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Sublingual sufentanil, a new opportunity for the improvement of postoperative pain management in Italy

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Abstract. – Despite the availability of national and international guidelines, adequate postoperative pain (POP) management is still a challenge in Italy. One of the potential reasons for the high incidence of surgical patients complaining moderate to severe pain is the difficult application of the currently recommended analgesic techniques in clinical practice. In particular, morphine, the most commonly used systemic opioid in the POP treatment, has some unfavorable pharmacodynamic and pharmacokinetic characteristics for POP management, suggesting a potential relevant improvement by using different opioids.

Many of sufentanil properties make it particularly suitable for POP control: a high affinity for the μ opioid receptor, the highest therapeutic index compared to any other opioid used in clinical practice and the absence of clinically relevant active metabolites.

The elevated potency, together with the high lipophilicity of sufentanil, allow the preparation of a nanotablet, 3 mm of diameter and 0.75 mm of thickness, containing 15 μg of active drug. The sublingual route allows a longer time of drug plasmatic permanence in comparison to IV route, overcoming the need for continuous dosing.

The patient-controlled system, considered in the present review, is preprogrammed to deliver one sublingual tablet of sufentanil with a 20-minute lockout period with a radiofrequency identification thumb tag allowing only the patient to activate the on demand button.

Phase II and III studies have assessed the efficacy of this system in POP management, showing that it was considered more satisfactory than the IV PCA morphine system by both patients and nurses.

The introduction of this simple and innovative system of patient-controlled analgesic administration could represent an opportunity for Italy to update the current practice in POP management.

Key Words:
PCA, Postoperative pain, Sublingual, Sufentanil.

Introduction

Inadequate post-operative pain (POP) management is still a major burden for most healthcare systems. About 70% of the 240 million post-surgical patients every year suffer from moderate to severe pain[1].

Uncontrolled POP may result in significant clinical and psychological changes that may lead to a number of medical complications, including pneumonia, infections, deep vein thrombosis, cardiovascular events, and depression. Pain relief has a key role in multimodal strategies to improve surgical outcome, together with preoperative assessment, information and optimization, reduction of surgical stress, rapid mobilization, and early oral nutrition[2].

In the current practice, the effectiveness of POP management is mainly evaluated through the cost of treatment, the length of stay, and the number of unanticipated readmission; however, these "here and now" outcomes could not be the right questions to ask. A good-quality perioperative care should be measured through patient-centred outcome studies in terms of patients' satisfaction, quality of recovery, quality of life, and incidence of long-term morbidities, such as chronic post-surgical pain (CPSP)[3].

International and national guidelines[4,5] recommend three analgesic techniques, including intravenous (IV) patient-controlled analgesia (PCA), epidural analgesia (EA), and continuous peripheral nerve blocks (CPNB).

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IV-PCA is nowadays the gold standard of acute pain control. The patient is directly involved in POP management and the dose of analgesics is tailored on real patient's need. These elements play a key role in providing better analgesia and superior patient satisfaction than PRN (*pro re nata* - as needed) parenteral opioids. There is no evidence that one opioid via IV-PCA is better than another, however, on an individual patient basis, one opioid may be more indicated than another (i.e. morphine for obese patients and fentanyl for patients with renal impairment)[6]. However, IV-PCA requires systematic information of patients and adequate caregivers training, which may need additional time in the perioperative period. Moreover, IV-PCA pumps are prone to technical problems, including operator errors (i.e. programming and drug mistakes, inappropriate prescription and concentration, accidental bolus administration during syringe change, misconnections) and patient's errors (i.e. failure to understand the device or activation of the pump by others, such as caregivers or relatives)[7].

Regional techniques are used alternatively to direct drug delivery in proximity to the receptor or near the target tissue.

EA provides better postoperative analgesia compared with parenteral opioids, regardless of analgesic drug, location of catheter placement, and type and time of pain assessment[8]. Moreover, EA has been shown to significantly reduce the incidence of postoperative pulmonary complications (PPCs) and to hasten return to postoperative gastrointestinal (GI) function[9]. However, EA is limited by the high rate of failure (about one-third of patients receiving either lumbar or thoracic epidural analgesia)[10], the potential for neurological damage subsequent to spinal hematoma (permanent injury 1:24,000 to 1:54,000 treated patients) and the risk of infections. The increasing use of chronic anticoagulant therapy for cardiovascular diseases, including new oral anticoagulants for atrial fibrillation, significantly limited the use of EA, in favor of alternative regional analgesic techniques, such as paravertebral blocks for thoracic surgery and Transversus Abdominus Plane (TAP) block for abdominal and gynecological surgery.

