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# Value of intrathecal lyophilized morphine in coronary artery bypass surgery

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Acronyms
**CABG:** coronary artery bypass surgery
**CPB:** cardiopulmonary bypass
**ITM:** intrathecal morphine
**IVM:** intravenous morphine
**SICU:** surgical intensive care unit

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**ABSTRACT**

***Introduction:*** Subarachnoid analgesia is a useful therapeutic method in cardiac surgery.

***Objective***: To compare the use of subarachnoid and intravenous morphine for postoperative analgesia in coronary artery bypass surgery.

***Method:*** A comparative longitudinal study was conducted in 40 patients, divided into two groups. The subarachnoid analgesia group received 15 mcg/kg of lyophilized morphine, and the intravenous morphine group received 0.3 mg/kg before and after surgery.

***Results:*** Female patients predominated. The average age and weights of both groups were similar ($p > 0.05$). In the subarachnoid morphine group, 90% of patients had excellent analgesia at 8 hours after surgery, and it ranged between excellent and good at 12 and 24 hours, respectively. On the other hand, only 50% of patients with intravenous morphine expressed they had a good analgesia at 8 hours after the operation; and at 24 hours they all complained of inadequate or poor analgesia ($p < 0.05$). The average total time of postoperative analgesia in the intrathecal morphine group was 24.41 hours, while in the intravenous morphine group it was 8.76 hours ($p < 0.01$). The main side effects were itching, for both groups, and hypotension and bradycardia for the intravenous morphine group, although differences were not significant.

***Conclusions:*** Subarachnoid morphine proved to be useful as an analgesic in coronary artery bypass surgery, with better and more prolonged analgesia than in those patients who were treated with intravenous morphine.

***Key words:*** Morphine hydrochloride, Lyophilized morphine, Subarachnoid analgesia, Coronary artery bypass surgery, Postoperative analgesia

## *Valor de la morfina liofilizada intratecal en la revascularización miocárdica quirúrgica*

**RESUMEN**

***Introducción:*** La analgesia subaracnoidea constituye un método terapéutico útil en la cirugía cardíaca.

***Objetivo:*** Comparar el uso de la morfina subaracnoidea e intravenosa para la analgesia postoperatoria de la revascularización miocárdica quirúrgica.

***Método:*** Se realizó un estudio comparativo, longitudinal en 40 pacientes, divididos en dos grupos. El de analgesia subaracnoidea recibió morfina liofilizada 15 mcg/kg, y el grupo de morfina intravenosa, 0,3 mg/kg previo y posterior a la cirugía.

***Resultados:*** Predominó el sexo femenino, las edades y los pesos promedio de ambos grupos fueron similares ($p > 0.05$). El 90 % de los enfermos del grupo de morfina subaracnoidea tuvo una analgesia excelente a las 8 horas de la intervención, y se mantuvo entre buena y excelente a las 12 y 24 horas posteriores, respectivamente; mientras que solo el 50 % de los pacientes de morfina intravenosa refirió una analgesia buena a las 8 horas de operados; y a las 24 horas, todos se quejaron de una analgesia insuficiente o mala ($p < 0.05$). El tiempo total promedio de analgesia postoperatoria obtenida en el grupo de morfina intratecal fue de 24,41 horas y en el de morfina intravenosa, de 8,76 horas ($p < 0.01$). Los principales efectos adversos fueron el prurito para ambos grupos, y la hipotensión y la bradicardia para el grupo con morfina intravenosa, aunque las diferencias no fueron significativas.

***Conclusiones:*** La morfina subaracnoidea demostró su utilidad como agente analgésico en la revascularización miocárdica quirúrgica, con mejor y más prolongada analgesia que los enfermos tratados con morfina intravenosa.

