

Physician-Pharmacist Comanagement of Postoperative Pain in Egyptian Patients: Patient Controlled Analgesia Using Morphine versus Nalbuphine

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Abstract:

Introduction: Patient controlled analgesia (PCA) is an interactive method of self drug administration that requires proper education to ensure safe and effective use. Morphine is the most popular opioid used for postoperative pain management using PCA; however it has many adverse effects. Nalbuphine, a mixed opioid agonist antagonist, is known to be safer than morphine. Ketorolac produce excellent analgesia when used alone or with opioids. Multimodal analgesic approach using morphine or nalbuphine combined with ketorolac for PCA administration has not been compared before. The study aimed to compare the clinical efficacy, adverse effects of multimodal analgesia using PCA and the effect of patient education regarding PCA use on patients' outcomes.

Patients and methods: Adult Egyptian patients ASA I and II who underwent different surgical procedures were selected and randomized either to receive PCA of morphine or nalbuphine combined with ketorolac. Patients from each drug group were further randomly selected to receive additional preoperative PCA education beside the usual care for pain management. Visual analogue scale (VAS), hemodynamic parameters, adverse effects and patient satisfaction were compared between groups.

Results: Of the total of 60 patients enrolled, 45 patients completed the study: 22 patients for morphine group (M) and 23 for nalbuphine group (N). VAS score was significantly lower in group (M) than group (N) at certain time points. Nalbuphine showed a significant lower incidence of itching than morphine (P: 0.03*). Pain control and overall satisfactions were better in the intervention groups (M2, N2) than in the control groups (M1, N1).

Conclusion: Morphine coadministered with ketorolac provides more potent analgesia than with nalbuphine. Preoperative patient education regarding PCA is crucial for proper postoperative pain control.

Keywords: Patient education, Morphine, Nalbuphine, PCA, Postoperative Pain.

I. Introduction

Effective postoperative pain management is a major concern to health care professionals [1]. It is not only providing pain relief but also decreases morbidity, facilitates rapid recovery and reduces hospital length of stay [2]. Patient controlled analgesia (PCA) is the most common used method to manage postoperative pain using intravenous (IV) opioids [3]. IV PCA is an interactive method of drug administration, in which a specific amount of medication (bolus dose) is delivered directly into patient's vein upon pressing a button of the device [4]. Basal background infusion may be combined with patient controlled bolus doses. Bolus doses are ignored during a lockout interval; if patient press the button during the lockout time, he will not receive any more medicine [4].

Morphine is the standard opioid used to manage postoperative pain using IV PCA [3]. However it is associated with several adverse effects like nausea, vomiting, pruritus, constipation, and respiratory depression [3]. Nalbuphine is a mixed agonist antagonist that produces analgesia through acting on kappa receptor. Nalbuphine is considered to be safer than morphine; it has a ceiling effect in its respiratory depression [5]. Incidence of adverse effects like pruritus and postoperative nausea and vomiting is lower with nalbuphine in comparison with morphine [6, 7]. To avoid morphine related adverse effects, many other analgesics can be used alone or in combination with opioids to manage postoperative pain such as nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol [8]. Ketorolac, a potent NSAID, provided excellent analgesic efficacy when used alone and has synergistic effect on reducing pain intensity when combined with opioid analgesics [8]. However morphine continues to remain the gold standard [9]. A multimodal analgesic approach using a combination of systemic opioids and NSAIDs can reduce postoperative pain. Such an approach also will ensure that the lowest possible dose of opioid is given to achieve adequate analgesia. As opioids cause dose dependent adverse effects such as nausea, vomiting, pruritus and respiratory depression [10].

Patient education is crucial for safe and effective use of PCA[11]. Proper use of PCA for opioid administration allow patient to balance pain against adverse effects. Education must be provided to patients prior to initiation of PCA[12]. Preoperative patient education can relief preoperative anxiety, reduces pain intensity, and decreases hospital length of stay[12, 13]. This study was conducted to compare the clinical efficacy and adverse effects of multimodal analgesic regimen of morphine and nalbuphine combined with ketorolac using IV PCA, and to study the effect of structured preoperative educational program on analgesic efficacy, incidence of adverse effects, and patients' satisfaction.

II. Patients and Methods

2.1 Patients

2.1.1 Patient Selection

The study was conducted at the department of anesthesia and pain management of the national cancer institute (NCI), Cairo, Egypt. Study subjects were selected, after full history taking, physical examination and complete investigations, from those patients who were admitted for different types of surgical procedures during the period between July 2013 and December 2014. The study was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice. The local ethics committees approved the protocol, and informed consent was obtained from all patients before study entry. Recruitment included patients with physical status of an American Society of Anesthesiologists (ASA) I and II, aged between 33 - 68 years. Exclusion criteria included: history of allergy to the study drugs, contraindication to the study drugs, refuse of using PCA as a pain management method, history of hepatic, cardiopulmonary or renal disease, hemodynamic instability, history of any chronic pain or drug history of analgesics, administration of opioid in the last 4 hours, history of substance abuse and psychiatric disorder.

2.2 Methods

2.2.1 Study Design

The study was prospective randomized double blinded, in which patients were randomized either to receive morphine for postoperative analgesia using PCA disposable infusion device (group M), or receive PCA nalbuphine for postoperative analgesia (group N). The study was double blinded using opaque sealed envelope; both patients and the anesthesiologists managing postoperative pain were blinded to knowledge of the group to which they belonged.

Patients were selected randomly from either morphine or nalbuphine group to attend additional structured preoperative educational program provided by the pharmacist. Accordingly, patients in morphine group were randomly sub classified into either morphine control group (group M1) or morphine intervention group (group M2); both groups received the usual hospital routine care for pain management. Similarly patients in nalbuphine group were randomly sub classified into either nalbuphine control group (group N1) or nalbuphine intervention group (group N2); both groups received the usual hospital routine care for pain management.

The intervention subgroups were subjected to an additional pharmacist care for pain management through patients and nurse counseling provided by the clinical pharmacist.

2.2.1.1 Patient Counseling

Education was provided to patients in the intervention subgroups of each morphine and nalbuphine; (group M2 and group N2). A structured preoperative educational program consisted of 15 minute session of verbal education on safe use of PCA was provided to patients. Also patients were instructed about the use of the visual analogue scales (VAS)[14], this consists of an ungraduated, straight 10-cm line marked at one end with the term " no pain" and at the other end "the worst possible pain". The patient is instructed to mark the line with a pencil slash at the point that corresponds best to the present level of pain intensity. A printed instruction sheet was given to reinforce the given information: (Appendix A). Instruction sheet were modified, adapted after Lam et al and Macintyre et al [15, 16], then translation into Arabic language was carried out to facilitate communication and understanding.

Also patients in the intervention groups were interviewed the day before the operation to be instructed in filling-in the revised American pain society patient outcome questionnaire (APS-POQ-R)[17]. It was designed to determine patients' satisfaction with their pain management with PCA and the incidence of adverse effects such as nausea, itching, dizziness, drowsiness or constipation. A validated Arabic translated form of questionnaire was downloaded from the American pain society website[18] to be suitable for the studied patients.

2.2.1.2 Nurse Counseling

Nurse education was conducted before surgery to those nurses who were responsible for patients in the intervention groups, the education included multiple sessions with each nurse group supported by an adapted instruction sheet (Appendix B) [19]. The instruction sheet was translated into Arabic language to facilitate understanding.

