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Comparison of Hemodynamic Effects of Morphine and Remifentanil in Traumatized Patients Requiring Mechanical Ventilation

Lida Fadaizadeh , Behrooz Zaman , Valyollah Hassani

Department of Anesthesiology, Hazrate Rasool Akram Hospital, Iran University of Medical Sciences and Health Services, TEHRAN-IRAN.

ABSTRACT

Background: This study was conducted to compare the sedative and hemodynamic effects of morphine and remifentanil in traumatized patients requiring intubation and mechanical ventilation in intensive care unit of Rasool Akram Hospital, Iran University of Medical science during the years 2003-4.

Material and Methods: This was a randomized controlled clinical trial study in which all traumatized patients requiring mechanical ventilation in ICU were randomly enrolled into two groups. The first group was given a 5 mg bolus dose of morphine and the second group received an infusion of remifentanil starting with 0.05 µg/kg and the doses were sequentially increased to reach a sedation state of 3-4 according to Ramsey scale. The regimen was continued for 24 hours, during which blood pressure, heart rate, and respiratory rate was monitored. Data were analyzed using SPSS software version 11.5.

Results: A total of 60 patients aged 18-80 yrs with mean age of 42.53 ±18.5 yrs, consisting of 37 (61.7%) males and 23 (38.3%) females entered the study. The mean blood pressure was 109.12±1.68 mmHg in the morphine group and 90.01 ±6.66 mmHg in the remifentanil group ($p<0.00$). The mean heart rate of the aforementioned groups were 101.89 ±2.31 and 95.06±10.15 ($p<0.00$) respectively.

Conclusion: Remifentanil causes an initial decline in blood pressure but it maintains the pressure in a rather steady state during the period of infusion. This result was quite similar to that of morphine with the additional fact that there was no profound decline of blood pressure with morphine. (*Tanaffos* 2005; 4(14): 31-36)

Key words: Sedation, Morphine, Remifentanil

INTRODUCTION

An appropriate level of sedation is required for most patients admitted to intensive care units. Sedation consists of a combination of analgesia, amnesia, and anxiolysis (1) which is essential for relieving pain, anxiety, and fear of patients admitted

to the ICU. The above-mentioned are usually triggers to activate stress responses in patients which are mainly due to the both uncomfortable and noisy environment of the ICU and the different invasive procedures that are performed during the admission, including intubation and mechanical ventilation.

All this results in catecholamine release, rise in

Correspondence to: Fadaizadeh L

Email address: lfadaizadeh@yahoo.com

blood pressure and heart rate, and eventually increase in O₂ consumption and metabolism which put the patient into a catabolic state. Control of this status results in a better general condition and therefore prompt recovery of patients (2).

No uniform protocol for sedation in ICU exists to date and the major criterion for drug selection is either availability or individual preference. Therefore, to decrease the delay in drug administration, proposing a single protocol for the purpose is essential.(3)

Much attention has been paid to narcotics, mainly due to their analgesic effect, and among them morphine has been considered as the drug of choice (4). But the main disadvantage of this drug is its active metabolites which usually accumulate in patients with multi-organ failure, which is not uncommon in ICU patients.

On the other hand, there is remifentanyl which is rapidly metabolized by plasma esterase and has a shorter half life and therefore seems to be a better choice in these patients.

This drug has the advantage of sedative effect in addition to analgesic effect, which reduces the need for complementary drugs (5, 6, 7, 8). But the role of this drug in the ICU setting and especially its hemodynamic effects has yet to be defined.

Therefore, the main aim of this study was to compare the hemodynamic effects of morphine and remifentanyl in traumatized and intubated mechanically ventilated patients admitted to ICU of Rasool Akram Hospital, Iran University of Medical Sciences, to better elucidate the role of this drug as a sedative in ICU.

MATERIALS AND METHODS

This study, which was designed as a randomized controlled clinical trial, was conducted in the Intensive care unit of Rasool Akram Hospital during the years 2003-4.

