Eficácia do Emprego da Metadona ou da Clonidina no Intraoperatório para Controle da Dor Pós-Operatória Imediata após Uso de Remifentanil *

Efficacy of Intraoperative Methadone and Clonidine in Pain Control in the Immediate Postoperative Period after the Use of Remifentanil

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RESUMO

Simoni RF, Cangiani LM, Pereira AMSA, Abreu MP, Cangiani LH, Zemi G - Eficácia do Emprego da Metadona ou da Clonidina no Intraoperatório para Controle da Dor Pós-Operatória Imediata após Uso de Remifentanil.

JUSTIFICATIVA E OBJETIVOS: Por suas características farmacocinéticas, o remifentanil não promove efeito analgésico residual no pós-operatório imediato. O objetivo deste estudo foi comparar a eficácia da metadona e da clonidina no controle da dor pós-operatória de intervenções cirúrgicas videolaparoscópicas sob anestesia venosa total com infusão alvo-controlada de remifentanil.

MÉTODO: Participaram deste estudo aleatório, duplamente encoberto e placebo-controlado, 126 pacientes com idade entre 18 e 65 anos, ASA PS 1 e 2 de ambos os sexos, que estavam previamente programados para a realização de intervenções cirúrgicas laparoscópicas. Após venopunção, os pacientes receberam por via venosa cetoprofeno e dipirona. A indução e manutenção da anestesia foram realizadas com infusão alvo-controlada de remifentanil e propofol. Antes do início da operação, os pacientes recebiam por via venosa a solução contendo metadona 0,1 mg.kg^{-1} (grupo metadona), clonidina 2,0 µg.kg^{-1} (grupo clonidina) ou solução fisiológica a 0,9% (grupo placebo). Na sala de recuperação pós-anestésica, a dor pós-operatória foi avaliada através da escala numérica verbal (ENV). Foi considerado paciente sem dor quando a ENV ≤ 2 e paciente com dor quando ≥ 3.

RESULTADOS: A incidência de dor no grupo metadona foi significativamente menor em relação ao grupo clonidina e grupo placebo (11, 21 e 23, respectivamente; p < 0,02). Não houve diferença significativa na incidência de dor entre pacientes do grupo clonidina e placebo.

CONCLUSÕES: Em relação ao controle da dor pós-operatória de intervenções cirúrgicas videolaparoscópicas sob anestesia venosa total com uso de remifentanil, o emprego da metadona foi mais eficaz que a clonidina; e usar clonidina não foi melhor que não usar.

Unitermos: ANALGÉSICOS: clonidina, metadona; DOR: pós-operatória

SUMMARY

Simoni RF, Cangiani LM, Pereira AMSA, Abreu MP, Cangiani LH, Zemi G – Efficacy of Intraoperative Methadone and Clonidine in Pain Control in the Immediate Postoperative Period after the Use of Remifentanil.

BACKGROUND AND OBJECTIVES: Due to its pharmacokinetic characteristics, remifentanil does not promote residual analgesia in the immediate postoperative period. The objective of this study was to compare the efficacy of methadone and clonidine in the control of postoperative pain of videolaparoscopic surgeries under total intravenous anesthesia with target-controlled remifentanil infusion.

METHODS: One hundred and twenty-six patients, ages 18 to 65 years, ASA I and II, of both genders, scheduled for laparoscopic surgeries, participated in this randomized, double- blind, placebo-controlled study. After venipuncture, intravenous ketoprofen and dypirone were administered. Target-controlled infusion of remifentanil and propofol was used for induction and maintenance of anesthesia. Before beginning the procedure, an intravenous solution containing 0.1 mg.kg^{-1} of methadone (methadone group), 2.0 µg.kg^{-1} of clonidine (clonidine group), or NS (placebo group) was administered. In the post-anesthetic care unit, postoperative pain was evaluated by the Verbal Numeric Scale (VNS). Absence of pain was defined as a score ≤ 2, and pain as a score of ≥ 3.

