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TRACHEA! INTUBATION;
COMPARISON BY USING THIOPENTOL AND VARYING DOSES OF REMIFENTANIL, WITHOUT MUSCLE RELAXANTS.

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ABSTRACT... hameedchohedritgjyahoo.com. Background: Administration of remifentanil followed by thiopental provides adequate conditions for tracheal intubation without muscle relaxants. However, controversy still remains on the best dose of remifentanil. Objectives: To identify the optimum dose of remifentanil in which the best intubating conditions could be achieved. Design: prospective randomized double biind clinical trial Period: From June 2004 to November 2005. Material & Methods: In a randomized, double blind study, 90 ASA I or II patients were randomly divided into three equal groups (n=30). Intubating condition and hemodynamic changes were assessed after injection of remifentanil 2.0 pg/kg (group A), 3.0 (jg/kg (group B) and 4.0 (jg/kg (group C). This was followed by thiopental 5mg/kg. Ninety seconds after administration of the hypnotic agent, laryngoscopy and intubation were attempted. Intubating conditions were assessed as excellent, satisfactory, fair or unsatisfactory on the basis of ease of ventilation, jaw relaxation, position of the vocal cords, and patient response to intubation and slow inflation of the endotracheal tube cuff. Hemodynamic changes were recorded at baseline, 1 min after induction, 1, 3 and 5 minutes after intubation. Results: Excellent intubating conditions were observed in 13.3% (n= 4), 46.7% (n=14), 83.3% (n=25) of patients in Groups A, B and C, respectively. Overall conditions at intubation were significantly (P<0.05) higher with 4pg/kg remifentanil compared with other doses. Conclusion: Intubation conditions were best when using thiopental 5 mg/kg combined with remifentanil at 4 mg/kg and no muscle relaxant.

Keywords: Thiopental, Remifentanil, Tracheal Intubation, Hemodynamic Change, Anaesthetics.

INTRODUCTION

Tracheal intubation following anaesthesia induction has "been commonly facilitated by the use of muscle relaxants. Previous studies have showed that thiopental in combination with short acting opioids such as alfentanil and remifentanil can provide adequate conditions for laryngoscopy and tracheal intubation without using muscle relaxants[1]. Thiopental has been previously shown that can achieve a satisfactory tracheal intubation when used in doses of 5-6 mg/kg[2,3.] Remifentanil has unique properties and undergoes rapid hydrolysis by non-specific blood and tissue esterases. Although onset of effect is similar to that of alfentanil, within one to two minutes, it has a shorter half-life and the time to recovery is not greatly influenced by the dose[4]. These clinical properties make remifentanil the short acting opioid of choice for circumstances in which an intense opioid effect of short duration is required. However, controversy still remains on the optimum dose of remifentanil.

This study was designed to assess intubation conditions and hemodynamic changes in three groups of patients scheduled for elective surgery. Three doses of remifentanil (2,3 &4 pg/kg) supplementing induction with thiopental 5 mg/kg were compared in order to find the optimum dose.

MATERIAL AND METHODS

In prospective randomized double blind clinical trial, 90 ASA grade l-ll elective surgical patients referred for operation to an educational hospital from June 2004 to November 2005 affiliated to Shiraz University of Medical Sciences were included Ethical Committee had approved the study. The patient's age ranged from 14 to 60 years. Exclusion criteria included history of hypertension. Asthma, drug or alcohol abuse, cardiovascular disease, reactive airway disease, allergies to any of the study drugs, or any suspicion of a difficult intubation (Modified Mallampati classification of airway anatomy of III and IV)[5,6].

On arrival in the operating room, an 18 gauge cannula was inserted into a peripheral vein, non-invasive arterial pressure, electrocardiogram (ECG) and pulse oximeter $(Sp0_2)$ were attached, and baseline measurements were recorded (pre-induction).

Ten minutes prior to induction, Midazolam, 0.03 mg/kg was intravenously given as pre-medication. The patients were hydrated with normal saline 0.9%, 7 ml/kg before induction of anaesthesia. Additionally, Lidocaine 1 mg/kg was given intravenously, 3 minutes prior to induction.

