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Preventive Multimodal Analgesia Versus Morphine in Cancer Patients Undergoing Major Abdominal Surgeries

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Abstract

Background: Opioids are the corner stone for perioperative analgesia in major surgeries. The aim of this study was to compare the efficacy of preventive multimodal analgesia versus morphine on post-operative pain and total morphine consumption.

Aim of Study: To compare the efficacy of preventive multimodal analgesia versus morphine in cancer patients undergoing major abdominal surgeries.

Patients and Methods: This prospective randomized study was done from March 2018 to September 2018 after approval of the institutional board review of National Cancer Institute. Forty cancer patients were randomly allocated in the study; patients were divided into 2 groups; multimodal group (n=20) received Ketamine, magnesium, ketorolac, paracetamol, with TAB (transverse abdominis plane) block before surgical incision and morphine group (n=20) received morphine sulphate 0.1mg/kg before surgical incision.

Results: There was statistically significant difference in intraoperative fentanyl consumption *p*-value (<0.001) and total morphine consumption in the first 24 hours postoperatively *p*-value (0.001) between the 2 studied groups being higher in the morphine group.

Conclusion: Preventive multimodal analgesia has superior analgesic profile than morphine regarding perioperative analgesia and morphine consumption in the first 24 hours post-operatively.

Key Words: *Preventive – Multimodal analgesia – Morphine – Post-operative pain – Cancer patients.*

Introduction

UNTREATED post-operative pain can be a significant cause of morbidity following surgical trauma. Acute pain control is essential to avoid long term sequale of untreated pain. These sequale can affect the process of pain sensitivity, may lead to long term negative impacts on pain neurophysiology and sensitivity. Preventive multimodal analgesia concept targets perioperative pain control through different antinociceptive mechanisms [1].

Opioids are considered the gold standard drugs for post-operative pain control. Morphine is the most commonly used opioid in perioperative settings [2]. However opioid side effects are not always tolerated and can be dose dependent side effects. Applying multimodal analgesia can potentially reduce opioid related side effects through combining smaller doses of opioids with nonopioid analgesics (and adjuvant agents) acting on multiple different sites within the central and peripheral nervous systems [3,4].

Drugs used as a part of multimodal approach for pain control include opioids, nonsteroidal anti-inflammatory drugs and acetaminophen. Adding ketamine shows to augment the multimodal analgesic effect especially when magnesium sulphate is added to it [5]. In addition to pharmacological drugs, interventions as peripheral nerve blocks, neuraxial blocks (e.g epidural analgesia) and truncal blocks (e.g Transversus Abdominis Block (TAB), Quadratus Lumborum Block (QLB), rectus sheath block (RB) are successfully used as an approach for multimodal analgesia [6,7].

The analgesic approach should be adjusted and tailored for every patient according to his current and past medical condition, type of surgery aiming to improve the outcome and minimize the side effects [8].

Proper understanding of the mechanisms involved in acute post-operative pain results in evolution from the 'preemptive analgesia' concept into

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another broader concept of 'preventive analgesia'. The difference between preemptive and preventive analgesia depends on the timing of analgesic drug administration [6].

Pre-emptive analgesia refers to analgesia applied before surgical skin incision to prevent acute post-operative pain and modulate central sensitization. Preventive analgesia, aim to modulate nociception throughout the perioperative period leading to reduce post-operative pain along with decreasing post-operative analgesic consumption [9].

Transversus Abdominis Plane block (TAP) can be effectively used as one of the regional modalities for analgesia in abdominal surgeries. Its analgesic effect is thought to be through blocking sensory innervation of the anterior abdominal wall before sensory nerves pierce the muscles for innervation [10].

This study aim was to compare the effect of preventive multimodal analgesia versus morphine in cancer patients undergoing major abdominal surgeries regarding effect on 24 hours post-operative morphine consumption, perioperative pain and possible side effects.

Patients and Methods

This prospective randomized controlled study was conducted from March 2018 to September 2018 after approval of the Institutional Review Board of the National Cancer Institute (IRB-NCI), Cairo University, IRB no. (201617033.2P). A written informed consent was taken from all patients undergoing the study.

