COMPARING THE EFFECTIVENESS OF INTRAVENOUS MORPHINE VERSUS FENTANYL FOR IMMEDIATE POST-OPERATIVE PAIN AFTER MAJOR SPINAL SURGERY UNDER REMIFENTANIL-BASED GENERAL ANESTHESIA

Lily Hii[1], MD, Nadia Md Nor[2], MBBChBaO , MMed (Anaes),
Siti Nidzwani Mohamad Mahdi[2], MBBS, MMed (Anaes),
Azlina Masdar[2], MD, FCAI, Ahmad Fairuz Abdul Shokri[2], MBBChBaO,
Syarifah Noor Nazihah Sayed Masri[3], MD,
Azarinah Izaham[2*], MD, MMed (Anaes)

Abstract

Background: Post-operative pain management in major spine surgery is important to ensure early ambulation and good functional outcome. This study compared the effectiveness of intravenous (IV) fentanyl 4 μg/kg to IV morphine 0.1 mg/kg for immediate post-operative pain after major spinal surgery under remifentanil-based anesthesia.

Methods: Seventy-eight patients undergone major spine surgery were randomly assigned to two groups: Group A received IV fentanyl 4 μg/kg and Group B received IV morphine 0.1 mg/kg given at skin closure. Total dosage of intra-operative remifentanil and the time taken for extubation were recorded. The immediate post-operative pain was assessed using the behavioural pain score (BPS) or visual analogue scale (VAS). The time to the first rescue analgesia, total cumulative morphine given and number of patients required rescue analgesia, pain score and sedation score were recorded. The assessments were done at 10 minutes interval upon patient arrival at recovery for one hour. The side effects of fentanyl or morphine were recorded.

Results: There was a delayed time for extubation in Group A compared to Group B (23.39 ± 6.1 *vs* 14.78 ± 6.8 minutes; p<0.001). The median time to the first rescue analgesia was longer in Group A compared to Group B (30(20-60) *vs* 20(10-60) minutes; p<0.001). The number of patients required rescue analgesia and the total cumulative morphine dosage in the first 30 minutes in the recovery were both less in Group A compared to Group B (24 *vs* 34 patients, p=0.027; 1(1-7) *vs* 2(0.5-4) mg, p<0.001). Median sedation score up to T_{40} showed statistically significant difference between two groups (p<0.05). At T_{10} and T_{20}, median BPS was lower in Group A compared to Group B (1(1-1) *vs* 1(1-2), p<0.01; 0(0-0), 2(0-2), p<0.022). However, there was no statistically significant difference in VAS from 20 minutes to 60 minutes for both groups. No other opioids side effects were noted.

1 Department of Anaesthesiology & Intensive Care, Hospital Umum Sarawak, Sarawak, Malaysia.
2 Department of Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia.
3 Department of Anaesthesiology & Intensive Care, Hospital Umum Sarawak, Sarawak, Malaysia.
* **Mailing address of the corresponding author:** Azarinah Izaham, MD, MMed(Anaes), Department of Anaesthesiology & Intensive Care, Faculty of Medicine, Universiti Kebangsaan Malaysia. Mailing address: Jalan Yaakob Latif, 56000 Kuala Lumpur, Malaysia. Telephone number: +60391455555, Email address: azaizaham@yahoo.com

Conclusion: Fentanyl provided comparable analgesia and safety properties compared to morphine as immediate post-operative analgesia after remifentanil-based anesthesia despite delayed in extubation without any adverse effects. However, fentanyl significantly delayed awakening from anesthesia.

Keywords: Fentanyl, morphine, remifentanil, spine surgery

Introduction

Major spinal surgeries are generally associated with considerable post-operative pain as it often involves extensive dissection of subcutaneous tissues, bones and ligaments. Adequate pain management is important to ensure early ambulation and good functional outcome.[1,2] Anesthetic challenges presented by major spinal surgery include the need to provide profound intra-operative analgesia and to facilitate intra-operative neurophysiologic monitoring of the spinal.[3,4] Intra-operative infusion of remifentanil is an established technique that is commonly used to meet this need.

