COMPARISON THE EFFICACY OF IV-PCA BETWEEN FENTANYL AND MORPHINE AFTER BURN NECROSIS EXCISION AND SKIN GRAFT SURGERY

Nguyen Ngoc Thach[1], Nguyen Van Quynh[1], Pham Thai Dung[2]

[1]Le Huu Trac National Burn Hospital
[2] Military Medical Hospital 103

ABSTRACT

***Objectives**: To compare the postoperative analgesic efficacy of IV-PCA Fentanyl with Morphine in patients undergoing burn necrosis excision and skin graft surgery.*

***Subjects and methods:** A comparative prospective study was conducted in 70 burn cases divided into 2 groups with 35 cases in each group having indications for burn necrosis excision and skin graft surgery. After the surgery, they were given IV-PCA Fentanyl (group F) or morphine (group M) for postoperative pain control. When the patients were painful (VAS ≥ 4), analgesics were titrated as following: In the group F, 0.025mg Fentanyl was intravenously injected and repeated every 5min until VAS < 4, then IV-PCA was started. The total titration dose of Fentanyl was below 0.1mg.*

In group M, 1mg Morphine was intravenously injected and repeated every 5 minutes until VAS < 4, then IV-PCA was started. The total titration dose of Morphine was below 10mg. IV-PCA setting were bolus 1ml (Fentanyl 0.025mg or Morphine 1mg), lockout time 10min, basal continuous infusion 1ml/h (Fentanyl 0.025mg/h or Morphine 1mg/h), maximum dosage 15ml/4h (Fentanyl 0.375mg/4h or Morphine 15mg/4h).

***Results:** In group F, the minimum and maximum of the visual analog scores (VAS) at rest after started IV-PCA were 2.03 ± 0.17 and 2.23 ± 0.64, respectively. In group M, minimum and maximum VAS at rest after started IV-PCA were 2.03 ± 0.2 and 2.14 ± 0.4, respectively. In group F, minimum and maximum VAS on movement after started IV-PCA were 3.03 ± 0.17 and 3.14 ± 0.49, respectively. In group M, minimum and maximum VAS on movement after started IV-PCA were 3.03 ± 0.2 and 3.23 ± 0.6, respectively. VAS at rest and on movement were statistically insignificant differences between the two groups (p > 0.05). The proportion of unsatisfied patients in group F was statistically significantly lower than that in group M (5.7% versus 20%) (p < 0.05).*

***Conclusions:** The analgesic efficacy of IV-PCA between Fentanyl and Morphine after burn necrosis excision and skin graft surgery was similar but the only proportion of satisfied patients in the IV-PCA Fentanyl group was higher than that in the IV-PCA Morphine group.*

***Keywords:** Fentanyl, Morphine, IV-PCA, burn necrosis excision and skin graft.*

[1] *Corresponding author:* Nguyen Ngoc Thach, Department of Anaesthesia, Le Huu Trac National Burns Hospital
Email: thachgmhs@yahoo.com.vn

1. INTRODUCTION

Patients with much deep burn area usually undergo many times necrosis excision and skin graft surgery causing postoperative severe pain. Therefore, postoperative pain management is essential. At present, there are many analgesic methods for burn patients, however, the use of the opioid group analgesics with IV-PCA is effective in pain management without an increased rate of side effects compared with conventional analgesia techniques [1] [2].

IV-PCA with Morphine is common [3], however, Morphine releases histamine and can cause oversedation in patients with renal failure due to accumulation of active metabolite Morphine-6-glucuronide. In contrast, Fentanyl is more potent than Morphine, it has a rapid onset after intravenous injection and without active metabolites. By way of consequences, if there is a contraindication for morphine use, IV-PCA with Fentanyl in place of Morphine is a proper choice.

Up to now, there hasn't been any study to compare IV-PCA Fentanyl with Morphine for postoperative pain management of burn necrosis excision and skin graft. Therefore, we conducted the study with the aim of comparing the postoperative analgesic efficacy of IV-PCA Fentanyl with Morphine in patients undergoing burn necrosis excision and skin graft surgery.

