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The safety and efficacy of remifentanil compared to fentanyl in pediatric endoscopy

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Aim: To compare propofol combinations with low induction doses of remifentanil and fentanyl in respect to the complication frequency and efficiency in ease of procedure in children undergoing esophagogastroduodenoscopy.

Materials and methods: Sixty-four patients, aged 3–14 years and undergoing elective esophagogastroduodenoscopy, were included in the study. The patients received an induction dose of 0.25 μg kg^{-1} remifentanil and 2 mg kg^{-1} propofol (group R), or 0.5 μg kg^{-1} fentanyl and 2 mg kg^{-1} propofol (group F) before the procedure. The procedure began with a sedation score of ≥5. Hemodynamic values, movement, ease and duration of the procedure, the time to awakening, and any requirement for additional doses of propofol/opioids and adverse events were recorded.

Results: Although frequency of apnea after induction was higher and the duration of apnea was longer in group R, during procedure and postprocedure follow-up, there were no apnea episodes in either group ($P < 0.05$, $P > 0.05$). Intraoperative respiratory rate, time to eye opening, opioid consumption, and duration of recovery were significantly shorter in group R ($P < 0.05$).

Conclusion: Remifentanil, when combined with propofol, can provide as efficient and safe anesthesia as fentanyl propofol combination for procedures like esophagogastroduodenoscopy.

Key words: Anesthesia, pediatric, remifentanil, fentanyl, upper gastric endoscopy

1. Introduction

As a parallel to the increased usage of endoscopic examination of the upper gastrointestinal system on an outpatient basis, the need for anesthesia and sedation gradually increases, especially in children, who need deeper sedation than adults (1,2). Ideal pediatric endoscopy requires control of anxiety, amnesia, pain, and combative behavior, and prompt patient recovery with high safety and effectiveness (3).

Anesthetic agents with rapid onset and short duration of action along with minimum suppression of the vital signs are preferred for outpatient procedures (4). Propofol, which is preferred due to its short duration of action, has been reported to provide a deep sedation and rapid recovery, but when used alone, propofol cannot provide adequate immobility and a relatively higher dose of propofol is required to enable adequate sedation (2,5,6). At times, such high doses may result in hypotension, respiratory depression, and unintended duration of anesthesia (7).

Opioids have been reported to reduce the need for propofol, in addition to providing hemodynamic stability and increasing the performance of the endoscopist by providing ease of procedure (2,6–10). Different combinations of these agents were studied in pediatric anesthesia literature (2,8,10,11). Fentanyl is a frequently used opioid agent proven to be efficient and safe for pediatric procedures, but its potency is intermediate and blood clearance is slow, which usually leads to much longer anesthesia duration than that of endoscopic procedures (2,8,10,11). Remifentanil, which is a more potent agent with shorter duration of action, is frequently used in pediatric outpatient anesthesia in bone marrow aspiration, bronchoscopy, and cardiac catheterization, as well as in laser photocoagulation in premature infants (12–15). Remifentanil has been used in adult endoscopic procedures in combination with propofol, which gave better results than fentanyl (9). Results of pediatric studies that compared remifentanil with fentanyl in combination with propofol are contradictory and study protocols are relatively complicated.

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We planned a study with a much lower induction dose of opioids with propofol (remifentanil and fentanyl) and additive doses that were given when required during the procedure in order to decrease complication rates and increase the quality and efficiency of anesthesia in pediatric esophagogastroduodenoscopy (EGD) procedures.

2. Materials and methods

The effect of propofol and remifentanil sedation was prospectively studied in 64 unpremedicated children undergoing gastrointestinal endoscopy under sedation. The children were aged between 3 and 14 years and with American Society of Anesthesiologist (ASA) scores of I. Exclusion criteria were as follows: having pulmonary or cardiac insufficiency, history of hypersensitivity to any medication used in the study, and history of severe vomiting, bleeding, or regurgitation. Approval was obtained from the institutional local ethics committee of Gaziantep University and informed consent was obtained from parents of the children.

