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Sufentanil Sublingual Tablet System: from rationale of use to clinical practice

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Abstract. – The control of post-operative pain in Italy and other western countries is still suboptimal. In recent years, the Sufentanil Sublingual Tablet System (SSTS; Zalviso; Acel-Rx Pharmaceuticals, Redwood City, CA, USA), which is designed for patient-controlled analgesia (PCA), has entered clinical practice. SSTS enables patients to manage moderate-to-severe acute pain during the first 72 postoperative hours directly in the hospital setting. However, the role of SSTS within the current framework of options for the management of post-operative pain needs to be better established. This paper presents the position on the use of SSTS of a multidisciplinary group of Italian Experts and provides protocols for the use of this device.

Key Words:
SSTS, Neuropathic pain, Surgery, Clinical practice.

Introduction

With approximately 250 million surgical procedures performed annually, whose 4 million are performed in Italy, post-operative pain represents a major healthcare concern[1]. Remarkably, proper management of post-operative pain reduces post-surgical morbidity, shortens the length of hospital stay and diminishes costs for the healthcare system[2]. However, post-operative pain is still poorly managed worldwide[3], and, with specific reference to Italy, more than 80% of surgical patients report moderate-to-severe post-operative pain[4].

Proper selection of analgesic therapy is crucial to allow post-operative analgesia. According to the SIAARTI (Società Italiana di Anestesia, Analgesia, Rianimazione e Terapia Intensiva) guidelines, paracetamol, NSAIDs, weak and strong opioids and local anesthetics should be used alone or in combination with adjuvants for the control of post-operative pain[2,5]. The method of administration for these drugs should be set in line with the specific pharmacokinetic and pharmacodynamic properties of each drug. Strong opioids should not be avoided but optimized in dose and duration[2,5]. Continuous infusion techniques without flow control meters are not recommended, due to the lack of evidence supporting their use to infuse analgesic drugs[1]. Patients should rather receive an appropriate epidural analgesia, patient-controlled analgesia (PCA), or continuous peripheral nerve blocks[2]. However, data from the Italian POPSI-2 survey, published in 2015 and referring to 2012, showed

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that continuous intravenous (IV) analgesia with an elastomeric infusion system remain the most frequently used technique (50%), with only 12% of patients on epidural analgesia and only 9% on PCA (7% IV PCA and 2% epidural)[1].

In recent years, the Sufentanil Sublingual Tablet System (SSTS; Zalviso; AcelRx Pharmaceuticals, Redwood City, CA, USA), which is designed for PCA, has entered clinical practice[6]. SSTS enables patients to manage acute moderate-to-severe post-operative acute pain directly in the hospital setting, during the first 72 hours post-surgery.

However, the role of SSTS within the current framework of options for the management of post-operative pain is worthy of further discussion. This paper presents the position on the postoperative use of SSTS of a multidisciplinary group of Italian Experts.

Elastomer and PCA: Pros and Cons

Elastomeric infusion systems are a cheap and easy-to-use system; however, they present some major drawbacks (Table I)[1]. First, they do not provide tailored postoperative analgesia and they must be set to provide a given dosage based on the anesthesiologist's prescription. Moreover, the administration of opioids by an elastomeric infusion pump requires special attention, due to the lack of a safety alarm. Lastly, elastomeric pumps typically provide continuous dosing over 24-48 hours without matching the increased needs of analgesia during the first 24 hours after surgery. The patient on elastomeric infusion systems may thus experience inadequate pain control on post-operative day 1 and excessive analgesia on the following day[1].

While PCA systems provide tailored analgesia, they are actually more complicated to use than elastomeric infusion pumps and require some level of patient education, as well as continuous maintenance (Table I). The newly developed SSTS device for sublingual PCA can be more useful in a setting with limited sources and/or when IV PCA is not possible. Based on this, the use of sublingual PCA has recently been listed, by the SIAARTI, in the Good Clinical Practice document among suggested treatments for the management of acute post-operative pain[7]. SSTS allows PCA with sufentanil, an opioid characterized by high affinity for the μ-opioid receptor. It has the highest therapeutic index compared with any other opioid used in clinical practice and with an absence of clinically relevant active metabolites[6].

In detail, SSTS is a hand-held, non-invasive delivery system administering sufentanil 15 μg nanotablets sublingually (Figure 1)[6]. SSTS is programmed with a 20-minute lockout interval, which cannot be altered by patients or healthcare professionals, and this leads to a low risk of programming errors. Only the patient can self-administrate the dose device thanks to a radio-frequency identification thumb tag. Remarkably, the prolonged half-time with sublingual administration can provide a more appropriate duration of analgesia when compared with the administration via the IV route[8]. The pharmacokinetic properties

Table I. Pros and cons of elastomeric infusion pumps, standard PCA systems and SSTS, according to Authors' experience.

