



Universiteit
Leiden

The Netherlands

Improving outcomes of pancreatic surgery

Groen, J.V.

Citation

Groen, J. V. (2023, June 29). *Improving outcomes of pancreatic surgery*.

Retrieved from <https://hdl.handle.net/1887/3628261>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3628261>

Note: To cite this publication please use the final published version (if applicable).

CHAPTER 14

Sublingual sufentanil versus standard-of-care (patient controlled analgesia with epidural ropivacaine/ sufentanil or intravenous morphine) for postoperative pain following pancreatoduodenectomy: a randomized trial

J.V. Groen, S.C. Boon, M.W. Minderhoud, B.A. Bonsing, C.H. Martini, H. Putter, A.L. Vahrmeijer, M. van Velzen, J. Vuijk, J.S.D. Mieog, A. Dahan

ABSTRACT

Background: The optimal treatment strategy for postoperative pain following pancreatoduodenectomy remains unknown. The aim of this study was to investigate whether sublingual sufentanil tablets (SST) is a non-inferior analgesic compared to our standard-of-care (patient controlled epidural analgesia [PCEA] or PCA morphine) in the treatment of pain following pancreatoduodenectomy.

Methods: This was a pragmatic, strategy, open-label, non-inferiority, parallel group, randomized (1:1) trial. The primary outcome was overall mean pain score (Numerical Rating Scale: 0-10) on postoperative day 1 to 3 combined. The non-inferiority margin was -1.5, since this difference was considered clinically relevant.

Results: Between October 2018 and July 2021, 190 patients were assessed for eligibility and 36 patients were included in the final analysis: 17 patients were randomized to SST and 19 patients to standard-of-care. Early treatment failure in the SST group occurred in 2 patients (12%) due to inability to operate the SST system and in 2 patients (12%) due to severe nausea despite antiemetics. Early treatment failure in the standard-of-care group occurred in 2 patients (11%) due to preoperative PCEA placement failure and in 1 patient (5%) due to hemodynamic instability caused by PCEA. The mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI -0.72 – 0.52) and therefore the non-inferiority of SST compared to standard-of-care was demonstrated. The mean pain score, number of patients reporting unacceptable pain (pain score >4), Overall Benefit of Analgesia Score, and patient satisfaction per postoperative day, perioperative hemodynamics and postoperative outcomes did not differ significantly between groups.

Conclusion: This first randomized study investigating the use of SST in 36 patients following pancreatoduodenectomy showed that SST is non-inferior compared to our standard-of-care in the treatment of pain on postoperative day 1 to 3. Future research is needed to confirm that these findings are applicable to other settings.

INTRODUCTION

Epidural analgesia (EA) is the gold standard for perioperative analgesic management in most major open abdominal surgeries.¹ Recently, we performed a systematic review of the various analgesic treatment strategies after pancreatoduodenectomy in our own center² and in the current literature³. The reported use of EA in patients undergoing pancreatoduodenectomy varies from 9% to 85%.³ The potential benefits of EA are lower pain scores in the first postoperative days and fewer postoperative (pulmonary) complications.^{2, 3} The disadvantages of EA are the invasive nature, early failure rates, hemodynamic instability and notorious, albeit uncommon, complications (eg spinal hematoma and epidural infections).²⁻⁶ The most used alternative for EA is intravenous (iv) morphine.^{1-3, 7} The advantages of iv morphine are that most patients are eligible (eg patients with coagulation disorders or spine anatomy alterations) and it is a less invasive method compared to EA. The disadvantages of iv morphine are the suboptimal pain control and a higher consumption of opioids compared to EA with associated side effects.^{2, 3, 8} The anesthesia and surgical teams in our center recently concluded that our standard-of-care treatment strategies following pancreatoduodenectomy were currently not comprehensive, and hence alternatives are explored.

Among the available alternatives for EA and iv morphine is sublingual sufentanil tablets (SST). SST consists of a patient-controlled non-invasive hand-held device that delivers 15 µg sufentanil micro-tablets with a 20 min lockout time. The advantages of SST are: (1) it is a non-invasive method of analgesia; (2) sufentanil is highly lipophilic and is rapidly absorbed after which it passes the blood-brain barrier within minutes ($t_{1/2 k_{eo}}$ or blood-effect-site equilibration half-life about 6 min); (3) Due to the sublingual formulation peak concentrations are relatively low and consequently, concentration dependent side effects -such as acute respiratory depression- do not occur; and (4) Due to its rapid onset of action, there is little delay in pain relief between the moment of administration and the onset of pain reduction. The disadvantages of SST are the inability to set a background infusion and ability to operate the SST system.⁹ SST showed adequate pain control in earlier randomized studies in abdominal and orthopedic surgery and in a recent retrospective cohort analysis of nearly 300 of our patients after laparoscopic abdominal and orthopedic surgery, we observed low average pain scores (75% of patients with a pain score ≤ 4 on the first postoperative day).¹⁰⁻¹³ Nevertheless, no studies are available which investigated the use of SST in patients undergoing pancreatoduodenectomy.³

The PROSPECT group states that there might be shortcomings when using general analgesic guidelines for choosing the optimal treatment strategy for postoperative pain following a specific surgical procedure.¹⁴ Therefore, this study compares treatment strategies (rather than medication *per se*) and investigates whether SST is a non-inferior

analgesic compared to our standard-of-care strategy (patient controlled analgesia with EA (PCEA) or patient controlled analgesia with iv morphine (PCA morphine)) in the treatment of postoperative pain following pancreatoduodenectomy.

