Original Article

Sufentanil sublingual tablet system (Zalviso®) as an effective analgesic option after thoracic surgery: An observational study

ABSTRACT

Introduction: Sufentanil sublingual tablet system (SSTS) (Zalviso®) is a sublingual system for patient controlled analgesia, demonstrated to be an effective strategy for pain control after major abdominal and orthopedic surgery. We present a prospective observational study on the use of SSTS for the management of postoperative pain after thoracic surgery. The aim of this study was to assess the efficacy of Zalviso® in reducing pain scores and increasing respiratory ability during postoperative period.

Materials and Methods: There were about 40 patients underwent video assisted thoracoscopy were included in the study. All the enrolled patients signed the informed consent were educated to the use of the device. Pain numeric rating scale values (NRS) were recorded at awakening from anesthesia (T0) and during the next hours, both at rest and with cough. We evaluate the time to obtain a mean NRS value ≤3 and difference in pain scores between first and subsequent measurements as the primary outcomes. The ability to use incentive spirometer and eventual drug adverse effect were evaluated as secondary outcomes.

Results: All patients in recovery room experienced moderate to severe pain. Pain score at rest and coughing decreased to a mean NRS value ≤3 (mild pain) respectively after 2 and 6 hours and the pain score difference continued to increase significantly after repeated measurements. 67.5% of patients resumed the original spirometric ability in pod 1; 9.5% in pod 2; 12% in pod 3. Only three patients out of forty (7,5%) experienced nausea; one patient (2,5%) had a vomiting episode.

Conclusion: Our study showed SSTS as an effective option for postoperative pain management in thoracic surgery, improving pain scores and respiratory ability.

Key words: Anaesthesia; pain management; patient-controlled analgesia; postoperative care

Introduction

Pain after thoracic surgery is generally considered to be from moderate to severe and could affect pulmonary function by reducing deep breathing and coughing ability, resulting in reduced clearance of secretions, atelectasis and pneumonia;[1] nonetheless, severe postoperative pain in thoracic surgery is associated with a higher rate of pain chronicization.[2] For these reasons, optimal pain management after thoracic surgery is mandatory since without an effective pain control patients may have an adverse outcomes.[3]

Moderate to severe postoperative pain, is usually controlled with a multimodal strategy approach that includes the use of opioids and regional techniques. In thoracic surgery,

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intravenous patient controlled analgesia (PCA), thoracic epidural and continuous paravertebral block are strictly recommended by international guidelines.[4,5] However, these regional techniques are invasive, riskful,[6] requiring skilled operators and a challenging postoperative management. Moreover, continuous regional techniques may be at risk of failure, due to catheter displacement or infusion pump malfunction.[7,8]

Sufentanil sublingual tablet system (SSTS) (Zalviso®) is a sublingual PCA system, it is not invasive and it has an established, not modifiable program, set up by the healthcare professional [Figure 1].

To administer a dose, the patient places the dispenser tip under the tongue and, using the thumb with an ID Thumb Tag attached to it, presses the dosing button on the Controller to deliver a 15-µg (single tablet) Sufentanil dose.

Zalviso is indicated for postoperative moderate to severe pain. Analgesia with SSTS has been demonstrated to be an effective strategy for pain control after major abdominal and orthopedic surgery.[9-12]

Furthermore, compared to opioid-based intravenous PCA, SSTS proved to a more rapid onset of analgesia and higher rates of success, with an adverse event profile typical of that of other opioids and generally similar to that of placebo.[9]

Figure 1: The Zalviso system. The Zalviso® system consists of the following components: a disposable dispenser tip (1); a disposable dispenser cap (2); a cartridge of 40 Sufentanil sublingual 15 mcg tablets (approximately a two-day supply) in a disposable radio frequency identification and bar-coded cartridge (3); a reusable, rechargeable handheld controller (as pictured, nurse-side view) (4); an authorized access card (5) and a tether (6)

We described our experience with SSTS for the management of postoperative pain after thoracic surgery, investigating about its efficacy in treating moderate to severe postoperative pain, clinically identified by numeric rating pain scores >3.

