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Coadministration of Propofol and Remifentanil for Lumbar Puncture in Children

Dose–Response and an Evaluation of Two Dose Combinations

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Background: **The combination of propofol and remifentanil may be particularly suitable for short-duration procedures such as lumbar puncture. The authors undertook a two-part study to evaluate coadministration of propofol and remifentanil as an anesthetic technique for lumbar puncture in children.**

Methods: **The first part was a sequential allocation dose-finding study to determine the minimum effective dose of remifentanil when coadministered with 2.0 or 4.0 mg/kg propofol. The second was a randomized double-blind study to compare the intraoperative and recovery characteristics of 2.0 or 4.0 mg/kg propofol coadministered with the corresponding effective dose of remifentanil.**

Results: **Effective doses of remifentanil in 98% of children were 1.50 ± 1.00 and 0.52 ± 1.06 μg/kg when coadministered with 2.0 and 4.0 mg/kg propofol, respectively. The duration of apnea was longer (median, 110 *vs.* 73 s; $P < 0.05$) and the time to awakening was shorter (median, 10 *vs.* 23 min; $P < 0.05$) after 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil compared with 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil. No child experienced hypotension or postprocedure nausea or vomiting after either dose combination.**

Conclusions: **Both dose combinations (2.0 mg/kg propofol plus 1.5 μg/kg remifentanil and 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil) provide effective anesthesia for lumbar puncture in children. However, the intraoperative and recovery characteristics of the two dose combinations differ in that the duration of apnea increases whereas recovery time decreases as the dose of remifentanil is increased and that of propofol is decreased.**

THE administration of sedative, anesthetic and analgesic agents is commonly required for painful hemato-oncologic procedures in pediatric patients. The intravenous anesthetic propofol has a rapid onset and offset of action making it suitable for ambulatory hemato-oncologic procedures of short duration, such as lumbar puncture. Propofol provides amnesia, anxiolysis, and hypnosis but has no analgesic properties and therefore may not prevent movement in response to lumbar puncture needle insertion. In addition, propofol may produce myoclonic movements in 2–65% of children,[1,2] which can make the procedure difficult to perform. To ensure patient immobility, the dose of propofol is often increased, resulting in a duration of action that is excessive for lumbar puncture. Coadministration of propofol with adjuvant agents may decrease the dose of propofol required and the time for recovery.[3]

The ultrashort-acting opioid remifentanil can be used to provide analgesia for brief painful procedures that are associated with minimal residual pain. As the sole agent, remifentanil is associated with a high incidence of respiratory depression and/or arterial oxygen desaturation.[4–6] The use of remifentanil in combination with propofol is particularly suitable for short-duration procedures[7,8]; however, no study has evaluated this drug combination for lumbar puncture in children. We undertook a two-part study to evaluate the coadministration of propofol and remifentanil as an anesthetic technique for lumbar puncture in children. First, we performed a sequential allocation dose-finding study to determine the minimum effective dose of remifentanil when coadministered with 2.0 or 4.0 mg/kg propofol. Second, we undertook a randomized double-blind study to compare the intraoperative and recovery characteristics of coadministration of 2.0 or 4.0 mg/kg propofol and the corresponding ED_{98} dose (effective dose in 98% of children) of remifentanil.

Materials and Methods

Approval from the Research Ethics Board of the Hospital for Sick Children (Toronto, Ontario, Canada), parental consent, and, when necessary, patient assent were obtained. In total, 94 unpremedicated American Society of Anesthesiologists physical status II or III pediatric patients undergoing lumbar puncture for a hemato-oncologic disorder were studied. Excluded were children who were known or suspected to be difficult to ventilate by facemask, who were deemed medically unfit (significant cardiac, respiratory, metabolic, hepatic, or renal disease) to receive either of the two study medications, who were obese (weight for height > 95th percentile[9]), or who did not have an indwelling intravenous line.