METHODS

Study design and participants

This was a pragmatic, strategy, open-label, non-inferiority, parallel group, randomized trial in a single center according to the CONSORT guidelines.¹⁵ Inclusion criteria were: American Society of Anesthesiologists score 1 to 3; age ≥ 18 years; elective pancreatoduodenectomy (eg open or robot-assisted procedures). Exclusion criteria were: unable to give written informed consent; contra-indication for SST, PCEA or PCA morphine such as allergies or coagulopathies; presumed inability to operate the SST or standard-of-care; opioid use >12 weeks; complex chronic pain disorders; liver failure (Child Pugh class C). Patients received information regarding the study preoperatively at the outpatient clinic or by phone. All included patients signed an informed consent form prior to study-related activities. The original protocol and two amendments (also including robot-assisted procedures and changing the non-inferiority margin) were approved by the Medical Ethical Committee (P18.061) and the Board of Directors of the Leiden University Medical Center. A Data Monitoring Committee was deemed not necessary. The full study protocol was registered at Netherlands Trial Register (NTR7318; www.trialregister.nl) and is available at request.

Randomization and blinding

Patients were randomized (1:1) within the electronic data capture system CASTOR (www.castoredc.com), stratified by procedure type (open or robot-assisted; to ensure equal distribution in both groups of the study) and with varying block sizes (4, 6, 8). Patients randomized to standard-of-care received PCEA or PCA morphine at discretion of the attending anesthesiologist and was mainly dependent on procedural type: PCEA for open, PCA morphine for robot-assisted procedures. Blinding of study participants and investigators was not done since the treatment strategies were evidently different.

Treatment strategies

SST

Patients randomized to SST received iv sufentanil during surgery and long-acting iv opioids, such as morphine, 45-60 min prior to the end of surgery. In the Post Anesthesia Care Unit (PACU), pain scores were assessed using an 11-point Numerical Rating Scale (NRS; from 0, no pain to 10, most extreme pain imaginable). If needed, patients received 2 mg iv morphine bolus doses to reduce pain scores ≤ 4 , only when pain scores were ≤ 4

and patients were able to operate the SST system, the SST system was started. The SST system consists of a patient controlled non-invasive hand-held device that delivers 15 µg sufentanil micro-tablets for sublingual use at a 20 min interval (lockout). An unique adhesive tag on the patients' thumb can activate the device by radio-frequency. The device is fixed to the patients' bed and contains a cartridge with 40 micro-tablets. The Acute Pain Service can manage the SST system with a specific card (remove/replace cartridges, link the thumb tag to the device etc).

Standard-of-care

Patients in the PCEA group received patient controlled epidural analgesia. The PCEA catheter was inserted preoperatively at level Th6-Th10. Following induction of anesthesia, a 6-12 mL bolus containing ropivacaine 0.75% was administered epidurally, followed by a continuous infusion of a mixture of ropivacaine 0.2% and sufentanil 0.75 µg/mL, at 6-10 mL/h; with the possibility of giving an additional bolus. During surgery, patients received additional iv sufentanil if deemed necessary by the attending anesthesiologist. At the PACU, pain scores were assessed at regular intervals and the level of the epidural blockade was tested with an ice pack. In case of pain score >4, 2 mL boluses at a 20 min interval (lockout) from the PCEA system were permitted. In case of failure to place the epidural catheter preoperatively, patients received PCA morphine according to the PCA morphine protocol.

Patients with PCA morphine received patient controlled iv morphine. These patients received 0.1-0.2 mg/kg iv morphine 45-60 min prior to the end of surgery. During surgery, patients received iv sufentanil if deemed necessary by the attending anesthesiologist. At the PACU, pain scores were assessed at regular intervals. If needed, initially, patients received 2 mg iv morphine bolus doses to reduce pain scores ≤4, thereafter the PCA morphine device was started. A background infusion of 0.5 mg morphine per h was administered. Patient could additionally administer a 1 mg bolus at a 5 min intervals (lockout) with a maximum dosage of 28 mg per 4 hours.

Perioperative care

The full study protocol describes the pre, peri and postoperative care in detail and is available at request. All patients received paracetamol 1000 mg 4 times daily and if needed metamizole 1000 mg 3 times daily. In case of insufficient pain treatment (persistent pain scores >4) during the course of treatment, patients could receive rescue pain medication at discretion of the attending anesthesiologist, ie such as conversion to another of the mentioned techniques. If this did not help, iv ketamine could be added (up to 10 mg/h). On postoperative day 3, both the SST system and the standard-of-care were terminated and replaced by paracetamol and oral or subcutaneous (sc) opioids, although both the SST system and the standard-of-care could be prolonged until maximum postoperative day 6 at the discretion of the attending anesthesiologist.

Outcomes and comparisons

There was a single primary outcome, which was the overall mean pain score on postoperative day 1 to 3 combined. The non-inferiority margin was set at -1.5, since a difference greater than -1.5 points was considered to be clinically relevant.¹⁶ Secondary outcomes included mean pain score and patients reporting unacceptable pain per postoperative day, Overall Benefit of Analgesia Score (OBAS)¹⁷ and patient satisfaction score on postoperative day 1 to 3 combined and per postoperative day. Additional secondary outcomes were early treatment failure, perioperative hemodynamics (occurrence of hypotension, use and dosage of vasopressors, postoperative fluid balances) and several additional postoperative outcomes (complications related to analgesia, day of resumption of oral diet intake and day of urinary catheter removal, Clavien-Dindo classification¹⁸, mortality within 30 days, length of hospital stay, readmission).

Outcomes were compared by intention-to-treat analysis (SST *versus* standard-of-care). Predefined subgroup analyses of pain scores were performed by intended procedure type (open and robot-assisted procedure) and protocol version (original and amended protocol). To investigate if older patients had the ability to operate the SST system and achieve adequate pain control, post-hoc subgroup analyses of pain scores were performed by age subgroups of ≤ 65 and > 65 years.

