Comparative Study on the Effectiveness of Intravenous or Subcutaneous Morphine

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ABSTRACT

In this double-blind study, the effects of morphine administered for 72 hours either by continuous intravenous (IV) infusion or subcutaneous (SC) injections were compared in 55 patients undergoing abdominal or thoracic surgery. Twenty-six patients received a continuous IV infusion of morphine and a SC injection of sodium chloride 0.9% whereas SC injections of morphine every four hours and sodium chloride 0.9% was infused IV to 29 other patients. Total Pain (TOTAL) Score, Pain Index (PI), Pain Intensity Difference (PID) and the Sum of Pain Intensity Differences (SPID) values were calculated from the pain scores determined with a Visual Analog Scale (VAS) immediately before and one hour after each SC injection. Respiratory rate, sedation index and serum morphine levels were also determined. Respiratory depression was reported in three of the 29 patients in the SC injection group in comparison to none in the IV infusion group. Sedation scores were slightly but not significantly higher in the SC group while continuous IV infusion was associated with slight development of tolerance to the analgesic effect of morphine. The data suggest that severe postoperative pain is well controlled by both modes of administration. However, side effects appeared slightly but not significantly higher when morphine was administered SC.

Key Words: *analgesia, morphine, pain, intravenous, subcutaneous, surgery, pharmacokinetics*

RÉSUMÉ

Dans cette étude à double insu, on a comparé les effets de morphine administrée pendant 72 heures soit par infusion intraveineuse (IV) continue soit par des injections sous-cutanées (SC) chez 55 patients subissant une chirurgie abdominale ou thoracique. Vingt-six patients ont reçu une infusion IV continue de morphine et une injection SC de chlorure de sodium à 0.9% tandis que chez les autres 29 patients on a administré les injections SC de morphine toutes les quatre heures et une infusion IV de chlorure de sodium à 0.9%. L'indice de douleur totale (TOTAL), l'Indice des Douleurs (ID), la Différence d'Intensité des Douleurs (DID) et le Total de la Différence d'Intensité des Douleurs (TDID) ont été calculés d'après les échelles des douleurs déterminées avec une échelle analogique visuelle (EAV) juste avant et aussitôt une heure après chaque injection SC. Le taux respiratoire, l'indice de sédation et les taux sériques de la morphine ont aussi été déterminés. La dépression respiratoire a été signalée chez trois des 29 patients du groupe recevant des injections SC comparativement à aucun dans le groupe d'infusion IV. Les échelles de sédation étaient légèrement mais non significativement élevées dans le groupe SC tandis que l'infusion IV a été associée avec un léger développement de tolérance envers l'effet analgésique de morphine. Les données indiquent que la douleur postopératoire sévère est bien contrôlée par les deux méthodes d'administration. Cependant, les effets secondaires qui sont apparus légèrement élevés au moment de l'administration de morphine SC étaient non significatifs.

Mots clés: *analgésique, morphine, douleur, chirurgie, pharmacocinétique, intraveineux, sous-cutané*

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INTRODUCTION

Morphine is used to relieve severe postoperative pain but this type of pain is often difficult to manage. Indeed, it is estimated that about 80 percent of patients experiencing this type of pain cannot be relieved despite the use of morphine or meperidine.[1-3] Physicians are reluctant to prescribe morphine on a regular basis because they feel it can induce respiratory depression, physical dependence and tolerance are known to develop. On the other hand, intermittent intramuscular (IM) or subcutaneous (SC) injections of morphine have been associated with fluctuating plasma levels as well as with great variations in the effectiveness and the side effects of the drug.

Continuous intravenous (IV) or SC infusions have been recommended to solve these problems because these methods of administration are thought to produce more predictable and stable serum levels of morphine and a better control of pain. Studies carried out in the last six to eight years provided evidence to support this hypothesis but they were done on a limited number of patients receiving morphine for periods of 24 hours or less.[4-11]

The efficacy and the side effects produced by intermittent IV infusion of morphine have also been investigated.[12-15] This method is known as the Patient Controlled Analgesia (PCA) method because patients can activate an electronic infusion device in response to their pain. While some authors believed that both SC injections of narcotics around the clock and continued infusion methods may produce more side effects than the PCA method, others demonstrated that continuous IV administration of morphine produced more stable effects than those obtained with intermittent administration.[9,16,17] Miser et al also suggested that continuous IV administration of morphine could minimize the alternating period of euphoria and pain seen with the intermittent modes of administration.[9]

This study was designed to determine whether continuous IV infusion of morphine produced better analgesia and less side effects than regular every four hour injections. The research was carried out over 72 hours in patients undergoing abdominal or thoracic surgery.