Part 1

To determine the minimum effective dose of remifentanil, 64 children aged 3–11 yr were studied. Each child

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was randomly assigned to receive either 2.0 or 4.0 mg/kg propofol using a blocked randomization schedule derived from a table of random numbers. These doses of propofol are within the 95% confidence interval for the ED_{95} (effective dose in 95% of subjects) for loss of eyelash reflex in unpremedicated children.[10,11] Group assignments were kept in sealed, opaque envelopes until consent/assent was obtained. Standard monitors (electrocardiogram, noninvasive blood pressure, and pulse oximeter) were applied before induction of anesthesia, and baseline measurements were taken. No topical anesthetic cream was applied to the skin over the lumbar region. Two anesthesiologists were present for each case. An unblinded anesthesiologist administered propofol followed immediately by remifentanil, diluted with 0.9% saline to a volume of 3 ml and administered as a bolus. The intravenous line was then flushed with 10 ml saline, 0.9%. The initial dose of remifentanil was 1.0 μg/kg for children receiving 2.0 mg/kg propofol and 0.5 μg/kg for those receiving 4.0 mg/kg propofol. In accordance with the Dixon up-and-down method,[12] the dose of remifentanil was increased or decreased for subsequent children depending on the response of the previous child to lumbar puncture needle insertion, using a dose interval of 0.25 μg/kg. For the purpose of analysis, the patient's response to needle insertion was reported as "no movement" or "movement."[13] "No movement" was defined as the absence of gross purposeful muscular movement preventing advancement of the lumbar puncture needle. The anesthesiologist making the assessments was unaware of the doses of propofol and remifentanil administered.

After administration of the propofol and remifentanil, the child was placed in the left lateral decubitus position, and 100% oxygen was administered by facemask. The skin over the lumbar region was prepared with chlorhexidine antiseptic solution and draped by the oncologist. Oxygen saturation was maintained above 94% using assisted manual ventilation if required. Ninety seconds after administration of remifentanil, the oncologist inserted the lumbar puncture needle. If movement occurred, the study was terminated, and an additional bolus of 1.0 mg/kg propofol was administered at the discretion of the blinded anesthesiologist. If no movement occurred in response to the lumbar puncture needle, the patient was judged to be satisfactorily anesthetized. Oxygen saturation, heart rate, and respiratory rate were monitored continuously during the procedure, and blood pressure was recorded at 1-min intervals after induction of anesthesia. The duration of apnea was recorded, as were episodes of desaturation and/or hypotension.

Part 2

To compare the intraoperative (duration of apnea, hemodynamic variables, oxygen saturation) and recovery characteristics of 2.0 mg/kg propofol (group P2) or 4.0 mg/kg propofol (group P4) coadministered with the corresponding ED_{98} of remifentanil derived from the dose–response data acquired in part 1, 34 children aged 4–11 yr were studied. Randomization was performed as in part 1.

Standard monitors were applied before induction of anesthesia, and baseline measurements were taken. No topical anesthetic cream was applied to the skin over the lumbar region. Propofol was followed immediately by remifentanil, diluted with 0.9% saline to a volume of 3 ml and administered as a bolus, and flushed with 10 ml saline, 0.9%. After administration of propofol and remifentanil, the patient was placed in the left lateral decubitus position, and 100% oxygen was administered by facemask. The skin over the lumbar region was cleaned and draped by the oncologist. Ninety seconds after administration of remifentanil, the oncologist inserted the lumbar puncture needle. If movement occurred, an additional bolus of 1.0 mg/kg propofol was administered and repeated as necessary. If no movement occurred in response to the lumbar puncture needle, the patient was judged to be satisfactorily anesthetized. The study was blinded in that the investigator recording the data was unaware of the doses of propofol and remifentanil administered. The duration of apnea, defined as the time from remifentanil administration to detection of spontaneous respiratory efforts by direct visualization of the chest and abdomen, was recorded. If necessary, intermittent assisted manual ventilation was performed to maintain the oxygen saturation above 94%. Heart rate, oxygen saturation, and respiratory rate were recorded at baseline, at 1-min intervals during the procedure, on arrival to the recovery room, and at 15-min intervals thereafter for 1 h. Bradycardia was defined as a heart rate less than 60 beats/min, and hypotension was defined as a systolic blood pressure less than 60 mmHg. Postprocedure sedation was rated on a numeric scale of 1–5, defined as follows: 1 = completely awake; 2 = awake but drowsy; 3 = asleep but responsive to verbal commands; 4 = asleep but responsive to tactile stimuli; and 5 = asleep but not responsive to any stimuli.[14] The sedation score was recorded upon admission to the recovery room and every 5 min thereafter for 1 h. The time to awakening, defined as the time from remifentanil administration to sedation score of 2 or less, was recorded.

