Comparison between remifentanil and sufentanil as opioids for general anaesthesia in ophthalmologic surgery

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▶ **Citation:** Weber J, Defosse J, Wappler F, Schieren M: Comparison between remifentanil and sufentanil as opioids for general anaesthesia in ophthalmologic surgery.
Anästh Intensivmed 2023;64:152–157. DOI: 10.19224/ai2023.152

Summary

Background: Remifentanil is a short-acting synthetic opioid that can be used as an anaesthetic for short surgical procedures. Due to a delivery shortage, we used sufentanil instead of remifentanil for surgical procedures in ophthalmology over a period of eight months in 2017. The aim of our retrospective data analysis was to assess how the use of sufentanil instead of remifentanil for general anaesthesia in ophthalmic surgery affected the intraoperative anaesthetic course and postoperative recovery.

Methods: After a preselection of 3,085 datasets, a total of 620 datasets were matched into two different groups (Remifentanil (R) group and Sufentanil (S) group). The collection and analysis of data was performed using the digitalised anaesthesia protocols and SPSS. Primary outcomes were the intraoperative and postoperative course of anaesthesiologic treatment.

Results: After pairwise matching, the two groups displayed no significant differences in patient characteristics. During general anaesthesia with remifentanil, the administration of atropine (R group: 12.6 %, S group: 6.8 %, p = 0.014) or vasopressors (R group: 55.8 %, S group: 32.3 %, p <0.001) was more frequently required. The duration of general anaesthesia as well as the length of stay in the post-anaesthesia recovery area were comparable. Postoperative shivering was observed more frequently in the R group than in the S group (R group: 3.2 %, S group: 0.6 %, p = 0.020). At the time of their discharge from the recovery room, more patients in the S group were pain-free (numeric pain scale 0 on a scale from 0 to 10, where 0 represents ‚no pain at all' and 10 represents ‚the worst pain possible') (R group: 84.2 %, S group: 92.3 %, p = 0.002), whereas the intraoperative administration of a non-opioid analgesic drug was more frequent in the S group than in the R group (R group: 10.6 %, S group: 16.5 %, p = 0.035) and the postoperative administration of Piritramide was more frequent in the R group than in the S group (R group: 16.1 %, S group: 9.7 %, p = 0.017).

Conclusions: Sufentanil is a suitable alternative to remifentanil for short and painful ophthalmic operations and furthermore it also seems to have a positive effect on intraoperative haemodynamic stability and postoperative recovery.

Introduction

The synthetic opioid remifentanil was patented in the USA in 1991 and has been approved for human use in Germany since 1996 [1]. Since then, remifentanil has been used in clinical practice, particularly for perioperative analgesia in the context of general anaesthesia or sedation.

Although remifentanil is structurally related to fentanyl, its pharmacokinetic and dynamic properties differ significantly from other opioids used in clinical practice. Thus, it is the only opioid that is primarily metabolised extra-hepatically by non-specific tissue and plasma esterases. Due to the high plasma clearance

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Competing interests
The authors declare no competing interests.

Keywords
Opioids – Remifentanil – Sufentanil – Ophthalmic surgery

of 3 l/min and the short terminal half-life in the plasma of 10 to 21 minutes, remifentanil is considered easy to control. Therefore, it is particularly suitable for reducing undesirable residual opioid effects (e. g. bradypnea, somnolence) after sedation or general anaesthesia [2–4]. For these reasons, our clinic uses remifentanil as an opioid for general anaesthesia in ophthalmologic surgery. Due to a supply bottleneck lasting several months and the unavailability for remifentanil caused by this in 2017, the longer-acting sufentanil was used instead. The aim of this paper is to investigate to what extent the usage of sufentanil influences the perioperative course of anaesthesiological treatment in surgical eye-interventions compared to remifentanil.