2.2.2. Intraoperative Anesthesia and Analgesia

Drug doses for anesthesia and analgesia in this study were used and administered according to the hospital treatment protocol. For patients in group M, general anesthesia was standardized and induced with IV fentanyl 1-2 mcg/kg (Fentanyl-Janssen® 0.5 mg, JANSSEN CILAG pharmaceutical company, Cairo, Egypt), morphine 0.1 mg/kg (Morphine sulphate®, 10 mg/ml, Misr pharmaceutical company, Cairo, Egypt), thiopental sodium 5mg/kg (Thiopental sodium® 500 mg, EIPICO pharmaceutical company, Cairo, Egypt), and atracurium 0.5 mg/kg (Tracium® 25 mg, GlaxoSmithKline, Cairo, Egypt). For group N general anesthesia was standardized and induced with 0.2 mg/kg nalbuphine (Nalufin® 20mg/ml, Amoun pharmaceutical company, Cairo, Egypt), thiopental sodium 5 mg/kg (Thiopental sodium® 500 mg, EIPICO pharmaceutical company, Cairo, Egypt), and atracurium 0.5 mg/kg (Tracium® 25 mg, GlaxoSmithKline, Cairo, Egypt). Atracurium and isoflurane were adjusted during surgery to maintain muscle relaxation and the depth of anesthesia.

2.2.3 Postoperative Care

After surgical procedures, fully awake patients were transferred to post anesthesia care unit (PACU) and remained in there for at least two hours. Thereafter, patients were shifted back to the wards after receiving routine standard instruction for postoperative analgesia. Morphine was administered in a loading dose of 0.1 mg/kg, while nalbuphine was given in dose of 0.2 mg/kg via IV route according to the hospital treatment protocol. Then, alerted patient was connected to a disposable silicon PCA infusion device.

2.2.4 Preparation and administration of PCA

For group M the disposable silicon PCA device (Accufuser Plus®, Woo Young Medical Co, Korea) was prepared with 300 ml total volume normal saline containing 60 mg morphine (Morphine sulphate®, 10 mg/ml, Misr pharmaceutical company, Cairo, Egypt), 60 mg ketorolac (Ketolac®, 30mg/ml, Amirya pharmaceutical industry, Cairo, Egypt) and 8 mg ondansetron (Zofran® 4mg/ml, GlaxoSmithKline, Cairo, Egypt). For group N the disposable silicon PCA device (Accufuser Plus®, Woo Young Medical Co, Korea) was prepared with 300 ml normal saline containing 120mg nalbuphine (Nalufin® 20mg/ml, Amoun pharmaceutical company, Cairo, Egypt), 60 mg ketorolac (Ketolac® 30mg/ml, Amirya pharmaceutical industry, Cairo, Egypt) and 8 mg ondansetron (Zofran® 4mg/ml, GlaxoSmithKline, Cairo, Egypt). For both drug groups PCA was programmed to provide 4 ml /hr by continuous infusion and 1 ml bolus dose with lockout interval of 15 minutes (A safety timer called a lockout; if patient press the button during the lockout time, he/she will not receive any more medicine). Patients with inadequate analgesia received additional IV bolus dose of either morphine or nalbuphine.

2.2.5 Postoperative Assessment

2.2.5.1 Primary Outcomes

The primary outcomes measured postoperatively were pain intensity using VAS, systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), heart rate (HR). Assessment was carried out at zero time (time to shift to PACU) and every 1/2 hour for the first 4 hours then every 2 hours till the end of the second postoperative day.

2.2.5.2. Secondary Outcomes

The secondary outcomes included level of sedation using the Ramsey Sedation Scale [20] (ranged from score 1; anxious, agitated to 6: no response can be elicited), and total cumulative opioid doses (morphine equivalents of). Incidences and severity of adverse effects (nausea, drowsiness, dizziness and itching) and patient satisfaction were assessed using APS-POQ-R. Arterial blood sample was taken at 0, 12, 14, 36, 48 postoperative hours to assess partial pressure of carbon dioxide (PaCO₂), and oxygen saturation (SaO₂).

2.3 Statistical Analysis

The SPSS version 22 software (copy right IBM Corporation and other(s), 1989, 2013) and Microsoft office excel 2010 were used for statistical analysis. Results are presented as means ± standard deviations (SD) for continuous data, median and range for ordinal data, and as frequencies and percentages for categorical data. Analysis of normality was performed using the Kolmogorov-Smirnov test. Categorical data and proportions were analyzed using the χ^2 test or the Fisher's exact test as required. Student's t test was used to compare the

means of the 2 groups with normal distributions, and the Mann-Whitney U test was used to compare variables with non-normal distributions. All tests were 2-tailed, P value < 0.05 was considered statistically significant.

III. Results

3.1 Patient Enrollment and Baseline Characteristics

A total of 60 patients were enrolled and screened to be eligible for the study according to the inclusion and exclusion criteria. Ten patients were excluded; therefore 50 patients with a mean age of 49.5 ± 10.7 years (CV% 21.7) were consented and randomized into two groups. Five patients were withdrawn after randomization while 45 patients completed the study: 22 patients for morphine group (M) and 23 for nalbuphine group (N). Flow chart of patient enrollment, reasons for exclusion and withdrawal are summarized in Figure 1.

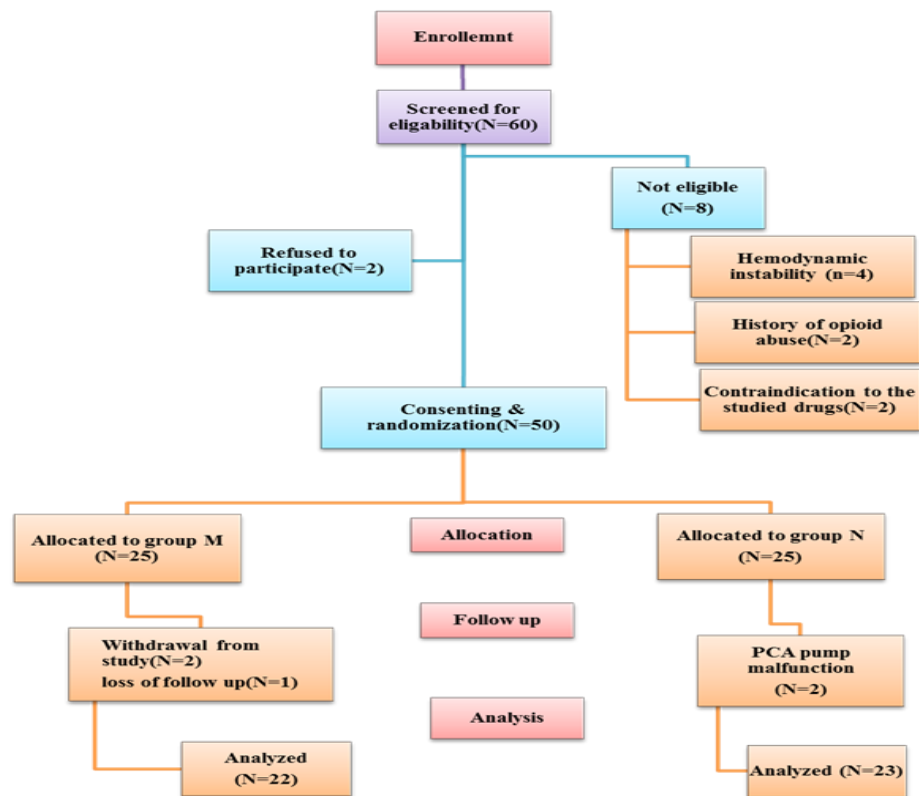


Figure 1: Flow chart of patient enrollment and reasons for exclusion and withdrawal

Forty five patients who completed the study comprised 21 males (47%) and 24 females (53%), with mean age of 49.4 ± 10.8 (CV%:21.9%). Baseline demographics of the analyzed groups are summarized in Table 1. The two drug groups were comparable with respect to sex, age, weight, ASA, comorbidities, drug history and type of surgery.

