

Combination effect of low dose fentanyl and propofol on emergence agitation in children following sevoflurane anesthesia

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ABSTRACT

الأهداف: لمعرفة اثر إعطاء جرعة صغيرة من عقار الفنتانيل مع جرعة صغيرة من عقار البروبوفول على الإثارة التي تحدث عند الإفادة من التخدير في الأطفال الذين تم تخديرهم بعقار السيفوفلوران أثناء عمليات استئصال اللحمية واللوزتين.

الطريقة: أجريت دراسة عشوائية شملت 120 طفلاً تراوحت أعمارهم ما بين 2-6 سنوات، مستشفى سعد التخصصي - الخبر - المملكة العربية السعودية، خلال الفترة ما بين 2007م وحتى 2008م. كان من المقرر إجراء عمليات استئصال اللحمية واللوزتين لهؤلاء الأطفال تحت تأثير التخدير العام باستخدام الأنبوية الحجرية عن طريق الفم. تم تقسيم الأطفال عشوائياً إلى ثلاث مجموعات. تم استخدام عقار السيفوفلوران في بدء التخدير والاستمرار فيه لجميع الأطفال. تلقى الأطفال محلول ملحي عن طريق الوريد عند نهاية العملية في المجموعة (C) وعددهم 40 طفل. تم استخدام عقار الفنتانيل بجرعة 1.5mcg.kg⁻¹ عن طريق الوريد عند بدء الجراحة وتم إعطاء 0.1ml.kg⁻¹ محلول ملحي عن طريق الوريد عند نهاية العملية في المجموعة (F) وعددهم 40 طفل. كما تم إعطاء 1.5mcg.kg⁻¹ من عقار الفنتانيل، و 1mcg.kg⁻¹ من عقار البروبوفول في نهاية العملية الجراحية للمجموعة (PF) والتي شملت 40 طفل. تم تسجيل حدوث أي آثار جانبية خلال ساعة بعد العملية.

النتائج: لم يوجد اختلاف إحصائي بين المجموعات الثلاث بخصوص البيانات الديموغرافية. وقد تم تسجيل حدوث الإثارة عند الإفادة من التخدير في 21 طفلاً (53%) في مجموعة التحكم، و 14 طفلاً (35%) في المجموعة (F)، و عند 7 أطفال (18%) في المجموعة (PF).

خاتمة: ثبت إن إعطاء جرعة صغيرة من الفنتانيل قبل العملية والبروبوفول عند نهاية العملية يقلل من احتمال حدوث الإثارة عند الإفادة من التخدير في الأطفال الذين تم تخديرهم بعقار السيفوفلوران عند خضوعهم لعملية استئصال اللحمية واللوزتين.

Objectives: To investigate the combination effect of low dose fentanyl and subhypnotic dose of

propofol on emergence agitation in children receiving sevoflurane for adenotonsillectomy procedure.

Methods: After ethical approval, a prospective, randomized, clinical study was performed in Saad Specialist Hospital, Al-Khobar, Kingdom of Saudi Arabia in 2007-2008. One hundred and twenty children in physical status of I according to the American Society of Anesthesiologists, aged 2-6 years, scheduled for adenotonsillectomy under general anesthesia were allocated into 3 groups randomly. Anesthesia was induced and maintained by sevoflurane in all groups. Children received 0.1 ml.kg⁻¹ normal saline at the end of surgery in group C (n=40), 1.5 mcg.kg⁻¹ fentanyl during induction, and 0.1 ml.kg⁻¹ normal saline at the end of surgery in group F (n=40), and 1.5 mcg.kg⁻¹ fentanyl during induction and 1 mg.kg⁻¹ propofol at the end of surgery in group FP (n=40). Postoperative agitation was recorded, if any, for the first postoperative hour.

Results: Three groups were comparable with regard to demographic data. Twenty-one patients (53%) in the control group, 14 patients (35%) in group F and 7 (18%) patients in group FP experienced postoperative agitation.

Conclusion: The combination of low dose fentanyl before surgery and propofol at the end of surgery decreases the incidence and level of emergence agitation in children after adenotonsillectomy procedure under sevoflurane anesthesia.