The patients were randomly assigned to one of the study groups using sealed numbered envelopes. In group R (n = 32), EGD was performed after 0.25 μg kg^{-1} bolus dose of remifentanil (Ultiva, GlaxoSmithKline, United Kingdom) followed by 2 mg kg^{-1} propofol that was slowly injected (Propofol, Fresenius Kabi, Germany) before the procedure (16). The children in group F (n = 32) received 0.5 μg kg^{-1} bolus dose of fentanyl (Fentanyl-Janssen, Janssen-Cilag, Belgium) followed by 2 mg kg^{-1} propofol that was slowly injected. All of the children received oxygen via a nasal cannula (4 L min^{-1}) during the procedure. All of the EGD procedures were performed by means of a pediatric fiber optic video gastroscope (Fujinon EG, Saitama, Japan) by an experienced pediatric gastroenterologist in the endoscopy room. Physiological parameters of all patients, such as mean arterial pressure (MAP), heart rate (HR), respiratory rate (RR), and oxygen saturation (SpO_2) were monitored via a computerized monitor. The measurements were obtained before the administration of the drugs, before inserting the gastroscope, every 3 min during the procedure, every 5 min after the procedure until the patient's Aldrete score was above 8 in the recovery room, and before discharge. Head and body movements, coughing and gagging during the gastroscope insertion, apnea lasting for 20 s or longer, the duration of the procedure, the time to awakening, and any requirement for additional doses of propofol and opioids were recorded (Table 1) (17). Patients who developed apnea were ventilated using oxygen via a balloon mask. Ease of the procedure was assessed on a scale of 1 to 4 by the same gastroenterologist immediately after the EGD (1: very easy, 2: fairly easy, 3: difficult, and 4: failure to complete examination), who was unaware of the drug combination that was administered. The patients' movements during the insertion of the gastroscope were graded on a scale of 0 to 3, where 0: none, 1: mild (no additional assistance needed), 2: moderate (the child needed to be kept still by an assistant), and 3: severe (procedure could not be carried out). An additional dose of 0.5 mg kg^{-1} propofol was only administered when the movement score exceeded 1, and 0.5 mg kg^{-1} propofol plus 0.2 μg kg^{-1} fentanyl or remifentanil (maximum of 1 μg kg^{-1} remifentanil and 2 μg kg^{-1} fentanyl) were administered

Table 1. PACU recovery and discharge scorings (modified Aldrete score).*

Parameters	Description of the patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respiration	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mmHg > preanesthetic level	2
	Is 20 to 50 mmHg > preanesthetic level	1
	Is 50 mmHg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level > 90% when breathing room air	2
	Requires supplemental oxygen to maintain level > 90%	1
	Has level < 90% with oxygen supplementation	0

*Maximum total score is 10; a score of ≥9 is required for discharge.

when the movement scores exceeded 2 or 3. The level of sedation was assessed by a modified Ramsay scale (Table 2) (18). The procedure began with a sedation score of ≥5, and the time to awakening was recorded when the patient attained a sedation score of 3 (induction of anesthesia–eye opening with verbal orders). The awakening was recorded by a nurse who was blinded to the kind of opioid that was used. Adverse effects were recorded during the procedure and in the recovery room. Children with an Aldrete score of ≥9 (Table 1), oriented, cooperating, and with SpO_2 of >95 at room conditions were discharged from the recovery room. Duration of recovery (from the end of the procedure to discharge from the recovery room) was recorded. Perioperative adverse events like dizziness, hypotension, bradycardia, bronchospasm, apnea, nausea, vomiting, and duration of apnea periods were also recorded. Balloon-mask ventilation was applied to the children when the SpO_2 was <90 and/or apnea lasted for 20 s or longer (prolonged apnea). When spontaneous ventilation started, children ventilated via a balloon mask device were allowed to continue with the procedure. Adverse events with no need for special treatment were considered as being minor, whereas those requiring pharmacologic treatment or ventilatory support were defined as significant adverse events.

Table 2. Ramsey sedation scores.

Nervous, agitated, and/or restless	1
Cooperative, orientated, quiet patient	2
Only obeying orders	3
Sleeping, hitting the glabella, and responding to high voices suddenly	4
Sleeping, hitting the glabella, and responding to high voices slowly	5
No response to any of this stimulation	6

2.1. Statistics

With reference to locally collected data, a study population size of the 64 patients was calculated to give a confidence interval of 95% in opioid consumption. All data were expressed as mean ± standard deviation (SD). For statistical analysis, comparison of groups was carried out using a nonparametric Mann–Whitney U test for movement score, ease of operation, and balloon-mask ventilation (patients with apnea duration longer than 20 s). Student's t-test was used for age, weight, duration of operation, RR, HR, MAP, SpO_2, propofol and opioid consumption, time of awakening, duration of postanesthesia care unit (PACU) stay, number and duration of apnea, and chi-square results for the evaluation of the remaining data (sex, ASA score, adverse events). In-group comparisons according to the baseline values of RR, HR, MAP, and SpO_2 were carried out with a paired t-test. All statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

3. Results

The clinical and demographic characteristics of the patients in both groups were similar (Table 3). The indications for the need of EGD in our patients were dyspepsia, suspicion of celiac disease, hematemesis etiology, foreign body extraction, and dysphagia.

