

Randomized, Double Blind, Double-Masked, Parallel-Group Clinical Study to Compare the Effectiveness of Oral Transmucosal Fentanyl 200 µg vs Morphine Hydrochloride 2 mg IV in the Treatment of Postoperative Pain

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Abstract

Postoperative pain is an acute pain that appears due to the surgical act, reaching its maximum intensity in the first 24 - 48 hours after surgery. Postoperative pain control reduces possible postoperative complications, as well as the patient's stay in the medical institution. **Objective:** This study compared the effectiveness and side effects of oral transmucosal fentanyl citrate (OTFC) with IV morphine in the control of postoperative pain. **Methods:** Seventy-three patients (Fentanyl group: 27, morphine group: 46) were included. Changes in pain were evaluated with Visual Analog Scale (VAS) and Pain Relief Scale, Pain Intensity Differences (PID), Sum of Pain Intensity Differences (SPID), and Total Pain Relief (TOTPAR). At time zero, 15, 30, 45 min and 1, 2, 3, 4, 5 and 6 h. **Results:** The decrease in pain intensity measured by VAS was similar in both groups with no significant differences at any of the measurement points. Both products produced a significant increase in the Pain Relief scale, with no differences between groups at any of the measurement times. There were no differences between groups when comparing PID. Comparing SPID between groups, there were no differences at 15, 30 minutes, then there were significant differences in favor of the Fentanyl group up to 6 hours. Both products produced a significant increase in the TOPAR scale, with no differences between groups at any of the measurement times. The appearance of adverse effects was similar in both groups. **Conclusions:** Both products produced a significant reduction in the measures of pain intensity (VAS), increase of

SPID, as well as a significant increase in the Pain Relief scale, a significant increase in the TOPAR scale, with no differences between the groups. The number of adverse effects was similar. The convenience of OTFC administration allows its administration without the special conditions needed for the administration of IV morphine.

Keywords

Postoperative Pain, VAS, PR, PID, SPID, TOTPAR, Fentanyl, Morphine

1. Introduction

Postoperative pain is an acute pain that appears due to the surgical act and reaches its maximum intensity in the first 24 - 48 hours after surgery progressively decreasing in the following days [1]. It is the most frequent symptom during the postoperative period and is characterized by being predictable and self-limited in time. It is a nociceptive type of pain, associated with vegetative, psychological, emotional and behavioral reactions. The International Association for the Study of Pain (IASP) defines pain as “an unpleasant, sensorial and emotional sensation or experience that is associated with actual or potential tissue injury.” [2].

From a pathophysiological view, postoperative pain generates by the manipulations inherent to the surgical intervention (tissue tractions and sections) and by the release of allogenic substances capable of activating the receptors responsible for processing the nociceptive sensation. Its control is essential since its relief is associated with a decrease in the incidence of postoperative complications. Adequate analgesia provides less cognitive deterioration in the postoperative period and a lower risk of the appearance of chronic postoperative pain.

Postoperative pain is an unresolved problem: approximately 70% of patients experience severe pain and 30% moderate pain [3]. In these last two decades there have been considerable advances related to the pathophysiology of pain, the introduction of new drugs and the development of new techniques and modes of administration.

For the effective treatment of postoperative pain, several factors must be revised, such as: the time between the surgical intervention and the appearance of pain, the type of intervention, the pre-surgical preparation, the incision, anesthetic technique, perioperative complications and post-surgical care, without disregarding the patient's personal tolerance threshold to pain, a fact that makes its measurement difficult.

All surgical interventions are followed by the appearance of pain, which may increase endocrine and metabolic responses, autonomic reflexes, nausea, ileus, muscle spasm and also postoperative morbidity and mortality. Postoperative pain is more frequent and intense after intrathoracic, intra-abdominal, renal interventions, spinal surgeries, surgeries of large joints, trauma surgery of the hand and

foot, and, in general, any other major surgical procedure [4].