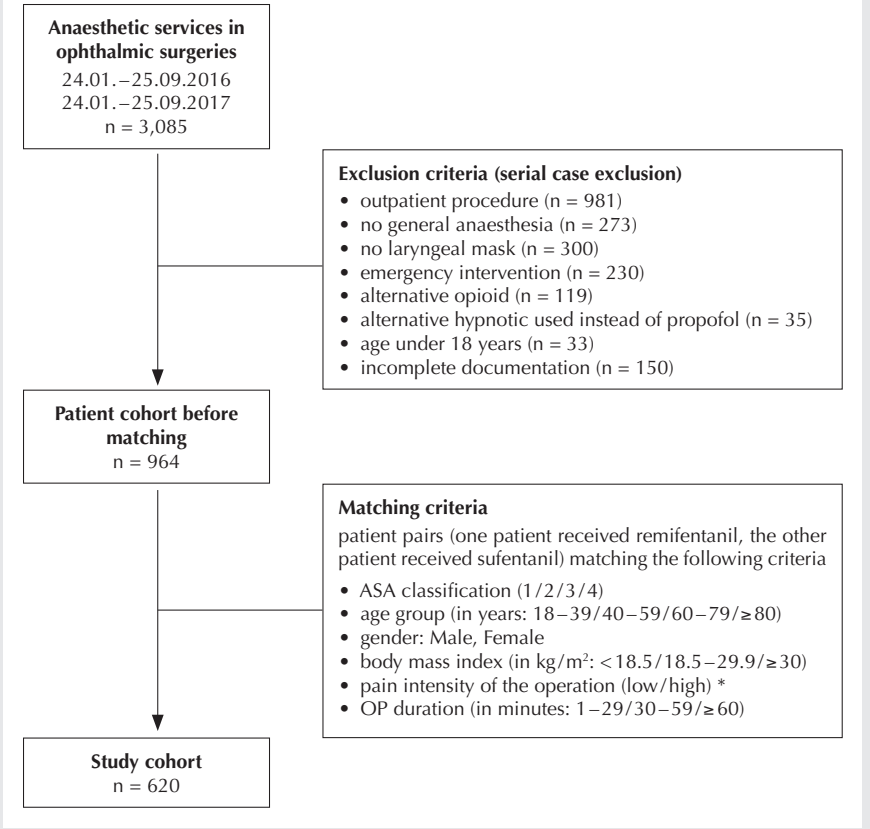
Methodology

The study was approved by the Ethics Committee of the University Witten/Herdecke, the observation period of this retrospective data analysis was the eight-month period between January 24, 2017 to September 25, 2017. Due to this, sufentanil was used for analgesia (sufentanil (S) group) during this time. Patients who had been treated in the corresponding period from the previous year (01/24/2016 – 09/25/2016) were included as the comparison group (remifentanil (R) group). The intraoperative and postoperative course of anaesthesiological treatment up to transfer from the recovery room were evaluated and compared as target parameters. The data was collected by using the digitised anaesthesia protocols. These included, amongst other things, the duration of the general anaesthesia, drug interventions (e. g. for circulatory stabilization or the additional need for analgesics), complications (e. g. shivering, nausea and vomiting, unintentional wakefulness, pain) and the time until the decision was made to transfer the patient onwards from the hospital recovery room.

A total of 3,085 datasets gathered from digitised anaesthesia protocols (Medlinq Softwaresysteme GmbH, Hamburg) were examined according to specific inclusion and exclusion criteria. All patients that received a general anaesthesia for opthalmologic surgery during the observational period were included. After applying defined exclusion criteria (Fig. 1), the patient cohort was comprised of 964 datasets. In order to identify study groups that were as comparable as possible, a matching procedure was then implemented for pairwise assignment into two groups (R and S group). This was based on several assignment criteria, namely: remifentanil or sufentanil for induction and maintenance of perioperative general anaesthesia, age (18–39 years, 40–59 years, 60–79 years, ≥80 years), ASA classification (ASA: American Society of Anesthesiologists; 1, 2, 3, 4), gender (female, male), body mass index (BMI) and surgical pain level (painful, less painful; Fig. 1). Painful surgical interventions were defined as the following: pars plana vitrectomies, enucleations, strabismus surgeries, keratoplasties, lacrimal duct surgeries and other reconstructive interventions.

The following were defined as less painful surgical interventions: cataract surgeries, surgeries to replace an anterior chamber lens, eyelid surgeries, and surgeries for an ectropion or entropion [5]. Using these criteria, 620 data sets (S group: n = 310, R group: n = 310) were identified for statistical analysis (Fig. 1). Furthermore, a subgroup analysis to differentiate between opioid-induced and noradrenaline-induced bradycardia was performed. For this purpose, those patients received an administration of atropine and of a vasopressor were identified and eliminated from the study

Fig. 1



Flow chart of patient selection and matching process.

