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Original Contribution

Remifentanil and worse patient-reported outcomes regarding postoperative pain management after thyroidectomy☆,☆☆

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Abstract

Background: Intraoperative remifentanil has been associated with postoperative hyperalgesia, higher visual analogic pain scores, and increased postoperative morphine consumption. However, this has not been investigated from patient's perspective by using a patient-reported outcomes (PROs) approach with a validated questionnaire.

Methods: We joined the largest prospective observational study on postoperative pain, PAIN OUT Project (NCT02083835), and collected data for 2 years. We studied the effects of remifentanil (R+) vs nonremifentanil (R−) anesthesia on PROs regarding their pain management after elective thyroidectomy. We selected 5 primary PROs (worst pain experienced, time spent in severe pain, relief received by treatment, satisfaction about pain management, wish for more pain treatment) and five secondary PROs (drowsiness, itching, nausea, dizziness, waking up due to pain) from the validated International Pain Outcomes questionnaire.

Results: The analysis included 317 patients, 208 in the R+ group (65.6%) and 109 in the R− group (34.4%), the latter receiving fentanyl as intraoperative opioid. Although the R+ group received more frequently intraoperative nonopioids (202/208, 97.1% vs 86/109, 78.9%; $P < .0001$) and opioids (184/208, 88.5% vs 38/109, 34.9%; $P < .001$), it reported higher worst pain (5.1±2.1 vs 4.3±2.1, $P < .005$), lower satisfaction (7.4±2.0 vs 8.1±2.1, $P < .001$), and worse results in 4 secondary PROs. A sensitivity analysis performed matching 67 couples of patients yielded similar results in primary PROs.

Conclusions: Our study suggests that remifentanil-based anesthesia is associated with worse pain-related PROs in patients undergoing thyroidectomy despite more frequent intraoperative analgesic administration. This study adds further evidence to the growing literature about opioid- and remifentanil-induced hyperalgesia.

☆ The authors declare that they have no conflict of interest.

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1. Introduction

Remifentanil holds unique pharmacological properties, making it the ideal opioid for total intravenous anesthesia. However, opioids are associated with induction of hyperalgesia with a sensitization of pronociceptive mechanisms even after a single dose [1], and an association between remifentanil and opioid-induced hyperalgesia has been shown both in human volunteers [2] and in clinical studies [3–7]. The clinical impact of remifentanil-induced hyperalgesia (RIH) has been probably underestimated until a recent meta-analysis demonstrated that anesthesia conducted with remifentanil is associated with higher pain scores and morphine consumption in the first 24 postoperative hours [8].

Despite advances in pain management, many patients still experience moderate to severe postoperative pain [9]. Regional, national, and continental surveys have documented that hospitalized patients receive a suboptimal pain treatment, and a US survey found 50%-70% of patients reporting moderate to severe postoperative pain [10–12]. Patient-reported outcomes (PROs) research is a growing approach to research, aiming at extending the concept of patient-centeredness from the daily health care delivery into health care research [13]. We participated in the international, observational, prospective, and PROs study on postoperative pain: PAIN OUT Project (www.pain-out-eu). From the data collected at our center, we aimed at investigating the effects of intraoperative remifentanil-based anesthesia on patients' perspectives about their pain management after thyroidectomy.

2. Methods

2.1. PAIN OUT participation

The PAIN OUT Project is an observational study, and its methodology has been published [14]. More detailed information is provided separately as Supplemental Digital Content–Appendix.

After the approval by the local Ethical Committee (26 Feb 2010; prot. no. 371) and for 2 consecutive years (April 2010-March 2012), trainees of the School of Anesthesia and Intensive Care of the University of Catania (Italy) prospectively collected observational data according to the PAIN OUT Project design in 5 hospitals associated with the university. Before starting data collection, in the period from January to March 2010, the trainees received a standardized introduction to the PAIN OUT Project with weekly meetings consisting of frontal teaching and hands-on training sessions to allow their familiarization with the study design and the charts for data collection. Importantly, because of the observational nature of the study, the trainees were not allowed to influence the anesthetic technique or the postoperative pain management strategies. Patients participating to the study were asked to fill in a dedicated questionnaire (International Pain Outcomes [IPO] questionnaire) on the first postoperative day at least 6 hours after their return to the ward. The IPO questionnaire has been validated in 10 different languages [15]. We planned to perform analyses of primary and secondary PROs (Table 1) in different surgical populations.

2.2. Aim of the present study

In the present study, we report PRO results of patients undergoing thyroidectomy (partial or complete, *International Classification of Diseases, NINTH Revision*, code 06.2 and 06.4, respectively—irrespective of the type of surgical indication) under general anesthesia. With the aim to investigate an association between remifentanil and worse postoperative pain outcomes, we divided the patients into 2 groups: those anesthetized with remifentanil infusion (R+) and those not (R−).

Patients were excluded from the analysis if they answered less than 2 primary PROs and/or lacked data about the intraoperative analgesics. We compared groups with regard to the intraoperative administration of drugs for postoperative pain relief, dividing these analgesics into 2 classes: opioids and nonopioids. Unfortunately, PAIN OUT Project design does not allow an accurate calculation of the dose of intraoperative remifentanil, and thus, an analysis of high-dose or low-dose remifentanil was not feasible. Although it was not possible to find out directly from the database, the administration technique for remifentanil was performed in manually controlled technique (μg/[kg min] dosing), and target controlled infusion was not implemented at the time of data collection.

Because the PAIN OUT charts were collected in a variable time frame after the operation (roughly between the 15th and the 30th postoperative hour), we avoided calculating the postoperative analgesic drug consumption because this is affected by the timing of data collection.

Data were downloaded directly from the central database of the project. The PAIN OUT Publication Board was informed of our analysis design and gave consent for this.

Table 1 Patient-reported outcomes

Primary end points	Scale	Secondary end points	Scale
Worst pain	0-10	Drowsiness	0-10
Time spent in severe pain	%	Itching	0-10
Pain relief received by treatments	%	Nausea	0-10
Satisfaction with pain management	0-10	Dizziness	0-10
Wish more pain treatment (Y/N)	%	Waking up due to pain (Y/N)	%

Five primary and 5 secondary end points were considered for the analysis in Catania's center participating in PAIN OUT.