Sedation for Short Hemato-Oncologic Invasive Procedures in Children: Comparison of Propofol-Remifentanil and Propofol-Fentanyl

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Introduction: Short hemato-oncologic procedures are often painful in children, and sedation should be performed outside the operating room.

Aim: The study aims to compare the effects of remifentanil with those of fentanyl administered during short hemato-oncologic interventions in children.

Materials and Methods: A prospective, randomized study was planned for 29 ASA I to III children (aged, 2 to 18 y) to undergo a total of 60 short oncologic interventions. The patients were placed into 2 groups: propofol-remifentanil (group PR) and propofol-fentanyl (group PF). Group PR was first administered propofol (2 mg/kg) and then remifentanil bolus (0.5 μg/kg). Group PF was first administered propofol (2 mg/kg) and then fentanyl bolus (0.5 μg/kg). Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure, respiratory rate, peripheral oxygen saturation, and heart rate were recorded every 3 minutes during the intervention and every 5 minutes after the operation. Postanesthetic recovery scores, eye-opening time to speech, and recovery time were recorded.

Results: Comparison of diastolic arterial pressure in groups at minute 3 of the procedure showed significant difference ($P < 0.05$). Eye-opening to speech ($P = 0.043$) and recovery times ($P = 0.002$) were shorter in group PR.

Conclusions: During short hemato-oncologic interventions in children, the PR combination is a suitable one for early recovery.

Key Words: children, short oncologic procedures, sedation, propofol, remifentanil, fentanyl, bolus

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Currently, for diagnosis and treatment, several intervention methods can be applied outside an operating room, which leads to special problems and complications.[1] Standards of patient care used outside the operating room are not different from those used in the operating room.[1–2] Basic standards such as appropriate equipment and monitoring must be ensured without disregarding the safety. Depending on the characteristics of the patient and the procedure, either general anesthesia or sedation analgesia can be applied.[1] In most of the childhood cancer cases the short, painful, and repeated interventions such as bone marrow aspiration (BMA), bone marrow biopsy (BMB), and lumbar puncture (LP) are applied.[3] Although many adults can tolerate these interventions performed outside the operating room under local anesthetic infiltration, in children sedation should be applied to ensure stress control and motionlessness. In terms of patient safety, anesthetists are required to use techniques that ensure rapid recovery after the procedure. There are studies conducted on different anesthetic agents used for sedation or anesthesia during painful hemato-oncologic interventions in pediatric patients.[3–5] It has been indicated that propofol anesthesia maintained by intermittent boluses in children is sufficient to provide amnesia and patient comfort during elective oncologic procedures.[6] In painful hematologic procedures performed in children with the diagnosis of acute hematologic malignancies (acute leukemia or lymphoma): for sedation, propofol was administered alone or in combination with fentanyl and it was determined that when fentanyl was added to propofol, the amount of propofol in total dose and side effects decreased.[7] In Cechvala et al's study[8] conducted on families' preferences, propofol or propofol-fentanyl (PF) combination was administered to children diagnosed with acute leukemia who were to undergo LP. Most of the patients (or families) preferred PF combination because it has been reported that this combination causes fewer side effects and recovery from anesthesia is faster. In a study investigating anesthetic techniques to provide rapid recovery during short painful oncologic procedures, sevoflurane-propofol-nitrous oxide was compared with propofol-remifentanil (PR). The recovery time was found significantly shorter in the PR group than in the other group and the parents mostly preferred PR combination.[3] Conscious sedation with remifentanil and midazolam was applied to children during painful procedures, and it was considered that administering remifentanil with midazolam would provide adequate analgesia and sedation. It was reported that this drug combination was effective but could cause respiratory depression at subtherapeutic levels.[9] Administration of propofol alone or in combination with remifentanil during BMA was compared. It was observed that adding remifentanil to propofol during the procedure led to a reduction in the total dose of propofol but increased the risk of respiratory depression.

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Sedation is applied to children who frequently undergo invasive procedures due to hematologic and oncologic diseases.