RESULTS: The incidence of pain in the methadone group was significantly lower than in the clonidine and placebo groups (11, 21, and 23, respectively; p < 0.02). Significant differences in the incidence of pain in the placebo and clonidine groups were not observed.

CONCLUSIONS: Methadone was more effective than clonidine in the control of postoperative pain in videolaparoscopic surgeries under total intravenous anesthesia with remifentanil; and using clonidine was not better than not using it.

Keywords: ANALGESICS: clonidine, methadone; PAIN: postoperative,

Efficacy of Intraoperative Methadone and Clonidine in Pain Control in the Immediate Postoperative Period after the Use of Remifentanil

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INTRODUCTION

Videolaparoscopic surgical techniques are responsible for better postoperative evolution and consequently shorter hospitalizations, with or without overnight hospital stay. The use of multimodal analgesia with the preoperative administration of dexamethasone, infiltration of the surgical wound with local anesthetics, and the use of non-steroidal anti-inflammatories is usually adequate to control postoperative pain without using opioids routinely [1]. However, postoperative pain is more severe in the first postoperative hour, especially in patients with residual pneumoperitoneum [2].

The development of intravenous anesthetics with short elimination half-lives, restricted distribution volume, and organ-independent metabolism facilitated the intraoperative titration of anesthesia, short awakening time, and safe early extubation. Remifentanil is an opioid that possesses those characteristics, which are responsible for an extremely short context-dependent half-life (4 to 6 minutes) regardless of the duration of the infusion [3].

This intraoperative advantage becomes a disadvantage in the post-anesthetic care unit (PACU) when control of post-operative pain becomes the major problem. Due to its pharmacokinetic characteristics, remifentanil does not promote residual analgesia in the immediate postoperative period [1]. Besides, some authors have warned us on the potential risks of postoperative hyperalgia and secondary acute tolerance associated with the use of remifentanil, which can increase both the incidence and severity of post-operative pain [4-10]. It can manifest early, occurring after in-fusions of low doses (0.1 $\mu g.kg^{-1}.min^{-1}$) for a short time (30 minutes) [11]. However, studies have demonstrated that the concomitant use of agonists of NMDA receptors and remifentanil decreases or prevents its development, leading to more effective control of postoperative pain [11-13].

Methadone is an opioid with prolonged latency and duration of action, rarely used in anesthesia. Its analgesic potency is similar to that of morphine when used intravenously. It has an elimination half-life of 24 hours, which can vary from 13 to 50 hours. However, its analgesic effect lasts 4 to 8 hours. The recommended dose of this drug varies from 0.10 to 0.15 $mg.kg^{-1}$. Due to the discrepancy between its plasma half-life and duration of the analgesic effect, repeated doses can lead to accumulation of the drug [14]. The R(-) isomer of methadone is a μ-agonist, while the S(+) isomer is almost inactive in this receptor. However, this isomer is an NMDA antagonist. Consequently, the R(-) and S(+) isomers of methadone are synergistic on promoting the antinociceptive effect [15]. Studies on the use of methadone to control postoperative pain after the use of remifentanil were not found in the literature.

When used in the usual intravenous doses, clonidine promotes sedation, analgesia, and a sympatholytic effect in 10 to 30 minutes [16-18] and the duration of the analgesic action varies according to the dose [19-21]. The synergism between α_2-agonists and opioids has been demonstrated in several studies [22,23]. The intraoperative administration of clonidine, a bolus of 3.0 $\mu g.kg^{-1}$ followed by the infusion of 0.3 $\mu g.kg^{-1}.h^{-1}$ is necessary in standard inhalational anesthesia without opioids for the effective control of postoperative analgesia with a low incidence of adverse effects (bradycardia and hypotension) [18,24]. However, low doses of clonidine (1.0 to 2.0 $\mu g.kg^{-1}$) can be effective when used in association with opioids [25,26]. A study with healthy volunteers showed that when clonidine was administered during the infusion of remifentanil the intensity of the anti-analgesic effect and the area of hyperalgia was reduced [11].