Data collection and definitions

Pain scores were assessed on a 11-point NRS ranging from 0 (no pain) to 10 (most extreme pain imaginable). Pain scores were assessed by the Acute Pain Service (a dedicated and specialized team of nurses and anesthesiologists who visit the patient twice daily and who are responsible for [early] postoperative pain treatment) or nursing staff at least 3 times daily according to local and national protocol.^{19, 20} Several training sessions were organized before and during the trial to ensure standardized assessment of pain scores. The OBAS was measured by the Acute Pain Service on the morning on postoperative day 1 to 3. The OBAS is a composite score of pain scores, side-effects, and patient satisfaction, ranging from 0 to 28, in which a lower score is superior to higher scores.¹⁷ Patient satisfaction scores were recorded by the patients themselves at the end of each hospital day (11-point NRS ranging from 0 [not satisfied at all] to 10 [fully satisfied]). Additional data were collected from the electronic medical records. The day of surgery was considered as postoperative day 0. Perioperative hypotension was defined as a mean arterial pressure < 55 mmHg. Unacceptable pain was defined as a reported pain score > 4 . Early treatment failure was defined as ending the use of the SST system or termination of standard-of-care before postoperative day 3 due to problems, such as preoperative placement failure, inadequate pain control, hemodynamic instability, or side effects impeding further treatment. The Clavien-Dindo classification was used to score overall postoperative complications.¹⁸

Sample size and statistical analysis

Based on a non-inferiority margin of -1.5 for the primary outcome (overall mean pain score for postoperative day 1 to 3 combined), 36 patients were required to be 90% certain that the lower limit of the 95% confidence interval was above the non-inferiority limit (PASS Software version 15.0.4). The primary outcome was tested at the p -value <0.05 level for significance. Mean differences were reported with 95% confidence intervals. In case the confidence interval included the inferiority limit, non-inferiority was considered demonstrated. Further analysis compared groups using independent samples t -test or Mann-Whitney test, depending on their distribution, for continuous variables. Chi-square test and Fisher's exact tests were used for categorical variables. Statistical analyses were performed using the SPSS statistical software package version 26.

RESULTS

Baseline characteristics

Between October 2018 and July 2021, 190 patients were assessed for eligibility of which 38 patients were included (Figure 1). The main reasons for exclusion were temporary stop of study activities in our institution during the peak of the COVID pandemic ($n = 40$) and logistics ($n = 38$). Randomization allocated 19 patients in the SST group and 19 patients in the standard-of-care group. Two patients in the SST group were excluded (exclusion criterium found after randomization [$n = 1$] and no resection being performed [$n = 1$]) and therefore 36 patients were included in the final analyses.

Baseline characteristics did not differ between the two groups (Table 1). In the SST group, 10 patients (59%) underwent an open procedure, 5 patients (30%) underwent a robot-assisted procedure and 2 (12%) underwent a robot-assisted procedure converted to an open procedure, compared to 11 (58%), 7 (37%) and 1 patients (5%) in the standard-of-care group, respectively ($p = 0.739$).

In the SST group, early treatment failure occurred in 2 patients (12%) due to the inability to operate the SST system and in 2 other patients (12%) due to severe nausea despite antiemetic treatment (Figure 2). In the standard-of-care group, 10 patients were intended for PCEA and 9 patients were intended for PCA morphine. Early treatment failure occurred in 2 patients (11%) due to preoperative placement failure of PCEA and in 1 patient (5%) due to hemodynamic instability caused by the PCEA. The rate of early treatment failure did not differ between groups ($p = 0.558$).

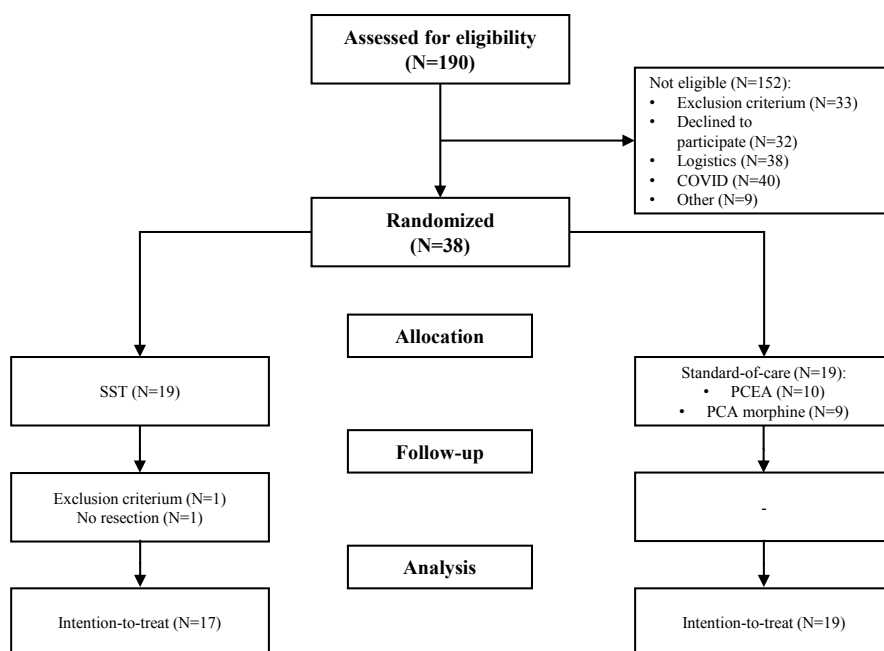


Figure 1. Flow chart of inclusion

Primary outcome

The mean (SD) pain score on postoperative day 1 to 3 was 2.24 (1.00) in the SST group and 2.24 (0.77) in the standard-of-care group. The mean difference was -0.10 (95% CI -0.72 – 0.52) (Table 2). The lower limit of the 95% CI was higher than the predefined limit for non-inferiority (-1.5), and therefore the non-inferiority of SST compared to standard-of-care was demonstrated.

Secondary outcomes

Pain scores

The mean pain score and patients reporting unacceptable pain (pain score >4) per postoperative day did not differ between groups (Table 2; Figure 3). In both groups an increase was observed of patients reporting unacceptable pain on postoperative day 3 compared to day 2.

Overall Benefit of Analgesia Scores (OBAS)

The median (IQR) OBAS on postoperative day 1 to 3 was 7 (3-10) in the SST group and 3 (3-6) in the standard-of-care group ($p = 0.126$) (Table 2). Also, the median (IQR) OBAS per postoperative day did not differ between groups.