Materials and Methods

After ethical committee approval (prot. 13.17 TS ComEt CBM), we carried out a descriptive observational study with the SSTS for postoperative analgesia in 40 patients underwent VATS (video assisted thoracoscopy).

Before starting the study, nurses staff, and clinicians of the thoracic surgery ward have been trained to the management of the system. There are patients under 18 years of age, ASA status IV, with visual or upper limbs impairment, with history of opioid abuse or with psychiatric or neurological diseases were excluded from the study. Our primary endpoint was to assess the effectiveness of the SSTS as sole drug for postoperative analgesia, thus pain score values (numeric rating scale, NRS) at rest and coughing, were recorded at awakening from anesthesia (T0), then at 2, 6, 12, 24, 36, 48 and 72 hours after surgery. This outcome was evaluated considering:

- Time to obtain a mean NRS value ≤3
- Difference in pain score between first and subsequent measurements.

Tablet consumption and tablet requests in the lockout period were recorded as well.

As secondary endpoints were studied: the ability of the patient to perform deep inspiration, recording efficacy in the use of a three balls incentive spirometer (Triflo®) and time of returning to preoperative normal values; the incidence of nausea or vomiting and other adverse effects; the postoperative day of the first bowel movement; the number of calls for help or for pain; the number of night awakening episodes due to pain; the overall patient's satisfaction about the method, taking into account easiness of use and quality of analgesia.

Before the surgery, after obtaining informed consent, all the enrolled patients were educated to the use of the device. All patients were managed with i.v. preemptive analgesia (dexamethasone 8 mg, acetaminophen 1 g, ketorolac 30 mg), general anesthesia with selective left endobronchial intubation, maintained with fentanyl 5-10 mcg/kg, sevoflurane (MAC 1.0), remifentanil TCI 0,5/2 ng/ml. After the

surgery, all patients were transferred to the post anesthesia care unit (PACU) and after complete recovery from general anesthesia, the first NRS value was pointed out (T0) and all the patients took the first Sufentanil tablet under the guidance and supervision of the anesthesiologist. All patients had scheduled antiemetic prescription along the entire period of SSTS administration, in order to prevent opioid related nausea and vomiting.

Continuous variables are presented as means with standard deviations (SD) and categorical variables as frequencies. Repeated pain scores are compared using the sum of pain intensity difference (SPID) at 12, 24, 36 and 48 hours.

Variables are compared in subgroups (young vs. elderly patients) using Student's T-test (software Microsoft Excel version 14.6.5).

Results

The primary endpoint results (pain scores at rest and with cough) expressed as mean plus standard deviation can be seen in Tables 1 and 2.

The patients tablet consumption can be seen in Figure 2.

The number of doses requested in the lockout period and not delivered can be seen in Table 3.

Regarding performance at spirometry, 67.5% of patients resumed the original ability to use the triflo® in the first post-operative day (POD) [Figure 3].

There were only three patients (7,5%) experienced nausea; one patient (2,5%) had a vomiting episode. First bowel movement was recorded within the 72 hours of observation in all the subjects, 97,5% in the first 48 hours. No episodes of respiratory depression were observed.

No patients called at the staff because of pain. 13 patients called for ID band malfunction and replacement. No patients reported night awakening due to pain. No episodes of delirium or pruritus were pointed out. Three patients wanted to discontinue the treatment. No other

Table 1: Pain scores at rest

Time after surgery	NRS at rest (mean±SD)	TW - SPID	AUC - SPID
0 h	4.56±1.91	-	-
2 h	3±1.31	-	-
6 h	2.08±1.32	-	-
12 h	1.81±1.41	29.54	25.33
24 h	1.73±1.19	63.5	58.81
36 h	1±1.37	-	-
48 h	0.49±1.02	155.06	142.93
72 h	0.27±0.84	258.02	243.25

NRS: Numeric rating scale; SD: Standard Deviation; h: Hours; SPID: Summed pain intensity difference analysis; TW: Time weighted; AUC: Area under the curve.