2. SUBJECTS AND METHODS

Following approval of the Hospital Ethics Council and informed consent of patients and their relatives, 70 cases at the intensive care unit (ICU) in National Burn Hospital with indications for elective surgery of burn necrosis and skin graft under general anesthesia from April 2018 to May 2019 have participated in the study.

Patients aged 16 to 60 with ASA I, II, III were included in the study. Patients with contraindications for Morphine and Fentanyl, burn shock, mechanical ventilation, mental disorders, severe hepatic impairment, severe renal failure, pregnancy, history of drug addiction, burn-in both hands, complications of surgery were excluded from the study.

The study method was a prospective comparative study. The patients were randomly divided into 2 groups. The group F included 35 cases given IV-PCA Fentanyl and group M included 35 cases given IV-PCA Morphine for postoperative pain management of burn necrosis excision and skin graft.

At the operating room, the patients were monitored for heart rate, non-invasive blood pressure, respiratory rate, SpO_2, $EtCO_2$. Premedication with intravenous injection of midazolam 0.05mg/kg and Fentanyl 1mcg/kg was performed 5 minutes before general anesthesia. Anesthesia induction was made with intravenous injection of Propofol 2 - 3mg/kg, Ketamine 1mg/kg and then laryngeal mask airway (LMA) was inserted. Anesthesia maintenance was made with intravenous infusion of propofol 5 - 10mg/kg/h. Intraoperative analgesia was made with intravenous injection of Fentanyl 0.1mg/time whenever the heart rate and/or systolic blood pressure increased over 20% of basal values before the premedication. When the surgery finished, patients were awake and adequate spontaneous breathing as soon as LMA was extubated. Then the patients were transferred to the recovery room to monitor vital signs and evaluate postoperative pain level.

Before general anesthesia, the patients were educated on how to use the IV-PCA device (Perfusor Space) of B.Braun company (Germany) and the visual analog score (VAS) ruler of Astra-Zeneca company (Sweden). In the recovery room, one-milligram Fentanyl was diluted with distilled water to make 40ml of Fentanyl solution 0.025mg/ml for IV-PCA in group F. Fifty milligram Morphine was diluted with distilled water to make 40ml of Morphine solution 1mg/ml for IV-PCA in the group M. IV-PCA setting were bolus 1ml (Fentanyl 0.025mg or Morphine 1mg), lockout time 10min, basal continuous infusion 1ml/h (Fentanyl 0.025mg/h or Morphine 1mg/h), maximum dosage 15ml/4h (Fentanyl 0.375mg/4h or Morphine 15mg/4h).

When the patients were painful (VAS ≥ 4), analgesics were titrated as following: In the group F, 0.025mg Fentanyl was intravenously injected and repeated every 5min until VAS < 4, then IV-PCA was started. The total titration dose of Fentanyl was below 0.1mg. In group M, 1mg Morphine was intravenously injected and repeated every 5min until VAS < 4, then IV-PCA was started. The total titration dose of Morphine was below 10mg.

During IV-PCA usage, if VAS was still greater than 4 despite three effective continuous boluses, 30mg Kevindol was intravenously injected for “pain rescue”. IV-PCA was stopped when the respiratory rate was below 10 breaths/min and/or SpO_2 < 90%.

A/D index at finished IV-PCA times, postoperative pain levels at rest and on movement according to VAS, from 0 (“no pain”) to 10 (“worst pain imaginable”), the proportions of patients with “pain rescue”, levels of patient satisfaction with IV-PCA including very satisfied patient-no pain and no side effects, satisfied patient - minor pain or only one side effect, and unsatisfied patient - severe pain requiring “pain rescue” or at least two side effects were recorded.

Data were collected at times as following: Just after extubated LMA with VAS ≥ 4 (H_s), started IV-PCA (H_0), after started IV-PCA 1h (H_1), 2h (H_2), 3h (H_3), 6h (H_6), 9h (H_9), 12h (H_{12}) and finished IV-PCA at 8 o’clock next morning (H_{kt}). Data were processed by SPSS software version 20.0 and p < 0.05 was considered a statistically significant difference.

