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ORIGINAL ARTICLE

Patient-controlled sublingual sufentanil tablet system versus intravenous opioid analgesia for postoperative pain management after lumbar spinal fusion surgery

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Abstract

Purpose This retrospective cohort study investigated the efficacy of a sublingual sufentanil tablet system (SSTS) in comparison to intravenous patient-controlled analgesia (IV-PCA) with piritramide for the management of postoperative pain following lumbar spinal fusion surgery.

Methods This was a retrospective analysis of patients undergoing single- or two-level lumbar spinal fusion surgery and receiving the SSTS or IV-PCA for postoperative pain relief as part of multimodal pain management that included IV paracetamol and oral metamizole. The following variables were collected: postoperative pain intensity and frequency scores using the numerical rating scale (NRS), hospital anxiety and depression scale (HADS), occurrence of nausea, postoperative mobilization, and patient satisfaction (MacNab criteria).

Results Sixty-four patients were included. Those receiving the SSTS ($n=30$) had significantly lower pain intensities on the operative day (NRS: 4.0, CI: 3.6–4.3 vs. 4.5, CI: 4.2–4.9; $p<0.05$) and one day postoperatively (NRS: 3.4, CI: 3.1–3.8 vs. 3.9 CI: 3.6–4.3; $p<0.05$) compared to patients receiving IV-PCA ($n=34$). No differences were observed on postoperative days 2 to 5. SSTS patients experienced more nausea than IV-PCA patients ($p=0.027$). Moreover, SSTS patients had a higher percentage of early mobilization following surgery than IV-PCA patients ($p=0.040$). Regarding patient satisfaction, no significant differences were seen between the groups.

Conclusion The SSTS is a potentially advantageous alternative to opioid IV-PCA for use within a multimodal approach to managing postoperative pain after lumbar fusion surgery. Furthermore, the potentially higher emetic effect of SSTS should be considered, and the patient should be able to perform the application.

Keywords Postoperative pain · Lumbar fusion surgery · Sublingual sufentanil tablet system · Intravenous patient-controlled analgesia · Opioids

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Introduction

Postoperative pain after spinal surgery is still a significant problem that is far from being successfully managed [1, 2]. Patients with suboptimal pain management may develop chronic pain after surgery, less satisfaction, increased length of hospital stay and decreased mobility due to postoperative pain [3]. Early mobilization is a crucial factor in improving postoperative recovery [4]. Therefore, postoperative pain management needs to be optimized without restrictions. Administration of opioids to postoperative patients using intravenous patient-controlled analgesia (IV-PCA) results in lower pain scores and higher patient satisfaction than nurse-administered modalities [5]. Several drawbacks include the requirement of a patent IV line and tethering of the patient to an IV-PCA pump, resulting in the risk of infection, reduced mobility, and analgesic gaps due to IV catheter infiltration or IV tubing obstruction [6].

Moreover, postoperative guidelines recommend oral over intravenous opioids in patients who can use the oral route [7]. Consequently, PCA devices such as the sublingual sufentanil tablet system (SSTS) have been developed. Compared to IV-PCA, the SSTS, due to its noninvasive design, avoids the risk of pump-programming errors and other complications (e.g., infections and analgesic gaps). It also imposes less restriction on postoperative mobility. Therefore, the SSTS provides an effective alternative to opioid-based IV-PCA for managing acute, moderate-to-severe postoperative pain [8].

The current study's objective was to investigate the efficacy and safety of an SSTS compared with an IV-PCA system in the management of postoperative pain in adult patients who had undergone lumbar spinal fusion surgery. Our primary hypothesis was that patients treated with the SSTS would show a better improvement in pain intensity and frequency within the first five days following surgery than would patients treated with IV-PCA. Our secondary hypothesis was that patients treated with the SSTS would have (a) a similar frequency of nausea, (b) earlier mobilization and (c) greater satisfaction than patients treated with IV-PCA.

