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Original Article

THE EFFECT OF REMIFENTANIL ON INTUBATION CONDITIONS IN PATIENTS UNDERGOING CESAREAN DELIVERY UNDER GENERAL ANESTHESIA: COMPARISON OF TWO DOSING REGIMENS

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Abstract. *The objective of our study was to compare the effects of two remifentanil dosing regimens, used during induction-delivery period of cesarean section, and of remifentanil-free control on maternal intubating conditions and hemodynamic response to endotracheal intubation as well as on neonatal outcome. Seventy seven ASA physical status I–II women with singleton term pregnancy, who were scheduled for elective cesarean section in general anesthesia and have given written informed consent, were enrolled in this prospective, randomized controlled study and divided in three groups: A – 31 patient received 1 μg/kg remifentanil bolus before the induction of anesthesia, followed by 0.15 μg/kg/min remifentanil infusion that was stopped after the skin incision; B – 27 patients received only 1 μg/kg remifentanil bolus; C – 19 patients did not receive remifentanil until the delivery of the baby. Intubating conditions were qualified as excellent, good or poor. Group A had significantly higher number of patients with excellent intubating conditions ($p = 0.011$); majority of patients with good intubating conditions were in group C ($p = 0.017$). Systolic, diastolic, main arterial pressure and heart rate raised significantly in group C compared to A and B ($p < 0.001$). Neonatal outcome did not differ between groups – all neonates were vital with first minute Apgar scores ≥ 8. In conclusion, our dosing regimen of remifentanil 1μg/kg bolus given immediately before the induction followed by 0.15 μg/kg/min interrupted after skin incision provided the best compromise between the achievement of excellent intubating conditions, attenuation of maternal hemodynamic stress response to endotracheal intubation and avoidance of neonatal respiratory depression.*

Key words: *anesthesia, obstetrical, endotracheal intubation, remifentanil*.

Introduction

The time interval from induction to anesthesia to the delivery of the baby (induction-delivery, I-D interval) during caesarean section performed under general anesthesia (GA) represents very vulnerable period concerning both maternal and fetal/neonatal wellbeing. All medications that the mother receives (except muscle relaxants) will cross uteroplacental membrane and affect the fetus directly (hearth and respiratory rate, muscle tone) and indirectly (by influencing maternal hemodynamics, uteroplacental perfusion, uterine tone) [1–3]. This is the reason why the doses of anesthetics are traditionally reduced as much as possible, which could lead to light anesthesia with increased risk of maternal intraoperative awareness (reported incidence of 0.2-0.9%) [4, 5] and exaggerated neuroendocrine stress response to laryngoscopy, endotracheal intubation and surgical stimuli. Mechanical stimulation of pharyngeal and laryngeal proprioceptors during direct laryngoscopy, endotracheal intubation and cuff inflation activates hypothalamo-pituitary-adrenal axis, with subsequent increase in hearth rate (up to 20%), blood pressure (40–50%), capillary wedge, intracranial and intraocular pressure, possibly leading to severe cardio- and cerebrovascular complications [6–9]. Increasing number of vulnerable patients in obstetrics population nowadays makes this problem more and more serious. We can expect much more parturients with high-risk pregnancies, advanced age, morbid obesity and complex comorbidities and, consequently, much more need for some drug that could help us blunting the unwanted effects of endotracheal intubation [9, 10].

Among different pharmacological options used to attenuate hemodynamic response to endotracheal intubation and surgical incision (direct vasodilatators, β-blockers, calcium channel blockers, α_2 agonists, anticonvulsant drugs such as gabapentin, magnesium, local anesthetics) opioids are still the most extensively used

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[11, 12]. It seems that remifentanil, ultra-short acting synthetic opioid, due to its specific pharmacokinetics, could be the appropriate drug to use during I-D interval, where a brief but intense analgesia without prolonged effect is desirable [13–18].

Remifentanil has a rapid onset of action (1–1.5 min), rapid redistribution and context sensitive half time 3-5 min; its metabolism depends on nonspecific tissue and plasma esterases [19]. Remifentanil does cross the placenta, but, unlike other opioids, appears to be rapidly metabolized and redistributed in the fetus leaving the smaller possibility of unwanted consequences (mainly neonatal respiratory depression, muscle rigidity, low Apgar and neurobehavioral scores) [19–21].

In the present study we investigated the effects of two remifentanil dosing regimens on intubating conditions and maternal blood pressure and heart rate response to the intubation in attempt to find the most effective remifentanil dose that would not adversely affect neonatal outcome.

