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# Does Simple Oral Route of Administration Affect Acute Post Operative Pain?(Oral Pregabalin Versus Oral Morphine Sulphate) for Acute Post Operative Pain following Cancer Surgeries

**Alaa Ali M. Elzohry, MD[1], Ahmed Fetouh Abdelrahman, MD[2], Ahmed Ahmed, MSc[3] Bahaa Gamal Saad, MSc[4], Ahmed Mohamed Ashmawy, MD[5]**

[*1]Lecturer of Anesthesia, ICU and Pain Relief, South Egypt Cancer Institute, Assiut University

[2]Lecturer of Anesthesia, ICU and Pain Relief, Faculty of Medicine, Tanta University

[3]Postdoctoral Fellow Anaesthesiology, The Ohio State University Wexner Medical Center, Columbus, USA

[4]Assistant Lecturer of Anesthesia, ICU and Pain Relief, South Egypt Cancer Institute, Assiut University

[5]Lecturer of Internal Medicine Department, Faculty of Medicine, Assiut University.

*alaa.zohiry@hotmail.com*

***Corressponding Author:** Alaa Ali M. Elzohry, MD, Department of Anesthesia, ICU and Pain Relief, South Egypt Cancer Institute, Assiut University, Arab Republic of Egypt.*

## Abstract

***Background and Objectives:** Major cancer surgeries cause severe pain that may lead to serious risks. Preemptive analgesia with oral pregabalin and oral morphine may be used as a non invasive and simple route of administration to decrease this pain and decrease postoperative analgesic consumption. The aim of the study was to assess the analgesic efficacy of oral pregabalin versus oral morphine tablet as simple route of administration, in patients undergoing elective major cancer surgery.*

***Materials and Methods:** This randomized, blinded, study was approved by local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut – Egypt and include Sixty patients (ASA II, III) who underwent elective major cancer surgery were divided into two groups of 30 patients each. Patients of (Group I) received oral pregabalin 300 mg two hours preoperative, and patients of (group II) received oral morphine sulphate 30 mg two hours preoperative, After induction of GA, heart rate and mean arterial pressure were recorded intraoperatively , and postoperative NRS, heart rate , mean blood pressure, side effects and total analgesic consumption were also recorded.*

***Results:** Pain scores by NRS, were comparable in both groups but postoperative total analgesic consumption there was reduction in the total amount of postoperative morphine consumption in group I (7.34±4.39) in comparison by group II (13.74±4.73) with ($p<0.044$). Also there was a significant optimization in intra-operative mean arterial pressure (MAP); and heart rate in group I in comparison to group II. The incidence of postoperative side effects such as nausea, sedation and vomiting were comparable in both groups.*

***Conclusion:** We concluded that oral route of administration is effective and both oral drugs are efficient in acute pain control and pre-operative use of oral pregabaline showed that; better intra and postoperative haemodynamic profile with better pain relief total and associated with less postoperative analgesic consumption than oral morphine after major cancer surgery.*

**Keywords:** *Major cancer surgery, acute post operative pain, morphine sulphate tablets (MST), pregabaline- NRS.*

## Introduction

Major cancer surgeries are usually accompanied by sever postoperative pain, and a significant component of the pain experienced after surgery is due to surgical incision. (1)

Controlling of this pain reduces post-operative insulin resistance, stress response, improves patient satisfaction and allows early patients

mobility, which itself is important to reduce secondary complications such as chest infection and DVT. (2)

Opioid analgesia remains the primary pharmacologic intervention for managing pain in hospitalized patients; however, as with any medication, opioids cancause adverse effects. Unintended advancing sedation and respiratory depression are among the most serious side effects. (3)

Management of acute postoperative pain has received great attention in recent years with considerable concurrent advancement in the field (4). Despite this advancement, postoperative pain continues to be a challenge and is often inadequately treated; leading to patient anxiety, stress and dissatisfaction, inadequately treated pain can lead to detrimental physiological effects and may also have psychological, economic and social adverse effects (5).

