Comparison between propofol-remifentanil total intravenous anaesthesia and desflurane-remifentanil balanced anaesthesia with regard to post-anaesthetic functional recovery measured with the Quality of Recovery-40 questionnaire on the day of vitrectomy

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Directed by Professor Min-Soo Kim

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ABSTRACT

Comparison between propofol-remifentanil total intravenous anaesthesia and desflurane-remifentanil balanced anaesthesia with regard to post-anaesthetic functional recovery measured with the Quality of Recovery-40 questionnaire on the day of vitrectomy

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Background: Total intravenous anaesthesia (TIVA) and inhalation anaesthesia are now commonly and safely used for general anaesthesia in outpatient surgery. Few studies have examined whether the TIVA has an advantage related to the functional recovery on the day of surgery. This study compared the degree of functional recovery following TIVA and inhalation anaesthesia using the Quality of Recovery-40 questionnaire (QoR-40) on the day of vitrectomy under general anaesthesia.

Methods: In this prospective, double-blinded, randomized study, 83 patients (20-80 years old) undergoing elective vitrectomy were randomized into two groups. The PRO group received effect-site target-controlled infusion (TCI) of propofol and remifentanil and the DES group received desflurane inhalation with effect-site TCI of remifentanil. Functional recovery at 6 h after surgery was assessed using the QoR-40. Other data such as emergence time, nausea/vomiting, and additional use of analgesic agent for agitation rescue or antiemetic drug in the post-anaesthesia care unit were collected.

Results: In the PRO group, the QoR-40 score on the day of surgery was significantly higher (P=0.033) than in the DES group (181.0 vs 169.5 in PRO

and DES groups, respectively). In particular, PRO group had significantly higher scores for physical comfort and physical independence dimensions. The amount of remifentanil administered was significantly higher and the emergence time was significantly longer in PRO group. However, there were no significant differences in other complications between the two groups.

Conclusion: TIVA showed better results in the quality of recovery on the day of surgery than inhalation anaesthesia.

Key words : anaesthetics inhalation, desflurane; anaesthetics i.v., propofol; recovery, anaesthesia recovery period

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I. INTRODUCTION

Outpatient surgery is increasing due to advances in minimally invasive procedures, anaesthesia with fewer side effects and faster recovery, and financial considerations. The important point for outpatient surgery is that recovery from anaesthesia should be quick enough to return to normal activity.[1] Total intravenous anaesthesia (TIVA) and inhalation anaesthesia are commonly and safely used. Comparative various adverse effects have been studied for these two anaesthetic methods.[2-7] However, these partial factors do not fully reflect overall recovery. The Quality of Recovery-40 questionnaire (QoR-40) is used to measure the overall recovery and has been validated.[8-10]

Recently, vitrectomy may be performed in an outpatient setting.[11-13] In vitrectomy under general anaesthesia, appropriate recovery on the day of surgery may be an important factor in the feasibility of outpatient surgery. Although a study by Lee and colleagues compared quality of recovery following TIVA and inhalation anaesthesia, the QoR-40 was completed for postoperative days 1 and 2.[14] Therefore, any difference in functional recovery on the day of surgery can be used in the selection of general anaesthetic method for outpatient surgery.

This study compared the degree of functional recovery following TIVA and inhalation anaesthesia using the QoR-40 on the day of vitrectomy.

II. MATERIALS AND METHODS

1. Study population

This study was a single-centre, prospective, double-blind, randomized controlled trial registered with ClinicalTrials.gov (NCT02212340). The study protocol was approved by the Institutional Review Board at Gangnam Severance Hospital (3-2014-0104), and written informed consent was obtained from all participants. Adult patients (20-80 years old and American Society of Anesthesiologists [ASA] class I-III), who underwent elective vitrectomy with general anaesthesia were invited to participate. Patients with allergy to the anaesthetic agents, anticipated difficult airway, body mass index (BMI) more than 30, chronic obstructive pulmonary disease, heart failure, or unstable angina were excluded. Each patient was allocated to the PRO or DES group by a random-number list created without dividing blocks from a website (http://www.random.org). Patient recruitment and randomization were conducted by a researcher who was not involved in anaesthetic management and data collection. Independent, experienced anaesthesiologists provided anaesthesia care in the same way, according to the assigned group. Because of distinct differences between the two anaesthetic methods, attending anaesthesiologists were aware of the group allocation. The patients, operating surgeons, postoperative outcome data evaluators, and data analysts did not know the group allocations.