Patients were randomized using a random number generator (computer randomization) to one of three groups to receive the following in a double blind manner: remifentanil 2pg/kg followed y thiopental 5mg/kg (Group A, n=30); remifentanil 3pg/kg followed by thiopental 5mg/kg (Group B, n=30); or remifentanil 4|jg/kg followed by thiopental 5mg/kg (Group C, n=30). The induction sequence was conducted using two pre-prepared syringes. The first syringe contained remifentanil 2, 3 or 4 pg/kg and was filled with 0.9% saline to a volume of 10ml. Syringe 2 contained thiopental 5 mg/kg. The coded test syringes were prepared by a nurse who did not take part in the study. Injection of all syringes was performed behind a drape so that the intubating anaesthesiologist was blinded to the drug's dose administered. Remifentanil was administered as a slow bolus infusion over SOSeconds. Sixty seconds after beginning remifentanil thiopental was given over 40 seconds. Baseline heart rate (HR) and mean arterial pressure (MAP) were recorded. Once the patient became unconscious, as judged by loss of response to command and loss of eyelash reflex, mask ventilation was initiated, After pre-oxygenation for 90 seconds with 100% oxygen the patient was intubated. Laryngoscopy and intubation were

attempted with a Macintosh 3 laryngoscope blade and 7.5 or 8.0 mm endotracheal tube. The anaesthesiologist who performed intubation was blind to the drug's dose in syringe number one. The anaesthetist performing intubation assessed five variables: exposure of the vocal cord, position of the vocal cord, jaw relaxation, laryngoscopy, and patient response to intubation (coughing, limb movement) and slow (five seconds) inflation of the endotracheal tube cuff. Intubating conditions were judged as excellent when the mouth was completely open, jaw muscles were completely relax, vocal cords were completely separated and visible. Satisfactory when the mouth could be easily opened, muscles of the jaw were not completely relax, vocal cords were hardly seen and had mild movement. Fair when the jaw muscles were not completely relax, vocal cord was hardly seen and intubation was hard. When the jaw muscles were poorly relax, the vocal cords were not seen and intubation was difficult the condition was recorded as unsatisfactory, Patient's post-induction vital signs were recorded. One minute after study drug administration, and 1, 3 and 5 minuted after intubation.

Patients in whom intubation was impossible at the

first attempt were given scoline 1 mg/kg and intubation was tried once more. In the event of a decrease in MAP of greater than 25% of the baseline, ephedrine 5-10 mg was administered. In the event of bardycardia (HR less than 50 beat/min), atropine 20 [jg/kg was administered. Anaesthesia was maintained with 50% oxygen, 50% N?0 and 0.5-1 % halothane.

All data were analyzed and computed by SPSS (Chicago, IL) software, version 10.0 and Microsoft Excel (Microsoft, Redmond, WA) software. Data are expressed as mean tstandard deviation (SD) and 95% confidence interval (Cl) was also given when essential. The association between variables was assessed by Student's T-test; Fisher's exact, x2 test and Mann Whitney U-test when appropriate. P values less than 0.05 were considered statistically significant.

RESULTS

Ninety patients, age range 14-60 years, were studied in three groups of equal size. Demographic characteristics are shown in (Table I). The three groups were comparable in age, sex, ASA classification and weight.

| Table-l. Demographic characteristics (age, weight & sex) and ASA classification of 90 patients enrolled in the study.				
	Group A (n = 30)	Group B (n = 30)	Group C (n = 30)	P Value
Age (Years)	30.86114,02	33.53i15.05	33,03±14.63	NS
Weight (Kg)	57.60±09.41	59.70±09.96	62.13+10,10	NS
Sex Ratio (M/F)	16/14	13/17	14/16	NS
ASA Grade l/ll	25/5	26/4	26/4	NS
MAP - mean arterial pressure, NS = Not Significant, P > 0.05 Date are shown as (SD).				

Intubation was excellent in 43 of 90 patients (71.6%) using remifentanil and thiopental 5 mg/kg [4 of 30 patients (13.3%) in group A, 14 of 30 (46.7%) in group B and 25 of 30 (83.3%) in group C]. The intubation conditions are shown in (Fig I). Excellent condition was significantly higher in

