Sublingual Sufentanil Tablet System for Postoperative Pain Relief after Spinal Lumbar Neurosurgery. A Retrospective Comparison with IV Morphine Patient Controlled Analgesia

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Abstract

Background: An enhanced and rapid recovery after surgery has become the new challenge to reduce postoperative complications and length of hospital stay. This retrospective study evaluated the benefits provided by the new sufentanil sublingual tablet system (SSTS) compared to patient controlled analgesia (PCA) with intravenous (IV) morphine in the specific context of spinal lumbar neurosurgery.

Method: We selected 80 patients undergoing 1-2 levels lumbar laminectomy and/or discectomy to evaluate the SSTS. A second group was retrospectively constituted with 80 patients having benefited from the same surgery with IV morphine PCA during the period just preceding the SSTS test period. All patients received similar intraoperative multimodal analgesia. In post anesthesia care unit, piritramide (SSTS group) or morphine (IV PCA group) was titrated intravenously to insure a pain score below 4/10 before PCA initiation. The acute pain service evaluated on Day 1 and Day 2 the pain intensity (visual analogic score at rest and during mobilization) and opioid related side effects. Results were compared using Mann-Whitney-Wilcoxon test, p<0.05 was considered significant. Any comments of the health care personal were collected during the SSTS test.

Results: The mean uptake after 48 hours was 34.99 mg IV morphine and 18.60 sufentanil tablets. Except for Day 1 at rest, pain intensity evaluations were significantly different between both groups, in favor of the IV PCA. There was no significant difference in side effects between groups. Valuable technical and practical comments were collected from patients and nurses, and were discussed.

Conclusion: Despite a significant difference in postoperative pain scores, we demonstrated the overall satisfaction of the patients and the health care personal for the innovative system but some questions and problems were highlighted and would benefit from technical improvements, administrative refinements and further dedicated studies.

Introduction

Since the last few decades, prevention and alleviation of postoperative pain has become a priority in most surgical departments. Patient-controlled analgesia (PCA) with intravenous (IV) morphine has been an important component of postoperative care after major or painful surgery [1]. However, too many patients still experience moderate to severe pain after surgery [2]. Thus, enhanced and rapid recovery after surgery has become the new challenge in the process of reducing postoperative complications and the length of hospital stay [3,4]. Even when properly managed by acute pain services, IV PCA with morphine has some limitations that interfere with postoperative recovery. The intravenous line increases the risk of catheter infection, infiltration, or obstruction leading to analgesic gaps, and limits the patient’s mobility. Morphine sulphate equilibrates slowly from the plasma to the central nervous system, and its active metabolite morphine-6-glucuronide leads to delayed adverse events [5].

In this context, a new development in postoperative PCA is challenging the classic IV PCA. A new sublingual sufentanil tablet system (SSTS) marketed as Zalviso™ by Grünenthal GmbH (Aachen, Germany) was launched in Belgium in 2016. This rechargeable hand-held device is pre-programmed to deliver a sublingual nanotablet containing 15 µg of sufentanil on patient demand with a 20-min lockout interval. Each cartridge contains 40 nanotables and is available for 72 hours. An authorized access
card allows healthcare personnel to interact with the controller, which is tethered to the patient’s bed. A radiofrequency identification thumbtag secures the patient access [6]. Sufentanil has pharmacokinetic and pharmacodynamic properties that make it suitable for sublingual administration, allowing for a rapid rise in plasma concentration that is still smoother than the increase obtained with an IV bolus [7]. Yet, sufentanil achieves faster central nervous system equilibrium than morphine, allowing for rapid and sustained relief from moderate to severe postoperative pain [8]. Sufentanil has a high therapeutic index, no active metabolites, and a low oral bioavailability, making the sublingual route especially interesting for postoperative analgesia [6].

The SSTS is indicated for patient-controlled treatment of moderate to severe postoperative pain in the hospital setting. The preliminary clinical benefits were already demonstrated after major abdominal and orthopedic surgery (hip and knee arthroplasty) [9-12].