Finally, in orthopaedic surgery, regardless of catheter location, CPNBs have been shown to provide superior analgesia and fewer opioid-induced side effects[11]. When compared with single-shot peripheral nerve blocks, CPNBs present a number of advantages, including prolonged site-specific local anaesthetic (LA) delivery, better analgesia, and prevention of premature analgesic block regression[12]. However, even with the introduction of ultrasound, PNBs are associated with an increased risk of infection and likelihood of hematoma compared with systemic analgesia[13]. Moreover, CPNBs require additional time to discuss with the patient, to perform the block, and to obtain the onset of analgesia[14].

The most interesting question is why these techniques and drugs introduced over the past 20 years for acute pain management have not improved postoperative outcomes. One possible explanation is the gap between a clinically meaningful advantage and the availability of resources necessary to use these techniques, including the greater risk of possible complications that require additional clinical surveillance[15].

Recognizing the barriers to effective POP management is the first step to achieving optimal post-operative analgesia[16].

In Italy, two surveys have been conducted in 2006 (Post Operative Pain Survey in Italy - POPSI)[17] and 2012 (POPSI-2)[18] on POP management, including data on commonly used analgesic techniques and protocols, healthcare professionals (HCPs) education, availability of Acute Pain Services (APS), and perceived barriers to clinical improvement. Both surveys included about 600 Italian anaesthesiologists with homogeneous regional distribution across the Country. Despite the growing interest in Italy on the topic of "pain", in particular after the introduction of Law 38/2010, that assures the right of citizens to have access to pain therapy, the most recent survey showed no progress in the treatment of acute pain, confirming the suboptimal management, probably related to organizational, cultural, and economic obstacles[18]. A recent survey involving about 300 Italian nurses, who daily play a key role in pain management and spend more time with patients than any other HCP, showed a low level of knowledge in the assessment and management of POP[19]. Implementation of specific training for all the actors involved in the perioperative period (anaesthesiologists, nurses, surgeons, physiotherapists, patients, and relatives) is mandatory. However, according to the results of POPSI-2, in the last years in Italy there was a significant reduction of continuing medical education in postoperative pain control, probably related to the lack of interest by pharmaceutical and medical device companies, which may support the financial expenses of scientific sessions[18].

The most upsetting result of these surveys is that in Italy the most commonly used analgesic technique is the continuous IV infusion of analgesics through elastomeric pump systems (Figure 1). There is no scientific support for the IV use of these devices, as neither randomized controlled trials have ever tested their efficacy against proved analgesic techniques, nor recommendations and guidelines include them among the suggested analgesic approaches. Furthermore, few papers are available on elastomeric pumps use for LA continuous infusion (perineural or near the surgical wound). However, 50% of Italian patients continue to be treated with continuous infusion of opioids or other analgesics. Use of elastomeric pumps presents a number of limitations. They do not guarantee tailored postoperative analgesia and often their use is accompanied by under-dosing of opioids to avoid the risks of a continuous infusion without any safety feedback. The main reasons for not using PCA pumps in Italy resulted the costs that limit the availability, and the length of training for caregivers. Lack of economic resources is also the main reason for the limited number of APS in the Country. Consequently, most of the used protocols are not universally accepted, but have been written in the hospital local setting and often are not completely shared even among anaesthesiologists of the same unit[18].

The introduction of simple and innovative systems of PCA delivery could represent an opportunity for Italy to update the current practice in POP management.

The Ideal Opioid for Patient-Controlled Analgesia

Moderate to severe POP is usually controlled using a multimodal approach, including opioids. Although it is clear that all opioids share the same mechanism of actions, the single molecules have specific pharmacodynamic and pharmacokinetic characteristics that should drive the choice of the opioid according to the type of pain that need to be treated, the most convenient route of administration, and the characteristic of each patient[20-22].

The theoretical characteristics for and ideal opioid for post-operative pain control are:

- a rapid and consistent onset of action supported by a fast equilibration between plasma and the central nervous system (CNS) with a limited efflux transporter effect;
- be devoid of active metabolites that may accumulate post-operatively increasing the risk for prolonged sedation or other adverse effects;
- a limited effect of hepatic or renal dysfunction on clearance;
- an acceptable tolerability profile.

Morphine has some unfavorable pharmacodynamics and pharmacokinetic characteristics for POP treatment, suggesting a relevant improvement by using different opioids; However, it represents the most commonly used opioid for POP control in Italy[18,22-24].