Table 1: Baseline Patient Demographics and Preoperative Clinical Data of Both Drug Groups

Parameter	Group M (N = 22)	Group N (N = 23)	P value
Sex Male/ Female N (%)	9/13 (41/59%)	12/11 (52/48%)	0.45
Age (Mean ± SD)	51.4 ± 11.6	47.6 ± 11.7	0.36
Weight (kg)	61.2 ± 7.4	63.7 ± 10.0	0.35
ASA Physical Status Classification 1/2 N (%)	12/10 (55/45%)	12/11 (55/45%)	0.61
Type of Surgery: Abdominal/Thoracic N (%)	17/5 (77/23%)	15/8 (65/35%)	0.37
Abdominal(N): HIPEC/Gastric pull p/Whipple/hysterectomy/gastrectomy/Radical cyctectomy/Abdominal exploration	3/4/2/2/3/2/1	5/2/2/1/2/1/2	
Thoracic (N): Lung lobectomy/ Chest wall mass	2/3	5/3	

Co morbidities: (N)			
• Hypertension	5 (23%)	7 (30%)	0.50
• Diabetes mellitus	6 (27%)	5 (22%)	0.73
• Ischemic heart disease	1 (4.5%)	1 (4%)	1.00
• Bronchial asthma	1 (4.5%)	0 (0%)	0.30
• Smoking	2 (9%)	3 (13%)	0.80
Drug history: (N)			
• B-blocker	2 (9%)	3 (13%)	0.80
• Ca ⁺⁺ channel blocker	2 (9%)	2 (8.7%)	1.00
• Diuretics	5 (23%)	3 (13%)	0.40
• Oral hypoglycemic and /or insulin	6 (27%)	5 (22%)	0.73
• B ₂ agonist	1 (4.5%)	0 (0%)	0.30

ASA: American society of anesthesiologists, HIPEC:hyperthermic intraperitoneal chemotherapy, P* $<$ 0.05

Morphine control group; M1, and morphine intervention group; M2, each comprised eleven patients. On the other hand nalbuphine control group; N1, comprised eleven patients while nalbuphine intervention group; N2, comprised twelve patients. Regarding baseline, there was no significant difference in sex, age, weight, ASA, and type of surgery between each of control and intervention group “Table2”.

3.2. Postoperative Assessment

3.2.1. Primary Patients` Outcomes

3.2.1.1. Pain Intensity

Median visual analogue score during the 48 postoperative hours in both drug groups presented in Figure 2. It revealed a statistically significant lower VAS score, for patients in group M, at 0.5, 6, 8, 10, 12, 14, 16, 18, 22, 26, 28, 32, 34, 36, 38, 42, 44, 46, and 48 hour when compared with those patients in group N. Adequate analgesia (VAS \leq 4) was reached 1.5 hour after surgery for group M, while after 2 hours in group N.

Table 2: Baseline Patient Demographics of Both Control and Intervention Groups

Parameter	Group M1 (N=11)	Group M2 (N=11)	P Value	Group N1 (N=11)	Group N2 (N=12)	P Value
Sex Male/Female N (%)	4/7 (36/64%)	5/6 (45/55%)	0.67	8/3 (73/27%)	4/8 (33/67%)	0.06
Age (years) (Mean \pm SD)	51.9 \pm 9.1	49.9 \pm 12.8	0.42	51.2 \pm 9.3	44.9 \pm 11.4	0.17
Weight (kg)	61.5 \pm 7.5	60.9 \pm 7.7	0.84	60.1 \pm 9.1	66.9 \pm 10.0	0.11
ASA Physical Status 1/2 N (%)	6/5 (55/45%)	6/5 (55/45%)	1.00	5/6 (45/55%)	7/5 (58/42%)	0.54
Type of Surgery: Abdominal/Thoracic N (%)	9/2 (82/18%)	8/3 (73/27%)	0.61	6/5 (55/45%)	9/3 (75/25%)	0.30

ASA: American society of anesthesiologists, P* $<$ 0.05

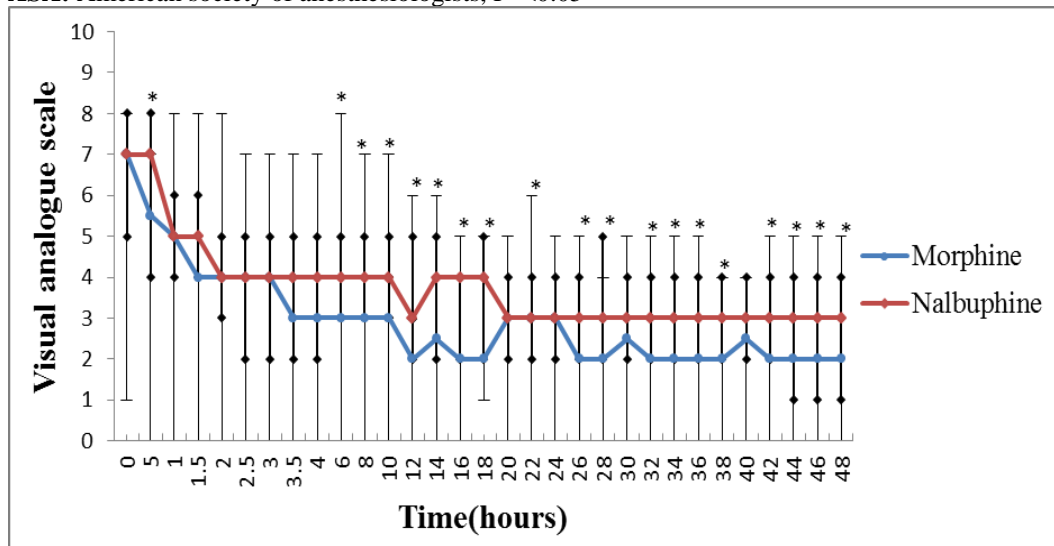


Figure 2: Visual analogue scale during the 48 postoperative hours in both drug groups, data are presented as median (range), P* $<$ 0.05

3.2. 1. 2 Hemodynamic Parameters

Mean SBP values were significantly lower for patients in group M when compared with group N at certain time points(0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 16, and 18 hour)as shown in Figure 3. Similarly,significantly lower meanDBPvalues were clear for patients in group M when compared withthose patients in group N at0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 8, 14, 16, 18, 20, 30, 34, 36, and 40 hourafter surgery “Fig 4”. With respect to HR,findings in Figure 5 revealed significantly higher values, only during the early postoperative hours (0, 0.5, 1, and 1.5), in group N as compared with group M. Although mean RRvalues weresignificantly lower in group Mat certain time points(1.5, 2, 2.5, 3, 3.5, 4, 6, 10, 12, 14, 16, 18, 20 , 22, 24, 26, 28, 34, 38, 40, 44, 46, and 48 hour)as compared with group N“Fig 6”, no patients had any episodes ofrespiratory depression (RR< 8 breaths/min).

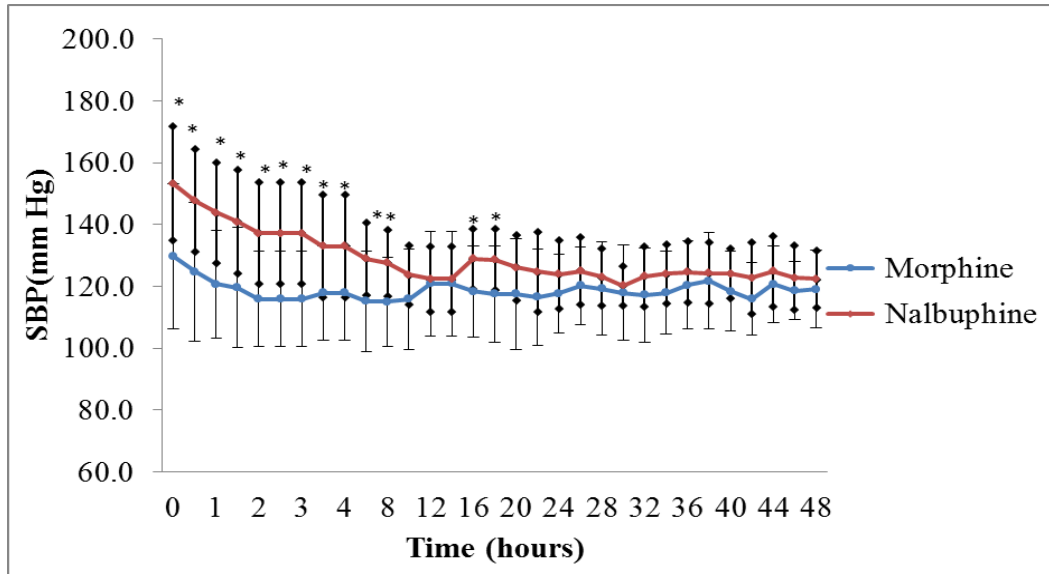


Figure 3: Systolic blood pressure in both drug groups during the 48 postoperative hours, data are presented as mean ± SD, P* < 0.05