* The following procedures were defined as painful: pars plana vitrectomy, enucleation, strabismus surgery, keratoplasty, lacrimal duct surgery and other reconstructive procedures. The following were defined as less painful: cataract surgery, surgery to replace an anterior chamber lens, eyelid surgery, and surgery for ectropion or entropion [5].

cohort. The frequency of intraoperative administration of atropine and vasopressors between the two groups was then re-examined.

The functional status of all anaesthetic-relevant organ systems was surveyed and examined as part of the preoperative evaluation of each patient. The risk-stratification method created by Apfel et al. was used to evaluate the risk of postoperative nausea and vomiting (PONV). As part of the data analysis, we subsequently differentiated between patients with an Apfel risk scor of ≤3 (low to medium risk) and 4 (high risk).

General anaesthesia was performed according to our internal hospital standards. In addition to patient monitoring (electrocardio-graphy, oxygen saturation measured by pulse oximetry, non-invasive measurement of arterial blood pressure; Infinity® Delta XL, Dräger Medical, Lübeck), a 18–20 G venous catheter was used to apply general anaesthesia intravenously. After preoxygenation, general anaesthesia was induced and maintained either by intravenous administration of remifentanil (0.2–0.4 µg/kg (ideal body weight) /min, Fresenius Kabi, Bad Homburg vor der Höhe) via a continous administration (Perfusor Space, B. Braun SE, Melsungen) or by intravenous bolus administration of sufentanil (Sufentanil-hameln, hameln pharma GmbH, Hameln) (0.2–0.5 µg/kg ideal body weight).

To induce general anaesthesia, a bolus dose of propofol (Fresenius Kabi) was administered, adapted to age, vital signs and other individual patient factors. A continuous propofol infusion was then continously administered to maintain general anaesthesia. Since the usage of propofol to induce and maintain general anaesthesia was part of the inclusion criteria, cases in which another hypnotic was used for induction or an inhalational anaesthetic was applied were excluded from the data analysis.

The airway was secured during total intravenous general anaesthesia using a laryngeal mask (Aura Once/Aura Gain, Ambu GmbH, Bad Nauheim). Mechanical ventilation was performed using pressure-controlled ventilation (Primus®, Drägerwerk AG & Co. KGaA, Lübeck).

The intraoperative volume requirement was moderated with the administration of a balanced full electrolyte solution (Jonosteril®, Fresenius Kabi). Arterial hypotension was treated with either an noradrenaline infusion (Sanofi-Aventis, Frankfurt am Main) and/or the fractionated administration of a 1:10 diluted cafedrin/theoadrenaline solution (Akrinor®, ratiopharm GmbH, Ulm). Atropine (initially 0.5 mg, B. Braun SE) was applied to treat bradycardia. Other drug interventions, such as the administration of antiemetics, piritramide, non-opioid analgesics, or antihypertensive drugs were also documented. Postoperative monitoring and subsequent therapy took place in a recovery room. All postoperative anaesthetic complications were recorded using a standartised recovery room protocol.

Postoperative shivering, nausea and vomiting, hypothermia, and hypotension requiring treatment were carefully documented. Pain was assessed using an 11-point numerical rating scale (0 = no pain, 10 = severe pain). As soon as the standardised hospital-internal transfer criteria were met, the decision to transfer to a general ward was made. The duration of the general anaesthesia, the operation and the time of the decision to transfer out of the recovery room were documented with a temporal resolution of five minutes.

The digitised anaesthesia protocols (Medlinq Softwaresysteme GmbH, Hamburg) and SPSS (IBM Corp., Armonk, USA) were used for data collection and analysis. The Shapiro-Wilk test was used to test the hypothesis of normal distribution. A p-value greater than the 5 % significance level rejected the null hypothesis that the sample was normally distributed. For normally distributed parametric data, t-tests for independent samples were used, for non-normal distributed continuous variables, the Mann-Whitney U test was used to examine the samples. Categorical data was analysed for differences between the two groups using Pearson's chi-square test. A level of significance was defined by a p-value ≤0.05. Unless otherwise indicated, continuous variables are reported as mean (standard deviation).