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Sevoflurane with its ease and speed of inhalational induction, cardiovascular stability, and speed of recovery became very popular in pediatric anesthesia. However, emergence delirium, and postoperative agitation is well described with sevoflurane in children.^{1,2} Many factors contribute to the occurrence of emergence agitation in children. Hypoxemia, metabolic disturbances, postoperative pain, and age are some of the postulated risk factors.³ Effects of using propofol for induction or maintenance,^{4,5} changing of volatile agent after induction,⁶ using opioids⁷ or clonidine⁸ are all studied to reduce the postoperative agitation after surgical procedures performed in children. Emergence agitation following sevoflurane anesthesia still remains a problem with the incidence varying between 20-80% depending on the definition used, and monitored time interval after emergence.⁹ Propofol maintenance was said to abolish emergence agitation.¹⁰ In addition, both propofol, and fentanyl were reported to decrease the rate of emergence agitation after sevoflurane and desflurane anesthesia in separate settings.¹⁰⁻¹³ The aim of this study was to investigate the combination effect of a low dose fentanyl administered before surgery, and a subhypnotic dose of propofol at the end of surgery on emergence agitation in children following sevoflurane anesthesia for adenotonsillectomy.

Methods. This prospective, randomized, clinical study was performed in the Department of Anesthesiology, Saad Specialist Hospital, Al-Khobar, Kingdom of Saudi Arabia, in 2007 to 2008. After hospital ethics committee approval and parents' informed written consent, 120 children aged 2-6 years in a physical status of I according to American Society of Anesthesiologists (ASA) guidelines, scheduled for adenotonsillectomy with or without bilateral myringotomy, and insertion of tubes under general anesthesia with endotracheal intubation were included in the study. Patients with history of previous anesthesia, bad hospital experience, and known allergy to any of the drugs used during the study period, any diagnosed psychological or behavioral problems, and patients who required propofol or fentanyl in any stage of anesthesia other than planned were excluded from the study. After 4-6 hours of fasting period, patients were randomly allocated into one of the 3 groups. All patients were premedicated with 0.5 mg.kg⁻¹ oral midazolam 20-30 minutes before operation. Group C (n=40) consisted of the children receiving 0.1 ml.kg⁻¹ normal saline with a maximum of 3 ml at the end of surgery, group F (n=40) consisted of the children receiving fentanyl 1.5 mcg.kg⁻¹ before the surgery started and 0.1 ml.kg⁻¹ normal saline with a maximum of 3 ml at the end of surgery, and finally group FP (n=40) consisted of the children receiving fentanyl 1.5 mcg.kg⁻¹ before the surgery started, and 1

mg.kg⁻¹ propofol with a maximum dose of 30 mg at the end of surgery. Induction of anesthesia was performed by 7% sevoflurane in 50% oxygen and nitrous oxide (O₂-N₂O) mixture, and an intravenous line was established thereafter. Following the intravenous access, 0.5 mg.kg⁻¹ atracurium was given intravenously to the children in all groups. In groups F and FP, 1.5 mcg.kg⁻¹ fentanyl was also added intravenously. With the achievement of intubation, children were given 40 mg.kg⁻¹ paracetamol rectal suppository and positioned for adenotonsillectomy. Anesthesia was maintained with age corrected minimum alveolar concentration (MAC) levels of sevoflurane monitored, and kept constant all through the procedure in a 50% mixture of O₂-N₂O. At the end of surgery, which was defined as the time that the mouth opener was removed, the children in group C, and F received 0.1 ml.kg⁻¹ normal saline with a maximum of 3 ml while the children in group FP received 1 mg.kg⁻¹ propofol intravenously, and anesthetic gases were discontinued. Controlled ventilation was maintained with the same settings with 100% O₂ without stimulating the patient. With the return of cough reflex followed by spontaneous regular breathing, facial grimacing, and purposeful movements, patients were extubated. After emergence they were followed in the recovery unit until they reached modified Aldrete score 9.¹⁴ Patients were observed for an hour and assessed for emergence agitation at 10 minute intervals by another anesthesiologist, who had not been in the operating room during the study period with the help of a 10 point scale (1- calm or sleepy, and 10- the highest level of agitation possible). The highest score of each patient was accepted as the postoperative agitation score of that patient. The patient was accepted to have no agitation with a score of 1, mild agitation with a score of 2-4, medium with a score of 5-7, and severe with a score of 8-10. Propofol with a dose of 1 mg.kg⁻¹ was given intravenously for the patients who had agitation score of 5, or more for more than 5 minutes.