Statistical Analyses

Statistical analysis was performed using GraphPad Prism 5 for Windows (Graphpad Software Inc., San Diego, CA) and SAS 9.1 (SAS Institute Inc., Cary, NC). Patient age, patient weight, and duration of procedure were compared between groups using an independent sample two-tailed Student *t* test. Categorical data were analyzed using a two-tailed Fisher exact test. In part 1, the minimum effective dose of remifentanil for each group was calculated by the method described by Dixon for quantal responses.[12] Values were obtained by calcu-

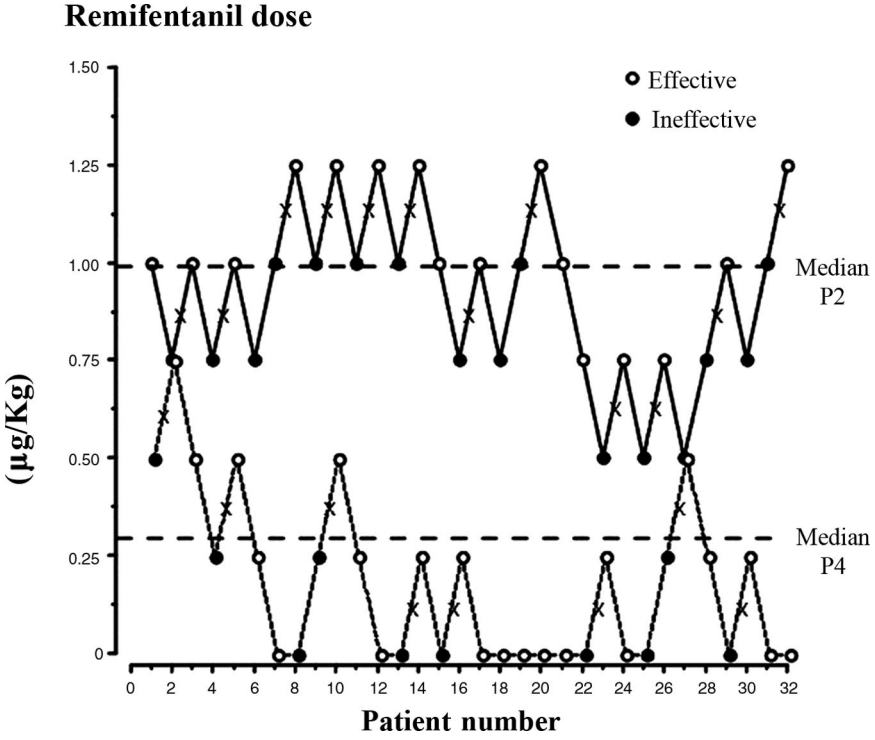

Fig. 1. Dixon up-and-down determinations for the two study groups (*solid curve* = 2.0 mg/kg propofol; *dashed curve* = 4.0 mg/kg propofol). *Horizontal dashed lines* show the minimum effective dose of remifentanil in children receiving 2.0 mg/kg propofol (Median P2) and 4.0 mg/kg propofol (Median P4). The *X*s correspond to the average of independent crossover pairs (ineffective–effective). The minimum effective dose of remifentanil was calculated as the average of the crossovers.

lating the midpoint remifentanil concentration for independent pairs of patients in which one patient moved and the next did not ("movement"–"no movement" crossover) (fig. 1). At least six independent crossovers were necessary in each group to provide a reliable estimate of the minimum effective dose using the Dixon up-and-down method.[12] In addition, data were analyzed using a logit regression model to determine the effective dose of remifentanil for lumbar puncture needle insertion in 50% and 98% of children (ED_{50} and ED_{98}, respectively).

For part 2, the primary outcome measure was the duration of apnea. To estimate the sample size required for part 2, we used data from part 1 showing that the mean duration of apnea after successful lumbar puncture with 2.0 mg/kg propofol and remifentanil was 93 ± 45 s. For the study to have the ability to detect a difference of 1 SD in duration of apnea (effect size = 1), with a two-tailed α of 0.05 and β of 0.2, we estimated that 17 patients would be needed in each group. Secondary outcome measures included time to awakening and hemodynamic variables. Data were tested for normality using the Kolmogorov–Smirnov test. Because data for duration of apnea and time to awakening deviated significantly from normality, the Mann–Whitney test was used for between-group comparisons. Repeated-measures analysis of variance with Tukey–Kramer posttest analysis was used to compare parametric variables. Data are reported as median and range, or mean ± SD, as appropriate. $P < 0.05$ was considered statistically significant.