In this study, the aim is to compare the effects of remifentanil with those of fentanyl administered during short hemato-oncologic interventions in children on vital signs, the need for additional doses of propofol, physician satisfaction, eye-opening time, and recovery time.

MATERIALS AND METHODS

Ethical approval for this human study (Ethical Committee 1472) was provided by the Ethical Committee of the Ministry of Health, Ankara, Turkey (Chairman Dr Hanefi Özbek) on 01-09-2010.

Interventions were applied to 29 pediatric patients (aged, 2 to 18 y/American Society of Anesthesiologists status I/III) who electively planned to undergo 60 short-invasive procedure (such as LP and intrathecal chemotherapy, BMA, biopsy, etc.) be accompanied by sedoanalgesia. Children undergoing a similar procedure again within 2 weeks were also recruited.[3] In this study, the exclusion criteria for the patients were as follows: ASA physical status > III, cannot answer verbal commands, who already have pain and nausea, sedative or analgesic medication taken within the last 12 hours, a history of concomitant disease (obstructive sleep apnea, cardiorespiratory disease, obesity, malignant hyperthermia, or other muscle disease), a history of allergy to the drugs used in the study, known or anticipated difficult airway presence, and inappropriate fasting time.[3]

The study design was planned as randomized and prospective. Children, parents, and the initiative team did not have information about the drugs that were used. Assignment to the groups was determined by random drawing of consecutively numbered envelopes containing the labels PF-PR.

The patients were included in the list the day before the procedure. Preanesthetic assessment was performed a day before the procedure for hospitalized patients. In the outpatient group, preanesthetic evaluation was carried out before the procedure. Procedures and sedation were performed in isolated clinic rooms or beds in the in the Pediatric Hematology-Oncology Clinics.

Noninvasive blood pressure, peripheral oxygen saturation (SpO_2), and respiratory rate (RR) measurements and DII derivative ECG were monitored in patients in the Pediatric Hematology and Pediatric Oncology Clinics.

Sedation was administered through the port catheter if available or through a 22- or a 24-G IV cannule (according to the age) on the right hand and a 0.9% saline infusion was started. Midazolam (0.05 mg/kg IV) (Dormicum; Roche Industry, London) was administered as premedication in both groups.

Group PR: remifentanil (0.5 μg/kg) (Ultiva; GlaxoSmithKline, Belgium) was administered after 1% propofol (2 mg/kg) (Fresenius; Fresenius Kabi, Sweden)

Group PF: fentanyl (0.5 μg/kg) [Fentanyl (0.05 mg/mL) ampul Jansen Pharmaceutica N.V., Belgium] was administered after propofol (2 mg/kg).

The bolus doses of drugs were administered for 1 to 4 minutes. The procedure was initiated 90 seconds after the opioid administration. Oxygen (6 L/dk) with face mask was applied to the cases at the beginning of the process of sedation and continued until the end of the recovery process.[10] Continuous SpO_2 and heart rate (HR) were observed. Systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure, the RR, SpO_2, and HR[11,12] were measured and recorded every 3 minutes during the process and every 5 minutes during recovery.[3] Spontaneous respiration was allowed to continue, in the case of RR < 10 or SpO_2 < 90%; assisted respiration through balloon pulmonary valve mask system was planned.

Movements were observed and recorded during the process. Observed movements were classified as follows[3–4]: severe, aimed movements preventing the process to continue; moderate, partial aimed movements not preventing the process to continue; none, no motion or myoclonic contraction.

In case of observing signs of inadequate anesthesia in both groups (movements aimed at preventing intervention, sweating, or tear, >30% increase in SAP), a further bolus doses of propofol (0.3 to 0.5 mg/kg) was given every 30 to 60 seconds.[4] To eliminate the pain of injection, lidocaine (0.04 mg) (2% Aritmal bulb; Biosel Pharmaceutical Industry, Istanbul) was added to the injector for each 1 mg of propofol.[13]

Sedation was stopped when the needle applied was pulled out of the body.[4] The cases were the compiled transaction. The interval between termination of the initiative and eye-opening (calling by name every minute till eyes are open), compiled to be ready for output (PMAS ≥ 9), and physician satisfaction score (excellent, moderate, poor) were recorded.[14]