***Palabras clave:*** Clorhidrato de morfina, Morfina liofilizada, Analgesia subaracnoidea, Revascularización miocárdica quirúrgica, Analgesia postoperatoria

## INTRODUCTION

Postoperative pain has a major incidence on cardiac surgery, so it has an important place in our attention[1]. Proper treatment is essential to ensure a quality care of the surgical patient. The use of opium for pain relief is proverbial. It was described in various ancient treatises. In recent centuries, different derived, semi-synthetic and synthetic compounds have been developed. They are generically known as opiates or opioids, and their prototype is the morphine[1,2]. When opioids settle locally in the vicinity of the spinal cord, they bind with pre-and postsynaptic receptors, and prevent the release of new transmitters at this level, thereby blocking the transmission of nociceptive information at the dorsal horn of the spinal cord[2], so they offer quality analgesia for a long time[3-6].

Coronary artery bypass surgery (CABG) without cardiopulmonary bypass (CPB) or with partial CPB, and the use of quick recovery anesthetic agents (isoflorane or sevoflurane, propofol, remifentanil, or lower doses of "classic" opioids such as fentanyl and surfentanil), has achieved a faster recovery of patients, with short postoperative mechanical ventilation time (<6 hours) and a shorter stay in the surgical intensive care unit (SICU), which has led to a higher incidence of postoperative pain[4,5].

Numerous strategies have been tried to fight it, ranging from the use of nonsteroidal anti-inflammatory drugs to parenteral injection of tramadol, meperidine or morphine. However, these drugs retain their pharmacological effect for short periods, usually 4-6 hours, and their cumulative effect plus the narrow margin between therapeutic and toxic doses reduce their effectiveness[4-6]. The use of intrathecal (IT) morphine for postoperative pain management in cardiac surgery may be an alternative to intravenous (IV) administration of opioids.

The objective of this research was to compare the effect of the administration of subarachnoid morphine with that of IV morphine, for postoperative analgesia in CABG.

## METHOD

A comparative, prospective and longitudinal study was conducted in two groups of patients undergoing CABG at the Cardiocentro Ernesto Che Guevara of Santa Clara, Cuba, from January to December 2012. A random selection (according to Torres Delgado *et al.*[9]) was conducted among adult patients under 70 years of age who were in the American Society of Anesthesiology

functional class III and the New York Heart Association (NYHA) functional class II-III[4], with good previous ventricular function (ejection fraction greater than 50%), without valve abnormalities or left ventricular regional wall motion abnormalities, preoperatively medicated with atenolol and nitro-derivatives, and who consented to participate in the study.

Patients with reduced ventricular function, myocardial infarction in the last 6 months, known hypersensitivity to drugs used in the study, mechanical ventilation and intraaortic balloon counterpulsation or inotropic support drugs prior to surgery were excluded; as well as surgical emergency patients or those who had absolute or relative contraindications for IT drug administration (puncture of the subarachnoid space). The exclusion criteria also included patients with lung disease, endocrine, metabolic or serious neurological disease, and those who did not complete the study period due to complications during the postoperative period (e.g. pneumothorax, major bleeding, severe pulmonary atelectasis), and finally patients with less than 150,000 platelets/$mm^3$, those who received preoperative heparin or other drugs known to affect coagulation, antiplatelet therapy or both, and those with a history of abnormal bleeding.

The sample consisted of 40 patients, divided into two random groups, each group with 20 participants. In the control group, IV morphine hydrochloride (IVM) 0.3 mg/kg was used, together with general anesthesia, before and after surgery. In the study group, a subarachnoid spinal block or lumbar IT block ($L_2$-$L_3$ or $L_3$-$L_4$) was used in the ratio of 15 mcg/kg of lyophilized IT morphine (ITM).

**Techniques and procedures**

After receiving the patients in the surgical unit, they were premedicated with intravenous midazolam 2 mg. They were taken to the operating room where their vital signs were recorded and they underwent a subarachnoid spinal block, in the above mentioned intervertebral spaces for this group, which received lyophilized IT morphine (ITM). The lateral decubitus position was used to carry out the dural puncture, using a 25G trocar. Once a clear, transparent and normotensive cerebrospinal fluid was obtained, 15 mcg/kg of lyophilized morphine, which had been dissolved in sodium chloride 0.9%, were added until reaching a volume of 6 ml. Subsequently, the patients stayed in supine position and were given supplemental oxygen by mask. The left radial artery was cannulated to measure blood pressure; and heart rate, the oxygen pulsatile saturation of hemoglobin and the continuous electrocardiography (lead II) were monitored.