The gabapentinoid class of drugs, which includes gabapentin and pregabalin, has an established role in the management of neuropathic pain. (6) Gabapentinoids can bind to the alpha2delta subunit of presynaptic voltage-gated calcium channels, thus reducing calcium influx into presynaptic terminals. (7)

Pregabalin is a lipophilic gamma-amino-butyric acid (GABA) analog with anticonvulsant, anxiolytic and sleep-modulating properties. Also, it is effective in several models of neuropathic pain and a matter of debate in perioperative acute pain management. (8)

Morphine sulphate is the pentahydrate of the sulphate of 7,8-didehydro-4,5-epoxy-17-methyl morphinan-3,6-diol. Regularly dosed oral morphine has gained acceptance as the treatment of choice for patients with chronic cancer pain but also can be used to treat acute postoperative pain and decrease the total postoperative analgesic consumption. (9)

The aim of the study was to assess efficacy of oral route administration and to assess the analgesic efficacy of oral pregabalin versus oral morphine tablet, in patients undergoing elective major cancer surgery.

## Materials and Methods

This Clinical study was approved by local ethics committee of South Egypt Cancer Institute, Assiut University, Assiut – Egypt, and included patients from surgical oncology department and post-operative intensive care unit at south Egypt cancer institute hospital, Assuit University. After obtaining a written informed consent from each patient, Sixty patients (age ≥21 years) classified as ASA grade II and III, scheduled for elective major cancer surgery were randomly assigned into two groups, 30 patients each; who were scheduled for elective major upper abdominal cancer surgery under general anesthesia.

We excluded from the study, Patients with a history of relevant drug allergy, opioid dependence, morbid obesity (body mass index more than 40 kg/m2), sepsis, and those with psychiatric illnesses that would interfere with perception and assessment of pain. Preoperative data were collected one day before surgery as; demographic data, medical, surgical history, physical examination and routine laboratory investigations. Pre operative medications in the form of oral ranitidine tablet, 50 mg and lorazepam tablet, 3 mg on the night of surgery were given to all patients. All patients were taught- The day before surgery- how to evaluate their own pain intensity using the numerical rating scale (NRS), scored from 0 to 10 [21] (where 0=no pain and 10= worst pain imaginable) and how to use the patient controlled analgesia (PCA) device (Abbott Laboratories, North Chicago, IL, USA).

And after medical optimization and complete medical fitness performed by Internal Medicine physician who was blinded to studied groups, 60 Patients were assigned into 2 groups, 30 patients in each group:

Group I (Pregabalin group): patients received gabapentin capsules 300 mg 2 hrs. preoperatively.

Group II (morphine group): patients received morphine sulphate 30 mg tab 2 hrs. preoperatively.

## Standard General Anesthesia

After preoxygenation for 3 min, induction of anesthesia was done with IV propofol (2.5 mg/kg) and fentanyl 2 µg/kg plus 0.15 mg/kg Cisatracurium to facilitate Tracheal intubation. Anesthesia was maintained by isoflurane 1–1.5 minimum alveolar concentration (MAC); cisatracurium 0.03 mg/kg was administered when indicated. Patients were mechanically ventilated to maintain end tidal CO2 between 35 and 40 mmHg. The inspired oxygen fraction (FIO2) was 50% using oxygen-and-air mixtures. At the end of surgery, neuromuscular block was antagonized in all patients with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg and the patients were extubated in the operating room.

Hypotension was determined as systolic blood pressure <85 mmHg and was managed with IV fluid plus IV ephedrine 0.1 mg/kg. Bradycardia was determined as HR slower than 50 beats /min and was treated by atropine 0.01 mg/kg.

Intra-operatively, all patients in both groups were followed up for vital signs (heart rate and the mean arterial pressure reading) every one hour was recorded.

Post-operatively, all patients were admitted to post-operative care unit (PACU) and were followed up and assessed immediately postoperative for; NRS, total morphine consumption in 24 hours and side effects and heart rate and the mean arterial pressure reading were recorded.

Data analysis: Statistical analysis was carried out on a personal computer using SPSS ® version 20 software. Normality of continuous data distribution was tested using the Kolmogorov-Smirnov test. Data were presented as number, percentage, mean and standard deviation. Chi-square test was used to compare qualitative variable among studied groups. Independent samples t- test was used to compare quantitative variables between the two studied groups. P Value < 0.05 was considered statistically significant.

Sample size estimation: It was determined based on a previous clinical trial assessing neuroplastic effects of tDCS on painful symptoms reduction in chronic hepatitis C: with sample size of 28 patients divided into two groups (14 per group) in order to detect a 1.5 cm reduction in VAS level intensity (average standard deviation 0.8 cm) with a power of 0.8 (37). To account for the multiple outcomes and dropouts we increased the sample size to 20 per group.