After intrathoracic, upper abdominal, and renal surgery, the movements that cause tension on the incision (deep breathing, coughing, and body movement) will aggravate the intensity of the pain.

Postoperative pain control reduces the patient's stay in the medical institution; this control improves by creating specific protocols that include analgesia guidelines based on the combination of drugs. The continuous search by anesthesiologists for better pain treatment has led to the association of various drugs and/or techniques, with better results than monotherapy.

Preventive analgesia initiated before surgical stimulation has taken on special interest. The administration of opioids and/or local anesthetics before a noxious stimulus prevented the development of spinal cord hyperexcitability induced by the injury and an increased perception of pain [5]-[7].

Opioids are considered the Gold Standard for postoperative pain management despite their adverse events [8] [9]. Of all the analgesics, these are the ones with the widest range of efficacy, providing the safest method to achieve rapid relief of moderate to severe pain. The analgesic effect of opioids occurs through their action on the central nervous system where we find the target receptors, which are found in other organs. The best known and most widely used is Morphine, which is an analgesic with pure agonist activity. The dose described for postoperative analgesia is 10 - 60 µg/kg and subsequently by infusion 15 - 200 µg/kg/h [10].

Fentanyl is a pure and selective agonist of the *mu* opioid receptor, with a potency between 50 and 150 times greater than that of morphine. It has a high lipid solubility, so it crosses cell membranes and the blood-brain barrier very well. Its great potency and good cardiovascular tolerability give it a very favorable therapeutic index, making it the most widely used opioid in cardiovascular surgical anesthesia and in intensive care units. The pharmacokinetics of fentanyl follow a three-compartment pattern, with a central compartment formed by the most vascularized organs (brain, heart, lung, liver and kidney). After intravenous administration, it penetrates the CNS very rapidly, reaching the maximum central action in 4 - 5 min [11].

It is absorbed through the gastrointestinal tract but undergoes intestinal and hepatic metabolism (first-pass metabolism) that gives it a bioavailability of only 30%. These limitations stimulated the development of other fentanyl formulations, such as transdermal, long acting, and Transmucosal [12].

2. Objectives

Primary: To compare the efficacy of Oral Transmucosal Fentanyl 200 µg versus IV Morphine Hydrochloride 2 mg, in the relief of moderate to severe postoperative pain after elective abdominal surgeries. Pain was evaluated through the Visual Analogue Scale (VAS) score and TOPAR pain relief scale at 15, 30, 45, 60 minutes, and at 2, 3, 4, 5 and 6 hours after administration of the study drugs.

Secondary: a) To determine the use of rescue doses of Morphine Hydrochloride

through SAP (Sedo-analgesia for procedures) or IV administration in case SAP is not available or IV boluses of Ketoprofen 75 mg.

b) To evaluate the safety and tolerability of Oral Transmucosal Fentanyl versus IV Morphine Hydrochloride in postoperative patients.

3. Materials and Methods

We conducted a randomized, comparative, double-blind, parallel-group phase 3 study. The study was conducted in two centers in the city of Caracas, Venezuela, Policlínica Las Mercedes and Dispensario Padre Machado.

Inclusion criteria

Patients of both sexes, aged between 18 - 75 years (at the time of signing the Informed Consent) were included.

Patients with pre-anesthetic assessment ASA I or II, scheduled for elective abdominal surgeries, who, during the postoperative period, present pain, with a value on the Visual Analogue Scale ≥ 5 (VAS: 0 - 10), in the first 8 hours of the postoperative period and who have signed their informed consent before starting the clinical study.

Exclusion criteria

Patients who, after surgery, require concomitant medication that interferes with the analgesic response to be evaluated, who have used opioids in the last seven (07) days before surgery, patients with chronic intake of opioid and non-opioid analgesics, with a history of alcohol abuse, with a history of abuse of legal and illicit drugs, as well as addiction.