Results

With regard to the patient characteristics, comparable study groups were created after pairwise assignment based on the predifined criteria (Tab. 1). Both groups were comparable with regard to the duration of the general anaesthesia (R group: 60.4 minutes, S group: 61.0 minutes, p = 0.525), the complexity of the surgical procedure and the expected pain. With regard to the Apple score, there was a non-significant tendency towards higher scores in the S group (apple score = 4: R group: n = 26 (8.4 %), S group: n = 41 (13.2%), p = 0.052; Tab. 2).

There was a significant difference in the frequency of intraoperative administration of vasopressors (R group: n = 173 (55.8 %), S group: n = 100 (32.3 %), p<0.001). The administration of atropine was documented in the R group in 39 (12.6 %) and in the S group in 21 (6.8 %) of the data sets (p = 0.014). Additionally, more patients in the R group required the administration of atropine and vasopressors during their anaesthesia (R-group: n = 29 (9.4 %), S-group: n = 13 (4.1 %), P = 0.011). After excluding the cases in which atropine and vasopressors were administered at the same time, the frequency of intraoperative administration of atropine was comparable between the two groups (R group: n = 10 (3.6 %), S group: n = 8 (2.7 %), p = 0.550). Interestingly, in the subgroup analysis, more patients in the R group received intraoperative administration of vasopressors than in the S group (R group: n = 144 (51.3 %), S group: n = 87 (29.3 %), p<0.001). In contrast, there was a significant difference in the frequency of intraoperative administration of non-opioid analgesics (R group: n = 33 (10.6 %), S group: n = 51 (16.5 %), p = 0.035). We discovered that there was no difference with regard to the frequency of intraoperative administration of piritramide (R group: n = 9 (2.9 %), S group: n = 7 (2.3 %), p = 0.612; Tab. 2).

In contrast to this, the post-operative administration of piritramide more frequent in the R group than in the S group (R group: n = 50 (16.1 %), S group: n = 39 (9.7 %), p = 0.017). In addition to

Tabelle 1
Patient characteristics (n = 620).

	Remifentanil-group (n = 310)	Sufentanil-group (n = 310)	p
Age (years)	68.7 (13.8)	67.7 (13.7)	0.382
Sex (n) female / male	154/156	154/156	1.000*
ASA 1 (n)	5 (1.6 %)	5 (1.6 %)	1.000*
ASA 2 (n)	171 (55.2 %)	171 (55.2 %)	1.000*
ASA 3 (n)	134 (43.2 %)	134 (43.2 %)	1.000*
Weight (n)	79.5 (16.5)	79.6 (18.3)	0.735
Height)cm)	169 (10.3)	169 (10.2)	0.634
BMI ($kg \cdot m^{-2}$)	27.8 (5.4)	27.9 (5.6)	0.936
Apple-score	1.4 (0.8)	1.5 (0.9)	0.272
Apple-score = 4 (n)	26 (8.4 %)	41 (13.2 %)	0.052

ASA: American Society of Anesthesiology; **BMI:** Body-Mass-Index.
The Apple score is used to assess the risk of postoperative nausea and vomiting (PONV). One point is added to the total for each of the following: female gender, non-smoker, motion sickness or postoperative nausea. Unless otherwise indicated, values are mean (standard deviation).
* Matching criterion.

Tabelle 2
Intraoperative course of treatment (n = 620).

	Remifentanil-group (n = 310)	Sufentanil-group (n = 310)	p
Duration of operation (min)	36.9 (29.0)	37.2 (27.8)	0.522
Time from induction of general anaesthesia to removal of laryngeal mask (min)	60.4 (32.5)	61.0 (30.8)	0.525
Complex / painful procedure (n)	120 (38.7 %)	120 (38.7 %)	1.000*
Intraoperative administration of atropin (n)	39 (12.6%)	21 (6.8%)	0.014
Intraoperative administration of vasopressors (n)	173 (55.8%)	100 (32.3%)	<0.001
Intraoperative administration of both atropin und vasopressors (n)	29 (9.4 %)	13 (4.1 %)	0.011
Intraoperativer administration of non-opioid analgetics (n)	33 (10.6 %)	51 (16.5 %)	0.035
Intraoperative administration of piritramid (n)	9 (2.9%)	7 (2.3%)	0.612

