Fentanyl is more effective than remifentanil at preventing increases in cerebral blood flow velocity during intubation in children

[Le fentanyl est plus efficace que le rémifentanil à prévenir des augmentations de la vitesse circulatoire cérébrale pendant l'intubation chez les enfants]

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Purpose: Controlling the cerebral and systemic hemodynamic responses to laryngoscopy and tracheal intubation may play a role in determining clinical outcome in pediatric neurosurgical patients. This study compared the effects of remifentanil and fentanyl on cerebral blood flow velocity (CBFV) and hemodynamic profile during laryngoscopy and tracheal intubation in children under sevoflurane anesthesia.

Methods: Sixty healthy children aged two to six years undergoing dental surgery under general anesthesia were enrolled. Each child was randomly assigned to receive a remifentanil or fentanyl infusion, at a rate of 0.75, 1.0, or 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after induction of anesthesia with 2% sevoflurane. Middle cerebral artery blood flow velocity was measured by transcranial Doppler (TCD) sonography. Once a baseline set of hemodynamic variables and TCD measurements were recorded, the opioid infusion was started. Measurements were taken at two-minute intervals, starting four minutes prior to laryngoscopy until four minutes following naso-tracheal intubation.

Results: Remifentanil caused a more significant decrease in mean arterial pressure and CBFV prior to tracheal intubation than did fentanyl ($P < 0.001$). During laryngoscopy and for two minutes following tracheal intubation, CBFV increased in all remifentanil groups ($P < 0.05$), whereas it remained stable in all fentanyl groups.

Conclusion: This study suggests that fentanyl was more effective than remifentanil at preventing increases in CBFV during and immediately following laryngoscopy and tracheal intubation in children undergoing sevoflurane anesthesia. Fentanyl also seemed to provide a more stable hemodynamic profile prior to laryngoscopy and tracheal intubation when compared to remifentanil.

Objectif : *Le contrôle des réponses hémodynamiques cérébrale et générale à la laryngoscopie et à l'intubation trachéale peut influencer de façon déterminante l'évolution clinique des enfants de neurochirurgie. La présente étude a comparé les effets du rémifentanil et du fentanyl sur la vitesse du flux sanguin cérébral (VFSC) et sur le profil hémodynamique pendant la laryngoscopie et l'intubation trachéale chez des enfants soumis à une anesthésie au sévoflurane.*

Méthode : *Soixante enfants en bonne santé devant subir une intervention dentaire sous anesthésie générale ont été choisis pour l'étude. Chaque enfant a été assigné au hasard pour recevoir une perfusion de rémifentanil ou de fentanyl selon une vitesse de 0,75, 1,0 ou 1,5* $\mu g \cdot kg^{-1} \cdot min^{-1}$*, après l'induction de l'anesthésie avec du sévoflurane à 2 %. La vitesse circulatoire de l'artère cérébrale moyenne a été mesurée par Doppler transcrânien (DTC). La perfusion a commencé après la réalisation des mesures de base des variables hémodynamiques et du DTC. Les mesures ont été prises aux deux minutes, en commençant quatre minutes avant la laryngoscopie jusqu'à quatre minutes après l'intubation nasotrachéale.*

Résultats : *Avant l'intubation trachéale, le rémifentanil, comparé au fentanyl, a causé une baisse plus importante de la pression de l'artère moyenne et de la VFSC (*$P < 0,001$*). Pendant la laryngoscopie et pendant deux minutes après l'intubation trachéale, la VFSC a augmenté avec le rémifentanil (*$P < 0,05$*) alors qu'elle est demeurée stable avec le fentanyl.*

Conclusion : *Cette étude montre que le fentanyl a été plus efficace que le rémifentanil à prévenir des hausses de la VFSC pendant et immédiatement après la laryngoscopie et l'intubation trachéale chez des enfants sous anesthésie avec du sévoflurane. Le fentanyl, comparativement au rémifentanil, semble fournir aussi un profil hémodynamique plus stable avant la laryngoscopie et l'intubation trachéale.*

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Laryngoscopy and tracheal intubation may cause significant cerebral and systemic hemodynamic responses, including tachycardia, hypertension and increased intracranial pressure.[1–3] Controlling these responses on induction of anesthesia may be an important factor in improving outcome in pediatric neurosurgical patients. Remifentanil is a μ-opioid receptor agonist, rapidly metabolized by nonspecific esterases throughout the blood and tissues. The elimination half-life of remifentanil is less than ten minutes, compared to 219 min for fentanyl.[4–6] It does not accumulate after prolonged continuous infusion and the blood brain equilibration time is rapid.[5,7] Its use is characterized by rapid and complete offset of opioid effects within minutes of infusion discontinuation.[4] These distinctive pharmacokinetic and pharmacodynamic characteristics make remifentanil a potentially attractive opioid for use in pediatric anesthesia. Comparative data assessing cerebral blood flow velocity (CBFV) on induction and tracheal intubation with remifentanil and fentanyl has not been documented in the pediatric population.