Patients under treatment with psycho suppressants (Benzodiazepines, Barbiturates), pregnant or lactating women, patients with coagulation disorders, with liver disorders and/or alterations in liver tests, patients with renal pathology, patients with uncontrolled Diabetes Mellitus, patients with uncontrolled arterial hypotension, patients with a history of Bronchial Asthma and/or Chronic Obstructive Pulmonary Disease (COPD). Patients with psychiatric pathologies. Patients with hypersensitivity to opioid analgesics.

The selected patients were informed about the aspects inherent to the clinical study, including the scales that will be used for the evaluation of postoperative pain, and they were asked to sign the Informed Consent (IC) document.

The surgical intervention and general anesthesia were performed according to the usual practice of the Medical Institution where the clinical study was carried out. The medications used during surgery were not limited. However, these medications must be recorded in detail in the Data Collection Notebook (DC).

Some patients received controlled analgesia through a "Postoperative Analgesia System (PAS)" for a minimum of twelve (12) hours, using Morphine Hydrochloride at a dose of 20 $\mu\text{g}/\text{kg}/\text{min}$, by a continuous infusion pump. At approximately 6 a.m., the day after the surgical intervention, controlled analgesia (PAS) was suspended and patients who experienced moderate to intense pain ($\text{EVA} \geq 5$) in the following eight (08) hours entered the clinical study.

In those cases in which PAS was not used, the patient entered the clinical study if he/she experienced moderate to intense pain ($VAS \geq 5$) in the following 8 post-operative hours, receiving the study medication according to the established randomization.

The rescue therapies used in this period were Morphine Hydrochloride through SAP or by intravenous (IV) boluses of Ketoprofen at a dose of 75 mg, at the discretion of the main investigator, when the patient spontaneously manifests a $VAS > 7$.

The data analysis was performed by intention to treat, using a paired Student T test for the variable VAS within the group and unpaired between groups.

The variables PIDS, SPIDS and TOPAR were analyzed using the Wilcoxon test within the group, and Mann Whitney test between groups and the number of patients who took rescue medication, using the Fisher Exact Test for an $\alpha = 0.05$ $\beta = 0.1$.

4. Results

Twenty-seven patients were admitted to the group that received Fentanyl, and 46 patients to the group that received morphine.

The imbalance between the groups was due to the expiration of Transmucosal Fentanyl, which could not be replaced because the supplier who initially supplied it was not available.

However, the researchers, evaluators and patients remained blind until the end of patient admission.

Table 1. Description of the evaluated population.

Variable	Fentanyl N° 27	Morphine N° 46	P
Age	44.74 (25 - 79)	48.0 (25 - 73)	0.39*
Sex (f/m)	22/5	41/10	0.96**
Weight (Kg)	68.8 ± 16.9	71.6 ± 23.2	0.56*
Size (m)	1.6 ± 0.1	1.6 ± 0.4	0.84*
IMC	26.9 ± 5.0	27.9 ± 5.8	0.56*
Main diagnosis	Cholelithiasis 14 (52%) Hysterectomy 7 (26%) Inguinal hernia 3 (11%) Tumor lesions 2 (7.4%) Vaginal prolapse 2 (7%)	Cholelithiasis 18 (40%) Hysterectomy 16 (35.5%) Inguinal hernia 1 (2%) Tumor lesions 8 (17%) Vaginal prolapse 1 (2%) Prostatic hypertrophy 1 (2%)	
Adverse effects	4 patients moderate arterial hypotension required administration of parenteral fluids, of these patients one presented headache and another vomiting	Hypotension 1 moderate Vomiting 1 patient moderate Skin rash 1 patient	

*Unpaired Student T test, **Chi Square.

At study entry, the patient groups were very similar in anthropometric variables and preoperative diagnosis, with the exception of more patients with tumor lesions in the group that received morphine (**Table 1**).

