LETTER TO THE EDITOR

SUBLINGUAL SUFENTANIL NANOTAB PATIENT-CONTROLLED ANALGESIA SYSTEM/15 MCG IN A MULTIMODAL ANALGESIC REGIMEN AFTER VERTEBRAL SURGERY: A CASE-SERIES ANALYSIS

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To the Editor,

Acute post-operative pain (POP) is an important public health issue worldwide. Undertreatment of POP can result in increased morbidity, limitation of active rehabilitation, delayed discharge, worsening of outcome, and it is highly predictive of chronic post-surgical pain.

Intravenous (IV) Patient-Controlled Analgesia (PCA) with morphine has been considered the gold standard for acute severe pain management, but fell into disuse in our clinical practice, given the invasive route and the workload on medical and nursing staff. Moreover, IV morphine can delay early mobilization and negatively interfere with gut function, affecting recovery. A multimodal, opioid-sparing approach has thus gained increasing popularity, according to Enhanced Recovery After Surgery (ERAS) protocols.

Recently, a Sufentanil Sublingual Tablet System (SSTS) has been marketed in Europe by Grünenthal GbmH (Aachen, Germany) (1). The SSTS is a PCA system approved for the management of acute moderate-to-severe pain in adult patients in hospital setting (2, 3). This pre-programmed drug/device combination product delivers a fixed dose of 15 mcg of sufentanil tablets as needed, in a non-invasive sublingual dosage form. Sufentanil is a μ-opioid agonist which lacks active metabolites, has a high therapeutic index and a rapid plasma/CNS equilibration half-life, ensuring a rapid and consistent onset of action (4, 5). The sublingual route of administration overcomes the high peak levels and short duration of action associated with IV administration due to sufentanil's highly lipophilic nature, also avoiding the first-pass metabolism associated with the "per os" route of administration (5-9).

The primary objective of this study was to determine the efficacy of the SSTS as part of multimodal analgesia by assessing POP intensity at 24 h. Secondary endpoints included patients' reports of pain intensity at 48 and 72 h, patients' satisfaction at discharge, side effects, length of hospital stay after surgery and nursing team satisfaction.

MATERIALS AND METHODS

A retrospective analysis of 19 consecutive patients

Key words: pain; postoperative; sublingual sufentanil; spinal fusion; spondylolisthesis

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scheduled for elective lumbar fusion surgery who received SSTS 15 mcg with a 20-minute lockout interval in the postsurgical period was performed. The study protocol and statement of informed consent to data treatment were approved by the local ethics committee (31120/18). Participants gave written informed consent to data analysis and publication. The study was registered at ClinicalTrials.gov on February 20, 2018 [CTN03459404].

Exclusion Criteria to post-operative sublingual sufentanil administration were:

- Age <18 yrs or >75 yrs
- Opioid tolerance
- Documented sleep apnoea or home oxygen therapy
- History of alcohol or drug abuse
- Allergy or hypersensitivity to opioids.

The patients enrolled were suffering from intractable lumbar pain, with or without lower limb radiation, walking limitation (neurogenic claudication) and different degrees of daily life activity limitation. The most frequent pathogenesis of the lumbar pain was degenerative or isthmic spondylolisthesis, lumbar stenosis, and spinal deformities. The surgical treatment consisted in decompression of neurologic structures (when required) and different procedures of vertebral fusion. On the day before surgery, patients were instructed on the use of the device.

Intraoperative management was standard (general anaesthesia inducted with propofol, fentanil or sufentanil, rocuronium and desflurane). In the post-anaesthesia care unit (PACU), patients were given SSTS when awake and cooperative (score 1 in Modified Wilson Sedation Scale) (10). They consequently self-administered SSTS as needed for pain relief for a maximum duration of 72 h. All patients were given acetaminophen, ketoprofen and metoclopramide "per os" in an 'around-the-clock' (ATC) dosing regimen. Ondansetron was prescribed as rescue drug in case of persistent nausea or vomiting. Tramadol "per os" was prescribed as rescue drug for pain control. Pain intensity was estimated during the 72 h after surgery using an 11-point NRS, ranging from 0 (no pain) to 10 (the worst pain imaginable). NRS was quantified before the surgical procedure and post-operatively at baseline (in PACU before the first administration of sublingual sufentanil), at 30 min, 1, 2, 6, 12, 24, 48 and 72 h. Side effects (nausea, vomiting, sleepiness, itching, dizziness, others) and length of stay after surgery were also reported.