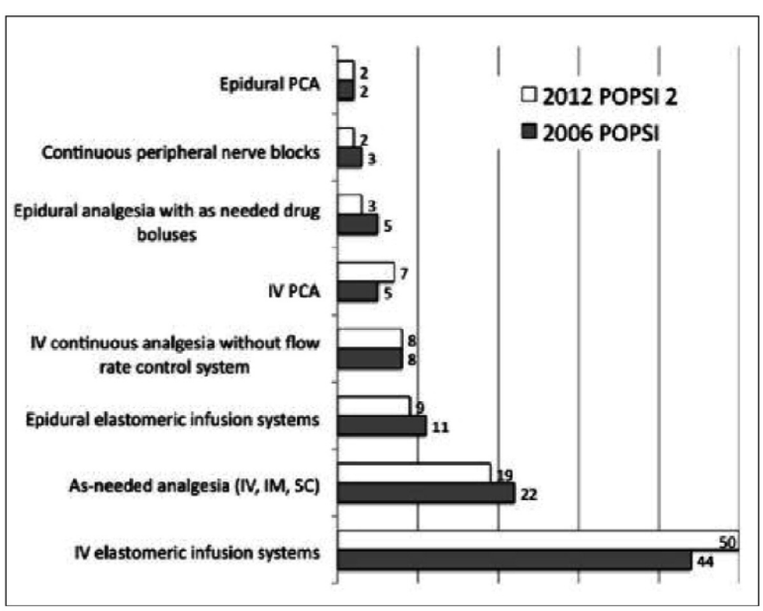

Figure 1. Analgesic techniques in 2006 vs. 2012 in Italy.

Table I. Main pharmacodinamic and pharmacokinetic properties of opioids commonly used for POP treatment.

Opioid	Therapeutic index*[28]	Active metabolites[31]	Plasma/CNS equilibration half-life ($t_{1/2ke0}$) min
Fentanyl	277	No (CYP3A4)	6.6[22,32]
Morphine	71	M3G-M6G	168.0[22-23],
Sufentanil	26716	No (CYP3A4)	6.2[32]

*Therapeutic index is the ratio of LD_{50}/ED_{50} in preclinical studies; M3G: Morphine-3-glucuronide; M6G: Morphine-6-glucuronide

Clinical Pharmacology of Sufentanil

Sufentanil is a highly lipophilic synthetic piperidine derivative opioid, synthesized in the mid-1970s and since then used in anesthesiology for intravenous, epidural and subarachnoid administration[25,26].

This molecule has many pharmacodynamic properties that make it particularly suitable for post-operative pain control. Sufentanil has a high affinity for the μ opioid receptor[27]; it is 300-400 fold more potent than morphine and 5-10 fold more potent than fentanyl[28-30].

The preclinical pharmacology indicates that sufentanil has the highest therapeutic index (ratio between the toxic drug dose and the dose that gives a therapeutic effect in animal studies) compared to any opioids used in the clinic (Table I)[28]. In support to clinical relevance of the high therapeutic index a few clinical studies have suggested a lower incidence of respiratory depression than fentanyl and morphine (Figure 2)[24,30].

Sufentanil, as well as fentanyl, is metabolized in the liver by CYP3A4 and have no clinically relevant active metabolites (Table I)[31]. In contrast, morphine glucuronide metabolites (Morphine 3-Glucuronide and Morphine 6-Glucuronide) are active, and their accumulation represents a risk for a prolonged duration of action and untoward effects. A phase III study, comparing sufentanil sublingual tablet versus IV morphine PCA over a 48-hour dosing period, showed a significant accumulation of plasma morphine 3-Glucoronide in the morphine group[30].

Rate of Equilibration Between the Plasma and Effector Sites (Opioid Receptor) in Central Nervous System

An important parameter to be considered in the choice of the optimal opioid for PCA is the equilibration half-life between the plasma and the μ-opioid receptor site in the CNS, known as $t_{½Ke0}$[22,23].

Obviously, opioids function at CNS receptors, and the plasma/CNS equilibration half time is a reliable parameter for predicting onset of action. The $t_{½Ke0}$ is experimentally calculated by evaluating an objective CNS opioid effect (such as miosis or EEG) and comparing the kinetic of this effect with plasma drug concentration, therefore, determining

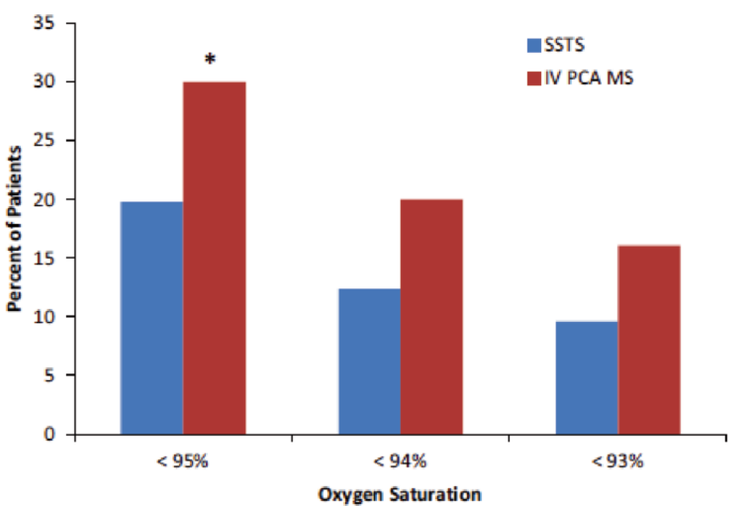

Figure 2. Oxygen desaturation events in a phase III study SSTS vs. IV PCA MS[30].