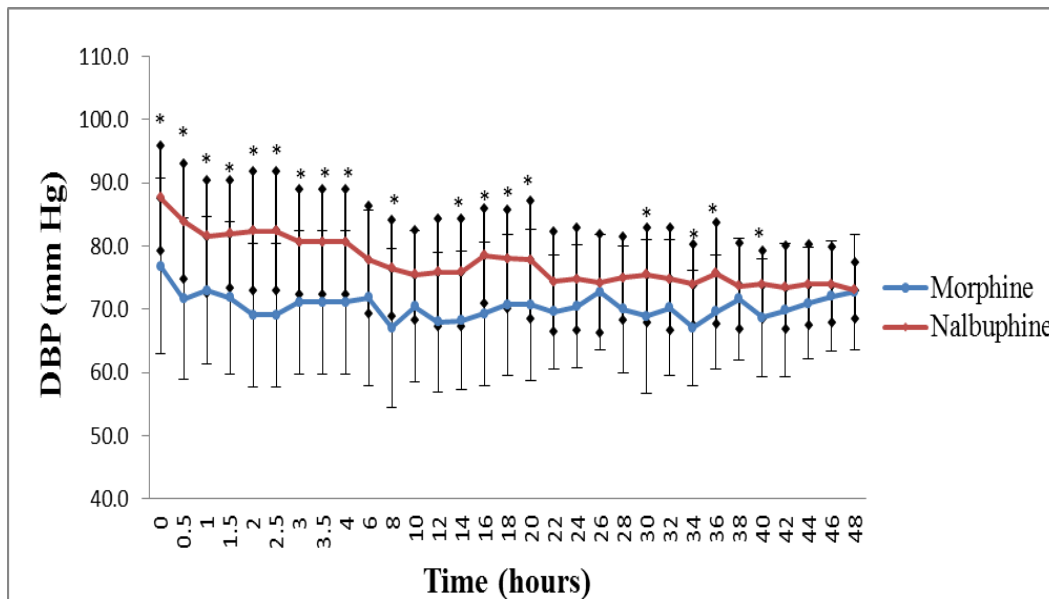


Figure 4: Diastolic blood pressure in both drug groups during the 48 postoperative hours, data are presented as mean ± SD, P* < 0.05

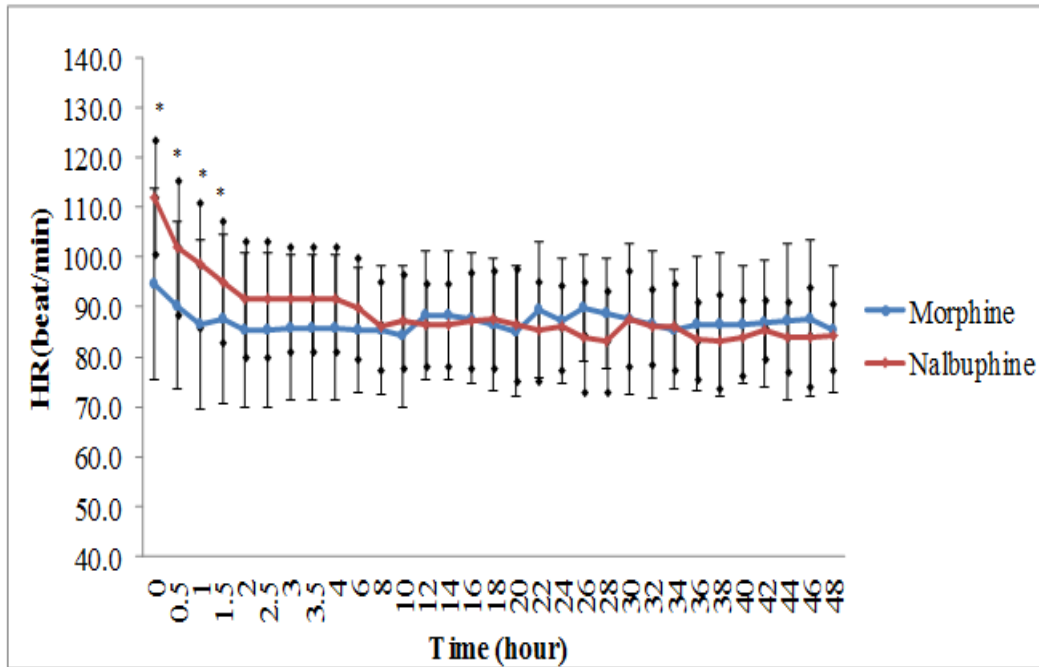


Figure 5: Heart rate during the 48 postoperative hours in both drug groups, data are presented as mean \pm SD, *P<0.05

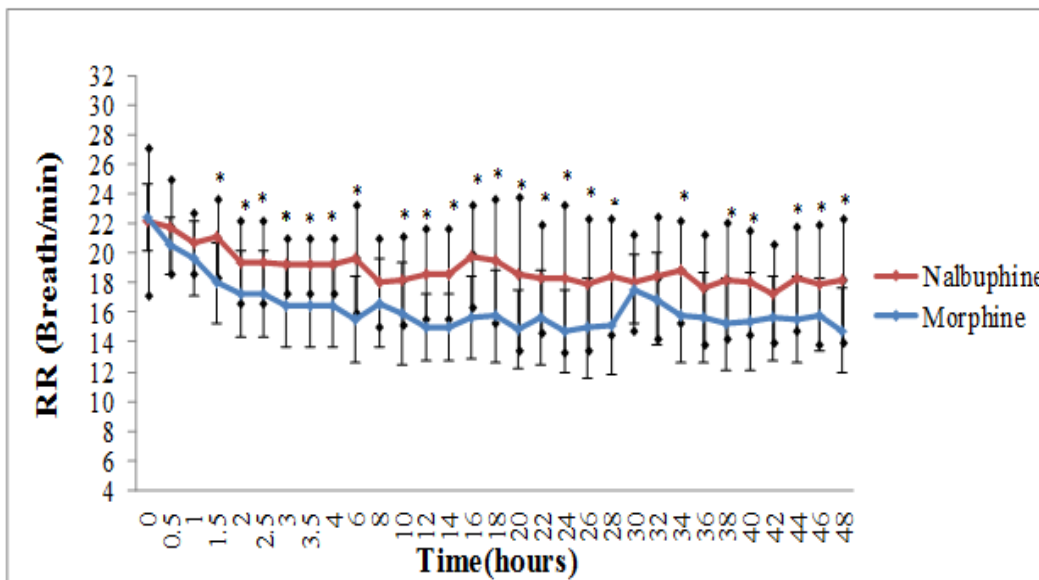


Figure 6: Respiratory rate during the 48 postoperative hours in both drug groups, data are presented as mean \pm SD, *P<0.05

3. 2. 2. Secondary patients` outcomes

3. 2. 2.1 Arterial Blood Gases

PaCO₂ levels were significantly lower in group N when compared with group M at each of 36 and 48 postoperative hours. However, no patient in the 2 drug groups had any episode of respiratory depression (PaCO₂ > 50 mmHg). The corresponding mean values, at the 36 hour, were (34.5 \pm 4.4) mmHg and (36.8 \pm 1.3) mmHg for groups N and M, respectively (P:0.02*). Similarly, the corresponding mean values, at the 48 hour, were (32.2 \pm 4.2) mmHg and (37.1 \pm 1.8) mmHg for groups N and M, respectively (P < 0.01*). With respect to SaO₂ levels, postoperative data were similar in both drug groups “Table 3”, no patient had any episode of hypoxemia (SaO₂<90%).