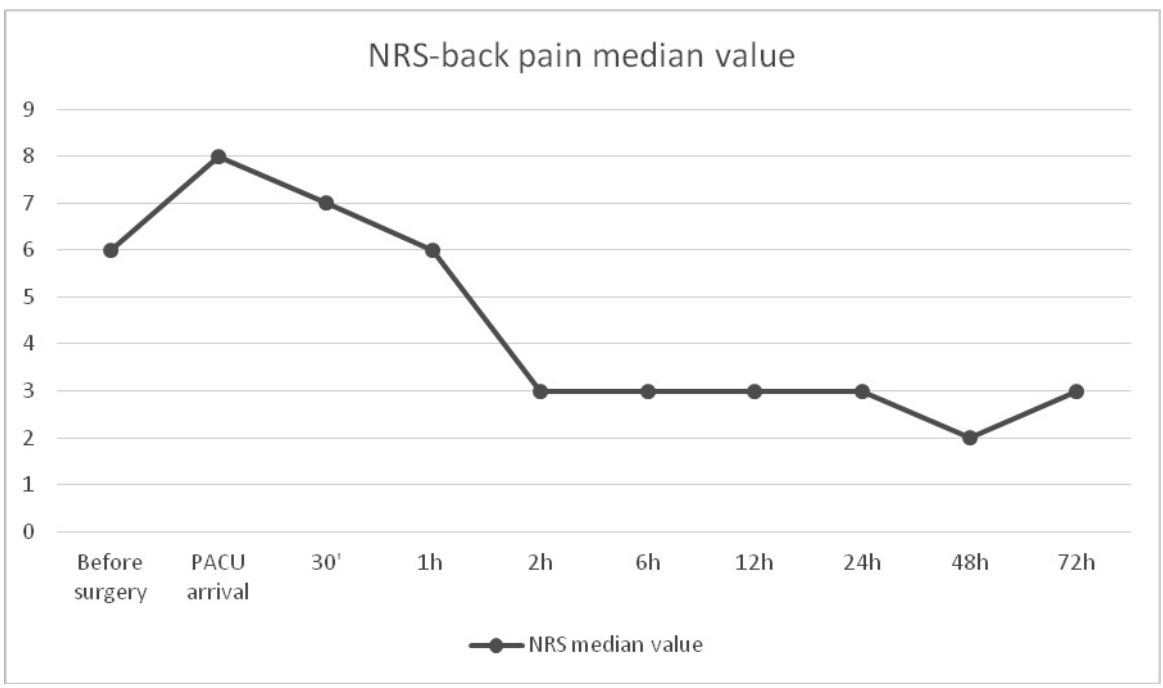

Fig. 1. *NRS median value.*

Patient and nurse satisfaction were assessed using a specific Ease-of-Care (EOC) Questionnaire, each adapted from validated patient (11) and nurse (12) EOC Questionnaire. The patient EOC Questionnaire included 20 questions, 18 of which were collected into 6 categories (confidence with the device, understanding, comfort with the device, movement, dosing confidence, pain control) and scored on a scale of 0 to 3 (0 not at all, 1 somewhat, 2 a great deal, 3 a very great deal). The remaining 2 questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) were scored on a scale of 0 to 3 (from extremely dissatisfied to extremely satisfied). The nurse EOC Questionnaire had 9 questions, 7 of which focused on the time-consuming and bothersome features of the device and were scored on a scale of 0 to 2 (0 not at all, 1 somewhat, 2 a great deal). The remaining 2 questions (satisfaction with level of pain control and satisfaction with the device) were scored on a scale of 0 to 2 (0 unsatisfied, 1 satisfied, 2 extremely satisfied). Statistical analysis was performed using SPSS 15.0. Data are expressed as mean and standard deviation.