Forty cancer patients aged 18-65 years with ASA (American Society of Anesthesiology) II-III, referred to the anesthesia department in NCI requiring major abdominal surgeries were included in the study. Patients with coagulation defects, abnormal kidney and liver functions, local infection at site of injection or known allergy to any of the used drugs were excluded from the study.

Upon arrival to the holding area all the patients were monitored by standard monitoring (ECG, pulse oximetry and non-invasive automated arterial blood pressure). Then all patients were premedicated with midazolam (2-3mg IV) after fixation of 20G cannula. Induction of anesthesia was done by propofol 2mg/kg, fentanyl 2 t/kg and rocuronium 0.7mg/kg followed by single lumen endotracheal intubation and controlled mechanical ventilation with 50% Fio2, then after anesthesia was maintained by sevoflurane and rocuronium for both groups.

Patients were randomly allocated into 2 equal groups, 20 patients each. Multimodal group: Received bilateral TAP block, intravenous ketamine 0.5mg/kg, magnesium sulphate 1g, NSAID (ketrolac 30mg), paracetamol (perfalgan 1g). Morphine group: Received 0.1mg/kg morphine sulphate. In Multimodal group: After induction of general anesthesia patients were positioned in supine position. A SonoSite M-Turbo ultrasound machine with a multifrequency linear probe 6-13Hz (FUGIFILM Sonosite, Inc. Bothel, WA 98021, USA) was used. After skin preparation and sterilization, the ultrasound probe was moved across the abdomen from midline laterally to identify fascial plane of transversus abdominis at anterior axillary line between the 12th rib and iliac crest. An 18-G Tuohy needle was advanced through the skin piercing the external oblique and the internal oblique muscles reaching the fascial plane between the internal oblique and transversus abdominis then after negative aspiration injection of 20ml of bupivacaine 0.25% was slowly injected with a maximum dose not exceeding 2.5mg/kg bupivacaine.

Starting from induction of anesthesia HR, Spo2 was continuously monitored and SBP, DBP was recorded every 15 minutes. In order to ensure adequate analgesia throughout the operation all patients was closely observed and upon appearance of signs of inadequate analgesia e.g increase in HR or systolic blood pressure 20% above the baseline, fentanyl rescue doses of 0.5 t/kg was supplemented and recorded. Both groups received morphine 0.1mg/kg for post-operative pain control when there VAS score >4, or paracetamol 1g not exceeding 4g/d when VAS score <4.

Sample size calculation:

Sample size was calculated based on the previous paper of El-Dawlatly et al., 2009 [12] in which the morphine consumption within each subject group was normally distributed with standard deviation (4.3). If the true difference in the TAP group and control group means is 25%, we will need to study 20 patients in each group to be able to reject the null hypothesis that the population means of the study groups are equal probability (power) 95%. The type I error probability associated with this test of this null hypothesis is 0.05.

Results

The two studied groups were comparable in demographic data, duration and type of surgery Tables (1-3).

There was no statistically significant difference between both groups in their systolic and diastolic blood pressure in the holding area and baseline measurements, however there was a statistically significant difference between both groups in the intraoperative period being lower for the multimodal group Figs. (1,2). Both groups showed no statistically significant difference in heart rate measurement and arterial oxygen saturation values (SpO2).

There was a statistically significant difference between both groups in intraoperative fentanyl consumption being lower (38±20) [illegible] for multimodal group than morphine group (78±36) [illegible] p <0.001. Total morphine consumption for the first 24 hours post-operatively showed statistically significant difference between the 2 groups being higher in the morphine group (10±3) mg/24hrs than the multimodal group (7±2) mg/24hrs, p 0.001. Time to first dose morphine was statistically longer for the morphine group (8±2) hours than the multimodal group (6±3) hours p=0.017, (Table 4).

There was no statistically significant difference between both groups in median VAS score within the first 12 hours however; the median VAS score was statistically significant lower in the multimodal group at 18 and 24 hours (p=0.043, 0.028) respectively, (Table 5). There were no reported cases of nausea and vomiting in both groups.

Table (1): Age and duration of surgery.

