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ORIGINAL ARTICLE

Recovery of psychomotor function after total intravenous anesthesia with remifentanil–propofol or fentanyl–propofol

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Abstract
Purpose Total intravenous anesthesia (TIVA) with propofol combined with remifentanil or fentanyl has commonly been used to achieve general anesthesia. The purpose of this study was to examine recovery of psychomotor function, by use of the Trieger dot test, after TIVA with remifentanil–propofol or with fentanyl–propofol.
Methods Forty patients were randomly divided into two groups of 20, to receive TIVA with either remifentanil–propofol (group R) or fentanyl–propofol (group F). Anesthesia was induced by intravenous injection of propofol. In group R, remifentanil at 0.3 μg/kg/min was infused continuously during surgery. In group F, 3 μg/kg fentanyl was injected as an initial dose and 1 μg/kg fentanyl was administered intravenously every 30 min during surgery. Psychomotor function, as measured by the Trieger dot test, was evaluated before anesthesia and 30, 60, 90, 120, and 150 min after the end of TIVA.
Results From assessment of the Trieger dot test, the number of dots missed in group R from 30 to 120 min after the end of TIVA was significantly lower than in group F. The maximum distance of dots missed in group R from 30 to 120 min after the end of TIVA was significantly shorter than in group F. The average distance of dots missed in group R from 30 to 120 min after the end of TIVA was significantly shorter than in group F.
Conclusion Recovery of psychomotor function in TIVA with remifentanil–propofol is faster than that in TIVA with fentanyl–propofol.

Keywords Psychomotor function · Trieger dot test · Remifentanil · Fentanyl · Propofol

Introduction

Total intravenous anesthesia (TIVA) with propofol combined with remifentanil has been widely used for ambulatory surgery because of rapid recovery from anesthesia [1]. However, remifentanil [2] and propofol [3] have psychomotor effects in the early recovery stage after continuous infusion, so it may be difficult to evaluate recovery status after TIVA with remifentanil–propofol. Despite this, monitoring of recovery of psychomotor function is recommended for determination of the observation period after TIVA with remifentanil–propofol. There have so far been few reports on the recovery of psychomotor function after TIVA with remifentanil–propofol [4].

Various psychomotor indices have been suggested to measure intermediate or late recovery from anesthesia. The Trieger dot test is widely used for assessment of intermediate and late recovery of cognitive and psychomotor functions after anesthesia. Gupta et al. [5] reported the Trieger dot test was more sensitive than the others for evaluation of recovery of psychomotor function after general anesthesia. We have previously used the Trieger dot test to study recovery of psychomotor function after propofol sedation and showed its validity for evaluation of psychomotor function in the early recovery state [6].

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In this study we used the Trieger dot test to examine recovery of psychomotor function after TIVA with remifentanil–propofol, and these results were compared with those after TIVA with fentanyl–propofol.

Materials and methods

After obtaining the approval of the ethics committee of Dokkyo Medical University School of Medicine and informed consent, 40 ASA physical status 1 or 2 patients 34–60 years of age, within 15% of ideal body weight, who were scheduled to undergo elective oral surgery, for example extraction of impacted teeth, cystectomy, open reduction of fractures, sequestrectomy, and resection of leukoplakia, under TIVA, were studied. Exclusion criteria were a history of cardiac, pulmonary, hepatic, or renal disease, or disabling neuropsychiatric disorders. No patients were receiving medication.

The Trieger dot test, a psychomotor function test, was performed before and after anesthesia. The test was conducted by a single anesthesiologist who was unaware of the drugs used. The test consists in joining together 42 dots with a line to form a drawing. The number of dots missed (NDM) is the total number of dots that are not connected. The maximum distance of the dots missed (MDDM) is the longest distance (in millimeters) between the drawn line and the missed dots. The average distance of dots missed (ADDM) is the mean of the cumulative distance (in millimeters) between the drawn line and the missed dots.