3. RESULTS

Table 1. Patients’ characteristics

Variables	Group F	Group M	p
Age (year)	35.3 ± 10.2	34.6 ± 11	> 0.05
Weight (kg)	54.6 ± 7.4	54.2 ± 9.8	> 0.05
Gender (male/female)	21/14	19/16	> 0.05
ASA (II/III)	19/16	13/22	> 0.05
Total burn area (%)	41.6 ± 15	43.9 ± 13.2	> 0.05
Deep burn area (%)	16.9 ± 11.9	18.5 ± 12.7	> 0.05
Surgical area (%)	10.9 ± 3.4	9.7 ± 3.2	> 0.05
The number of used opioid times in the hospital before the study	9.7 ± 7.7	13.3 ± 9	> 0.05

The data were shown as $\overline{X} \pm SD$ or frequency.

Table 2. Titrated analgesic doses, titration time, IV-PCA duration, the analgesic dosage used for IV-PCA, A/D ratio at finished IV-PCA times

Variables	Group F	Group M
Titrated analgesic doses (mg)	0.04 ± 0.01	1.7 ± 0.6
Titration time (min)	5.9 ± 1.6	8.3 ± 3
IV-PCA duration (h)	20.9 ± 0.87	20.9 ± 0.92
Analgesic dosage used for IV-PCA (mg)	0.57 ± 0.08	22.8 ± 1.9
A/D ratio at finished IV-PCA times (%)	90.4 ± 10.2	94.7 ± 9.9

The data were shown as $\overline{X} \pm SD$

Table 3. VAS at rest

Times	Group F	Group M	p
H_s	5.03 ± 0.17	4.97 ± 0.2	> 0.05
H_0	2.06 ± 0.23*	2.14 ± 0.4**	> 0.05
H_1	2.11 ± 0.4*	2.08 ± 0.3**	> 0.05
H_2	2.06 ± 0.34*	2.06 ± 0.2**	> 0.05
H_3	2.06 ± 0.23*	2.06 ± 0.2**	> 0.05
H_6	2.14 ± 0.49*	2.06 ± 0.2**	> 0.05
H_9	2.03 ± 0.17*	2.06 ± 0.2**	> 0.05
H_{12}	2.23 ± 0.64*	2.03 ± 0.2**	> 0.05
H_{kt}	2.03 ± 0.17*	2.03 ± 0.2**	> 0.05

The data were shown as $\overline{X} \pm SD$

**p < 0.05 when comparing VAS at times from H_0 to H_{kt} with at H_s in the group F*

***p < 0.05 when comparing VAS at times from H_0 to H_{kt} with at H_s in the group M.*

Table 4. VAS on movement

Times	Group F	Group M	p
H_s	6.03 ± 0.17	5.88 ± 0.5	> 0.05
H_0	3.06 ± 0.23*	3.23 ± 0.6**	> 0.05
H_1	3.11 ± 0.4*	3.08 ± 0.3**	> 0.05
H_2	3.06 ± 0.34*	3.06 ± 0.2**	> 0.05
H_3	3.06 ± 0.23*	3.06 ± 0.2**	> 0.05
H_6	3.14 ± 0.49*	3.06 ± 0.2**	> 0.05
H_9	3.03 ± 0.17*	3.06 ± 0.2**	> 0.05
H_{12}	3.23 ± 0.64*	3.03 ± 0.2**	> 0.05
H_{kt}	3.03 ± 0.17*	3.03 ± 0.2**	> 0.05

The data were shown as $\overline{X} \pm SD$

** p < 0.05 when comparing VAS at times from H_0 to H_{kt} with at H_s in the group F*

*** p < 0.05 when comparing VAS at times from H_0 to H_{kt} with at H_s in the group M*

Table 5. "Pain rescue" and levels of patient satisfaction

Variables	Group F		Group M		p
	n	%	n	%	
"Pain rescue"	2	5.7	4	11.4	> 0.05
Unsatisfied patient	2	5.7	7	20	
Satisfied patient	31	88.6	17	48.6	< 0.05
Very satisfied patient	2	5.7	11	31.4	

The data were shown as frequency and percentage.