Results

No significant differences in patient age, weight, sex, and duration of procedure were found between groups (table 1).

Part 1

The minimum effective doses of remifentanil required to prevent movement are shown in figure 1 and table 2. The percentages of patients who exhibited movement were 50% and 34% after 2.0 and 4.0 mg/kg propofol, respectively. ED_{50} values determined by logit regression

Table 1. Demographics and Duration of Lumbar Puncture

	Study 1		Study 2	
	2.0 mg/kg Propofol	4.0 mg/kg Propofol	2.0 mg/kg Propofol + 1.5 μg/kg Remifentanil	4.0 mg/kg Propofol + 0.5 μg/kg Remifentanil
Age, yr	5.2 ± 2.1	5.6 ± 2.6	6.2 ± 1.6	7.2 ± 2.4
Weight, kg	20.6 ± 6.4	22.7 ± 7.6	26.4 ± 11.3	29.9 ± 9.7
M/F	19/13	22/10	13/4	15/2
Duration of procedure, s	229 ± 68	211 ± 38	227 ± 48	219 ± 52

Patient demographics and duration of procedure were comparable between groups within each study. Values are mean ± SD or ratios.

Table 2. Effective Doses of Remifentanil When Coadministered with Propofol

	2.0 mg/kg Propofol	4.0 mg/kg Propofol
Dixon minimum effective dose, μg/kg	0.96 ± 0.23	0.28 ± 0.22
ED_{50}, μg/kg	0.86 ± 1.00	0.12 ± 1.02
ED_{98}, μg/kg	1.50 ± 1.00	0.52 ± 1.06

The Dixon minimum effective doses of remifentanil were determined by calculating the midpoint remifentanil concentration for independent pairs of patients in which one patient moved and the next did not ("movement"–"no movement" crossover). The ED_{50} and ED_{98} of remifentanil were calculated using a logit regression model. Values are mean ± SD.

were comparable to the minimum effective dose as determined by the Dixon up-and-down method (table 2). The ED_{98} values of remifentanil were 1.50 ± 1.00 and 0.52 ± 1.06 μg/kg after 2.0 and 4.0 mg/kg propofol, respectively (table 2). The duration of apnea for patients who did not move during the procedure was 93 ± 45 s. There were no episodes of bradycardia or hypotension in either group.

Part 2

The duration of apnea was significantly longer with 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil (group P2) (110 s, 0–228 s) than with 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil (group P4) (73 s, 0–110 s; $P < 0.05$; fig. 2). In each group, 88% of children developed apnea after study drug administration, and the majority of these required intermittent assisted manual ventilation. Time to awakening in group P4 (23 min, 5–69 min) was more than double that in group P2 (10 min, 4–70 min; $P < 0.05$; fig. 3). Intraoperative heart rate, respiratory rate, and mean arterial pressure decreased significantly compared with baseline in group P2 (table 3). In contrast, intraoperative heart rate and respiratory rate did not change significantly but mean arterial pressure decreased significantly compared with baseline in group P4 (table 3). There was a significant group–time interaction effect for intraoperative respiratory rate ($P < 0.0001$). Intraoperative bradycardia (heart rate 56 beats/min) occurred in one patient in group P2 and resolved spontaneously. There were no episodes of bradycardia in group P4 and no episodes of hypotension in either group. One patient in group P2 required a bolus dose of 1.0 mg/kg propofol for movement during the procedure. During the recovery phase, heart rate, respiratory rate, mean arterial pressure (table 4), and oxygen saturation were comparable between groups. No patient experienced nausea or vomiting during the recovery phase.

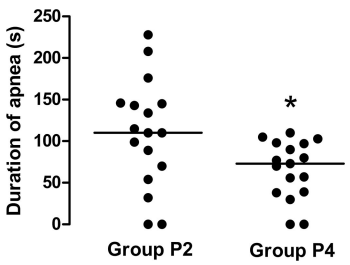

Fig. 2. Scatter plot showing duration of apnea after remifentanil administration. The time to resumption of spontaneous ventilation was significantly shorter in group P4 (4.0 mg/kg propofol plus 0.5 μg/kg remifentanil) compared with group P2 (2.0 mg/kg propofol plus 1.5 μg/kg remifentanil) (* $P < 0.05$). *Circles* represent values for individual patients. *Horizontal bars* indicate group median values.