METHODS

Fifty-five patients undergoing thoracic or abdominal surgery were included in this double-blind study. Table I summarizes the characteristics of the patients included in the study. Patients older than 70 years and those with clinical signs of chronic pulmonary obstructive disease, hepatic and/or renal failure as well as known allergy to morphine and related opiates were excluded from the study. No sedatives, hypnotics or antiemetics were allowed during the study period. None of the patients received opiates or any other analgesics 12 hours before the surgery. Morphine was the only analgesic administered during the three-day study. Fentanyl was used during the surgery as an adjunct to other general anesthetics but it was discontinued as soon as the patients were released from the operating room. The protocol was approved by the Committee on Ethics in human experimentation of Hôpital du St-Sacrement and a written informed consent was obtained from all patients prior to their inclusion in the protocol.

Table II summarizes the protocol used in this experiment. Patients were randomly assigned to receive either a continuous IV infusion of morphine for three days or a SC injection of the opiate every four hours for three days. A bolus injection of morphine or sodium chloride 0.9% was administered to each patient at their return from the operating room. All patients included in the study were submitted to both modes of administration to ensure that the double-blind procedure was respected. The study began immediately with the arrival of the patient at the intensive care unit and the dosing schedule was established at this moment.

Criteria used to increase or decrease morphine doses after the beginning of treatment were as

Table I: Patient Characteristics

Treatment Groups	Mean		Sex		Types of surgery		
	Age (y)	Weight (Kg)			Thoracotomy	Intestinal Resection	Others[a]
SC injection (n=29)	54±2.2	61±2.4	F M	10 19	17	7	5
IV infusion (n=26)	55±1.6	65±2.5	F M	10 15	15	8	3

a. The other types of abdominal or thoracic surgery were: thymectomy (n=3), splenectomy (n=1) and aortobifemoral bypass (n=4).

follows: an increase in the morphine dose was allowed when the pain evaluated with a Visual Analog Scale (VAS) was two or higher whereas a lower dose of the analgesic drug was prescribed usually when the respiratory rate was below 13 respirations/minute and/or when the sedation score was higher than 4/6. The adjustment of the dose was done by increasing or decreasing the morphine dosage by 0.5 mg/h in the infusion group and by 2 mg/4 h in the SC group. All adjustments required after the beginning of the experimental protocol were made as a function of the patient's needs.

Morphine and sodium chloride 0.9% were administered with volumetric infusion pumps (LIFECARE 3 from Abbott Laboratories, Montréal, Canada; and INFUTROL IV 6000 from Valleylab Inc., Toronto, Canada).

A Visual Analog Scale was used to assess the degree of pain. The patients were asked to describe their pain according to the following numbered and coloured choices: (0) white: no pain; (1) green: mild pain; (2) yellow: moderate pain; (3) orange: severe pain; (4) red: very severe pain; (5) purple: agonizing pain. The day prior to surgery, the patients were instructed on the appropriate use of the pain scale. Assessments of pain were made by the same nursing staff throughout the study. To ensure standardization in pain assessment, nurses were instructed on the appropriate use of the pain scale three weeks before the start of the study. Pain assessment was made immediately before and one hour after each SC injection but it was not done when the patient was asleep at the time of data collection.

The analgesic effect of morphine was determined using the data obtained from the pain score. As suggested by Sriwatanakul et al, the tests used were Total Pain Score (TOTAL), Pain Index Score (PI), Pain Intensity Difference (PID) score and Sum of Pain Intensity Differences (SPID).[18] Pain score is a test indicating pain intensity. In this study, the TOTAL score was the 24-hour sum of pain score recorded immediately before and one hour after each SC injection. Thus, the 24-hour score was based on 12 assessments/patient/day. The TOTAL values varied between 0 and 60 and maximum relief of pain was obtained when the values were close to 0. Pain Index Score is an estimation of the degree of pain over 24 hours; this index varied between 0 and 500. For example, a patient who had 10 pain scores of two recorded in a period of 18 hours and a score of one for a six-hour period had a calculated PI of: (2 x 18/24 x 100% + 1 x 6/24 x 100%) = 175. Finally, the PID score was the difference between the PAIN score determined immediately before and one hour after morphine administration whereas the sum of PID (SPID) value was the 24-hour arithmetic sum of PID.[19] The SPID values represent the sum of six PID/day/patient since morphine or sodium chloride 0.9% were administered every four hours. In this study SPID values smaller than 10 were considered as an indicator of a constant analgesic effect.