	Pros	Cons
Elastomeric infusion pumps	• Cheap • Easy to handle	• Do not provide tailored postoperative analgesia • Dosage set according to anesthesiologist's prescription • Continuous dosing over the first 48 hours • Lack of safety alarm
Standard PCA systems	• Tailored analgesia • Presence of safety alarm	• Complex to use • Require proper patient's education • Require continuous maintenance • Safety alarm can generate additional workload for nurses
SSTS	• Tailored analgesia • Easy to use • Less invasive than standard PCA • No increased risk of use in special subgroups • Low risk of programming errors • Can fit into existing protocols	• Requires proper patient's education • Lack of dedicated standardized protocols at the moment

PCA: Patient-controlled analgesia; SSTS: Sufentanil Sublingual Tablet System.

Figure 1. SSTS device and its three main components.

of repeated dose administration were shown to support the 20-minute lockout interval[8]. Compared with standard, morphine-based IV PCA, SSTS has faster onset of analgesia and is associated with a higher rate of successful pain control[6]. Moreover, given the lack of any IV line or risk of flow interruption, SSTS may be associated with a low incidence of infections or analgesic gaps.

SSTS: Clinical Evidence

Clinical Trials

The efficacy of SSTS in controlling pain after open abdominal and orthopedic surgery has been documented in three randomized studies, which compared the use of this device *vs*. morphine[9-11].

In a 48-hour non-inferiority trial in 357 subjects with an open-label design, Melson et al[9] compared patient satisfaction with SSTS against IV PCA morphine sulfate 1 mg with a 6-minute lockout interval for the control of pain after major open abdominal or orthopedic surgery. The primary outcome was the proportion of patients giving an evaluation of "good" or "excellent" ("success") at 48 hours after surgery on the Patient Global Assessment (PGA48). Overall, this goal was achieved by 78.5% of patients on SSTS and by 65.6% of patients on IV PCA, thus showing non-inferiority (p<0.001) and a statistical advantage for SSTS (p=0.007). Moreover, SSTS was associated with faster onset of analgesia and increased ease of care by nurse compared with IV PCA. The tolerability profile was similar in the two groups, but patients on SSTS experienced less cases of oxygen desaturations below 95% compared with those on IV PCA (p=0.028).

In another randomized trial, with a placebo-controlled design, Ringold et al[10] evaluated the efficacy and safety of SSTS in patients undergoing open abdominal surgery with a pain intensity at baseline ≥4 on a numeric rating scale (NRS). The primary endpoint was the time-weighted summed pain intensity difference (SPID) over 48 hours, while secondary endpoints included SPID and total pain relief (TOTPAR) up to 72 hours, as well as patient and healthcare provider global assessments. SPID over 48 hours was higher in the SSTS group than in the placebo group (least square mean±SEM, 105.60±10.14 *vs*. 55.58±13.11; p=0.001). Likewise, SPID and TOTPAR scores were higher in the SSTS group than with placebo at all time points from 1 hour (SPID) or 2 hours (TOTPAR) up to a total time of 72 hours (p<0.05). Patient's and healthcare provider's global assessment ratings of good or excellent were greater with SSTS than placebo at all time points (p<0.01), and the tolerability profile of SSTS was similar to that of placebo.

Last, in a placebo-controlled trial, patients were randomly assigned to either SSTS (n=315) or placebo (n=104) after knee or hip arthroplasty[11]. SPID was higher with SSTS group compared with placebo (76±7 *vs*. -11±11, p<0.001). In the SSTS group, more patients and nurses judged SSTS as "good" or "excellent" on the global assessments compared with placebo (p<0.001). Overall, the above-mentioned data were confirmed in a recent pooled analysis[12].

Observational Experiences

Observational experiences on the use of SSTS in real-life are now being increasingly published, as a consequence of the mounting use of this device in clinical practice[13-19]. In a study conducted in The Netherlands, SSTS was evaluated within a multi-modal treatment, including paracetamol and NSAIDs, in 280 patients subjected to different procedures, mainly laparoscopic abdominal or orthopedic surgery[13]. Median pain intensity, assessed by NRS, decreased over time in a similar fashion for all different surgeries. Mean number of tablets used was 19 (range 0-86). Nausea occurred in 34% of patients. Overall satisfaction was high in 73% of patients and was

