,13,15–17]. Patients in the xenon group showed significantly faster recovery with respect to time to reaction on demand than groups treated with other inhalational anesthetics (MD, −5.35 minutes; 95% CI, −6.59 to −4.11 minutes; $P < .00001$; $I^2 = 97\%$).

Three studies recorded BIS values at time to reaction on demand (Fig. 4*B*) [13,15,16]. At those time points, BIS values showed significantly lower levels in the xenon groups than other inhalational anesthetics groups (MD, −7.49 minutes; 95% CI, −13.48 to −1.51 minutes; $P < .00001$; $I^2 = 96\%$).

Two studies recorded OAA/S scores at the time to reaction on demand (Fig. 4*C*) [13,16]. There was no difference between xenon groups and other inhalational anesthetics (MD, −0.00 minutes; 95% CI, −0.0.5 to 0.05 minutes; $P = .28$; $I^2 = 13\%$).

3.4. Extubation

Eleven studies reported time to extubation (Fig. 5*A*) [2,3,11–19]. Patients in the xenon group showed significantly faster recovery with respect to time to extubation than patients treated with other inhalational anesthetics (MD, −4.49 minutes; 95% CI, −5.4 to −3.58 minutes; $P < .00001$; $I^2 = 96\%$).

Three studies recorded BIS values at the time point extubation (Fig. 5*B*) [13,15,16]. At the time points, BIS values showed significantly lower levels in the xenon groups than other inhalational anesthetics groups (MD, −7.95 minutes; 95% CI, −13.05 to −2.85 minutes; $P < .00001$; $I^2 = 97\%$).

Two studies recorded OAA/S scores at the time to extubation (Fig. 5*C*) [13,16]. There was no difference between the xenon groups and other inhalational anesthetics groups (MD, 0.20 minutes; 95% CI, 0.12 to 0.28 minutes; $P = .79$; $I^2 = 0\%$).

3.5. Orientation

Seven studies reported time to orientation (Fig. 6*A*) [2,3,12,13,15–17]. Patients in the xenon group showed