Table 1. Baseline characteristics

		Type of analgesia		P
		SST (N=17)	Standard-of-care (N=19)	
		N (%)	N (%)	
Total		17 (47.2)	19 (52.8)	-
Sex	Male	8 (47.1)	14 (73.7)	0.102
	Female	9 (52.9)	5 (26.3)	
Age, median (IQR)		68 (59-74)	63 (57-77)	0.612
BMI, median (IQR)		25.7 (23.3-28.5)	27.7 (23.6-28.4)	0.601
Preoperative acetaminophen use		7 (41.2)	10 (52.6)	0.492
Preoperative NSAID use		0	0	-
Preoperative opioid use		0	2 (10.5)	0.487
ASA-score	I-II	11 (64.7)	14 (73.7)	0.559
	III-IV	6 (35.3)	5 (26.3)	
Type of procedure	Open	10 (58.8)	11 (57.9)	0.739
	Robot-assisted	5 (29.4)	7 (36.8)	
	Conversion to open	2 (11.8)	1 (5.3)	
Type of incision	Midline	12 (70.6)	12 (63.2)	0.732
	Minimally invasive	5 (29.4)	7 (36.8)	
Type of analgesia	PCEA	-	10 (52.6)	-
	PCA morphine	-	9 (47.4)	
Type of resection	PPPD	10 (58.8)	12 (63.2)	0.790
	Classic Whipple	7 (41.2)	7 (36.8)	

SST, sublingual sufentanil tablets; IQR, interquartile range; BMI, Body Mass Index; NSAID, non-steroidal anti-inflammatory drugs; ASA, American Society of Anesthesiologists; PCEA, patient controlled epidural analgesia; PCA morphine, patient controlled analgesia with morphine; PPPD, pylorus-preserving pancreaticoduodenectomy

Patient satisfaction scores

The median (IQR) patient satisfaction score on postoperative day 1 to 3 was 7 (5-9) in the SST group and 8 (7-9) in the standard-of-care group ($p = 0.337$) (Table 2). Median (IQR) patient satisfaction scores per postoperative day did not differ between groups.

Perioperative hemodynamics

Perioperative characteristics did not differ between groups (Table 3). The use and total dosage of vasopressors did not differ between groups. In the SST group, 7 patients (41%) experienced perioperative hypotension compared to 5 patients (26%) in the standard-of-care group ($P = 0.345$). Fluid balances on postoperative day 0 to 5 did not differ between groups.

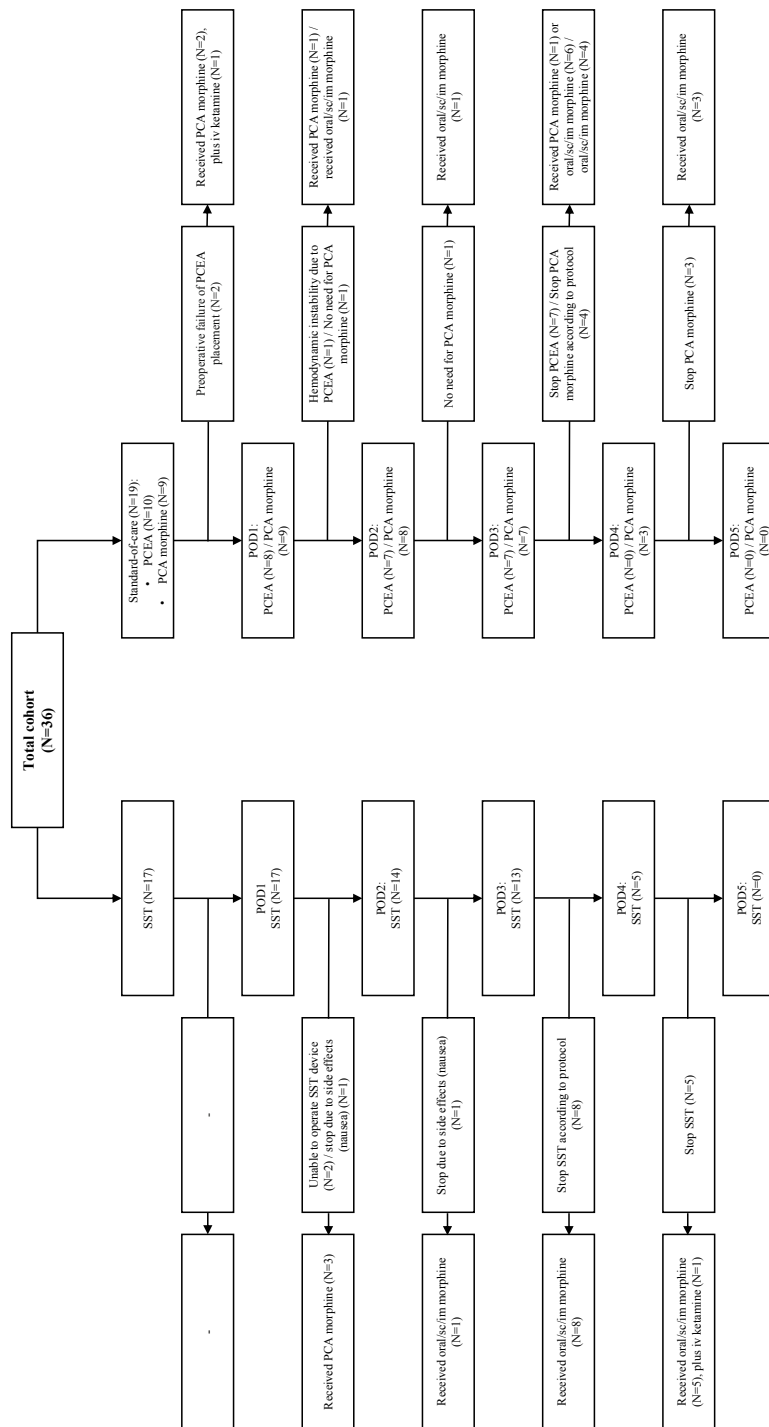


Figure 2. Flow chart of the use of SST and standard-of-care per postoperative day