## Results

The flow of the patients through the study is illustrated in (Figure 1). The demographic data and the characteristics of the patients were similar between groups (Table 1). In analysis of intraoperative heart rate (HR) variable it was found that there was statistical significant reduction in group I compared by group II at time point ($P \leq 0.018$), but at baseline was insignificant differences ($P > 0.05$) as shown in the figure (2).

Figure (3), showed that intra-operative mean arterial pressure (MAP) was significantly reduced in Group I compared by Group II in the early intra operative hours ($P>0.011$), but there was statistically insignificant difference between groups in the baseline ($p > 0.05$).

The post-operative heart rate was reduced significantly in patients of group I compared to group II in the early postoperative period but not over the remaining period ($P > 0.01$) as shown in table (2) and figure (4).

In this study we reported that there was statistically significant difference between studied groups as regards post-operative MAP in the first hour ($P> 0.01$), as shown in table (3) and figure (5).

There was reduction in pain scores, table (4) and the total amount of postoperative morphine consumption in group I (8.43±4.39) in comparison by group II (14.74±4.73) with ($p<0.044$) as shown in table (5).

And finally, side effects were comparable between the two groups as shown in table (6).

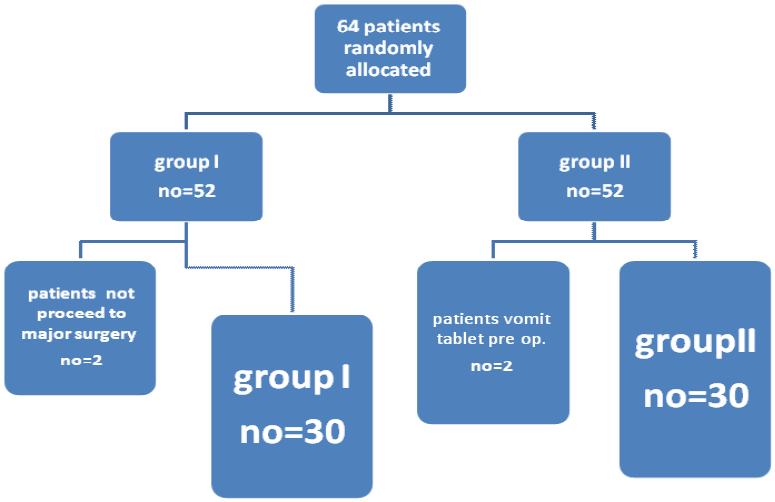


**Figure 1.** *Flow diagram of patients*

**Table 1.** *Demographic data of the studied groups.*

| | Group (n=30) | Group (n=30) | P. value |
|---|---|---|---|
| **Age: mean±SD** | 63.73 ± 5.61 (55-74) | 61.73 ± 6.07 (5574) | 0.191 |
| **Gender, M/F** | 18/20 | 12/10 | 0.592 |
| **BMI, kg/m 2: mean±SD** | 22.1 ±3.3 | 23.9 ±1.5 | 0.066 |
| **ASA , n (%)** | | | |
| II | 14 (46.7) | 12 (40.0) | 0.501 |
| III | 16 (53.3) | 9 (60.0) | |
| **Operative duration** (hours), **mean±SD** | 5.64 ± 0.7(4.4 - 7) | 5.41 ± 0.68(4.3 - 7) | 0.196 |
| **Type of Surgery:** | | | |
| -Gastrectomy | 17 (56.7%) | 15 (50.0%) | 0.795 |
| -Whipple's surgery | 7 (23.3%) | 8 (26.7%) | 0.998 |
| -Pelvic surgeries | 6 (20.0%) | 7 (23.3%) | 0.976 |

Data expressed as (Mean ± SD) and number (%) Group (I): pregabalin group, Group (II): Morphine sulphate tablets group