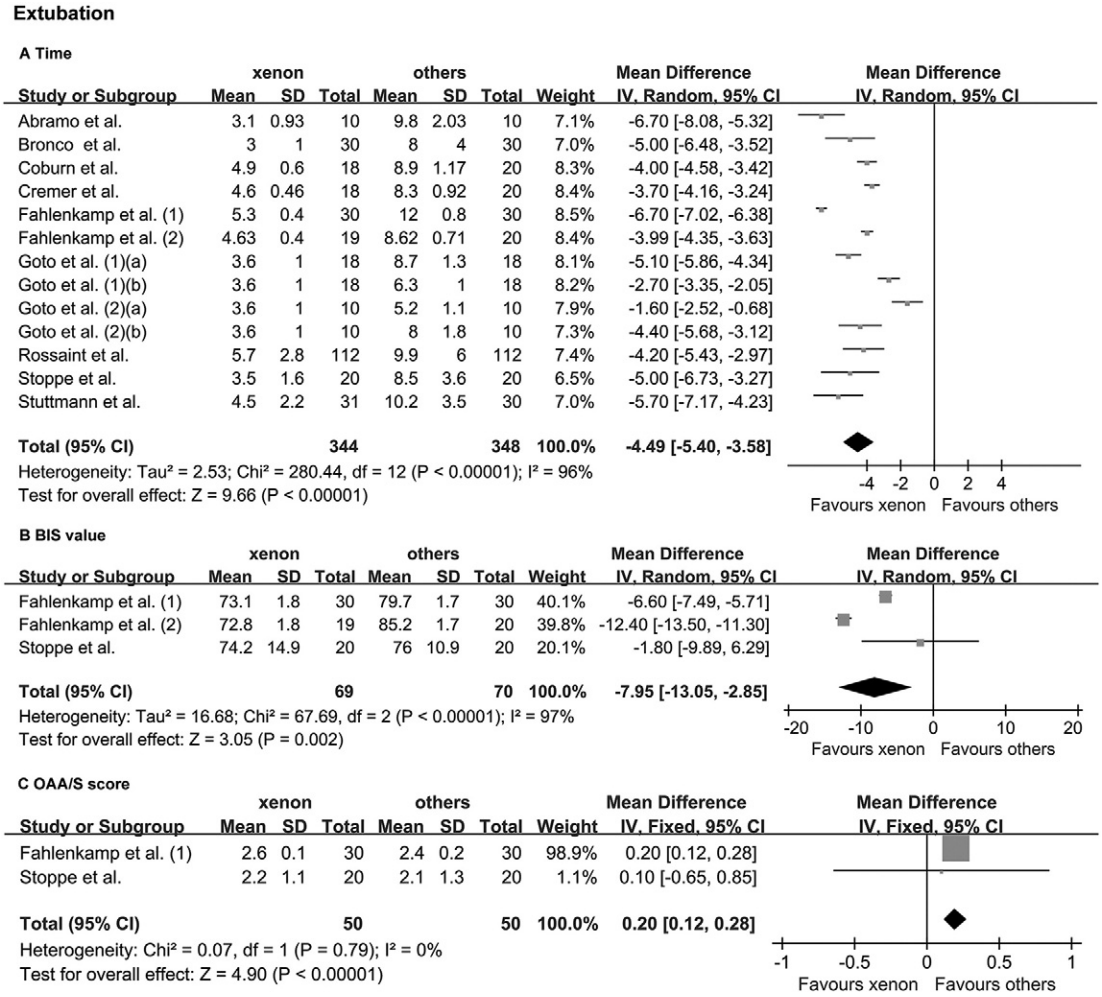

Fig. 5 Forest plot of meta-analysis of trials comparing xenon anesthesia with other inhalation anesthesia on the time to recovery (extubation) and anesthetic parameters at the time points. (**A**) Time to extubation. (**B**) BIS values at the time point extubation. (**C**) OAA/S scores at the time point extubation. Studies with the same first author were numbered [author et al (number)]. Studies of the same first author with more than one intervention group were numbered [author et al (number) (alphabet)]. Xenon, xenon anesthesia; others, other inhalation anesthesia.

significantly faster recovery with respect to time to orientation than patients in other inhalational anesthetics groups (MD, −4.99 minutes; 95% CI, −6.45 to −3.52 minutes; $P < .00001$; $I^2 = 97\%$).

Three studies recorded BIS values at the time point orientation (Fig. 6*B*) [13,15,16]. At the time points, BIS values showed significantly lower levels in xenon groups than other inhalational anesthetics groups (MD, −3.80 minutes; 95% CI, −4.39 to −3.22 minutes; $P = .58$; $I^2 = 0\%$).

Two studies recorded OAA/S scores at the time point orientation (Fig. 6*C*) [13,16]. There was no difference between the xenon group and other inhalational anesthetics (MD, −9.65 minutes; 95% CI, −28.36 to 9.07 minutes; $P < .00001$; $I^2 = 100\%$).

4. Discussion

Conventional volatile inhalational agents, in general, are thought to produce anesthesia via interaction with receptor targets such as γ-aminobutyric acid receptors [20]. Xenon exerts its anesthetic properties mainly by noncompetitively inhibiting *N*-methyl-D-aspartate receptors [21,22], and 80% xenon has been shown to reduce *N*-methyl-D-aspartate–activated currents by approximately 60%. As an anesthetic reagent, xenon possesses favorable properties such as hemodynamic stability [12,23] and cardioprotective [24] and neuroprotective effects [24,25]. Xenon was used as a clinical anesthetic agent for more than 50 years until the late 1940s [26]. However, its clinical use has been limited because of the high costs [27].