Table 3:Oxygen Saturation Levels and Partial Pressure of Carbon Dioxide in Both Drug Groups

Time (hour)	PaCO ₂ Group M	PaCO ₂ Group N	P Value	SaO ₂ Group M	SaO ₂ Group N	P Value
0	36.5 ± 6.1	37.5 ± 9.7	0.49	95.2 ± 7.8	95.4 ± 1.9	0.92
12	36.1 ± 3.0	38.3 ± 8.1	0.27	95.9 ± 8.7	95.4 ± 1.7	0.64
24	37.3 ± 2.0	38.0 ± 11.2	0.76	95.1 ± 4.6	96.2 ± 2.1	0.40
36	36.8 ± 1.3	34.5 ± 4.4	0.02*	91.8 ± 9.9	95.7 ± 2.3	0.11
48	37.1 ± 1.8	32.2 ± 4.2	<0.01*	95.8 ± 5.2	95.9 ± 1.9	0.97

3.2.2.2 Opioid Requirement

Postoperative results revealed a statistically significant higher (P <0.01*) cumulative opioid doses consumption “Table 4” for patients in group N compared with those in group M (as morphine equivalents; on basis of that 1mg nalbuphine=0.7 mg morphine). On the other hand, numbers of patients that required additional analgesic doses (additional dose of the study opioid drug) were not statistically different in the two drug groups (P: 0.37).

Table 4:Comparison of Opioid Requirement between the Two Drug Groups

Parameter	Group M (n=22)	Group N(n=23)	P Value
Cumulative opioid doses (Mean ± SD)	68.6 ± 6.2	92.2 ± 6.8	< 0.01*
Number of patients received additional analgesia (%)	17(77%)	15(65%)	0.37

Opioid doses (in morphine equivalent mg; 1mg nalbuphine=0.7 mg morphine)[21], P* <0.05

3. 2. 2.3.Sedation

Median Ramsey scores were significantly lower for patients in group N when compared with those in group M at 0, 0.5, 1, 20, 22, 24, 26, and 28 hours after surgery “Fig 7”

3.2.2.4. Incidence and Severity of Adverse Effects

Regarding incidence and severity of adverse effect postoperatively “Table 5”, Median score of itching measured using APS-POQ-R questionnaire, ranged from 0 no itching to 10 severe itching, was lower in group N than group M (P: 0.03*). Incidences of postoperative nausea, drowsiness, dizziness were not statistically different in the two drug groups.

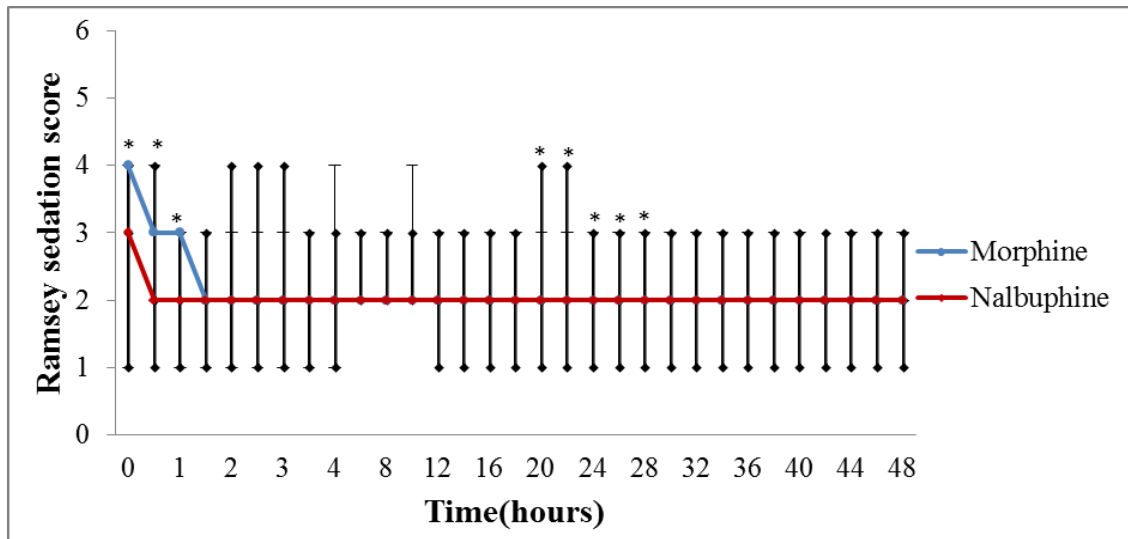


Figure 7: Median Ramsey sedation score 48 hours after surgery in both drug groups, data are presented as median (range), P* <0.05

Table 5: Incidence and Severity of Adverse Effects

Incidence and severity of adverse effects	Group M	Group N	P value
P6a: Nausea	0(0-4)	0(0-2)	0.22
P6b: Drowsiness	0(0-2)	0(0-2)	0.68
P6c: Itching	0(0-2)	0(0-0)	0.03*
P6d: Dizziness	0(0-2)	0(0-2)	0.27

3.2.2.5. Patient satisfaction with pain management

Median score of the least pain in the first 24 postoperative hours was significantly lower in group M than in group N ($P < 0.01^*$) as shown in Table 6. Also patients in group N experienced a significantly higher percentage of time experience of severe pain during the first 24 hours than those patients in group M ($P: 0.02^*$). While other scores of satisfaction were similar between morphine and nalbuphine group.

3. 3. Effect of Structure Preoperative Education on Patients' Outcomes

3.3.1 Visual Analogue Scale

Patients in group M2 showed a significant lower median VAS score than those patients in group M1 at 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 postoperative hours “Table 7”, while patients in group N2 showed a significant lower scores only at 0, 0.5, 1 postoperative hours compared to patients in group N1.

3.3.2 Incidence and Severity of Adverse Effects

There were no statistical different between the intervention and control groups with respect to the score of each of nausea, drowsiness, itching and dizziness “Table 8”.

Table 6: Patient Satisfaction with Pain Treatment in the First 24 Hour after Surgery in Both Drug Groups

Item of APS-POQ-R	group M	group N	P value
P1: The least pain the first 24 hours	2 (0-3)	4.5(2-6)	<0.01*
P2: The worst pain in the first 24	4(1-8)	4 (2-8)	0.98
P3. The percentage of time experience of severe pain during the first 24 hours	20%(0-70)	30%(0-70)	0.02*
P4a: Pain interfered or prevented from doing activities in bed	3(2-6)	3(2-5)	0.20
P4b: Pain interfered or prevented from doing activities out of bed	4(2-6)	4(3-6)	1.00
P4c: Pain interfered or prevented from Falling asleep	3.5(1-5)	4(1-5)	0.78
P4d: Pain interfered or prevented from staying asleep	3(0-4)	4(1-5)	0.50
P5a: Feeling anxious	2(0-6)	1(0-4)	0.49
P5b: Feeling depressed	0(0-5)	0(0-3)	0.49
P5c: Feeling frightened	0(0-6)	0(0-3)	0.12
P5d: Feeling helpless	0(0-3)	0(0-1)	0.72
P7: One percentage that best showed how much relief they have received from all of pain treatments	80%(50-100)	90%(60-100)	0.87
P8: Participation in decisions about pain treatment	0(0-7)	4(0-8)	0.07
P9: Satisfaction with the results of pain treatment while in the hospital	9(0-10)	7(5-10)	0.92
P10: How helpful the information about pain treatment options	6(0-10)	7(0-10)	0.73
P11: Number of patients that received non-medicine methods used to relieve pain (walk and deep breathing) N (%)	10 (45%)	12 (52%)	0.65
P12: How often a nurse did or doctors encourage to use non-medicine methods to control pain? N (%) Never Sometimes often	9(41%) 5(23%) 8(36%)	8(35%) 10(43%) 5(22%)	0.30
P13: Number of patient received help in filling-in the questionnaire N (%)	7(32%)	8(34%)	0.83

Data are represented as median (range) for ordinal data, or frequencies and (percentage) for categorical data, $P^* < 0.05$

Table 7: Comparison between Median Visual Analogue Scale between the Interventions and Control Groups