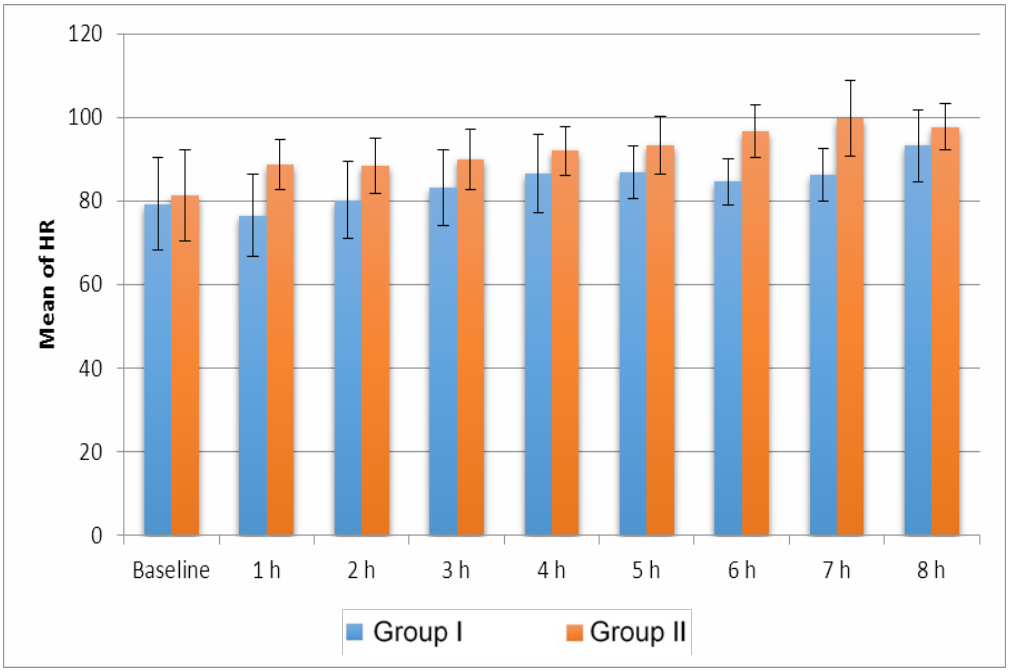


**Figure 2.** *Intra-operative heart rate (HR) (beat/ min)*

**Data** expressed as (Mean ± SD) and number (%) **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group

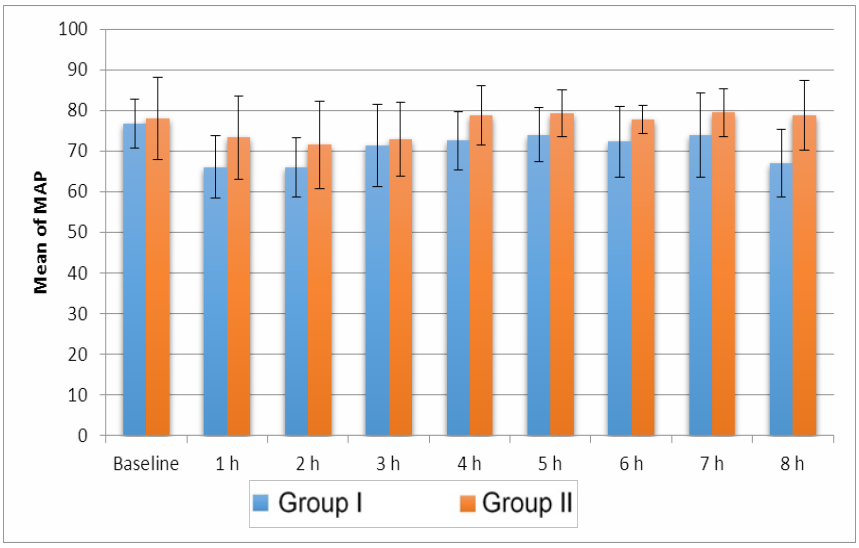


**Figure 3.** *Intra-operative mean arterial pressure (MAP) mmHg*

**Data** expressed as (Mean ± SD) and number (%) **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group

**Table 2.** *Postoperative heart rate (beats/ min)*

| HR (bpm) | Group (I) | | Group (II) | | P. value |
|---|---|---|---|---|---|
| | Range | Mean±SD | Range | Mean±SD | |
| **0.5 h** | 60-106 | 80.13±9.61 | 66-108 | 81.33±9.97 | 0.005** |
| **1 h** | 60-110 | 73.6±10.13 | 65-110 | 78±10.65 | 0.107 |
| **2 h** | 60-95 | 75.27±8.2 | 63-106 | 79.8±11.77 | 0.089 |
| **4 h** | 62-99 | 78.37±10.42 | 64-103 | 82.53±8.91 | 0.101 |
| **6 h** | 69-103 | 91.53±8.01 | 60-100 | 89.8±9.76 | 0.565 |
| **12 h** | 65-108 | 82.3±9.1 | 70-98 | 83±7.76 | 0.730 |
| **24 h** | 72-98 | 84.07±6.73 | 69-100 | 82.67±7.49 | 0.449 |

