Journal of Clinical Anesthesia (2016) **33**, 514–520

ELSEVIER

Journal of Clinical Anesthesia

Original Contribution

Remifentanil infusion during emergence moderates hemodynamic and cough responses to the tracheal tube: A randomized controlled trial

Mohammad Reza Ghodraty[a], Valiollah Hasani[b], Amirhossein Bagheri-Aghdam[a], Mohammad Mahdi Zamani[a], Alireza Pournajafian[a], Faranak Rokhtabnak[a], Alireza Kholdebarin[a], Nader D. Nader[c,*]

[a]*Department of Anesthesiology, Firoozghar Hospital, Iran University of Medical Sciences, Tehran, Iran*
[b]*Department of Anesthesiology, Rasoul Akram Medical Complex, Iran University of Medical Sciences, Tehran, Iran*
[c]*Department of Anesthesiology & Perioperative Care, VA Western NY Healthcare System, SUNY-Buffalo, Buffalo, NY, USA*

Received 23 July 2014; revised 23 July 2015; accepted 9 September 2015

Keywords:
Coughing;
Extubation;
Emergence;
Hemodynamic;
Straining;
Remifentanil

Abstract
Objective: To examine the severity of cough and straining at the time of emergence from anesthesia.
Design: Double-blind randomized, placebo-controlled study.
Setting: University-affiliated hospital.
Patients: Sixty-two American Society of Anesthesiologists 2 patients undergoing craniotomy and excision of supratentorial cerebral tumors.
Intervention: Intravenous infusion of remifentanil (REM) at 0.05 μg/kg/min or normal saline (NS) upon termination of the surgical procedure.
Measurements: Heart rate (HR) and mean arterial pressure (MAP) along with the frequency and severity of cough response (Modified Minogue Scale) to the endotracheal tube were recorded at different time points. The frequency of cough and straining was analyzed with χ^2 tests. HRs and MAP were analyzed by repeated-measures analysis of variance between REM and NS groups.
Main Results: There was no case of significant cough in the REM group, and all of the patients in the NS group developed some extent of cough varying from mild retching to severe coughing episodes ($P < .001$). Both the HR and MAPs were consistently lower in the REM group compared to the NS group.
Conclusion: Infusion of REM at the end of craniotomy procedures results in significant reduction of the frequency and severity of coughing and straining. Compared to placebo, REM moderates increases in MAP upon emergence from general anesthesia until the time of extubation.
Published by Elsevier Inc.

1. Introduction

Smooth emergence from anesthesia is highly desired after any type of surgery, but it is critical after neurosurgical operations to prevent inadvertent rises in intracranial

* Correspondence: Nader D. Nader, VA Western NY Healthcare System, Rm. 204C, 3495 Bailey Ave, Buffalo, NY 14215, USA.
E-mail address: nnader@buffalo.edu (N.D. Nader).

http://dx.doi.org/10.1016/j.jclinane.2015.09.001
0952-8180/Published by Elsevier Inc.

pressures [1-3]. Upon termination of surgical procedures, after discontinuation of the anesthetic, the depth of anesthesia is lessened, although the patient remains in need of ventilatory support until the endotracheal tube can safely be removed. While in place, the physical stimulation of the trachea by a foreign body results in varying degree of coughing and straining which is associated with activation of the sympathetic nervous system manifesting with arterial hypertension, tachycardia, and increases in intracranial pressures [4,5]. The majority of severe anesthesia-related complications such as myocardial infarction and different types of dysrhythmias occur during this phase of emergence [6].

Hemodynamic changes during emergence phase of anesthesia have a great impact on surgical physiology of the brain. Cerebral blood flow increases up to 60% compared to the awake levels during removal of the endotracheal tube, and this hyperemia lasts at least 30 minutes afterward independent of the type of anesthesia [1]. The altered hemodynamic status causes blood-brain barrier dysfunction, cerebral edema, and even hemorrhage in severe cases [5,7,8]. Although direct correlation between the observed hemodynamic changes and a poor outcome has not yet been established, it is reasonable to avoid predisposing clinical conditions that may lead to increased pressures of the intracranial cavity [4]. The pharmacological control of emergence-associated hyperdynamic states has been tried by several investigators using local anesthetic agents [9] and vasoactive drugs such as β-adrenergic blocking drugs [10,11], calcium-channel blockers [12,13], and angiotensin-converting enzyme inhibitors [14]. Dexmedetomidine has recently been used to moderate the rises in arterial blood pressures during emergence from anesthesia [15]. Although there has been a relative success associated with any of these therapies, this clinical challenge has yet to be solved completely.

