Journal of Clinical Neuroscience 38 (2017) 96–99

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Case study

Safety of remifentanil in transsphenoidal surgery: A single-center analysis of 540 patients

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ARTICLE INFO

Article history:
Received 31 May 2016
Accepted 26 December 2016

Keywords:
Transsphenoidal surgery
Remifentanil
Safety
Complication

ABSTRACT

Although some studies have examined the efficacy and safety of remifentanil in patients undergoing neurosurgical procedures, none has examined its safety in transsphenoidal operations specifically. In this study, all transsphenoidal operations performed by a single author from 2008 to 2015 were retrospectively reviewed to evaluate the safety of remifentanil in a consecutive series of patients. During the study period, 540 transsphenoidal operations were identified. Of these, 443 (82.0%) patients received remifentanil intra-operatively; 97 (18.0%) did not. The two groups were well-matched with regard to demographic categories, comorbidities, and pre-operative medications ($p > 0.05$), except pre-operative tobacco use ($p = 0.021$). Patients were also well-matched with regard to radiographic features and surgical techniques. Patients who received remifentanil were more likely to harbor a macroadenoma (78.1% vs. 67.0%, $p = 0.025$), and had slightly longer anesthesia time on average (269.2 min vs. 239.4 min, $p = 0.024$). All pathologic diagnoses were well-matched between the two groups, except that patients receiving remifentanil were more likely to harbor a non-functioning adenoma (46.5% vs. 26.8%, $p < 0.001$). Analysis of post-operative complications showed no significant difference between patients who received remifentanil and those who did not, and length of stay and prevalence of ICU stay did not differ between the two groups. In a well-matched series of 540 patients undergoing transsphenoidal surgery, remifentanil was found to be a safe anesthetic adjunct. There were no significant differences in post-operative hospital course or complications in patients who did and did not receive intra-operative remifentanil.

1. Introduction

Remifentanil is frequently used during neurosurgical procedures as an anesthetic adjunct during short periods of intense noxious stimulation or to control blood pressure rapidly, and has been shown in many studies to be a safe and equivalent alternative or adjunct to other commonly-used anesthetics [1–10]. Along with a quick and smooth emergence from sedation, patients given remifentanil have been found to have increased functional ability in the 24 h following sedation, as well as a shorter post-operative recovery time [11–16]. Unlike many similar synthetic opioids, remifentanil is metabolized by rapid hydrolysis by tissue and plasma esterases rather than hepatically, yielding a short half-life even after prolonged infusion [17,18].

For transsphenoidal surgery in particular, prevention of coughing during emergence from sedation is preferred in order to avoid excess bleeding or disruption of the surgical wound or nasal packing. Multiple studies have found that remifentanil is an appropriate anesthetic agent for cough suppression in nasal surgery, and it has previously been reported that remifentanil suppresses both cough incidence and severity without prolonging wake-up time [19,20]. Additionally, long-acting opioids that are used in other intracranial procedures are sometimes inappropriate for use in transsphenoidal surgery, due to the lack of an incision through the skin and skull, and a generally shorter operative duration [15]. The rapid onset and offset and beneficial hemodynamic properties of remifentanil have previously been documented specifically in transsphenoidal surgery [15].

Additional benefits of the use of remifentanil include a relatively lower incidence of post-operative nausea and vomiting than

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http://dx.doi.org/10.1016/j.jocn.2016.12.011
0967-5868/

some of its counterparts, especially when used in conjunction with propofol [3,21]. When combined with propofol, remifentanil was found to be an equivalent alternative to other anesthetic methods regarding extubation time [5].

Although many studies have examined the efficacy of remifentanil in patients undergoing neurosurgical procedures in general, to our knowledge, none has examined its safety in transsphenoidal operations specifically [2,14,16]. Remifentanil may produce adverse events characteristic of other mu opioids, including respiratory depression, apnea, tachycardia, bradycardia, remifentanil-induced hyperalgesia, and skeletal muscle rigidity [4,18,19]. Together, these complications can lead to prolonged hospital stay, the necessity of ICU support, or readmission. Here, we present the single-center experience of 540 patients undergoing transsphenoidal surgery to evaluate the relative safety of intra-operative use of remifentanil.

2. Methods

All transsphenoidal operations performed by a single author (E.R.L.) at Brigham and Women's Hospital from 2008 to 2015 were retrospectively reviewed. Patients with missing anesthesia records were excluded. Patient data, including demographics, co-morbidities, pre-operative medications, peri-operative characteristics, pathological analysis, and post-operative complications and hospital course were collected and compared. For all tests, $p < 0.05$ was considered statistically significant.

