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

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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 µgr/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

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blood pressure and heart rate, and eventually increase in $O_2$ 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 remifentanil 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 remifentanil 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 remifentanil 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 remifentanil, 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 remifentanil 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 ± 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 μg/kg/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 |
|---|---|---|---|---|---|
| 1st Systolic BP | Remifentanil | 106.33 | 22.51 | 1.11 | P<0.416 |
| | Morphine | 110.00 | 9.46 | 1.72 | |
| 2nd 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 | |
| 1st Diastolic BP | Remifentanil | 57.33 | 22.42 | 4.09 | P<0.006 |
| | Morphine | 70.00 | 6.94 | 1.26 | |
| 2nd 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 | |
| 1st Heart rate | Remifentanil | 119.63 | 32.60 | 5.95 | P<0.44 |
| | Morphine | 106.16 | 13.77 | 2.51 | |
| 2nd 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 | |

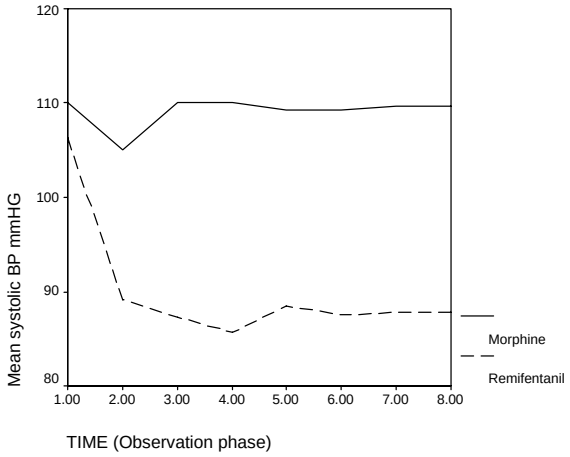


Figure 1. Systolic blood pressure changes during 24 hours of observation, remifentanil and morphine groups.

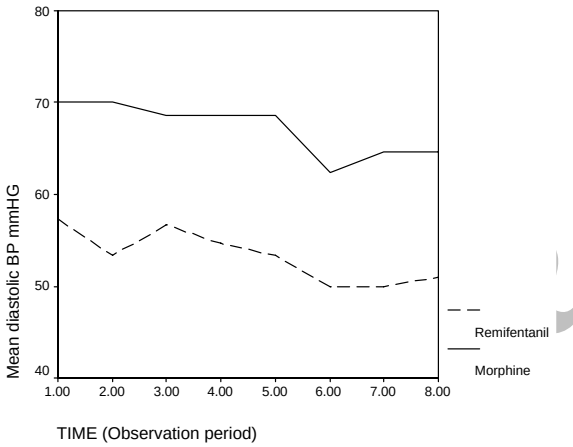


Figure 2. Diastolic blood pressure changes during 24 hours of observation, remifentanil and morphine groups.

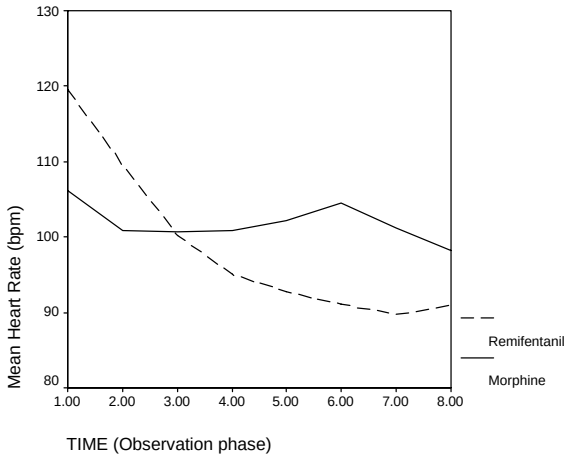


Figure 3. Heart Rate changes during 24 hours of observation, remifentanil and morphine groups.

By comparing the changes of this value between the two groups, it was revealed that the decline in systolic blood pressure in remifentanil 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 remifentanil 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 remifentanil 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 remifentanil group and $p<0.000$ for morphine group). Inter-group comparison revealed that during the 24 hours period the remifentanil 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 heat rate (Table 1, fig 3) .

## DISCUSSION

This study was conducted to compare the hemodynamic effects of morphine and remifentanil 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, remifentanil 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 remifentanil 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 remifentanil 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 remifentanil administration to patients with unstable hemodynamic status, hemorrhagic disease, and cardiovascular instability.

One special result of our study was that in the remifentanil 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 remifentanil, this decline was not statistically different from the baseline. Therefore, this may be the reason why remifentanil 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 remifentanil 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

Remifentanil 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.

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