The objective of the present study was to compare the efficacy of methadone and clonidine in the control of pain in the immediate postoperative period of videolaparoscopic surgeries under total intravenous anesthesia with target-controlled infusion of remifentanil. The hypothesis of whether methadone is more effective than clonidine in the control of postoperative pain under those circumstances was tested.

METHODS

After approval by Ethics on Research Committee and signing of the informed consent, 126 patients, ages 18 to 65 years, ASA I and II, of both genders scheduled for non-gynecological videolaparoscopies participated in this randomized, double-blind, placebo-controlled study. The size of the study population was based on a prior pilot study. Considering that the placebo group showed an incidence of pain of 60%, the power of the analysis with 1% alpha and 20% beta showed that for a 25% reduction in the incidence of pain, each group should have 42 patients. Patients who used alcohol or illicit drugs, chronic users of H_2 inhibitors, tricyclic antidepressants, or calcium channel blockers, with psychiatric disorders, dementia, or hypersensitivity to the drugs used in the study were excluded.

Patients were randomly divided in three equal groups: methadone group (MG), clonidine group (CG), and placebo group (PG). Before the beginning of the study, a table of random numbers was generate by a computer specifying the group that each patient would belong to. An opaque enveloped, sealed and numbered sequentially, which contained the group the patient was allocated, was prepared for each

patient. Before anesthesia induction, an anesthesiologist not involved with the anesthetic procedure opened the envelope and prepared a syringe with 10 mL of a solution containing methadone, clonidine or normal saline. Anesthesiologists involved in the control of anesthesia or collection of the data were not aware of the group the patient belonged to. In case of an emergency, the anesthesiologist responsible for the procedure was allowed to open the study. Patients did not receive pre-anesthetic medication.

After tracheal intubation, patients were monitored with non-invasive mean arterial pressure (MAP), cardioscope, pulse oximeter (SpO_2), bispectral index (BIS), and capnograph.

After venipuncture, patients received intravenous ketoprofen (1.5 mg.kg^{-1}) and dypirone (30 mg.kg^{-1}) administered over 10 minutes. Ringer's lactate, 10 mL.kg^{-1}, was administered before the pneumoperitoneum, and 5.0 mL.kg^{-1}.h^{-1} were administered intraoperatively.

Anesthesia was induced with target-controlled infusion (TCI) of remifentanil and propofol at a target dose of 6.0 ng.mL^{-1} and 4.0 µg.mL^{-1}, respectively. After loss of consciousness observed by failure of the corneal-palpebral reflex and confirmed by bispectral index (BIS < 60), cisatracurium (0.15 mg.kg^{-1}) was administered to facilitate tracheal intubation. Immediately after the tracheal intubation the target dose of remifentanil was reduced to 3.0 ng.mL^{-1} while the target dose of propofol was reduced to 2.0 to 3.5 ng.mL^{-1} to maintain BIS between 40 and 50.

Five minutes before surgery, patients in the MG group received an intravenous solution containing methadone 0.1 mg.kg^{-1}, clonidine 2.0 ng.kg^{-1} in CG, or NS in PG.

At the beginning of the surgery, the target dose of remifentanil was increased to 5.0 ng.mL^{-1} and varied in the intraoperative period to maintain MAP ± 15% of baseline levels while the target dose of propofol varied to maintain BIS between 40 and 50.

Mean arterial pressure and HR were observed on the following moments: when the patient arrived at the operating room, after induction of anesthesia, tracheal intubation, pneumoperitoneum, 10, 20, and 30 minutes after the pneumoperitoneum, at the end of surgery, and after tracheal extubation.

At the end of the procedure, the residual neuromuscular blockade was reversed with atropine (10 µg.k^{-1}) and neostigmine (20 µg.kg^{-1}). Remifentanil and propofol infusions were then turned off. Pneumoperitoneum was reversed without additional efforts to remove the gas from the abdominal cavity.