All patients were premedicated by intramuscular injection of 0.5 mg atropine sulfate 30 min before the induction of anesthesia. After arriving in the operation room, pulse oximetry (Satlite; Datex-Ohmeda, Madison, WI, USA), capnography (Capnomac; Datex-Ohmeda), and bispectral index monitoring (BIS; model A1050, version 3.4; Aspect Medical Systems, USA) were started. Forty patients were prospectively randomized, via sealed envelope assignment, to one of two groups of 20 patients each to receive TIVA with either remifentanil–propofol (group R) or fentanyl–propofol (group F).

A face mask was used to administer 100% oxygen 6 l/min. In both groups, propofol was injected until loss of consciousness, when intravenous target-controlled infusion was commenced (TCI pump, Marsh's model, TE-371, Terumo, Japan) with a blood concentration of 3.0 μg/ml. After the induction of anesthesia, mask ventilation with oxygen was started. The trachea was intubated after intravenous injection of 0.1 mg/kg vecuronium, and the ventilator was started with 66% air in oxygen. During surgery the rate of infusion of propofol was adjusted to maintain an appropriate level of anesthesia by use of BIS values (range 40–60). In group R, 0.3 μg/kg/min remifentanil was continuously infused during surgery. In group F, 3 μg/kg fentanyl was injected as an initial dose and intravenous injection of 1 μg/kg fentanyl was administered every 30 min during surgery.

End-tidal carbon dioxide tension (Et_{CO_2}) was maintained between 35 and 40 mmHg during surgery. All patients received a continuous infusion of acetate Ringer's solution at a rate of 5 ml/kg/h during the study.

Fentanyl was not administered within 30 min of the end of surgery, and propofol and remifentanil were discontinued at the end of surgery. The lungs were ventilated with 100% oxygen at a fresh gas flow of 6 l/min after TIVA. Residual neuromuscular block was reversed by use of 2 mg neostigmine, as a mixture with 1 mg atropine sulfate, after spontaneous ventilation was observed. Extubation was conducted when adequate spontaneous ventilation and response to verbal command were established. The early recovery time from the end of TIVA to opening of the eyes on command and the time from the end of TIVA to extubation were noted by a single anesthesiologist. The Trieger dot test was performed before anesthesia and 30, 60, 90, 120, and 150 min after the end of TIVA. If patients complained of postoperative pain, 50 mg flurbiprofen axetil was to be administered. If flurbiprofen axetil was not adequate to relieve postoperative pain, 15 mg pentazosine was to be administered intramusculary and those patients would be excluded from the study.

All data are expressed as mean ± SD. Intergroup differences were analyzed by two-way analysis of variance for the repeated-measures design. When a significant overall effect was detected, Scheffé's test was used for comparison of the mean values for the two variables. Comparison between both groups was by application of Scheffé's test. The threshold for statistical significance was $P < 0.05$.

Results

Age, gender, height, weight, duration of surgery, duration of anesthesia, and BIS values during anesthesia were not significantly different between the two groups (Table 1). Although the total amount of propofol was no different between the two groups (957 ± 258 mg in group R; 830 ± 274 mg in group F), the average effect site concentration of propofol in group R during surgery was significantly lower than that in group F (2.8 ± 0.3 μg/ml in group R; 3.1 ± 0.3 μg/ml in group F; $P < 0.05$). The effect site concentration of propofol using TCI at the end of surgery in group R was significantly lower than that in group F (2.7 ± 0.4 μg/ml in group R; 3.1 ± 0.5 μg/ml in group F; $P < 0.01$). The total amounts of remifentanil and fentanyl were 3.1 ± 1.7 and 0.37 ± 0.1 mg, respectively.

The early recovery time from the end of TIVA until patients opened their eyes on command differed significantly between the groups (10 ± 3 min in group R; 13 ± 7 min in group F; $P < 0.05$). A statistically significant difference was observed in the time from the end of TIVA to extubation between both groups (14 ± 4 min in group R; 17 ± 6 min in group F; $P < 0.01$).