Material and Methods

The study was approved by the local ethics committee. Seventy-seven ASA physical status I-II women with singleton term pregnancy, who were scheduled for elective caesarean section in general anesthesia and have given written informed consent, were enrolled in this prospective, randomized controlled study. Exclusion criteria were known cardiac, respiratory, neurologic, renal, endocrine, psychiatric disorders, history of drug or alcohol abuse, morbid obesity, preeclampsia, predicted difficult airway management (Mallampati score > 2a), active labor, known fetal congenital abnormalities or signs of fetal compromise. All patients refused regional anesthesia, or had absolute/relative medical contraindications to regional anesthesia.

In the operating room patients were placed supine with left uterine displacement, standard monitoring (noninvasive blood pressure, electrocardiography, pulse oximetry, capnography – using bedside monitor, model BSM-2301k, Nihon Kohden Corporation, Tokyo, Japan and bispectral index – BIS electroencephalogram, using BIS-Vista monitoring system Norwood, Massachusetts, USA) was initiated and two intravenous lines established, one for remifentanil infusion (using Perfusor fm B/Brown , Melsungen AG, Germany), the other for the administration of other medications and fluids.

Patients were randomly allocated (using envelope method) to one of the following groups:

1. group (A) – 31 patient received 1 μg/kg remifentanil bolus, given over 30 s, before the induction of anesthesia, followed by 0.15 μg/kg/min remifentanil infusion that was stopped after the skin incision.

2. group (B) – 27 patients received 1μg/kg remifentanil bolus, given over 30 s, just before the induction of anesthesia

3. control group (C) – 19 patients did not receive remifentanil until the delivery

After 3 minutes of preoxygenation through a facemask and remifentanil administration in A and B group, anesthesia was induced with thiopentone, starting with 3 mg/kg over 20 s, followed by additional boluses (if needed) of 25 mg until adequate dept of anesthesia has been reached (BIS values under 60, but not below 40); succinylcholine 1.5 mg/kg was administered and after 60 s endotracheal intubation was performed by the anesthetist blinded to group assignment, who also estimated and graded intubating conditions as excellent, good or poor (Table 1). The intubating score was evaluated according to the consensus conference on Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents [22]. Anesthesia was maintained with 1–1.5% end-tidal sevoflurane and 50% nitrous oxide in oxygen. Further muscle relaxation has been provided with rocuronium 0.6 mg/kg. The lungs were mechanically ventilated to maintain end-tidal PCO_2 of 28–32 mmHg, with fresh gas flow of 6 l/min.

Beginning from the induction of anesthesia until delivery SAP, DAP, MAP (systolic, diastolic, main arterial pressure respectively) and HR (heart rate), were measured and recorded at 2 minutes interval. We specially

Table 1 Scoring conditions for endotracheal intubation

Variables	Intubating conditions		
	Clinically acceptable		Clinically unacceptable
	excellent	good	poor
Laryngoscop			
Jaw relaxation	relaxed	not fully	poor
Resistance to laryngoscope	none	slight	active
Vocal cords			
Position	abducted	intermediate	closed
Movements	none	moving	closing
Reaction to tube insertion and cuff inflation			
Limb movements	none	slight	vigorous
Cough	none	slight	sustained (>10s)

Conditions: excellent – if all the answers are 'excellent'
good – if the answers are 'excellent' or 'good'
poor – if one or more answers are 'bad'

recorded values measured after induction to anesthesia (T1) and 30 s after endotracheal intubation (T2).

After delivery, pediatrician blinded to group assignment assessed the neonate and recorded the time to sustained respiration, Apgar score at 1st and 5th minute and resuscitative measures (if required), that might have included the use of tactile stimulation, beg-mask ventilation, endotracheal intubation or naloxone administration.

Statistical analyses

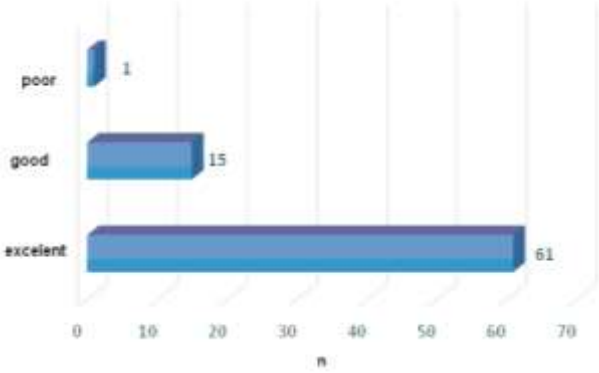
Statistical analysis was performed using SSPS statistic package, version 13. Normal distribution was evaluated with Kolmogorov-Smirnov test. Analysis of variance (ANOVA) was used for parameters comparison between three groups, with subsequent post hoc analysis. In cases of irregular data distribution Kruskal-Wallis test was utilized, with subsequent post hoc analysis with Mann-Whitney U test. The Chi-square test was used to verify the relation between categorical variables. The statistic hypothesis was tested on the significance level for risk of α=0.05; the difference between samples was considered significant if p was < 0.05.