According to Lesin et al. [5] the following surgeries were designated as complex/painful surgeries: vitreous removal surgery, enucleation, strabismus surgery, keratoplasty, lacrimal duct surgery, and other reconstructions. The following were rated as less complex/less painful interventions: cataract surgery, implantation of an anterior chamber lens. Non-opioid analgesics: Nonsteroidal anti-inflammatory drugs. Unless otherwise indicated, values are given as mean (standard deviation).
* Matching criterion.

that, postoperative shivering were also documented more frequently in the R group than in the S group (R group: n = 10 (3.2 %), S group: n = 2, (0.6 %), p = 0.020). The frequency of PONV was comparable between both groups (R group: n = 9 (2.9 %), S group: n = 12 (3.9 %), p = 0.505). Moreover, a higher rate of patients could be transferred without pain (NRS, numerical rating scale = 0) in the S group, than in the R group (NRS = 0, R group: n = 261 (84.2 %) S group: n = 286 (92.3 %), p = 0.002). Nonetheless, there was no difference in the decision to transfer to the general ward (R group: 71.9 minutes, S group: 73.8 minutes, p = 0.539) in the postoperative period (Tab. 3).

Discussion

The primary aim of this retrospective data analysis was to investigate the use of remifentanil and sufentanil during general anaesthesia for short surgical procedures in ophthalmologic surgery. The results show that sufentanil can indeed be used as an alternative to remifentanil. Despite the longer duration of action, neither the duration of the general anaesthesia nor the time until the patient is released for transfer out of the recovery room differ. Additionally, the use of sufentanil seems to be advantageous with regard to the frequency of intraoperative arterial hypotension and bradycardia requiring treatment. Furthermore, more patients are transferred from the recovery room without pain and the incidence of postoperative shivering is lower.

Due to the different pharmacological properties of the aforementioned opioids, cardiocirculatory functions are affected in different ways. These are caused, among other things, by the stimulation of central and peripheral opioid receptors [6]. The negative chronotropic effect of the opioids is oftentimes explained by a stimulation of μ-opioid receptors in the dorsal nucleus of the vagus nerve and by a subsequent direct inhibition of the sinoatrial stimulus transmission [7–9]. In a systematic review of 58 clinical studies by Komatsu et. al. it was shown that the intraoperative use of remifentanil is associated with higher relative risks for arterial hypotension (relative risk: 1.68 (95 % confidence interval: 1.36–2.07)) and bradycardia (relative risk: 1.46 (95 % confidence interval: 1.04–2.05)) compared to other opioids [10].

The same review also observed that vasopressors had to be used more often when using remifentanil (relative risk: 1.40 (95 % confidence interval: 1.13–1.72)) [10]. Since perioperative arterial hypotension has a significant impact on perioperative morbidity [11,12], our study also compared the frequency

Tabelle 3
Postoperative course of treatment (n = 620).

	Remifentanil-group (n = 310)	Sufentanil-group (n = 310)	p
Time until decision to transfer out of recovery room (min)	71.9 (36.4)	73.8 (41.9)	0.539
Postoperative administration of piritramid (n)	50 (16.1 %)	30 (9.7 %)	0.017
Postoperative hypothermia* (n)	0	0	–
Postoperative administration of an antihypertensive drug in the recovery room (n)	18 (5.8%)	29 (9.4 %)	0.095
Postoperatives shivering in recovery room (n)	10 (3.2%)	2 (0.6 %)	0.020
PONV in recovery room (n)	9 (2.9%)	12 (3.9 %)	0.505
Administration of an antiemetic in recovery room (n)	7 (2.3%)	15 (4.8 %)	0.082
Transfer to general ward with NRS = 0	261 (84.2%)	286 (92.3 %)	0.002

* Body temperature < 36.6 °C; **PONV:** Postoperative Nausea and Vomiting; **NRS:** Numerical Rating Scale. Unless otherwise indicated, values are mean (standard deviation).

of bradycardia requiring treatment and arterial hypotension when using remifentanil and sufentanil in ophthalmologic surgery. In the context of our retrospective study, comparable effects of the negative impairment of intraoperative hemodynamics after the administration of remifentanil were likewise observed. The negative chronotropic effects of noradrenaline must also be taken into account with regard to the more frequent administration of atropine in the R group. For this purpose, a subgroup analysis was performed excluding those cases in which atropine and vasopressors were given together. After excluding those cases, the subgroup analysis showed a comparable frequency of intraoperative administration of atropine between the groups. Therefore, the more frequent use of vasopressors can be assumed to be the reason for the more frequent administration of atropine in the R group. However, due to the small number of cases for this, no clear causal connection can be assumed at this point.