After approving the project by the review board regarding scientific and ethic issues, written informed consent was obtained from the patients or

their near relatives in charge of the patient. Thereafter, all traumatized patients requiring intubation and mechanical ventilation with an age range of 18-80 were enrolled in the study. Patients with hemodynamic instability and accompanying disorders of liver, kidney, heart (congestive heart failure, valvular heart disease, etc.), and lung (asthma, COPD, etc.) were excluded from the study. Type of trauma was also quite similar in all patients; ie, all patients had chest trauma and minor extremity injuries. Patients with head trauma were excluded from the study, even with no alterations in level of consciousness.

Initially liver function (SGOT, SGPT, Bil, ALP) and renal function (BUN, Cr) tests were performed to determine their basal status. Ramsey scale was used to assess their conscious level.

To administer sedative drugs, all patients were randomly categorized into two groups, the first was given bolus doses of 5 mg morphine (intravenous) and the second underwent remifentanyl infusion with minimal dose of 0.05µg/kg/min.

Our goal was to reach the Ramsey scale sedation stage of 3-4; therefore, the patients were assessed after administration of drugs and if still not sedated enough, after reaching the time of peak effect of each drug which is 20 minutes for morphine and 5 minutes for remifentanyl, the dose of each drug was doubled. This procedure was repeated until the required sedation level was reached. Thereafter the patients were monitored for 24 hours and during this period the first group of patients received bolus doses of 5 mg morphine every 4 hours to keep the Ramsey level of 3-4, and the second group received the last adjusted dose of remifentanyl as infusion through 24 hours. During this period the patients were monitored every 4 hours for blood pressure and heart rate alterations and the drug administration was adjusted as required according to the Ramsey level of sedation to keep it at 3-4. Therefore blood pressure (systolic and diastolic) and heart rate were recorded at 8 stages; baseline, after reading the required sedation

level, and every 4 hours thereafter up to 24 hours.

After computerizing the data, statistical analysis was performed using SPSS software version 11.5.

Mean \pm standard deviation was calculated for each variable (BP and HR) and t-student test was used to determine their statistical difference.

RESULTS

A total of 60 patients enrolled in the study. The patients were randomly categorized into morphine and remifentanil groups. The mean age of total patients was 42.53 ± 18.59 and the mean age for morphine and remifentanil groups was 44.36 ± 20.58 and 40.70 ± 16.5 , respectively, with no statistically significant difference between the two groups ($p < 0.06$).

Considering gender, a total of 37(61.7%) males and 23 (38.5%) females were studied which were allocated to each group as follows: 19(63.3%) males and 11 (36.7%) females in remifentanil group and 18 (60.0%) males and 12 (40%) females in morphine group. It is noteworthy that difference between the

two genders was statistically significant inside each group ($p < 0.000$) but non-significant between the two groups ($p < 0.09$).

The total effective dose for each drug to reach the Ramsey scale of 3-4 was $0.10 \mu\text{g}/\text{kg}/\text{min}$ infusion for remifentanil and 12.83 ± 2.52 mg initial bolus dose for morphine.

The mean systolic pressure was 109.12 ± 1.68 mmHg for the total patients and for each group this parameter was 106.33 ± 22.5 mmHg for remifentanil and 110.00 ± 9.46 mmHg for morphine.

During the 24 hours period of the study, 8 stages of evaluation were performed, the mean value of which is stated in table 1. Figure 1 shows the trend of mean systolic blood pressure changes during the 24 hours of the study for both groups.

As demonstrated in Fig 1, a considerable decline in mean systolic blood pressure occurred between stage one and two of evaluation in both groups with a statistically significant difference within each group ($P < 0.000$).

Table 1. Comparison between 1st, 2nd, and last blood pressure, and heart rate, in patients of both groups.