Methods

This was a monocentric, retrospective, matched (1:1) cohort study designed to investigate the effect of a change in the spine surgery department's practice, i.e., the postoperative administration of an SSTS after single- or two-level spinal fusion surgery. The study was approved by the ethics committee of the University Hospital Jena, Germany (No. 2021–2433-Daten). All methods were carried out according to relevant guidelines and regulations based on the approval. Written informed consent for patient information and images to be published was provided by the patients or a legally authorized representative.

Patients were included if they were scheduled to undergo primary single- or two-level spinal fusion surgery with a posterior approach due to single- or two-level lumbar segment degeneration with associated back pain and radiculopathy. Cases of mental health and physical problems, previous lumbar surgery, multilevel (> 2) lumbar fusion surgery, opioid-tolerant patients (use of > 15 mg oral morphine equivalent per day within the past three months), and alcohol or drug abuse were excluded to prevent falsification through a potentially changed perception of pain or application error in the postoperative PCA. In addition, documented sleep apnea or a need for outpatient oxygen therapy was contraindications for PCA.

Group size was calculated using G*Power Version 3.1 (University of Düsseldorf, Germany) for the main outcome parameter (NRS), except for an effect size of $f = 0.35$ (medium-to-strong effect; $\alpha = 0.05$, $\beta = 0.2$, repeated measures correlation coefficient of 0.85 based on postoperative NRS measurements of a historical cohort) for 6 measurement time points (repeated measures ANOVA), resulting in a total sample size of 60 patients (30 per group).

Two groups were defined by the kind of patient-controlled postoperative analgesia application during the first 48 h after surgery (group SSTS and group IV-PCA).

Based on known factors associated with postoperative pain and the operative course, the groups were matched (1:1) for age, body mass index, HADS, and type of surgery (single- or two-level lumbar fusion surgery) [9].

Treatment with the SSTS was initiated as another option for standard therapy in patients undergoing lumbar fusion surgery from January 2020 to December 2020. The SSTS (Zalviso®, Grünenthal, Aachen, Germany) has a preprogrammed 20-min lockout interval and uses a radiofrequency identification (RFID) thumb tag to personalize the device upon setup of the system, which is completed without a need for programming decisions. The nurse inserts a small cartridge containing 40 sufentanil tablets into the dispenser tip, locked into the controller base, and the system is tethered to the bedside or other secure locations. The controller base has a graphic user interface screen that facilitates patient training by the nurse and displays setup instructions and system data for authorized healthcare professionals. Sublingual sufentanil has a 300 to 400 potency factor and 60% bioavailability compared to IV morphine. One sufentanil tablet contains 15 µg. The synthetic opioid piritramide was used for IV-PCA. Piritramide is a long-lasting opioid with an equianalgesic potential of 0.65–0.75 to standard morphine and is

frequently used to manage postoperative pain [10]. Consequently, the sufentanil dose in the SSTS, which is available every 20 min, reflects an approximately equianalgesic dose to the standard 1 mg piritramide that is on demand every 5 min with typical IV-PCA settings (approximately 3 mg IV-Morphine equivalent every 20 min for both groups).

Based on our standard hospital protocol, IV opioids were allowed as needed for analgesia during surgery. All patients were operated on under general anesthesia. Following surgery, IV morphine, hydromorphone, or fentanyl were administered as required to keep the patient comfortable in the postanesthesia care unit (PACU). Antiemetic prophylaxis and treatment were allowed.

Patients leaving the PACU who did not require further intensive medical care after lumbar fusion surgery were treated with either the SSTS (15 µg sufentanil every 20 min) or IV-PCA (1 mg piritramide every 5 min) in random allocation. The maximum dose was limited to 30 mg piritramide per day. The duration of treatment using postoperative PCA (SSTS or IV-PCA) was 48 h. Thus, the approximately maximum available morphine equivalent dose over 48 h was 140 mg of IV-morphine in the SSTS group and 45 mg of IV-morphine in the IV-PCA group.

Postoperative PCA was part of multimodal pain management that included IV acetaminophen (1 g on demand four times daily) and oral metamizole (1 g three times daily).