The goal of this retrospective study was to evaluate the benefits provided by the new SSTS in comparison with IV PCA in the specific context of spinal lumbar neurosurgery, an elective and reproducible procedure requiring opioid-based patient-controlled postoperative analgesia and rapid recovery. In comparison with a retrospective similar group of patients treated with IV morphine PCA, the primary outcome was the postoperative pain score and the secondary outcome was the incidence of opioid-related adverse events. The patients and healthcare personnel were invited to rate and comment on the use of the new device.

Methods

Patient selection

The neurosurgery department (including surgeons and ward nurses) was selected for the SSTS test period according to the reproducibility of the perioperative management. We selected patients who underwent lumbar laminectomy and/or discectomy at 1-2 levels because these procedures benefited from accurate standardized care provided by the Acute Pain Service (APS) and required routine IV PCA with a mean consumption of 35 mg per 48 hours. All healthcare personnel involved in the test were educated and trained to use the SSTS before starting the evaluation.

After obtaining informed consent and providing preoperative instructions on the use of the SSTS, we prospectively enrolled 80 adult patients (18 to 80 years old) with ASA status I-III in the clinical assessments from July 2016 to February 2017.

A second group was retrospectively constituted with 80 patients who had undergone the same surgery during the period just preceding the SSTS test period (January to May 2016). These patients’ perioperative care was almost identical, including the same multimodal analgesia and anesthesia drugs and protocols, except the use of postoperative morphine titration in the recovery room and IV PCA (programmed as follows: morphine, 1-mg bolus; lockout interval, 5 minutes; maximum dose, 25 mg/4 hours).

Anesthesia and analgesia

The patients were premedicated with alprazolam 0.5 mg on request. Standard monitoring, including ECG, non-invasive blood pressure cuff measurements, pulse oximetry, and neuromuscular transmission assessment (Philips Intellivue, Boeblingen, Germany), was applied on arrival in the operating room. An IV line containing Ringer’s lactate solution was inserted into a forearm vein. Anesthesia was induced with sufentanil 0.15 µg/kg, lidocaine 1 mg/kg, propofol 2-3 mg/kg, and rocuronium 0.5 mg/kg. Dexamethasone 5 mg was administered to patients who had experienced postoperative nausea or vomiting (PONV) previously. After tracheal intubation, the patients were ventilated to maintain EtCO₂ in the 35-40 mmHg range and anesthesia was maintained with desflurane or sevoflurane to target a minimal alveolar concentration of 1-1.2 depending on the patient’s need (Zeus Infinity empowered anesthesia machine; Drägerwerk AG and Co., Lübeck, Germany). Complementary multimodal analgesia included ketorolac 20-30 mg, ketamine 0.5 mg/kg, magnesium sulphate 2 g, and clonidine 1-2 µg/kg titrated according to the need to spare opioids and ensure hemodynamic stability. As a part of the department’s protocol, a urinary catheter was inserted under general anesthesia in all patients and removed at the end of the PCA treatment. The patients maintained a ventral decubitus position during the surgical procedure.

At the end of the procedure, the patients received paracetamol 1 g, tramadol 100 mg, and alizapride 50 mg. The residual neuromuscular block was reversed with neostigmine-glycopyrrolate to ensure a train-of-four ratio > 0.9 before tracheal extubation.

Once the patient arrived in the post-anesthesia care unit (PACU), PONV was recorded and treated with IV ondansetron 4 mg if needed. The patients were asked to evaluate their pain intensity with a 10-grade numerical scale. If necessary, piritramide (SSTS group) or morphine (IV PCA group) was titrated intravenously to ensure a pain score below 4 before PCA initiation. The patients received a final explanation regarding the use of the SSTS or IV PCA device and the first tablet or IV bolus was self-administered to confirm that the patient was able to use the device properly.

The patients were then transferred to the ward, where nurses provided standardized postoperative care. The postoperative medication regimen included paracetamol 1 g/6 h and diclofenac 75 mg/12 h systematically with IV PCA or SSTS always available at the bedside. On the morning of days 1 and 2, as a part of daily practice (identical in both groups), the APS nurse evaluated the pain intensity with a visual analog scale (VAS) ranging from 0 to 100, and recorded and treated any opioid-related side effects or adverse events that occurred during the past 24 hours. The IV line was removed on day 1 if the patient was able to drink and eat and did not need IV drugs anymore. PCA (IV or SSTS) administration was interrupted after 48 hours. If necessary, oral tramadol and oxycodone were administered to ensure the same level of comfort.