TABLE 1. Demographic Data of Patients

	Group PF (n = 30)	Group PR (n = 30)	*P*
Age (y)	9.25 ± 3.95	8.10 ± 4.44	0.294
Weight (kg)	34.30 ± 15.08	30.58 ± 15.31	0.347
Female [n (%)]	11 (44.0%)	14 (56.0%)	0.610
Male [n (%)]	19 (54.3%)	16 (45.7%)	0.432
ASA-I [n (%)]	0 (0.0%)	1 (3.3%)	0.420
ASA-II [n (%)]	22 (73.3%)	23 (76.7%)	0.271
ASA-III [n (%)]	8 (26.7%)	6 (20.0%)	0.328

$P > 0.05$.

ASA indicates American Society of Anesthesiologists Physical Status Classification; PF, propofol-fentanyl; PR, propofol-remifentanil.

TABLE 2. Diagnoses of Patients

	n (%)		
	Group PF (n = 30)	Group PR (n = 30)	Total
Leukemia	20 (66.7%)	23 (76.7%)	43 (71.7%)
Lymphoma	3 (10.0%)	3 (10.0%)	6 (10.0%)
Rhabdomyosarcoma	1 (3.3%)	1 (3.3%)	2 (3.3%)
Myelosarcoma	4 (13.3%)	1 (3.3%)	5 (8.3%)
Ewing Sarcoma	1 (3.3%)	0 (0%)	1 (1.7%)
Hypereosinophilic Syndrome	1 (3.3%)	0 (0%)	1 (1.7%)
Neuroblastoma	0 (0%)	1 (3.3%)	1 (1.7%)
Aplastic anemia	0 (0%)	1 (3.3%)	1 (1.7%)
Total	30 (100%)	30 (100%)	60 (100%)

PF indicates propofol-fentanyl; PR, propofol-remifentanil.

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TABLE 3. Implement Procedure for Groups

	n (%)		
	Group PF (n = 30)	Group-PR (n = 30)	Total
Lumbar puncture	11 (36.7%)	19 (63.3%)	30 (50.0%)
Bone marrow aspiration	6 (20.0%)	3 (10.0%)	9 (15.0%)
Bone marrow aspiration-biopsy	1 (3.3%)	4 (13.3%)	5 (8.3%)
Bone marrow aspiration-lumbar puncture	4 (13.3%)	1 (3.3%)	5 (8.3%)
Bone marrow aspiration-lumbar puncture	4 (13.3%)	2 (6.7%)	6 (10.0%)
Bone marrow biopsy-lumbar puncture	4 (13.3%)	1 (3.3%)	5 (8.3%)
Total	30 (100%)	30 (100%)	60 (100%)

PF indicates propofol-fentanyl; PR, propofol-remifentanil.

Statistical Analysis

When the eye-opening time was considered, it was determined that the number of the interventions should be 60 (n = 30) if the power of the study was to be 95.5%. Results were given as mean ± SD and in percentages. Statistical analysis was performed using SPSS 16.0 for Windows. The Student *t* test was used to determine the mean difference between the 2 groups, and the χ^2 and the Mann-Whitney *U* tests were used to determine the difference between the groups. $P < 0.05$ was considered significant.

RESULTS

There was no statistical significant difference between demographic characteristics of patients such as age ($P = 0.294$), body weight ($P = 0.347$), sex (female, male: $P = 0.420$, respectively), ASA (I/II/III: $P = 0.420$, 0.271, 0.328, respectively) physical status classification (Table 1), the diagnoses of patients (Table 2), and implement procedure for groups (Table 3 ($P < 0.05$).

SAP, mean arterial pressure, and HR of the groups in procedure time did not show a statistically significant difference ($P > 0.05$) in the end (Figs. 1, 2, 3). Comparison of DAP in groups at minute 3 of the procedures showed significant difference ($P < 0.05$) (Fig. 4).

