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Dose-Response of Propofol for Tracheal Intubation in Children Correlated to Intubation Condition Score and Cerebral State Index. Randomized, Double-Blinded Trial

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Abstract

Background: Avoiding neuromuscular blocking drugs may prevent the potential complications of their use if they are not required for the planned procedure. This study was designed to estimate dose-response of propofol for tracheal intubation in children correlated to Intubation Condition Score and Cerebral State Index (CSI) without neuromuscular blocking drugs.

Methods: 56 children (ages 3-8 years), ASA physical status I and II, weight 13-35 Kg, admitted for adenotonsillectomy were included. Children were randomly divided into four groups to receive propofol by Target Controlled Infusion (TCI) at different concentrations: 3.0 μg•ml^{-1}, 3.5 μg•ml^{-1}, 4.0 μg•ml^{-1}, 4.5 μg•ml^{-1}. At time T_0 remifentanil infusion 0.5 μg•kg^{-1}•min^{-1} was started. After 4 min, time T_1, children received propofol according to their group. At time T_2 (8 min after T_0) tracheal intubation was carried out, Intubation Condition Score and CSI values at time T_2 were assessed.

Results: The results show that increasing propofol plasma concentrations from 3.0 μg•ml^{-1} to 4.5 μg•ml^{-1}, the number of patients with acceptable intubating conditions, increased to 100%. There was a statistically significant difference with respect to Intubating Condition Score: 3.0 μg•ml^{-1} vs 4.5 μg•ml^{-1} and 3.0 μg•m^{l-1} vs 4.0 μg•ml^{-1}. With reference to CSI values, a statistically significant difference was observed between 4.5 μg•ml^{-1} and the other 3 concentrations. We observed a significant difference in patients with CSI≤50 versus CSI>50 among the four propofol groups. Therefore, we detected a significant difference in the Intubation Condition Score between the CSI≤50 and CSI>50 groups.

Conclusions: The administration of propofol at 4 and 4.5 μg•ml^{-1}, coadministered with remifentanil 0.5 μg•kg^{-1}•min^{-1}, provided clinically acceptable conditions for tracheal intubation. In our opinion the use of CSI monitoring may be of practical value in producing acceptable intubating conditions in children.

Keywords: Propofol; Children; Target controlled infusion; Intubation condition score; Remifentanil; Cerebral state index

Abbreviation: TCI: Target Controlled Infusion; CSI: Cerebral State Index; CSM: Cerebral State Monitor; BS: Burst Suppression; BP: Blood Pressure; HR: Heart Rate; SpO_2: Peripheral Oxygen Saturation; UMSS: University of Michigan Sedation Scale.

Introduction

After induction of anesthesia, tracheal intubation is commonly facilitated by the use of neuromuscular blocking drugs. In particular situations the use of neuromuscular blocking drugs should be avoided [1] or the use of succinylcholine is contraindicated [2-3]. Moreover, it is known that excessive or unnecessary neuromuscular blockade is one of the contributing factors to awareness under general anesthesia [4,5]. For the above reasons we were prompted to investigate alternative drugs to facilitate tracheal intubation.

In pediatric patients we studied the dose-response of different propofol concentrations by Target Controlled Infusion (TCI) [6,7] for tracheal intubation in children, co-administering 0.5 μg•kg^{-1}•min^{-1} remifentanil and without neuromuscular blocking drugs. For a better understanding of the degree of depth of anesthesia we used the Cerebral State Monitor (CSM) that is an EEG derived monitor (CSI TM, Danmeter, and Odense, Denmark). The CSM calculates an index (CSI) from the raw EEG signals using an algorithm based on power analysis of the beta, alpha, and beta-alpha ratio. The monitor also evaluates the amount of instantaneous burst suppression (BS) in each 30-s period of EEG, which is expressed as a percentage [8].

Aim of the study was to correlate different propofol concentration with Intubation Condition Score [9,10] and CSI values at intubation time. Secondary end point was to correlate CSI values with Intubation Condition Score.

Materials and Methods

Approval was obtained from the Ethical Committee of Azienda Ospedaliera Universitaria Policlinico, Catania, Italy and informed consent was obtained from the parents after the aim and the possible risks of the study were fully explained. We studied 56 ASA I–II children,

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aged 3 to 8 years, weight 13 to 35 kg [11] scheduled for elective adenoidectomy and tonsillectomy under general anesthesia surgery. Exclusion criteria were allergy to medications and obesity (greater then 95th percentile for age and gender) [12,13].