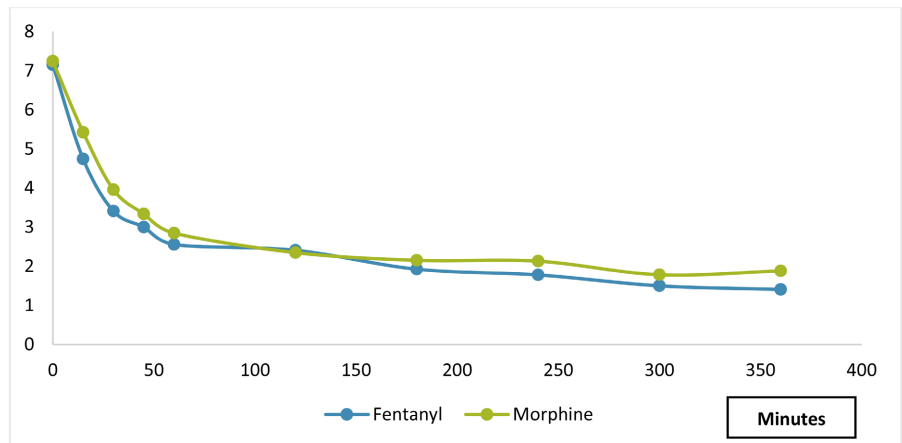


Figure 1. Pain Intensity/PI.

In both groups, there was a significant decrease in VAS values at measurement intervals up to 60 minutes in the group receiving Fentanyl and up to 2 hours in the group receiving morphine. (Wilcoxon Rank Test). The decrease in pain intensity measured by VAS 1 - 10 was similar in both groups with no significant differences at any of the measurement points. (Mann-Whitney Rank Test) (**Figure 1**).

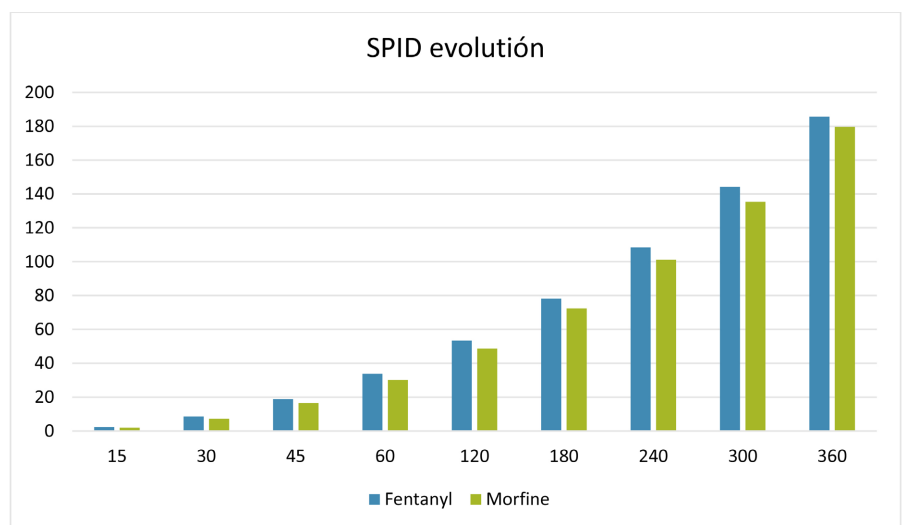


Figure 2. Sum of differences in SPID-6 h pain intensity (Pain Intensity/PI).

In both groups, there were increases in SPID from 15 min to 6 h (Wilcoxon Rank Test).

When compared between groups there were no differences at 15, 30 minutes, then there were significant differences in favor of the group that received Fentanyl

up to 6 hours. (Mann Whitney U Rank Test) (See p value in boxes) (**Figure 2**).