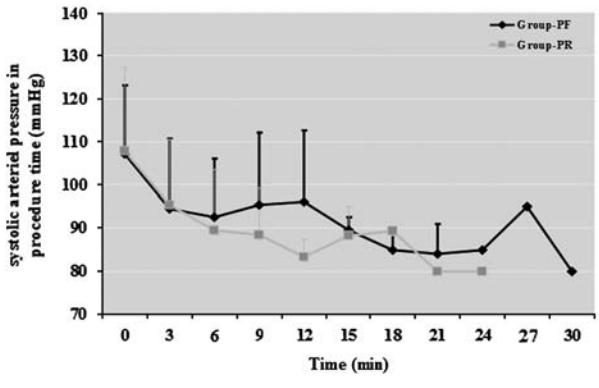


FIGURE 1. Systolic arterial pressure data of patients (mm Hg) ($P > 0.05$).

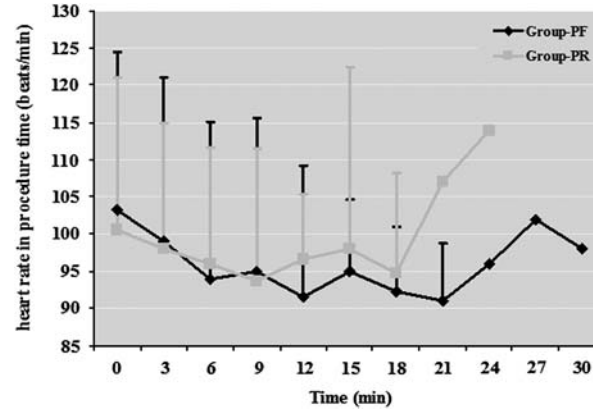


FIGURE 2. Heart rate data of patients (beats/min) ($P > 0.05$).

Mean values of SpO_2 during and after the procedure did not show significant difference between the groups ($P > 0.05$) (Fig. 5). There was no significant difference between the mean RRs of the groups after the procedures ($P > 0.05$). PMAS measured after the procedure did not show statistically significant difference either ($P > 0.05$). Statistically significant difference was not observed between (Pediatric Hematology and Oncology) physician satisfaction of the groups ($P > 0.05$) (Fig. 6).

There was no significant difference between the groups for amount of propofol, fentanyl, and remifentanil used ($P > 0.05$). For each patient, mean propofol dose used was 70 mg for group PF and 60 mg for group PR. Additional propofol doses were needed at a ratio of 16.7% for group PF and 26.7% for group PR. Procedure time did not show a statistically significant difference ($P > 0.05$ and 0.257). Eye-opening time with call ($P = 0.043$) and recovery time ($P = 0.002$) were lower in group PR, which were statistically significant ($P < 0.05$).

Groups did not show a significant difference in observed movements ($P > 0.05$). Adverse effects according to groups were hypotension (group PF = 5, group PR = 6 patients) and bradycardia observed in one of the patients (group PF).

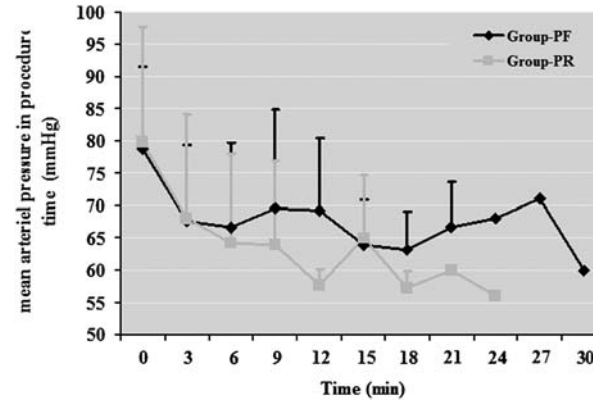


FIGURE 3. Mean arterial pressure data of patients (mm Hg) ($P > 0.05$).

