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ORIGINAL RESEARCH

Remifentanil-Induced Secondary Hyperalgesia Is Not Prevented By Preoperative Acetazolamide Administration In Patients Undergoing Total Thyroidectomy: A Randomized Controlled Trial

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Purpose: Acute administration of remifentanil may lead to opioid-induced hyperalgesia (OIH). Studies in mice suggest that OIH is mediated by impaired anionic homeostasis in spinal lamina I neurons due to a down-regulation of the K^+-Cl^- co-transporter KCC2, which was reverted using acetazolamide (ACTZ), a carbonic anhydrase inhibitor. We propose that ACTZ prevents remifentanil-mediated OIH in humans.

Patients and methods: We conducted a randomized, double-blind, placebo-controlled clinical trial between December 2016 and September 2018. Patients were randomly allocated to receive ACTZ (250 mg of ACTZ 2 h before surgery) or placebo. To detect hyperalgesia, mechanical pain threshold (MPT) were measured before and after surgery using hand-held von Frey filaments in the forearm. Anesthesia was maintained with remifentanil at a target effect site of 4.5 ± 0.5 ng/mL, and sevoflurane at an end-tidal concentration of 0.8 MAC corrected for age.

Results: In total, 47 patients completed the study. Both groups were comparable in the baseline characteristics and intraoperative variables. Baseline MPT were similar in both groups. However, MPT in the forearm significantly diminished in the time in both groups. Finally, postoperative pain and morphine consumption were similar between groups.

Conclusion: Both groups developed remifentanil-mediated OIH at 12–18 h after surgery. However, ACTZ did not prevent the MPT reduction in patients undergoing total thyroidectomy.

Keywords: anesthesia, chloride dysregulation, carbonic anhydrase, pain

Introduction

Opioid-induced hyperalgesia (OIH) is a sensitization process in which opioids, paradoxically, cause pain hypersensitivity.[1,2] A hypersensitivity in a distant place from the surgery site is secondary hyperalgesia, which is manifested as a decline in the mechanical pain threshold (MPT).[2,3] The relevance of OIH and secondary hyperalgesia in humans is controversial. Nonetheless, clinical trials show consistently that high-dose of opioids during surgery increases postoperative pain and opioid consumption after surgery.[3] Particularly in patients who receive the ultra-short-acting μ-opioid receptor agonist, remifentanil.[4–6] Moreover, a high intraoperative dose of remifentanil is associated with OIH manifested as a diminished in the MPT surrounding the surgical wound on the day after surgery (ie, primary hyperalgesia).[7]

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The canonical mechanism related to OIH is the activation of N-methyl-D-aspartate (NMDA)-dependent pronociceptive systems leading to a reduction in the nociceptive thresholds.[2,8] However, some studies suggest that OIH might also be explained by alternative mechanisms (Figure 1A and B) in animal models.[9] Briefly, it has been proposed that OIH may be mediated, at least in part, by a downregulation of the K-Cl co-transporter 2 (KCC2) expression in the spinal dorsal horn in rats.[10] This would lead to an intracellular accumulation of chloride (Cl^-) in neurons, and consequently, $GABA_A$ receptor inhibition might be abolished by depolarization of the Cl^- reversal potential (ie, chloride dysregulation).[11] In normal conditions, $GABA_A$ receptors inhibition depends on the influx of Cl^-, which is counterbalanced by an efflux of bicarbonate ($HCO3^-$) as $GABA_A$ receptors are permeable to Cl^- and $HCO3^-$ in a 4:1 permeability ratio.[12–14] Thus, chloride dysregulation could be reverted by reducing the HCO_3^- efflux (Figure 1C). One way to attenuate HCO_3^- efflux is to block the reaction catalyzed by carbonic anhydrase that restores the intracellular HCO_3^- levels.[15] Indeed, spinal inhibition of carbonic anhydrase reduced neuropathic allodynia in rats,[16] and also avoided morphine-induced hyperalgesia in mice.[11] To demonstrate that chloride dysregulation is an alternative mechanism of OIH in humans, we propose that inhibition of carbonic anhydrase by acetazolamide (ACTZ) might revert OIH.

Thus, the aim of this clinical trial was to test whether preoperative administration of 250 mg of ACTZ during sevoflurane-remifentanil anesthesia diminishes the postoperative remifentanil-induced secondary hyperalgesia in patients undergoing total thyroidectomy.