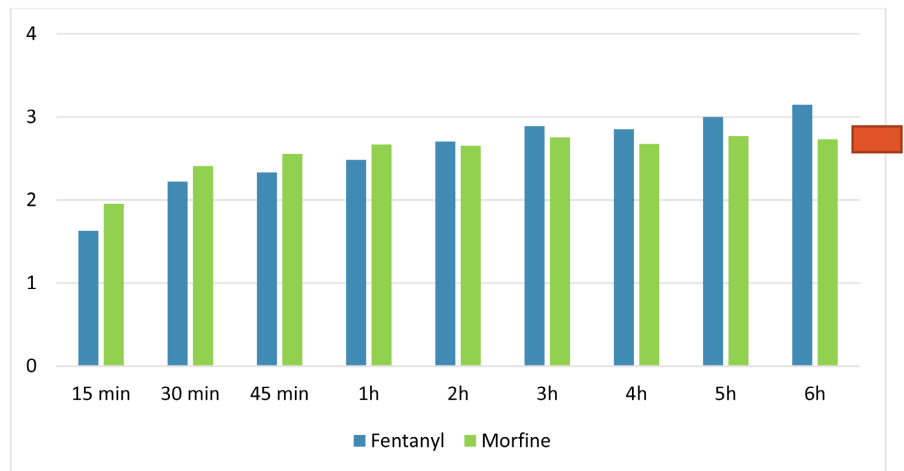


Figure 3. Pain relief.

Both products produced a significant increase in the Pain Relief scale, at the first evaluation times (30 min for Fentanyl and at times 30 and 45 for Morphine) and between the beginning and hour 6 of evaluation (Wilcoxon Rank Test).

There were no differences between the groups at any of the measurement times (Mann Whitney U test) (**Figure 3**).

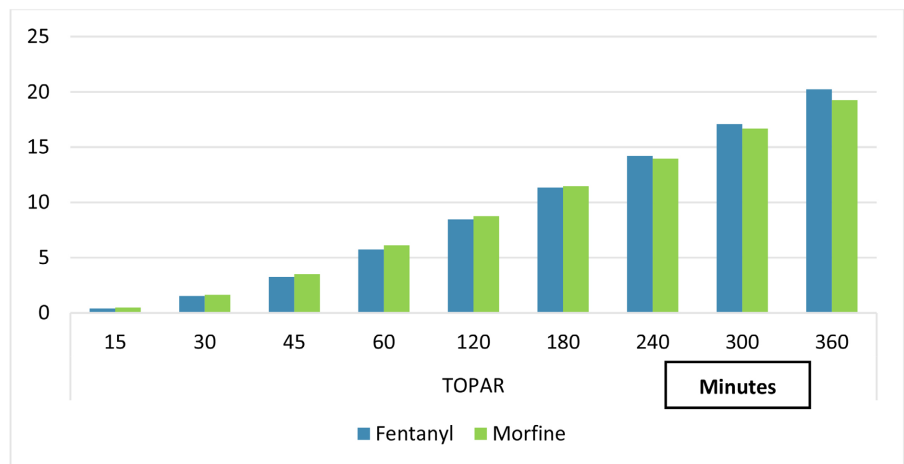


Figure 4. Evolution of the TOPAR scale in 6 hours

Both products produced a significant increase in the TOPAR scale, with no differences between the groups at any of the measurement times (Mann Whitney U test) (**Figure 4**).

The time to reach a decrease in the VAS 0 - 10 scale of 1, was similar: 20.3 minutes for fentanyl vs 23.7 minutes with morphine.

Rescue medication: 22.2 % of the Fentanyl group and 19.6 % of the morphine group received rescue medication with no difference between the groups (Chi-

square).

The survival analysis for time to rescue medication showed no difference between both arms of the study, (fentanyl or morphine) as can be seen through the Chi-square test or the Kaplan Meier survival curves.

Analysis of the time to start rescue medication using Kaplan Meier survival curves (**Table 2** and **Figure 5**).

The appearance of adverse effects was similar in both groups.

Table 2. Survival analysis (Chi-square test).