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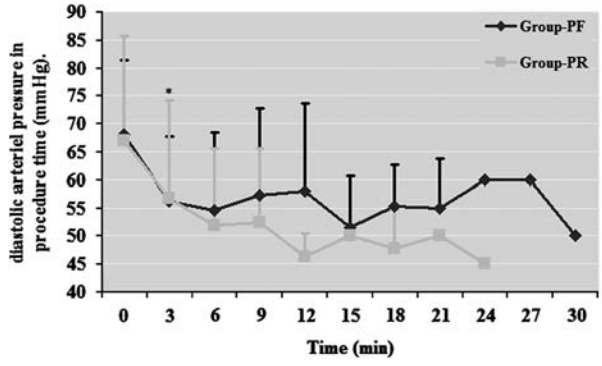


FIGURE 4. Diastolic arterial pressure data of patients (per min) (mm Hg). ($P < 0.05$, significantly different during between comparisons at minute 3).

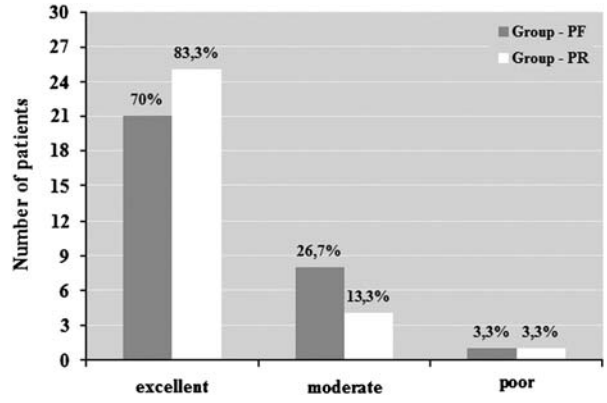


FIGURE 6. Physician's satisfaction data ($P > 0.05$, 0.257).

DISCUSSION

Among the treatment steps for childhood malignancies are short painful procedures such as LP and BMA.[3] Anesthesia methods to be implemented in children include various degrees of general anesthesia or sedation. As these processes are usually performed in an operating room, children and families suffer enormous stress.[15]

In the literature, it is reported that various sedative hypnotic drugs and opioid analgesics are combined for patient comfort during sedation.[3,5,16,17]

Maunuksela et al[16] administered a combination of flunitrazepam and fentanyl to 96 children who underwent bone marrow intervention. In this study, 5 of the children reported respiratory depression and 10% of them reported inadequate sedation.

Marx et al[17] administered ketamine-atropine-midazolam and meperidine-midazolam combinations to 32 pediatric cancer patients as premedication before implementing such painful interventions. They found that ketamine-atropine-midazolam combination produced better sedation, faster onset, fewer side effects, and faster recovery.

Jayabose et al[18] found that administrating propofol with fentanyl, midazolam, or fentanyl-midazolam to children with cancer during painful procedures was safe and effective.

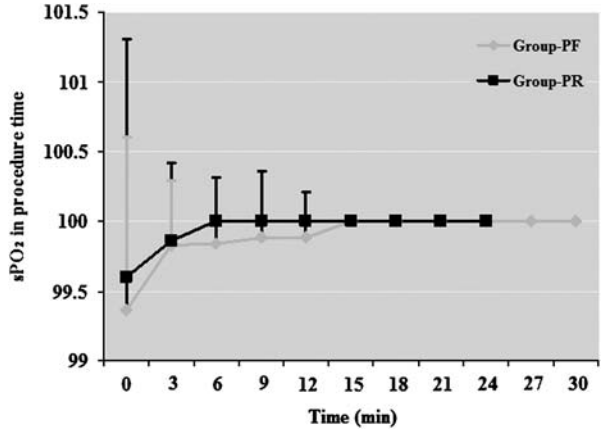


FIGURE 5. SpO_2 data of patients ($P > 0.05$).

Glaisyer and Michael[3] evaluated the recovery time after administering PR or propofol-nitrous oxide-sevoflurane during pediatric short painful oncologic procedures in their study in 21 children. It was observed that the time that elapsed to ensure criteria for discharge from the recovery room was 19 minutes shorter in the PR group than in the other group.

Antmen et al[19] compared the effects of remifentanil (1 μg/kg), alfentanil (20 μg/kg), remifentanil-midazolam (0.5/0.05 μg/kg), alfentanil-midazolam (20/0.05 μg/kg) combinations on sedation levels in children who underwent BMA.