RESULTS

Nineteen consecutive patients eventually met inclusion criteria for SSTS use. In 2 patients the treatment was interrupted (1 for intractable post-operative vomiting and 1 for technical malfunction of the device). The 17 remaining patients were analysed: 11 women and 6 men, mean age 59±10 years, mean Body Mass Index (BMI) 22.5±3.53. Average surgery time was 250 min (mean 258±73.9 min). In the PACU, mean time to first SSTS use after recovery from anaesthesia was 22.5±5.6 min.

During the pre-anaesthetic interview, patients estimated the intensity of their low-back pain as moderate. At the arrival in PACU, NRS score median value was 8, reduced to 6 at 1 h and 3 at 2, 6 and 12 h

Table I. *NRS and tablets consumption, mean and median values. Tablet consumption refers to each span of time from the previous entry.*

	NRS ***Mean value ±DS***	**NRS** ***Median value***	**Tablets consumed** ***Mean value ±DS***	**Tablets consumed** ***Median value***
Before surgery	6.05±2.5	6	-	-
PACU arrival	7±2	8	-	-
30'	6.6±2.1	7	0.9±0.2	1
1h	5.7±2.1	6	0.7±0.6	1
2 hrs	3.5±2	3	0.9±1	1
6 hrs	2.8±2.2	3	1.1±0.9	1
12 hrs	3.5±1.9	3	1.3±1.1	1
24 hrs	2.8±2	3	3.8±2.5	3
48 hrs	1.9±1.5	2	6.4±4.4	6
72 hrs	2.3±1.5	3	4.4±5.6	3.5

Table II. *Patient and Nurse EOC Questionnaire.*

Patient EOC Questionnaire		
		Mean±DS
	CONFIDENCE WITH THE DEVICE	**2.6±0.4**
1	I liked being in control of my pain medication.	2.47±0.6
2	I have never been worried that the device would run out of medication.	2.7±0.7
3	I have never been afraid of having to ask for help to use the device.	2.8±0.3
	UNDERSTANDING	**2.7±0.1**
4	The instructions provided by the nurse/doctor were useful.	2.8±0.3
5	I understood how often I could press the button to get my pain medication.	2.7±0.4
6	I have never needed help from nurses to use and/or adjust the device.	2.7±0.4
	COMFORT WITH THE DEVICE	**2.8±0.2**
7	I never had problems pressing the button because I was drowsy and/or feeling weak.	2.7±0.5
8	The device was easy to use.	2.9±0.2
9	Releasing the drug was easy, regardless the position in which I was lying in the bed.	2.8±0.3
	MOVEMENT	**2.6±0.5**
10	I have never been afraid of walking away from the device (in order to reach the chair, the bathroom, the unit hallway..).	2.7±0.8
11	It is easy to carry.	2.5±0.8
	DOSING CONFIDENCE	**2.7±0.4**
12	I have never been worried that nurses or doctors were not monitoring how much pain medication I was taking.	2.9±0.2
13	I have never been afraid of becoming addicted to the pain medication.	2.6±0.7
14	I have never been worried that I might be taking more medication than I was supposed to.	2.8±0.5
15	I have never been worried that I might not assume enough medication to control pain.	2.6±0.7
	PAIN CONTROL	**2.1±0.5**
16	Problems with device use have never prevented me from controlling pain.	2.8±0.3
17	Pain never woke me up from sleep.	1.8±0.8
18	Pain never went up and down (i.e. sometimes the pain was bad and other times it was under control).	1.7±0.8
	SATISFACTION	**Mean±DS**
19	How satisfied were you with the level of the pain control?	**2.4±0.5**
20	How satisfied were you with the way in which your pain medication was administered?	**2.5±0.5**

Nurse EOC Questionnaire		
	I considered time-consuming/bothersome..	**Mean±DS**
1	Learn how to use the device.	0.7±0.4
2	Maintaining device function.	0.2±0.4
3	Changing or adjusting the device due to malfunction.	0.3±0.6
4	Educating/ re-instructing patient on how to use the device.	0.5±0.5
5	Positioning, moving or transferring the patient with the device.	0.1 ± 0.3
6	Managing breakthrough pain.	0.1 ±0.3
7	Treating patient problems related to the device (identification thumb tag damage, problems with drug release..).	0.2 ± 0.5
	SATISFACTION	
8	How satisfied were you with the pain control provided by the device?	**1.7±0.4**
9	Please rate your overall satisfaction with the device	**1.7±0.4**