Data expressed as (Mean ± SD) and range Group (I): pregabalin group **Statistically significant difference ($p<0.01$) Group (II): Morphine sulphate tablets group bpm; beat per minute

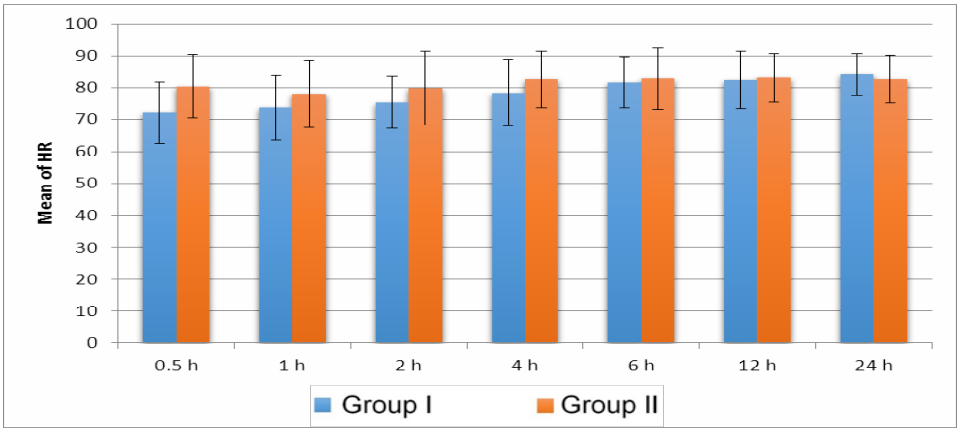


**Figure 4.** *Post operative changes in post-operative HR (beats per minutes)*

Data expressed as (Mean ± SD) and number (%) Group (I): pregabalin group Group (II): Morphine sulphate tablets group

**Table 3.** *Postoperative mean blood pressure (MAP)*

| MAP (Mmhg) | Group (I) | | Group (II) | | P. value |
|---|---|---|---|---|---|
| | Range | Mean±SD | Range | Mean±SD | |
| **0.5 h** | 70-95 | 80±7.8 | 70-100 | 87.33±7.96 | 0.001** |
| **1 h** | 70-90 | 71.83±7.48 | 70-110 | 85.5±11.17 | 0.006** |
| **2 h** | 70-100 | 84.83±7.13 | 70-110 | 87.5±9.63 | 0.228 |
| **4 h** | 70-100 | 86.67±9.86 | 80-110 | 89.17±9.01 | 0.309 |
| **6 h** | 70-110 | 91±7.81 | 70-105 | 90.5±8.74 | 0.816 |
| **12 h** | 70-115 | 90.67±10.06 | 70-110 | 88.33±8.24 | 0.330 |
| **24 h** | 70-105 | 91.83±7.6 | 75-100 | 86.5±6.97 | 0.141 |

**Data** expressed as (Mean ± SD) and range **MAP;** mean arterial blood pressure ** Statistically significant difference (p<0.01) **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group