The aim of this study was to compare the effects of remifentanil and fentanyl on CBFV and hemodynamic profile during laryngoscopy and tracheal intubation in children under sevoflurane anesthesia.

Methods

With Regional Ethics Board approval and written parental consent, 60 unpremedicated children aged two to six years, ASA I or II, undergoing dental surgical procedures requiring general anesthesia were enrolled. Exclusion criteria included emergency surgery, central nervous system or cardiovascular disease. Using a randomization table, patients were prospectively assigned to receive either a remifentanil or fentanyl infusion, at a rate of 0.75, 1.0 or 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In each child, anesthesia was induced with sevoflurane in oxygen, with the inspired sevoflurane concentration being kept at 2% upon loss of consciousness. A peripheral *iv* catheter was then inserted. Monitoring of the patient included the standard anesthesia monitors. A transcranial Doppler (TCD) probe with a 2-mHz emitted ultrasonic frequency was placed appropriately to measure middle cerebral artery (MCA) blood flow velocity (Vmca) at the M1 segment. A custom designed head frame was used to prevent the probe from moving during the study period.[8] Once a baseline set of variables [heart rate (HR), respiratory rate, oxygen saturation, peak airway pressure, non invasive blood pressure, axillary temperature, end-tidal CO_2 concentration and Vmca] was recorded, the opioid infusion was started. These variables were recorded at two-minute intervals, starting

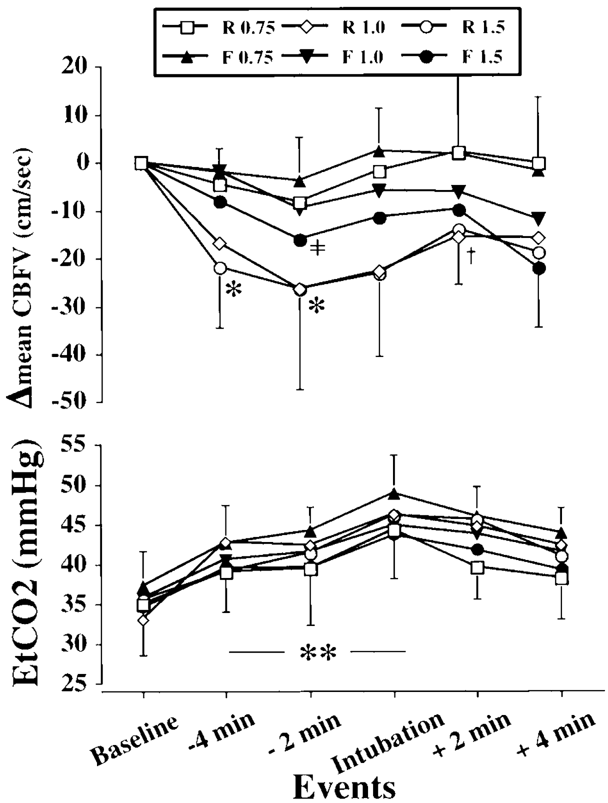

FIGURE 1 Changes in cerebral blood flow velocity (CBFV) and $ETCO_2$ over time comparing fentanyl and remifentanil infusions. * represents a decrease in CBFV with remifentanil 1.0 and 1.5 when compared to baseline ($P < 0.001$). † indicates an increase in CBFV after laryngoscopy and tracheal intubation with remifentanil 1.0 and 1.5 ($P < 0.05$). ‡ denotes a decrease in CBFV with fentanyl 1.5 when compared to baseline ($P < 0.001$). ** indicates an increase in $ETCO_2$ in all groups when compared to baseline ($P < 0.001$).

four minutes prior to laryngoscopy, until four minutes post naso-tracheal intubation, at which point the infusion was discontinued. Manual face-mask ventilation was instituted to maintain normocapnea in those patients who became apneic prior to tracheal intubation. All patients were horizontal and supine throughout the study.