Time (hour)	VAS Group M1	VAS Group M2	P Value	VAS Group N1	VAS Group N2	P Value
0	7(3-8)	5(1-8)	0.18	8(7-8)	5(5-8)	<0.01*
0.5	6(3-7)	5(0-7)	0.12	8(7-8)	5(4-8)	<0.01*
1	6(2-8)	4(0-6)	0.12	6(5-6)	4(4-6)	0.01*
1.5	6(3-8)	3(0-6)	0.02*	5(4-6)	4(4-5)	0.23
2	5(3-8)	3(0-7)	0.04*	4(3-5)	4(3-5)	0.83
2.5	5(3-7)	3(0-5)	0.04*	4(2-5)	4(3-5)	0.28
3	5(2-7)	3(0-5)	0.04*	8(7-8)	5(5-8)	0.93
3.5	5(2-7)	3(0-5)	0.02*	4(2-5)	4(3-5)	0.79
4	4(2-7)	2(0-5)	0.04*	4(2-5)	4(3-5)	0.10
6	3(2-8)	2(0-4)	0.02*	4(2-4)	4(3-5)	0.19
8	4(2-7)	2(0-5)	0.04*	4(3-5)	3(3-5)	0.61

VAS: visual analogue scale, Data are presented as median (range), $P^* < 0.05$

Table 8: Incidence and Severity of Adverse Effects between the Interventions and Control Groups

Adverse Effect	Group M1 (N=11)	Group M2 (N=11)	P Value	Group N1 (N=11)	Group N2 (N=12)	P Value
P6a: Nausea	0(0-3)	0(0-4)	0.54	0(0-2)	0(0-2)	0.49
P6b: Drowsiness	0(0-2)	0(0-2)	1.00	0(0-2)	0.5(0-2)	0.38
P6c: Itching	0(0-2)	0(0-2)	1.00	0(0-0)	0(0-0)	1.00
P6d: Dizziness	0(0-1)	0(0-2)	0.92	0(0-2)	0(0-1)	0.26

Data are presented as median (range), $P^* < 0.05$

3.3.3 Additional Analgesia and Cumulative Opioid Doses

Numbers of patients that required additional analgesic doses (additional opioid doses) and the cumulative opioid doses (as morphine equivalents) were comparable in the intervention and control groups “Table 9”.

Table 9: Opioid Requirement in both Control and Intervention Groups

Parameter	Group M1 (N=11)	Group M2 (N=11)	P Value	Group N1 (N=11)	Group N2 (N=12)	P Value
Cumulative opioid doses (Mean ± SD)	67.3 ± 4.1	70.0 ± 7.7	0.32	92.3 ± 7.4	92.2 ± 6.6	0.97
Number of patients received additional opioid doses (%)	10 (90%)	7 (63%)	0.46	7(63%)	8(72%)	0.88

3.3.4 Patient Satisfaction

The median score of the least pain, worst pain, and the percentage of time experience of severe pain in the first 24 hours were significantly lower in group M2 as compared with group M1 (P: <0.01*, <0.01* and 0.03*, respectively). Similarly, scores of patients in group N1 were significantly higher than those patients in group N2 (P: <0.01*, <0.01* and 0.01*, respectively) “Table 10”. Satisfaction scores with the results of pain treatment and the percentages of pain relief from pain treatment were significantly higher for patients in group M2 and group N2 compared with those patients in either group M1 or group N1 (P<0.01*). Patients in the intervention groups (M2 and N2) noted that, the given information about pain management options were helpful, while patients in the control groups (M1 and N1) didn’t see that (P<0.01*). Seven patients in group M1 received help in filling in the questionnaire, while two patients only in group M2 did not fill the questionnaires themselves (P: 0.03*). Also eight patients in group N1 required nurse help for filling in the questionnaire and nine patients in group N2 Filled in the questionnaire themselves (P :0.02*).

Table 10: Patient Satisfaction with Pain Management of the Intervention and Control Groups.

Item Of APS-POQ-R	Group M1 (N=11)	Group M2 (N=11)	P Value	Group N1 (N=11)	Group N2 (N=12)	P Value
P1: The least pain the first 24 hours	3(0-3)	1(0-2)	<0.01*	5(4-6)	2(2-6)	<0.01*
P2: The worst pain in the first 24	7(4-8)	2(1-4)	<0.01*	7(5-8)	3 (2-4)	<0.01*
P3. The percentage of time experience of severe pain during the first 24 hours	30%(10-70)	0%(0-20)	0.03*	50%(20-70)	20%(0-30)	0.01*
P4a: Pain interfered or prevented from doing activities in bed	3(2-6)	3(2-5)	0.25	3(2-5)	3(2-5)	0.78
P4b: Pain interfered or prevented from doing activities out of bed	5(3-6)	4(2-5)	0.18	4(4-6)	4(3-6)	0.10
P4c: Pain interfered or prevented from Falling asleep	2(1-4)	3(1-5)	0.54	4(3-5)	4(2-5)	0.41
P4d: Pain interfered or prevented from staying asleep	2(0-4)	3(0-4)	0.23	4(2-5)	4(2-4)	0.19
P5a: Feeling anxious	1(0-4)	2(0-6)	0.20	2(0-4)	1(0-2)	0.15
P5b: Feeling depressed	0(0-0)	0(0-5)	0.12	0(0-3)	0(0-1)	0.21
P5c: Feeling frightened	0(0-0)	0(0-6)	0.72	0(0-3)	0(0-1)	0.24
P5d: Feeling helpless	0(0-1)	0(0-3)	0.92	0(0-1)	0(0-0)	0.29
P7: One percentage that best showed how much relief they have received from all of pain treatments	60%(50-90)	100%(80-100)	<0.01*	80%(60-90)	100%(90-100)	<0.01*
P8: participation in decisions about pain treatment	0(0-6)	0(0-7)	0.49	5(0-8)	2.5(0-8)	0.52
P9: Satisfaction with the results of pain treatment while in the hospital	7(6-10)	9(0-10)	<0.01*	5(5-6)	8.5(7-10)	<0.01*
P10: How helpful the information about pain treatment options	0(0-4)	10(8-10)	<0.01*	1(0-9)	9(7-10)	<0.01*
P11: Number of patients that received non-medicine methods used to relieve pain (walk and deep breathing) N (%)	6 (55%)	5(45%)	0.67	5(45%)	7(58%)	0.53
P12: How often a nurse did or doctors encourage to use non-medicine methods to control pain? N (%) Never Sometimes often	3(27%) 3(27%) 5(46%)	2(18%) 2(18%) 7(64%)	0.69	4(36%) 4(36%) 3(28%)	4(33%) 6(50%) 2(17%)	0.75
P13: Number of patient received help in filling-in the questionnaire. N (%)	7(64%)	2(18%)	0.03*	8(73%)	3(25%)	0.02*

Data are represented as median (range) for ordinal data, or frequencies and (percentage) for categorical data, P* < 0.05

IV. Discussion

Postoperative pain is a major problem, for health care professionals, which requires intense workup for effective management [1]. Postoperative pain control decreases morbidity, facilitates rapid recovery and reduces hospital length of stay [2]. Opioids are commonly used for postoperative pain control; however, nausea, vomiting, pruritus, constipation, and respiratory depression are major associated drawbacks [10]. So pain control should be balanced against these adverse effects. PCA is commonly used postoperatively to manage pain, however little is known about PCA itself. Patient may neglect pain and avoid activation of PCA due to fear of addiction from opioids or occurrence of adverse effects when use it frequently [11, 22].

Morphine is an opioid that produces analgesia through acting on mu receptors [7]. The many adverse effects of morphine are related to mu receptor binding. Nalbuphine, on the other hand, acts as an agonist on kappa receptors which provides analgesia and as an antagonist on mu receptor[23]. Nalbuphine has a ceiling effect in its respiratory depression and is considered to be safer than morphine with minimum incidence of postoperative pruritus, nausea and vomiting [6, 7]. The analgesic effect of nalbuphine through kappa receptors reaches a ceiling effect [5, 24,25]. This can lead to unpredictable analgesic efficacy for surgical procedures. So the analgesic efficacy depends on its complex pharmacodynamic profile rather than pharmacokinetic [9]. Results of comparative studies between morphine and nalbuphine are inconsistent. There is no evidence to indicate which is better for pain control [26].