Data gathering was performed uniformly by the same person [11] for all groups since the data were gathered as part of standard treatment. Based on the current average hospital stay in this country after a single- or two-level lumbar fusion surgery of 7–8 days (5–7 days in our hospital), retrospective data collection was performed for 5 days postoperatively. The following baseline characteristics were collected: age, sex, body mass index (BMI), and American Society of Anesthesiologists score [7]. To determine the difference in anxiety and depression between the groups, all patients were assessed before surgery using the hospital anxiety and depression scale (HADS). The HADS is an easy-to-use questionnaire with already proven validity and reliability consisting of 14 questions that examine the symptoms of depression with seven questions and the symptoms of anxiety with seven questions [12]. Total scores between 0 and 7 indicate no abnormality; scores of 8 and above indicate anxiety or depression [13].

The primary outcome parameters, pain intensity, and frequency of pain were assessed on an NRS, where 0 = no pain and 10 = worst possible pain and 0 = no pain and 10 = persistent pain, respectively. The daily average NRS score was collected from both groups until the 5th postoperative day. At this, patients were asked about their average pain intensity and pain frequency once a day as part of the daily medical consultation. Secondary outcome parameters included nausea, early mobilization following surgery (no later than the 1st day following surgery), and patient satisfaction. Satisfaction with the treatment was assessed using the MacNab criteria with four levels of categorization: excellent, good, fair, and poor [14].

All outcome parameters were compared between the groups.

Statistical analysis

The statistical evaluation of this work was performed using SPSS Statistics Version 24 software for Macintosh (IBM, Armonk, USA).

The demographic data were assessed using Student's *t* test for independent samples, and the normal distribution of the data was assessed in advance using the Kolmogorov–Smirnov test. Categorical data were evaluated using Pearson's X^2 test, and continuous data were evaluated using Student's *t* test. Given that the primary target values were measured at 6 points in time, the scores were subjected to a two-way ANOVA for repeated measures using post hoc Bonferroni tests. The Greenhouse–Geisser correction was used to assess the sphericity. A double-sided significance check was performed for all tests, and a p value < 0.05 was assumed to indicate statistical significance for all statistical tests.

Results

Baseline demographics

Of the 1115 patients operated on during the study period, 60 patients were matched and analyzed (Fig. 1). Thirty patients received SSTS treatment, and 30 patients received IV-PCA as postoperative analgesia. Patients treated with the SSTS received a mean of 14.35 (CI: 12.3–15.5) tablets of sufentanil 15 µg, and those treated with IV-PCA received a mean of 28.5 mg (CI: 25.25–30 mg) piritramide. Baseline characteristics are shown in Table 1. There were no age or BMI limits on patient enrollment, resulting in an age range of 34 to 82 years and a BMI range of 19 to 40 kg/m2 [15]. There were no statistically significant differences between treatment groups for any demographic or baseline characteristics.

Primary outcome parameters

Regarding pain intensity scores, there was a significant reduction in both groups over the whole observation period ($p < 0.001$).

In the post hoc analysis, patients receiving SSTS treatment had significantly lower pain intensity scores on the day of surgery (NRS: 4.0, CI: 3.6–4.3 vs. 4.7, CI: 4.4–5.0;