Data collection and statistical analysis

The following parameters were recorded in the same standardized way by the APS nurse for further analysis:

- Pain intensity evaluated with VAS at rest (supine position) and during mobilization (sitting on the side of the bed) on the morning of days 1 and 2.
- Amount (in mg) of IV morphine or number of sufentanil tablets administered over 24 hours.
• Occurrence (yes or no) of opioid-related side effects (PONV, pruritus, sedation, respiratory depression).
• IV line removal on day 1 (only in the SSTS test).
• Patient satisfaction evaluated on a 10-grade scale. Any comments of the healthcare personnel were collected (only during the SSTS test).

Categorical and numerical variables were compared among both groups by chi-squared and Mann-Whitney-Wilcoxon tests respectively. P < 0.05 was considered significant.

Results

All results are presented as mean ± SD.

The characteristics of the patients included in both groups are presented and compared in Table 1. There are no differences between the two groups.

On arrival in the PACU, 18 patients received IV morphine (1.3 ± 2.3 mg; range, 2-12 mg) before managing the IV PCA by themselves. In the other group, 5 patients received titrated pirpiramide (0.35 ± 1.5 mg; range, 2-10 mg) before being allowed to use the SSTS and self-administer the first sufentanil tablet.

All the 80 patients included were evaluated on day 1, and day 2 data were missing for two patients in the IV PCA group (the patients were removed on day 1 because they reported no residual pain). Eight patients were excluded from the SSTS group after 24 hours (see below).

The amount of morphine and the number of sufentanil tablets taken on postoperative days 1 and 2 are presented in Table 2. The mean uptake after 48 hours was 34.99 ± 24.97 mg (range, 1-96 mg) IV morphine and 18.60 ± 11.47 (range, 1-40) sufentanil tablets.

Postoperative (day 1 and day 2) pain intensity on the VAS at rest and during mobilization in both groups are presented and compared in Table 3. Except for the scores obtained at rest on day 1, pain intensity evaluations were significantly different between both groups in favour of the IV PCA.

The opioid-related side effects noted during the postoperative period are presented and compared in Table 4. There was no significant difference in PONV between groups. Only 3 and 2 patients in the IV PCA and SSTS groups, respectively, required postoperative ondansetron. Except one patient who complained of pruritus with morphine, none of the other patients reported side effects.

In the SSTS group, the IV line could be removed on day 1 in 61% of the cases. The SSTS evaluations provided by patients showed a good satisfaction rate (74%). The APS and ward nurses also recorded positive and valuable comments:

• The novelty of the SSTS increased the interest in postoperative pain management among healthcare personnel and patients.
• Sublingual administration is well tolerated and compatible with early mobilization.
• The absence of responsibility in programming the device relieved the staff of the risk of human error.
• The IV line was not needed for sufentanil administration and, therefore, was removed (or not replaced) earlier than in IV PCA. This contributed to reducing the nurses’ workload.

However, some problems occurred, and several questions have arisen over the course of the SSTS test. Most of them have the potential for improvement.

• Error “300” occurred during cartridge initialization, necessitating a restart with a new cartridge. This happened 47 times over the first 40 patients. The problem was solved in January 2017, and never appeared subsequently.
• The radiofrequency identification tag did not stick well enough on the thumb and came off frequently (33 out of 80 patients). Some tags were lost. This necessitated re-identification of the patients with new tags. During this period, the SSTS was not available for pain relief.
• Five patients complained about the intensity of the device’s green light during the night.
• A few sufentanil nanotablets were found in some patients’ beds. This reflected their difficulty in perceiving sublingual delivery of the small and light tablets. In particular, five patients expressed difficulty in determining if the tablet was properly administered or not.
• Sublingual administration with the SSTS required coordination of movements and a good understanding of the operating mode. This was difficult (or even impossible) in the strict supine position, which was imposed by the surgeon in some patients. It was also unpredictable in patients with even mild cognitive impairment or hand-