The degree of sedation was assessed by a six-point scale with the following choices: (1) patient fully alert; (2) patient responding to his/her name; (3) patient remaining alert for five minutes; (4) patient alert only when the observer touched him/her slightly; (5) patient alert for less than five minutes; (6) patient asleep. The nursing staff determined the degree of sedation every day at 1000h, 1400h and 1900h for three days.

The respiratory rate was determined every four hours for 72 hours after surgery. Patients whose respiratory frequency was less than 10 respirations/minute were considered to have respiratory depression. When respiratory depression was observed, naloxone (0.4 mg) was administered intravenously and repeated every 15 minutes until a normal respiratory rate was

Table II: Experimental Protocol

	Continuous IV Infusion	SC Injection
Number of Patients	26	29
Modes of Drug Administration:		
1. Continuous IV infusion		
• Substances used	morphine	sodium chloride 0.9%
• Initial dose used	≤59 kg: 2 mg/h 60-79 kg: 2 mg/h ≥80 kg: 3 mg/h	——
2. SC injection		
• Substances used	sodium chloride 0.9%	morphine
• Initial dose used	——	40-50 kg: 8 mg 60-79 kg: 10 mg ≥80 kg: 12 mg
3. Bolus injection		
• Substances used	sodium chloride 0.9%	morphine
• Dose used	——	0.6 mg/m^2

obtained. The patients presenting respiration depression were excluded from the study.

To determine the serum levels of morphine, 5 mL of blood were withdrawn through an arterial blood catheter 12 times daily, immediately before and one hour after each SC injection. The samples were centrifuged immediately and frozen until assayed.

Morphine determination was made by a radioimmunoassay (RIA) method using the 1251-Mo kit (Abuscreen®, Roche Diagnostic Systems, Nutley, NJ 07110) as modified in our laboratories.[19] This method is similar to the one described by Edwards et al but an extraction procedure was done to remove metabolites such as morphine-3-glucuronide that are known to interfere with RIA tests.[20,21] Each sample was measured in duplicate and then within assay, between assay and total variations were respectively 6.5%, 10.3% and 12.1% at the level of 10.3 ng/ml (n=25) and 7.9%, 11.1% and 13.6% at the level of 31.7 ng/ml (n=22). The lower limit of detection was 1.7 ng/ml and the range was 0-50 ng/ml while the recovery of morphine added to drug-free serum samples was 103% at the level of 10 ng/ml (n=25) and 105.6% at 30 ng/ml (n=22). Droperidol, fentanyl and morphine-glucuronide did not interfere with the RIA assay.

Data obtained from assessments of pain (TOTAL, PI, PID, SPID) and sedation were analysed with the Mann-Whitney rank-sum test. General data such as patient's age and weight were analysed with the 2-tailed Student's *t* test. A Chi-square analysis of contingency was used to compare proportions of patients who had respiratory depression in both groups. Finally, the degree of correlation between the dose of morphine administered and the serum level of the drug was determined with the Pearson product-moment correllation coefficient test. The statistical analysis were performed as described by Glantz and values of $P<0.05$ were considered statistically significant.[23-25]

RESULTS

Table I shows that the majority of patients included in each group underwent thoracotomy and it indicates that there was no difference in the number of patients in each group of the study or in the mean age and weight of these patients. A total of 52 patients completed the three-day study. One patient withdrew from the study after 24 hours and two withdrew on the second day. These three patients had been included initially into the SC group; the first patient withdrew because the protocol was cumbersome for him; the second patient was an alcoholic who developed a psychotic reaction while the third patient needed to undergo surgery again.

Table III shows that patients receiving morphine by SC injections every hours had TOTAL values comparable to those in the continuous infusion group. However, it is interesting to note that TOTAL values were slightly smaller in the SC group throughout the three-day period. From day one to day three, the differences in TOTAL score between the two groups were 4.4, 5.2 and 1.8, respectively. Statistical analysis of the data on day two indicated that mean TOTAL score ± SD of 11.2 ± 1.4 obtained in the SC group was significantly smaller ($P<.05$) than the 16.4 ± 1.9 score found in the IV group. In both groups of patients, there was no significant difference in TOTAL values obtained on day one and day three of the study.