Results

Seventy seven ASA status I-II parturients were included in this study. Patient's characteristics and surgical details are summarized in Table 2; no differences between groups have been observed.

Hemodynamic variables measured after the induction to anesthesia did not show statistical difference between groups (Table 3). After the intubation all hemodynamic variables in group C have raised significantly compared to groups A and B. The increase in variables was also greater in group B compared to A, but the difference did not reach statistical significance (Table 3)

The intubation conditions were excellent in 61 parturient (79.2%), good in 15 (19.5%) and poor in one parturient (1.3%) (Graph 1).



Graph 1 Intubation condition in our patients

The intubation scores showed significant difference between groups (Table 4.).

Table 2 Parturients characteristics and surgical details

	Group			F	p
	A	B	C		
Age (years)	31.74 ± 4.46	31.22 ± 5.22	30.89 ± 1.04	0.202	0.818
Gestation weeks	38.94 ± 0.72	39.04 ± 1.09	39.47 ± 0.90	2.162	0.122
Weight (kg)	77.19 ± 13.27	82.37 ± 9.52	79.26 ± 11.84	2.216	0.918
I-D interval (minutes)	11.22 ± 1.67	10.04 ± 1.81	10.37 ± 1.71	3.639	0.031
U-D interval (seconds)	57.39 ± 18.93	58.00 ± 14.92	60.42 ± 22.25	0.165	0.848

F-ANOVA

Table 3 Hemodynamic variables after the induction to anesthesia (T1) and 30 s after the intubation (T2)

	T_1			F	p	Post Hoc
	A	B	C			
SAP1	110.03 ± 14.16	107.14 ± 12.59	116.89 ± 9.93	3.364	0.040	c
SAP2	119.61 ± 13.95	121.89 ± 13.82	149.00 ± 14.50	29.302	<0.001	b, c
DAP1	67.93 ± 10.99	71.28 ± 10.51	75.31 ± 14.60	2.313	0.106	
DAP2	75.71 ± 12.93	81.56 ± 10.65	98.21 ± 15.01	18.750	<0.001	b, c
MAP1	85.80 ± 13.21	84.22 ± 13.01	91.05 ± 13.17	1.590	0.211	
MAP2	91.06 ± 12.60	96.70 ± 12.49	116.68 ± 14.76	23.292	<0.001	b, c
HR1	97.06 ± 9.88	94.70 ± 9.96	103.15 ± 11.64	3.819	0.026	c
HR2	100.68 ± 8.92	102.41 ± 11.02	109.68 ± 9.61	5.165	0.008	b, c

F-ANOVA,
a (A vs B), b (A vs C), c (B vs C)
Abbreviations: SAP1 – systolic arterial pressure after the induction to anesthesia (mm Hg), SAP2 – systolic arterial pressure after the endotracheal intubation, DAP1 – diastolic arterial pressure after the induction to anesthesia (mm Hg), DAP2 – diastolic arterial pressure after the endotracheal intubation (mm Hg), MAP1 – main arterial pressure after the induction to anesthesia (mm Hg), MAP2 – main arterial pressure after the endotracheal intubation (mm Hg), HR1 – heart rate after the induction to anesthesia (beat per minute), HR2 – heart rate after the induction to anesthesia (beat per minute)

Table 4 Intubation conditions

Score (in % of patients)	Group			χ^2	p
	A	B	C		
Poor	0.0	0.0	5.3		
Good	6.5	18.5	42.1	13.276	0.010
excellent	93.5	81.5	52.6		

χ^2 – chi square test

Table 5 Newborns characteristics

		Group			χ_{KW}^2 /*F	p
		A	B	C		
Ap^1		8.81±0.55	8.81±0.48	8.63±0.49	2.969	0.227
Ap^5		9.03±0.31	8.93±0.26	8.89±0.32	2.972	0.226
Breathing*	immediately	77.4	81.4	73.7		
(% of newborns)	tactile stimulation	12.9	7.4	15.8		
	bag mask ventilation	9.7	11.1	10.5	4.365*	0.359

F-ANOVA

χ_{KW}^2– Kruskal-Wallis test

Abbreviation: Ap^1 – Apgar score in 1st minute, Ap^5 – Apgar score in 5th minute

The greater percent of patients in group A had excellent sore ($\chi^2 = 6.471$; $p = 0.011$), while in group C 42.1% of patients had good score ($\chi^2 = 5.617$; $p = 0.017$). Patients with good score in group A (two patients) had intermediate vocal cords position and moving. All patients with good score in group B (five patients) had intermediate vocal cord position and moving; two of them (7.4%) additionally had slight cough. All patients with good score in group C had intermediate vocal cord position; four of them (21.2%) additionally had not fully relaxed jaw, one (5.3%) slight cough. Patient with poor intubation score had poor jaw relaxation, vocal cords in closed position and slight limb movements.

