Effects of remifentanil on the recovery quality among pediatric candidates for dental procedures under general anesthesia

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ABSTRACT

Background: Remifentanil is a short-acting synthetic opioid, seems to facilitate hospital discharge, induce less agitation and better recovery quality. The aim of this study was to investigate the effects of remifentanil on the quality of recovery among healthy children who were candidate for dental procedures under general anesthesia.

Materials and Methods: This study was a double blind randomized controlled clinical trial on healthy children who referred to the Department of Pediatric dentistry, School of Dentistry, Isfahan University of Medical Sciences. Both groups were anaesthetized using 5 mg/kg thiopental sodium, 1 μg/kg fentanyl and 0.6 μg/kg atracurium. The first group received propofol to maintain anesthesia and the second group was given remifentanil along with propofol. Then, the time span to regain consciousness, level of agitation during recovery and time of discharge were monitored and compared between the two groups. Data were analyzed using the Mann-Whitney U-test, and the Kruskal–Wallis test at \( P < 0.05 \) level of significance.

Results: Findings showed that the propofol + remifentanil group recovered faster than the propofol group. Chi-square test showed a significant difference in recovery time between the two groups \( (P < 0.05) \). About 45 min after regaining consciousness, the mean pediatric anesthesia emergence delirium score in the propofol group was 4.02 ± 2.19 and was significantly higher than the propofol + remifentanil group \( (3.02 ± 2.83) (P < 0.05) \). In addition, the mean Postanesthetic Discharge Scoring System score in the propofol group was 6.04 ± 1.74 and was significantly higher than the propofol + remifentanil group \( (7.58 ± 2.14) (P < 0.05) \).

Conclusion: Combination of propofol and remifentanil significantly reduced the time taken for recovery, discharge and agitation level compared to propofol.

Key Words: Child, general anesthesia, propofol, remifentanil

INTRODUCTION

Dental fear and anxiety is one of the major concerns in pediatric dentistry.¹ Dentists and parents prefer nonpharmacological behaviors to overcome children’s fear, however, general anesthesia is a recommended alternative for treating agitated and anxious children, patients with underlying disorders, and children...
Propofol is a well-known drug for induction and maintenance of anesthesia. The major advantages of propofol is its rapid induction of anesthesia, easy intubation process, and its deep anesthetic property while maintaining cardiovascular parameters. Recovery from the anesthetic effects of propofol is remarkably rapid, with approximately 6–8 min with minimal complications, including agitation, nausea, and vomiting in the postoperative period, which facilitate early patient discharge. Propofol alone can be helpful, but high doses might be needed to decrease pain-induced movements, as mentioned in two other studies where the average dose of propofol used was 5–8.8 mg/kg. Therefore, most studies have suggested propofol alone with other drugs, e.g. remifentanil, to induce and maintain anesthesia. Remifentanil is a short-acting synthetic opioid widely used by anesthesiologists to induce and maintain anesthesia. Remifentanil has several unique properties. It induces rapid and profound anesthesia with minimal suppression of the central nervous system and, more importantly, it is metabolized by esterase’s and not dependent on hepatic or renal function for excretion. Therefore, it has a very short half-life (about 3–8 min), regardless of the patient’s age, comorbidities, or duration of drug administration.

Postanesthetic agitation is a common phenomenon experienced by patients in varying degrees based on the type of anesthesia, age, sex, history of prior surgery, preoperative anxiety, type of surgery, and time taken to regain consciousness. In a study by Glaisyer et al. among 2–10-year-old children under oncology treatment, children discharged earlier following recovery with propofol + remifentanil than propofol, sevoflurane, and nitrous oxide combination. In Choi et al. study among 80 children aged between 3 and 7 years, continued injections of low-dose remifentanil during the recovery phase reduced the incidence of agitation in children under sevoflurane anesthesia. Other previous studies reported that remifentanil reduced the incidence of agitation, recovery duration, and induced less pain. Considering the findings of previous studies, remifentanil seems to facilitate hospital discharge, induce less agitation and better recovery quality.

Given the significant increase in general anesthesia in pediatric dentistry and the lack of evidence regarding the efficacy of remifentanil on improving the quality of recovery in this group, further studies is required to determine the definitive effects. The aim of this study was, therefore, to determine the effects of remifentanil on the quality of recovery in healthy children aged 3–6 years who were candidate for dental practices under general anesthesia.

**MATERIALS AND METHODS**

The present study was a double-blind randomized controlled clinical trial. The study was ethically approved by the Regional Bioethics Committee of Isfahan University of Medical Sciences, IR.MUI.RESEARCH.REC.1398.466. Clinical trial registration code is IRCT20170624034726N2.

In this study, participants were selected from the School of Dentistry of Isfahan University of Medical Sciences. Subjects were chosen by convenience sampling method based on inclusion and exclusion criteria. Inclusion criteria included consent to participate in this study, healthy children between 3 and 6 years old referred for dental procedures under general anesthesia, no pre-existing medical conditions. Exclusion criteria included any surgeries or complex tooth extraction and any other procedures which requires general anesthesia for <30 min and more than 90 min.