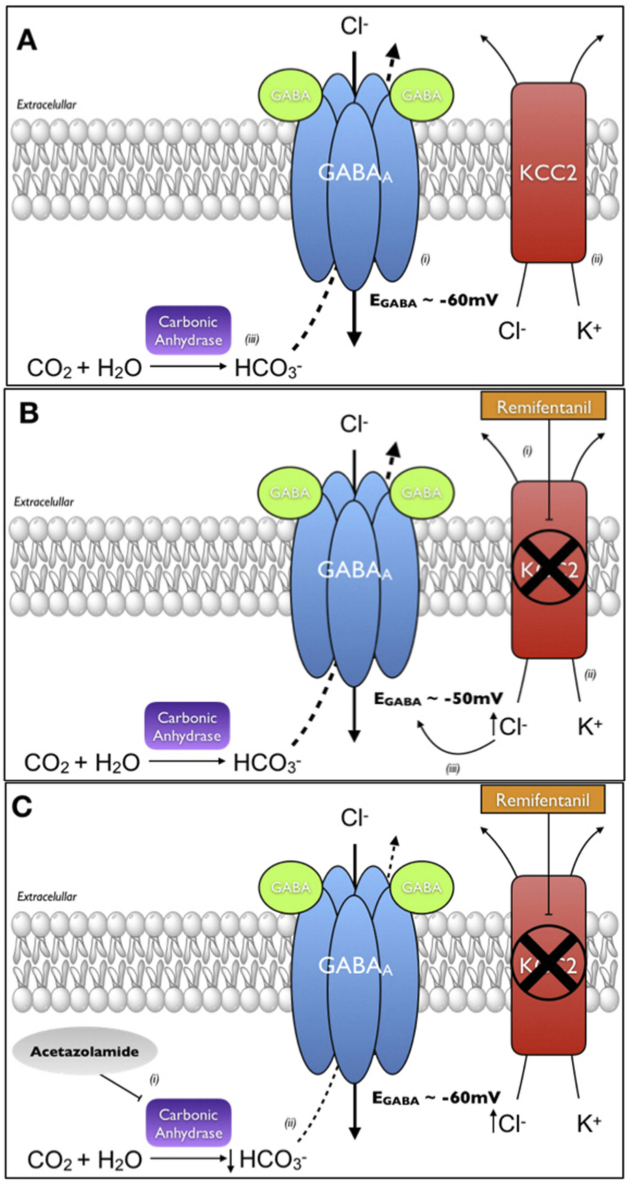

Figure 1 Scheme representing the molecular mechanism of acetazolamide (ACTZ) to revert hyperalgesia generated by chloride-dysregulation induced for opioids. (**A**) Normal condition: i) $GABA_A$ receptors activation leads to a Cl^- influx and $HCO3^-$ efflux; ii) KCC2 maintains a low Cl^- intracellular concentration, and thus, the reversal potential for $GABA_A$ receptor (E_{GABA}) is approximately −60 mV. E_{GABA} depends on Cl^- and $HCO3^-$ with 4:1 ratio of permeability. (**B**) Remifentanil-induced hyperalgesia by downregulation of the KCC2: i) Remifentanil leads to a downregulation of the KCC2 expression by a BDNF-mediated mechanism[11] generating an increase in the intracellular Cl^- concentration and therefore changing the Cl^- gradient; ii) E_{GABA} is depolarized to approximately −50 mV. (**C**) Acetazolamide reverses the chloride-dysregulation by inhibition of the carbonic anhydrase: i) Acetazolamide inhibits carbonic anhydrase leading to a reduction in the intracellular HCO_3^- concentration; ii) E_{GABA} is consequently hyperpolarized to approximately −60 mV.

Materials And Methods

This trial was registered in ClinicalTrials.gov, ID number: NCT02992938 and was conducted in accordance with the Declaration of Helsinki. After obtaining ethics committee approval (Hospital Clínico de la Universidad de Chile, Santiago, Chile) we conducted a randomized, double-blind, placebo-controlled clinical trial between December 2016 and September 2018. We included patients between 18 and 65 years, American Society of Anesthesiologist (ASA) I or II, scheduled for total thyroidectomy without neck dissection. Exclusion criteria were chronic pain history, previous partial thyroidectomy, analgesic use in the last 48 h, body mass index > 30 $kg \cdot m^{-2}$, contraindication to receive ACTZ or a sevoflurane-based anesthesia, and unable to use a patient-controlled analgesia (PCA) device.