In their study, no significant difference was observed between the groups in terms of CHEOPS and visual analog scale scores.

In contrast, in our study, the children's stability, movements, eye-opening to speech (calling the name of the patient), and recovery times during interventions were compared when the PF or PR combinations was administered for sedation during short painful procedures. Although no differences were observed in both groups in the vital signs, observed movements, and physician satisfaction during and after (PF-PR) administration, eye-opening to speech and recovery times were shorter in the PR group.

Repeated short oncologic procedures are painful in children. During these interventions, administration of propofol alone requires high doses of propofol and this causes respiratory depression.[3] In 2 different studies, the mean dose of propofol administered alone ranged from 5 to 8.8 mg/kg.[6,19] In one of these studies, Hollman et al[7] administered propofol or PF to children with acute leukemia or lymphoma for sedation during LP and determined that the amount of propofol needed decreased by 34.8% when fentanyl was added, and this decrease was considered statistically significant.

In our study, after the administration of propofol (2 mg/kg IV bolus), additional bolus doses were administered when necessary (according to the movement scale), and although it was administered with remifentanil or fentanyl, no respiratory depression or airway obstruction occurred; therefore, no airway or respiratory support was needed. In addition, in our study, no significant difference was observed between the PR and PF groups in terms of needs for additional doses of propofol.

Respiratory depression is a common side effect of remifentanil; however, this effect is short lived as is the

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analgesic effect.[4] In their study, Keidan et al[4] applied 0.1 μg/kg/min infusion of remifentanil after administering 0.15 mg bolus of remifentanil, and of the 41 patients, 8 developed respiratory depression and 8 moved during the procedure.

In our study, we observed movements in 3 patients in both groups to such an extent that they prevented us from continuing the interventions. No movement was observed in 10 (33.3%) patients in the PF group and in 9 (30%) patients in the PR group. None of the patients needed respiratory support.

Bradycardia and hypotension are unwanted but potential side effects of the remifentanil.[3] In their study, Antmen et al[19] administered remifentanil, alfentanil, remifentanil-midazolam combination and alfentanil-midazolam combination to children who underwent BMA, and they did not observe deep sedation, respiratory depression, hypotension, bradycardia, or hypoxemia in any of the groups. When Cechvala et al[8] administered propofol or PF combination to the children who underwent LP, they observed side effects in 4 of the 22 patients administered propofol and fentanyl and 11 of the 22 patients administered propofol alone. In their study, Hayes et al[5] administered propofol and remifentanil combination at 2 different doses to children who were to undergo LP and they observed no episodes of bradycardia or hypotension. With increasing doses of remifentanil and decreasing doses of propofol, the duration of apnea prolonged whereas the recovery time shortened. In our study, hypotension was observed during 11 interventions (5 in group PF and 6 in group PR) and bradycardia during 1 intervention (group PF). Hypotension occurring after drug administration in children returned to normal when the interventions began. There was a statistically significant difference between the groups in terms of DAP only at minute 3 during intervention ($P = 0.03$). In the PR group, significantly lower DAP values were measured at that minute.

The majority of children to undergo short painful hematologic and oncologic interventions have complex diseases, which necessitate them being included in treatment programs and staying in a hospital for months or even years.

In studies involving repeated oncologic interventions (LP and/or BMA) in which propofol sedation was performed not in the operating room but in the clinic, higher satisfaction scores were observed in children and their parents.[15]

In their study, Cechvala et al[8] administered first propofol/placebo combination and then propofol/fentanyl combination to 22 children with acute leukemia who underwent LP (44 interventions), and then families were asked which sedation regime they would prefer for their children in the next LP intervention. Of the families, 16 preferred propofol/fentanyl combination because the discharge time after recovery was shorter in the patients receiving propofol/fentanyl combination than in the patients receiving propofol alone.

In the literature, there are various studies carried out to evaluate the use of remifentanil in children.[20,21] Eck and Lynn[20] indicated that infants with complex medical conditions could be administered remifentanil, without a prolonged opioid effect necessitating ventilation and providing stable hemodynamic conditions. Foubert et al[21] reported that remifentanil produced appropriate and rapid recovery and stable hemodynamic conditions in children with congenital heart disease when they underwent cardiac catheterization.