2. Measurements

The patients were not premedicated prior to anaesthesia induction. The electrocardiogram, pulse oxygen saturation, non-invasive blood pressure, end-tidal carbon dioxide (EtCO2), and the bispectral index (BIS, AspectA-2000, Aspect Medical Systems Inc., Newton, MA, USA) were monitored at regular intervals. In the PRO group, propofol and remifentanil were administered with a commercial target-controlled infusion (TCI) system (Orchestra® Base Primea, Fresenius Vial, Brezins, France) for anaesthesia induction and maintenance. In the DES group, anaesthetic induction was established with a bolus administration of propofol 1.5-2 mg kg^{-1}, and the anaesthetized state was maintained with desflurane inhalation and remifentanil infusion through the TCI

system. The effect-site concentrations of propofol and remifentanil infused through the TCI system were determined by Schnider's and Minto's pharmacokinetic models, respectively.[15,16] The anaesthetics administered in each group were adjusted to provide a BIS value of 40 to 60 and mean arterial pressure (MAP) within 20% of pre-induction values. Rocuronium 0.6 mg kg^{-1} was injected to facilitate orotracheal intubation during the induction period. After tracheal intubation, mechanical ventilation was initiated with a tidal volume of 8 ml kg^{-1} and respiratory rate was adjusted to maintain an EtCO2 of 4.6-5.3 kPa with 50% oxygen/air mixture.

Ramosetron 0.3 mg for prophylactic anti-emesis and propacetamol 1 g for analgesia were intravenously administered 10 min before the end of the operation. Once the operation was completed, neostigmine 0.04 mg kg^{-1} and glycopyrrolate 0.005 mg kg^{-1} were given intravenously, and all the anaesthetic agents were discontinued. The stimulus to awaken the patients was confined to continuous verbal commands to open their eyes.[17] When adequate response to verbal command and sufficient spontaneous respiration were observed, tracheal extubation was performed. Every patient was admitted to the postanaesthesia care unit (PACU) after stable vital signs and spontaneous breathing with airway patency were confirmed.

From the time of discontinuation of anaesthetic agents, the durations to the first verbal command and extubation were recorded. The total amount of remifentanil and phenylephrine, BIS value, and respiratory rate at the time of extubation were also recorded. Emergence was defined as the time period from the discontinuation of anaesthetic agents and 2 min after tracheal extubation.[17] During emergence, the grade of agitation and cough was assessed using the Ricker sedation-agitation scale and a four-point scale, respectively (Table 1).[18-20] A sedation-agitation scale score $\geq$ 5 was considered as the presence of emergence agitation. A sedation-agitation scale score = 7 was regarded as dangerous agitation.[19,20] Vital signs including MAP and heart rate were recorded before anaesthesia induction, at 10 and 30 min after initiation of the operation, at the end of the operation, and at 1 and 2 min after tracheal extubation. In addition,

BIS score at tracheal extubation and adverse events such as desaturation (SpO2 < 90%), airway obstruction, and laryngospasm were also recorded during emergence.

In the PACU, the scores on the sedation-agitation scale at the time of arrival, an 11-point numerical rating scale (NRS) for postoperative pain (0=no pain and 10=worst pain imaginable), and a four-point nausea and vomiting scale (0=no nausea, 1=mild nausea, 2=severe nausea requiring antiemetics, and 3=retching, vomiting, or both) were recorded. Residual sedation was defined as a sedation-agitation scale score ≤3 at the time of arrival. If NRS was 5 or more, fentanyl 50 μg was administered intravenously. When the four-point nausea and vomiting scale score was 2 or more, metoclopramide 10 mg was administered intravenously. Discharge from the PACU was permitted when the Aldrete score was 9 or more.[17]

The quality of functional recovery at 6 h after surgery was assessed using the QoR-40 questionnaire.[10] The QoR-40 questionnaire is a 40-item quality-of-recovery questionnaire, which includes five dimensions of recovery: emotional state (9 items), physical comfort (12 items), physical independence (5 items), psychological support (7 items), and pain (7 items). A five-point Likert scale is used for scoring of each item. Positive items were scored from 1 (worst) to 5 (best). The scoring was reversed for negative items. The total score on the QoR-40 questionnaire ranges from 40 (extremely poor) to 200 (excellent).