	Estimation	SE	IC 95%	
			Lower limit	Upper limit
Fentanyl	6.185	0.358	5.484	6.887
Morphine	6.087	0.293	5.512	6.662
Global	6.123	0.221	5.691	6.555
		Chi-square	gl	Sig.
Log Rank (Mantel-Cox)		0.111	1	0.739

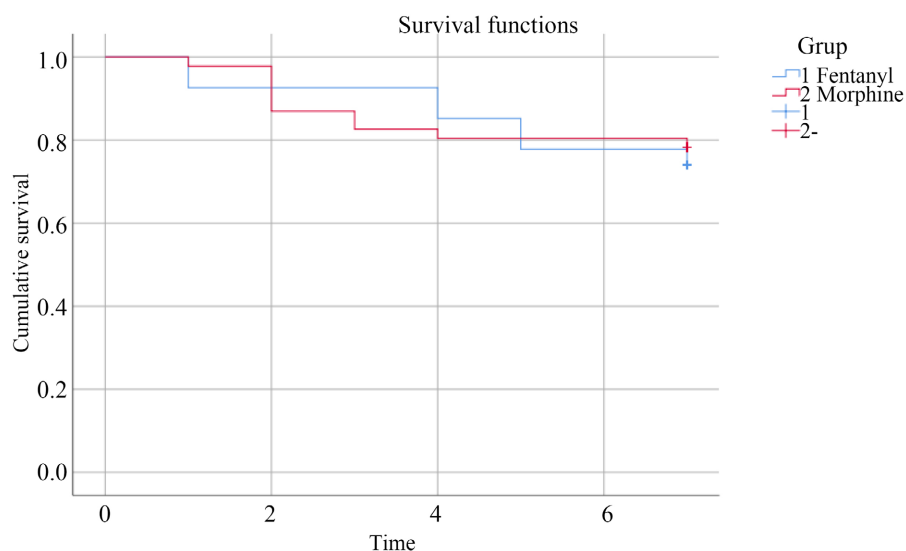


Figure 5. Survival analysis for time to rescue medication.

5. Discussion

Acute postoperative pain can be classified as nociceptive, inflammatory, or neuropathic. Nociceptive pain is mediated by activated unmyelinated C fibers, and is the type of pain that occurs in response to noxious stimuli, such as direct intraoperative tissue injury (e.g., making a skin incision). Inflammatory pain occurs when nociceptive fibers become sensitized in response to the release of inflammatory mediators such as cytokines. Neuropathic pain is the result of injury to neuronal structures (e.g., peripheral nerves), so pain occurs due to increased axonal sensitivity to stimuli. Neuropathic pain will occur in the immediate postoperative

period and may persist as chronic postoperative pain [13].

The goal of postoperative pain control is to reduce the negative consequences of postoperative pain and help the patient return to normal life without problems. Traditionally, opioid analgesic therapy has served as the mainstay of acute postoperative pain management. The misuse of opioids has led to an increased demand for more research efforts to develop pain management strategies that emphasize the use of a multimodal approach.

Optimized postoperative pain control is very important to improve immediate outcomes, reduce hospital stays, and improve overall patient satisfaction [13].

Commonly used medications for postoperative pain control include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, steroids, gabapentin or pregabalin, IV ketamine, and IV lidocaine. Intramuscular medications are not recommended. Oral administration of opioid medications is preferable to the intravenous route. Adding acetaminophen or NSAIDs is associated with lower opioid consumption and better pain control than opioid use alone [14]-[18].

In a randomized, prospective, double-blind study that included patients with severe postoperative pain, rescue was performed in one group with morphine 0.1 mg/kg and in another with fentanyl 1 mcg/kg, every 5 min intravenously, until the pain was reduced from severe to mild (VAS < 4). Thirty patients were included in both groups.