the time needed for equilibration between site of effect and plasma concentration. For opioids that are lipophilic such as fentanyl and sufentanil this equilibration is rapid (Table I)[28,31]. The presence of efflux transporters such as Glycoprotein P represents a limiting factor for a fast equilibration. Sufentanil is not a substrate for Glycoprotein P, thus guaranteeing a fast and repetitive onset of action[33]. In contrast morphine and its metabolites are more hydrophilic, have a limited ability to diffuse in a lipidic environment (CNS) and are substrate for efflux transporters[33]; as a consequence the plasma/CNS equilibration of morphine and its metabolites can take hours at difference with the few minutes needed for sufentanil and fentanyl (Table I). In the IV PCA setting, the delayed equilibration may be overcome by a possible initial overshoot of drug administration by patients or by rescue drug bolus, adding a risk for side effects.

Therefore, based on its therapeutic index, lack of active metabolites and short $t_{1/2Ke0}$, sufentanil has optimal characteristics for postoperative PCA. The obvious question is why this molecule is not routinely used for IV PCA. The answer is that sufentanil when injected IV has a rapid high Cmax, followed by a short alpha-redistribution half-life, thus resulting in a rapid onset, as described above, but also in a very short duration of action requiring a high redosing frequency. This pharmacokinetic problem has been overcome by administering sufentanil via the sublingual route rather than IV.

Pharmacokinetic of Sufentanil Sublingual Tablet

The elevated potency together with the high lipophilicity of sufentanil allows the preparation of nanotablet, 3 mm diameter and 0.75 mm thick, containing 15 μg of active principle (sufentanil sublingual tablet 15 μg, SST). The small dimensions of the nanotablet are intended to minimize taste and salivation, when placed under the tongue, reducing swallowing of saliva containing drug and maximizing transmucosal uptake.

Sublingual absorption of SST was evaluated in several studies, and results demonstrated the favorable pharmacokinetics that is obtained coupling sufentanil with the sublingual route of administration[34,35].

SST, delivered sublingually as single dose, demonstrated a media plasma half time ($Pt_{1/2}$, i.e. the time from Tmax to time at which plasma concentration reached half of Cmax after drug discontinuation) of 2.2 hours, significantly longer than that measured after IV administration of 0.2 hours (Table II)[34]. The sublingual route allows a longer time of drug permanence in plasma, and one of the main concern of using sufentanil for IV PCA, that was the need for too frequent dosing, was therefore overcome.

Sufentanil undergoes a significant first pass effect by the liver, that causes bioavailability by os to be low, <10%[34]. As already reported above, the high potency of sufentanil can be exploited in the nanotablet adhesive formulation that reduces the amount of sufentanil solubilized in the saliva and inadvertently swallowed; together with sublingual route of administration there is guarantee for a rather high bioavailability, that in relation to IV administration is 59%.

The pharmacokinetic properties of a single-dose administration of sufentanil 15 μg by IV route of administration reached a mean Cmax of 445 pg/ml, while the measured Cmax after sub-

Table II. Pharmacokinetic properties of 15 μg of sufentanil administered as IV bolus or as SST in single and repeated-dose[34-35].

Parameter	Sufentanil 15 mcg			
	IV	Sublingual single dose	Sublingual after repeated doses	Sublingual 40 repeated doses
$AUC_{0\text{-}inf}$ (h.pg/ml) Mean (SD)	273.8 (61.1)	125.5 (47.7)	4216.6 (1225)	75.1 (22.4)
C_{max} (pg/ml) Mean (SD)	445.1 (312.0)	35.0 (12.2)	276 (77)	249.6 (72.1)
T_{max} (h) Mean (SD)	0.1 (0.0)	0.9 (0.3)	10.9(0.5)	0.4 (0.2)
$PT_{1/2}$ (h) Mean (SD)	0.2 (0.1)	2.2 (0.9)	ND	2.5 (0.6)