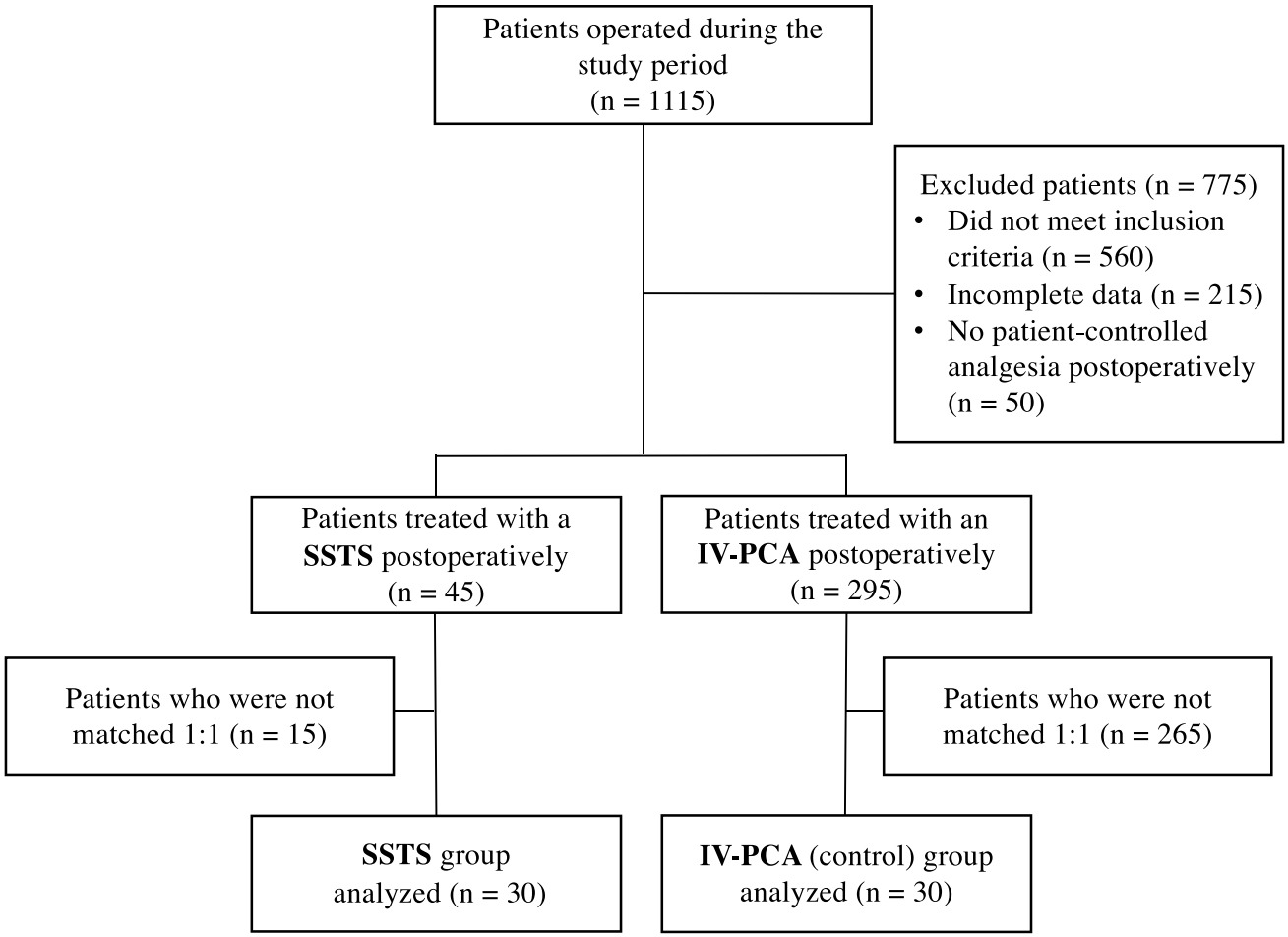

Fig. 1 Flow chart diagram. SSTS—sublingual sufentanil tablet system, IV-PCA—intravenous patient-controlled analgesia

$p = 0.016$) and one day after surgery (NRS: 3.4, CI: 3.1–3.8 vs. 4.1 CI: 3.8–4.4; $p = 0.027$) compared to those of patients receiving IV-PCA. On days 2 to 5, there were no differences in pain intensity scores (Table 2, Fig. 2).

Regarding pain frequency, there was a significant reduction in both groups over the whole observation period ($p < 0.001$). No difference was observed between groups in NRS scores (Table 2, Fig. 3).

Secondary outcome parameters

The results of the secondary outcome parameters are listed in Table 3.

Nausea

Patients treated with the SSTS experienced more nausea than patients treated with IV-PCA (47 vs. 20%, $p = 0.024$).

Postoperative mobilization

Patients treated with the SSTS had a higher percentage of early mobilization following surgery than patients treated with IV-PCA (80 vs. 57%, $p = 0.043$).

Patient satisfaction

Both groups mainly reported good and excellent results (70% of IV-PCA patients and 83% of SSTS patients) concerning postoperative pain management. No significant differences were noted between the groups ($p = 0.179$).