directly correlated with pain relief ($p<0.001$) and inversely correlated with occurrence of nausea ($p=0.01$). In another retrospective study, conducted in the Italian scenario, Scardino et al[14] compared SSTS (n=95) with their standard of care [continuous femoral nerve block (cFNB) within a multimodal analgesic, n=87] after total knee arthroplasty. While NRS at rest was lower with cFNB, NRS on movement improved with SSTS at all time-points, compared with standard of care. Adverse effects were less frequent with SSTS than with cFNB (6% *vs*. 74%; $p<0.001$), and rescue analgesics were needed by 5% and 60% of patients, respectively. The use of SSTS was also associated to improved walking ability, with all patients of the SSTS group being able to stand and walk for 10 m at day 1, compared with 40% of those receiving cFNB. Remarkably, all patients of the SSTS group remained in hospital for only 4 days, according to the institution protocol, compared with only 36% of those on cFNB. In another recently published prospective study on 341 adults with post-operative moderate-to-severe pain, SSTS reduced resting pain intensity from NRS score of 5.2±2.3 (at SSTS handover) to 1.8±1.6 (day 3 after handover)[15]. Overall, 87.1% of patients reported the method of pain control to be "good" or "excellent", 91.8% were "extremely/very satisfied" or "satisfied" with the level of pain control; and 95.9% were at least satisfied with the method of administration. Turi et al[17] retrospectively investigated the use of SSTS in 308 patients undergoing major surgery within an Enhanced Recovery After Surgery (ERAS) protocol. Overall, compared with the first SSTS administration, pain intensity decreased by 79% over the observation period [median NRS: from 6 (baseline) to 0 (day 3)]; this reduction was already evident at day 1. Patient satisfaction was high: 89% of patients judged the device as "easy" or "very easy" to use. Other experiences on the use of SSTS have been published, evaluating patients undergoing thoracic[18], gynecological[19] or vertebral surgery[16]. Overall, all these studies are consistent in encouraging the routine application of SSTS in the above-mentioned settings.

SSTS: Place in the Therapy

The authors of the present report have an extensive experience in the use of SSTS for the treatment of pain after several types of surgery, involving approximately 3000 patients.

In the authors' experience, SSTS has been directly included and applied, by replacing the main drug/technique, into the clinical protocols for post-operative analgesia (Table II). However, these protocols are applied on several types of surgeries (abdominal, thoracic, urological/gynecological, vascular, orthopedic) and depend upon the specific experience of each Center. Hence, they are quite heterogeneous at present but, at the same time, they show the wide applicability of SSTS for postoperative pain control.

Overall, SSTS appears to be a safe, less invasive than IV PCA and effective tool for post-operative analgesia, associated with a high level of patient's satisfaction and improvement in quality of life. Interestingly, experience of the Authors showed as SSTS is frequently used during the first day after surgery, a key period for rehabilitation often not covered by currently used single-shot and/or fixed analgesic approaches, which lose their effect already 12-24 hours after administration (Table I). Remarkably, clinical experiences suggest that SSTS is not associated with increased risk in special subgroups of patients, such as obese, those with renal/liver insufficiency or elderly[13].

On the base of our experiences and what already seen in previous evidence[17], SSTS is easy to understand and use, allows a prompt canalization, is associated with good quality of sleep and, given the possibility of self-administration, can be linked to improved adherence. The use of SSTS does also optimize the nurse workflow, influencing positively the management of the surgical wards.

However, this system still shows some margins of improvement, such as a clearer explanation of its use (eg to elderly patients) and proper training protocols. It should be kept in mind that SSTS enables to manage moderate-to-severe acute pain during the first 72 hours after surgery. Moreover, SSTS is associated with a low risk of programming errors. It has been observed that some patients treated with SSTS present dry mouth, an event which can be avoided by nebulizing water into the mouth before taking a tablet. However, patients should be adequately evaluated (e.g., previous abuse, comorbidities etc.) before using this system. SSTS in a multimodal vision of post-operative analgesia could be associated with new techniques of peripheral or parietal blocks, such as Erector Spinae block in spine surgery[20].

A special effort is warranted to organize multicenter studies enrolling a large number of patients, with the aim to verify the effectiveness of SSTS to counteract the occurrence of chronic

Table II. Peri- and post-operative analgesic protocols with SSTS.