Sample size was calculated using the formula suggested for parallel studies. We considered type 1 error of 5%, type 2 error of 20% (power = 80%), and agitation as a key variable and reached the sample size of 43 participants in each group. To ensure having sufficient participants at the end of the study, 50 individuals in each group were selected according to the above-mentioned inclusion criteria. Oral assent was obtained from all participants, and informed written consents was obtained from their parents. This study was registered at Iranian website for registry of clinical trials (IR.MUI.RESEARCH.REC.1398.466). The study was ethically approved by the Regional Bioethics Committee of Isfahan University of Medical Sciences.
Study procedures
Anesthesia was induced in both groups equally using 5 mg/kg thiopental sodium (Ciron Drugs, India), 1 μg/kg fentanyl (Aburaihan, Iran) and 0.6 μg/kg atracurium (Caspian, Iran). Then, the nasal endotracheal tube was passed through the nose and the patient was connected to an anesthesia machine at a rate of 10 cc/min and with a respiratory rate of 15 cc. The volume and number of breaths were controlled using a capnograph. As initial loading dose, the first group received 1 mg/kg propofol. Then, for anesthesia maintenance, the first group received 100 μg/kg/min propofol, 50% N2O and 50% oxygen (Dongkook Pharm. Co. Ltd. Korea).[19] As initial loading dose, the second group received 1 mg/kg propofol, and for anesthesia maintenance 100 μg/kg/min propofol and 50% N2O and 50% oxygen.[20] At the same time as starting the infusion of propofol, the second group received 0.4 μg/kg/min remifentanil (Laboratoris Norman, S.A, Spain) for anesthesia maintenance.

Recovery condition assessment
Agitation was assessed by the anesthesiologist every 15 min for 45 min starting from the child’s entry to the recovery room. Pediatric anesthesia emergence delirium (PAED) was used in this study to evaluate children’s agitation.[21] PAED contains 5 items and each item with a score ranging from 0 to 4 points. Items are: (1) The child makes eye contact with the caregiver. (2) The child’s actions are purposeful. (3) The child is aware of his/her surroundings. (4) The child is restless. (5) The child is inconsolable eventually. Items 1, 2, and 3 are reverse scored as follows: 4 = not at all; 3 = just a little; 2 = quite a bit; 1 = very much; and 0 = extremely. Items 4 and 5 are scored as follows: 0 = not at all; 1 = just a little; 2 = quite a bit; 3 = very much; and 4 = extremely, these points summed up and each child’s final score was between 0 and 20. In this study, a score of more than 10 was considered as inappropriate recovery conditions. The degree of agitation is directly proportional to the increase in total score. The validity and reliability of this tool have been shown in previous studies.[21] The duration of recovery (the time that the child wakes up till the time of discharge) was also recorded in both groups.

Patient discharge time assessment
The Postanesthetic Discharge Scoring System (PADSS) tool was used to determine patient discharge time.[22] The tool sets 6 criteria for discharge: Vital signs (including blood pressure, pulse and heart rate), ability to walk, absence of nausea and vomiting, pain, surgical bleeding, and urinary excretion. Each criterion was given a score between 0 and 2. If a child received a score of 9 or higher, he or she was eligible for discharge. Each patient was discharged based on thorough counseling and provision of a phone number for emergency calls.

Statistical analysis
Descriptive statistics were presented as mean, standard deviation and frequency. Since distribution of PAED and PADSS was not normal, nonparametric tests were used for these variables. To do this, the Mann–Whitney U-test was used to compare these variables in the two groups (within group) and the Kruskal–Wallis test was used to compare changes over time. All statistical analyses were done using the Statistical Package (version 20; SPSS Inc.). \( P < 0.05 \) was considered statistically significant.

RESULTS
Mean age of 100 participants in our study was 3.8 years in the propofol + remifentanil and 3.9 years in the propofol group. All participants completed the study [Figure 1]. Findings showed that propofol + remifentanil group had shorter recovery period compared to the propofol group. Chi‑square test showed a significant difference in recovery time period between the two groups \(( P < 0.05 )\) [Table 1]. After 45 min of recovery, the mean PAED in the propofol group was 4.02 ± 2.19 and was significantly higher than the propofol + remifentanil group (3.02 ± 2.83) \(( P < 0.05 )\) [Table 2]. In addition, the mean PADSS in the propofol group was 6.04 ± 1.74 and was significantly higher than the propofol + remifentanil group (7.58 ± 2.14) \(( P < 0.05 )\) [Table 3]. No adverse effects was reported.

| Time (min) | Propofol, \( n (%) \) | Propofol + remifentanil, \( n (%) \) |
|-----------|-----------------------|--------------------------------------|
| 15        | 0 (0)                 | 1 (2)                                |
| 30        | 4 (8)                 | 14 (28)                              |
| 45        | 46 (92)               | 35 (70)                              |

\( P \) value: Chi‑Square test
DISCUSSION

Given the significant increase in general anesthesia in pediatric dentistry and the lack of evidence regarding the efficacy of remifentanil on improving the quality of recovery, the aim of this study was to determine the effects of remifentanil on the quality of recovery in healthy children aged 3–6 years who were candidate for dental practices under general anesthesia.