The PI values obtained in both groups of patients are also presented in Table III. The data obtained in the IV group indicate that maximal decrease of PI values was found on day two and no further reduction in pain level was found thereafter. In the SC group, the PI values recorded from day one to day three of the study were significantly lower ($P<.05$) than those obtained in the other group. This is even more impressive on day three as the mean PI values of the SC group were 54% lower than the IV group. Table III shows also that mean PID values ± SE of on day one were statistically significantly higher in the SC than in the IV group (0.61 ± 0.07 vs 0.95 ± 0.15) whereas no other significant difference was found on the two other days. Finally, mean SPID values

Table III: Evaluation of the Analgesic Effect of Morphine

Postoperative Period (in days)	Total		PI		PID		SPID	
	IV	SC	IV	SC	IV	SC	IV	SC
1	22.3±1.8	17.9±34.4	194±15	151±10*	0.61±0.07	0.95±0.2*	3.6±0.5	5.7±0.9*
2	16.4±1.9	11.2± 1.4*	128±16	164± 6*	0.41±0.08	0.53±0.4	2.6±0.5	3.2±0.5
3	10.9±1.7	9.1± 0.4	129±16	70±10*	0.41±0.05	0.36±0.3	2.5±0.4	2.1±0.4

* Indicates a significant difference ($P\leq0.05$) between the values of the IV and SC groups on each day.

± SD of 3.6 ± 0.5 and 5.7 ± 0.9, were found on day one in the IV and SC group, respectively. There was a statistical difference ($P<.05$) between these two values but the SPID levels were comparable in both groups on day two and three.

The degree of sedation produced by morphine administration is presented in Table IV. From day one to day three, there was no statistical difference ($p>.05$) in the sedation produced by the two modes of morphine administration. Respiratory depression was observed in 3/29 patients receiving morphine by SC injection and naloxone administration (0.4 mg IV) was needed to restore normal respiratory rate. No case of respiratory depression was recorded in patients receiving morphine by the continuous infusion method. Statistical analysis of the morphine effect on respiration did not reveal any statistically significant difference ($p>.05$) between the two groups. Nausea and vomiting were not evaluated in this study. These side effects of morphine did not cause any major problem to the patients included in the study.

Table V shows the mean doses of morphine administered to both groups. Morphine requirements were comparable in both groups for the first two days of the study; on day three however, the dose was 15% smaller for patients in the SC (2.4 ± 0.3 mg/h) than in the IV (2.8 ± 0.8 mg/h) group. A statistical analysis indicated a significant difference ($P<.05$) between the daily dose of morphine required in these last two groups. The serum concentrations of morphine were stable in the infusion group whereas the peak and valley phenomenon was obtained in patients receiving SC morphine every four hours (see Table V). The serum concentrations of morphine in the SC group were slightly but not significantly lower on day three than on day one and two. Mean serum morphine levels in the three patients who experienced respiratory depression was 41 ng/ml which is slightly higher than the drug levels (36 ng/ml) determined in the other patients of the same group.

Although the correlation between the daily dose administered and the serum morphine levels seems to increase with time after the beginning of the treatment, the statistical analysis did not reveal any significant correlation in these data during the three days of the experiment. The statistical analysis also did not indicate a correlation between serum morphine levels and sedation score in both treatment groups.

DISCUSSION

The evaluation of pain in clinical trials relies mainly on the cooperation, the willingness and the ability of patients to estimate the intensity of their pain. Therefore the pain scale must be easy to understand and to use by the patients. Better data on morphine-induced relief could perhaps have been obtained if a second specific pain relief scale had been used in our study.[26] However, the simultaneous use of two pain scales during the post-operative period could confuse the patient and the reliability of the pain estimation would be reduced. This is important in the immediate post-operative period because patients are still under the influence of anesthetic drugs. Thus, we used a single pain intensity scale and the analgesic effect of morphine was evaluated from the pain score through determination of TOTAL, PI and SPID values.

The patients included in both

Table IV: Assessment of Morphine-Induced Sedation

Postoperative Period (in days)	Mean Sedation Score ±		
	IV Infusion	SC Injections	P
1	5.0±0.5	5.0±0.4	NS
2	3.3±0.2	3.8±0.4	NS
3	3.1±0.2	3.6±0.5	NS

NS = not significant.

Table V: Comparative Morphine Requirements and Serum Concentrations

Postoperative Period (in days)	Morphine Requirements mg/h			Mean Serum Morphine Levels ng/mL		
	IV Infusion	SC Injections	P	IV Infusion	SC Injection Peak	SC Injection Trough
1	2.6±0.1	2.4±0.1	NS	26.4±1.6	38.6±2.5	9.7±0.9
2	2.8±0.3	2.5±0.1	NS	26.8±1.6	36.0±2.0	9.1±0.7
3	2.8±0.2	2.4±0.1	<.01	27.7±1.9	32.1±2.3	8.7±0.7

NS = not significant.