EMLA® cream was applied on the expected site of the venipuncture at least 45 min before arrival in the operating room. Orally midazolam 0.5 mg•kg^{-1} (max 7 mg) was given as premedication, 30 min before induction of anesthesia.

In the operating room, while intravenous access was secured, routine monitoring of ECG, pulse oximetry, and automated non-invasive blood pressure were begun. To minimize the effects on the infusion system dead volume, flow rates during total intravenous anesthesia, we used the same infusion system architecture and a standardized fluid administration (saline solution) at 45 ml•h^{-1} in all children [14]. CSI monitor electrodes were applied: two electrodes were positioned on the forehead and one on the mastoid process behind the ear, according to the manufacturer's instructions.

To compare the propofol plasmatic concentrations for tracheal intubation in children, patients were randomized into four groups to receive different concentrations of propofol during TCI infusion (P_1:3.0 μg•ml^{-1}; P_2:3.5 μg•ml^{-1}; P_3:4.0 μg•ml^{-1}; P_4:4.5 μg•ml^{-1}). Randomization was achieved by using a schedule derived from a table of random numbers generated by a computer.

At 'T_0' time all patients received a continuous infusion of remifentanil 0.5 μg•kg^{-1}•min^{-1}; after 4 min, 'T_1' time, they received propofol according to their group. Propofol was administrated in TCI, using the Alaris Asena PK® syringe pump (Alaris Medical System, Basingstoke, UK) and the pharmacokinetic parameters used were those determined by Kataria et al. based on a pediatric model [6,7].

Four minutes after beginning propofol infusion, at 'T_2' time, laryngoscopy and tracheal intubation were performed using a Macintosh laryngoscope by an experienced anesthesiologist (one of the authors), who was unaware as to the dose of propofol the patient had been given. At the same time Intubation Condition Score and CSI were recorded. At each time (T_0, T_1, T_2), blood pressure (BP), heart rate (HR), CSI and peripheral oxygen saturation (SpO_2) were recorded by blinded observers.

Intubating conditions were assessed using a four-point scoring system [9,10] based on: condition of laryngoscopy, jaw relaxation, position of vocal cords, degree of coughing, limb movement and we added changes in HR (Table 1). Intubating conditions were as follows: excellent when all scores were 1, good when all scores were ≤ 2, and poor if any score was ≥ 3. Excellent and good intubating conditions were considered clinically acceptable [10]. For patients with a poor Intubation Condition Score, the lungs were ventilated with oxygen by face mask, and rocuronium (0.3 mg•Kg^{-1}) was administered before a second attempt at intubation. In these patients the Intubation Condition Score in the database remained unchanged and was classified as poor, in comparison to the second Intubation Condition Score.

Score	1	2	3	4
Jaw relaxation	*Complete*	*slight tone*	*stiff*	*Rigid*
Laryngoscopy	*Easy*	*fair*	*difficult*	*impossible*
Vocal cord position	*Open*	*moving*	*closing*	*Closed*
Coughing	*None*	*slight*	*moderate*	*Severe*
Limb movement	*None*	*slight*	*moderate*	*Severe*
Heart Rate	*Unchanged*	*increased by 20%*	*increased by 30%*	*Increase greater then 30%*

Table 1: Intubation Condition Score [10] modified with the introduction of the heart rate value.

The same 56 patients were divided into two groups on the basis of their CSI value at T_2 time: CSI ≤50 and CSI >50, independently of their propofol plasmatic concentration. We chose to use a cut-off of 50 for the CSI value, because it is in the middle of the range (40-60) of adequate depth for surgical anaesthesia, according to the manufacturer's instructions [15].

These two groups were compared based on propofol plasma concentrations and Intubation Condition Score.

Statistical Analysis

Based on our clinical experience we used an effect size large of 40 % with a power over 0.80 and an alpha value of 0.05. We would need to study 10 children for each group to be able to reject the null hypothesis. We recruited 14 patients per group to allow protocol violations and drop outs.

Kruskal Wallis test (followed by Dunn's Multiple comparison test) was used to compare the scores of jaw relaxation, laryngoscopy, vocal cord position, coughing, limb movement, HR and intubating condition score between the four groups.