Surgical setting	Pre-operative protocol	Intra-operative protocol	Post-operative protocol before the introduction of SSTS	Post-operative protocol after the introduction of SSTS
Major spine surgery	Midazolam 0.05 mg/kg IV Ranitidine 50 mg IV	General anesthesia (balanced or TIVA) Paracetamol 1 g IV Ketoprofen 100 mg IV Metoclopramide 10 mg IV Dexamethasone 0.05 mg/kg IV	Tramadol 4 mg/kg/day and SF 0.9% qs 96 ml for 2 days by elastomer (2 ml/h) or oxycodone 5/10 mg/day IV Paracetamol 1 g IV TID Ketoprofen 100 mg IV BID Metoclopramide 10 mg IV BID Rescue: Tramadol 50 mg PO (max 6/day) Ondansetron 4 mg IV (max 3/day) Regional analgesia: No	SSTS Paracetamol 1 g IV TID Ketoprofen 100 mg IV BID Metoclopramide 10 mg IV BID Rescue: Tramadol 50 mg PO (max 6/day) Ondansetron 4 mg IV (max 3/day) Regional analgesia: No
Abdominal surgery		General balanced anesthesia Morphine 0.05-0.1 mg/kg IV Ketorolac 30 mg IV Paracetamol 1 g IV Ondansetron 4 mg IV Dexamethasone 4 mg IV	Morphine bolus 1 mg (PCA), 10 minutes lock-out, max dose 4 mg/h Ketorolac 30 mg IV or Paracetamol 1 g IV at fixed times Regional analgesia: No	SSTS Ketorolac 30 mg IV or Paracetamol 1 g IV at fixed times Regional analgesia: No
Major pancreatic surgery and liver surgery		General anesthesia (balanced/TIVA-TCI) Blended anesthesia (general/epidural)	Tramadol/morphine in continuous infusion by elastomer ± NSAIDs/ paracetamol (69% of cases) Epidural analgesia (local anesthetic + opioid; 21% of cases) Other (10% of cases) Regional analgesia: Yes	SSTS ± NSAIDs or Paracetamol (morphine on demand if these are not indicated or ineffective) Regional analgesia: Yes
Thoracic surgery		General anesthesia (TIVA/TCI) TPVB single shot Ropivacaine 5 mg/ml (7 ml T3-T4 + 7 ml T5-T6) Paracetamol 1 g IV Ketorolac 30 mg IV Ondansetron 4 mg IV Dexamethasone 0.1 mg/kg IV	Sufentanil 0.1 µg/kg (transitional analgesia) Morphine 30–40 mg IV continuous infusion (48 h) Ondansetron 4 mg IV BID Paracetamol 1 g IV 4-times a day Ketoralac 30 mg IV TID Regional analgesia: Yes	Sufentanil 0.1 µg/kg (transitional analgesia) SSTS Paracetamol 1 g IV 4-times a day Ondansetron 4 mg IV BID Rescue: Ketorolac 30 mg IV Regional analgesia: Yes

Table Continued

Table II *(Contijued)*. Peri- and post-operative analgesic protocols with SSTS.

Surgical setting	Pre-operative protocol	Intra-operative protocol	Post-operative protocol before the introduction of SSTS	Post-operative protocol after the introduction of SSTS
Thoracic surgery and abdominal surgery		Thoracic: general anesthesia (TIVA) Abdominal: general anesthesia (balanced)	Thoracic: Morphine + ketorolac by elastomer Rescue: Paracetamol Abdominal (open): epidural analgesics Abdominal (laparoscopic/robotic): Ketorolac + paracetamol (PCA) Regional analgesia: Yes	Thoracic: SSTS + Paracetamol Rescue: Ketorolac Abdominal (open): SSTS or epidural analgesics Abdominal (laparoscopic/robotic): SSTS + paracetamol, ketorolac on demand Regional analgesia: Yes
Urological and gynecological surgery	Ranitidine 50 mg IV	General balanced anesthesia Ketorolac 30 mg IV Ondansetron 4 mg IV Dexamethasone 4 mg IV DBP 0.625 mg IV	Ropivacaine 0.2% + sufentanil 0.75µg/mL 4-6 mL/h Rescue: Paracetamol 1 g/8 h IV Ondansetron 4 mg/12 h IV Regional analgesia: Yes	SSTS Paracetamol every 1 g/8 h IV Ketorolac 30 mg/12 h IV Ondansetron 4 mg/12 h IV Regional analgesia: No
Major surgery (urological, gynecological, thoracic, liver, bariatric and vascular)	Midazolam or sufentanil	General anesthesia (balanced/blended) After induction: Dexamethasone, droperidol Before awakening: Morphine as needed, ondasetron as needed Paracetamol Sufentanil	Morphine + droperidol/metoclopramide ± ketorolac by elastomer 240 ml Morfina + droperidol/metoclopramide (PCA IV) Ropivacaine 0.2% or Levobupivacaine 0.125% ± fentanyl or sufentanil by peridural catheter or PainFusor® catheter and elastomer 300 ml Continuous peri-nervous block by elastomer 300 ml (ropivacaine 0.2% or levobupivacaine 0.125%) Tramadol ± metoclopramide ± ketorolac IV Rescue: Paracetamol/ketorolac/tramadol/ morphine IV Regional analgesia: Yes	SSTS Rescue: Paracetamol or ketorolac Regional analgesia: Yes

Table Continued

Table II *(Contijued)*. Peri- and post-operative analgesic protocols with SSTS.