After inducing anesthesia with lidocaine 2 mg/kg, thiopental 3 mg/kg, fentanyl 10 mcg/kg, and vecuronium 0.2 mg/kg IV, the central venous pressure, diuretic rhythm, capnography and central temperature were monitored. An endotracheal tube and a nasogastric tube were placed. Mechanical ventilation was performed with the tidal volume calculated at 7 ml/kg, respiratory rate of 12 to 16 per minute and $FiO_2$ of 50%, in controlled mode, and it was readjusted so that $PaCO_2$ was between 35 and 45 mmHg.

Anesthetic maintenance was carried out with isoflurane at 0.8-1.0%, and supplemental intravenous doses of fentanyl, 5 mcg/kg, depending on the requirements of surgical stimulation. With regard to the group that was given IV morphine, once the induction of anesthesia was concluded, morphine hydrochloride (0.3 mg/kg) was administered prior and after aorto-coronary graft. Intraoperative hydration was kept at 10 ml/kg/hour with crystalloids, plus replacement fluids, depending on the extraordinary losses and individual hemodynamic needs. All patients underwent a blood conservation program through intentional normovolemic hemodilution with autologous blood donation (≈ 500 ml per patient). Replacement of bleeding was carried out with colloids (gelofusin or hemohes). Autologous blood was recovered before the transfer of the patient to the SICU. The hemodynamics of the patients was supported with norepinephrine, dobutamine and nitroglycerin, according to the individual needs. A close monitoring of blood pressure, heart rate and respiratory frequency, arterial oxygen saturation and echocardiographic rhythm was conducted.

After the completion of surgery, the IVM group received a dose of morphine hydrochloride, previously calculated at 0.3 mg/kg. Then, all patients were transferred to the SICU where the monitoring of their vital parameters continued. Mechanical ventilation and its shutdown was performed according to the hospital protocol (usually before 6 hours after arrival at the SICU), and hemodynamic support was maintained depending on the needs of the patients.

The intensity and duration of pain were assessed at 8, 12 and 24 hours after the arrival at the SICU. The visual analog scale (VAS), from 0 to 10, was used for

this purpose, with 0 representing no pain; from 1 to 3, mild pain; from 4 to 6, moderate pain; from 7 to 9, severe pain; and 10, unbearable pain. In the same way, it was considered that the quality of analgesia was good when the pain was mild (1-3), so-so when pain was moderate (4-6), and poor when the pain was severe (≥ 7). When there was no pain it was considered as excellent (VAS = 0). A table was devised with the results obtained from the implementation of the VAS. It shows the quality of postoperative analgesia in both groups over time. The time of postoperative analgesia was determined as the time elapsed between IT or IV injection of the drug and first analgesic dose needed by the patient. Once the drugs were administered in each group, both intraoperatively and postoperatively, there was a monitoring of side effects, reported by the person or observed clinically by the anesthesiologist. Those effects attributable to other identifiable causes were dismissed. All data were collected in an individual survey.

The extubation time was calculated from the moment the patient was admitted to the SICU. The respiratory rate and blood gas were measured on admission, one hour later, at extubation, and then every 6 hours. Residual sedation was assessed by the Ramsay scale (according to Congedo *et al.*[10]). Additional IV morphine consumption was recorded in both groups during 24 hours after extubation. It was also recorded the presence of pruritus, nausea, vomiting and other postoperative complications (e.g. post-dural-puncture headache or presence of epidural hematoma).