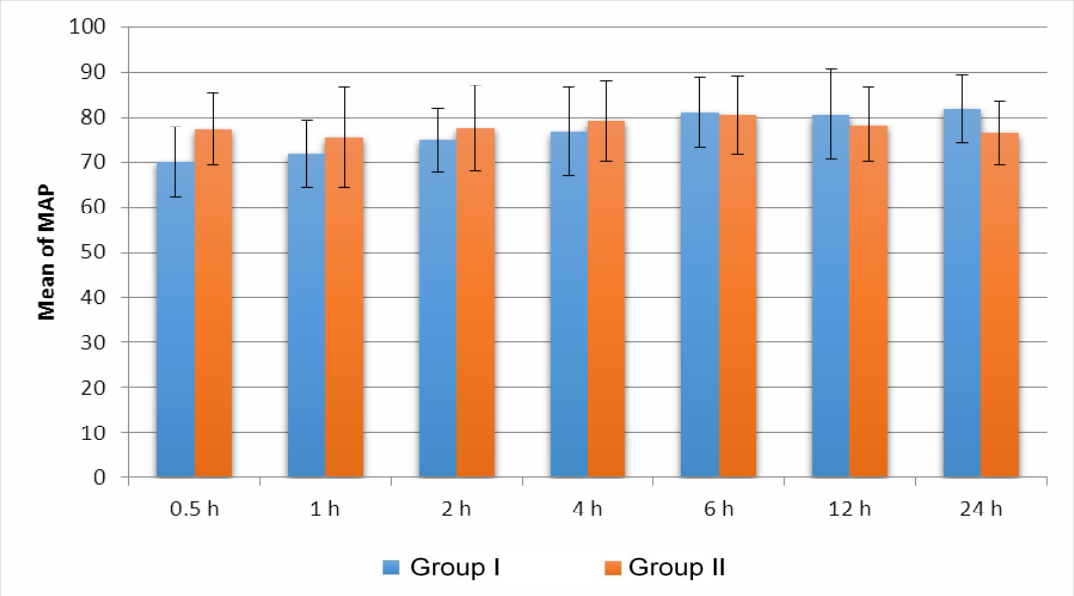


**Figure 5.** *Postoperative mean blood pressure (MAP)*

**Data** expressed as (Mean ± SD) and range **MAP;** mean arterial blood pressure ** Statistically significant difference (p<0.01) **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group

**Table 4.** *Pain NRS score during the postoperative 24 hours in the two studied groups*

| NRS score | Group I (n=30) | Group II (n=30) | p value |
|---|---|---|---|
| 1 hour | 3 (1-4) | 2 (2-4) | 0.824 |
| 2 hours | 2 (1-3) | 2 (1-4) | 0.513 |
| 6 hours | 2 (1-3) | 1.5 (1-2) | 0.948 |
| 12 hours | 1 (1-2) | 1 (1-2) | 0.359 |
| 24 hours | 1 (1-2) | 1 (1-2) | 0.735 |

Data are expressed as median (range) **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group NRS=Numerical rating scale, h=hour. P. value < 0.05 considered statistically significant.

**Table 5.** *total analgesic consumption*

| | Group (I) | | Group (II) | | P. value |
|---|---|---|---|---|---|
| | Range | Mean±SD | Range | Mean±SD | |
| **Total morphine consumption (mg)** | 0-18 | 7.34±4.39 | 0-24 | 13.74±4.73 | 0.009** |

**Data** expressed as (Mean ± SD) and range **Group (I):** pregabalin group ** Statistically significant difference (p<0.01) **Group (II):** Morphine sulphate tablets group

**Table 6.** *Post-operative complications from the studied drugs*

| | Group I (n=30) | Group II (n=30) | P. value |
|---|---|---|---|
| No complication | 17(56.7%) | 24(80%) | 0.319 |
| Vomiting | 3(10%) | 0(0%) | 0.383 |
| Pruritus | 1(3.3%) | 0(0%) | 0.059 |
| Respiratory depression | 2(6.7%) | 1(3.3%) | 0.798 |
| Bradycardia | 2(6.7%) | 5(16.7%) | 0.178 |

Data are expressed as mean ± SD, **Group (I):** pregabalin group **Group (II):** Morphine sulphate tablets group P. value < 0.05 considered statistically significant. There was no significant difference between two groups.

## Discussion

Major cancer surgeries lead to severe acute post operative pain, which if treated inadequately, can cause shallow breathing, atelectasis, retention of secretions and lack of cooperation in physiotherapy. This increases the incidence of post-operative morbidity and leads to delayed recovery. (10).

Classically for control of pain specially after major abdominal or pelvic surgeries, neuro-axial block used for this goals but Spinal anesthetics are typically limited to procedures involving most structures below the upper abdomen (11). To administer a spinal anesthetic to higher levels may affect the ability to breathe by paralyzing the intercostal respiratory muscles, or even the diaphragm in extreme cases (called a "high spinal", or a "total spinal", with which consciousness is lost), as well as the body's ability to control the heart rate via the cardiac accelerator fibers. (12, 13)

Gabapentinoid drugs, which include gabapentin and pregabalin, play an established role in the management of neuropathic pain. However, whether preoperative administration of gabapentinoids has a beneficial role in controlling acute pain after cancer surgery is unknown. (5, 14)

So in this study we used drugs that administered orally as the oral administration is non–invasive and may be less intimidating for the patient, allowing it to be easily used as preoperative medication and it seems to be a simple and inexpensive preoperative method to produce "preemptive" analgesia.