After signed a written informed consent, patients were randomly allocated to the ACTZ group (250 mg of ACTZ 2 h before surgery) or to the control group (placebo 2 h before surgery). Placebo tablets were the same in terms of color and shape to those containing ACTZ. Patients were allocated to each group using a random-number table whose

information was kept in sealed envelopes. After the enrollment of a patient, the respective envelope was opened, and the medication was administered according to the information in the envelope.

To determine the secondary hyperalgesia (ie, in a distant place from surgical site), the MPT was measured using hand-held von Frey filaments in the right forearm as previously described.[7,17] All the evaluations were performed by the same operator (RG). Baseline MPT measurement was performed before the surgery, and at 2 h and 12–18 h after surgery in the forearm without peripheral venous catheter. Since, we did not include patients scheduled at first hour in the morning, the 12–18 h interval evaluation corresponds to the morning at the day after surgery. General anesthesia induction was standardized as follows: remifentanil infusion was guided by Minto's model[18] to an effect-site target of 6 $ng \cdot mL^{-1}$, propofol 2 $mg \cdot kg^{-1}$, lidocaine 40 mg, and rocuronium 0.6 $mg \cdot kg^{-1}$ to facilitate orotracheal intubation. After tracheal intubation, patients were protectively ventilated to normocapnia with 40–50% oxygen without nitrous oxide. Patients received intravenous ketorolac 60 mg and acetaminophen 1 g before the incision. Anesthesia was maintained with remifentanil at target effect-site of 4.5 ± 0.5 $ng \cdot mL^{-1}$, and sevoflurane at an end-tidal concentration of 0.8 MAC corrected for age. Thirty minutes before the anticipated end of surgery, a 0.1 $mg \cdot kg^{-1}$ bolus dose of morphine was given intravenously, and then, a morphine PCA device was connected, which was programmed with a 1 mg bolus of morphine and a lockout interval of 8 min. All participants were preoperatively instructed on the PCA use. Ketamine was not used in any patient in this protocol.

The primary endpoint was to detect a higher MPT at 12–18 h in the ACTZ group respect to control group. Based on previous results[17] the number of patients needed to find a difference of 20 g (65 g vs 45 g) in the MPT was 19 per group, with a power of 0.80 and an α of 0.05. Assuming a dropout rate of 30%, we calculated a sample size of 25 patients per group. Secondary outcomes were pain evaluated with a numeric pain rating scale (NPRS) and morphine consumption during the first 24 h after surgery. Any adverse event was registered and follow up during the hospital stay.

The analysis of the von Frey measurement, NPRS, and morphine consumption was performed using two-way ANOVA. Demographics and intraoperative data were analyzed with Fisher exact test or *t* test as corresponded. A p value <0.05 was considered statically significant.

Results

Fifty patients were enrolled in the study. Three patients were excluded due to the suspension of surgery (n=2) and unplanned neck dissection (n=1). Therefore, 47 patients completed the study and were included in the final analysis (Figure 2). There were no differences between groups in comorbidities, morphometric and demographic characteristics, while women were predominant in our population (Table 1). Between ACTZ administration and the anesthesia induction, the mean time was the same in both groups (Control 113.7 ± 38.8 min vs ACTZ 113.1 ± 30.8 min, p=0.9). Duration of surgery and anesthesia were also similar between groups. Finally, both groups received the same total dose of remifentanil during surgery (Control 1186 ± 341.8 µg vs ACTZ 1286 ± 359.4 µg, p=0.4).

There were no differences in the baseline forearm MPT between patients receiving placebo and those receiving ACTZ (Figure 3). In the postoperative evaluations at 2 and 12–18 h, we did not find any differences in the forearm MPT between the groups. However, MPT in the forearm significantly diminished in the time in both groups (two way ANOVA, effect of time: $F_{(2,44)} = 6.8$, p=0.02; effect of treatment: $F_{(1,22)} = 0.13$, p=0.7; and effect of interaction: $F_{(2,44)} = 0.2$, p = 0.2. Tukey post hoc test, Placebo: 2 h vs 12–18 h, p<0.05; ACTZ: baseline vs 12–18 h, p=0.001 and 2 h vs 12–18 h, p<0.05).