When benzodiazepines and opioid analgesics are combined, they have synergistic interaction, which causes respiratory depression.[22,23] Litman[9] identified a high incidence of respiratory depression in children undergoing painful procedures when they were administered benzodiazepine-remifentanil combination.

Keidan et al[4] administered propofol and PR combination to pediatric hemato-oncologic disease group during BMA intervention. The addition of remifentanil increased the quality of sedation, reduced the total propofol dose, and decreased the time needed to go home, but led to an increased risk of respiratory depression. However, when compared with other drugs, remifentanil seems to be more advantageous as it has more rapid onset of action and shorter duration of action.[5]

Antmen et al[19] reported that administering remifentanil in bolus doses produced satisfactory sedation and analgesia in short, painful hemato-oncologic procedures and prevented undesirable adverse respiratory effects. In another study of healthy volunteers, 30 seconds after remifentanil bolus (0.5 μg/kg), the postrespiratory effect of the drug reached a peak at 2.5 minutes and ended at 15 minutes[24]

In our study, no patient suffered respiratory depression that would necessitate the use of balloon valve mask for respiration (SS < 10 or SpO_2 < 90%). According to the results of our study data, the eye-opening time to speech and recovery time were shorter in group PR ($P = 0.043$, 0.002).

Peacock et al[24] reported that the safe dose of remifentanil should be 0.025 to 0.05 μg/kg/dk to maintain appropriate spontaneous breathing. Hayes et al[5] designed their study in 2 parts in which remifentanil and propofol were administered to children to undergo LP. In the first part, remifentanil was administered with 2.0 and 4.0 mg/kg of propofol and the minimum effective dose was assessed as 1.50 ± 1.00 and 0.52 ± 1.06 μg/kg, respectively, in 98% of the children. In the second part, the goal was to compare respiratory effects and recovery time and the patients were divided into 2 groups. The first group was administered 2.0 mg/kg of propofol and 1.5 μg/kg of remifentanil and the second group was administered 4.0 mg/kg of propofol and 0.5 μg/kg of remifentanil. In the first group, the duration of apnea was longer and the recovery period was shorter.[5]

In our study, as the time required for the formation of a stable blood concentration for propofol to produce an adequate effect was longer than that of remifentanil, we first administered propofol. When propofol and remifentanil were administered together, the central volume of distribution and clearance of remifentanil decreased. After remifentanil bolus injection, the increase in the plasma concentration of remifentanil is rapid.[5]

As there are no specific units for postanesthesia care in the departments of our hospital, the patients recovered where the interventions were carried out. Therefore, the duration of drug action and postanesthesia recovery time gain great importance. Patients should recover safely as soon as possible and be transferred to the physician and/or nurse in the clinic. In our study, the time between the termination of the intervention and the eye opening was identified and then evaluated with the Modified Aldrete Score, an objective indicator of discharge from recovery. In our study, eye opening to speech and recovery times were shorter in group PR than in group PF.

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Children under 2 years of age were not included in the study, which was the study's limitation. There are no data available regarding drug-dose adjustments in children of this age group. As the main purpose of this study was to compare the eye opening to speech and recovery times, no parameters related to the preoperative and postoperative pain were investigated and thus recorded. In interventions outside the operating room, in children, whatever the anesthesia method is, the efficacy of bispectral index use to assess the depth of anesthesia is not clear.[10,25] Therefore, it was not planned to use bispectral index monitoring. Family satisfaction and preference were not assessed either, because parents were not allowed into the intervention room until the patient opened his/her eyes to speak. BMA and BMB are longer interventions than LP is. Intraoperative and/or postoperative pain may increase from time to time. Therefore, bolus propofol and remifentanil administrations could be inadequate and the need for additional doses may increase.

In our study, there was no difference between the PR group and PF group in terms of hemodynamic and respiratory parameters; however, eye opening to speech and recovery times were shorter in the PR group. Therefore, remifentanil can be used as boluses for procedures outside the operating room for children older than 2 years of age, in combination with propofol and midazolam.

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