Pregabalin has been reported to be a well-tolerated and safe drug. Some side effects were usually reported after long-term gabapentin use and usually diminish with time but may be bothersome in an acute setting to a postoperative patient. (14)

In this study, we reported that both intra and postoperative HR and MAP were reduced significantly in patients of Group I than Group II - although both HR and MAP were within normal range in both groups-, In a similar study, attenuation of the hemodynamic response to intubation and surgical stress and the level of this response was directly associated with the dose of administered Pregabalin. (15)

This beneficial effect was also revealed by Kaya et al., They showed that the use of oral gabapentin 800 mg two hours before surgery which have the mechanism as Pregabalin, effectively attenuate the increase in HR and MAP secondary to endotracheal intubation. (16)

In this study we found that total morphine consumption was significantly reduced in patients of Group I than patients of Group II.

In a previous meta-analysis of the use of gabapentinoids in the management of postoperative pain after lumbar spinal surgery, the findings suggested that both gabapentin and pregabalin were efficacious in reducing postoperative pain. (17) However, only 2 studies included in the meta-analysis compared pregabalin with placebo for spinal surgery.

Jiang et al (18) reported that preoperative use of pregabalin was efficacious in the reduction of postoperative pain, total morphine consumption, and the occurrence of nausea following spine surgery. However, the sample size and the number of included studies were limited.

Dong et al (19) performed a meta-analysis of the use of pregabalin for reducing pain after knee surgeries and found that pregabalin was effective in reducing pain intensity after TKA. Morphine-related complications were also compared between the gabapentinoid and control groups. Significant reductions were found in the incidence of postoperative nausea, vomiting, and pruritus following spinal surgery.

Other clinical studies have shown that Pregabalin can reduce acute postoperative pain, decreasing the need for opioids. For example, a gabapentin dose of 1.2 grams per day 1 hour before surgery and for 2 days after CABG surgery showed that postoperative pain scores at 1, 2, and 3 days as well as the consumption of tramadol given as a rescue analgesic were significantly lower in the gabapentin group when compared to the placebo group. (20)

Preoperative medication with oral morphine offers some advantages, in fact the non–invasive administration may be less intimidating for the patient. Moreover, it seems to be a simple and inexpensive preoperative method to produce “preemptive” analgesia.

We found that oral morphine (30 mg) in our study was effective as a post-operative analgesic by decreasing the VAS scores, and prolong the time of first analgesic request, but not equal in effect as Pregabalin, similar to us. Borracci et al., who studied Sixty patients undergoing major abdominal surgery and were randomly assigned to premedication with 0.5 mg/kg oral morphine sulphate (oral morphine group) or 0.05 mg/kg oral midazolam (active placebo group). (21)

Primary outcome was efficacy of morphine premedication on opioid administration of Intravenous Patient Controlled Analgesia (IVPCA) doses, at 4, 24, and 48 hours after completion of surgery and reducing static and dynamic visual analogue scale (sVAS and dVAS) scores (22.23) .but in our study we gave a fixed dose of oral morphine (30 mg) preoperative for all patients in group II which may explain the less effect of this dose of morphine than the effect of gabapentin in group I.

While some studies suggest that oral morphine sulphate does not significantly reduce postoperative pain scores or opioid consumption, as Ana et al., who performed a study investigating the effects of Preoperative oral administration of fast-release morphine sulfate on postoperative piritramide consumption, this study found that the two groups of patients who received either morphine sulfate pentahydrate or placebo as premedication before orthopedic surgery were compared for postoperative consumption of piritramide. Pain scores were not significantly different between the two groups, therefore the postoperative consumption of piritramide in the morphine and placebo groups was equi-analgesic. (24)

We concluded that oral route of administration is effective and both oral drugs are efficient in acute pain control and pre-operative use of oral pregabaline (300 mg) showed that; better intra and postoperative haemodynamic profile with better pain relief total and associated with less postoperative analgesic consumption than oral morphine (30 mg) after major cancer surgery.

## Study limitations

Our study has many limitations. Short follow up period, second, small sample size, and finally, we should include patients with ASA physical status classes > III.

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