3. Statistical analysis

The primary endpoint of this study was the total QoR-40 score at 6 h after surgery. The sample size was calculated on the basis of assumed clinical significance when the difference in QoR-40 score was more than 15 points. The mean and standard deviation of the postoperative QoR-40 from a previous study were respectively 167 and 23.[10,21] According to the results of the calculations (α of 0.05 and a power of 80%), 37 patients were needed in each group. Assuming a dropout rate of 10%, 84 patients were included and randomized. QoR-40 was compared between the two groups using an independent t-test. Other continuous variables were analysed with an independent t-test or Wilcoxon rank-sum test

after Shapiro-Wilk normality testing. The chi-square test or Fisher's exact test was used to compare categorical variables. A *P*-value of <0.05 was considered statistically significant.

Table 1. Ricker sedation-agitation scale and four-point cough scale scores during emergence.

Ricker sedation-agitation scale	**Score**
Minimal or no response to noxious stimuli	1
Arousal with physical stimuli but does not communicate	2
Difficult to arouse but awakens to verbal stimuli or gentle shaking	3
Calm and follows commands	4
Anxious or physically agitated and calms with verbal instructions	5
Requires restraint and frequent verbal reminders of limits	6
Pulling at tracheal tube, trying to remove catheters or striking at staff	7
Four-point scale	**Score**
No cough	0
Single cough	1
Persistent cough lasting < 5 s	2
Persistent cough lasting ≥ 5s or bucking	3

III. RESULTS

The study initially assessed and enrolled 84 patients. The enrolled patients were randomly assigned to each group. One patient withdrew and 83 completed the study. Figure 1 shows the CONSORT flow diagram for the number of patients in the two groups at each stage. Patient characteristics were similar in the PRO and DES groups (Table 2). There were no significant differences in operative time, anaesthesia time, or baseline vital signs between the two groups.

Table 3 shows QoR-40 scores for the PRO and DES groups on the day of surgery. The total score was significantly higher (P=0.033) in the PRO group than in the DES groups (181.0 vs 169.5 in PRO and DES groups, respectively). In particular, the PRO group demonstrated significantly higher scores in physical comfort and physical independence (P=0.031 and P=0.045, respectively). Other dimensions did not show significant differences between the two groups.

Perioperative data are shown in Table 4. The MAP and heart rate were not significantly different between the groups before anaesthesia induction, at 10 and 30 min after initiation of the operation, and at the end of the operation. However, at 1 and 2 min after extubation, the DES group had a significantly higher MAP and heart rate (P<0.001) (Figure 2). In the intraoperative period, the amount of phenylephrine administered was similar between both groups, and the amount of remifentanil administered was significantly higher in the PRO group (P<0.001). The response time to verbal commands and extubation time were significantly longer in the PRO group (P<0.001). However, the BIS, agitation incidence and score, cough score, desaturation events, and airway obstruction showed no significant differences between groups. In the PACU, agitation score, pain score, and nausea/vomiting events showed no significant differences; there was no significant difference between groups in the additional use of antiemetic drug or analgesic agent for agitation rescue.

Table 2. Patient characteristics in the PRO and DES groups.

	PRO group (*n*=41)	DES group (*n*=42)
Age (y)	59.0 (51.0-64.0)	60.0 (50.0-70.0)
Sex (M/F)	17 (41.5)/24 (58.5)	19 (45.2)/23 (54.8)
Height (cm)	162.7 (8.7)	162.4 (10.0)
Weight (kg)	64.1 (10.7)	63.9 (11.5)
Diabetes mellitus	13 (31.7)	5 (11.9)
Hypertension	12 (29.3)	15 (35.7)
Coronary artery disease	1 (2.4)	1 (2.4)
ASA class (I/II/III)	14 (34.1)/19 (46.3)	15 (35.7)/18 (42.9)
	/8 (19.5)	/9 (21.4)
Operation time (min)	60.0 (44.0-79.0)	62.0 (48.0-91.0)
Anaesthesia time (min)	100.0 (95.0-125.0)	110.0 (100.0-135.0)
Baseline vital signs		
Mean arterial pressure (mm Hg)	101.7 (18.0)	99.3 (14.9)
Heart rate (beat min^{-1})	71.0 (62.0-80.0)	72.0 (63.0-81.0)

Data are presented as mean (SD), median (IQR), or n (%) as appropriate. PRO, propofol; DES, desflurane; SD, standard deviation; IQR, interquartile range; ASA, American Society of Anesthesiologists

Table 3. QoR-40 scores for the PRO and DES groups on the day of surgery.