Table 2. Mean difference in pain scores, Overall Benefit of Analgesia Score (OBAS) and patient satisfaction scores per postoperative day

	Type of analgesia		P
	SST (N=17)	Standard-of-care (N=19)	
Mean differences (95% CI)			
Pain score POD 1 to 3	-0.10 (-0.72 – 0.52)		0.738
Pain score POD 0	-0.03 (-1.42 – 1.37)		0.969
Pain score POD 1	0.17 (-0.60 – 0.94)		0.658
Pain score POD 2	0.17 (-0.70 – 1.04)		0.688
Pain score POD 3	-0.50 (-1.44 – 0.45)		0.293
Pain score POD 4	-0.24 (-1.12 – 0.64)		0.585
Pain score POD 5	-0.51 (-1.52 – 0.50)		0.309
	Median (IQR)	Median (IQR)	P
OBAS POD 1 to 3	7 (3-10)	3 (3-6)	0.126
OBAS POD 1	8 (4-9)	3 (2-6)	0.144
OBAS POD 2	5 (1-11)	4 (2-6)	0.762
OBAS POD 3	5 (2-8)	3 (2-5)	0.140
Patient satisfaction POD 1 to 3	7 (5-9)	8 (7-9)	0.337
Patient satisfaction POD 1	6 (1-9)	9 (8-10)	0.105
Patient satisfaction POD 2	8 (5-8)	8 (8-10)	0.050
Patient satisfaction POD 3	8 (6-9)	7 (3-9)	0.609

SST, sublingual sufentanil tablets; CI, confidence interval; POD, postoperative day; OBAS, Overall Benefit of Analgesia Score, IQR, interquartile range;

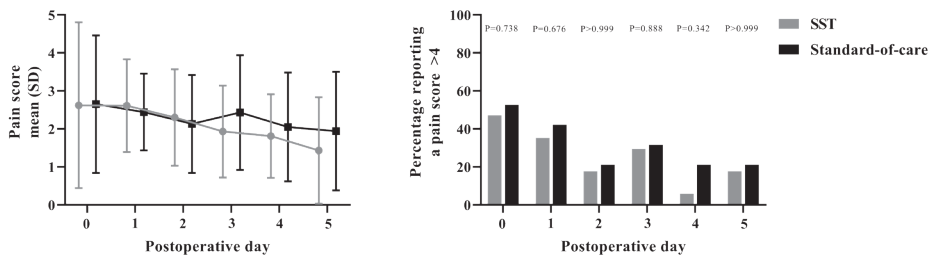


Figure 3. Mean (SD) pain score per postoperative day (left), and percentage of patients reporting a pain score >4 per postoperative day (right)

Additional postoperative outcomes

Postoperative characteristics did not differ between groups (Table 3). In both groups, 1 patient (SST group: 6%, standard-of-care group: 5%) experienced a complication related to analgesia (SST group: respiratory depression with good effect of naloxone treatment, standard-of-care group: hemodynamic instability with good effect of stopping PCEA).

Subgroup analysis

Predefined subgroup analysis by intended type of procedure

Patients undergoing an intended open procedure (SST [$n = 10$] versus standard-of-care: PCEA [$n = 10$] and PCA morphine [$n = 1$]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference -0.23 [95% CI $-1.22 - 0.75$]). The mean (SD) pain score on postoperative day 3 was significantly lower in the SST group compared to the standard-of-care group (1.19 [0.97] versus 2.75 [1.84]; $p = 0.03$). Other pain scores per postoperative day did not differ between these groups. Patients undergoing an intended robot-assisted procedure (SST [$n = 7$] versus standard-of-care: PCA morphine [$n = 8$]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference 0.02 [95% CI $-0.58 - 0.62$]). The mean (SD) pain score on postoperative day 1 was significantly lower in the SST group compared to the PCA morphine group (2.42 [0.83] versus 3.22 [0.44]; $p = 0.033$). Other pain scores per postoperative day did not differ between these groups.

Predefined subgroup analysis by original and amended protocol

Patients during the original protocol (SST [$n = 3$] versus standard-of-care [$n = 5$]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference 0.98 [95% CI $-2.23 - 2.56$]). The mean (SD) pain scores on postoperative day 0 and 1 were significantly higher in the SST group compared to the standard-of-care group (3.67 [1.1] versus 1.62 [1.17]; $p = 0.05$ and 3.83 [1.74] versus 1.28 [0.82]; $p = 0.027$). Other pain scores per postoperative day did not differ between these groups. Patients during the amended protocol (SST [$n = 14$] versus standard-of-care [$n = 14$]) showed similar results for mean pain score on postoperative day 1 to 3 (mean difference -0.17 [95% CI $-0.80 - 0.47$]). Pain scores per postoperative day did not differ between these groups.

Post-hoc subgroup analysis by age

Patients ≤ 65 years (SST [$n = 8$] versus standard-of-care [$n = 10$]) and >65 years (SST [$n = 9$] versus standard-of-care [$n = 9$]) showed similar results for mean pain score on postoperative day 1 to 3 and mean pain score per postoperative day (data not shown).