3. Results

Within the study period, 540 transsphenoidal operations were performed. Of these operations, 433 (82.0%) patients received remifentanil intra-operatively, while 97 (18.0%) patents did not (Table 1). These two groups were well-matched ($p > 0.05$) with regard to demographic categories, including sex, age, and BMI, pre-operative comorbidities, including hypertension, coronary artery disease, diabetes, cardiac disease, CVA/stroke, hyperlipidemia, and obesity, but were not well-matched by pre-operative tobacco use ($p = 0.021$). The two patient groups were also well matched for all pre-operative medications. All patients who received remifentanil received it as an anesthetic adjunct.

With regard to surgical techniques and radiographic features, the two patient groups were generally well-matched ($p > 0.05$) (Table 2). Patients who received remifentanil intra-operatively were more likely to harbor a macroadenoma (78.1% vs 67.0%, $p = 0.024$), and had a slightly longer average anesthesia time (269.2 min vs. 239.4 min, $p = 0.024$). All pathologic diagnoses were well-matched between the two groups, except patients receiving remifentanil were more likely to harbor a non-functioning adenoma (46.5% vs. 26.8%, $p < 0.001$, Table 3).

Analysis of post-operative hospital course and complications showed no significant difference between patients who received remifentanil intra-operatively and those who did not ($p > 0.05$) (Table 4). Hospital length of stay did not differ significantly between patients receiving remifentanil and those who did not (3.51 days vs. 3.29 days, $p = 0.410$), and similar proportions of patients in each group required a stay in the Intensive Care Unit (12.9% vs. 16.5%, $p = 0.330$) and readmission (8.9% vs. 4.3%, $p = 0.204$). Other complications analyzed in this report were divided into endocrine complications (e.g., SIADH, transient diabetes insipidus), infectious complications (e.g., sinus infection, meningitis), and surgical complications (e.g., CSF leak, epistaxis, visual field deficit). No complications analyzed differed significantly between the two groups.

4. Discussion

Remifentanil has been shown in multiple studies to be an effective anesthetic, with desirable effects including reduction in patient coughing after extubation [19], reduction of patient time in the PACU, improved recovery times [8,13], and an equivalent or superior sedation side effect profile [3–9,11,13,19]. Remifentanil may reduce post-operative nausea and vomiting and may preclude the use of long-acting opioids [8,16,20].

Table 1
Demographics of patients undergoing transsphenoidal surgery with and without the use of remifentanil.

Characteristic	Total ($n = 540$)	With remifentanil ($n = 443$)	Without remifentanil ($n = 97$)	P-value
Male sex, no. (%)	252 (46.7)	198 (44.7)	54 (55.7)	0.056
Age, mean (range)	46.8 (16–89)	47.1 (16–89)	48.5 (16–82)	0.423
BMI, mean (range)	29.1 (18.0–56.1)	29.1 (18.0–56.1)	29.6 (18.6–51.2)	0.516
Prior medical history, no. (%)				
Hypertension	183 (34.6)	149 (34.3)	34 (35.8)	0.812
Coronary artery disease	19 (3.6)	15 (3.5)	4 (4.2)	0.760
Diabetes	64 (12.1)	53 (12.2)	11 (11.6)	1.000
Cardiac disease	40 (7.6)	33 (7.6)	7 (7.4)	1.000
CVA/stroke	13 (2.5)	12 (2.8)	1 (1.1)	0.480
Hyperlipidemia	116 (22.0)	95 (21.9)	21 (22.1)	1.000
Tobacco use	102 (19.3)	75 (17.3)	27 (28.4)	0.021
Obesity	89 (16.9)	76 (17.6)	13 (13.7)	0.449
Pre-operative medications, no. (%)				
Levothyroxine	109 (20.2)	90 (20.4)	19 (19.6)	1.000
Liothyronine	4 (0.8)	3 (0.7)	1 (1.1)	0.550
Oral glucocorticoids	57 (10.8)	48 (11.1)	9 (9.5)	0.719
Growth hormone	5 (0.9)	5 (1.2)	0	0.591
Desmopressin	19 (3.6)	17 (3.9)	2 (2.1)	0.549
Insulin	17 (3.2)	15 (3.5)	2 (2.1)	0.750
Oral glucose-lowering agents	34 (6.5)	30 (6.9)	4 (4.2)	0.232
Anti-hypertensive	160 (30.3)	131 (30.3)	29 (30.5)	1.000
Beta blocker	65 (12.3)	53 (12.3)	12 (12.6)	0.865
Lipid-lowering agent	114 (21.6)	96 (22.2)	18 (19.1)	0.582
Cabergoline	48 (9.1)	38 (8.8)	10 (10.5)	0.558
Bromocriptine	8 (1.5)	6 (1.4)	2 (2.1)	0.639
Somatostatin analog	18 (3.4)	13 (3.0)	5 (5.3)	0.342
Prior pituitary surgery, no. (%)	118 (22.3)	97 (22.4)	21 (22.1)	1.000
Prior radiation to pituitary, no. (%)	16 (3.0)	13 (3.0)	3 (3.2)	1.000