## RESULTS

Table 1 shows the characterization of the patients included in the study. Age (ITM group 67 ± 9.69 years and IVM group 68 ± 9.71 years) and body weight (ITM 65 ± 7.0 kg and IVM 63 ± 8.5 kg) were similar (p > .05). Females predominated in both groups, and most patients underwent 2 or more aorto-coronary bypass grafts. The procedure was performed on the beating heart with or without partial CPB; it was similar in both groups. No statistical differences were found between groups (p > 0.05), which ensured comparability.

**Table 1.** Characterization of patients according to the group (study or control).

| Caracteristics | ITM Group | IVM Group |
|---|---|---|
| Number of patients | 20 | 20 |
| Mean age ± SD (years) | 67 ± 9,69 | 68 ± 9,71 |
| Sex (Female/Male) | 8/2 | 9/1 |
| Mean weight ± SD (kg) | 65 ± 7,0 | 63 ± 8,5 |
| Number of grafts/patient: | | |
| - 1 | 5 (25 %) | 6 (30 %) |
| - 2 | 8 (40 %) | 6 (30 %) |
| - 3 or more | 7 (35 %) | 8 (40 %) |
| Use of CPB: | | |
| - With CPB | 12 (60 %) | 10 (50 %) |
| - Without CPB | 8 (40 %) | 10 (50 %) |

p > 0.05

The degree of post-operative analgesia is summarized in Table 2. According to the VAS, 90% of patients in the ITM group had excellent analgesia at 8 hours after surgery, and it remained from good to excellent even at 12 hours after surgery; at 24 hours, 80% maintained a good level of analgesia. In these patients, there were no cases with high VAS scores in any of the measurements. Conversely, 50% of patients in the IVM group reported a good analgesia at 8 hours after surgery, which decreased to 30% of patients at 12 hours. All the patients in this group were afflicted

**Table 2.** Comparing the degree of analgesia obtained in both groups, according to the VAS.

| Degree of analgesia | ITM Group [n (%)] | | | IVM Group [n (%)] | | |
|---|---|---|---|---|---|---|
| | Hours after surgery | | | | | |
| | 8 | 12 | 24 | 8 | 12 | 24 |
| **Excellent** | 18 (90 %) | 12 (60 %) | 10 (50 %) | - | - | - |
| **Good** | 2 (10 %) | 6 (30 %) | 6 (30 %) | 10 (50 %) | 6 (30 %) | - |
| **So-so** | - | 2 (10 %) | 4 (20 %) | 10 (50 %) | 7 (35 %) | 6 (30 %) |
| **Poor** | - | - | - | - | 7 (35 %) | 14 (70 %) |

p < 0.05

by insufficient or poor analgesia at 24 hours of surgery. Significantly, in this group, there was no patient with "excellent" analgesia in any of the measurements. The differences between the groups were statistically significant ($p < 0.05$).

In both groups, the average total time for postoperative analgesia remained at 50% or more of patients, with a VAS score of less than 4 (Table 3). However, highly significant differences were found between the groups ($p < 0.01$). Thus, the average time of analgesia in the ITM group was 24.41 hours; while it was just 8.76 hours in the IVM group, 3 times less than in the patients of the study group.

Extubation times were similar in both groups and no statistically significant difference was found (ITM 8.41 ± 1.33 vs. IVM 7.32 ± 1.55 hours; $P > 0.05$); and the level of sedation in the Ramsay scale was similar in the two groups during the 24 hours after extubation, hence most of the patients were in level 2 of sedation (cooperative, orientated and tranquil).