The most important pharmacokinetic property of xenon is its blood-gas coefficient. In the late 1990s, Goto et al [2,3] reported that recovery from xenon anesthesia was not only fast but also smooth; no patients exhibited agitation or restlessness. Our systematic review of previous studies has confirmed that xenon has a more rapid recovery time than other inhalational anesthetics. This effect is likely due to its blood-gas partition coefficient, which is significantly lower than that of other inhalational agents (xenon = 0.115[4] vs nitrous oxide = 0.47,

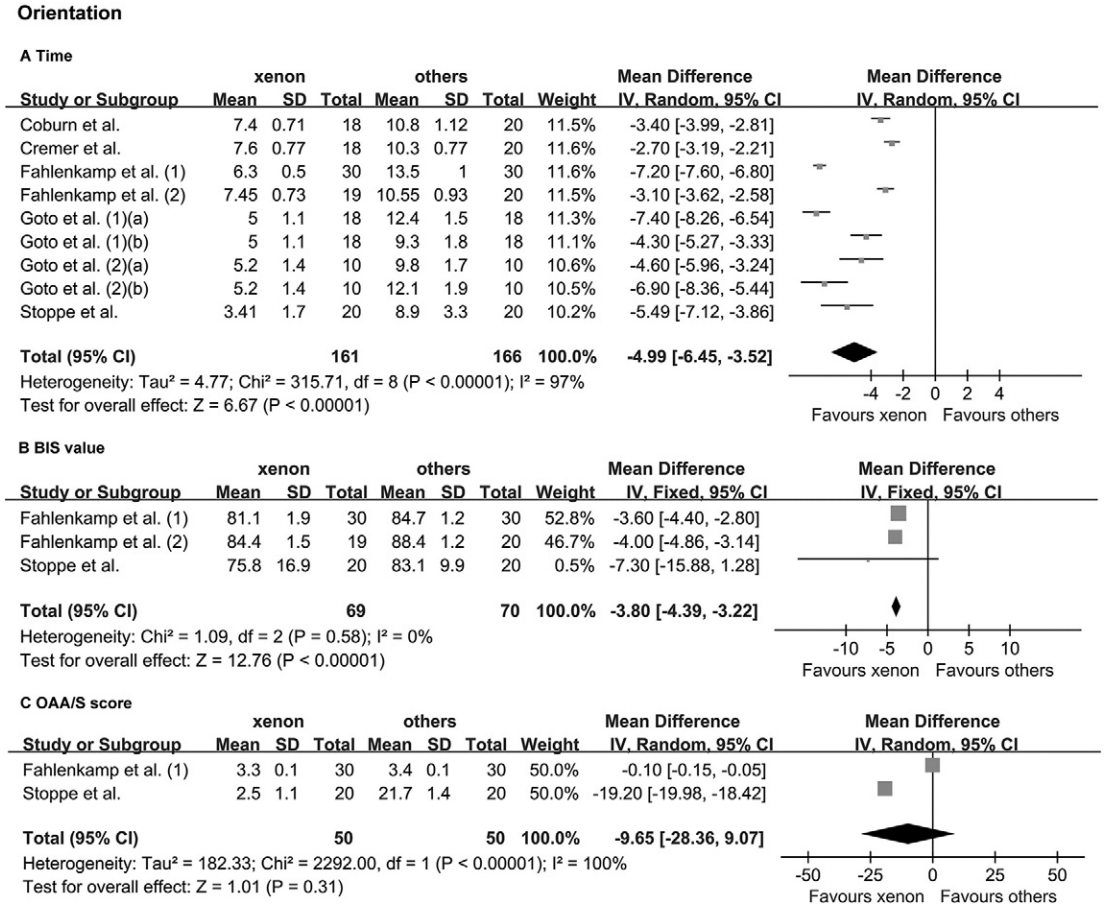

Fig. 6 Forest plot of meta-analysis of trials comparing xenon anesthesia with other inhalation anesthesia on the time to recovery (orientation) and anesthetic parameters at the time points. (**A**) Time to orientation. (**B**) BIS values at the time points orientation. (**C**) OAA/S scores at the time point orientation. Studies with the same first author were numbered [author et al (number)]. Studies of the same first author with more than one intervention group were numbered [author et al (number) (alphabet)]. Xenon, xenon anesthesia; others, other inhalation anesthesia.