Postoperative pain scores evaluated on a visual analogue scale did not significantly differ between the groups 2 h after the end of TIVA (50 ± 8 mm in group R; 52 ± 11 mm in group F). There was no significant difference in the number of patients who asked to use flurbiprofen axetil within the 24 h postoperative period between group R (10/20; 50%) and group F (8/20; 40%). No patient in either group requested additional analgesics postoperatively.

Figure 1 shows the NDM results before and after TIVA. Before TIVA there were no significant differences in NDM between the two groups. In group R, NDM increased significantly from 30 to 90 min after the end of TIVA compared with the baseline value. In group F, NDM increased significantly from 30 to 120 min after the end of TIVA compared with the baseline value. NDM in group R was significantly lower than that in group F from 30 to 120 min after the end of TIVA.

As shown in Fig. 2, before TIVA there were no significant differences in MDDM between the two groups. In group R, MDDM increased significantly from 30 to 60 min after the end of TIVA compared with the baseline value. In group F, MDDM increased significantly from 30 to 120 min after the end of TIVA compared with the baseline value. MDDM in group F increased significantly from 30 to 120 min after the end of TIVA compared with that in group R.

Figure 3 shows the ADDM results before and after TIVA. Before TIVA there were no significant differences in ADDM between the two groups. In group R, ADDM increased significantly from 30 to 60 min after the end of TIVA compared with the baseline value. In group F, ADDM increased significantly from 30 to 120 min after the

Table 1 Demographic data in total intravenous anesthesia (TIVA) with remifentanil–propofol (group R) or with fentanyl–propofol (group F)

	Group R	Group F
Age (years)	49 ± 19	51 ± 18
Gender (male/female)	8/12	10/10
Height (cm)	162 ± 10	161 ± 7
Weight (kg)	62 ± 12	56 ± 9
Duration of surgery (min)	95 ± 40	81 ± 34
Duration of anesthesia (min)	162 ± 41	150 ± 40
Highest BIS value during anesthesia	56 ± 5	55 ± 3
Lowest BIS value during anesthesia	43 ± 3	42 ± 3
BIS value at the end of TIVA	50 ± 4	49 ± 3

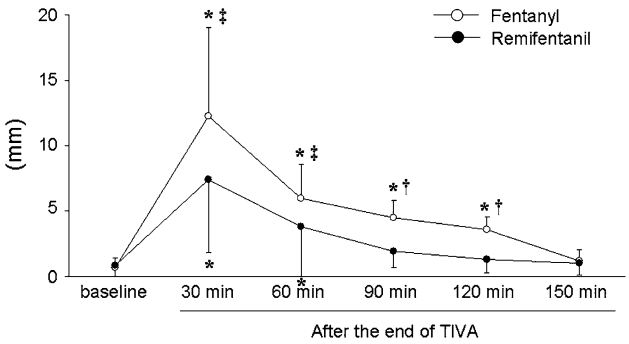

Fig. 2 The maximum distance of dots missed before and after total intravenous anesthesia (*TIVA*) with remifentanil–propofol (group R) or fentanyl–propofol (group F), using the Trieger dot test. *$P < 0.01$ versus baseline. †$P < 0.01$ versus group R. ‡$P < 0.05$ versus group R. Values are shown as mean ± SD