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### Table 1: Patients characteristics

<table>
<thead>
<tr>
<th>Patients</th>
<th>IV PCA (n=80)</th>
<th>SSTS (n=80)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>41/39</td>
<td>43/37</td>
<td>NS</td>
</tr>
<tr>
<td>Age (y.o.)</td>
<td>60 ± 15</td>
<td>58 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>78 ± 18</td>
<td>79 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169 ± 10</td>
<td>169 ± 10</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2: IV morphine mg and sublingual sufentanil tablets uptake on postoperative Day 1 and Day 2

<table>
<thead>
<tr>
<th>Uptake in 24h</th>
<th>IV PCA (mg)</th>
<th>SSTS (tablets)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>23.73 ± 20.45</td>
<td>9.34 ± 7.24</td>
</tr>
<tr>
<td>Day 2</td>
<td>11.26 ± 15.65</td>
<td>9.26 ± 8.70</td>
</tr>
</tbody>
</table>

### Table 3: Postoperative pain intensity (Visual Analogic Scale 0-100) at rest and on mobilization

<table>
<thead>
<tr>
<th>Postoperative pain</th>
<th>IV PCA</th>
<th>SSTS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 VAS rest</td>
<td>30.24 ± 24.77</td>
<td>34.37 ± 24.59</td>
<td>NS</td>
</tr>
<tr>
<td>Day 1 VAS dynamic</td>
<td>47.86 ± 22.45</td>
<td>58.33 ± 24.41</td>
<td>0.006</td>
</tr>
<tr>
<td>Day 2 VAS rest</td>
<td>14.87 ± 18.26</td>
<td>21.04 ± 20.81</td>
<td>0.043</td>
</tr>
<tr>
<td>Day 2 VAS dynamic</td>
<td>32.36 ± 21.88</td>
<td>41.03 ± 22.53</td>
<td>0.027</td>
</tr>
</tbody>
</table>

### Table 4: Opioid related side effects.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>IV PCA</th>
<th>SSTS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV in PACU</td>
<td>5</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>PONV Day 1</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>PONV Day 2</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1</td>
<td>0</td>
<td>NS</td>
</tr>
</tbody>
</table>
shaking because the administration required well-coordinated movements. During the test period, eight patients (10%) had to give up SSTS and resort to another analgesic technique (IV PCA or oral opioids).

• The price of the cartridge was considered important, especially in the context of the Belgian honorarium for acute pain management. The patient was charged for the cartridge (112 Euros, reimbursed by most individual insurance plans), whereas the APS could not receive the INAMI/RIZIV honoraria (202333–202344, K56) dedicated to support postoperative management with IV PCA.

• The cartridge contained a fixed number of tablets (40), which seemed adequate for some patients and excessive for others.

Discussion

Since postoperative pain management was already a priority in our neurosurgical department, this study provided a great opportunity to test the new SSTS in clinical practice as soon as it was available in Belgium and to compare the results with our long-term experience with IV PCA. We demonstrated that patients and healthcare personnel were satisfied overall with the innovative system, but our findings highlighted some questions and problems that indicate the need for technical improvements, administrative refinements, and further dedicated studies.

The new hand-held opioid delivery system sparked the interest of anesthesiologists, acute pain nurses, and all the care providers in the surgical ward. The implementation of the project was an opportunity to bring all the actors together for the management of the patients undergoing spinal lumbar neurosurgery and refine the approach employed in postoperative recovery by including fewer IV lines and drains. The new device would become a part of daily practice, and the reliability of its benefits would have to be validated before concluding that it can enhance pain management and recovery after surgery.

The SSTS provided satisfactory pain relief in the selected population, as assessed by the frequent high patient satisfaction rates. However, the pain scores were unexpectedly higher than those recorded with IV PCA (see Table 3). Severe pain was frequently described on mobilization on the first day while the SSTS was available, and the patient was able to self-administer a supplemental dose if he thought it necessary. As a choice of the manufacturer, the SSTS program was fixed to one 15-µg sufentanil tablet every 20 min maximum. This limited access to the drug might explain some of the high postoperative pain scores, especially on mobilization. Patient education could be improved in order to better prevent painful events with the anticipated administration of sufentanil.