Table 2: Pain scores with cough

Time after surgery	NRS with cough (mean±SD)	TW - SPID	AUC - SPID
0 h	6.65±1.91	-	-
2 h	4.54±1.31	-	-
6 h	3.78±1.32	-	-
12 h	3.54±1.41	34.36	31.81
24 h	3.19±1.19	75.88	71.23
36 h	2.08±1.37	-	-
48 h	1.45±1.02	193.12	178.03
72 h	1.03±0.84	328.24	307.99

NRS: Numeric rating scale; SD: Standard Deviation; h: Hours; SPID: Summed pain intensity difference analysis; TW: Time weighted; AUC: Area under the curve.

Table 3: Doses requested in the lockout period and not delivered

Time after surgery	Mean	Standard deviation
0 h - 2 h	1.14	1.01
2 h - 6 h	1.31	1.04
6 h - 12 h	0.81	1.1
12 h - 24 h	0.47	0.83
24 h - 36 h	0.12	0.33
36 h - 48 h	0.49	1.29
48 h - 72 h	0.09	0.28
0 h - 72 h	4.41	2.51

Number of times a patient requested one dose in the lock-out period

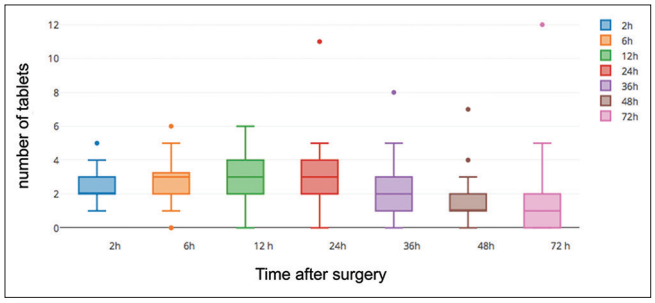

Figure 2: Delivered Sufentanil tablets. h: hours

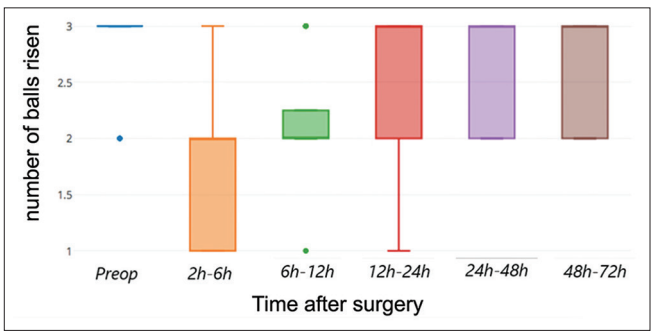

Figure 3: Performance with spirometer. h: hours; Preop: preoperative period

interruptions were observed due to inadequate pain control or adverse effects.

Moreover, in a 5 degrees subjective satisfaction level score, 72% of patients reported a very high level of satisfaction while no patients reported low satisfaction [Figure 4].

As an adjunct to these results, we decided to divide the group in two subgroups on the basis of age: group A (24 patients over 65 years of age) and group B (16 patients under 65 years of age) and search for differences between them: we found out that younger patients consumed more tablets compared with older patients with a statistically significant difference [Table 4]. All the other results were evaluated and compared in the two groups, but resulted no other differences.

Discussion

The NRS results showed the efficacy of SSTS after its administration.

All patients in recovery room (T0) experienced moderate to severe pain with a score around 5 at rest and around 7 at cough; all of them experienced a fast benefit from first and second tablet intake, as pain score at rest and coughing quickly decreased to a mean NRS value ≤3 (mild pain) respectively after 2 and 6 hours. Furthermore, the pain score difference continued to increase significantly after repeated measurements, both at rest and with cough.