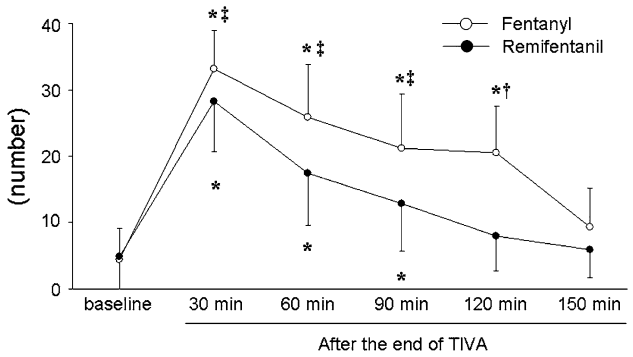

Fig. 1 The number of dots missed before and after total intravenous anesthesia (*TIVA*) with remifentanil–propofol (group R) or fentanyl–propofol (group F), using the Trieger dot test. *$P < 0.01$ versus baseline. †$P < 0.01$ versus group R. ‡$P < 0.05$ versus group R. Values are shown as mean ± SD

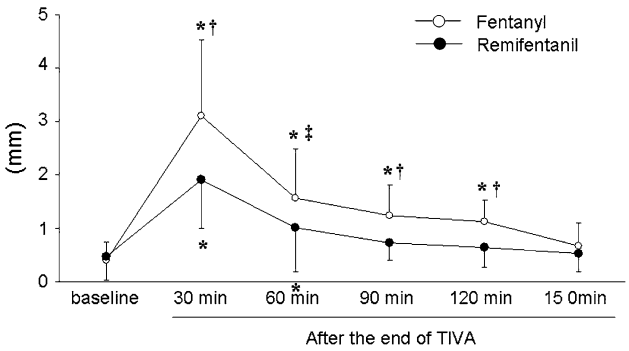

Fig. 3 The average distance of dots missed before and after total intravenous anesthesia (*TIVA*) with remifentanil–propofol (group R) or fentanyl–propofol (group F), using the Trieger dot test. *$P < 0.01$ versus baseline. †$P < 0.01$ versus group R. ‡$P < 0.05$ versus group R. Values are shown as mean ± SD

end of TIVA compared with the baseline value. ADDM in group R from 30 to 120 min after the end of TIVA was significantly shorter than that in group F.

Et_{CO_2} was maintained between 35 and 39 mmHg during TIVA in both groups.

Discussion

Remifentanil is the newest ultra-short-acting μ-opioid receptor agonist. The elimination half-life of remifentanil metabolized by tissue and plasma esterases is 8–20 min [7], whereas that of fentanyl metabolized by the liver is 3–4 h [8]. Furthermore, the context-sensitive half-life of remifentanil is considerably less than that of fentanyl [9]. Therefore, remifentanil is preferable to fentanyl as an opioid during TIVA for surgery because of faster emergence from anesthesia, few postoperative side effects, and early discharge from hospital [10–12]. Coskun et al. [13] reported that eye opening time, and extubation time for TIVA with remifentanil–propofol were significantly shorter than those for TIVA with fentanyl–propofol. These were similar to our results. They also found that the time of orientation (i.e., recalling name and date of birth) in TIVA with remifentanil–propofol was significantly shorter than that of TIVA with fentanyl–propofol (4.9 and 7.6 min, respectively). However, little is known about the different effects on psychomotor function after anesthesia by TIVA with remifentanil–propofol compared with TIVA with fentanyl–propofol. NDM, MDDM, and ADDM from the Trieger dot test are used to assess complete recovery from anesthesia. Greater numbers of dots missed and longer distances from a drawn line to dots are associated with delayed recovery of psychomotor function after anesthesia.

In this study, according to the Trieger dot test, recovery of psychomotor function after TIVA with remifentanil–propofol was significantly faster than after TIVA with fentanyl–propofol. The recovery of psychomotor function, which is associated with sophisticated and elaborate functions, after TIVA with remifentanil–propofol does not exceed 120 min after anesthesia; that after TIVA with fentanyl–propofol may take 150 min after anesthesia, from our results. We also demonstrated that NDM, MDDM, and ADDM of the Trieger dot test in group F increased significantly from 30 to 120 min after anesthesia compared with those in group R. All of our results consistently showed that TIVA with remifentanil resulted in faster recovery of psychomotor function than that with fentanyl. Because impairment of psychomotor function due to TIVA may be detrimental to patients' well-being after anesthesia, a more prolonged and attentive observation period may be necessary for patients receiving TIVA with fentanyl–propofol compared with TIVA with remifentanil–propofol.