Perioperative blood pressure was similar in both groups (Table 4). However, during the procedure, HR was significantly higher in the fentanyl group ($P < 0.05$). Intraoperative and postoperative hemodynamic values did not differ significantly according to baseline values between groups.

Apnea occurred after induction and reversed before the beginning of the procedure in all of the cases. Prolonged apnea was recorded in 14 (43.8%) children in group R and in 11 (33.3%) children in group F. None of them required endotracheal intubation. Mean duration of apnea as detected in groups R and F was 23.9 ± 19 and 18.8 ± 16.8 s, respectively, and the difference was not significant ($P > 0.05$, Table 5). There was no other adverse event during

Table 3. Demographic values.

	Group R (n = 32) (mean ± SD)	Group F (n = 32) (mean ± SD)	P-value*
Age (years)	9.7 ± 3.9	8.90 ± 4	0.417
Sex (boys/girls)	11/21	16/16	0.255
Weight (kg)	26.96 ± 10.29	27.75 ± 11.58	0.773
ASA I/II	27/5	26/6	0.970
Duration of procedure (min)	9.21 ± 2.93	9.3 ± 2.29	0.898

ASA: American Society of Anesthesiologists. *: 95% confidence interval.

Table 4. Intraoperative hemodynamic values.

	Group R (n = 32) (mean ± SD)	Group F (n = 32) (mean ± SD)	P-value
SpO_2 (%)	97.07 ± 0.90	96.6 ± 1.25	0.098
HR (beats min^{-1})	88.96 ± 10.94	94.15 ± 19.72	0.197
MAP (mmHg)	84.5 ± 9.11	84.87 ± 5.72	0.246
RR (breaths min^{-1})	14.66 ± 2.71	16.36 ± 1.69	0.03

SpO_2: peripheral oxygen saturation, HR: heart rate, MAP: mean arterial pressure, RR: respiratory rate.

the procedures. The difference between intraoperative SpO_2 measurements was not statistically significant ($P > 0.05$). Intraoperative RR, the time to awakening, opioid consumption, and duration of PACU stay were significantly shorter in group R than in group F ($P < 0.05$, Table 5). The propofol consumption, movement score, and ease of operation (endoscopist satisfaction) were similar between groups ($P > 0.05$, Table 5). No postoperative complications such as hypotension, bradycardia, bronchospasm, apnea, or hypoxia were detected. Nausea was detected in 1 patient in group R and in 3 patients in group F ($P > 0.05$).

4. Discussion

Endoscopy is a very effective practice in the diagnosis and treatment of gastrointestinal diseases. Children and uncooperative adults cannot tolerate the endoscopic procedures without anesthetic support (2). Although there is no ideal sedation protocol, intravenous sedation, during which the child breathes spontaneously without an artificial airway, is a frequently used technique. Propofol is a potent and predictable IV anesthetic that can be used in low doses to sedate children and it has been successfully used in endoscopic procedures in children (2,7). However, the sedative dose of propofol can easily be exceeded, leading to unintended anesthesia and higher risk of respiratory depression. To prevent respiratory depression, propofol is slowly injected (16).

In this study, we tested the quality and safety of deep sedation using a low induction dose of remifentanil or standard dose of fentanyl in combination with propofol for children undergoing an upper endoscopic procedure. Our results showed that both remifentanil and fentanyl when used at a dose of 0.25 μg kg^{-1} and 0.5 μg kg^{-1}, respectively, lead to satisfactory anesthesia with no severe complications such as respiratory depression.

There are limited studies that compared the effectiveness of the combination of remifentanil and fentanyl in children undergoing endoscopic procedures (2,8,10,11).

Disma et al. studied the effect of the addition of fentanyl to propofol and found that this hypnotic addition leads to a significant decrease of used additional doses of propofol (2). They also found that the addition of fentanyl also increased the ease of the procedure. Their results were comparable to our results; however, the dose of fentanyl in the present study was lower than in their study and our remifentanil group provided a satisfactory sedation at a low dose. Recovery time duration was also lower in the present study compared to Disma et al.