The results were evaluated using statistical software package SPSS 9.01[®] with ANOVA, Chi-square, and Fisher's exact tests and post hoc least significant difference test where appropriate, and significance was set at the level of 0.05. Power analysis was managed with GPower 3.0[®]. Total sample size for chi-square test was 108 when effect size w=0.3, α -error probability 0.05, and power (1- β error probability) was 0.8. Also

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for ANOVA test, for effect size 0.3, α -error probability 0.05, and power ($1-\beta$ error probability) 0.8, calculated sample size was 111.

Results. Fifty-six male and 64 female, totaling 120 children were enrolled in this prospective, randomized, controlled study. The mean age of the study population was 4.8 ± 1.9 years, and mean body weight was 21.4 ± 3.3 kg. There were 40 children in each of the 3 groups. The groups were comparable in demographic characteristics, duration of surgery, recovery, and hospital stay (Table 1). There was no difference in blood pressures, or heart rates recorded with 5 minutes intervals during the anesthesia, and 15 minutes intervals during the recovery stay

Table 1 - Demographic data, duration of operation, recovery and hospital stay of the patients according to groups (mean \pm SD).

Demographic data	Group C (n=40)	Group F (n=40)	Group FP (n=40)
Age (years)	4.6 ± 1.5	5.1 ± 1.9	4.8 ± 1.9
Body weight (kg)	20.6 ± 3.3	21.4 ± 3.3	22.3 ± 3.1
Gender (male/female)	24/26	25/25	27/23
Duration of operation (minutes)	44.8 ± 6.5	45.3 ± 6.8	43.3 ± 6.6
Recovery time (minutes)	26 \pm 4	28 \pm 7	31 \pm 8
Discharge time (minutes)	202 \pm 36	222 \pm 36	212 \pm 36

Group C - received 0.1 ml.kg $^{-1}$ normal saline with a maximum of 3 ml at the end of surgery, Group F - received fentanyl 1.5 mcg.kg $^{-1}$ before the surgery started and 0.1 ml.kg $^{-1}$ normal saline with maximum of 3 ml at the end of surgery, Group FP - received fentanyl 1.5 mcg.kg $^{-1}$ before the surgery started, and 1 mg.kg $^{-1}$ propofol with a maximum dose of 30 mg at the end of surgery

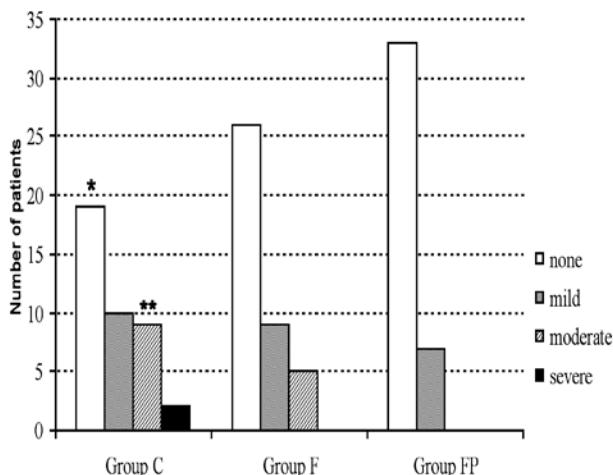


Figure 1 - Distribution of patients by the group according to their level of emergence agitation. * $p=0.027$, ** $p=0.018$. None - agitation score 1, mild: agitation score 2-4, moderate: agitation score 5-7, severe: agitation score 8-10.

between the groups. None of the patients developed any complication related with either anesthesia or surgery in the operating room, and recovery unit. The total number of patients with emergence agitation was 42 (35%) out of 120 children. Emergence agitation was observed in 21 (53%) children in the control group, 14 (35%) children in group F, and 7 (18%) children in FP group. It was statistically highest in group C ($p=0.027$, Figure 1). Figure 1 shows that the number of children that experienced mild agitation was statistically similar in the 3 groups. The number of children experiencing moderate agitation was statistically higher in the group C than the group F and FP ($p=0.018$). There was no patient with moderate, and severe agitation in group FP. There were 2 (5%) children with severe agitation during their recovery stay in all study groups, both being in the group C (Figure 1). Six of the children in the control group required propofol treatment of the emergence agitation in the recovery unit, which was statistically higher than the number of children that required treatment in the group F and group FP ($p=0.021$). The number of children receiving propofol during their recovery stay was one in group F, and none in group FP. Following propofol administration, all agitation scores recorded until the end of the recording period was one, regardless of the group of patient.