Remifentanil is a potent, selective 4-anilidopiperidine μ-opioid receptor agonist that has a rapid onset and short duration of action independent of the duration of infusion with a context sensitive half-time of 4 minutes.[4-7] The pharmacokinetics properties of remifentanil result in termination of analgesic effect within minutes of discontinuing an infusion.[8] Thus, a transition must be made from remifentanil to some other longer-acting analgesics.[9] The most commonly used opioids for surgical pain are morphine and fentanyl, with the former being the mainstay of pain management after spine surgery.[10] It offers a good balance between the speed of action onset (15-30 minutes) and the maintenance of analgesia as it is relatively hydrophilic with a long duration of action.[11] Fentanyl also has favourable pharmacokinetics, theoretically having a more rapid onset (<60 seconds) with a half-life of 90 minutes and duration of action close to 30-60 minutes.[12] This may allow the reduction of total opioid dosage used, thus reducing the dose-dependent opioid-related side effects.

Furthermore, an important concern with intra-operative infusion of remifentanil is the possible development of opioid induced hyperalgesia, causing as increased post-operative analgesic requirement, especially with potent opioids.[13] Crawford et al. demonstrated that the initial 24-hour post-operative morphine consumption was increased by 30% in adolescents who had received infusion remifentanil for scoliosis repair compared with those who received intermittent morphine alone.[3] Previous study showed that intravenous (IV) morphine bolus of 0.25 mg/kg administered 30 minutes before the end of major surgery significantly reduced Verbal Pain Score (VPS) at 60 minutes compared to 0.15 mg/kg ($p<0.001$).[14] However, three cases of post-operative respiratory depression occurred in 0.25 mg/kg group. In their study, they also suggested that an acute tolerance had occurred during remifentanil infusion or rapid offset of remifentanil. The postulation of the phenomenon was the opioid receptor coupled with the slower attachment of opioids with lesser affinity, and hence, causing the pain and agitation seen following cessation of remifentanil.

The present study was conducted with the objective of comparing the effectiveness of IV fentanyl 4 μg/kg versus IV morphine 0.1 mg/kg for immediate post-operative pain after major spinal surgery under remifentanil-based general anesthesia. We also evaluated the incidence of opioids side effects such as post-operative nausea and vomiting (PONV), pruritus, respiratory depression and over sedation.

Methods

This prospective double-blind and randomised study was conducted after obtaining approval by the Research Committee of Department of Anaesthesiology & Intensive Care, Universiti Kebangsaan Malaysia Medical Centre and the Medical Research & Ethnics Committee UKMMC (FF-2018-083).

Patients aged 12 to 60 years old with American Society of Anesthesiologists (ASA) I or II classfications and scheduled for major spine surgery requiring patient-controlled analgesia (PCA) post-operatively were included in the study. The exclusion criteria were patients with known allergies to the study drugs, history of substance abuse, chronic use of opioids and patients who could not understand the Visual Analogue

scale (VAS). Patients were recruited one day prior to the operation and were kept fasting for at least 6 hours prior to their surgery. The written informed consent was taken and all patients did not received premedication. The VAS (Appendix 1) was explained to all patients and the baseline VAS was assessed and recorded. Patients' demographic data, which included age, gender, race, ASA physical status, weight, height, diagnosis and surgical procedure planned, were recorded. Patients were randomly assigned into one of the two study groups by using a computer-generated randomization table. Group A received IV fentanyl 4 µg/kg (lean body weight) while Group B received IV morphine 0.1 mg/kg (lean body weight) 30 minutes before the end of surgery (defined as starting of skin closure). The specified drug was prepared by the primary investigator and was given to the patients by the medical officer in the operating theater (OT), who was blinded to the study.