The duration of surgery, time until awakening (spontaneous opening of the eyes and/or BIS ≥ 70), total dose of remifentanil infused per lean body mass, and the total dose of propofol per total body weight were recorded. Patients were extubated in the operating room and transferred to the post-anesthetic care unit (PACU) receiving oxygen through a nasal cannula.

In the PACU, postoperative pain was evaluated by the Verbal Numeric Scale (VNS). The patient was considered pain free when VNS ≤ 2, while patients with VNS ≥ 3 were considered as being in pain. Intravenous tramadol (1.5 mg.kg^{-1}) was the rescue analgesic if the patient reported pain. The incidence of nausea and vomiting (PONV) was also observed. All patients remained in the PACU for at least two hours.

Continuous parameters with normal distribution were expressed as means and standard deviation and evaluated by Analysis of Variance (ANOVA). Scheffeé's test was used as a *post hoc* test. Counting (proportions) parameters were analyzed by the Chi-square test. Differences were considered significant when p was lower than 0.05.

RESULTS

Table I shows the demographic data and type of surgery in both groups. Groups did not differ regarding mean propofol consumption, intraoperative BIS levels, and mean duration of surgery (Table II). Mean remifentanil consumption was

Table I – Demographic and Morphometric Data and Types of Surgeries

	Methadone Group	Clonidine Group	Placebo Group	p
Age (years)	45 ± 12	42 ± 15	40 ± 10	0.1232
Weight (kg)	79 ± 16	75 ± 16	76 ± 17	0.4469
Height (cm)	168 ± 11	166 ± 10	166 ± 9	0.4044
Lean Body Mass (kg)	55 ± 10	52 ± 11	51 ± 10	0.2942
Gender (M/F)	16/26	13/29	11/31	0.4986
Physical Status (ASA I/II)	35/7	34/8	30/12	0.3716
Type of Surgery				0.6292
Cholecystectomy	32	35	35	
Hiatal Hernia	10	7	7	

Results expressed as Mean ± SD or number of patients

Table II – Postoperative Consumption of Remifentanil and Propofol, Hemodynamic Data, Duration of the Surgery, Time until Awakening, and Incidence of Postoperative Nausea and Vomiting (PONV)

	Methadone Group	Clonidine Group	Placebo Group	p
Remifentanil ($\mu g.kg^{-1}.min^{-1}$)	0.245 ± 0.055	0.236 ± 0.059 *	0.268 ± 0.059	0.0377
Propofol ($\mu g.kg^{-1}.min^{-1}$)	107.1 ± 25.9	109.0 ± 20.4	108.0 ± 29.3	0.9439
MAP (mmHg)	88 ± 5	80 ± 5 +	86 ± 5	0.0073
HR (bpm)	68 ± 5	65 ± 4	71 ± 9	0.2537
Duration of the surgery (min)	65 ± 20	58 ± 15	57 ± 15	0.0606
Time until awakening (min)	7.6 ± 4.1	9.1 ± 3.9	5.1 ± 2.7 ++	< 0.0001
PONV (S/N)	4/38	2/40	7/35	0.1960

Results expressed as Mean ± SD.
*vs. Placebo Group; + vs. Methadone and Placebo Groups; ++ vs. Methadone and Clonidine Groups
MAP – non-invasive mean arterial pressure; HR – heart rate

Table III – Pain in the Immediate Postoperative Period

	Methadone Group	Clonidine Group	Placebo Group	p
With	11	21	23	0.0183 *
Without	31	21	19	

Results expressed in number of patients
* Methadone Group vs. Clonidine and Placebo Groups

significantly lower in the methadone and clonidine groups than in the placebo group; however, a significant difference between the methadone and clonidine groups was not observed (p < 0.05; Table II). Intraoperatively, mean MAP was significantly lower in the clonidine group than in the methadone and placebo groups (p < 0.008; Table II). Mean HR was similar in all three groups (Table II). Mean awakening time was significantly lower in the placebo group than in the clonidine and methadone groups (p < 0.0001; Table II), but statistically significant differences between the methadone and clonidine groups were not observed.