Table 4: Tablet Consumption among different ages

	Group A	Group B	*P*
Mean	14.85	20	0.0144
Standard deviation	4.7	7.59	-

Group A: ≥65 years of age; Group B: ≤65 years of age

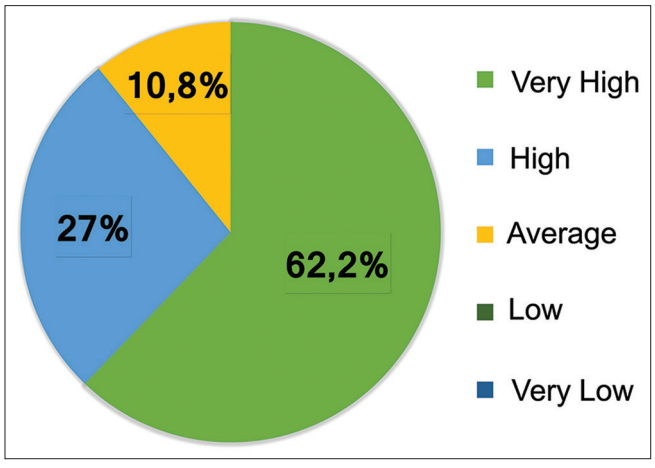

Figure 4: Patients satisfaction. 5 degrees subjective satisfaction level score (very high; high; average; low; very low)

Moreover, the effectiveness of SSTS for thoracic surgery is confirmed by the results we obtained with the three ball incentive spirometer. All the patients had a reduced efficacy in the first few postoperative hours, this reduction was related to the pain evoked by the forced inspiration, for this reason almost a ball less then preoperatively was risen by all the patients but the 67,5% of them regained the original ability within 24 hours. It has been interesting to see that in some patients, in the first 6 hours, the ability to rise an extra ball was achieved within 10 minutes after taking a tablet.

We assume this as a proof of the effectiveness of the drug in managing acute, incident pain.[13]

Despite the early oral feeding we observed a very low incidence of nausea (7,5%), and the only vomiting episode (2,5%, 1 out of the 3 experiencing nausea) was related to a missed prescription of the antiemetic drugs. Constipation was not observed, maybe early oral feeding helped to prevent this adverse effect of opioids.

These results could be taken into account for further research in order to evaluate SSTS prescription in ERAS protocols.[14]

After data analysis, we observed a patient sample of more than 66 years of mean age, thus we decided to divide the analysis into two groups, in order to evaluate the safety of this system in the aged population. The results showed a reduced mean tablet intake in elderly people along all the observation period. This reflects the, well known, age related, pharmacokinetic modifications, especially for lipophilic drugs like Sufentanil.[15] Global reduction of body water and relative increase in fat of aged, results in a faster onset and in a prolonged half-life, with an apparent increase of potency of the drug.[16] The older patients, obtained same effects by reducing the doses. Absence of adverse effects, especially delirium or respiratory depression, indicated the SSTS as a safe method for postoperative analgesia in the aged population.

This study lacks a control group, as we assumed pain relief and the increase in spirometry performance as the proof of efficacy for SSTS: this represent a limitation, and it underlines the need of more studies.

Conclusion

Our study showed SSTS as an effective alternative to regional analgesia techniques for postoperative pain management in thoracic surgery. Despite the opioid based strategy, noninvasiveness and low incidence of adverse effects, make

the system a considerable choice in ERAS protocols. SSTS is safe, quick and a rescue dose itself. The most important requirement is the patient's education and this objective could be achieved only through a comprehensive staff education. Our data derived by a small sample analysis. Randomized controlled trial are needed to confirm our findings.

Author's Contribution

All authors participated in drafting the article or revising it critically for important intellectual content and all authors approved the final version.

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Conflicts of interest

There are no conflicts of interest.

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