Appendix 1
Visual Analogue Scale (VAS)
0 mm (no pain) to 100 mm (unbearable pain)

In the OT, standard monitoring which included non-invasive or invasive blood pressure, electrocardiography, pulse oximetry and capnography were applied. The IV access was established using a 18G branula and IV Hartmann's solution was commenced followed by the Holliday Segar formula for maintenance fluid requirements.[15] All patients were induced and maintained using total intravenous anesthesia (TIVA) with target-controlled infusion (TCI) of propofol and remifentanil using the Schnider and Marsh model, respectively. The intra-operative TIVA infusion dose was according to the anesthesiologist in charge. Patients were intubated with an appropriately sized endotracheal tube and positioned prone for the spine surgery. Intravenous dexamethasone 8 mg and IV paracetamol 15 mg/kg were given after induction of anesthesia.

At skin closure, all patients were given the study drug prepared earlier, depending on randomisation, with TCI propofol discontinued and 1mg of granisetron administered as PONV prophylaxis. The TCI remifentanil was discontinued when dressing was applied to the surgical wound. All patients were extubated following the standard extubation criteria and sent to recovery area for monitoring. Total dose of remifentanil used intra-operatively was recorded. The time for extubation which was defined as the time from the termination of remifentanil infusion to removal of endotracheal tube was also recorded. Patient was considered drop-out from the study if he/she failed to be extubated 30 minutes after discontinuation of remifentanil infusion.

At 10 minutes after arrival at recovery area (T_{10}), patient's sedation score was assessed using the Ramsay sedation scale (Appendix 2). Should the score be ≥4, pain assessment was done using the Behavioural Pain Score (BPS) (Appendix 3). If the Ramsay sedation score was <4, pain was evaluated using the VAS. Similar assessment was done every 10 minutes for a 60-minute duration, recorded as T_{20}, T_{30}, T_{40}, T_{50} and $T_{60,}$ respectively. A BPS of ≥ 2 or VAS ≥ 40 mm was considered as inadequate analgesia, following which an IV morphine 1 mg bolus was given as a rescue analgesia and titrated to effect until a VAS ≤ 40 mm or BPS < 2 was reached. The time to the first rescue analgesia and total cumulative morphine given as rescue analgesia in the recovery area were also recorded. All patients were given a PCA morphine before being discharged to the ward upon fulfilling the standard discharge criterias. The presence of opioid side effects such as nausea, vomiting, respiratory depression and pruritus were also recorded during the first hour in the recovery area and treated accordingly.

Appendix 2
Ramsay sedation score
1- agitation and uncomfortable
2- cooperated and orientated
3- do simple directions
4- sleep and strongly reply to stimulation
5- sleep and slowly reply to stimulation
6- sleep and do not reply to stimulation

Appendix 3
BPS
0- calm patient with no verbal or behavioural manifestation of pain
1- behavioural or verbal expression of pain
2- intense behavioural or verbal manifestation of pain (cry, extreme agitation).

The sample size was calculated using the PS Software version 3.0 (Dupont & Plummer, 2011) based on Schlesselman's (1982) formula.[15,16] Fletcher et al. showed that there was a significant difference between patients with a VPS of ≥2 who received intra-operative IV morphine 0.25 mg *vs* 0.15 mg/kg (40.5% *vs* 70.5%), 60 min after discontinuation of remifentanil.[14] A sample size was designed based on these results, with an α value of 0.05 and a power (1-β) of 0.80. It was calculated that each group required 38 subjects. We therefore enrolled 86 patients (43 per group) to allow for 10% dropouts. Data analysis was performed using SPSS for Windows version 23.0 (IBM Corp, Armonk, NY. USA). Independent t-test or Mann-Whitney U test were used for normally distributed continuous data and not normally distributed data, respectively. The qualitative data (e.g Race, Gender, ASA status) was analysed using Chi-square or Fisher exact test if insufficient numbers were present. A *p* value of <0.05 was considered statistically significant.

Results

A total of 86 patients who underwent major spinal surgery were recruited in this study. Eight patients dropped out from the study: five patients from Group A because of delayed extubation and three patients from Group B due to massive blood loss and were kept ventilated post-operatively. The demographic data of both groups were comparable (Table 1).