The incidence of pain in the methadone group was significantly lower than in the clonidine and placebo groups (11, 21, and 23, respectively; p < 0.02; Table III). The incidence of pain was not significantly different in the clonidine and placebo groups. The incidence of PONV was similar in all three groups (Table II).

DISCUSSION

In the present study, methadone was more effective in controlling postoperative pain over two hours in PACU in patients who underwent videolaparoscopy than clonidine and placebo, and it did not increase significantly the time until awakening or the incidence of nausea and vomiting during this period. The incidence of pain did not differ between the clonidine and placebo groups.

Cholecystectomy was the most common surgery in the three study groups. Postoperative pain in patients undergoing videolaparoscopic cholecystectomy is more severe in the first postoperative hour in patients with residual pneumoperitoneum[2]. Most patients probably had residual pneumoperitoneum since additional techniques for its removal were not used. For those reasons, it was decided not to follow-up patients for more than two hours.

As mentioned before, the use of multimodal analgesia, including dexamethasone, infiltration of the surgical wound with local anesthetic, and non-steroidal anti-inflammatories is enough to control postoperative pain[1]. However, the authors did not make a deeper analysis of the clinical assays in which remifentanil was used as intraoperative analgesic.

One should be aware of the possible development of acute tolerance and postoperative hyperalgia secondary to the use of remifentanil [4-9]. Although it was not the objective of this study, it is known that postoperative hyperalgia can increase the incidence and severity of postoperative pain [4-9]. Studies have emphasized that the preemptive control of postoperative pain with modulation of secondary hyperalgia is more effective [27-28]. We decided against the preemptive administration of the study drugs, since the patient could report the presence of any clinical feelings to the anesthesiologist responsible for the study at the time of infusion, compromising the double-blind nature of the study.

The intra- and postoperative use of continuous infusion of low doses of ketamine has been suggested by some authors to decrease the incidence of postoperative pain and consumption of analgesics [11-13]. However, its use has limited practicability since more than one infusion system is necessary.

Recently, it has been demonstrated that the administration of fentanyl (1.5 µ.kg^{-1}) before and after the infusion of remifentanil did not decrease pain and analgesic consumption in the first four postoperative hours when compared to patients who received fentanyl (3.0 µg.kg^{-1}) after the infusion [29]. It has not been reported yet whether fentanyl has antagonistic actions in NMDA receptors. It is known that, to obtain the same effect with morphine, it is necessary to use doses up 16 times higher than its usual dose.

The differential of methadone relies in its µ-agonist and NMDA-antagonist actions, promoting better nociceptive effects. Its use is convenient because due to its long half-life another infusion system is not necessary facilitating its use in clinical practice. Studies on the use of methadone to control postoperative pain and hyperalgia after the use of remifentanil were not found in the literature. However, other drugs have been used to achieve this effect.

Due to its analgesic and sedative actions clonidine was used in healthy volunteers demonstrating that in patients who received intravenous clonidine (2.0 µg.kg^{-1}) during the infusion of remifentanil the incidence of pain was lower after the discontinuation of the opioid [11]. In the present study, the same dose of clonidine was used; however, it was ineffective in controlling postoperative pain since the incidence of pain in this group was similar to that of the placebo group.

It is possible that the dose used in the present study was not enough to provide postoperative analgesia. In fact, some authors recommend doses between 3.0 and 5.0 µg.kg^{-1} and continuous infusion of 0.3 µg.kg^{-1}.h^{-1} in the intraoperative period to obtain effective analgesic effect in the postoperative period [19-21]. However, one study demonstrated that low doses of intravenous clonidine intraoperatively were effective in controlling postoperative pain with very few side effects. But the authors did not use remifentanil as the opioid [18].