In this study, recovery time in children receiving propofol + remifentanil was shorter in comparison to the propofol group. Agitation was also lower in the propofol + remifentanil group compared to the propofol group. In addition, children in the propofol + remifentanil group were discharged sooner than those in the propofol group.

Agitation includes disturbance in consciousness, accompanied by hyperactive motor behaviors such as kicking and unbearable crying immediately after anesthesia. This can harm child and put a lot of pressure on the medical staff. In this study, we found that the children who received propofol + remifentanil were less agitated than children who received propofol for anesthesia maintenance. This finding could be due to the sedative effect of remifentanil in the postoperative period, but its exact mechanism is not fully understood. In fact, remifentanil is often prescribed to provide a level of relaxation to relieve anxiety and agitation. In Choi et al. study on 80 children aged 3–7 years, continued injections of low doses of remifentanil during the recovery phase reduced the incidence of agitation in children under sevoflurane anesthesia. In Choi et al. study of 3–9-year-old having an ophthalmic surgery under anesthesia with sevoflurane showed that remifentanil injection

**Table 2: Comparison of the mean score of agitation between the two groups over recovery time**

| Time (min) | n  | Mean±SD       | P   |
|-----------|----|---------------|-----|
|           |    | Propofol     | Propofol + remifentanil |
| 0         | 50 | 12±0         | 12±0 | - |
| 15        | 50 | 11.08±3.11   | 9.92±2.63 | 0.052 |
| 30        | 50 | 8.92±3.24    | 7.36±3.32 | 0.020 |
| 45        | 50 | 4.02±2.19    | 3.02±2.83 | 0.002 |

\*P value: Freidman. P value: Mann–Whitney U test. SD: Standard deviation

**Table 3: Comparison of the mean score of Postanesthetic Discharge Scoring System over recovery time**

| Time (min) | n  | Mean±SD       | P   |
|-----------|----|---------------|-----|
| 0         | 50 | 0.94±0.76     | 0.86±0.78 | 0.59 |
| 15        | 50 | 4.40±1.16     | 5.46±1.32 | <0.001 |
| 30        | 50 | 5.12±1.62     | 6.89±2.62 | 0.001 |
| 45        | 50 | 6.04±1.74     | 7.58±2.14 | 0.001 |

\*P value: Freidman. P value: Mann–Whitney U-test. SD: Standard deviation
reduced the incidence of agitation without significant hemodynamic changes. In another study by Eshghi et al. on anxious and noncooperative children aged 3–7 years, intravenous sedation technique with remifentanil compared to ketamine induced a much more effective and safe sedation with less pain, more forgetfulness, and a shorter recovery period in children undergoing dental procedures. Agitation is influenced by factors like rapid anesthesia, preoperative anxiety, pain, young, age, use of sevoflurane, and type of surgery. Since pain is an important factor in causing agitation, the analgesic properties of remifentanil during the postoperative period could contribute greatly to reducing the incidence of agitation.

In the present study, children who received remifentanil with propofol for anesthesia had a shorter recovery phase in contrast to children who received propofol for anesthesia maintenance. In addition, children in the propofol + remifentanil group were discharged faster than children in the propofol group. In Glaisyer et al. study of 2–10-year-old undergoing oncology treatments, children were ready to be discharged 19 min earlier from the recovery section following propofol + remifentanil than the combination of propofol, sevoflurane, and nitrous oxide. Taking these findings into account, remifentanil appears to reduce agitation, reduce recovery time period, and reduce the length of hospital stay in children.

To the best of our knowledge, this is the first study examined the effects of remifentanil on the quality of recovery in healthy children candidate for dental procedures under general anesthesia. However, the present study has some limitations which must be considered when interpreting our results. First of all, although PAED is a validated and reliable tool for assessing the level of agitation that can reduce the rate of error in the clinical assessment of agitation, it seems researchers need to use another new indicator that is easier to assess in children. Secondly, we have not been able to constantly measure the level of agitation in children. This is because, agitation in children occurs at different times and is unpredictable, which may result in lower PAED scores.

CONCLUSION

In conclusion, the results of the present study showed that combination of remifentanil and propofol reduced recovery time while improved quality of recovery, reduced agitation level and hospital stay compared to propofol.

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Informed consent
Oral assent was obtained from all participants, and informed written consents was obtained from their parents.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
The authors of this manuscript declare that they have no conflicts of interest, real or perceived, financial or nonfinancial in this article.

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