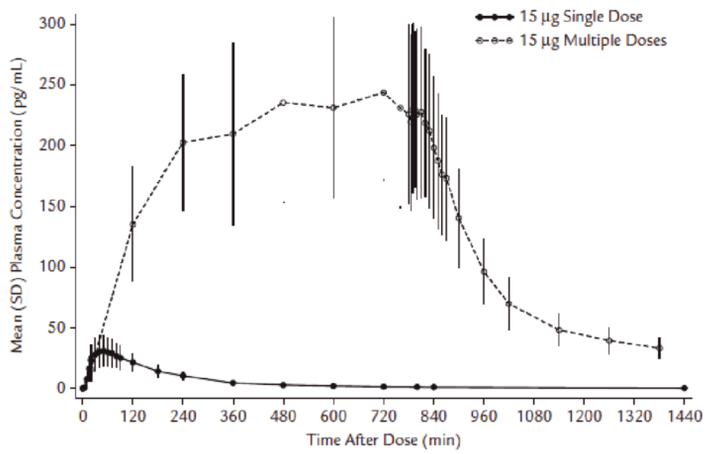

Figure 3. Sufentanil plasma concentration after single and repeated SST doses[34].

lingual route of the same dose was 35.0 pg/ml (Table II)[34,35]. These data clearly indicate that sublingual administration avoids the peak plasma concentrations that can be of concern for safety.

In the treatment of POP, the patients can self administer repeated doses of SST with a lockout period of 20 minutes. The pharmacokinetic parameters of repeated dosing of SST, one tablet every 20 minutes for 40 doses was assessed in healthy volunteers. As expected both Cmax and AUC were greater after repeated administration compared with those after single dose of SST (Table II)[34,35]. However, it is important to underline that the mean Cmax measured with repeated sublingual administration of sufentanil tablets at maximal frequency of dosing (every 20 minutes) was 249.6 pg/ml, that remained lower than that achieved after a single IV dose of sufentanil (445.1 pg/ml). These results suggest a great margin of tolerability for SST also after repeated dosing, avoiding rapid high plasma concentrations that may produce undesirable adverse effects (Figure 3).

Another important parameter that needs to be taken into consideration in the patient– controlled self administration paradigm with repeated sufentanil dosing administration, is the $Pt_{1/2}$ following the last dose of SST after 40 sequential doses every 20 minutes compared to a single dose. It is important that this parameter would remain fairly stable allowing a predictable and consistent offset of the analgesic effect of sufentanil after the last administration, avoiding the risk of delayed adverse effects. The mean $Pt_{1/2}$ after a single dose administration of SST was calculated to be 2.2 hours, that become 2.5 hours after the last repeated (of 40 sequential doses) dose, indicating no risk of drug accumulation (Table II). It has also to be underlined that in this study[34], SST was administered at the maximum allowed frequency (every 20 minutes), while in the phase 3 studies, the median interval between dosing in patients was 80-100 minutes[30,35,37].

In contrast, for fentanyl it has been reported that a prolonged infusion over 4 hours results in a relevant increase of its $Pt_{1/2}$, due to high volume of distribution and its long elimination half-life ($Pt_{1/2}$ = 180 minutes after 4 hours and 290 minutes after 8 hour infusion)[38].

Risk of Drug Interactions

Sufentanil is metabolized in the liver by the CYP3A4 enzyme, and as a consequence co-administration of drugs that affect CYP3A4 may alter sufentanil metabolism. Indeed in a phase 1 study, ketoconazole a well known CYP3A4 inhibitor was co-administered, and a slightly higher but not significantly different sufentanil peak plasma levels were measured (mean Cmax of 40 pg/ml with sufentanil alone and 46 pg/ml together with ketoconazole)[35]. The clinical relevance of interactions in the post-operative context is however questionable, considering the short time of opioid administration in a well-controlled hospital environment. Moreover, the patient-controlled nature of this type of analgesia allows the patients to adjust for any altered metabolism of sufentanil.

Use of SST in Renal or Hepatic Impairment

In a phase 3 study[30] there were no significant differences in plasma sufentanil concentrations measured at 24 or 48 hours between patients with renal impairment (glomerular filtration rate esti-

Table III. Main efficacy results of the phase II studies, sublingual sufentanil tablets versus placebo[35].