There was a statistically significant delay for time to extubation after remifentanil infusion discontinuation between Group A (23.39 minutes) and Group B (14.78 minutes) ($p<0.001$). In addition, the median time to the

to Group B (30 minutes *vs* 20 minutes; $p<0.001$). The median of total cumulative morphine dosage in Group A showed a statistically significant lower dose compared to Group B for the first 30 minutes in the recovery area (1(1-7) *vs* 2(0.5-4) mg, ($p<0.001$) (Table 2). Similarly, the number of patients that required rescue analgesia in the first 30 minutes in the recovery was significant lower in Group A compared to Group B, 24 (63.2%) *vs* 34(85.0%) ($p=0.027$).

There were a statistically significant difference in the median Ramsay sedation score between Group A and Group B for the first 40 minutes in the recovery area (Table 3).

The difference in median BPS at T_{10} between Group A (1(1-1)) and Group B (1(1-2)) was statistically significant (Table 4). Two types of assessment were conducted according to the Ramsay sedation score at T_{20}. The median BPS score in Group A was significantly

Table 1
Demographic characteristics of study patients

	Group A (n= 38)	**Group B (n= 40)**	**p-value**
Age, years	17.6 (12-34)	16.0 (13-33)	0.0415
Gender, n (%) Female Male	 33 (86.8) 5 (13.2)	 36 (90.0) 4 (10.0)	0.734
BMI, kg/m^2	18.1±2.5	18.0±2.6	0.820
Duration of surgery (min)	128.5±38.0	138.0±43.9	0.312
ASA, n (%) 1 2	33 (86.8) 5 (13.2)	30 (75.0) 10 (25.0)	0.185
Surgical procedure, n (%) Scoliosis Non-scoliosis	36 (94.7) 2(5.3)	40 (100.0) 0(0)	0.234

Values are expressed as median (25th percentile – 75th percentile), mean ± SD or number of patients (percentage)

Table 2

Intra- and post- operative anesthesia properties

	Group A (n=38)	**Group B** (n=40)	**p value**
Baseline VAS score, mm	0 (0-7)	0 (0-5)	0.945
Total dose of intra-operative remifentanil (ng)	1555 ± 584	1757 ± 647	0.153
Time to extubation (minute)	23.39 ± 6.1	14.78 ± 6.8	<0.001
Time to first rescue analgesia (minute)	30 (20-60)	20 (10-60)	< 0.001
Total cumulative morphine dose in recovery (mg) 0- 30 minute 30-60 minute	3.0 (0-9) 1 (1-7) 3.5 (2-9)	3.5 (0-6) 2 (0.5-4) 4 (1-6)	0.164 <0.001 0.156
Number of patient requiring rescue analgesia in first 30 minutes, n (%)	24 (63.2)	34 (85)	0.027

Values are expressed as median (25^{th} percentile – 75^{th} percentile) or mean ± SD

Table 3

Post-operative Ramsay sedation score at recovery

	Group A (n=38)	**Group B (n=40)**	**p value**
$\mathbf{T_{10}}$	5 (5-5)	4 (2-4)	<0.001
$\mathbf{T_{20}}$	5 (4-5)	2 (1-4)	<0.001
$\mathbf{T_{30}}$	4 (2-4)	2 (2-2)	<0.001
$\mathbf{T_{40}}$	2 (2-4)	2 (2-2)	0.001
$\mathbf{T_{50}}$	2 (2-2)	2 (2-2)	0.234
$\mathbf{T_{60}}$	2 (2-2)	2 (2-2)	0.284

* Values are expressed as median (25^{th} percentile - 75^{th} percentile)

Table 4

Postoperative Behavior Pain Score (BPS) and Visual Analogue Scale (VAS)

Time	**Group A (n=38)**		**Group B (n=40)**		**p-value**
	BPS,median (25^{th}-75th percentile)	VAS, median (25^{th} percentile - 75^{th} percentile)	BPS,median (25^{th}-75th percentile)	VAS, median (25^{th} percentile - 75^{th} percentile)	
T_{10}	n=38 1 (1-1)	n=0	n=40 1 (1-2)	n=0	<0.01
T_{20}	n=30 0 (0-0)	n=8 4 (1-6)	n=5 2(0-2)	n=35 6 (5-8)	0.022_{BPS} 0.078_{VAS}
	VAS, median (25^{th} percentile - 75^{th} percentile)				
T_{30}	5 (0-9)		5 (0-8)		0.215
T_{40}	6 (0-9)		5 (1-9)		0.620
T_{50}	5 (0-8)		5 (2-8)		0.207
T_{60}	4 (0-7)		4 (2-8)		0.366

Values are expressed as median (25^{th} percentile - 75^{th} percentile)

lower compared to Group B at T_{20} (0 (0-0) *vs* 2(0-2), *p* =0.022). However, there was no significant difference in VAS from 20 to 60 minutes for both groups.