**Table 3.** Total average times of postoperative analgesia and extubation.

| Time (hours) | ITM Group | IVM Group | p |
|---|---|---|---|
| **Analgesia** | 24,41 ± 5,13 | 8,76 ± 2,13 | p < 0.01 |
| **Extubation** | 8,41 ± 1,33 | 7,32 ± 1,55 | p > 0.05 |

The most frequent side effects, once the above mentioned medications were administered, were bradycardia and hypotension (Table 4). And, although they were not significantly different in the two groups, they predominated in the IVM group (hypotension 45% and bradycardia 40%). There were no other reactions of interest during the intra-operative period. Already in the postoperative period, the occurrence of pruritus in the recovery room was similar in both groups, with an expected incidence between 40-45%, somewhat higher in the ITM group. Other side reactions attributable to the use of morphine by any route include nausea (8 patients in the ITM group vs. 6 patients in IVM group) and somnolence (2 patients in the ITM group vs. 1 patient in the IVM group). There were no statistical differences between the groups in these parameters ($p > 0.05$), nor cases of shortage of breath or respiratory depression, or other allergic manifestations. Likewise, no patient had the typical complications of lumbar puncture (infection, meningitis, epidural hematoma, etc.).

**Table 4.** Complications and side effects found, attributable to the anesthetic technique.

| Efectos colaterales | ITM Group [n (%)] | IVM Group [n (%)] |
|---|---|---|
| **Hypotension** | 7 (35 %) | 9 (45 %) |
| **Bradycardia** | 7 (35 %) | 8 (40 %) |
| **Nausea and vomiting** | 8 (40 %) | 6 (30 %) |
| **Pruritus** | 9 (45 %) | 8 (40 %) |
| **Somnolence** | 2 (10 %) | 1 (5 %) |

$p > 0.05$

## DISCUSSION

The use of spinal subarachnoid block techniques associated with general anesthesia brings benefits to the patient, not only because it disrupts the spinal reflex arc, but also by the possibility of providing postoperative analgesia. In thoracic surgery, it is generally preferred the dorsal location of an epidural catheter (T4 to T10), likewise, the lumbar subarachnoid block has proven to be very effective. The use of lyophilized morphine in CABG increases the benefits of anesthesia in thoracotomy, because it allows a "light" general anesthesia technique with reduced effects of residual respiratory depression[11-15].

The use of IT morphine as analgesic technique in patients undergoing cardiac surgery was initiated by the work of Matthews and Abrams, which was published in 1980[3]. In a multicenter study, it was found that about 8% of anesthesiologists routinely carried out spinal anesthesia techniques in patients undergoing cardiac surgery. The administration of IT morphine for postoperative pain management in cardiac surgery is an alternative to the use of IV morphine. However, its intrathecal administration may involve the appearance of serious side effects: meningitis, post-lumbar puncture headache, epidural hematoma and respiratory depression[13,14]. To be able to consider

IT morphine administration as a routine analgesic technique, it should provide more advantages over these potential problems. This study demonstrates that IT morphine administration, as an analgesic regimen after cardiac surgery, offers some advantages compared with conventional intravenous analgesic on-demand regimen, especially from the point of view of pain relief, because the patients who received IT morphine required less use of intravenous pain medication. So, the adverse effect profile and postoperative recovery of patients were similar in both groups.

To date, the optimal analgesic dose of IT morphine for the postoperative period after cardiac surgery is still not well defined[16-18]. The administration of high doses of IT morphine (4 mg), immediately before the induction of anesthesia achieves excellent postoperative pain control, but it is associated with delayed awakening, postoperative sedation and delay in extubation. The administration of lower doses of IT morphine (250 µg to 2 mg) provides residual analgesia in the postoperative and lowers the analgesic requirements, without delaying extubation and with minimal side effects[19]. Currently, it is considered that the majority of patients undergoing cardiac surgery may be extubated 2 - 4 hours after surgery, regardless of the use of epidural or intradural techniques, or patient-controlled analgesia in IV boluses[18-20].

In this study, long extubation times could be attributed to the fact that postoperative recovery was performed slowly to allow sufficient time for reheating the patient, for the haemodynamic stability with minimal need for inotropic and vasoactive support, and minimal bleeding through chest tubes. In addition, it is necessary to mention that in our country we still use fentanyl for analgesia, which has a delayed elimination half-life, unlike others such as remifentanil, which could relatively justify to some extent an important delay in extubation.