group C who received thiopental and 4 pg/kg of remifentanil compared to the other 2 groups (p < 0.05). Intubation was impossible in 2 patients in group A and one patient in group B. All subjects given additional neuromuscular blocking drug were subsequently intubated successfully. Subjects who required neuromuscular blocking agent were defined as having unsatisfactory intubating conditions. Individual assessment of jaw relaxation, view at laryngoscopy, vocal cord position, limb movement and coughing improved significantly as the dose of remifentanil was increased. There was a statistically significant difference in overall intubation conditions between groups A,B and C (p<0.05). Hemodynamic responses to induction and intubation are (Fig-2). The baseline hemodynamic variables were similar in the three groups (Fig-2). There was a statistically significant decrease in MAP and heart rate after induction in all three groups compared to baseline values (p < 0.05) but this was not clinically

significant. None of the patients required atropine. There was no significant difference in arterial pressure between groups at any time.
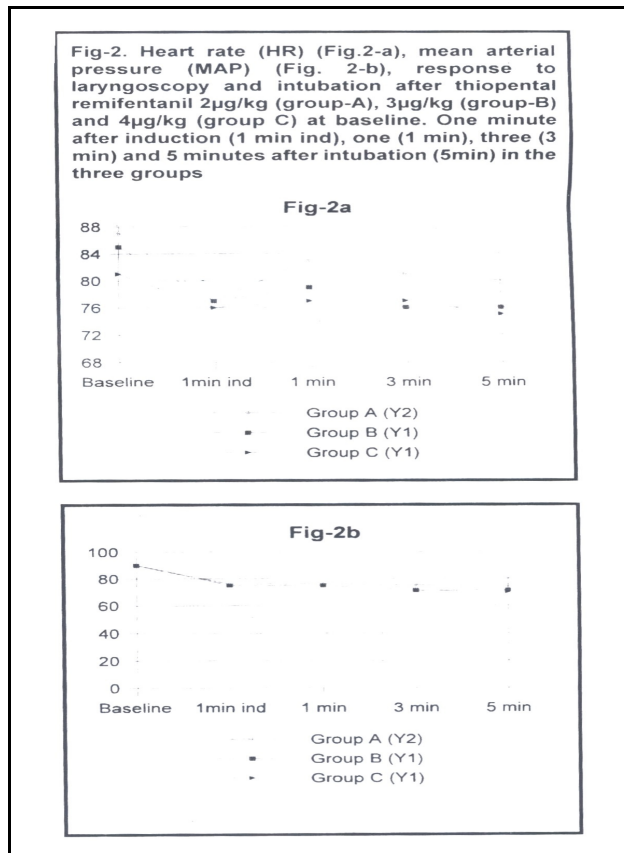
airway anatomy. Remifentanil 3 pg/kg administered with thiopental 5 mg/kg provided excellent or satisfactory conditions in 83.4% of patients whereas remifentanil 2 pg/kg provided acceptable conditions in only 46.6% of patients. Excellent intubating conditions were achieved in 83%, 47% and 13% of patients in the 4, 3 and 2 pg/kg groups respectively, suggesting remifentanil 2 and 3 pg/kg were inferior to 4 [jg/kg when combined with thiopental 5 mg/kg.

Previous studies have shown that remifentanil 3pg/kg administered with propofol 2 mg/kg provides good or excellent intubating conditions in 93.3% of pre-medicated patients with a favorable airway anatomy2. In the same study, remifentani!3 pg/kg combined with thiopental 6 mg/kg provided acceptable conditions in 66.7% of the patients which is similar to the overall result obtained in our study, in all the patients (71.6% in allot the studied patients)2. Similar studies have tried to prove that propofol is superior to thiopental in intubating without muscle relaxant[7].

Fig-1. Intubation condition in the 90 patients studies.
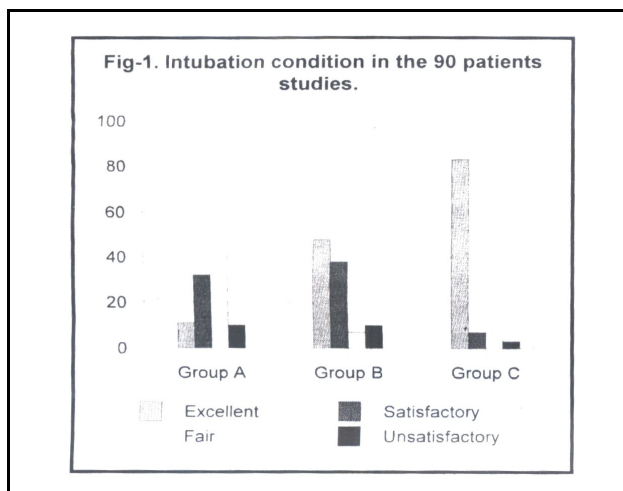
DISCUSSION
The results of this study suggest that remifentanil 4 ug/kg combined with thiopental 5 mg/kg provides excellent or satisfactory intubating conditions in 90.0% of pre-medicated patients with favorable