As is commonly observed in postoperative pain management, individual requirements were highly different, ranging from 1 to 40 tablets over 48 hours. A second cartridge never had to be used during the test period even if some patients used all the 40 tabs. On the other hand, some other patients self-administered very few tablets; 20 tablets would have been sufficient for half of them. Thus, it might be interesting to provide patients with different programs according to their actual needs, and also use other cartridges with limited amounts of tablets with the goal of reducing the overall cost of the therapy.

Interestingly, we recorded a low rate of opioid-related adverse events (see Table 4). Only 10% of the patients experienced one episode of postoperative nausea in the PACU or in the ward. No other side effects were recorded while using the SSTS. This is a significantly lower rate than that previously published in studies investigating the effects of sublingual sufentanil monotherapy [12]. However, these rates were also lower with IV morphine PCA before the introduction of the SSTS in the neurosurgical department. Thus, the low rates might be the result of a combination of several factors, including the use of opioid-sparing anesthesia without N.O, multimodal analgesia, and systematic PONV prevention [13,14].

The security of opioid administration with the SSTS was based on different controller-specific factors, including the fixed program with a 20-min lockout period and the authorized access card. This was mandatory to initialize the cartridge and to tether the device to the patient’s bedside. A patient’s thumb identification tag is mandatory to self-deliver a sufentanil tablet on demand. Unfortunately, challenges related to several aspects of this strategy were encountered during the study, including the recurring error “300” during cartridge initiation, the availability of the access card before moving the patient from his bed, loose or lost thumb tags, and the administration errors (not sublingual or not in the mouth), with some tablets found in the bed. The findings also indicated the potential for illicit use of opioids by other people (healthcare personnel, other patients, families, and visitors).

The SSTS was considered to be simple to use. This was confirmed by the majority of patients. However, the different problems encountered indicate the need for some technical improvements. Moreover, even after repeated explanations, using the SSTS was not as simple as expected for all patients. Some physical constraints limited the feasibility of sublingual self-administration, like the strict supine position. On the other hand, a limited understanding of the device operation mode or even a mild postoperative cognitive impairment—quite frequent in the elderly, for example—could interfere with proper administration of sublingual tablets and reduce the effectiveness of PCA, thereby forcing the patient to give up the system. These findings support the need for preoperative selection of patients likely to benefit from SSTS and anticipation of alternative treatment approaches to avoid any analgesic gap.

In Belgium, the new SSTS had a financial impact on the patient—who was charged for the cartridge—and on the APS as well: even considering the reduced inconvenience related to the IV line, it remains important to provide patients and the ward with a pain-related dedicated follow-up assessment to ensure that each patient underwent an appropriate pain management protocol [15]. Since 2003, the anesthesiology department and APS have been supported by a dedicated honorarium for postoperative IV PCA management. This should continue and be applied to new technologies (including SSTS) to support the developments in acute pain therapy that will undoubtedly impact postoperative recovery [3].

The major limitation of this study was its retrospective design. However, the sample size was substantial and both groups of patients were demonstrated to be similar. Every aspect of the intraoperative protocol and postoperative care...
was identical except the drug delivered by the PCA device. Few patients received piritramide or morphine to alleviate pain if VAS > 4 before using the PCA (see results section). The goal was to achieve the same pain level before initiating the postoperative treatment. In accordance with the neurosurgery department protocol, the urinary catheter was maintained until the end of PCA (IV or SSTS) treatment. This could undoubtedly be improved to favor patient mobilization.

Finally, thanks to its novel administration mode for effective PCA, the SSTS has the potential to improve recovery after surgery. Further dedicated studies should demonstrate its positive impact on early feeding and mobilization, ability in physiotherapy and rehabilitation programs, incidence of postoperative complications, and length of hospital stay.

After some refinements, the inherent advantages of the new SSTS to treat postoperative pain could challenge the classic IV PCA and favor enhanced recovery after surgery, which still needs to be demonstrated in surgical departments.

References