Efficacy parameter	Total knee arthroplasty				Open abdominal surgery		
	Sublingual sufentanil			Placebo (n = 24)	Sublingual sufentanil		Placebo (n = 30)
	5 µg (n=24)	10 µg (n=25)	15 µg (n=20)		10 µg (n=29)	15 µg (n=29)	
SPID-12, LS mean (SEM)	3 (6)	1 (6)	13 (6)*	-7 (6)	22 (4)**	28 (4)**	3 (3)
TOTPAR-12	17 (2)	13 (2)	19 (3)	12 (2)	23 (2)**	26 (2)**	14 (2)
Discontinuation due to inadequate analgesia, n (%)	13 (54)	11 (44)	5 (25)**	16 (67)	7 (24)**	3 (10)**	21 (71)

*p<0.05 compared with placebo; **p<0.001 compared with placebo.

mate based upon creatinine) and those with normal renal function. Moreover, no significant differences for plasma sufentanil were measured when comparing those patients with mild to moderate hepatic impairment (as assessed by aspartate and alanine aminotransferases and total bilirubin) and those with normal hepatic function. Indeed, as reported above, sufentanil does not possess active metabolites that could eventually accumulate in renal impairment.

The efficacy of SST in the Treatment of Acute Postoperative Pain

SST, the new sublingual formulation of sufentanil, was object of two phase 2 studies evaluating different dosages in the management of POP following elective total knee replacement (TKR) and open abdominal surgery (OAS)[36]. In the post-anesthesia care unit patients were randomized to receive placebo, or an active treatment with sublingual sufentanil (5, 10, or 15 µg in the TKR study and 10 or 15 µg in the OAS trial). The study drug was administered by an investigator as needed at the request of the patient with a minimum interval of 20 minutes. One-Hundred-One and 94 patients were respectively enrolled and randomized in the TKR and the OAS study. The summed pain intensity difference (SPID) scores for the 15 µg dose were higher than placebo at all time points in the TKR study and at all time points starting from the first 3 hours for the OAS study. The percentages of patient discontinuation in the studies due to inadequate analgesia were dose related. The average interdosing interval for the patients treated with the 15 µg dosage was 73 to 101 minutes and confirmed the hypothesis that the sublingual administration of sufentanil can effectively treat POP without the need of frequent on demand doses. The prevalence of adverse events (AEs) was similar among groups, except for a higher incidence of pruritus in the groups treated with sufentanil.

The phase 2 dose-finding studies showed that the dose of 15 µg of sublingual sufentanil (SST) was the optimal dosage in terms of efficacy and safety (Table III and Table IV) and it was the one tested in the phase 3 program.

In the phase 3 studies, SST was administered with a preprogrammed, noninvasive patient-controlled system (sufentanil sublingual tablet sys-

Table IV. Adverse Events of the phase II studies, sublingual sufentanil tablets versus placebo[35].

Possibly or probably related AEs occurring in ≥5% in any group	Open abdominal surgery or total knee arthoplasty (%)			
	5 µg (n=24)	10 µg (n=55)	15 µg (n=49)	Placebo (n=54)
Nausea	29	40	37	32
Vomiting	8	11	6	6
Dizziness	13	4	2	2
Pruritus	4	7	12*	0

AE: Adverse event, *p=0.042 vs. placebo.

Table V. Adverse events in the phase III study comparing SSTS vs. IV PCA MS (AE > 5% in either treatment group)[30].

Adverse Event occurring in ≥5% in any group	SSTS % (n = 177)	IV PCA MS (%) (n = 180)
Nausea	42.9	40.0
Vomiting	13.0	11.1
Constipation	11.3	8.3
Oxygen saturation decreased	9.6	9.4
Headache	7.9	6.7
Hypotension	6.2	11.1
Dizziness	5.6	3.3
Pruritus	4.0	7.8

IV PCA MS, Intravenous patient-controlled analgesia morphine sulfate, SSTS, sufentanil sublingual tablet system.

tem – SSTS; Zalviso®). The device was preprogrammed to deliver one sublingual tablet of sufentanil with a 20-minute lockout period. A radiofrequency identification thumb tag allows only the patient to activate the on demand button. To better understand the results of these studies, it is important to underline that patients involved were not treated with a multimodal approach and the enrollment was not limited by age and body mass index (BMI).

Two placebo-controlled trials and one active comparator study were conducted in patients undergoing major abdominal and orthopedic surgeries[30,37,39].

The two placebo-controlled studies evaluated the efficacy and safety of SSTS for the management of moderate to severe acute postoperative pain in patients undergoing major open abdominal or orthopedic surgery[37,39]. Patients were randomized to receive SSTS 15 μg or an identical system containing placebo tablets. Patients treated with the SSTS showed a significantly higher SPID and total pain relief (TOTPAR) scores compared with patients in the placebo group. The effectiveness of sufentanil was confirmed by a greater drop in pain intensity compared with baseline (PID score) than in the placebo group. In both the studies patients in the SSTS group showed an average interdosing time significantly higher compared with the 20 minutes preprogrammed lockout period. In the majority of the patients, a single cartridge of 40 nanotablets was enough to provide analgesia for at least 48 hours[39].