There were no significant differences in the percentage of patients with reduction from severe to mild POP at 5 min after injection of morphine or fentanyl, or in the subsequent rescue analgesia intervals ($p > 0.05$). Similarly, there were no significant differences in the mean VAS (95% CI) in the morphine or fentanyl groups starting 5 min after the first analgesic dose ($p > 0.05$) between the groups [19].

Another study evaluated the effectiveness and safety of IV fentanyl as compared to IV morphine for patients requiring analgesic medications for a traumatic injury during transport via a physician-staffed air medical service. Trauma patients were grouped by even and odd days (even-morphine 4 mg, odd-fentanyl 50 µg). During the flight, medical crew assessed numeric pain score, vital signs, and incidence of pruritus or nausea. There were 103 patients enrolled in the morphine arm and 97 patients in the fentanyl arm. There were no significant differences in analgesia between fentanyl and morphine. Average number of morphine doses was 3 ± 1.2 . For fentanyl, average number of doses was 3 ± 1.3 . The study concluded that there was not a significant difference in analgesic effectiveness between morphine and fentanyl. There was no significant difference in the incidence of adverse effects between the two drugs [20].

Two additional studies compared the effectiveness of fentanyl vs. morphine in severe postoperative pain, with the difference that fentanyl was supplied in the form of a lollipop-type tablet that is absorbed through the oral mucosa (OTFC), a highly practical administration route that can be used almost anywhere. In both postoperative settings, OTFC produced rapid pain relief similar to that produced

by IV morphine [21] [22].

In our study, despite the fact that the planned number of patients in the group that received Fentanyl was not completed because the product was not available once it had expired, the double blind was never broken.

The results show that both products produce a significant reduction in the measures of pain intensity (VAS) and, in terms of SPID. When the groups were compared there were no differences at times 15 and 30 minutes, then there were significant differences in favor of the group that received Fentanyl up to 6 hours. This represents an advantage of fentanyl over morphine, since the use of additional medications is avoided for a longer period, reducing the risk of side effects that can occur with the use of morphine.

The use of OTFC represents an advantage also in the administration route, since the patient can control the pain at home, without requiring a parenteral route, as has been demonstrated in previous studies [21] [22].

Both products produced a significant increase in the Pain Relief scale, at the first evaluation times (30 min for Fentanyl and at times 30 and 45 for Morphine) and between the beginning and hour 6 of evaluation, with no differences between the groups at any of the measurement times.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Miranda, A. (1992) Dolor postoperatorio: Estudio, valoración y tratamiento. *JIMS*.
- [2] Vervest, A.C. and Schimmel, G.H. (1988) Taxonomy of Pain of the IASP. *Pain*, **34**, 318-321. [https://doi.org/10.1016/0304-3959\(88\)90129-7](https://doi.org/10.1016/0304-3959(88)90129-7)
- [3] Carr, D.B. and Gordas, L.C. (1999) Acute Pain. *The Lancet*, **353**, 2051-2058. [https://doi.org/10.1016/S0140-6736\(99\)03313-9](https://doi.org/10.1016/S0140-6736(99)03313-9)
- [4] Bonica, J.J. (1990) Postoperative Pain. In: Bonica, J.J., Ed., *The Management of Pain*, 2nd Edition, Lea & Febiger, 1.
- [5] Dahl, V. and Ræder, J.C. (2000) Non Opioid Postoperative Analgesia. *Acta Anaesthesiologica Scandinavica*, **44**, 1191-1203. <https://doi.org/10.1034/j.1399-6576.2000.441003.x>
- [6] Vadivelu, N., Mitra, S., Schermer, E., Kodumudi, V., Kaye, A.D. and Urman, R.D. (2014) Preventive Analgesia for Postoperative Pain Control: A Broader Concept. *Local and Regional Anesthesia*, **7**, 17-22. <https://doi.org/10.2147/LRA.S62160>
- [7] Ramirez Guerrero, A. (1995) Tratamiento del Dolor Posoperatorio en el Adulto. *Rev Mex Anest*, **18**, 75-83.
- [8] Ritchey, R.M. (2006) Optimizing Postoperative Pain Management. *Cleveland Clinic Journal of Medicine*, **73**, S72-S76.
- [9] Poggi Machuca, L. and Ibarra Chirinos, O. (2007) Manejo del dolor agudo posquirúrgico. *Acta Médica Peruana*, **24**, 39-45.
- [10] Omoigui S. (1995) The Anesthesia Drugs Handbook. *Mosby Segunda Edición*, 235-240.