groups of the study received doses of morphine that were large enough to produce a satisfactory control of their pain. Clinical experience indicates that maximal pain relief is obtained when the TOTAL score is under 10 and when the PI value is under 200. Our data (see Table III) shows that the TOTAL scores and PI values in this study were within this accepted range. The daily doses of IV morphine (2.6 to 2.8 mg/h) administered were comparable to those used by Waldman et al (2.0 to 3.5 mg/h) and Dalhström et al (2.6 mg/h).[11,22] However, it is interesting to note that the patients receiving a continuous IV infusion of morphine for 72 hours had a mean PI on day three at the same level as on day two (see Table III) and the sedation scores (see Table IV) recorded on day two and three of the study were slightly smaller than those found in the patients from the SC group. These data suggest that the continuous IV infusion of morphine produced a rapid development of tolerance to the effects of the drug. Marshall et al and Pickar et al presented similar evidence.[28,29] They suggested also that surgical stress could release β-endorphins.[28,29] The continuous IV infusion of morphine could decrease further the plasma concentration of β-endorphins and the interaction of the narcotic with the endogenous analgesic system could block morphine receptors. Larger doses of morphine could be needed to overcome this blockade and this could be interpreted by authors as an indication that tolerance has developed. Further research is needed to confirm this.

It is of interest to determine which mode of morphine administration produced maximal pain relief and minimal side effects. As indicated above, both modes of morphine administration produced satisfactory analgesia but some data presented in Table III suggest that the pain relief may have been slightly better when morphine was administered by SC injections every four hours while others indicate that the IV infusion mode was preferable. In patients receiving morphine subcutaneously every four hours, the PI values obtained on day one and day three were significantly lower than in the IV group while mean PID or mean SPID values were significantly higher on day one and TOTAL score was significantly less on day two. The higher analgesia produced by the SC injection mode could probably be explained by the large fluctuations of serum morphine levels (the peak and valley phenomenon) associated with the SC injections every four hours. On the other hand, no significant difference has been detected in mean TOTAL scores of day one and three, in mean SPID and PID of day two and day three. Thus, a complete analysis of the data obtained with the different tests used to measure pain intensity suggests that the two modes of morphine administration produced a comparable degree of analgesia in our patients.

Another approach to determine the best method of morphine administration is to look at the side effects produced by each technique of drug administration. The sedation scores were slightly but not significantly higher in the SC group (see Table IV) while respiratory depression was noted in 3/29 patients of this same group but was not reported in the IV group. There was no statistical difference in the data on respiratory depression. Because we did not observe many cases of undesired effects in this study, our data on sedation index and respiratory depression cannot be used to determine the best mode of morphine administration.

Further research on larger groups of patients is needed in this area.

Graves et al and Batenhorst et al suggested that SC and IV morphine administration produced more side effects than the PCA method.[16,17] They suggested that the inability to predict an ideal maintenance infusion rate and the difficulty to individualize treatment are the main deficiencies of continuous IV infusion therapy. To our knowledge however, no extensive study has been carried out to compare the desired and undesired effects of morphine administered by the PCA method or a continuous IV infusion. Until such research is done, it will not be possible to determine whether morphine adminsitration by the PCA or the continuous IV infusion method produces the best results in a given clinical situation.

Frequent determination of drug serum levels is thought to be one method to monitor the effects of the drug when a correlation has been established between plasma levels and drug effectiveness. In agreement with many other investigators our pharmacokinetic data indicate that the effective serum concentrations of morphine and the analgesic response was highly variable among individuals.[9,13,14,22] For instance, 96 percent of all patients receiving SC injections of morphine had trough serum levels of the drug below the minimal effective concentration (MEC) of 20 ng/ml but they had satisfactory relief of their pain.[8,22] Eighty percent of the patients receiving IV infusion of morphine maintained a serum morphine concentration above 20 ng/ml. A correlation could not be found between the serum morphine levels, the daily doses of the drug and the sedation

score during the first day of treatment while a better but not statistically significant correlation was found on day three. Mean serum levels of morphine were 14 percent higher in patients with respiratory depression than in the other patients of both groups who did not have this side effect. Thus, the pharmacokinetic data can be used as an indicator of morphine effects but it should be associated to specific tests (VAS, TOTAL, PID, SPID) to maximize and to individualize the dose of morphine.

In summary, the data obtained with the present study indicate that IV infusion of morphine over three days is a predictable, effective and safe method of morphine administration to patients undergoing thoracic or abdominal surgery. Its use is associated with slightly but not significantly less sedation or less respiratory depression than what was obtained after around the clock SC injections of morphine for three days. The maximal efficacy of morphine administered by continuous infusion was obtained during the first day after surgery the effectiveness was reduced slightly on the second and third day of administration. The SC injection method produced a slightly better analgesic effect than the IV infusion method during the second and the third days of the study.

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