Newborn characteristics are presented in Table 5, with no differences between groups in any of the estimated variables. All neonates were vital (Apgar score ≥ 8). The reanimation of neonates who did not start to breathe immediately consisted only of brief (1–2 minutes) tactile stimulation or beg- mask ventilation.

Discussion

The number of studies reporting the use of remifentanil during I-D period of caesarean section is increasing. The dosing regiments were different and so were maternal effects and neonatal outcomes [13–15, 17, 18, 21, 23]. The suppression of exaggerated neuroendocrine response to endotracheal intubation and surgical stress was sometimes achieved at the expense of maternal hypotension or neonatal respiratory depression and lower first minute Apgar scores, so optimal remifentanil dosing regimen was yet to be determined.

In presented article we compared the effects of two remifentanil dosing regimens with remifentanil-free control, (meaning traditionally performed anesthesia, with omission of opioids during I-D interval), hypothesizing that remifentanil beneficial effects could justify its use. Group B received remifentanil bolus just before the induction to anesthesia. In group A remifentanil bolus was followed by infusion, meant to extent its analgesic effect to whole I-D period. The infusion was interrupted after skin incision; taking into account the average length of I-D period of caesarean section performed at our Clinic (10–11 min) and remifentanil context sensitive half-time of 3 min, we believed this should leave enough time for remifentanil redistribution and metabolism in fetal circulation, thus diminishing the probability of neonatal respiratory depression.

According to our results both remifentanil dosing regimens successfully blunted maternal hemodynamic response to endotracheal intubation. SAP, DAP, MAP and HR, measured 30 s after the intubation, were significantly higher in group C than in groups A and B. The elevation of blood pressure after endotracheal intubation was even less in group A than in group B, but at this point of the operation the difference did not reach statistical significance (this will be reached as soon as at skin incision, but further analysis of maternal hemodynamic was beyond the scope of this article).

Intubating conditions (Table 5) in group A were also significantly better than in other groups. The excellent conditions were noted in 93.5% patients, compared to 81.5% in group B and 52.6% in group C; the difference between groups B and C was significant as well.

This finding did not come as a surprise, because it is known that remifentanil, used with propofol or thiopentone to facilitate endotracheal intubation, is an acceptable alternative to neuromuscular blocking drugs, since it may potentiate depression of the laryngeal reflexes [24]. Remifentanil boluses of 2–4 μg/kg (depending on a study) with propofol 2 mg/kg or thiopentone 5 mg/kg, provided satisfactory or excellent intubating conditions [25–28]. Remifentanil-hypnotics synergism could be particularly useful in cases in which muscle relaxants are contraindicated, e.g. myopathies or choline-esterase enzyme deficiency [28]. Alexander et

al. [29] reported successful use of 0.5 μg/kg remifentanil followed by 0.25 μg/kg/min, together with thiopentone for endotracheal intubation in a parturient with suxamethonium apnea.

Even when used with muscle relaxants, as in our study, remifentanil could be of great help in ameliorating intubating conditions, especially in cases where difficult intubation is anticipated. Due to physiologic changes of pregnancy, like airway edema, enlarged breasts, weight gain, change in Mallampati score, the risk of difficult/failed intubation is increased [1, 3]. The incidence of difficult and failed intubation in obstetric patients is 1–6% and 0.13–0.6% respectively (0.13–0.3% in general surgical population); additionally, the tolerance to apnea is reduced as a consequence of reduced pulmonal functional residual capacity and increased metabolic rate and oxygen consumption. This could lead to respiratory complications, like coughing, bucking, laryngospasm and bronchospasm, hypercarbia and hypoxia [1, 7, 10], making airway management problems one of the leading causes of anesthesia-related maternal mortality [2]. According to our results, the addition of remifentanil will help provide smooth endotracheal intubation, ameliorate intubation conditions and attenuate excessive hemodynamic response. This effect could be particularly beneficial in parturients with serious comorbidities, e.g. preeclampsia, but also in healthy obstetric population.

Opposite to the data from the literature [15, 17, 18, 21, 23], remifentanil regimens applied in our study did not affect neonatal outcome. First minute Apgar scores were ≥8 in all cases, without difference between groups. Majority of neonates (77.4% in group A, 81.4% in group B, 73.7% in group C) started breathing within few seconds after delivery. Resuscitative measures applied to the neonates with respiratory depression consisted of tactile stimulation and brief beg-mask ventilation with no significant difference between groups. There was no need for endotracheal intubation or for naloxone administration, and no muscular rigidity was observed.

Conclusion

Our dosing regimen of remifentanil 1μg/kg bolus given immediately before the induction followed by 0.15 μg/kg/min interrupted after skin incision provided the best compromise between achievement of excellent intubating conditions, attenuation of maternal blood pressure and heart rate response to endotracheal intubation, and avoidance of neonatal respiratory depression.

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