Compared with the patients treated with placebo, a higher percentage in the SSTS group reported "success" on the patient global assessment (PGA) as well as, at the same time points, more health care professionals reported "success" on the health care professional global assessment (HPGA).

Patients in the SSTS group showed a similar safety profile in terms of AEs considered potentially related to study drug compared with patients in the placebo system group. This data is relevant due to the fact that the population in the two placebo-controlled studies can be considered at high risk of AEs. In fact, a significant percentage of patients enrolled were older than 65 years of age or with a BMI ≥30 kg/m^2, reflecting the real-life.

The active comparator study was conducted and published by Melson et al[30], to evaluate the efficacy and safety of SSTS compared to the gold standard IV PCA morphine sulfate (IV PCA MS). To test the analgesic efficacy of the drugs involved in the study, as well as the delivery method, the two groups (SSTS vs IV PCA MS) were compared in terms of 48 hours patient global assessment (PGA 48) of method of pain control. The parameters selected for the IV PCA MS (bolus of 1 mg with a lockout period of 6 minutes) were based on the daily practice of many hospitals. Moreover, they allowed an equivalent dose of morphine compared to sufentanil in the same 20 minute time period (15 μg SST = 3 mg IV MS based on 300 to 400 potency factor and 60% bioavailability of SST).

Three hundred fifty-seven patients undergoing open abdominal or orthopedic major joint surgery (SSTS [n = 177] and IV PCA MS [n = 180]) were treated and the 79% completed the 48 hours study period. There were no significant differences between the two groups related to the proportion of patients who discontinued from the study due to an AE or inadequate analgesia. The 78.5% of the patients in the SSTS group achieved "success" on the PGA 48 compared to the 65.6% in the IV PCA MS group, demonstrating a statistical superiority. Also, the HPGA was statistically in favor of SSTS at all time points. The two groups did not present significant differences in terms of SPID and TOTPAR scores, even if patients treated with sublingual sufentanil showed a faster onset of pain reduction with a significantly greater PID at 1, 2, and 4 hours (Figure 4). The faster onset of the analgesic effect of SSTS compared with IV PCA MS was confirmed by the time required to achieve a mean PID of 1.3 (1.3 hours *vs*. 7 hours) which has been demonstrated clinically significant in the treatment of acute pain[40].

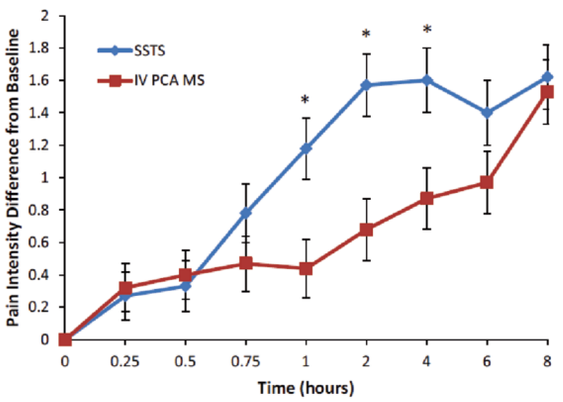

Figure 4. PID over the first hours of treatment in the phase III study comparing SSTS vs. IV PCA MS[30].

The mean interdosing interval during the study period was 81 minutes and 47 minutes, in the SSTS and IV PCA MS groups respectively.

There were no significant differences for any adverse event between treatment groups (Table V). Nevertheless, in a high-risk population (for age (52.4% ≥ 65 years) and BMI (42.9% ≥ 30) a lower percentage of patients in the SSTS group compared with IV PCA MS experienced oxygen desaturation episodes (< 95% recorded on pulse oximetry) (Figure 2). This difference between the two groups can be explained by the fact that morphine has a lower therapeutic index and a delayed effector site penetration compared with sufentanil. Moreover, the morphine active metabolite morphine-6-glucuronide (M6G) could increase the risk of oxygen desaturation in particular in patients with renal impairment.

Based on the easy-of-care (EOC) questionnaire completed by patients and nurses the SSTS was considered easier to use compared with the IV PCA system and more satisfactory by both, patients and nurses (Table VI).

Conclusions

Even nowadays, the treatment of acute postoperative pain remains a challenge. Despite the availability of national and international guidelines, a significant percentage of patients still experiences moderate to severe pain after surgery[16]. These guidelines recommend continuous regional analgesic techniques (epidural or peripheral nerve blocks) or the systemic administration of opioids trough a patient-controlled device as therapies of choice after scheduled surgeries characterized by moderate to severe pain[4,5]. One of the possible reasons that can justify the high incidence of uncontrolled pain in the postoperative period is the poor adherence to these guidelines[17,18]. In fact, in Italy the most commonly used pain treatment in the postoperative context is a continuous infusion of morphine through an elastomeric pump. Even

Table VI. EOC questionnaire in the phase III study comparing SSTS vs. IV PCA MS[35].