Fig-2. Heart rate (HR) (Fig.2-a), mean arterial pressure (MAP) (Fig. 2-b), response to laryngoscopy and intubation after thiopental remifentanil 2µg/kg (group-A), 3µg/kg (group-B) and 4µg/kg (group C) at baseline. One minute after induction (1 min ind), one (1 min), three (3 min) and 5 minutes after intubation (5min) in the three groups

However, the results obtained were in an acceptable range of difference. Additional in our setting, propofol is approximately 4 times more expensive than thiopental and is less available. Therefore, due to above mentioned reasons and similar results achieved in administering propofol and thiopental we decided to use thiopental. In our study, however instead of remifentanil 3pg/kg we administered three doses of remifentanil and observed that with administering remifentanil 4 pg/kg success rate in achieving an acceptable intubation condition increased to 90% which is similar to the results obtained with the combination of remifentanil 3 (jg/kg and propofol mg/kg.

Stevens et al used thiopental 4 mg/kg. However they did not lead to satisfactory intubating conditions8. Therefore, we used a higher dose of thiopental to 5 mg/kg and obtained better results compared to those of Stevens et al. Additionally, it has been reported that propofol 2.5 mg/kg and thiopental 5 mg/kg are equipotent and due to satisfactory results obtained by Erhan et al using propofol 2 mg/kg of thiopental[9].

The effects of remifentanil are short acting, and timing to achieve the maximum effect of the combination of propofol and remifentanil is important[10]. Using a computerized pharmacokinetic model, Grant et al determined that peak blood concentrations would be approximately 90 s after infusion of remifentanil[11]. The most important side effects of remifentanil are apnea, bardycardia and hypotension[12]. In a study performed by Thompson et al, remifentanil 1 pg/kg bolus over 30 sec followed by an infusion of 0.5 pg/kg/min was associated with bardycardia or hypotension, or both, in 50% of the patients[12]. None of their patients had received anti-cholinergic or vagolytic agents. In our study, no patients was treated for hypotension even in patients who had received 4|jg/kg of remifentanil. This may be because we pre-hydrated all of our patients with normal saline 0.9% (7 ml/kg) before the induction of anaesthesia and an anti-cholinergic agent was given. Therefore, we recommended that in order to prevent these two side effects of remifentanil, the patients should be pre-hydrated and received anti-cholinergic agents.

Remifentanil has a short duration of action and therefore has a reliably short duration of apnea. This is its main advantage compared to alfentanil. Remifentanil is metabolized by non-specific tissue esterases and has a reliable context-sensitive half life of approximately 3 min[13]. The reliably short duration of apnea is the main advantage of remifentanil compared with alfentanil. It has been noted by Erhan et al that the duration of apnea is similar to that with succinylcholine2. Therefore, this side effects was also not significant, In a study performed by McNeil et al the intubating conditions, hemodynamic responses and duration of apnea was evaluated in 60 healthy adult patients

after propofol 2 mg/kg combined with either a bolus of remifentanil 2 pg/kg, or succinylcholine 1 mg/kg was administered[14].

The patients that were intubated following remifentanil showed dose-dependent intubating conditions, similar at 4 pg/kg to the conditions produced with succinylcholine. Post induction mean arterial pressure decreased from baseline values by 21%, 28% and 8% in the remifentanil 2pg/kg, remifentanil 4pg/kg and 2mg/kg groups, respectively. The mean (SD) duration of apnea following induction was 9.3 (2.6) min and 12.8 (2.9) min in the remifentanil 2 pg/kg and 4 pg/kg groups, and 6.0(0.9) min in the succinylcholine group. Interestingly, they observed significant, dose related cardiovascular depression associated with the use of a large dose of remifentanil[14]. However, these levels of hypotension were well tolerated, by their subjects. In our study none of our patients developed hypotension and we therefore, once more emphasis on the essentiality of pre-hydration in all patient in whom high dose of remifentanil (4pg/kg) is to be applied. High doses of potent opioids are also well recognized to cause muscle rigidity[15]. In our study, no difficulty in hand ventilating the patients related or observed. This may be due to the rather moderate injection rate of the opioids.