Discussion. The results of this study reveal that fentanyl with a dose of 1.5 mcg.kg $^{-1}$ applied during induction is effective to decrease emergence agitation, especially moderate, and severe agitation, and the addition of a subhypnotic dose of propofol at the end of surgery to the fentanyl given previously helps to decrease the emergence agitation more. Emergence agitation is a well described time limited phenomenon defined as a period of restlessness, agitation, inconsolable crying, disorientation, delusion, and hallucination plus cognitive, and memory impairment.¹⁵ The exact etiology of postoperative agitation is not yet well understood. The patient population chosen for this study was preschool children, as they are known to have this phenomenon more often.¹⁶ Although pain is an important factor leading to emergence agitation, it has already been published that this phenomenon can occur in pain-free children.¹⁷ It was assumed that paracetamol suppository in a dose proven to be effective for children having tonsillectomy,^{17,18} and fentanyl with its known analgesic effect lasting until 60 minutes¹⁹ would exclude any contributing factor of pain. In addition, in this study after application of propofol as a rescue medication patients were free of agitation until the end of study, suggesting that the major problem was agitation rather than pain. Fentanyl is a short-acting opioid analgesic that has sedative effects, and reported to be effective in decreasing the incidence of emergence agitation in a dose of 2.5 mcg.kg $^{-1}$ in patients receiving sevoflurane anesthesia for adenoidectomy.¹² In the pilot

study performed before the current one, fentanyl was used in a $3 \text{ mcg} \cdot \text{kg}^{-1}$ dose before the surgery started. Emergence time was increased significantly with that dose of fentanyl, especially when used with propofol in that pilot study. Thus, in the current study the dose was preferred to be lower since propofol was also planned to be given. Abu-Shahwan¹¹ claimed that delayed emergence, and smoothing the recovery might be the reasons for the decreased emergence agitation incidence. However, Cohen et al²⁰ reported that induction of anesthesia was not effective in decreasing the incidence of emergence agitation when anesthesia was maintained by desflurane. On the other hand, emergence agitation could be eliminated after anesthesia induction with high dose sevoflurane inhalation followed by propofol infusion for maintenance.⁴ An euphoric state, caused by propofol itself may be the reason for a decreasing incidence of bad experience called emergence agitation. Any possible adverse effect of propofol such as hypotension, bradycardia, apnea, airway obstruction, and consequent desaturation was not observed in this study with a dose of $1 \text{ mg} \cdot \text{kg}^{-1}$. Nevertheless, none of the 40 children receiving propofol experienced these problems, as the dose is limited to a maximum of 30 mg. In addition, it was also reported that administration of subhypnotic doses of propofol also decreases the likelihood of laryngospasm.²¹

The important limitation of this study was the difficulty of differentiation between pain and emergence agitation. This limitation can be discarded by topical application of different types of drugs for the relief of postoperative pain and discomfort in a different study design.²²

As a conclusion, the combination of low dose fentanyl applied before surgery with the subhypnotic dose of propofol applied at the end of surgery has a decreasing effect on emergence agitation after adenotonsillectomy procedures in children following sevoflurane anesthesia. However, further studies can be carried out by different analgesic modalities to minimize the effect of pain on agitation.