One-way ANOVA of variance for the comparison of CSI at intubation time (T_2) was used for the four groups followed by Newman-Keuls Multiple Comparison Test.

$P < 0.05$ was considered significant.

Chi-square Pearson test was used to compare the number of patients with four different propofol concentrations between the two CSI groups. The same test was used to compare Intubation Condition Score between the two groups.

$P < 0.05$ was considered significant.

Results

Demographic data and baseline hemodynamic variables were similar in all four groups, as well as age, weight and gender (Table 2). Each propofol group contained 14 patients.

There were no significant differences between the four groups of propofol with respect to laryngoscopy, coughing, limb movement and HR (Figure 1).

Jaw relaxation was judged to be complete in 64% of patients in P_1 group, 100% in P_2, 93% in P_3 and 100% in P_4, with a statistically significant difference ($P < 0.05$) between P_2 and P_4 vs P_1. There was a statistical difference with respect to vocal cord position between P_3 and P_1 ($P < 0.05$) and between P_4 and P_1 ($P < 0.01$). Vocal cord position was judged to be open in 21% of patients in P_1 group, 57% in P_2, 71% in P_3 and 78% in P_4 (Figure 1).

Intubating Condition Score was significantly different between P_1 group compared with P_4 group ($P < 0.01$) and P_3 group ($P < 0.05$). Intubating condition was judged to be *excellent* in 21.4% of patients in P_1 group, 29% in P_2, 64% in P_3 and 71% in P_4. Intubating condition was

	P_1	P_2	P_3	P_4	*P*
Age (month)	77.2±17.7	66.4±17.9	72.6±15.8	75.4±21.6	NS
Weight (Kg)	22.4±6.2	22.4±8.0	22.9±5.22	25±7.4	NS
Male/Female	9/5	7/7	9/5	9/5	NS

Table 2: Demographics in each group of propofol. Data are mean ± SD or ratios. *P*<0.05 was considered statistically significant.

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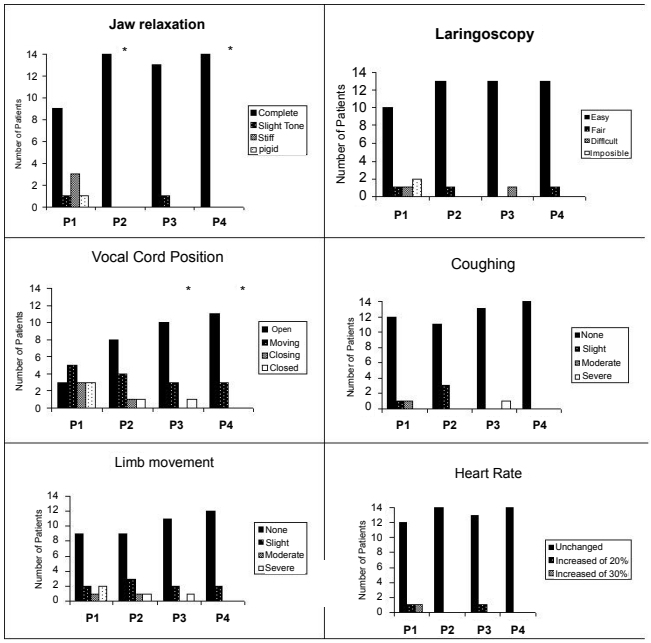

Figure 1: Score for jaw relaxation, laryngoscopy, vocal cord position, coughing, limb movement and heart rate during intubation in each propofol group. (*) P <0.05 vs P_1; (* *) P<0.01 vs P_1.

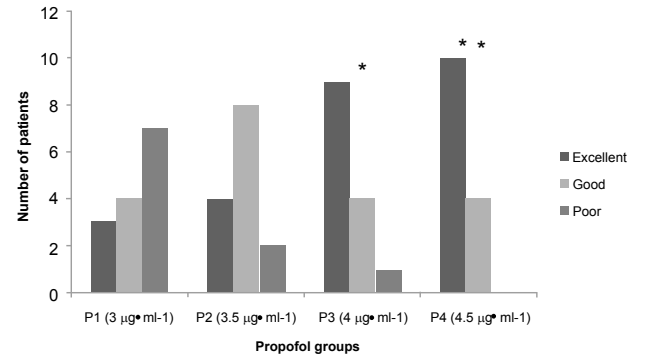

Figure 2: Overall intubating conditions. * P <0.05 vs P1(3 µg•ml^{-1}) ; * * P<0.01 vs P1(3 µg•ml^{-1}).