Table 3. Perioperative hemodynamics and postoperative outcomes

	Type of analgesia		P
	SST (N=17)	Standard-of-care (N=19)	
	N (%)	N (%)	
PERIOPERATIVE HEMODYNAMICS			
Intraoperative use of vasopressors	17 (100)	18 (94.7)	1.00
Noradrenaline	16 (94.1)	18 (94.7)	1.00
Phenylephrine	12 (70.6)	11 (57.9)	0.429
Ephedrine	8 (47.1)	10 (52.6)	0.738
Postoperative MC/ICU use of vasopressors	8 (47.1)	10 (52.6)	0.738
Noradrenaline	8 (47.1)	10 (52.6)	0.738
Phenylephrine	0	0	-
Ephedrine	0	2 (10.5)	0.487
Total dose of noradrenaline (mg), median (IQR)*	0.60 (0.28-2.08)	1.08 (0.56-4.76)	0.358
Total dose of phenylephrine (mg), median (IQR)*	150 (0-300)	50 (0-250)	0.359
Total dose of ephedrine (mg), median (IQR)*	0 (0-5.0)	3.0 (0-12.5)	0.243
Cumulative fluid balance			
POD 0 (mL), median (IQR)	2517 (2291-4187)	2625 (1836-3196)	0.522
POD 1 (mL), median (IQR)	3736 (3361-5342)	3590 (3029-6195)	0.968
POD 2 (mL), median (IQR)	4927 (4172-6241)	5601 (4640-7750)	0.262
POD 3 (mL), median (IQR)	6219 (3773-6532)	6397 (4854-7674)	0.137
POD 4 (mL), median (IQR)	6718 (3597-7979)	7369 (5711-8219)	0.233
POD 5 (mL), median (IQR)	7965 (5268-9381)	9015 (6577-9885)	0.233
POSTOPERATIVE OUTCOMES			
Complications related to analgesia**	1 (5.9)	1 (5.3)	0.935
Day of resumption of oral diet intake, median (IQR)***	3 (3-5)	3 (2-5)	0.571
Day of urinary catheter removal, median (IQR)	3 (3-4)	3 (2-4)	0.544
Clavien-Dindo classification			0.357
No complications	11 (64.7)	8 (42.1)	
I-II	1 (5.9)	3 (15.8)	
III-V	5 (29.4)	8 (42.1)	
30-day mortality	0	0	-
Length of hospital stay (days), median (IQR)	9 (7-12)	8 (7-14)	0.778
Readmission	2 (11.8)	6 (31.6)	0.182

IQR, interquartile range; MC/ICU, Medium Care/Intensive Care Unit; mg, milligram; IQR, interquartile range; POD, postoperative day;

* Missing data for SST group (N=2)

** In the SST group: respiratory depression, in the standard-of-care group: hemodynamic instability

*** Missing data for SST group (N=1) and standard-of-care group (N=2)

DISCUSSION

This first randomized study investigating the use of SST in 36 patients following pancreateo-duodenectomy showed that the SST treatment strategy, as part of a multimodal approach, is a non-inferior analgesic compared to our standard-of-care (PCEA or PCA morphine) in the treatment of pain on postoperative day 1 to 3. Early treatment failure occurred in 24% of patients in the SST group and in 16% of patients in the standard-of-care group. Additional outcomes such as pain scores, OBAS and patient satisfaction scores did not differ between the two groups. Also, perioperative hemodynamics and postoperative outcomes did not differ between the two groups.

The mean difference in pain score on postoperative day 1 to 3 was -0.10 (95% CI $-0.72 - 0.52$) and therefore non-inferiority of SST was demonstrated. No previous randomized data were available that report mean postoperative pain scores with SST. An observational study of our first clinical experience with SST did show comparable postoperative pain scores in laparoscopic abdominal and orthopedic surgery.¹⁰ Previous randomized trials with (PC)EA and PCA or iv morphine showed similar pain scores during the first postoperative days.²¹⁻²⁴ This suggests that our results regarding pain scores might be applicable to other settings. It should be noted that this study investigated multimodal treatment strategies, including standard use of paracetamol and if needed metamizole and ketamine besides SST, PCEA or PCA morphine, and therefore no conclusions can be drawn on the effectiveness of the individual components of the treatment strategy. An increase was observed of patients reporting unacceptable pain on postoperative day 3 compared to day 2 in in both groups. This may have been caused by the termination of SST and standard-of-care and (painful) transition to paracetamol and oral or sc opioids.² Evidently, more efforts are needed to improve this transition and prevent an upsurge in pain scores when the primary treatment strategy is ended.

The OBAS did not differ significantly between groups. The reported OBAS of the SST group was somewhat higher (a lower score is better) than the standard-of-care group and also higher than reported in a study comparing continuous wound infiltration plus PCA morphine to (PC)EA in patients undergoing open hepato-pancreato-biliary surgery.²⁴ As we did not separately analyze side effects (mainly nausea, dizziness), we can only hypothesize that OBAS of the SST group was somewhat higher due to more frequently experienced side effects of the SST, and not due to higher pain scores. This possibly also explains why patient satisfaction score were slightly lower in the SST group. A more proactive administration of antiemetics and communication with the patient could be a solution. We did not assess the level of sedation prior to pain scoring or OBAS. Sedation may have affected scores, but it is our experience that residual

sedation is minimal in our patient population following total intravenous anesthesia and preemptive morphine dosing.

Early treatment failure occurred in 24% of patients in the SST group and in 16% of patients in the standard-of-care group (all in the PCEA group; 30%). In a previous randomized trial with SST in open abdominal and orthopedic surgery, the early failure rate was 18%.¹² A disadvantage of SST is that patients need a good cognition, vision and hand-to-mouth coordination in order to operate the system, and careful patient selection (eg low risk for post-operative delirium) is therefore warranted. A meta-analysis performed by us showed similar data of early treatment failure in patients with EA (29%).³ We did not formally check the position of the PCEA catheter with eg radiography, as this is not part of our standard clinical practice. Patients were analyzed by intention-to-treat approach to avoid potential bias due to exclusion of patients and resemble standard clinical care as much as possible.

EA has been associated with significant vasoactive medication and fluid administration and even impaired anastomotic healing.^{25, 26} Perioperative hemodynamics did not differ between groups in this study, yet the sample size could have been too small to detect relevant and significant differences. This also applies to the other postoperative outcomes. The use of SST has a benefit over PCEA and PCA morphine as no epidural catheter or iv line is needed which can hinder the patient from early ambulation and early urinary catheter removal. Unfortunately, no difference was observed regarding urinary catheter removal in the current study.