	PRO group (n=41)	DES group (n=42)	*P*-value
Physical comfort	54.0 (50.0-57.0)	49.5 (47.0-56.0)	0.031
Emotional status	42.0 (40.0-44.0)	40.0 (35.0-43.0)	0.072
Physical independence	23.0 (21.0-25.0)	21.0 (16.0-25.0)	0.045
Psychological support	32.0 (27.0-35.0)	31.0 (27.0-34.0)	0.395
Pain	31.0 (27.0-34.0)	29.5 (25.0-33.0)	0.141
Total score	181.0 (163.0-191.0)	169.5 (155.0-184.0)	0.033

Data are presented as median (IQR). QOR-40, 40-item Quality of Recovery questionnaire; PRO, propofol; DES, desflurane; IQR, interquartile range.

Table 4. Perioperative data of the PRO and DES groups.

	PRO group (n=41)	DES group (n=42)	*P*-value
Intraoperative data			
Remifentanil dose ($\mu g\ kg^{-1}\ min^{-1}$)	0.066 (0.021)	0.049 (0.016)	< 0.001
Phenylephrine dose ($\mu g\ kg^{-1}\ min^{-1}$)	0.103 (0.133)	0.140 (0.129)	0.201
Emergence data			
Time to verbal response (s)	799.0 (665.0-975.0)	497.5 (400.0-622.0)	< 0.001
Time to extubation (s)	867.0 (700.0-1072.0)	523.0 (440.0-635.0)	< 0.001
BIS score at extubation	77 (75-78)	82 (75-86)	0.027
Agitation score during emergence (1/2/3/4/5/6/7)	0 (0) 4 (9.8) 5 (12.2) 28 (68.3) 4 (9.8) 0 (0) 0 (0)	0 (0) 0 (0) 4 (9.5) 27 (64.3) 10 (23.8) 1 (2.4) 0 (0)	0.104
Incidence of emergence agitation	4 (9.8%)	11 (26.2%)	0.097
Cough score during emergence (0/1/2/3)	18 (43.9) 13 (31.7)	15 (35.7) 13 (31.0)	0.765

	7 (17.1)	11 (26.2)	
	3 (7.3)	3 (7.1)	
Desaturation events during emergence	0 (0)	1 (2.4)	1.000
Airway obstruction during emergence	0 (0)	1 (2.4)	1.000
PACU			
Agitation score on arrival (1/2/3/4/5/6/7)	0 (0)	0 (0)	0.313
	0 (0)	0 (0)	
	2 (4.9)	1 (2.4)	
	39 (95.1)	39 (92.9)	
	0 (0)	2 (4.8)	
	0 (0)	0 (0)	
	0 (0)	0 (0)	
Maximum pain score	4.0 (2.0-4.0)	4.0 (3.0-4.0)	0.943
Maximum nausea/vomiting score (0/1/2/3)	41 (100%)	41 (97.6%)	1.000
	0 (0)	0 (0)	
	0 (0)	1 (2.4%)	
	0 (0)	0 (0)	
Use of analgesic	2 (4.9%)	2 (4.8%)	1.000
Use of antiemetic	0 (0.0%)	1 (2.4%)	1.000

Data are presented as mean (SD), median (IQR), or n (%) as appropriate. PRO, propofol; DES, desflurane; SD, standard deviation; IQR, interquartile range.