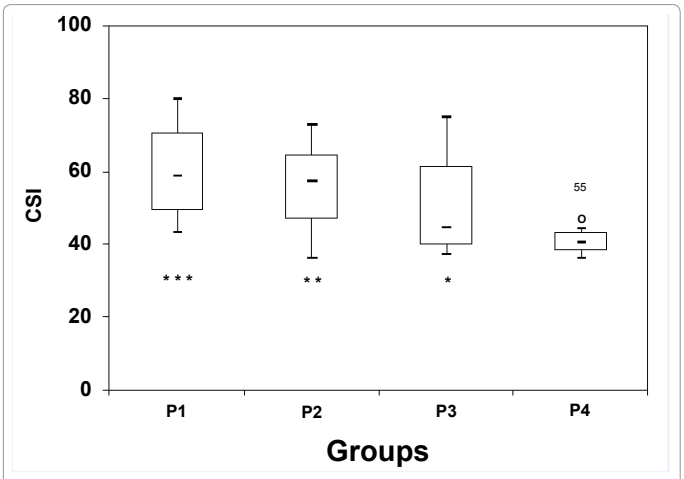

Figure 3: CSI during intubation in each propofol group. * * * P<0.001 vs P4, * * P<0.01 vs P4, * P<0.05 vs P4.

	CSI≤50	CSI≥50	*p*
Age (month)	73.3±20.6	72.3±15.6	NS
Weight (Kg)	23.6±6.6	22.6±6.9	NS
Male/Female	19/12	13/10	NS

Table 3: Demographics in each group of CSI. Data are mean ± SD or ratios. *P*<0.05 was considered statistically significant.

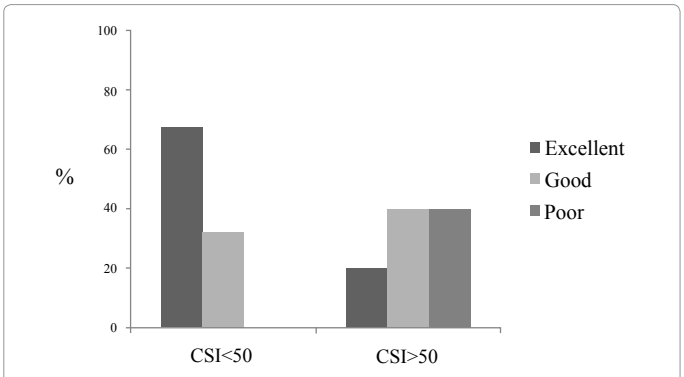

Figure 4: Intubation Condition Score between CSI≤50 and CSI>50 groups (P<0.001).

observed as *good* in 29% of patients in P_1 group, 37% in P_2, 21% in P_3 and 29% in P_4. Intubating condition was *poor* in 50% of patients in P_1 group, 14% in P_2, 14% in P_3, while we had no poor cases in P_4 group (Figure 2).

Figure 3 shows CSI measurements during intubation in each propofol group. A statistically significant difference was observed between P4 group and all the other groups, with $P < 0.001$ vs P_1, $P < 0.01$ vs P_2, $P < 0.05$ vs P_3. Increasing propofol concentrations decreased CSI values. Mean (± DS) CSI was 59 (± 11) in P_1 group, 56 (± 11) in P_2, 50 (± 13) in P_3 and 41 (± 5) in P_4.

For the secondary end point, demographics data are shown in table (Table 3); there were no differences between the two groups with regard to age, weight and gender.

At T_2 time, CSI was > 50 in 25 patients and ≤ 50 in 31.

We found significant differences in the number of patients with the four different propofol concentrations between the two groups with CSI ≤ 50 and CSI > 50 (P < 0.001)

We found a significant difference with regards to Intubation Condition Score between CSI ≤ 50 and CSI > 50 groups (P < 0.001). In the CSI ≤ 50 group we observed 68% (21 case) with excellent intubation, 32% (10 case) with good intubation and none with a poor score. Instead, in the CSI > 50 group we had only 20% (5 cases) with excellent intubation, 40% (10 cases) with good intubation and 40% (10 cases) with poor intubation (Figure 4).