Several subgroup analyses were performed to confirm the robustness of the results. In intended open procedures, pain scores on postoperative day 3 were lower in the SST group compared to the standard-of-care (PCEA) group. As already mentioned, this might be the result of the (painful) transition to paracetamol and oral or sc opioids.² During the original protocol, pain scores on postoperative day 0 and 1 were higher in the SST group compared to the standard-of-care (PCEA) group. We speculate this may be caused by a short learning curve in the use of SST in clinical practice following pancreatoduodenectomy. The subgroup analysis of >65 years showed similar results between SST and standard-of-care, though we would have expected higher pain scores in the SST group since the SST system is more difficult to operate compared to standard-of-care. A possible explanation may be that also for the standard-of-care group patients require a good understanding of the systems as these are also patient controlled methods. There is no one-size-fits-all type of analgesic treatment strategy and for choosing the most appropriate treatment strategy, in the process of shared decision making, the clinician together with the patients should weigh all relevant factors including patient characteristics and the potential advantages and disadvantages of each

different treatment strategy. Careful patient selection, a multimodal treatment strategy and a dedicated and specialized team, including an Acute Pain Service¹⁹, are pivotal for a successful postoperative pain treatment.

This study has several limitations. First, the sample size was small, although large enough to demonstrate non-inferiority of the primary outcome. Due to the small sample size, it is possible some relevant and significant differences were not found for the secondary outcomes (Type II or β error). Second, postoperative day 0 (day of surgery) was not included in the primary outcome since, in our experience, this day is used to establish an adequate level of pain control as modifications of treatment and repetitive instruction of the patient are often needed.² Another reason was that the antinociceptive treatment during surgery may have differed among patients with differences in their residual analgesic effects in the first postoperative hours. To investigate possible variations in pain scores during each postoperative day which were not reflected within the mean pain score, we also analyzed proportion of patients that report unacceptable pain and observed no significant difference. Third, the open-label design (no blinding) introduces a the risk of performance bias. Blinding was not done since the treatment strategies were evidently different and blinding of study participants and investigators is not pragmatic and does not resemble standard clinical care. Fourth, two relevant amendments were made to the protocol during the study (allow inclusion of robot-assisted procedures and changing the non-inferiority margin) which might have affected the outcomes. These amendments were reviewed and approved by an independent ethics committee (including a statistical review). Enlarging the inclusion criteria was done as the number of open pancreatoduodenectomies declined rapidly over the last two years in our center, partly related to the COVID-19 pandemic and to the wishes of surgeons and patients to perform a minimal invasive procedure. Minimally invasive pancreatoduodenectomy has been suggested to cause less pain and a faster recovery in non-randomized studies.²⁷ Stratification for procedure type was used to ensure equal distribution of open and robot-assisted procedures in both groups. The treatment strategies in the standard-of-care group changed due to the inclusion of robot-assisted procedures (from only PCEA to PCEA or PCA morphine). This amendment of the protocol was not in conflict with our goal which was to demonstrate that the SST treatment strategy is a non-inferior alternative to our standard-of-care following pancreatoduodenectomy. The change was regarded as statistically acceptable since our own retrospective data showed that patients with PCEA and PCA morphine following pancreatoduodenectomy reported similar overall mean pain scores on postoperative day 1 to 3 combined. Due to slow accrual, we changed the non-inferiority margin from -1.0 to -1.5 in order to decrease the required sample size. It should be noted that -1.5 is still somewhat strict, as other studies used a margin of -2.0.^{21, 28} Multiple subgroup analysis (eg by intended procedure type and protocol version) were performed to check the robustness of the outcomes. And lastly, we

chose not to include secondary outcomes investigating the pharmaco-economics. This should be included in future trials.

In conclusion, this study demonstrated that the SST treatment strategy is a non-inferior analgesic compared to our standard-of-care (PCEA or PCA morphine) in the treatment of pain following pancreatoduodenectomy. In our institution, SST can definitely be added to the pallet of postoperative pain treatment strategies following pancreatoduodenectomy. Future research is needed to confirm that these findings are applicable to other settings, preferably by studies with larger sample sizes and multicenter study designs.