Moreover, there have been prolonged endotracheal extubation times in patients receiving IT morphine (10 µg/kg) along with fentanyl (20 µg/kg). However, other authors note that with the use of small amounts of IV fentanyl (2-4 µg/kg), followed by IT morphine (10 µg/kg), it is possible to achieved endotracheal extubation in the operating room without increasing the incidence of respiratory complications[17,18].

In the ITM group, the incidence of the four classic adverse effects in the first 24 hours after administration of IT morphine (pruritus, nausea, vomiting and respiratory depression) was very low. It was similar to the IVM group and the findings of other studies[15,18,19]. In this study, no case of respiratory depression was detected, measured by an increase in $PaCO_2$ or respiratory rate decrease after extubation.

The most serious complication of IT morphine administration, especially in patients with systemic anticoagulation, is the epidural spinal hematoma[21,22]; however, it was not observed neither in this study nor in the other reviewed studies, in which heparin was used for systemic anticoagulation after a neuraxial procedure in patients undergoing cardiac surgery.

With the IT morphine doses that were used in this study (15 mg/kg), it was obtained adequate postoperative analgesia, without compromising extubation, and with a lower consumption of IV morphine, since only 30% of patients required additional IV boluses of the drug.

Patients treated with IT morphine showed lower VAS scores and, subjectively, felt better during the postoperative period. This is consistent with several reports in the referenced literature[21-25]. However, subarachnoid block is not without risks. Of all the side effects that are presented, the most common is hypotension, which appears with the use of opioids mainly due to the release of histamine and a manifest vasodilation, especially when they are used intravenously. This may affect the minimum values of heart and brain autoregulation, and cause damage to the perfusion of these organs. However, with adequate oxygenation, if vascular space is optimally filled with crystalloids and colloids, and vasopressors (ephedrine, phenylephrine or norepinephrine, dopamine) are used in an early and effective way, it is possible to counteract this disadvantage and minimize the risks[26,27]. With the use of parenteral opioids, and with neuraxial opioids in this case, it is much more frequent the occurrence of bradycardia due to the vagolytic effect of narcotics, coupled with the concomitant use of negative chronotropic agents (beta-blockers and calcium antagonists)[28], but this is easily solved with the use inotropic drugs.

The emetic effects of opioids, administered by any route, are well known, including those administered via the spinal cord. This is due to cephalic spread of the agent in the cerebrospinal fluid to the vomiting center in the medullary chemoreceptor zone. How-

ever, nausea and vomiting that are not caused by narcotics are common complications of anesthesia and surgery[29]. However, it is interesting the occurrence of pruritus, with a higher incidence in the ITM group. It is suggested that its occurrence could be the result of an acute or excessive release of histamine, or due to rostral spread of the narcotic, with direct effect on Mu receptors, resulting in alterations of cutaneous sensation and pain perception, especially at the dorsal horn of the spinal cord[1,2]. Other theories that have been raised include the action of sodium bisulfite, which is an additive in morphine vials[30], or the effect of the drug on the spinal trigeminal nucleus[31].

Several authors point out that pruritus is the most common adverse effect in their studies, as it has appeared in up to 50% of the cases[32-35]. Some studies have found its appearance after 18 hours. It usually has a higher incidence in obstetric women and is usually located on the face and thorax[36-39].

Delayed respiratory depression is very rare with low-dose spinal morphine (less than 0.2 mg) and the incidence of this adverse effect is 1.9-2.3% in the U.S., and 0.09% in Sweden[40-42]. In our series, there was no case of delayed respiratory depression because patients are kept intubated until they meet the clinical and blood gas criteria for extubation[43].

## CONCLUSIONS

Patients who were administered lyophilized subarachnoid morphine had better and more prolonged analgesia than patients treated with IV morphine hydrochloride alone. The mean duration of analgesia was 3 times higher with the addition of morphine to IT block. Pruritus was the most important postoperative adverse effect in most patients, with the highest incidence in the ITM group. There were no serious complications in any of the groups in the study.

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