From the results obtained in the present study, the synergistic action of remifentanil with clonidine seems to be limited to the intraoperative period since mean consumption of remifentanil in the clonidine group was slightly lower than the placebo group and similar to that of the methadone group. Other clinical assays are necessary to determine the relationship between the drugs studied with the area of hyperalgia and the incidence and severity of postoperative pain. Similarly to other studies, mean MAP levels were lower in the clonidine group than in the methadone and placebo groups [18-21]. This is due to the sympatholytic action of α_2-agonists [17,33]. However, its sedative property was not evident, since the consumption of propofol was similar in all three groups, which differs from other studies [21,30-34]. However, such studies used oral clonidine as pre-anesthetic medication while in the present study clonidine was used intravenously. It is known that the onset of action of intravenous clonidine varies from 10 to 30 minutes and, since the duration of the surgery in this clinical assay was relatively short, it is possible that the propofol sparing effect was not significant. One should not forget that mean intraoperative BIS levels were similar in all three groups.

The dose of clonidine used is another factor that can explain this result. A study demonstrated a reduction in BIS levels and, consequently, propofol consumption with doses of 4.0 µg.kg^{-1} of clonidine, the double of what was used in the present study [21]. However, even with the low dose of clonidine used, patients in the clonidine group showed a slightly higher time of awakening than the placebo group [19,31].

The analgesic and sedative effects of clonidine are most likely dose-dependent, since the dorsal spinal cord horn is the proposed initial site of action for those effects [35].

The main limiting factor of the present study is the lack of longer postoperative follow-up of patients, which hindered a more encompassing conclusion on postoperative pain.

The results of the present study allow us to conclude that regarding the control of postoperative pain in videolaparoscopic surgeries under total intravenous anesthesia with remifentanil the use of methadone is advantageous since it decreases the incidence of pain in the immediate postoperative period without prolonging too much the time until awakening and the incidence of nausea and vomiting.

To conclude from the results obtained it is possible to affirm that it is better to use methadone than not using it. Methadone was more effective than clonidine, whose response was similar to placebo.

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RESUMEN

Simoni RF, Cangiani LM, Pereira AMSA, Abreu MP, Cangiani LH, Zemi G - Eficacia del Empleo de la Metadona o de la Clonidina en el Intraoperatorio para Control del Dolor Postoperatorio Inmediato después del Uso de Remifentanil.

JUSTIFICATIVA Y OBJETIVOS: El remifentanil, por sus características farmacocinéticas, no genera un efecto analgésico residual en el postoperatorio inmediato. El objetivo de este estudio fue comparar la eficacia de la metadona y de la clonidina en el control del dolor postoperatorio de intervenciones quirúrgicas videolaparoscópicas bajo anestesia venosa total con infusión objeto controlada de remifentanil.

MÉTODO: Participaron en este estudio aleatorio, doble ciego y placebo-controlado, 126 pacientes con una edad entre los 18 y los 65 años, ASA PS 1 y 2 de ambos sexos, que estaban previamente programados para la realización de las intervenciones quirúrgicas laparoscópicas. Después de la venopunción, los pacientes recibieron por vía venosa cetoprofeno y dipirona. La inducción y el mantenimiento de la anestesia fue realizada con infusión objeto controlada de remifentanil y propofol. Antes del inicio de la operación, los pacientes recibieron por vía venosa la solución conteniendo metadona 0,1 mg.kg^{-1} (grupo metadona), clonidina 2,0 µg.kg^{-1} (grupo clonidina) o solución fisiológica a 0,9% (grupo placebo). En la sala de recuperación postanestésica, el dolor postoperatorio se evaluó a través de la escala numérica verbal (ENV). Se tuvo en cuenta el paciente sin dolor cuando la ENV era ≤ 2 y el paciente con dolor cuando había ≥ 3.

RESULTADOS: La incidencia de dolor en el grupo metadona fue significativamente menor con relación al grupo clonidina y al grupo placebo (11, 21 y 23, respectivamente; p < 0,02). No hubo diferencia significativa en la incidencia de dolor entre los pacientes del grupo clonidina y placebo.

CONCLUSIONES: Con relación al control del dolor postoperatorio de intervenciones quirúrgicas videolaparoscópicas bajo anestesia venosa total con el uso de remifentanil, el empleo de la metadona fue más eficaz que la clonidina. Y usar clonidina no fue mejor que no usarla.