There were no side effects (nausea, vomiting, pruritus and respiratory depression) noted among the participants.

Discussion

The current study showed that fentanyl could be considered as a post-operative analgesia after remifentanil-based anesthesia in major spine surgeries. The time required to first rescue analgesia was longer while the cumulative morphine dosage for 30 minutes in the recovery room was lower when fentanyl was given as a post-operative analgesia after remifentanil was discontinued. A delay in time to extubation and higher sedation scores were also seen when fentanyl was administered.

A study by Kochs et al. found that there was no differences in median time to extubation after equi-potent dose of morphine or fentanyl were given to patients undergoing major abdominal surgery, 25 minutes before terminating remifentanil-based anesthesia.[16] However, our result showed that there was a delay in extubation time when fentanyl was given as post-operative analgesia after remifentanil-based anesthesia. The study by Kochs et al. used a fixed dose of fentanyl and morphine whereas the dosage used in the present study was according to body weight.[16] We postulated that fentanyl's greater lipophilicity and potency allowed it to rapidly cross the blood-brain barrier, contributing to the peak effect of fentanyl at the time of extubation.[17] Contrary to the present findings, Kochs et al. showed no difference between morphine and fentanyl as a post-operative pain management after remifentanil-based anesthesia, regarding the time to first rescue analgesia in patients. A study by Albrecht et al., who compared the effectiveness of approximately equipotent doses of morphine and fentanyl given 20 minutes before the end of remifentanil-based anesthesia for major abdominal surgery, also showed similar median time to administration of first rescue opioids.[17] However, both studies used fixed dose of fentanyl and morphine instead of according to body weight which was in contrast to our study.

The current study showed that fentanyl had better analgesia property at the first 10 minutes in the recovery area. However, patients who received fentanyl were more sedated compared to morphine. At 20 minutes into recovery, 79% of the patients in the fentanyl group who were assessed using BPS had median score of 0 suggesting that fentanyl had better analgesic property at 20 minutes after remifentanil-based anesthesia. For the last 30 minutes into recovery, patients who received either drug showed moderate pain scores, requiring rescue analgesia. To the best of our knowledge, there has been no prior study assessing pain scores by using time intervals while in recovery. Kochs et al. showed a lack of difference in analgesic property between fentanyl and morphine after remifentanil-based anesthesia, with the pain score only being assessed once an Aldrete score of ≥ 9 was achieved.[16] At 60 minutes we found that patients had moderate pain with median pain score of 4, which was similar to the study done by Fletcher et al. who used 0.15 mg/kg morphine. We used 0.1 mg/kg morphine as a post-operative analgesia, which was comparable to the dosage used by Fletcher et al.[18]

We didn't observe any side effects when either drug was used for post-operative analgesia after remifentanil-based anesthesia in which both appeared to be safe. As the patients recruited were less than 40 years of age, the findings here cannot be extrapolated for patients > 40 years old. The assessment of respiratory components is also important in evaluating the effect of morphine and fentanyl. This includes time to spontaneous respiration, time to response to verbal command and time to achieve an Aldrete score ≥ 9. However, this was not taken into account in the present study.

In conclusion, fentanyl provided comparable analgesia and safety properties compared to morphine as immediate post-operative analgesia after remifentanil-based anesthesia. However, fentanyl 4μg/kg significantly delayed awakening from anesthesia.

Financial disclosures: None.

Conflicts of interest: None.

Acknowledgements: The authors would like to thank Ms Qurratu' Aini Musthafa for the statistical analysis.