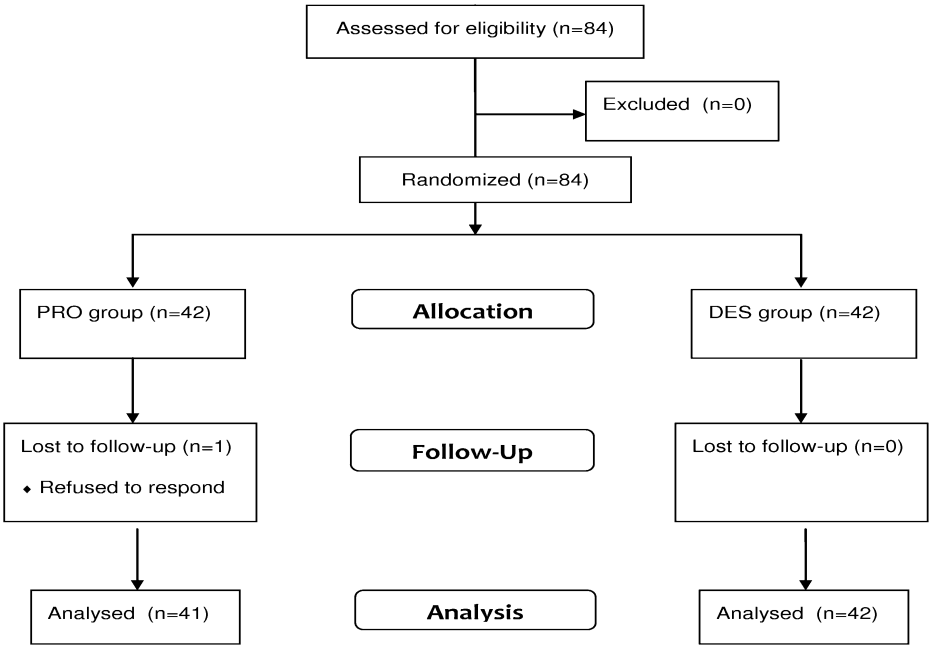

Figure 1. CONSORT flow diagram.

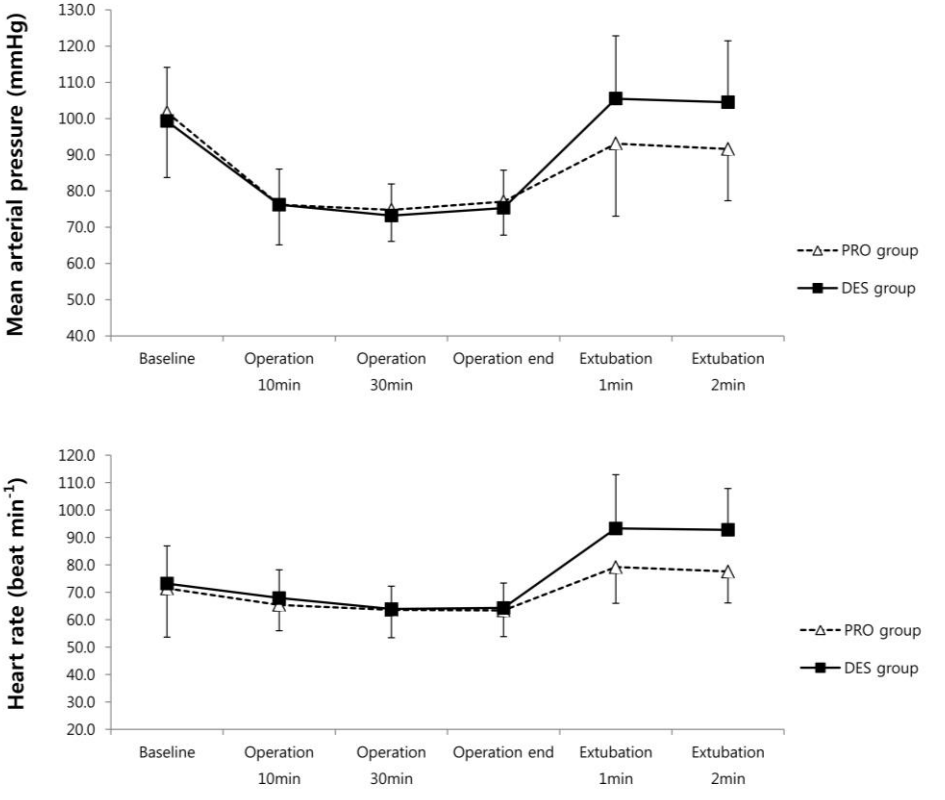

Figure 2. Mean arterial pressure and heart rate were significantly higher in the DES group at 1 and 2 min after extubation (P<0.001).