Demographic data are expressed as mean ± standard deviation. The number of patients needed to demonstrate a direct effect on CBFV was calculated with the assumption that a 20% change would be clinically relevant. Based on a statistical power of 0.8, an α_2 = 0.05 and a ß = 0.2, six patients per group was suggested. A total of ten patients per group was studied to account for methodological difficulties that

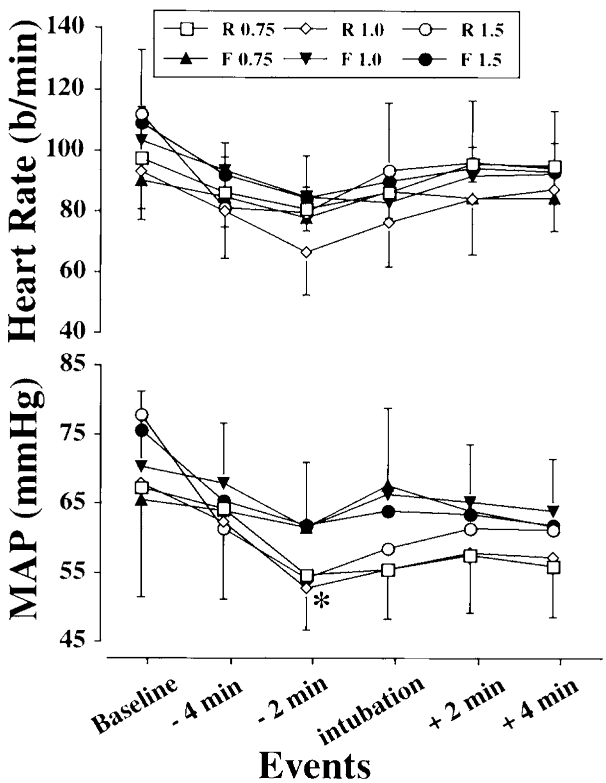

FIGURE 2 Changes in heart rate (HR) and mean arterial pressure (MAP) over time comparing fentanyl and remifentanil infusions. * represents a decrease in MAP for all remifentanil doses ($P < 0.05$).

could have led to exclusion from the study. Differences within groups in Vmca, HR, blood pressure and end-tidal CO_2 ($P_{ET}CO_2$) were analyzed with repeated measures ANOVA and the Student-Newman-Keuls test for multiple comparisons. Between groups statistical analysis was achieved using ANOVA and the Tukey test for multiple comparisons. Non-parametric data (apnea, score of intubation) were analyzed using the Kruskall-Wallis test. The analysis of each set of TCD measurements was carried out by an investigator unaware of the drug and the concentration administered. All patients were used as their own control. A *P* value less than 0.05 was accepted for statistical significance.

Results

Sixty patients were studied, with an average age and weight of 4.2 ± 1.3 yr and 17.6 ± 4.2 kg, respectively. There were no demographic differences between the groups. The TCD measurements were completed in all children and there were no complications that resulted from this study. Changes in CBFV and $P_{ET}CO_2$ are shown in Figure 1. Hemodynamic responses to induction and tracheal intubation are shown in Figure 2. When compared to baseline, there was a significant decrease in Vmca in the remifentanil 1.0 and 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ groups both at four and two minutes prior to tracheal intubation ($P < 0.001$), despite a concurrent increase in $P_{ET}CO_2$ (Figure 1). A decrease in Vmca was also seen in the fentanyl 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ group ($P < 0.001$), but only at two minutes pre-intubation. Remifentanil caused a more important decrease in mean arterial pressure (MAP) at two minutes prior to intubation than did fentanyl ($P < 0.001$; Figure 2). The MAP two minutes before intubation was lower in all remifentanil groups than any of the fentanyl groups ($P < 0.05$). There was a decrease in HR two minutes prior to intubation in the R1.0, R1.5 and F1.5 groups when compared to baseline ($P < 0.001$).

During laryngoscopy and for two minutes following tracheal intubation, Vmca increased in all remifentanil groups ($P < 0.05$), whereas it remained stable in all fentanyl groups during that same period (Figure 1). There were no significant changes in HR or MAP in any of the groups following tracheal intubation, and changes in $P_{ET}CO_2$ were similar in both the fentanyl and remifentanil groups. Except for the F0.75 group, in which only 50% of patients became apneic, greater than 80% of patients in all other groups including the R0.75 group became apneic prior to tracheal intubation. There was no difference in the incidence of apnea between the F and R groups at both 1.0 and 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Face-mask ventilation immediately prior to tracheal intubation was scored as easy in all children, and intubating conditions were excellent (jaw relaxed, vocal cords open, no coughing) in all patients. Peripheral oxygen saturation remained above 95% in all children throughout the study.