		Mean	Std. Deviation	Std. Error Mean	p-value
1 st Systolic BP	Remifentanil	106.33	22.51	1.11	P<0.416
	Morphine	110.00	9.46	1.72	
2 nd Systolic BP	Remifentanil	89.16	15.37	2.80	P<0.000
	Morphine	105.00	9.73	1.77	
Last Systolic BP	Remifentanil	87.83	17.35	3.16	P<0.000
	Morphine	109.66	14.73	2.69	
1 st Diastolic BP	Remifentanil	57.33	22.42	4.09	P<0.006
	Morphine	70.00	6.94	1.26	
2 nd Diastolic BP	Remifentanil	53.33	199.53	3.56	P<0.000
	Morphine	70.00	6.94	1.26	
Last diastolic BP	Remifentanil	51.00	16.04	2.93	P<0.000
	Morphine	64.66	8.60	1.57	
1 st Heart rate	Remifentanil	119.63	32.60	5.95	P<0.44
	Morphine	106.16	13.77	2.51	
2 nd Heart rate	Remifentanil	109.63	20.15	3.67	P<0.034
	Morphine	100.80	8.92	1.62	
Last Heart rate	Remifentanil	91.00	12.49	2.28	P<0.030
	Morphine	98.26	12.84	2.34	

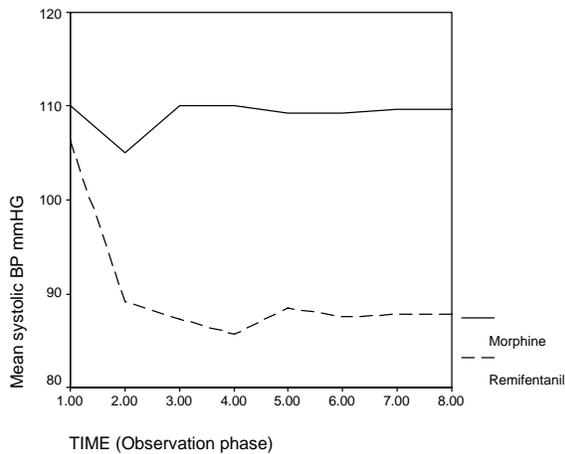


Figure 1. Systolic blood pressure changes during 24 hours of observation, remifentanyl and morphine groups.

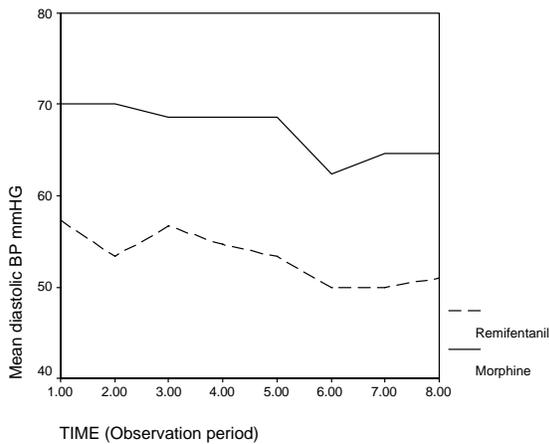


Figure 2. Diastolic blood pressure changes during 24 hours of observation, remifentanyl and morphine groups.

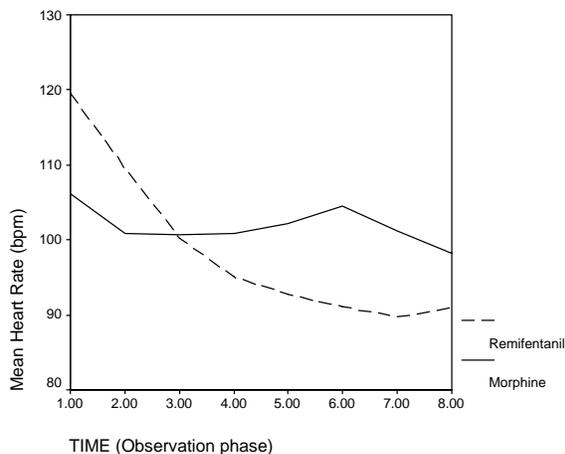


Figure 3. Heart Rate changes during 24 hours of observation, remifentanyl and morphine groups.

By comparing the changes of this value between the two groups, it was revealed that the decline in systolic blood pressure in remifentanyl group was considerably greater than the morphine group and the difference between the groups was statistically significant ($p < 0.000$).