4. DISCUSSION

For burn patients, apart from pain caused by a burn injury, they also experience pain after burn necrosis excision and skin graft surgery, especially at the donor site. Among analgesics used for burn patients, the opioid group analgesics are still the pillar of pain management. Burn patients often show an altered pharmacodynamics and pharmacokinetics drug response, requiring a highly individualized pain management plan [4].

IV-PCA with the opioid group analgesics is a safe and efficient method of achieving flexible analgesia in burn patients [2]. IV-PCA helps to maintain plasma opioid level and avoid peak phenomenon as well as a bottom phenomenon when an intermittent intravenous injection or intramuscular injection is used.

Currently, IV-PCA Morphine and Fentanyl are commonly used for burn patients [5] [6] [7] [8]. In our study, IV-PCA settings were based on the study of Yukitoshi Niyama and colleagues [9] who used IV-PCA Fentanyl with bolus 25mcg, lockout time 10min, background infusion 25mcg/h or IV-PCA Morphine with bolus 1mg, lockout time 10min, no background infusion for pain management after abdominal surgery. However, in group M in our study, Morphine background infusion 1mg/h was administered because morphine intravenous infusion is necessary for background pain in burn patients [2]. Burn patients are very different from other surgical ones that after hospital admission, they often need many times of the opioid group analgesic usage for hydrotherapy, dressing change, especially patients with large burn area in the intensive care unit (ICU). Specifically, the number of used opioid times in the hospital before the study in the groups F and M were 9.7 ± 7.7 and 13.3 ± 9, a statistically insignificant difference, p > 0.05 (Table 1).

In the study, we only maintained IV-PCA until 8 o'clock the next morning because of severe pain during dressing changes which need general anesthesia. Adequate postoperative pain management for patients in both groups was shown via the quite high A/D ratio at finished IV-PCA times and the relatively low proportion of "pain rescue". Specifically, when IV-PCA was finished, the A/D ratio was 90.4 ± 10.2% (table 2) and the proportion of "pain rescue" was 5.7% in the group F (Table 5), while they were 94.7 ± 9.9% and 11.4%, respectively in the group M; a statistically insignificant difference, p > 0.05. On the

contrary, Yukitoshi Niiyama and colleagues [9] found that the numbers of patients receiving supplemental analgesic were significantly smaller in the group F (4/20) than in group M (15/19), $p < 0.01$. The analgesic efficacy of IV-PCA Morphine and Fentanyl was also expressed via VAS at rest and on movement, levels of patient satisfaction during IV-PCA. Table 3 and Table 4 depicted that there was no statistically significant difference in mean VAS at rest and on movement between the two groups ($p > 0.05$), however, in each group, mean VAS at rest and on movement at times from H_0 (started IV-PCA) to H_{kt} (finished IV-PCA) was statistically significantly lower than that at H_s (IV-PCA was not started), $p < 0.05$.

Similarly, Paul R. Howell and colleagues [10] used IV-PCA Fentanyl and Morphine in postoperative pain control of cesarean delivery under general anesthesia and they reported that there was no difference in VAS between the IV-PCA Fentanyl and Morphine groups. Eman M.Nada and colleagues [11] compared IV-PCA Fentanyl with Morphine for postoperative pain control after liver resection in 40 liver donors and also found that there was no significant difference in VAS between the two groups. However, the demands requested by pressing the IV-PCA button were significantly lower in the Morphine group compared with the Fentanyl group. On the contrary, Yukitoshi Niiyama and colleagues [9] showed that in the group F, postoperative numerical rating scores were significantly lower at rest in the first 24 hours after surgery and when coughing at the first two hours after the end of abdominal surgery than those in the group M, perhaps due to the different surgical nature while the author studies IV-PCA after abdominal surgery, we study IV-PCA after-burn surgery.