Surgical setting	Pre-operative protocol	Intra-operative protocol	Post-operative protocol before the introduction of SSTS	Post-operative protocol after the introduction of SSTS
Hip/knee joint replacement		Spinal anesthesia: Bupivacaine 12/15 mg LIA with ropivacaine 400 mg at the end of surgery Metoclopramide 10 mg IV Ondansetron 4 mg IV Methylprednisolone 125 mg IV Ranitidine 50 mg IV	Continuous femoral block (ropivacaine 0.125% 5 ml/h) Oxycodone/naloxone10 mg/5 mg PO BID Ketoprofen 100 mg PO BID or paracetamol 1 g PO TID Rescue: Morphine 10 mg PO PONV prophylaxis: Metoclopramide 10 mg IV BID for 3 days Ondansetron as needed Regional analgesia: Yes	SSTS Eterocoxib 120 mg/day PO for 3 days Rescue: Oral Morphine 10 mg PONV prophylaxis: Metoclopramide 10 mg BID for 3 days Ondansetron as needed Regional analgesia: No
Spine stabilization		Ranitidine 50 mg IV General anesthesia (TIVA/TCI) Dexamethasone 4–8 mg IV Droperidol 0.625 mg IV MgSO4 1 g IV Ketorolac 30 mg IV	Paracetamol 1 g IV TID Ketorolac 30 mg BID Regional analgesia: No	SSTS Ondansetron 4 mg IV BID Rescue: Ketorolac 30 mg IV Regional analgesia: No
Major Shoulder Surgery	Midazolam 0.1 mg/kg IV Pantoprazole 40 mg IV	General anesthesia (balanced or TIVA) ± interscalene brachial plexus block (single shot with 0.75% ropivacaine up to 150 mg) Paracetamol 1g IV Ketorolac 30 mg IV Ondansetron 4 mg IV	Titration with IV morphine is needed (ie after GA with remifentanil) to NRS ≤4 Morphine IV in continuous infusion by elastomeric pump (up to 20 mg/die) Paracetamol 1g IV TID NSAIDs IV as needed Ondansetron 4 mg IV BID Regional analgesia: Yes/No	Titration with IV Morphine is needed (ie after GA with remifentanil) to NRS ≤4 SSTS Paracetamol 1 g IV TID Ondansetron 4 mg IV BID Regional analgesia: Yes/No
Major abdominal surgery		General anesthesia (± epidural anesthesia) TIVA/TCI Morphine 0.05-0.1 mg/kg at least 30 minutes before surgery end Ketorolac 30 mg IV Paracetamol 1 g IV Ondansetron 4 mg IV	Epidural analgesia (if available), ropivacaine 0.1% or levobupivacaine 0.125% 6-8 ml/h Paracetamol 1 g IV as rescue therapy OR Morphine bolus 1 mg (PCA) 10 minutes lock-out, max dose 5 mg/h Ketorolac 30 mg IV Paracetamol 1 g TID Regional analgesia: Yes	SSTS Paracetamol 1 gr TID Ondansetron 4 mg TID Rescue: Ketorolac 30 mg repeatable every 8 h if needed Regional analgesia: No

qs: quantum satis; BID: Twice daily; DBP: Diastolic Blood Pressure; IV: Intravenous; LIA: Local infiltration analgesia; NRS: Numeric Rating Scale; NSAID: Non-steroidal anti-inflammatory drug; PCA: Patient-controlled analgesia; PO: Orally; PONV: Postoperative nausea and vomiting; SSTS: Sufentanil Sublingual Tablet System; TCI: Target Controlled Infusion; TID: Three-times daily; TIVA: Total intravenous anesthesia; TPVB: thoracic paravertebral block.

postoperative pain. In particular, dedicated and shared protocols for the use of SSTS in different surgical settings should be developed, including proper anti-emetic therapy according to the specific type of surgery and risk of postoperative nausea and vomiting.

Conclusions

According to the available evidence and clinical experience, SSTS can represent a breakthrough in the management of post-operative pain, as it provides an effective patient-controlled analgesia in association with a favorable safety profile using an easy-to-use and error-free device. Shared treatment protocols on the use of SSTS should be developed to further increase its use and to improve the fight to postoperative pain.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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