Finally, we found no differences between groups in the postoperative pain evaluated using the NPR scale (Figure 4A) or in morphine consumption (Figure 4B). Both were evaluated during the first 24 h after surgery. Total morphine consumption was 7.7 ± 6.7 mg in the control group and 7.6 ± 11.0 mg in the ACTZ group. There was no serious adverse event related to the ACTZ administration. Three patients reported headache in the ACTZ group (3/23, 13%) and one patient in the control group (1/24, 4%). The headaches were not severe in any case. There were also no differences in the incidence of postoperative nausea and vomiting (Control: 4/24 (16%) vs ACTZ: 5/23 (21%), p=0.9).

Discussion

This is the first clinical trial aimed to test whether a single preoperative dose of ACTZ prevents remifentanil-induced secondary hyperalgesia in patients undergoing total thyroidectomy. We found an intraoperative remifentanil-induced hyperalgesia, which was defined as a decreased

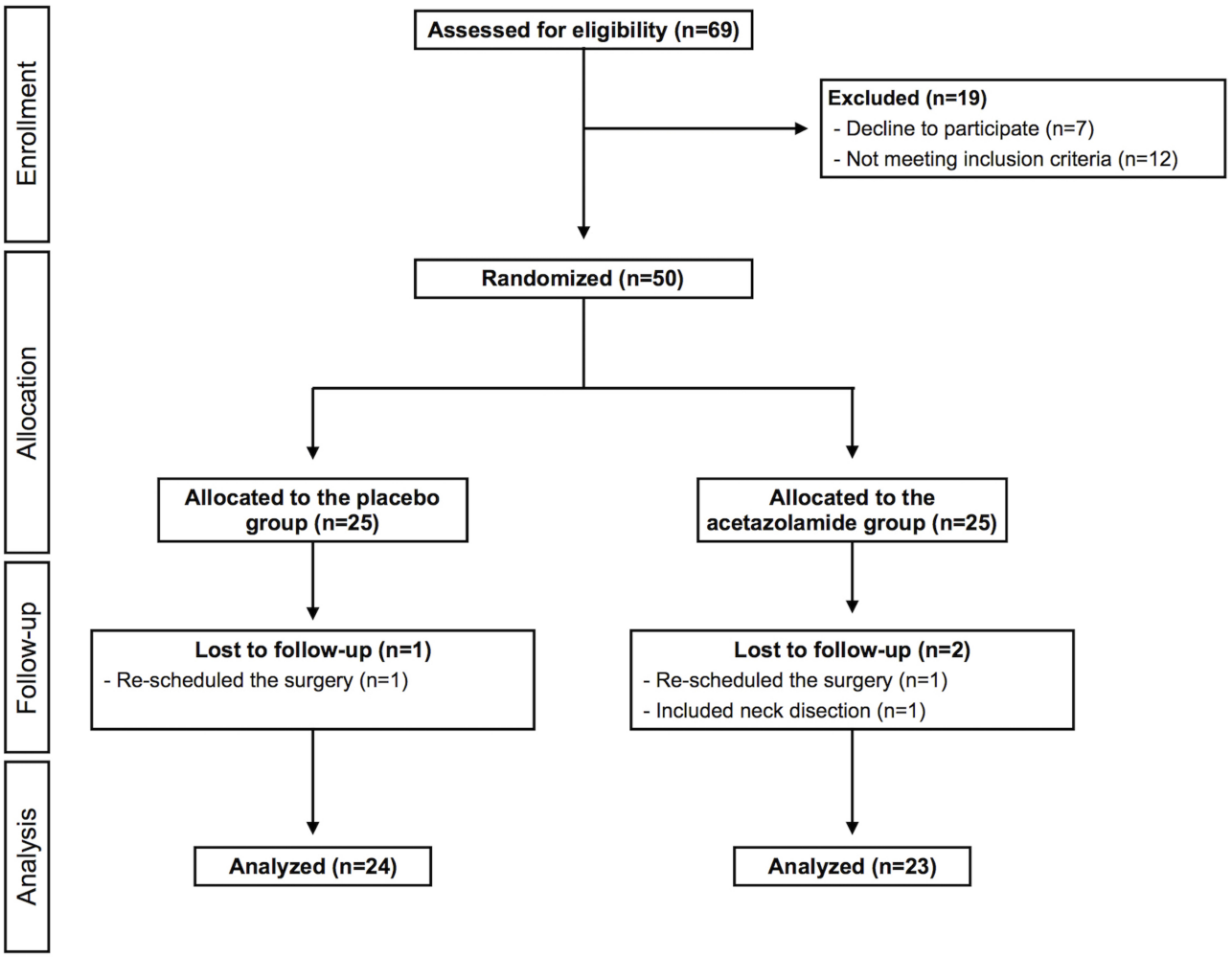

Figure 2 CONSORT diagram of patients' recruitment and retention through the trial.

in the MPT 12–18 h after surgery, but it was not prevented by ACTZ.