References

- Aono J, Ueda W, Mamiya K, Takimoto E, Manabe M. Greater incidence of delirium during recovery from sevoflurane anesthesia in preschool boys. *Anesthesiology* 1997; 87: 1298-1300.
- Lapin SL, Auden SM, Goldsmith LJ, Reynolds AM. Effects of sevoflurane anesthesia on recovery in children: a comparison with halothane. *Pediatr Anaesth* 1999; 9: 299-304.
- Tripi PA, Palermo TM, Thomas S, Goldfinger MM, Pineda IF. Assessment of risk factors for emergence distress and postoperative behavioural changes in children following general anesthesia. *Pediatr Anesth* 2004; 14: 235-240.
- Uezono S, Goto T, Terui K, Ichinose F, Ishquro Y, Nakata Y, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. *Anesth Analg* 2000; 91: 563-566.
- Bal N, Saricaoglu F, Uzun S, Dal D, Celebi N, Celiker V, et al. Perioperative anxiety and postoperative behavioural disturbances in children: comparison between induction techniques. *Eur J Anaesthesiol* 2006; 23: 470-475.
- Meyer RR, Munster P, Werner C, Brambrink AM. Isoflurane is associated with a similar incidence of emergence agitation/delirium as sevoflurane in young children- a randomized controlled study. *Pediatr Anesth* 2007; 17: 56-60.
- Cravero JP, Beach M, Thy BE, Whalen K. The effect of fentanyl on emergence characteristics of pediatric patients after sevoflurane anesthesia without surgery. *Anesth Analg* 2003; 97: 364-367.
- Tazeroualti N, De Groote F, De Hert S, De Ville A, Dierick A, Van der Linden P. Oral clonidine vs midazolam in prevention of sevoflurane-induced agitation in children. A prospective, randomized controlled trial. *Br J Anaesth* 2007; 98: 667-671.
- Cole JW, Murray DJ, McAllister JD, Hirshberg GE. Emergence behavior in children: defining the incidence of excitement and agitation following anesthesia. *Pediatr Anaesth* 2002; 12: 422-427.
- Uezono S, Goto T, Terui K, Ichinose F, Ishguro Y, Nakata Y, et al. Emergence agitation after sevoflurane versus propofol in pediatric patients. *Anesth Analg* 2000; 91: 563-566.
- Abu-Shahwan I. Effect of propofol on emergence behavior in children after sevoflurane general anesthesia. *Pediatr Anesth* 2008; 18: 55-59.
- Cohen IT, Hannallah RS, Hummer KA. The incidence of emergence agitation associated with desflurane anesthesia in children is reduced by fentanyl. *Anesth Analg* 2001; 93: 88-91.
- Cohen IT, Finkel JC, Hannallah RS, Hummer KA, Patel KM. The effect of fentanyl on the emergence characteristics after desflurane or sevoflurane anesthesia in children. *Anesth Analg* 2002; 94: 1178-1181.
- Aldrete JA. The postanesthesia recovery score revisited. *J Clin Anesth* 1995; 7: 89-91.
- Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. *Anesthesiology* 2004; 100: 1138-1145.
- Johr M. Postanaesthesia excitation. *Pediatr Anaesth* 2002; 12: 293-295.
- Anderson BJ, Kanagasundaram S, Woolard G. Analgesic efficacy of paracetamol in children using tonsillectomy as a pain model. *Anaesth Intensive Care* 1996; 24: 669-673.
- Capici F, Ingelmo PM, Davidson A, Sacchi CA, Milan B, Sperti LR, et al. Randomized controlled trial of duration of analgesia following intravenous or rectal acetaminophene after adenotonsillectomy in children. *Br J Anaesth* 2008; 100: 251-255.
- Dershawitz M, Rosow CE. Pharmacology of Opioid Analgesics. In: Longnecker DE, Brown DL, Newman MF, Zapol WM, editors. *Anesthesiology*. New York (NY): McGraw-Hill; 2008. p. 875.
- Cohen IT, Drewsen S, Hannallah RS. Propofol or midazolam do not reduce the incidence of emergence agitation associated with desflurane anesthesia in children undergoing adenotonsillectomy. *Pediatr Anaesth* 2002; 12: 604-609.
- Batra Y, Ivanova M, Ali SS, Shamsah M, Al Qattan AR, Belani KG. The efficacy of a subhypnotic dose of propofol in preventing laryngospasm following tonsillectomy and adenoidectomy in children. *Pediatr Anesth* 2005; 15: 1094-1097.
- Canbay O, Celebi N, Uzun S, Sahin A, Celiker V, Aypar U. Topical ketamine and morphine for postoperative pain. *Eur J Anaesthesiol* 2008; 25: 287-292.