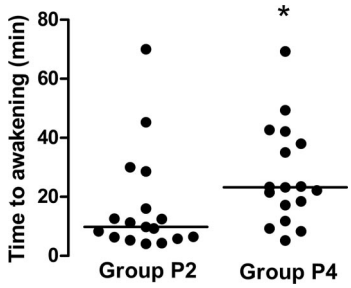

Fig. 3. Scatter plot showing time to awakening after remifentanil administration. The recovery time was significantly longer in group P4 (4.0 mg/kg propofol plus 0.5 μg/kg remifentanil) compared with group P2 (2.0 mg/kg propofol plus 1.5 μg/kg remifentanil) (* $P < 0.05$). *Circles* represent values for individual patients. *Horizontal bars* indicate group median values.

Discussion

The results indicate that the combination of propofol and remifentanil provides effective general anesthesia for lumbar puncture in pediatric patients. Although both dose combinations (2.0 mg/kg propofol plus 1.50 μg/kg remifentanil and 4.0 mg/kg propofol plus 0.52 μg/kg remifentanil) provided effective anesthesia for lumbar puncture, their intraoperative and recovery characteristics differed significantly. The duration of apnea after 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil was significantly longer than that after 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil. In addition, the time to awakening after 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil was approximately double that after 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil. In contrast to 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil, administration of 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil was associated with reductions in intraoperative heart rate and respiratory rate that did not require intervention and were of no clinical significance. The results indicate that increasing the dose of remifentanil and decreasing that of propofol increases the duration of apnea and decreases the recovery time.

To our knowledge, this study is the first to determine the effective dose of remifentanil when coadministered as a bolus with propofol in children. Previous studies have evaluated the dose-sparing effect of remifentanil on propofol requirements for ambulatory anesthesia in children.[7,8] The Dixon up-and-down method was used in one study to evaluate the pharmacodynamic interaction

Table 3. Intraoperative Hemodynamic and Respiratory Parameters

	Baseline	1 min	2 min	3 min	4 min
Heart rate, beats/min					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	100 ± 15	84 ± 13*	82 ± 13*	81 ± 10*	83 ± 11*
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	99 ± 10	88 ± 16*	92 ± 13	91 ± 11	93 ± 7
Respiratory rate, breaths/min					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	21 ± 2	4 ± 7*	6 ± 8*	11 ± 6*	16 ± 4
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	14 ± 10	8 ± 6	14 ± 3	16 ± 5	16 ± 2
Mean arterial pressure, mmHg					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	75 ± 7	71 ± 12	61 ± 10*	56 ± 7*	53 ± 5*
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	76 ± 10	71 ± 12	62 ± 12*	60 ± 8*	62 ± 5

Heart rate, respiratory rate, and mean arterial pressure were decreased compared with baseline at multiple time points after administration of 2.0 mg/kg propofol plus 1.5 μg/kg remifentanil (group P2). Mean arterial pressure was decreased compared with baseline at 2 and 3 min after administration of 4.0 mg/kg propofol plus 0.5 μg/kg remifentanil (group P4). Respiratory rate was decreased in group P2 compared with group P4 at 2 minutes. Values are mean ± SD.

* $P < 0.05$ compared with baseline.

of propofol and remifentanil in children undergoing upper gastrointestinal tract endoscopy.[7] Propofol was administered *via* a target-controlled infusion system alone or in combination with remifentanil. The addition of remifentanil decreased the plasma concentration of propofol associated with 50% effectiveness; however, increasing the remifentanil infusion rate greater than $0.25\ \mu g \cdot kg^{-1} \cdot min^{-1}$ increased the incidence of respiratory side effects without further reduction in propofol requirement. Another study showed that infusion of remifentanil reduced the total dose of propofol required but increased the incidence of bradypnea and desaturation in children undergoing bone marrow aspiration.[8] A study of propofol–remifentanil pharmacodynamic interaction in volunteers also demonstrated a significant propofol-sparing effect with relatively low doses of remifentanil.[15]

Other medications, such as fentanyl and midazolam, have been shown to reduce propofol requirement and shorten recovery time.[3] Remifentanil offers advantages when compared with other adjuvant agents, including its relatively rapid onset and short duration of action. When compared with propofol plus sevoflurane and nitrous oxide, bolus administration of propofol and remifentanil shortened recovery and discharge time after lumbar puncture in children.[16] In adults, propofol–remifentanil anesthesia was associated with a shorter recovery time compared with propofol–sufentanil or propofol–alfentanil anesthesia.[17–19] In addition, postoperative opioid-related side effects may be reduced after anesthesia with remifentanil compared with fentanyl.[20] In this study, no significant drug-related side effects occurred during the intraoperative or recovery periods; however, the study was not powered to evaluate the incidence of side effects.