The rationale for using ACTZ comes mainly from results obtained in pre-clinical studies. ACTZ has been widely used in different clinical scenarios and exhibits a secure profile in terms of adverse effects, thus ACTZ was potentially an excellent agent to prevent remifentanil-induced hyperalgesia. However, our results indicate that ACTZ did not avoid remifentanil-induced hyperalgesia. On the other hand, remifentanil-mediated OIH occurred in both groups of patients, even when thyroidectomy is a short-duration surgery (approximately 1.5 h) and the total dose of remifentanil was less than in other studies.[7,19] Remifentanil-induced secondary hyperalgesia has been previously reported by Schmidt et al.[19] They observed that an acute remifentanil administration was associated with the induction of hyperalgesia to painful pressure stimuli in a different site to the surgery localization and our data show that this phenomenon occurs also in this short-duration surgery.

Several factors could explain our negative results. First, ACTZ dose may not have been enough to avoid OIH. A larger dose, multiple doses or other timing of administration could have been beneficial. Nonetheless, we define the dose (250 mg) and the timing (2 h before surgery) of ACTZ administration based on a pharmacokinetic study in healthy volunteers.[20,21] The peak plasma concentration is reached after 2–3 h from oral administration and its elimination half-life is about 4–8 h.[20] Indeed, a single 250 mg dose led to a plasma concentration above 5 $\mu g \cdot mL^{-1}$ for at least 10 h since its administration in healthy Chilean volunteers[21] which is a concentration in the therapeutic range to inhibit carbonic anhydrase.[22] This plasma concentration is over the therapeutic range to inhibit carbonic anhydrase. Second, since the theoretical mechanism of ACTZ is based on restoring the Cl^- reversal potential in neurons, this drug will act

Table 1 Demographic And Clinical Characteristics Of Enrolled Patients

	Placebo (n=24)	Acetazolamide (n=23)	p Value
Morphometric and patient characteristic			
Sex (female)	21 (87.5)	22 (95.7)	0.6
Age (year)	48 (15.3)	40.8 (14)	0.1
Weight (kg)	66.7 (8.8)	65.3 (10.0)	0.6
Height (cm)	161 (0.1)	162 (0.1)	0.5
Body mass index ($kg \cdot m^{-2}$)	25.2 (2.8)	25.4 (2.8)	0.8
ASA physical status I	12 (50)	6 (26.1)	0.1
Intraoperative data			
Time between ACTZ administration and anesthesia induction (minutes)	113.7 (38.8)	113.1 (30.8)	0.9
Anesthesia duration (minutes)	122.1 (22.5)	121.5 (28.4)	0.9
Surgery duration (minutes)	81.4 (24.2)	81.7 (26.4)	0.9
Remifentanil, total dose administrated (μg)	1186 (341.8)	1286 (359.4)	0.4
Morphine, bolus dose administrated (mg)	5.4 (1.2)	5.9 (1.0)	0.2
Ephedrine, total dose administrated (mg)	14.3 (15.2)	15.1 (10.7)	0.8

Note: Values are expressed as mean (SD) or no. of patients (%).
Abbreviations: ASA, American Society of Anesthesiologist Physical Status Classification; ACTZ, acetazolamide.

once the chloride dysregulation has already been established. For the design of this trial, we expected that a single preoperative dose would be enough to prevent the Cl^- reversal potential after the surgery, based of its pharmacokinetics properties.[21] However, since we failed to demonstrate the hypothesis with our trial design, future studies with another