IV. DISCUSSION

In this study, we found that TIVA showed a significantly higher quality of recovery on the day of surgery than inhalation anaesthesia. In addition, TIVA required more remifentanil use and had a more delayed emergence time than inhalation anaesthesia, TIVA did not cause more complications.

Although regional anaesthesia techniques are preferred to ophthalmic surgery due to advantages including early ambulation and avoidance of complications and costs related to general anaesthesia, there are still several problems such as pain, fear and anxiety of patients and unexpected eye movement during intraocular procedures.[22,23] Various sedative agents such as propofol and midazolam have been applied to solve these problems during ophthalmic surgery. However, these drugs have several adverse effects including cardiovascular and respiratory depression related to over-sedation, non-cooperation, and disorientation during surgery.[23,24] In addition, regional block is not always safe due to serious complications i.e. globe perforation, bulbar haemorrhage, cardiovascular depression, and convulsion.[25] For these reasons, general anaesthesia is still playing an important role in ophthalmic surgery.[22]

Outpatient surgery has cost-effective financial advantages and permits the patient to recover comfortably in a familiar home environment on the day of surgery. Therefore, the quality of recovery from general anaesthesia on the day of surgery is important in outpatient surgery. For better quality of recovery, the selection of general anaesthetic method should be carefully considered. TIVA and inhalation anaesthesia are the most commonly used methods in general anaesthesia. There are many studies comparing TIVA and inhalation anaesthesia. Some previous studies have shown no significant differences between the two methods in various respects.[26,27] TIVA has the advantage of reducing contamination of the operating room and atmosphere by inhalation anaesthetics, but requires special equipment for the prevention of awareness. In recovery from anaesthesia, studies reported that patients undergoing TIVA showed better bronchociliary airway clearance than those receiving inhalation anaesthetic, a shorter time to spontaneous eye opening, response to comments, and extubation, and a lower

intensity of pain, incidence of postoperative nausea/vomiting, and usage of rescue medicine for pain and nausea/vomiting.[2-7] In addition, TIVA decreases intraocular pressure more significantly than inhalation anaesthesia for ophthalmic surgery.[28] In terms of quality of recovery, TIVA was reported to have a higher QoR-40 score than inhalation anaesthesia on postoperative days 1.[14] However, no other study has compared the quality of recovery on the day of surgery according to the anaesthetic method. In our study, there were no significant differences in complications between TIVA and inhalation anaesthesia. Despite the greater use of remifentanil and delayed awakening time, the results of TIVA were better for the quality of recovery on the day of surgery. These findings suggest that fragmentary clinical indicators do not fully reflect the quality aspects of recovery.

The QoR-40 is the most widely used method for assessing functional recovery after anaesthesia and surgery. The QoR-40 questions are scored from worst (one point) to best (five points), and the 40 questions are classified into five dimensions of emotional state, physical comfort, psychological support, physical independence, and pain. This questionnaire has been used in various studies to investigate the effect of surgery type, anaesthetic method, additional use of medication, sex, etc. on general anaesthesia and surgery, and validity has been proven.[29-34] In this study, compared to inhalation anaesthesia, TIVA showed significant differences in physical comfort and physical independence dimensions in the QoR-40 on the day of surgery. The physical comfort dimension is composed of questions related to breathing, sleep, eating, resting, nausea, vomiting, dry retching, restlessness, shaking or twitching, shivering, cold, and dizziness. The physical independence dimension is related to capability of return to normal daily life, including work, home activities, writing, speech, and washing. These dimensions help to understand the impact of postoperative or post-anaesthetic complications on patients undergoing outpatient surgery.[35] Each question allows the patient to select a score using a five-point scale. When the patent selects a score, subjective feelings may be reflected in the score. Therefore, even if there is no significant difference in complications observed by

the clinician, there may be a significant difference in the score of the dimensions.[21]