	Multi		Morphine		p-value
	Mean	SD	Mean	SD	
Age (years)	52	8	53	8	0.701
Duration (minutes)	125	30	123	29	0.872

SD: Standard deviation, $p \leq 0.05$ is statistically significant, analysis done by independent t-test.

Table (2): Patient gender.

	Multi		Morphine		p-value
	Number	%	Number	%	
Gender:					
Female	10	50.0	9	45.0	0.752
Male	10	50.0	11	55.0	

Table (3): Type of surgery.

Type of surgery	Multi		Morphine		p-value
	Number	%	Number	%	
• Cancer colon	7	35.0	6	30.0	
• Cancer pancreas	5	25.0	5	25.0	
• Anterior abdominal wall tumor	2	10.0	3	15.0	0.613
• Renal cell carcinoma	3	15.0	2	10.0	
• Retroperitoneal tumor	3	15.0	4	20.0	

Table (4): Total intraoperative fentanyl, total post-operative morphine consumption and time to first dose analgesic.

	Multi		Morphine		p-value
	Mean	SD	Mean	SD	
Fentanyl ([illegible]	38	20	78	36	<0.001
Morph (mg/24h)	7	2	10	3	0.001
Time to 1 st analg	8	2	6	3	0.017

SD: Standard deviation, $p \leq 0.05$ is statistically significant, analysis done by independent t-test.

Table (5): VAS score in the first 24 hours post-operatively.

	Multi			Morphine			p-value
	Median	Minimum	Maximum	Median	Minimum	Maximum	
VAS 0	2	1	4	2	0	4	0.657
VAS 2	3	1	4	3	1	8	0.132
VAS 4	3	1	7	3	0	8	0.420
VAS 6	3	1	7	3	0	7	0.923
VAS 8	3	0	7	4	1	8	0.545
VAS 12	2	0	8	3	0	8	0.248
VAS 18	3	0	4	3	1	4	0.043
VAS 24	2	0	4	3	1	6	0.028

$p \leq 0.05$ is statistically significant, analysis done by Mann Whitney test.

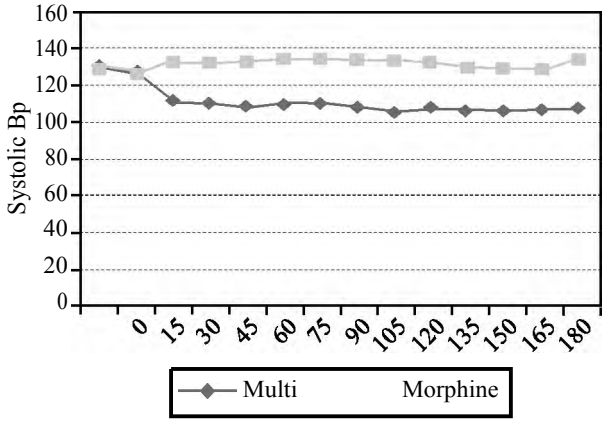

Fig. (1): Systolic blood pressure changes in the two studied groups.

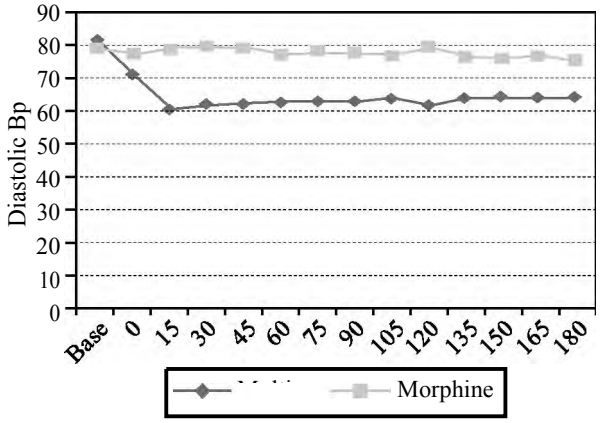

Fig. (2): Diastolic blood pressure changes in the two studied groups.

Discussion

Preventive analgesia targets to control pain throughout the perioperative period, furthermore applying multimodal analgesic approach help in reducing post-operative opioid consumption, as well as playing an important role in Enhanced Recovery After Surgery (ERAS) protocols [13].