REFERENCES

1. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane Database Syst Rev* 2005(1): CD004088.
2. Groen JV, Slotboom DEF, Vuyk J, Martini CH, Dahan A, Vahrmeijer AL, Bonsing BA, Mieog JSD. Epidural and Non-epidural Analgesia in Patients Undergoing Open Pancreatectomy: a Retrospective Cohort Study. *J Gastrointest Surg* 2019;23(12): 2439-2448.
3. Groen JV, Khawar AAJ, Bauer PA, Bonsing BA, Martini CH, Mungroop TH, Vahrmeijer AL. Meta-analysis of epidural analgesia in patients undergoing pancreatoduodenectomy. 2019;3(5): 559-571.
4. Axelrod TM, Mendez BM, Abood GJ, Sinacore JM, Aranha GV, Shoup M. Peri-operative epidural may not be the preferred form of analgesia in select patients undergoing pancreaticoduodenectomy. *J Surg Oncol* 2015;111(3): 306-310.
5. Low J, Johnston N, Morris C. Epidural analgesia: first do no harm. *Anaesthesia* 2008;63(1): 1-3.
6. Pratt WB, Steinbrook RA, Maithel SK, Vanounou T, Callery MP, Vollmer CM, Jr. Epidural analgesia for pancreatoduodenectomy: a critical appraisal. *J Gastrointest Surg* 2008;12(7): 1207-1220.
7. Groen JV, Henrar RB, Hanna Sawires RG, AlEassa E, Martini CH, Bonsing BA, Vahrmeijer AL, Besselink MG, Pecorelli N, Hackert T, Ishizawa T, Miller T, Mungroop TH, Samra J, Sauvanet A, Adham M, Demartines N, Christophi C, Morris-Stiff G, Mieog JSD. Pain management, fluid therapy and thromboprophylaxis after pancreatoduodenectomy: a worldwide survey among surgeons. *HPB (Oxford)* 2021.
8. Aloia TA, Kim BJ, Segraves-Chun YS, Cata JP, Truty MJ, Shi Q, Holmes A, Soliz JM, Popat KU, Rahlfs TF, Lee JE, Wang XS, Morris JS, Gottumukkala VNR, Vauthey JN. A Randomized Controlled Trial of Postoperative Thoracic Epidural Analgesia Versus Intravenous Patient-controlled Analgesia After Major Hepatopancreatobiliary Surgery. *Ann Surg* 2017;266(3): 545-554.
9. van de Donk T, Ward S, Langford R, Dahan A. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. *Anaesthesia* 2018;73(2): 231-237.
10. Meijer F, Cornelissen P, Sie C, Wagemans M, Mars A, Hobma T, Niesters M, Dahan A, Koopman JS, Steegers MA. Sublingual sufentanil for postoperative pain relief: first clinical experiences. *J Pain Res* 2018;11: 987-992.
11. Jove M, Griffin DW, Minkowitz HS, Ben-David B, Evashenk MA, Palmer PP. Sufentanil Sublingual Tablet System for the Management of Postoperative Pain after Knee or Hip Arthroplasty: A Randomized, Placebo-controlled Study. *Anesthesiology* 2015;123(2): 434-443.
12. Melson TI, Boyer DL, Minkowitz HS, Turan A, Chiang YK, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system vs. intravenous patient-controlled analgesia with morphine for postoperative pain control: a randomized, active-comparator trial. *Pain practice : the official journal of World Institute of Pain* 2014;14(8): 679-688.

13. Ringold FG, Minkowitz HS, Gan TJ, Aqua KA, Chiang YK, Evashenk MA, Palmer PP. Sufentanil sublingual tablet system for the management of postoperative pain following open abdominal surgery: a randomized, placebo-controlled study. *Reg Anesth Pain Med* 2015;40(1): 22-30.
14. Kehlet H, Wilkinson RC, Fischer HB, Camu F, Prospect Working G. PROSPECT: evidence-based, procedure-specific postoperative pain management. *Best Pract Res Clin Anaesthesiol* 2007;21(1): 149-159.
15. Blom JW, Muth C, Glasziou P, McCormack JP, Perera R, Poortvliet RKE, Numans ME, Thürmann P, Thiem U, Thio SL, Van Driel M, Beyer M, Van den Akker M, Knottnerus JA. Describing deprescribing trials better: an elaboration of the CONSORT statement. *J Clin Epidemiol* 2020;127: 87-95.
16. Cepeda MS, Africano JM, Polo R, Alcalá R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003;105(1-2): 151-157.
17. Lehmann N, Joshi GP, Dirkmann D, Weiss M, Gulur P, Peters J, Eikermann M. Development and longitudinal validation of the overall benefit of analgesia score: a simple multi-dimensional quality assessment instrument. *Br J Anaesth* 2010;105(4): 511-518.
18. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2): 205-213.
19. Rawal N, Berggren L. Organization of acute pain services: a low-cost model. *Pain* 1994;57(1): 117-123.
20. VMS-Veilighedsprogramma. Vroege herkenning en behandeling van pijn. https://www.vmszorg.nl/wp-content/uploads/2017/11/web_20090109_praktijkids_pijnpdf (accessed January 2018) 2009.
21. Hutchins JL, Grandelis AJ, Kaizer AM, Jensen EH. Thoracic paravertebral block versus thoracic epidural analgesia for post-operative pain control in open pancreatic surgery: A randomized controlled trial. *J Clin Anesth* 2018;48: 41-45.
22. Klotz R, Larmann J, Klose C, Bruckner T, Benner L, Doerr-Harim C, Tenckhoff S, Lock JF, Brede EM, Salvia R, Polati E, Königer J, Schiff JH, Wittel UA, Hötzel A, Keck T, Nau C, Amati AL, Koch C, Eberl T, Zink M, Tomazic A, Novak-Jankovic V, Hofer S, Diener MK, Weigand MA, Büchler MW, Knebel P. Gastrointestinal Complications After Pancreatoduodenectomy With Epidural vs Patient-Controlled Intravenous Analgesia: A Randomized Clinical Trial. *JAMA Surg* 2020;155(7): e200794.
23. Marandola M, Cilli T, Alessandri F, Tellan G, Caronna R, Chirletti P, Delogu G. Perioperative management in patients undergoing pancreatic surgery: the anesthesiologist's point of view. *Transplant Proc* 2008;40(4): 1195-1199.
24. Mungroop TH, Bond MJ, Lirk P, Busch OR, Hollmann MW, Veelo DP, Besselink MG. Preperitoneal or Subcutaneous Wound Catheters as Alternative for Epidural Analgesia in Abdominal Surgery: A Systematic Review and Meta-analysis. *Ann Surg* 2018.

25. Kulemann B, Fritz M, Glatz T, Marjanovic G, Sick O, Hopt UT, Hoepfner J, Makowiec F. Complications after pancreaticoduodenectomy are associated with higher amounts of intra- and postoperative fluid therapy: A single center retrospective cohort study. *Ann Med Surg (Lond)* 2017;16: 23-29.
26. Wright GP, Koehler TJ, Davis AT, Chung MH. The drowning whipple: perioperative fluid balance and outcomes following pancreaticoduodenectomy. *J Surg Oncol* 2014;110(4): 407-411.
27. Chen K, Pan Y, Liu XL, Jiang GY, Wu D, Maher H, Cai XJ. Minimally invasive pancreaticoduodenectomy for periampullary disease: a comprehensive review of literature and meta-analysis of outcomes compared with open surgery. 2017;17(1): 120.
28. Liu SS, Richman JM, Thirlby RC, Wu CL. Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. *J Am Coll Surg* 2006;203(6): 914-932.