References

1. Bajwa SJS, & Haldar R. Pain management following spinal surgeries: an appraisal of the available options. Journal of craniovertebral junction & spine 2015;6(3):105-10.
2. Bianconi M, Ferraro L, Ricci R, Zanoli G, Antonelli T, Giulia B, et al. The pharmacokinetics and efficacy of ropivacaine continuous wound instillation after spine fusion surgery. Anesthesia & Analgesia 2004; 98(1):166-72.
3. Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. Anesthesia & Analgesia 2006; 102(6):1662-7.
4. Egan TD, Lemmens HJ, Fiset P, Hermann DJ, Muir KT, Stanski DR, et al. The pharmacokinetics of the new short-acting opioid remifentanil (GI87084B) in healthy adult male volunteers. Anesthesiolog y: The Journal of the American Society of Anesthesiologists (1993); 79(5):881-92.
5. Glass PS, Hardman D, Kamiyama Y, Quill TJ, Marton G, Donn K, et al. Preliminary pharmacokinetics and pharmacodynamics of an ultra-short-acting opioid: remifentanil (GI87084B). Anesthesia & Analgesia 1993; 77(5), 1031-40.
6. Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, et al. Measured context-sensitive half-times of remifentanil and alfentanil. The Journal of the American Society of Anesthesiologists 1995; 83(5):968-75.
7. Westmoreland CL, Hoke JF, Sebel PS, Hug CC, Muir KT. Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. Anesthesiology: The Journal of the American Society of Anesthesiologists 1993; 79(5):893-903.
8. Yarmush J, D'Angelo R, Kirkhart B, O'Leary C, Pitts MC, Graf G, et al. A comparison of remifentanil and morphine sulfate for acute postoperative analgesia after total intravenous anesthesia with remifentanil and propofol. Anesthesiology: The Journal of the American Society of Anesthesiologists 1997; 87(2):235-43.
9. Bowdle TA, Camporesi EM, Maysick L, Hogue CW, Miguel RV, Pitts M, et al. A multicenter evaluation of remifentanil for early postoperative analgesia. Anesthesia & Analgesia 1996; 83(6):1292-7.
10. Seki H, Ideno S, Ishihara T, Watanabe K, Matsumoto M, Morisaki H. Postoperative pain management in patients undergoing posterior spinal fusion for adolescent idiopathic scoliosis: a narrative review. Scoliosis and spinal disorders 2018; 13(1):17.
11. Cadavid-Puentes A, Bermúdez-Guerrero FJ, Giraldo-Salazar O, Muñoz-Zapata F, Otálvaro-Henao J, Ruíz-Sierra J, et al. Comparison of the effectiveness of fentanyl versus morphine for severe postoperative pain management. A randomized, double blind, clinical trial. Colombian Journal of Anesthesiology 2017; 45(2):100-07.
12. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. British Journal of Anesthesia 2014; 112(6):991-1004.
13. Trivedi M, Shaikh S, Gwinnut C. Pharmacology of Opioids. Update in Anesthesia, 2007, Update in Anesthesia.
14. Dupont W, Plummer W. PS power and sample size calculations software version 3.0, 2011.
15. Schlesselman JJ. Case-control studies: design, conduct, analysis, 1982, Oxford University Press.
16. Kochs E, Cote D, Deruyck L, Rauhala V, Puig M, Polati E, et al. Postoperative pain management and recovery after remifentanil-based anesthesia with isoflurane or propofol for major abdominal surgery. Remifentanil Study Group. British Journal of Anesthesia 2000; 84(2):169-73.
17. Albrecht S, Fechner J, Geisslinger G, Maass A, Upadhyaya B, Moecke HP, et al. Postoperative pain control following remifentanil-based anesthesia for major abdominal surgery. Anesthesia 2000; 55(4):315-22.
18. Fletcher D, Pinaud M, Scherpereel P, Clyti N, Chauvin M. The efficacy of intravenous 0.15 versus 0.25 mg/kg intraoperative morphine for immediate postoperative analgesia after remifentanil-based anesthesia for major surgery. Anesthesia & Analgesia 2000; 90(3):666-71.