Discussion

To the best of our knowledge, this is the first investigation of the SSTS versus IV-PCA for patients undergoing lumbar spinal fusion surgery. Regarding our primary hypothesis, a more sufficient pain reduction following surgery was

Table 1 Baseline demographic and clinical characteristics

Variable	IV-PCA ($n=30$)	SSTS ($n=30$)	Total ($n=60$)	p value
Age, years (SD)	64.9 ± 11.8	60.3 ± 9.3	62.6 ± 10.8	0.090
Sex, n (%)				0.302
Male	15 (50)	12 (40)	27 (45)	
Female	15 (50)	18 (60)	33 (55)	
BMI, kg/m^2 (SD)	27.4 ± 4.4	28 ± 4.6	27.7 ± 4.5	0.622
ASA score (I/II/III)	4/18/8	4/19/7	8/37/15	0.960
Preoperative pain medication, n (%)				
Opioid	7 (23)	8 (27)	15 (25)	0.500
Nonopioid	26 (87)	23 (77)	49 (82)	0.253
Smoking-Status, n (%)				0.500
Smoker	12 (40)	11 (37)	23 (38)	
Non-smoker	18 (60)	19 (63)	37 (62)	
MPSS score (I/II/III)	17/13/0	16/14/0	33/27/0	0.524
HADS anxiety, n (%)				0.097
Anxious	1 (3)	5 (17)	6 (10)	
Non-anxious	29 (97)	25 (83)	54 (90)	
HADS depression, n (%)				0.212
Depressed	2 (7)	5 (17)	7 (12)	
Non-depressed	28 (93)	25 (83)	53 (88)	
Fusion-segments, n (%)				0.652
Single-level fusion	19 (63)	18 (60)	37 (62)	
Two-level fusion	11 (37)	12 (40)	25 (42)	

Analyzed with Student's t test for continuous variables and X^2 for categorical variables. *ASA* American Society of Anesthesiologists; *BMI* body mass index; *HADS* Hospital Anxiety and Depression Scale; IV PCA-IV patient-controlled analgesia; *MPSS* Mainz Pain Staging System; *SD* single standard deviation; *SSTS* sublingual sufentanil tablet system

Table 2 Comparison of Numeric Pain Rating Scale for pain intensity and pain frequency between the groups over time

Time n	Pain Intensity (NRS)		Pain Frequency (NRS)	
	IV-PCA (30)	SSTS (30)	IV-PCA (30)	SSTS (30)
	Mean (CI)	Mean (CI)	Mean (CI)	Mean (CI)
Day 0*	4.7 (4.4–5.0)	4.0 (3.6–4.3)	5.9 (5.4–6.4)	6.2 (5.6–6.7)
Day 1*	4.1 (3.8–4.4)	3.4 (3.1–3.8)	5.1 (4.7–5.5)	5.0 (4.6–5.4)
Day 2	3.6 (3.3–3.8)	3.5 (3.2–3.7)	4.7 (4.2–5.0)	4.7 (4.2–5.1)
Day 3	3.1 (2.9–3.4)	3.4 (3.2–3.7)	4.1 (3.7–4.4)	4.0 (3.6–4.4)
Day 4	2.8 (2.5–3.1)	3.1 (2.8–3.4)	3.6 (3.2–3.9)	3.7 (3.3–4.1)
Day 5	2.5 (2.2–2.8)	2.8 (2.5–3.1)	3.0 (2.7–3.3)	3.1 (2.8–3.4)
$p_{\textbf{treatment}}$	0.481		0.739	
$p_{\textbf{time}}$	< 0.001		< 0.001	
$p_{\textbf{treatment x time}}$	0.001		0.703	

p values from 2-sided 2-way ANOVA for repeated measures; * indicates a significant difference in post hoc tests between the means of pain intensity of the 2 groups at the specified time ($p<0.05$); *CI* confidence interval; *NRS* Numeric Pain Rating Scale; *IV-PCA* intravenous patient-controlled analgesia; *SSTS* sublingual sufentanil tablet system

achieved in the SSTS group, predominantly within the first 48 h. There was no difference in pain frequency between the groups. Furthermore, SSTS treatment led to (a) earlier mobilization after surgery but caused (b) more nausea than IV-PCA did. In the end, both PCA systems achieved comparable (c) patient satisfaction.