In the prospective study of Abu-Shahwan and Mack on 42 pediatric patients undergoing upper and lower gastrointestinal endoscopy, they reported that propofol and remifentanil infusion was very effective during the procedure, providing good hemodynamic control and fast recovery. The most definitive difference between their study and the present study is the duration of procedure. The complicated protocol reported in that study (after sevoflurane induction, propofol was administered as 1 mg kg^{-1} IV bolus and 80 μg kg^{-1} h^{-1} IV infusion was started, then a second bolus of 1 mg kg^{-1} propofol was given before the insertion of the endoscopy probe; propofol infusion was reduced from 80 to 50 μg kg^{-1} min^{-1} 5 min after the start of the procedure; remifentanil infusion was begun at 0.1 μg kg^{-1} min^{-1} without a bolus dose and the infusion of remifentanil was decreased to 0.05 μg kg^{-1} min^{-1} if the respiratory rate was reduced to less than 10 breaths per minute) might be appropriate for procedures with long durations, but not for EGD. Our protocol is much simpler and seems to be more appropriate for short procedures such as EGD. The other important difference was that they had given remifentanil as an IV infusion only, without a premedication bolus dose. Although they did not report as such, the usage of remifentanil as bolus treatment instead of infusion may cause respiratory complications like apnea, but this application is not appropriate for short-duration procedures. In our protocol, apnea was observed after induction in most patients, especially in the remifentanil group. However, this situation was not significant clinically, since spontaneous breathing started in all patients, either by themselves or with a simple intervention. No apnea was observed and SpO_2 values were over 97% in both groups during the procedure time period (11) (Table 4).

In anesthesia practice it is reported that the frequency of apnea becomes higher in pediatric patients. In addition, in children the incidence of perioperative complications such as bronchospasm, apnea, airway obstruction, and hypoventilation is expected to be higher as compared to adults. Therefore, in pediatric patients, an anesthesiologist who is experienced in airway management along with

Table 5. Duration of apnea and recovery, perioperative drug dosages, and scores.

	Group R (n = 32) (mean ± SD) or n (%)	Group F (n = 32) (mean ± SD) or n (%)	P-value
Movement score	0.96 ± 0.99	1.12 ± 0.99	0.539
0	13	10	
1	10	10	
2	6	9	
3	3	3	
Ease of operation scores	1.53 ± 0.62	1.93 ± 0.34	0.913
1	17	16	
2	13	15	
3	2	1	
4	0	0	
Propofol consumption (mg kg^{-1})	2.67 ± 0.77	2.74 ± 0.73	0.708
Number of additional narcotic doses	14	17	0.689
Time to awakening (min)*	10.78 ± 3.32	13.87 ± 3.0	0.0001
Duration of recovery (min)*	15.75 ± 5.11	21.39 ± 5.94	0.0001
Number of cases of apnea longer than 20 s	14 (43.75%)	11 (34.37%)	0.707
Duration of apnea (s)	26.56 ± 19.72	23.87 ± 20.45	0.592

*: Between groups, statistical significance at $P < 0.05$.

good monitoring could be said to be essential. Hassal, a pediatric gastroenterologist, reported that the sedation given by anesthesiologists was better in pediatric endoscopy procedures in terms of patient safety and satisfaction (19).

There is only 1 study comparing propofol and fentanyl with propofol and remifentanil in pediatric endoscopic procedures. We studied the same 2 drugs but with different doses and administration protocols.

Hirsh et al. compared the addition of remifentanil and fentanyl to propofol during EGD practice and evaluated the patient–endoscopist comfort, hemodynamic status, and recovery times, and they concluded that the remifentanil group had more efficient anesthesia but more respiratory depression, and likewise in our results. In our study, half of the dose of opioid used by Hirsh et al. for induction was used, and we did not observe any decrease of SpO_2 during the procedure. In the study by Hirsh et al., intraoperative mean SpO_2 values were reported as 82.3% and 90% in the remifentanil and fentanyl groups, respectively, but in our study mean SpO_2 values were 97.1% and 96.6%. Although the recovery duration was similar to previous studies that were reported before, in the present study, the mean propofol consumption was lower, also. The reason for this low consumption could be the simultaneous administration of propofol and opioid together when additional doses were needed. Recovery times in our study were similar (8).

In conclusion, we consider that combinations of propofol with remifentanil or fentanyl may provide safe and practical anesthesia for outpatient procedures like EGD in children. Low-dose induction with remifentanil seems to be enough for providing the same anesthesia quality with fentanyl without increasing the complication rate in this group of children.

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