TIVA may have been able to obtain better quality of recovery because the anaesthetic method had an effect on modulating the response to stress and inflammation caused by surgery and anaesthesia.[36] The inflammatory response during surgery is amplified by the increase in stress hormones and insulin resistance.[37] An enhanced inflammatory reaction can lead to increased complications and longer hospital stays.[38,39] TIVA using propofol has been reported to reduce the stress-induced inflammatory response more effectively than inhalation anaesthesia, and the secretion of stress hormones, neuroendocrine responses, and catecholamine release is less than that with inhalation anaesthetics.[40-43] Additionally, bronchociliary airway clearance may be significantly more impaired by inhalation anaesthesia than with TIVA.[2] Therefore, inhalation anaesthesia can cause more respiratory problems. In this regard, better bronchociliary airway clearance with TIVA may have affected the results of the QoR-40 by reducing patient physical comfort.

There are some limitations or considerations to this study. First, the preoperative QoR-40 was not evaluated. However, there was no difference in demographic data among patients. Additionally, each patient was randomized and none had a history of cognitive impairment or psychiatric medication. Some studies also obtained reliable results without preoperative QoR-40 scoring.[17,33] Therefore, the preoperative QoR-40 might not differ significantly between groups. Second, the Korean version of the questionnaire used in this study was not yet validated. However, the questionnaire used plain language that was not likely to change in meaning after translation. For this reason, the Korean version of the QoR-40 has been used in many studies.[14,17] Thus, the effect of language differences on the results of the study may not be significant. Finally, the exclusion criteria of this study did not include renal failure or liver cirrhosis. Previous studies reported that the metabolism of propofol, desflurane and remifentanil that were administered to patients enrolled in this study were not significantly affected by these organ failures.[44-49] In addition, the anaesthetics administered in each group

were adjusted to achieve a BIS value of 40 to 60 and MAP within 20% of pre-induction values.

V. CONCLUSION

In conclusion, TIVA showed better results in the quality of recovery on the day of surgery than inhalation anaesthesia. TIVA might be considered as a general anaesthetic method for outpatient surgery in terms of the quality of recovery on the day of surgery.

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ABSTRACT(IN KOREAN)

망막수술에서 propofol-remifentanil 전정맥마취와 desflurane-remifentanil 균형마취간의 QoR-40을 이용한 마취 후 일상회복정도의 비교

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정규희

배경: 전정맥마취 (TIVA)와 흡입 마취는 외래 수술의 전신 마취에 일반적으로, 안전하게 사용되는 마취방법이다. 전정맥마취가 수술 당일의 기능적 회복 면에서 이점이 있는지에 대해서는 거의 연구되지 않았다. 이 연구는 전신마취 하에서 유리체절제술 당일 QoR-40 설문지를 사용하여 전정맥마취 및 흡입마취후의 기능적 회복 정도를 비교하였다.

방법: 전향적 이중 맹검 무작위 연구방법에 따라, 계획된 유리체 절제술을 시행한 83명의 환자 (20세- 80세)를 무작위로 두 그룹으로 나누었다. PRO 그룹은 프로포폴과 레미펜타닐의 효과처 목표 농도 조절 주입 (TCI) 을 받았고, DES 그룹은 레미펜타닐의 효과처 목표 농도 조절 주입과 데스플루란 흡입마취를 받았다. 수술 후 6시간째의 기능회복을 QoR-40 설문지를 사용하여 평가하였다. 회복실에서의 각성 시간, 동요 (agitation) 해소를 위한 진통제의 사용, 오심/구토, 항구토제의 사용과 같은 기타 데이터를 수집하였다.

결과: PRO 그룹에서의 수술 당일 QoR-40 설문지의 점수는 DES 그룹보다 (PRO 및 DES 그룹에서 181.0 대 169.5) 유의하게 높았다 (P=0.033). 특히 PRO 그룹은 신체적 편안함과 신체적 독립성 측면에서 유의하게 높은 점수를 보였다. 투여된 레미펜타닐의 양과 각성 시간은 PRO 그룹에서 현저히 높았다. 그러나 다른 합병증에서는 두 그룹간의 유의한 차이를 보이지 않았다.

결론: 전정맥마취가 흡입 마취에 비해 수술 당일의 마취 회복의 질 측면에서 더 유리하였다.

핵심되는 말 : 데스플루란, 프로포폴, 회복, 마취 회복 기간