Compared to our postoperative pain therapy concept, the international guidelines recommend a multimodal therapy

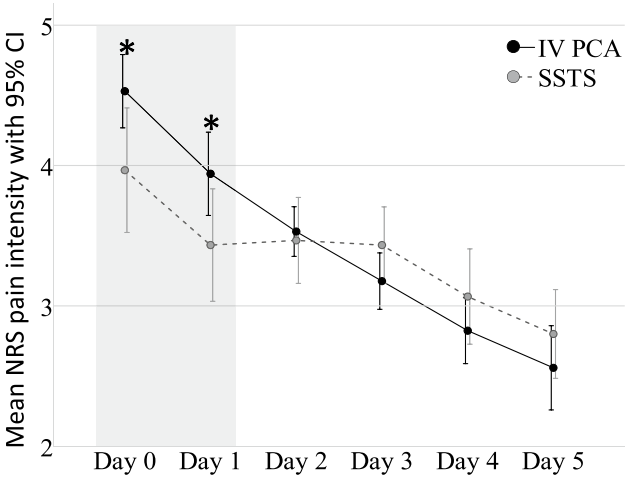

Fig. 2 NRS pain intensity presented as means. Gray background represents the period of treatment with patient-controlled analgesia. Whiskers represent the 95% confidence interval [21]. *Significant differences occurred between treatment groups on day 0 ($p=0.016$) and day 1 ($p=0.027$). IV-PCA—IV patient-controlled analgesia; SSTS—sublingual sufentanil tablet system

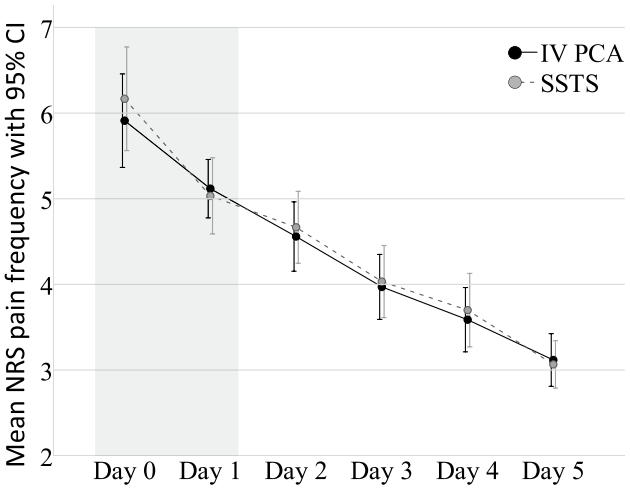

Fig. 3 NRS pain frequency presented as means. Gray background represents the period of treatment with patient-controlled analgesia. Whiskers represent the 95% confidence interval [21]. No significant differences occurred between treatment groups over the observation period. IV PCA—IV patient-controlled analgesia; SSTS—sufentanil sublingual tablet system

approach [7]. The aim is to reduce pain as quickly and effectively as possible to achieve faster mobilization and patient satisfaction. However, the literature data suggest that up to 85% of patients with acute pain after major surgical procedures experience moderate, severe, or extreme pain [2]. Therefore, assuming a pain intensity level of NRS 4 as the optimal limit value for mild to advanced pain [8], the results of the SSTS group show sufficient pain reduction after lumbar fusion surgery. By contrast, in the IV-PCA group, the mean NRS after 24 h was ≥ 4 and reached < 4 after 48 h of treatment only. Thus, these results represent an advantage of the SSTS over IV-PCA. Psychosocial factors such as depression or anxiety influence subjective pain perception and should be considered in studies examining the effectiveness of analgesic systems. However, based on the matched design of the present study, there was no significant difference in HADS scores between the groups.