Opioid agonists are known to block the cough response and increase the threshold of the patients to tolerate manipulation of the airways. However, the use of previous generations of this class of medications is associated with delays in emergence from anesthesia, prolonged suppression of ventilation, and subsequent hypercapnea, which may be equally detrimental in increasing intracranial pressures among neurosurgical patients. Recent advances are made with introduction of ultra-short-acting opioids that have enabled the anesthesia clinicians to efficiently block hemodynamic and cough responses to the endotracheal tube [16,17].

The main objective of this study was to examine the effects of remifentanil (REM) infusion on moderating the hemodynamic and cough responses to the endotracheal tube while emerging from anesthesia after intracranial surgeries. The frequency of cough from cessation of anesthesia until the removal of endotracheal tube was our primary end point. We hypothesized that cough and straining response will be effectively inhibited with infusion of REM.

2. Methods

This study was designed as a double-blind prospective clinical trial. The study protocol and informed consent process were reviewed and approved by the institutional review board and the ethics committee on research of Iran University of Medical Sciences. After its institutional approval, the trial was registered at the Islamic Republic of Iran Clinical Trials registry under the registration number of IRCT2012110711398N1.

From March 2012 to March 2013, 62 eligible patients for this study in 2 teaching hospitals (Rasool-e-Akram Hospital and Firouzgar Hospital) were enrolled after obtaining an informed consent from the participants. Inclusion criteria were all patients between 18 and 65 years old with the American Society of Anesthesiologists physical class of II undergoing elective craniotomy for supratentorial space-occupying lesions. All the patients meeting the following criteria were excluded from the study: (1) unable to understand and sign an informed consent, (2) preoperative Glasgow Coma Scale (GCS) <14, (3) history of essential hypertension, (4) chronic obstructive pulmonary disease including asthma, (5) chronic cough spells, (6) recent tracheobronchitis (during the last week), and (7) history of allergy to the drugs used in this study.

All enrolled patients were randomized by block randomization method to receive either intravenous infusion of REM or intravenous infusion of an equal volume of normal saline (NS) as controls. A research pharmacist prepared the study drug and calculated the infusion rate. The infusion bag was then labeled with the patient's name, the study number, and the rate of infusion. All members of the anesthesia team and surgeons were blinded to the nature of treatment.

The anesthesia team consisted of a resident trainee in anesthesiology and a board-certified anesthesiologist (faculty member of Iran University of Medical Sciences) for all cases. After their arrival to the operating room, all patients were preoxygenated with 100% oxygen for 5 minutes. All patients were monitored for invasive arterial pressures via radial arterial catheters in addition to the American Society of Anesthesiologists standard continuous monitoring. All patients were induced with intravenous injection of fentanyl citrate 3 μg/kg, lidocaine 1.0-1.5 mg/kg, midazolam 20 μg/kg, and sodium pentothal 4-5 mg/kg. Muscle relaxation was achieved by atracurium 0.5-0.6 mg/kg. The trachea was intubated with spiral tubes, and internal diameters of the tubes were 7.0 mm for female and 8.0 mm for male patients. The cuffs for the tracheal tubes were inflated to maintain pressures between 20 and 25 cm H_2O during the operation. General anesthesia was maintained with total intravenous anesthesia (TIVA) using propofol infusion at 100-120 μg/kg/min, REM at 0.1-0.2 μg/kg/min, and atracurium at 10 μg/kg/min. Mean arterial pressure (MAP) was maintained within 20% of the baseline. Near the end of operation, fentanyl citrate 1 μg/kg was administered intravenously, and muscle paralysis was reversed using intravenous neostigmine 0.05 mg/kg mixed with glycopyrrolate 6 μg/kg