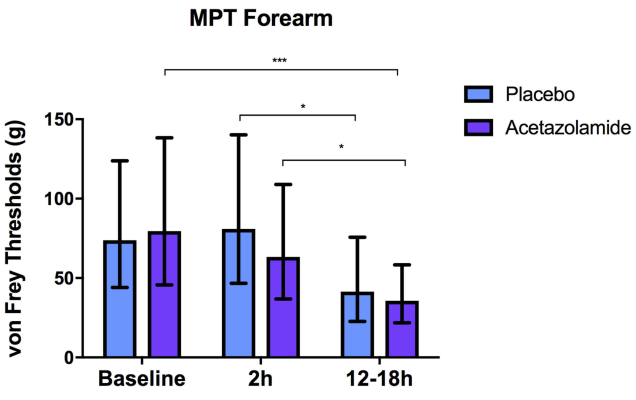

Figure 3 Mechanical pain threshold (MPT) measured using von Frey filaments at different times in both groups of patients. Values are presented as mean (95% CI) and statistical analyses was performed with two-way ANOVA and Tukey's test for multiple comparisons. *p<0.05, ***p=0.001.

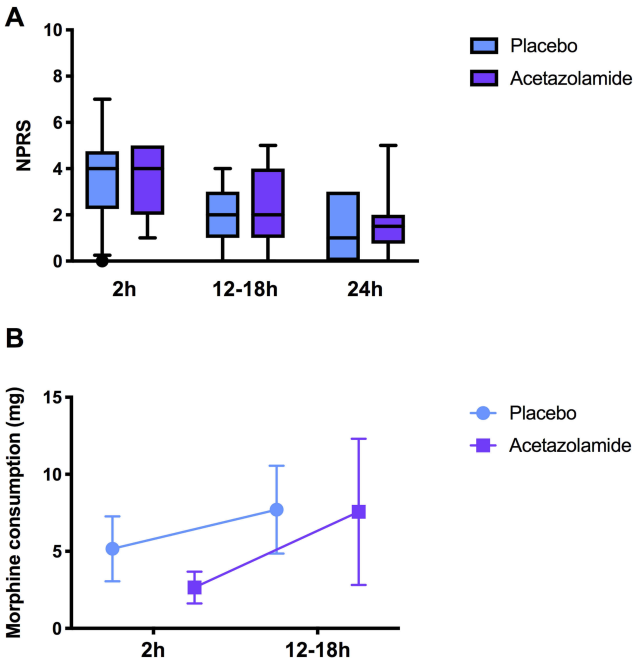

Figure 4 Pain and morphine consumption at different times in both groups of patients. (**A**) Postoperative pain scores using the numeric pain rating scale (NPRS). Values are presented as median (IQR). (**B**) Postoperative cumulative morphine consumption. Values are presented as mean (SD).

timing and dosages of ACTZ, including a postoperative administration (eg, when a change in MPT is actually observed), will be necessary to elucidate its potential role in reverting the OIH in humans. Indeed, in animals' models ACTZ is administered when the OIH is established, and therefore its role is not to prevent its occurrence, instead it is to revert it.[11] Third, it is possible that the KCC2-Chloride dysregulation mechanism of hyperalgesia may not be substantial in humans. Fourth, there is a potential confounder effect derived from morphine postoperative consumption, which is a potential limitation of this study. Morphine may probably affect pain perceptions compared with baseline measurements in areas distant to skin incision and possibly mask the OIH. However, in order to reduce this bias, we decided to conduct this trial in patients undergoing thyroidectomy, which has a mild surgical injury compared to other type of surgeries. In fact, morphine consumption was low in our patients and it principally occurred during the first postoperative hours. Fifth, our sample size could have been small to find a significant difference between groups. However, it was enough to detect a statically significant drop out in the MPT between the baseline and 12–18 h after surgery in a similar magnitude in both groups. Finally, the restoration of the MPT to the basal condition was not evaluated and it could have been different between the two groups.

Conclusion

In conclusion, both groups presented a reduction in the MPT in the forearm at 12–18 h compared to baseline, developing remifentanil-induced secondary hyperalgesia. However, ACTZ failed to prevent the MPT reduction in patients undergoing total thyroidectomy.

Data Sharing Statement

Individual participant data that underlie the results reported in this article, after deidentification will be shared upon request. The study protocol, statistical analysis plan, informed consent form and the analytic code will be also available immediately following publication and ending 5 years. This information will be shared to researches who provide a methodologically sound proposal to achieve the respective aims. Proposals should be directed to apenna@uchile.cl.

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Disclosure

The authors report no conflicts of interest in this work.

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