The Dixon up-and-down method is a simple technique to determine the effective dose at the 50th percentile.[21] An advantage compared with nonsequential design methods is that an equally accurate result is produced with a smaller sample size (20–40 patients are usually adequate).[21] Because this type of sequential design does not produce a dose–response curve, the estimated minimum effective dose may differ considerably from the true ED_{50} if the dose–response curve is steep at the 50th percentile. In addition, because the data are clustered around the ED_{50}, extrapolation to the ED_{98} has inherent limitations,[21] and calculated doses should be taken as an approximation only. Previous studies have shown good agreement between ED_{50} doses determined by the Dixon up-and-down method and logit regression, in agreement with our findings.[22–24] In our study, 33 of 34 children (97%) were adequately anesthetized, suggesting that our estimation of the ED_{98} doses of remifentanil were accurate and clinically useful.

The use of a bolus dose of remifentanil without an infusion is appropriate for short-duration procedures

Table 4. Hemodynamic and Respiratory Parameters during Recovery

	Admission	15 min	30 min	45 min	60 min
Heart rate, beats/min					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	87 ± 12	86 ± 15	90 ± 14	87 ± 11	89 ± 12
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	89 ± 11	85 ± 10	86 ± 10	89 ± 12	91 ± 9
Respiratory rate, breaths/min					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	24 ± 3	23 ± 2	22 ± 2	22 ± 2	22 ± 2
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	23 ± 4	23 ± 3	22 ± 2	22 ± 2	22 ± 2
Mean arterial pressure, mmHg					
2.0 mg/kg propofol + 1.5 μg/kg remifentanil	63 ± 8	66 ± 9	66 ± 10	66 ± 8	66 ± 8
4.0 mg/kg propofol + 0.5 μg/kg remifentanil	59 ± 18	62 ± 18	64 ± 18	64 ± 18	65 ± 18

Hemodynamic and respiratory parameters during recovery were comparable for the two groups. Values are mean ± SD.

such as lumbar puncture. Because propofol equilibrates more slowly with the effect compartment compared with remifentanil,[25] we administered propofol first, followed immediately by remifentanil. To minimize movement during lumbar puncture, the timing of needle insertion should coincide with the peak drug effect. Considering the time to peak effect of remifentanil after intravenous administration,[26] we inserted the lumbar puncture needle at 90 s. A study of the pharmacokinetic interaction between propofol and remifentanil demonstrated that propofol decreases the central volume of distribution and clearance of remifentanil, resulting in an increase in the plasma concentration of remifentanil after bolus administration.[27] These results are mainly applicable to clinical situations in which remifentanil is administered *via* target-controlled infusion to achieve a desired plasma-effect compartment concentration and not a clinical endpoint such as immobility.

A limitation of our study is that the applicability of the results to patients of different ages undergoing other hemato-oncologic procedures, such as bone marrow aspiration or biopsy, may be limited. Compared with lumbar puncture, bone marrow aspiration and biopsy typically take longer to perform and intraoperative and postoperative pain is often more severe. Therefore, a single bolus dose of propofol and remifentanil may be insufficient to maintain an adequate depth of anesthesia for the duration of the procedure. Because remifentanil has an ultrashort duration of action, longer-acting opioids, such as fentanyl or morphine, may be required. An additional limitation of this study is the lack of a standardized rating scale for movement. Therefore, the doses administered must be adjusted according to each patient's requirements.

In summary, the administration of a bolus dose of propofol and remifentanil is an acceptable general anesthetic technique for patients undergoing lumbar puncture. Increasing the remifentanil dose produces a propofol-sparing effect, which results in a shorter recovery time and, possibly, earlier discharge from the recovery room. This is an important consideration if resources such as physical space and time are limited. For these reasons, our clinical practice is to use a higher dose of remifentanil and lower dose of propofol. However, practitioners may not be comfortable with the longer duration of apnea, especially if the procedures are performed in a "satellite" or off-site location.

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