The present study was performed to compare the clinical efficacy and adverse effects of PCA morphine and nalbuphine combined with ketorolac in postoperative setting and evaluate the effectiveness of a constructed educational program for pain management on patients `outcomes. To accomplish the goal, a combination of opioid analgesics, either morphine (morphine group) or nalbuphine (nalbuphine group), and non-opioid analgesic ketorolac was used for PCA administration. Groups were subdivided into control and intervention groups. Patient and nurse education on safe and effective use of PCA was provided to the intervention groups.

No available data in literature compared the effect of morphine ketorolac combination versus nalbuphine ketorolac on postoperative pain management using PCA. Ketorolac is a NSAID with analgesic and antipyretic properties[27]. It has peripheral and central anti nociceptive effects; peripheral effect on neurons providing local anti-inflammatory activity[28] and may blunt central enhancement of pain impulse transmission by prostaglandins elaborated from disrupted tissue [29, 30]. Ketorolac can produce opioid sparing [31] and provide a synergistic analgesic effect in combination with morphine [32, 33]. Our study revealed a better analgesia produced from morphine ketorolac combination rather than nalbuphine ketorolac combination indicated by lower VAS scores measured from the PACU time shift up to the end of the second postoperative day at 0.5, 6, 8, 10, 12, 14, 16, 18, 22, 26, 28, 32, 34, 36, 38, 42, 44, 46, and 48 hours. This was consistent with result of the study conducted by Akshat et al, higher VAS scores was observed at ½, 2, 6, 12, 24 postoperative hours for morphine compared to nalbuphine in patients underwent open gynecological surgery using PCA morphine or nalbuphine for postoperative analgesia [9]. They used equivalent doses of both drugs for both intraoperative (0.1mg/kg) and postoperative analgesia (PCA settings of 1mg bolus, lockout time of 10 minutes, without any background infusion). While Minai et al concluded that nalbuphine provided better analgesia and greater hemodynamic stability using dose of 0.2 mg/kg, as a component of balanced anesthesia in lower abdominal surgery, with a lower incidence of nausea and vomiting in the postoperative period compared to morphine 0.1 mg/kg [6]. In the present study, morphine was administered in a dose of 0.1 mg/kg, while 0.2 mg/kg for nalbuphine and the PCA solution was prepared to provide basal rate of 0.4 mg/hr of morphine and 0.1 mg bolus dose versus 0.8 mg/hr basal rate for nalbuphine and 0.2 mg bolus dose; with lockout interval 15 minute for both PCA drugs. A higher analgesic efficacy of morphine compared with nalbuphine can be explained by that nalbuphine analgesic potency is equivalent to that of morphine, milligram to milligram for doses up to 10 mg/70kg while at higher doses morphine provides progressively improved analgesic efficacy [5, 34]. Also the studies conducted by Akshat et al and Minai et al. were undertaken in female population and the effect in a group of males may be different. Other studies observed that nalbuphine has different effects in females and males. Kappa-opioids affinity is more pronounced in females than males. Study conducted by Gear et al reported that men receiving the 5 mg dose of nalbuphine experienced significantly greater pain than those receiving placebo; only the 20 mg dose of nalbuphine in men produced significant analgesia compared to placebo. While a similar antianalgesic effect was not observed in women, only the 10 mg dose of nalbuphine produced significant analgesia compared to placebo[35]. A further study conducted by Gear et al compared the analgesic effect of nalbuphine in males versus females after bone-impacted third molar extraction, they found prolonged effect of analgesia in females compared with males using a predominately kappa agonist butorphanol and nalbuphine [36]. The unexpected anti-analgesic effect in males receiving nalbuphine than

females may be explained by that male sex hormone, testosterone interact negatively with kappa opioid agonist ; female related hormones such as progesterone or estrogen may potentiate the action of kappa opioid agonist [36]. Previous studies demonstrated that an opiate-sparing effect for ketorolac was reported when used postoperatively. Blackburn et al reported that the combination of an IV infusion of ketorolac with morphine after lower abdominal surgery has resulted in morphine- sparing effects with adequate analgesia in comparison with placebo [27]. Based on the above data, the present study used lower doses of opioids, compared with the previous studies [6, 9], in a promise to produce adequate analgesia with less adverse effects [8] when combined with ketorolac. Also patients enrolled in our study are cachexic and debilitated, so they may require a lower dose of opioids to decrease the incidence of adverse effects. Previous studies reported that sedation and life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients while receiving opioids as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [37, 38].

The significant rise of postoperative heart rate and systolic and diastolic blood pressure in nalbuphine group compared with morphine group may be due to inadequate pain relief indicated by higher median VAS scores and total equivalent morphine doses for patients who used nalbuphine. Inadequate analgesia, obtained in nalbuphine group, may have affected the overall hemodynamic results. This may explain in part the significance changes in patients' hemodynamics in nalbuphine group. This is consistent with the result of the study conducted by Gélinas et al, they reported a significantly increased in measurements of both mean arterial pressure (MAP) and heart rate (HR) ($p < 0.05$) after nociceptive procedures (i.e., turning, endotracheal suctioning) [39]. Also, morphine is known to cause bradycardia, probably by stimulation of vagal nuclei in medulla and direct depressant action on sinoatrial node, especially when coadministered with volatile anaesthetic agents [32].

The most relevant opioid-related adverse effect is respiratory depression. In postoperative patients the risk of opioid-induced respiratory depression is finite, and this may happen with both PCA and conventional analgesia. Therefore, patients receiving opioids by PCA or adequate amounts of opioids by the conventional route need surveillance [3]. In the current study, and at certain time points, respiratory rate was lowered significantly in morphine group compared with nalbuphine group, however respiratory depression ($RR < 8$ breaths/min) has not been observed among patients in both drug groups. Morphine is a pure agonist whereas nalbuphine is a partial agonist. Morphine has an agonist action on all opioid receptors whereas nalbuphine is kappa agonist and weak mu antagonist. Hence, morphine has both spinal and supraspinal components in its analgesic effect whereas nalbuphine has predominantly spinal components [40]. Respiratory depression caused by nalbuphine has a ceiling effect [5]. These differences in mechanisms between morphine and nalbuphine might produce the difference in actions. Also sedation scores, in the current work, showed significantly lower levels in nalbuphine group than morphine group at certain time points. Again, this can be explained by that, nalbuphine acts as an agonist on kappa receptor and has less effect on mu receptor so less likely to induce sedation or respiratory depression compared to morphine [7]. The incidences of other adverse effects in our study were statistically comparable in both drug groups excluding itching. Itching score was higher in morphine group than nalbuphine group 0 (0-2) versus 0 (0-0), ($P: 0.03^*$). As nalbuphine is an antagonist at mu receptors, it does not cause any pruritus [7]. It was reported that morphine causes pruritus, whereas nalbuphine does not share this adverse effect. In fact nalbuphine may be used to treat morphine induced pruritus. Many authors observed an absence of pruritus with nalbuphine when compared with morphine [6].

The objective of the present study, in part, is to study the effect of a structured preoperative educational program provided by the clinical pharmacist, on the analgesic efficacy, incidence of adverse effects, and patients' satisfaction of the used regimen. Pharmacists may be able to enhance patients' outcomes and adherence to therapy. In addition to dispensing medications, the pharmacy profession advocates that pharmacists offer pharmaceutical care to improve patients' health [41]. Pharmaceutical care activities include monitoring patients' symptoms, counseling patients about their medications, helping resolve drug-related problems, facilitating communication with physicians, and performing patient-specific interventions when appropriate [42]. Also clinical pharmacist had an important educational role before operation and at different stage of surgery to reduce patients' fears and apprehensions and to minimize the consequences of this very painful surgical experience, they tested the patients preoperatively to check their wellbeing and health condition [43].