From previous studies [6, 14–18], duration of anesthesia, depth of anesthesia, types of opioid, and age may affect psychomotor function after TIVA with opioid–propofol. Because there were no significant differences in the duration of anesthesia, the depth of anesthesia at the end of TIVA, the age in this study, and the types of opioid might affect our results. Veselis et al. [19] evaluated psychomotor function for several plasma fentanyl concentrations in healthy volunteers. In their study, fentanyl at concentrations above 2.5 ng/ml caused impairment of psychomotor function. Furthermore, there is a report describing an interaction between fentanyl and propofol during emergence from anesthesia [20]. Higher plasma concentrations of fentanyl required patients to eliminate propofol so as to lower plasma concentrations to regain consciousness. Therefore, combination of opioids with propofol may contribute to delayed recovery of psychomotor function compared with each drug alone. In this study, psychomotor function was impaired until 120 min after the end of surgery in group F, but only 90 min in group R. In group F, fentanyl was administered with intermittent boluses according to anesthesiologists' usual practice. This may have contributed to the slightly higher plasma fentanyl concentration until 120 min after surgery in group F.

Although plasma concentrations of fentanyl and remifentanil were not measured in this study, we estimated blood concentration of fentanyl and remifentanil after the end of TIVA by use of pharmacokinetic simulation software (TIVAtrainer® ver.8, eurosiva.org) in groups F and R, respectively. In group F, blood concentration of fentanyl was estimated as $0.79 \pm 0.1, 0.68 \pm 0.1, 0.63 \pm 0.1, 0.59 \pm 0.1$, and 0.57 ± 0.1 ng/ml at the end of TIVA and 30, 60, 90 and 120 min after the end of TIVA, respectively. In group R, blood concentration of remifentanil was estimated as 7.87 ± 1.4, 0.29 ± 0.1, 0.09 ± 0.02, 0.06 ± 0.01, and 0.04 ± 0.02 ng/ml at the end of TIVA and 30, 60, 90 and 120 min after the end of TIVA, respectively. It has been shown that the context-sensitive half-life of remifentanil is significantly less than that of fentanyl [9]. Therefore, our results may have been affected by the type of opioid administered in TIVA.

BIS monitoring is currently regarded as the accepted standard on depth of anesthesia. It is also used for reducing the average consumption of anesthetic agents [21]. In this study, the BIS values in both groups were maintained in the range 40–60 during surgery. However, the effect site concentration of propofol at the end of surgery in group R was significantly lower than that in group F. This result was consistent with previous studies [11, 12]. One reason why recovery of psychomotor function was earlier in group R might be the lower effect site concentration of propofol compared with that in group F. Adequate analgesia can

result in low effect site concentration of propofol with suitable BIS values [22].

Dressler et al. [4] showed that psychomotor function was impaired until 90 min after surgery under remifentanil–propofol anesthesia. This is consistent with our results. The context-sensitive half-life of remifentanil is much less than that of propofol. Recovery of psychomotor function may depend on effect site concentration of propofol at the end of surgery, compared with a residual effect of remifentanil after TIVA.

Postoperative pain and administration of analgesics may contribute to recovery of psychomotor function. There are reports that TIVA with remifentanil–propofol satisfied more postoperative analgesic requirements than TIVA with other opioid–propofol [23–25]. In this study, postoperative pain scores and the number of patients who requested analgesics after surgery were similar in both groups. Therefore, postoperative pain condition did not affect differences in recovery of psychomotor function between groups F and R.

In conclusion, we have demonstrated that TIVA with remifentanil–propofol results in more rapid and reliable recovery of psychomotor function than TIVA with fentanyl–propofol.

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