Table 3 Comparison of secondary outcome parameters between the groups

Variable	IV-PCA ($n=30$)	SSTS ($n=30$)	p value
Nausea, *n* (%)	6 (20)	14 (47)	0.024*
Early mobilization, *n* (%)	17 (57)	24 (80)	0.043*
Patient satisfaction, n (%)			0.179
Poor	0	0	
Fair	9 (30)	5 (17)	
Good	18 (60)	17 (57)	
Excellent	3 (10)	8 (26)	

Analyzed with Student's *t* test for continuous variables and Fisher's exact test for categorical variables; *indicates significant *p* values (< 0.05); *IV-PCA* intravenous patient-controlled analgesia; *SSTS* sublingual sufentanil tablet system

In recent years, "fast track" surgery has been developed in many surgical specialties to decrease perioperative morbidity, decrease hospital length of stay and save costs. According to this approach, physiotherapy and mobilization start on the first postoperative day in our center. In the presented study, a more significant proportion of patients treated with the SSTS achieved adequate mobilization. Possible reasons for the better mobilization in the SSTS group could be the more efficient pain reduction and the increased independence of the patient since an IV pump could be dispensed with here. However, it should be noted that the comparability with other studies that have tested the possible advantages of an SSTS over other PCA procedures is very limited concerning mobilization since different mobilization standards are used due to the different types of surgery.

Nausea is the most frequently described side effect concerning opiate use in the postoperative setting [16]. However, based on our results, there was a higher incidence of nausea in the SSTS group. The more frequent occurrence of nausea appears to be an effect of the sublingual administration of sufentanil, which is also described in the literature [17, 18]. In our clinical practice, antiemetics were only administered when nausea occurred. Thus, a reduction in this side effect can be achieved by implementing antiemetic prophylaxis and has already been described in comparative studies [17–19].

Patient satisfaction was high among patients treated with the SSTS and IV-PCA. However, the superiority in

pain reduction within the first 48 h and early mobilization in the SSTS group was not reflected in significantly higher patient satisfaction. In contrast to our results, a systemic literature review by Giacarri et al. regarding postoperative analgesia in patients undergoing major surgical procedures described a higher level of satisfaction of patients treated with SSTSs compared to IV-PCA systems [8]. A possible reason for the difference in findings could be the higher rate of nausea in the SSTS group in our study. Thus, the satisfaction in the SSTS group could be further improved with the administration of antiemetic prophylaxis.

The present study is not without limitations. First, based on the retrospective study design, we were unable to implement a placebo group and randomize patients. However, the effectiveness of SSTSs compared to placebo has already been reported in other studies [17, 19]. Second, the preoperative NRS value could not be determined. Preoperative pain condition could have an influence on the postoperative pain course and thus influence the presented results. However, the aim of the present study was to compare the postoperative acute wound pain of two analgesic systems, so that the influencing effect of the preoperative pain intensity cannot be excluded but should be marginal. Third, a cost calculation was not performed. Since the SSTS was only used temporarily for testing in our clinic as another option for standard therapy in patients undergoing lumbar fusion surgery, an exact cost comparison cannot be made. However, van Veen et al. reported significantly higher costs of the SSTS (approximately US$125 plus approximately US$1,750 for the device) compared to that of an opioid tablet ($0.75 per tablet) [20]. Fourth, we cannot draw any conclusion regarding the effect on length of hospital stay because the healthcare system in our country required a minimal hospital stay of 5 days for full reimbursement in the cases researched. Finally, we must admit that given the frequent occurrence of nausea, the lack of superiority in patient satisfaction, and higher costs associated with the SSTS, SSTS use was discontinued in our hospital despite its advantages.

In conclusion, the SSTS provides an effective and potentially advantageous alternative to IV-PCA with opioids for use as part of a multimodal approach to managing postoperative pain after lumbar fusion surgery. Given the potentially higher emetic effect of SSTS, the implementation of antiemetic prophylaxis should be considered. Future studies should ideally focus on evaluating the cost-effectiveness of the SSTS relative to opioid-based IV-PCA.

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Declarations

Conflict of interests The authors declare that there is no conflict of interest.

Ethical approval The present study was performed in accordance with the Ethical Principles for Medical Research Involving Human Subjects, outlined in the World Medical Association's Declaration of Helsinki revised in 2013. The approval of the Ethics Committee of the University Hospital Jena was granted via approval reference No. 2021–2433-Daten.

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