In a randomized, double-blind study performed on 80 healthy patients Erhan and coworkers, compared intubating conditions when remifentanil in three different doses (2,3 or 4 pg/kg) or alfentanil 40 pg/kg followed by propofol 2 mg/kg was administered[16]. Intubating conditions were assessed as excellent, good or poor on , the basis of ease of lung ventilation, jaw relaxation, laryngoscopy, position of the vocal cords, and patient response to intubation and slow inflation of the endotracheal tube cuff. They concluded that remifentanil 4 pg/kg and propofol 2 mg/kg administered in sequence intravenously provided good or excellent conditions for ~ tracheal intubation in all patients without the use of muscle relaxants16. They also obtained

similar results to our study. In another study done by Stevens and Wheatley, 80 ASA physical status I and II pre-medicated outpatients were randomly assigned to one of four groups (n = 20/group). Remifentanil 1, 2, 3 or 4 (jg/kg (Groups I-IV), respectively) was infused intravenously over 90 seconds17. Sixty seconds after beginning the remifentanil infusion, propofol 2 mg/kg was infused. Ninety seconds after the administration of the propofol, laryngoscopy and tracheal intubation were attempted and graded. Clinically acceptable intubating conditions (i.e. jaw relaxed, vocal cords open, and fewer than two coughs in response to intubation) were observed in 35%, 75%, 100% and 95% of patients in groups I-IV, respectively. Excellent intubating conditions (i.e. vocal cords open, no movement in response to intubation) were observed in 30%, 50%,, 80% and 80% of patients in Groups I-IV, respectively. Overall conditions at intubation were significantly (p < 0.05) better in Groups III and IV compared with Groups I and II. No patient manifested clinically significant muscle rigidity. The mean arterial pressure decreased 16%, 20%, 28% and 26% immediately before tracheal intubation in Groups I-IV, respectively. In their study they also didn't observe any patient with hypotension or bardycardia. They concluded that healthy, pre-medicated patients with favorable airway anatomy can be reliably intubated with good or excellent conditions 90 s after the administration of remifentanil 3-4 pg/kg and propofol 2 mg/kg.

In our study we observed marked similarity between the changes caused by different drug doses both after induction and intubation. The mean reductions after anaesthetic induction, approximately 20% in MAT and 12-a8% in HR, were of the same magnitude in the three groups. Barclay and Kluger determined the dose response of remifentanil in attenuating the hemodynamic response to tracheal intubation. Patients were allocated to one of four groups: placebo, remifentanil 1 pg/kg, remifentanil 2 (jg/kg and remifentanil 4 (jg/kg. Baseline non invasive blood

pressure and heart rate recordings were made prior to starting target controlled infusion, then at one minute intervals after loss of verbal contact for the duration of the study. They observed that following intubation, heart rate increased by 15% in the placebo group, 10% in 1 pg/kg group, with no changes in 2 and 4 pg/kg groups. Additionally, systolic blood pressure following intubation increased by 30% in the placebo group, 10% in the 1 (jg/kg group and remained unchanged in the 2 and pg/kg groups.

They concluded that remifentanil l pg/kg attenuated the rise in heart rate and systolic blood pressure. However, remifentanil 2 pg/kg blocked the hemodynamic response completely and no further benefit was shown from increasing the dose to 4 pg/kg[18]. Sebel et al observed that after remifentanil decreases in arterial pressure and heart rate, on average 20%, were independent of the given dose escalating from 2 to 30 mg/kg[19]. The authors suggested that a possible causative link for the absence of cardiovascular depression could be found in the pre-treatment with glycopyrrolate, which may had masked a dose related effect. However, Thompson et al, observed that when anticholinergic agents was not administered bardycardia or hypotension, or both, occurred in 50% of the patients[12]. In our study we administered anticholinergic agents and this might have contributed to the observed stability of heart rate in our study in contrast to the obtained by Stevens and Wheatley without using an anticholinergic agent[17].

In conclusion we suggest that the administration of remifentanil 4 pg/kg, in combination with thiopental 5 mg/kg, provided good to excellent conditions for endotracheal intubation, there by allowing successful tracheal intubation in most patients with favorable airway anatomy. The combination totally prevented the hemodynamic intubation response.

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