Pharmacists in Egypt have not yet implemented the pharmaceutical care into their practice. The health care system in Egypt expects pharmacists only to dispense medication according to physicians' prescription, pharmacists are not obliged to educate patient or monitor effectiveness or safety of their pharmacotherapy[44]. In the current work, education provided by the pharmacist, to patients and nurses in the intervention groups, on safe and or effective use of PCA, VAS and APS-POQ-R, resulted in a significant better percentages of pain

relief, which is a likely reason for improvement in pain control and satisfaction with pain management after surgery in the intervention groups because drug regimen did not differ along the study period for both of the control and the intervention groups as mentioned in the methods section. Improvement in pain control in the intervention groups appeared as a significant decrease in median VAS score and a significant increase in satisfaction score.

A significant decrease in pain intensity indicated by lower median VAS score was observed in our work, in patients in the morphine intervention group at 1.5, 2, 2.5, 3, 3.5, 4, 6, and 8 postoperative hours, and at 0, 0.5, and 1 postoperative hours for patients in the nalbuphine intervention group. Study reported by Hong et al support these findings, they reported a significant differences in the pain level measured at two, six and 24 hours after surgery between the experimental and control groups [11].

One of the most dramatic problems identified, in the current work during the structure educational program, was the extremely poor level of physicians, nurses, and patients' knowledge and understanding regarding the PCA device and its use. Adequately increasing patients' knowledge toward the PCA device and its use was one of the main targets in our study by making complete educational system as explained in the methods section. The structured educational program provided a basic knowledge on PCA and reduced patient fear while using the device; indicated by the better score on the given information on pain treatment methods in the intervention groups regarding PCA use compared with the control groups ($P < 0.01^*$). The education provided to the patient in the intervention groups could contribute to reinforce the information during the education sessions, regarding PCA use, instruction sheets and questionnaires that were described in the methods section. Moreover, our preoperative explanation of PCA technique, in the present study, allowed patients to be not confused between PCA button and the nurse call button, be familiar with PCA technique and reduce fear of addiction from frequent use of PCA. The significant higher levels of knowledge, and practice observed in patients who received the pharmaceutical care in this study could have a great impact in improving pain control, attitudes toward analgesics use and satisfaction with pain management after surgery. Data in the literature support our findings [11, 45,46]

Chumbley et al. observed that a PCA leaflet allowed patients to feel better informed and less confused[47]. Further study by the same authors revealed PCA leaflet written by professional was more attractive, more informative and which proved more satisfactory to patients [45]. In the present study, we reported improvement in satisfaction with the results of pain treatment and the percentages of pain relief were significant for patients in the intervention groups than those patients in the control groups ($P < 0.01^*$). Also, Hong et al. observed a higher satisfaction score in the experimental group than the control group 24 hour after surgery ($P < 0.0001$) [11]. Similarly, Knoerl et al. reported that patients who attended structured preoperative education had more positive attitudes toward analgesics use and better pain control and satisfaction with pain management after surgery [46]. Reports by Coleman et al. by the same way, support data in the literature and go hand in hand with our results. They reported that including an (American Pain Society) APS nurse in PCA administration, whose role is patient and staff education regarding PCA use, led to improvements in analgesia and patient satisfaction with PCA [48]. Preoperative patient education, on the other hand, is proved to relief preoperative anxiety, reduce postoperative pain, and shorten hospital stay [12, 13]. Thus the structured preoperative educational program has a positive impact attitude toward self-administration of analgesics, better pain control and satisfaction with pain management using PCA.

V. Conclusion

Morphine provides more effective postoperative analgesia than nalbuphine whencoadministerd with ketorolac. The combination of ketorolac allowed more pronouncedsynergistic effect with morphine than that with nalbuphine.Preoperative patient and nurse education improved analgesia and overall patient satisfaction with their pain treatment protocol; the patient can treat pain more in a more timely and individualized manner, thus, increasing pain-management satisfaction.Preoperative PCA education avoids patient's confusion between PCA button and the nurse call button, allows patients to be familiar with PCA technique and reduces fear of addiction from frequent use of PCA. Also education may allow patients to balance between administration of analgesics and adverse events by self-adjusting the dose of analgesic used.Limitation of the study: Pain intensity is not estimated during rest and at movement/coughingwhich is important to judge the analgesic efficacy.

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Conflict of Interest

The authors declare that they don't have any conflict of interest.

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(Appendix A)

Patient Instruction Sheet

Control Your Pain with Patient Controlled Analgesia infusion system

Why you need to control of your pain?

- Rapid recovery
- Reduce stress, so rapid wound healing
- You can breathe deeply or cough without pain
- Walk easily
- Avoid cardiopulmonary complications or formation of clots
- Decrease your hospital length of stay

What is patient controlled analgesia (PCA)?



(Accufuser, wen YOUNG MEDICAL CO., LTD.)

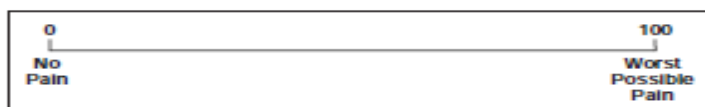
PCA is an infusion device which allows you to administer a small amount of painkiller through a balloon infuser connected to your vein. When you experience pain, press the green button on the PCA device, a small amount of painkiller will be delivered into your vein. The analgesic effect will be achieved within 15 minutes from pressing the button.

Advantages of PCA over conventional pain management methods

- You don't need to wait for nurse to receive your pain killer dose
- You get faster and better pain relief
- You need fewer painkillers with fewer adverse effects
- Low addiction probability due to short term use of PCA

How to assess your pain?

You can assess your pain through using visual analogue scale (VAS)



The scale shown above is ranged from 0–100 for pain with 0 being no pain and 100 being worst pain ever felt. Use a pencil to mark the line shown above at the point that corresponds best to the present level of pain you feel

How and when to use PCA?



When you begin to experience pain, press your PCA button then repeat pressing after 15 minute; if you press the button within the 15 minute interval you will not receive any additional doses. The PCA machine will then lock automatically to prevent an overdose of medicine from being released (safety lockout time)

Only you should press the button; not ask your family members or friends to press the button as it may lead to dangerous adverse effects.

You can press the button before doing activities like exercise, walking, physiotherapy, coughing, dressing change and deep breathing to avoid increase pain intensity

Avoid pressing the button in the following cases:

- You need to sleep or decrease anxiety
- You feel drowsy, or confused
- You experience any of drug adverse effects like nausea, vomiting, drowsiness, itching, and constipation

All of these adverse effects are of low incidences and can be managed, so call your nurse or doctor once you feel any of these adverse effects

When to call your nurse or doctor?

- You still have pain uncontrolled however pressing the button
- You experience any of drug adverse effects like nausea, vomiting, drowsiness, itching, and constipation

(Appendix B):

Nurse Instruction Sheet

Instructions given to patient before connecting PCA

- Demonstration of PCA and how to proper use it
- Mention the risk of dangerous adverseeffect if any family member or friend presses the button rather than the patient himself/herself, because itmisjudges level of sedation.
- Advice patient to press the button to release painkiller when he/she begin to experience pain, providing that he/she is fully awake and conscious
- Advice patient to press the button before doing activities like exercise, walking, physiotherapy, coughing and deep breathing to avoid increase pain intensity
- Advice patient not to press the button when he need to sleep, need to decrease anxiety or experience any of adverse effects like nausea, vomiting, itching, drowsiness, and constipation

The following parameters should be closely monitored

- Respiratory rate, heart rate, and blood pressure at zero time (time to shift to PACU) and every 1/2 hour for the first 4 hours then every 2 hours till the end of the second postoperative day. If you observes a marked decrease of respiratory rate (RR<8 breaths/min) stop PCA IMMEDIATELY.
- Level of sedation using Ramsey sedation scale.
- Pain intensity using VAS at zero time (time to shift to PACU) and every 1/2 hour for the first 4 hours then every 2 hours till the end of the second postoperative day.

When to stop PCA

- Marked over sedation or respiratory depression (RR<8 breaths/min)