sevoflurane = 0.65, isoflurane = 1.4, and desflurane = 0.42) [1,28,29]. The results are consistent with the widely accepted concept that the smaller the factor of blood-gas partition coefficients is, the faster is the wake up time from anesthesia. The studies included in this review did not report specifically on the comparison of recovery parameters between xenon and propofol anesthesia. Six studies [13–17,19] included in our meta-analysis had a study arm with patients receiving xenon and sevoflurane. All patients in the xenon group showed a significantly faster recovery with respect to time to open eyes, time to reaction on demand, time to extubation, and time to orientation. Similar outcomes were observed in comparative studies evaluating recovery parameters of xenon and isoflurane [18] or desflurane [12]. In addition, recovery from xenon anesthesia proved to be 2 or 3 times faster than recovery from equi-minimum alveolar concentration (MAC) nitrous oxide–isoflurane or nitrous oxide–sevoflurane anesthesia [2,3,11,30]. These studies suggested that anesthesia with xenon maybe a good option for postanesthesia recovery periods.

One study [19] has investigated the effect of xenon on the morbidly obese patients. Although obesity may increase the risk of recovery, it appears that there is no considerable difference of recovery times with respect to normal-weight patient trials. In the other 2 studies [11,18], investigators used a recovery index (RI) to describe the recovery after discontinuation of the anesthetic gas. The RI quotient uses eyes opening time, extubation time, and Aldrete score [11,18,31–33]. A difference in RI of 0.17 or higher was classified as a clinically relevant advantage. The xenon anesthesia group provided a distinctively faster recovery than in the isoflurane-N_2O group with a difference of 0.30.

Recently, monitoring depth of anesthesia raised concern about recovery from general anesthesia. In our systematic review, 3 measurements were used to monitor hypnotic depth: BIS, auditory-evoked potential index, and A-line autoregressive index [13,15,16]. The measurement of BIS is the most widely used assessment of the actual state of cerebral activity [34–36]. In this review, BIS values showed significantly lower levels in the xenon group than in other inhalation anesthesia groups at the time to open eyes, reaction on demand, extubation, and orientation. Although Goto et al [37] reported that the BIS values were lower than

50 while awake, the validity of the BIS monitoring remains controversial. This phenomenon may be due to an averaging of data and technical delays caused by the fast emergence from xenon anesthesia. Furthermore, display of BIS values during awakening might lag behind the true electroencephalogram processes. In our review, we found awakening at BIS values greater than 50. It is indicated that when BIS values were situated at the lower limit of the recommended range of emergence, we could attempt to rouse patients from anesthesia. In addition, the observer's determination of OAA/S scores was assessed at the predefined time points [38]. There was no difference between xenon and other inhalation anesthesia due to small amounts of data. Only 2 studies [13,16] reported the measurement of auditory-evoked potential index and A-line autoregressive index independently in this review, and we did not analyze those data.

The heterogeneous nature of the data included in this review was a limitation. Different types of anesthesia and surgerical methods may confound clinical outcomes. The comparative "other inhalational anesthesia" included a wide variety of mixtures that may have also resulted in clinical heterogeneity. In addition, there were no means to correct for studies of differing quality. Furthermore, the age and weight of patients, intraoperative opioids, isonipecotic acid consumption, and reported outcomes resulting in the heterogeneity could alter study outcomes. The impact of heterogeneity will have to be evaluated in future studies.

In conclusion, xenon anesthesia enables significantly faster recovery from anesthesia than other inhalation anesthetic agents. In spite of the high cost, xenon has characteristics that could make its use ideal in certain patient populations. Large and rigorous randomized trials in the future can focus on the recovery parameters and other outcomes such as postoperative cognitive dysfunction from xenon anesthesia.

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