The proportion of patients with very satisfied, satisfied and unsatisfied levels in the group F were 5.7%, 88.6%, and 5.7%, respectively and those in group M were 31.4%, 48.6% and 20%, respectively, a statistically significant difference, $p < 0.05$ (Table 5). Similarly, Yukitoshi Niiyama and colleagues [9] reported that Fentanyl IV-PCA provided greater patient satisfaction after abdominal surgery. On the contrary, Paul R. Howell and colleagues [10] found that there was no difference in patient satisfaction between the IV-PCA Fentanyl and Morphine groups, perhaps due to the different surgical nature while the author studies IV-PCA after cesarean section, we study IV-PCA after-burn surgery.

The limitation of the current study is that we have not used the analgesia nociception index, which is an objective tool for assessing postoperative pain levels.

5. CONCLUSIONS

Regarding the pharmacology of both analgesics, Fentanyl is 75 to 125 times more potent than Morphine but the analgesic efficacy of IV-PCA between Fentanyl and Morphine after-burn necrosis excision and skin graft surgery was similar and the only proportion of satisfied patients in the IV-PCA Fentanyl group was higher than that in the IV-PCA Morphine group in our study.

REFERENCES

1. **M. Choiniere, R. Grenier, and C. Paquette.** Patient-controlled analgesia: A double-blind study in burn patients. *Anaesthesia* 1992;47:467-472.

2. **Cornelia Griggs, Jeremy Goverman, Edward Bittner, and Benjamin Levi**. Sedation and Pain Management in Burn Patients. *Clin Plast Surg* 2017;44(3):535-540.
3. **Jeffrey A. Grass**. Patient-controlled Analgesia. *Anesth & Analg* 2005;101(5): 44-61.
4. **Lavrentieva A., Depetris N., Rodini I**. Analgesia, sedation and arousal status in burn patients: the gap between recommendations and current practices. *Annals of Burns and Fire Disasters* 2017;30(2):135-142
5. **Smita Prakash, Tazeen Fatima, and Mridula Pawar**. Patient-Controlled Analgesia with Fentanyl for Burn Dressing Changes. *Anesth Analg* 2004;99:552-5
6. **Siamak Rimaz, Cyrus Emir Alavi, Abbas Sedighinejad, Mohammad Tolouie, Sharareh Kavoosi, Leila Kouchakinejad**. Effect of Gabapentin on Morphine consumption and Pain after Surgical Debridement of Burn Wounds: A Double-Blind Randomized Clinical Trial Study. *Arch Trauma Res.* 2012;1(1):38-43
7. **In-Suk Kwak et al**. The Effect of Weight-Compensated Intravenous Patient-Controlled Analgesia in Burns. *J Korean Burn Soc* 2013;16:12-16
8. **Ying-Chun Lin, Chien-Chung Huang, Nuan-Yen Su, Chia-Lin Lee, Hsuan-Chih Lao, Chia-Shiang Lin, Chien-Chuan Chen**. Patient-controlled analgesia for background pain of major burn injury. *Journal of the Formosan Medical Association* 2019;118:299-304
9. **Yukitoshi Niiyama, Nobuyoshi Matsuoka, Reona Sugimoto and Michiaki Yamakage**. Efficacy of Intravenous Patient-Controlled Analgesia (IV-PCA) using Fentanyl compared with IV-PCA using morphine after abdominal surgery: a prospective randomized study. *J Anesth Clin Res* 2016;7(1):1-5
10. **Paul R. Howell, David R. Gambling, Timothy Pavy, Graham McMorland, M.Joane Douglas**. Patient-controlled analgesia following Caesarean section under general anaesthesia: a comparison of fentanyl with morphine. *Can J Anaesth* 1994;42(1):41-45
11. **Eman M.Nada, Abdulmajeed Alabdulkareem**. Morphine versus fentanyl patient-controlled analgesia for postoperative pain control in major hepatic resection surgeries including living liver donors: A retrospective study. *Saudi J Anaesth* 2018;12:250-5