Study of diastolic blood pressure changes showed that although a statistically significant difference existed between the two groups before initiation of the study ($p < 0.05$) with the remifentanyl group having a lower diastolic blood pressure, the subsequent decline after drug administration was not considerable in each group ($p < 0.23$). Considering the inter-group relation, diastolic blood pressure decline was greater in the remifentanyl group with a statistically significant difference comparing to the morphine group (0.083) (fig 2, Table 1).

Heart rate evaluation revealed that both groups experienced a considerable decline in heart rate and that the difference from baseline values was statistically significant ($p < 0.08$ for remifentanyl group and $p < 0.000$ for morphine group). Inter-group comparison revealed that during the 24 hours period the remifentanyl group experienced a profound, continuous and gradual decline of heart rate but the morphine group, in spite of an initial decline, experienced an overall higher level of heart rate (Table 1, fig 3).

DISCUSSION

This study was conducted to compare the hemodynamic effects of morphine and remifentanyl in ICU admitted patients. Results showed that both drugs were equally effective in reaching the required level of sedation, although with a significantly different time interval which is due to the kinetics of each drug. (9, 10, 11)

According to the previous studies, remifentanyl is a fast acting opioid (12, 13, 14, 15, 16, 17, 18, 19) with adequate sedative and analgesic effects (15, 16,

17). Also, this drug is referred to as an ultra short acting drug which is considered an advantage for its use in the ICU. All this is in contrast with the effects of morphine, the drug formerly known as the "drug of choice" for sedation in ICU. But what needs to be clarified is the hemodynamic effects of each drug in ICU patients who usually have failure of the cardiovascular system.

Results of this study showed that during the initial phase of drug administration, which is the time of drug administration till reaching the required level of sedation, patients of both groups experienced a sudden decline in blood pressure. This steep decline was continued with a smooth course throughout the 24 hours of observation in the remifentanyl group. On the contrary, the morphine patients first experienced a steep decline and thereafter a gradual rise of blood pressure to the baseline. Small fluctuations were seen during the course of study, which was probably due to the bolus administration of the drug.

According to former studies remifentanyl is considered as a drug which causes a high degree of hemodynamic stability (5, 6, 13). Although most of these studies have reported some levels of hypotension, but none of them considered this a complication or adverse effect and also have not reported a profound decline in blood pressure at the initial phase of drug administration (10, 11, 13). Therefore it is recommended that until this issue is fully clarified, special attention must be paid to remifentanyl administration to patients with unstable hemodynamic status, hemorrhagic disease, and cardiovascular instability.

One special result of our study was that in the remifentanyl group decline in systolic blood pressure was observed to be greater than diastolic blood pressure.

As previously mentioned, although a slight decrease in diastolic blood pressure was detected among the patients given remifentanyl, this decline

was not statistically different from the baseline. Therefore, this may be the reason why remifentanyl is considered safe regarding the hemodynamic status of the patients. But since no previous study has been performed on this issue, we should be cautious about our judgement and further clarification seems mandatory.

Tachycardia is considered a sign of pain and anxiety and also a major factor for evaluation of hemodynamic stability (10, 13), especially in anesthetized patients. We used this factor as an indicator of pain perception and level of sedation in our patients. Our results demonstrated that both drugs were effective in sedation and therefore initial decrease of pulse rate in patients but comparison of the groups showed that remifentanyl induced a gradual and continuous decline whereas morphine, in spite of an initial decline, showed a gradual return of pulse rate to baseline. Although this may be attributed to the mode of drug administration (bolus) in morphine group, it needs to be further investigated.

CONCLUSION

Remifentanyl with a rapid onset and therefore less experience of pain and anxiety for the patients, short duration of action, and no risk of accumulation is considered as an acceptable drug for ICU patients. But in spite of all favorable characteristics, much attention must be paid to the hemodynamic effects of this drug, especially in patients with unstable hemodynamic status.

REFERENCES

1. Nasernejad SH, Sadri B, Hasanie V. Administration of sedative drugs to patients with neurologic disorders in the intensive care unit. *Specialists' J.* No 3, pp 45-59.
2. Park GR. *Sedation and Analgesia in the critically ill.* 1st edition, Blackwell science Ltd. UK. P 9-11. 1995.