After analysing all used data sets (n = 3,085), the average patient age was 68.2 years and 43 % of the study cohort had an ASA physical status of 3. With regard to the average age and the risk profile of the study cohort, as well as the fact that perioperative arterial hypotension is associated with the occurrence of complications such as myocardial infarction, cerebral ischemia and (transient) renal dysfunction [13], avoiding negative cardiocirculatory effects is particularly important. In addition to that, there is a frequent occurrence of bradycardia and arterial hypotension during ophthalmologic surgery due to the oculocardial reflex due to vagal stimulation [14]. Bradycardia requiring treatment has been previously observed with a frequency of up to 65 % in strabismus operations [15]. The proportion of anterior segment surgeries (cataract surgeries: 29 %, vitrectomies: 24 %, surgeries to lower intra ocular pressure: 10 %) predominated in our cohort and the proportion of operations with relevant manipulation of the eyeball was very low (operations of the eye muscles: 3 %). Nevertheless, a difference in the frequency of bradycardia requiring therapy and arterial hypotension could still be determined in the present study.

The results of our analysis are congruent with the previously described dose-dependent effects of remifentanil on the incidence of postoperative shivering [16,17]. A separate meta-analysis based on 18 randomised controlled studies showed that postoperative shivering occurs more frequently after the use of remifentanil compared to other opioids [18]. Postoperative shivering is a relevant problem and should be avoided not only because of patient discomfort, but also because of the resulting increased oxygen demand that it causes.

The average length of time of the patient's stay in the recovery room was comparable between the two groups. After the use of sufentanil, a value of 0 as an NRS was more frequently documented in the examined data sets upon transfer out from the recovery room. This may well be due to sufentanil's longer half-life compared to remifentanil. It is imperative to mention, however, that non-opioid analgesics (either paracetamol or metamizol) were administered during the operative procedure within the S group. This leads us to presume an additive analgesic effect in regards to the higher rate of painlessness at the time of discharge from the recovery room. In contrast to that, piritramide was administered significantly more frequently in the recovery room in the R group, (R group: n = 50 (16.1 %), S group: n = 30 (9.7 %), p = 0.017; Tab. 2). We can therefore assume that the administration of piritramide had a stronger overall effect on postoperative analgesia than the application of a non-opioid during the operation itself.

The underlying pharmacological properties of sufentanil seem to not only have a positive influence on patient's intraoperative haemodynamic stability but also on their postoperative analgesia.

Due to the limited data set of the digitised anaesthesia protocol and the retrospective examination approach, the present study is subject to some limitations however.

The delivery bottleneck for remifentanil resulted in a type of „pseudo-randomisation" of the intraoperative opioid therapy. This is not comparable to a regular randomisation process, but allows for low-distortion group assignment and data analysis with regard to patient selection.

The exact dosage of each opioid, non-opioid analgesic, propofol, or vasopres-

sor could not be accurately examined as the administered dose was not digitally recorded. The same applies to the perioperative vital parameters. Anaesthesiological follow-up observations (e. g. arterial hypotension or bradycardia requiring therapy) on the other hand were specifically recorded, which allow conclusions to be drawn about perioperative organ function. Therefore, a pragmatic evaluation approach requires a corresponding need-based dose adjustment and reaction to vital function disorders according to anaesthesiological specialist standard. In view of the more frequent use of a non-opioid analgesic in the sufentanil group, a randomised controlled trial with a defined dose of a non-opioid analgesic in both groups needs to be carried out to exactly determine the effect on postoperative analgesia when using sufentanil instead of remifentanil during ophthalmologic surgery.

Conclusion

In terms of clinical effectiveness, sufentanil is at the very least a comparable alternative to remifentanil in the context of general anaesthesia in ophthalmologic surgery. We observed that the use of sufentanil required less intraoperative administration of atropine and vasopressors compared to remifentanil. In the S group, a non-opioid analgesic was administered more frequently intraoperatively. By contrast, piritramide was administered more frequently in the R group in the recovery room. Overall, more patients in the S group could be transferred from the recovery room without pain and had a lower frequency of postoperative shivering.

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