- [11] Fentanyl Citrate Injection, USP.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/016619s034lbl.pdf
- [12] Grape, S., Schug, S.A., Lauer, S. and Schug, B.S. (2010) Formulations of Fentanyl for the Management of Pain. *Drugs*, **70**, 57-72.
<https://doi.org/10.2165/11531740-000000000-00000>
- [13] Horn, R., Hendrix, J.M. and Kramer, J. (2024) Postoperative Pain Control. StatPearls.
- [14] McQuay, H.J. and Moore, R.A. (1998) An Evidence-Based Resource for Pain Relief. Oxford University Press.
- [15] Astudillo, W., Mendinueta, C., Astudillo, E. and Gabilondo, S. (1998) Principios básicos para el control del dolor total. *Rev. Soc. Esp. Dolor*, **6**, 29-40.
- [16] Rawal, N. (2016) Current Issues in Postoperative Pain Management. *European Journal of Anaesthesiology*, **33**, 160-171.
<https://doi.org/10.1097/EJA.0000000000000366>
- [17] Blichfeldt-Eckhardt, M.R. (2018) From Acute to Chronic Postsurgical Pain: The Significance of the Acute Pain Response. *Danish Medical Journal*, **65**, B5326.
- [18] Ghaffarpassand, F., Dadgostar, E., Ilami, G., Shoaee, F., Niakan, A., Aghabaklou, S., Ghadimi, M., Goudarzi, S., Dehghankhalili, M. and Alavi, M.H. (2020) Intravenous Acetaminophen (Paracetamol) for Postcraniotomy Pain: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *World Neurosurgery*, **134**, 569-576.
<https://doi.org/10.1016/j.wneu.2019.11.066>
- [19] Cadavid-Puentes, A., Bermúdez-Guerrero, F.J., Giraldo-Salazar, O., Muñoz-Zapata, F., Otalvaro-Henao, J., Ruíz-Sierra, J., *et al.* (2017) Comparación de la efectividad del Fentanilo versus morfina, en dolor severo post operatorio. Ensayo Clínico aleatorizado, doble ciego. *Revista Colombiana de Anestesiología*, **45**, 100-107.
<https://doi.org/10.1016/j.rca.2016.11.005>
- [20] Smith, M.D., Wang, Y., Cudnik, M., Smith, D.A., Pakiela, J. and Emerman, C.L. (2012) The Effectiveness and Adverse Events of Morphine versus Fentanyl on a Physician-Staffed Helicopter. *Journal of Emergency Medicine*, **43**, 69-75.
<https://doi.org/10.1016/j.jemermed.2011.05.018>
- [21] Lichtor, J.L., Sevarino, F.B., Joshi, G.P., Busch, M.A., Nordbrock, E. and Ginsberg, B. (1999) The Relative Potency of Oral Transmucosal Fentanyl Citrate Compared with Intravenous Morphine in the Treatment of Moderate to Severe Postoperative Pain. *Anesthesia & Analgesia*, **89**, 732-738.
<https://doi.org/10.1213/00000539-199909000-00038>
- [22] Ashburn, M.A., Lind, G.H., Gillie, M.H., de Boer, A.J., Pace, N.L. and Stanley, T.H. (1993) Oral Transmucosal Fentanyl Citrate (OTFC) for the Treatment of Postoperative Pain. *Anesthesia & Analgesia*, **76**, 377-381.