3. Ibrahim EH, Kollef MH. Using protocols to improve the outcomes of mechanically ventilated patients. Focus on weaning and sedation. *Crit Care Clin* 2001; 17 (4): 989-1001.
4. Shapiro B A, Peruzzi WT. Respiratory care. In: Miller RD: Anesthesia, 5th edition (2000), Churchill Livingstone . USA. Volume 4, P 2424.
5. Cohen J, Royston D. Remifentanyl. *Curr Opin Crit Care* 2001; 7 (4): 227- 31.
6. Chinachoti T, Kessler P, Kirkham A, Werawatganon T. Remifentanyl vs morphine for patients in intensive care unit who need short-term mechanical ventilation. *J Med Assoc Thai* 2002; 85 Suppl 3: S848- 57.
7. Myles PS, Hunt JO, Fletcher H, Watts J, Bain D, Silvers A, et al. Remifentanyl, fentanyl, and cardiac surgery: a double-blinded, randomized, controlled trial of costs and outcomes. *Anesth Analg* 2002; 95 (4): 805- 12.
8. Walder B, Elia N, Henzi I, Romand JR, Tramer MR. A lack of evidence of superiority of propofol versus midazolam for sedation in mechanically ventilated critically ill patients: a qualitative and quantitative systematic review. *Anesth Analg* 2001; 92 (4): 975- 83.
9. Glass PS, Gan TJ, Howell S. A review of the pharmacokinetics and pharmacodynamics of remifentanyl. *Anesth Analg* 1999; 89 (4 Suppl): S7- 14.
10. Muellejans B, Lopez A, Cross MH, Bonome C, Morrison L, Kirkham AJ. Remifentanyl versus fentanyl for analgesia based sedation to provide patient comfort in the intensive care unit: a randomized, double-blind controlled trial [ISRCTN43755713]. *Crit Care* 2004; 8 (1): R1- R11.
11. Kessler P, Chinachoti T, Van der Berg P. Remifentanyl vs. morphine for the provision of optimal sedation in the ICU patients. *Int Care Med* 2001; 27 (Supple 2): S 239.
12. Tipps LB, Coplin WM, Murry KR, Rhoney DH. Safety and feasibility of continuous infusion of remifentanyl in the neurosurgical intensive care unit. *Neurosurgery* 2000; 48: 596-601.
13. Karabins A, Hantson P, Speelberg B. A remifentanyl-based technique for analgesia and sedation in ICU patients with neurotrauma: preliminary data. *Int Care Med* 2001; 27 (2): S275; Abstract 549.
14. Chiaretti A, Pietrini D, Piastra M, Polidori G, Savioli A, Velardi F, et al. Safety and efficacy of remifentanyl in craniostomosis repair in children less than 1 year old. *Pediatr Neurosurg* 2000; 33 (2): 83- 8.
15. Kuhlen R, Putensen C. Remifentanyl for analgesia-based sedation in the intensive care unit. *Crit Care* 2004; 8 (1): 13- 4.
16. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H. Remifentanyl versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. *Anesthesiology* 2004; 101 (3): 640- 6.
17. De Bellis P, Gerbi G, Bacigalupo P, Buscaglia G, Massobrio B, Montagnani L, et al. [Experience with remifentanyl in the ICU]. *Minerva Anestesiol* 2002; 68 (10): 765- 73.
18. Karabinis A, Mandragos K, Stergiopoulos S, Komnos A, Soukup J, Speelberg B, et al. Safety and efficacy of analgesia-based sedation with remifentanyl versus standard hypnotic-based regimens in intensive care unit patients with brain injuries: a randomised, controlled trial [ISRCTN50308308]. *Crit Care* 2004; 8 (4): R 268- 80.
19. Wilhelm W, Dorscheid E, Schlaich N, Niederprum P, Deller D. [The use of remifentanyl in critically ill patients. Clinical findings and early experience]. *Anaesthesist* 1999; 48 (9): 625- 9.