EOC parameter, mean (SD)	Orthopedic and open abdominal surgeries		
	SSTS	IV PCA MS	*p*-value
Patient EOC			
n	177	180	
EOC total, mean (SD)	4.5 (0.5)	4.1 (0.7)	<0.001
Confidence with device	4.7 (0.6)	4.5 (0.8)	0.015
Comfort with device	4.5 (0.7)	4.3 (0.7)	0.041
Ease of movement	4.7 (0.7)	3.9 (1.4)	<0.001
Dosing confidence	4.7 (0.7)	4.5 (0.9)	0.003
Pain control	3.6 (1.3)	3.2 (1.4)	0.004
Knowledge/understanding	4.5 (0.9)	4.1 (1.1)	<0.001
Overall satisfaction	4.2 (1.0)	3.8 (1.0)	0.004
Nurse EOC			
n	44	43	
EOC total, mean (SD)	4.3 (0.6)	3.8 (0.8)	0.017
Time-consuming	0.9 (0.7)	1.2 (0.9)	0.076
Bothersome	0.5 (0.6)	1.1 (0.9)	0.006
Overall satisfaction	3.9 (0.7)	3.4 (0.6)	<0.001

AE: Adverse event, *p=0.042 vs. placebo.

where the electronic PCA devices are available, they are not used systematically probably due to some limitations of the currently available IV PCA devices. These limits include for instance the requirement of an IV line with a potential increased risk of infection and analgesic gaps due to IV catheter infiltration or IV tubing obstruction. Moreover, the possibility of program modifications of the electronic pump can lead to medical and nurse errors with an increased risk of under and over-treatment[41] and significant costs for each error event[42].

The sufentanil sublingual tablet system is instead preprogrammed and it does not require an IV line. The non programmable nature of SSTS in the fragile patient may be perceived as a limitation but if it is important to underline that data from the phase 3 program of SSTS showed an effective treatment of pain with a significantly higher mean interdosing interval compared with the preprogrammed lockout, giving the possibility to achieve the therapeutic dose through a wide range of on-demand administrations until the attainment of the 20 minutes interdosing interval. In this view, the choice not to limit the enrollment of patients in the phase 3 program by age and BMI, avoiding the selection of a population far from real practice, makes the safety profile showed by SSTS clinically significant. More data related to the effectiveness of the SSTS in the highly opioid-tolerant patients has to be collected, due to the fact that this small group of patients should probably benefit of a tailored approach to postoperative pain.

The selection of an opioid with a close association between patient dosing and peak of CNS effect is fundamental to avoid dose accumulation and to reduce the occurrence of side effects[34]. Morphine presents a slow-equilibrating time and sometimes requires multiple doses to optimize the analgesia in the initial period of treatment, potentially followed by a delayed opioid balance with CNS μ receptors, therefore producing AEs. The dose-stacking phenomenon is exacerbated by the fact that the active metabolite of morphine, M6G, has an even longer equilibration time with the CNS compared to morphine[43]. On the contrary, sufentanil presents a faster uptake from the plasma to the μ-opioid effector site in the CNS with a $t_{1/2Ke0}$ of 6.2 minutes.

In conclusion, a peak of plasma concentration of 18 min after repeated sublingual administration showed by Willsie et al, matching with the lockout period of 20 minutes preprogrammed for the SSTS device, a rapid equilibration time with CNS and the lack of active metabolites make sufentanil the ideal opioid for PCA administration. Moreover, to guarantee adherence to the guidelines, the nanotablets of sublingual sufentanil can be delivered only through a specific preprogrammed patient-controlled device, that potentially decreases the risk of and-over-treatment related to drug and/or medical errors. The SSTS was also favorably rated by HCP, including nurses.

A non-invasive and easy to use patient-controlled device with an effective and safe opioid like the SSTS system may hopefully represent an alternative to the too frequently used elastomeric pumps, improving the adherence of the Italian postoperative pain management to the currently available guidelines.

Further studies are needed to better understand the clinical role of SSTS within a multimodal approach to postoperative pain management.

Authors' Declaration of Personal Interests

Andrea Fanelli has served as speaker for Ibsa, as consultant for Abbvie, Angelini and Molteni and as advisory board member for Grunenthal.

Paola Sacerdote has served as Advisory Board Member for Grunenthal, and as speaker for Helsinn Healthcare.

Flaminia Coluzzi has served as Advisory Board Member for Grunenthal and as speaker for Angelini and Mundifarma.

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