The patient EOC Questionnaire included 20 questions, 18 of which were collected into 6 categories (confidence with the device, understanding, comfort with the device, movement, dosing confidence, pain control). The questions were scored on a scale of 0 to 3 (0 not at all, 1 somewhat, 2 a great deal, 3 a very great deal). The higher the score, the better the corresponding value. The remaining 2 questions (satisfaction with level of pain control and satisfaction with method of administration of pain medication) were scored on a scale of 0 to 3 (from extremely dissatisfied to extremely satisfied). The nurse EOC Questionnaire had 7 questions scored on a scale of 0 to 2 (0 not at all, 1 somewhat, 2 a great deal): a lower score meant a better experience in the use of the device. The remaining 2 questions (satisfaction with level of pain control and satisfaction with the device) were scored on a scale of 0 to 2 (0 unsatisfied, 1 satisfied, 2 extremely satisfied): higher value corresponded to a greater satisfaction. Data are expressed as mean and standard deviation.

from the arrival. At 24 h after surgery, median NRS value was 3 (primary endpoint, mean value 2.8±2). Median NRS values were 2 and 3 at 48 and 72 h, respectively (secondary endpoints). Table I and Fig. I show all mean and median NRS values recorded. The patients self-administered a total of 20 sufentanil tablets (median value, see Table I). Only 1 patient required a rescue dose of tramadol. Only 1 patient reported itching. 7 out of 17 patients experienced mild nausea (only 2 of them requested antiemetic rescue therapy). Many patients reported sleepiness (9 out of 17) and 4 patients felt dizziness. No other side effects were reported. After surgery, many patients spent 3 days in hospital (14 out of 17), but 1 patient was discharged prior to 48 h and 2 patients from 48 to 72 h. The patient satisfaction with level of pain control and SSTS method of administration corresponded to a median value of 2 (from 0 to 3) and 3 (from 0 to 3), respectively (see Table II). The nursing team also reported to be extremely satisfied with the method of drug administration (median value of 2 in a scale from 0 to 2, Table II).

DISCUSSION

Although a certain limit of this report is the lack of a control group and its snall sample, this preliminary investigation has the advantage of portraying our clinical practice.

A moderate-to-severe POP follows surgical treatment, mostly because of injury of paravertebral musculature and acute restoration of spinal sagittal balance and segmental lordosis. The peak of pain is generally experienced on the first days after surgery, causing a mobility restriction. Conversely, our patients portrayed a median NRS back pain value of 3 at 24 h post-op, with the greatest reduction in pain intensity experienced during the first 2 hours. Patients also began mobilization on post-op day 1, with a single physical therapy session a day. In our view, mobilization sessions were more beneficial compared to standard: the patients not only got to sit up on post-op day 1 (as common in our daily practice), but most of them managed to stand up and ambulate, promptly resuming activities of daily living. The improved pain control also shortened the length of hospital stay, permitting early discharge after surgery (less than 48 hours, against the usual discharge occurring in our experience at least 72–96 hours after surgery).

SSTS in a multimodal analgesic regimen proved to be safe: no major events or post-operative respiratory depression episodes occurred. At the end of the treatment, patients felt comfortable with self-providing pain medication, declaring a high level of satisfaction with the achieved pain control. The nursing team likewise expressed great satisfaction, evaluating the system both effective and inexpensive in terms of time and effort.

In conclusion, the SSTS, in multimodal analgesia, can be considered very effective in the management of moderate-to-severe POP in lumbar fusion surgery. The improvement in pain management and its 'easy-to-use' features could implement early mobilization protocols following major surgery, according to the new paradigms of ERAS.

DISCLOSURE

Alessandro Vergari has served as Advisory Board Member for Grünenthal Italia.

Grünenthal Italia srl sustained publication fees.

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