The current study results reported that multimodal regimen had higher perioperative analgesic efficacy as well as reduced total post-operative opioid consumption when compared to morphine alone. These results are supported by a population-based retrospective cohort study done by Cozowicz et al., [14], stating that receiving multimodal analgesic regimen showed to be superior to opioid only analgesia.

Adding non opioid analgesics as Non-Steroidal Anti-Inflammatory (NSAIDs) and paracetamol reduces postoperative morphine consumption. This is in accordance to the results of systematic review done by Maund et al., who found that there is reduction in 24 hours postoperative morphine consumption when NSAIDs, paracetamol were added to Patient Controlled Analgesia (PCA) morphine for post-operative pain control [15].

In 2017 Helander et al., [13], compared 15 institutional multimodal analgesic approaches who implement ERAS protocols. They concluded that paracetamol and NSAIDs are the most commonly used non-opioid analgesics which play an important role in post-operative analgesia with opioid sparing effect, in addition to reduction of post-operative ileus resulting in earlier ambulation.

Adding magnesium sulfate to multimodal regimen reduced perioperative pain and total post-operative morphine consumption. This is in agreement to the results of a meta-analysis done by Oliveira et al., in 2013 [16] who stated that perioperative use of magnesium decreases post-operative pain and can lead to reduction of post-operative opioid consumption. This was supported by the results of more recent studies in different surgical procedures as hepatectomy, laparoscopic gastrectomy and laparoscopic gynecological surgeries [17-19]. Using perioperative magnesium has a promising role in reducing post-operative opioid consumption [20].

Using ketamine in low dose can help in reducing perioperative opioid use as well as decreasing the need for long term postoperative opioids [21]. This is supported by a meta-analysis of 5 studies which investigated the effect of preemptive ketamine on postoperative pain [22]. It was reported that ketamine reduced the amount of postoperative morphine consumption as well as prolonging the time for first analgesic requirement additionally it didn't increase the incidence of nausea and vomiting [23]. We didn't report any side effects from low dose ketamine, same was mentioned by Benzon et al who reported no increase in the incidence of ketamine side effects when low doses are used [20].

Providing regional analgesia by Transversus Abdominis Plane block (TAB) enhances analgesia when compared to standard opioid analgesia. It helps in reducing perioperative opioid consumption [12]. Carney et al., stated that adding TAB block to multimodal analgesia resulted in better post-operative analgesia and reduced morphine consumption in patients undergoing total abdominal hysterectomy when compared to placebo effect [24].

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التسكين الوقائى متعدد الوسائط مقارنة بالمورفين فى مرضى السرطان الخاضعين لعمليات جراحية كبرى بالبطن

تعتبر العقارات الأفيونية هى حجر الأساس لتسكين الآلام أثناء العمليات الجراحية الكبرى.

تهدف هذه الدراسة إلى مقارنة جودة التسكين الوقائى متعدد الوسائط مقابل المورفين لتسكين الآلام ما بعد العمليات الجراحية ومعدل أستهلاك المورفين.

تمت الدراسة فى الفترة من شهر مارس ٢٠١٨ إلى شهر سبتمبر ٢٠١٨ وقد تضمنت الدراسة ٤٠ مريضاً بالسرطان خاضعين لعمليات جراحية بالبطن وتم تقسيمهم عشوائياً إلى مجموعتين متساويتان مجموعة المورفين (٢٠) مريضاً تلقت هذه المجموعة عقار المورفين بجرعة ٠.١مجم/كجم قبل بدء الجراحة. مجموعة متعدد الوسائط (٢٠) مريضاً تلقت هذه المجموعة عقاقير الكيتإين، الكيتولاك، الباراسيتامول، الماغنسيوم، إلى جانب حقن العضلة البطنية المستعرضة قبل بدء الجراحة.

وقد أوضحت النتائج أن إستخدام التسكين الوقائى متعدد الوسائل لمرضى السرطان كوسيلة لتسكين الألام الناتجة عن العمليات الجراحية الكبرى بالبطن يؤدى إلى تقليل إستخدام عقار الفنتانيل أثناء الجراحة وتقليل كمية عقار المورفين المستخدم فى أول ٢٤ ساعة بعد الجراحة.