Discussion

Our results demonstrate that propofol TCI 4 or 4.5 µg•ml^{-1} produced clinically acceptable intubating conditions (both excellent and good) in healthy premedicated children without the use neuromuscular blocking agents. For elective adenoidectomy and tonsillectomy without neuromuscular blocking the best conditions were achieved with propofol TCI 4.5 µg•ml^{-1}.

Batra Y.K et al. found that remifentanil (3 μg•Kg^{-1}), administered before propofol (3 mg•kg^{-1}), provided acceptable tracheal intubating conditions without neuromuscular blocking drugs, and completely inhibited the increase in HR and MAP associated with intubation [10].

Crawford M.W et al. found that the dose-response of remifentanil for tracheal intubation was similar in infants and children and that coadministration of propofol 4.0 mg•kg^{-1} and remifentanil 3.0 μg•kg^{-1} provided excellent or good conditions for tracheal intubation in infants [16].

Blair J.M et al. reported that adequate conditions for laryngoscopy and intubation were produced in healthy children with remifentanil 1.0, 2.0 or 3.0 μg•kg^{-1} in combination with propofol [17].

In the present study we used a fixed continuous infusion dose of remifentanil (0.5 μg•kg^{-1}•min^{-1}); this dose was in keeping with the findings of the other workers, but we chose a continuous infusion model because we considered that remifentanil with its short and stable context sensitive half-time is ideally suited for TIVA and Munoz et al. reported that children needed markedly higher infusion rates compared with adults [18]. For this reason the timing to achieve the steady effect of remifentanil and also of propofol in continuous infusion is important, and we waited 8 min after the start of remifentanil and 4 min after the administering of propofol TCI before attempting laryngoscopy. The vocal cord position in the patients of the P1 group was judged in 79% not to be open instead of 75% open in both the P3 and P4 Group; only 5% of the patients in the 4 groups experienced an increase in the heart rate. Muscle rigidity or difficulty with ventilation was not found in any study patients.

Our results are similar to those of other studies in adults that have suggested that propofol in combination with short-acting opioids such as alfentanil and remifentanil may provide adequate conditions for laryngoscopy and tracheal intubation without using neuromuscular blocking drugs [19].

We have also demonstrated that propofol produces a decrease in CSI values and a significant correlation exists between CSI at intubation time and predicted propofol concentrations. Several studies have recently been performed with CSI to demonstrate its possible use in children [20,21], however, to date, few studies of intubating conditions related to depth of anaesthesia have been carried out in paediatric patients using BIS, and none using CSI [22,23].

Park et al. investigated the relationship between BIS index and predicted plasma concentrations of propofol delivered by TCI in children, finding that BIS moderately correlated with the predicted plasma concentration of propofol and could be used in recovery from anaesthesia [24]. In a previous study we demonstrated that the CSI was able to distinguish light sedation with University of Michigan Sedation Scale (UMSS 0-1) from deep sedation (UMSS 3-4) [20]. Thus continuous analysis with both clinical and more objective monitoring tools is essential; in this regard, monitoring the hypnotic state by adding EEG-based monitors will probably soon become standard in pediatric anesthesia practice [25].

In conclusion, the administration of remifentanil 0.5 μg•kg^{-1}•min^{-1} with the co-administration of 4.5 μg•ml-1 propofol provided the "best" clinically acceptable conditions for tracheal intubation without using neuromuscular blocking drugs in healthy children. We found that during intubation, CSI values were lower in patients that received propofol 4.5 μg•ml^{-1} with respect to all the other patients. Intubation was easier in patients with CSI < 50 with respect to others. Our study demonstrates a good relationship between propofol plasma concentrations by TCI, CSI value, and Intubation Condition Score. This combination of drugs may be advantageous in children with normal airway anatomy undergoing brief surgical procedures (i.e adeno-tonsillectomy) or when neuromuscular blockade is contraindicated.

The quality of care and a better outcome represent the gold standard of the health care system. Physicians and medical staff know very well that to improve the care in perioperative medicine and surgery we should standardize procedures. Millions of children are submitted to adeno-tonsillectomy every year around the world [26]. The combination of drugs without the use of neuromuscular blocking agents is a standardized and safe procedure in our clinical practice.

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