Discussion

CBFV decreased early and significantly in the medium and high dose remifentanil groups prior to tracheal intubation, despite a concurrent increase in end-tidal CO_2. Furthermore, remifentanil was significantly less effective than fentanyl at preventing increases in CBFV during and immediately following laryngoscopy and tracheal intubation. Human adult and animal studies designed to assess the effects of different opioids on cerebral hemodynamics have yielded conflicting results. Narcotic infusions have been shown to increase,[9] decrease,[10] or cause no change[11] in CBFV. In the present study, end-tidal carbon dioxide levels increased equally in all groups prior to tracheal intubation, and since cerebrovascular reactivity to CO_2 is preserved with both remifentanil and fentanyl,[12] an increase in CBFV might have been expected, rather than the noted decrease. In clinical pediatric neuroanesthetic practice manual ventilation is often used during anesthetic induction to avoid hypercarbia. One may speculate then that in neurosurgical patients with intracranial hypertension, the decrease in CBFV and cerebral perfusion induced by remifentanil might be even more clinically relevant if $ETCO_2$ is kept lower. Opioid-induced decreases in CBFV have been theorized to be due to i) decreased cerebral metabolic rate for oxygen ($CMRO_2$),[13] ii) loss of cerebral pressure autoregulation, or iii) direct cerebral vasoconstriction.[14] Sufentanil has been shown in animal and adult human studies to decrease $CMRO_2$,[15,16] however the effect of remifentanil on $CMRO_2$ in children is unknown.

In the present study, remifentanil caused a more pronounced decrease in MAP prior to tracheal intubation than did fentanyl. In fact, there was a 30% drop in MAP prior to laryngoscopy in the high-dose remifentanil group. These findings are in agreement with adult studies, which demonstrated significant decreases in MAP when higher doses of remifentanil were used either as a bolus or continuous infusion.[17,18] The decrease in CBFV prior to tracheal intubation seemed to coincide with a decrease in MAP in the present study, suggesting that remifentanil may be associated with impaired cerebral blood pressure autoregulation. Alternatively, remifentanil may have decreased MAP to pressures below the lower limit of cerebral autoregulation. Establishing a cause-and-effect relationship between MAP and CBFV would require a demonstration that CBFV was maintained only when MAP was kept constant with the use of a vasopressor during the narcotic infusion period.

In adults, fentanyl 5–8 $\mu g \cdot kg^{-1}$ *iv* given before induction of anesthesia is effective in suppressing the cardiovascular responses to laryngoscopy and tracheal intubation.[19] In the present study fentanyl provided a more stable blood pressure profile prior to tracheal intubation than did remifentanil. Both agents were equally successful in maintaining stable hemodynamic parameters after tracheal intubation. In addition, both remifentanil and fentanyl offered equally good intubating conditions.

Sevoflurane was chosen as the background anesthetic agent in this study for several reasons. Like all other volatile agents, sevoflurane causes dose-dependent cerebral vasodilatation,[20] however this effect is not as pronounced as it is with isoflurane.[16] Sevoflurane has been shown to effectively preserve cerebral blood pressure autoregulation[21] and cerebrovascular CO_2 reactivity.[22] In addition, induction and maintenance of anesthesia for children with sevoflurane represents common pediatric practice.

In order to properly compare the effects of remifentanil and fentanyl on cerebral and systemic hemodynamics, it was essential that they be administered at equipotent doses. Although opinions vary regarding remifentanil's relative potency, most studies have found that it is 15–40 times more potent than alfentanil.[23,24] Electro-encephalographic studies estimate that remifentanil is 30 times more potent than alfentanil,[24] which puts it very close to fentanyl.[25,26] Although the elimination half-life of fentanyl is longer than that of remifentanil, in the context of a very brief infusion period (eight minutes in this case), the difference in terms of postoperative duration of action may be clinically insignificant. Postoperative discharge times were not delayed in any of the patients in the current study.

A full explanation of TCD methodology in children has been presented in a previous article.[8] TCD validation studies have found that changes in CBFV as measured by TCD sonography can accurately reflect changes in cerebral blood flow.[27,28] Nevertheless, some methodological limitations to TCD sonography interpretation deserve mention. Doppler flow measurements at the middle cerebral artery may not reflect changes in CBFV if the probe is positioned inappropriately, or if the probe angle or MCA diameter change during the study.[29] In order to minimize some of these pitfalls, an experienced operator applied the probe, which was then fixed in position,[8] ensuring that the patient's head position did not change throughout the study period. Studies have demonstrated that the caliber of the proximal cerebral arteries (such as the MCA) remains constant despite variations in blood pressure and end-tidal CO_2,[30] and that it is the more distal arterial branches that change in diameter during pressure changes.[31]

Understanding the possible limitations of using TCD sonography as a measure of cerebral blood flow, it can be concluded that in children undergoing sevoflurane anesthesia, remifentanil was associated with a more pronounced decrease in MAP prior to laryngoscopy and tracheal intubation when compared to fentanyl. In addition, remifentanil was less effective than fentanyl at preventing further increases in CBFV during and immediately following tracheal intubation. Therefore, we speculate that the potential benefits of using the ultra short-acting opioid remifentanil on induction of anesthesia in pediatric neurosurgical patients may be offset by its association with deleterious changes in cerebral and systemic hemodynamics preceding tracheal intubation.

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