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RESEARCH ARTICLE
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COMPARATIVE STUDY BETWEEN POSTOPERATIVE ANALGESIC EFFECTS OF ADDING INTRAINCISIONAL MEPERIDINE VERSUS INTRAINCISIONAL TRAMADOL TO BUPIVACAINE IN ELECTIVE CESAREAN SECTION UNDER SPINAL ANESTHESIA

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ABSTRACT

Background: Analgesic treatment has traditionally focused on central mechanisms associated with pain perception via the use of opioids. The aim of this work was to evaluate the postoperative analgesic effect of intra-incisional infiltration of meperidine added to bupivacaine versus tramadol added to bupivacaine in elective cesarean section (CS) under spinal anaesthesia.

Methods: This randomised controlled double blinded work had been conducted on 90 healthy full-term patients aged from 20 to 35 years old, planned for elective CS under spinal anaesthesia. Patients were divided into three equal groups: Meperidine Group: obtained 50 mg meperidine with 50 mg bupivacaine, Tramadol Group: received 50 mg tramadol with 50 mg bupivacaine and Bupivacaine Group: obtained 50 mg bupivacaine

Results: The amount of morphine given postoperative was significantly decreased in meperidine group and tramadol group than bupivacaine group ($P \leq 0.001$). The time of first dosage of morphine given postoperatively had been earlier in bupivacaine group contrasted to tramadol group than meperidine group ($P < 0.05$). Heart rate, systolic blood pressure, diastolic blood pressure at the studied times, sedation score and side effects had been insignificantly varied between the studied groups. Visual analogous scale (VAS) at rest and cough was significantly lower in meperidine group than tramadol group at 3, 6, 9, 12, 15 and 18 hours ($P < 0.05$). VAS at rest and cough was significantly lower in meperidine group than bupivacaine group at 3, 6, 9, 12, 15, 18 hours ($P \leq 0.001$).

Conclusions: The impact of the addition of intraincisional Meperidine or tramadol to bupivacaine caused adequate and prolonged analgesia. Meperidine when added to intraincisional bupivacaine provides significant analgesia better than intraincisional bupivacaine alone as lasting for a relatively long time.

Keywords: Meperidine, Tramadol, Bupivacaine, Analgesia, Cesarean Section.

INTRODUCTION

The predominant surgical intervention among women of reproductive age is the cesarean section

(CS) **[1].** Effective postoperative pain management is crucial in most surgeries to decrease morbidity and death in patients **[2].**

Surgical Surgical pain arises from inflammation caused by tissue trauma or direct nerve injury, whereby tissue damage stimulates free nerve endings known as pain receptors, or more scientifically, nociceptors. The patient perceives pain via the afferent pain pathway, that may be modified by numerous pharmacological drugs **[3].**

Analgesic treatment has traditionally focused on central processes of pain perception via the administration of opioids; nevertheless, it is now evident that a more effective strategy involves many drugs, each targeting distinct locations within the pain pathway **[4].**

The activity of pain receptors may be directly inhibited by medicines that include lidocaine and bupivacaine, or by anti-inflammatory medications like aspirin and nonsteroidal anti-inflammatory drugs, which reduce the local hormonal responses to injuries, so indirectly diminishing pain receptor activation. **[5].**

Good pain relief leads to earlier mobilization and reducing the elevated risk of thromboembolic illness throughout pregnancy, abbreviated hospitalizations, less hospital expenses, and enhanced satisfaction among patients **[6].**

Post-caesarean section analgesia can be provided by a variety of means. Pain management protocols ought not to be uniform; instead, they must be customized to the specific requirements of each patient, taking into account psychological, medical, and physical conditions; age; degree of fear or worry; personal preferences; and reactions to administered drugs **[7].**

Meperidine is intended for the management of moderate-to-severe pain and is administered as a hydrochloride salt in tablet form, as a syrup, or by subcutaneous, intramuscular, or intravenous injection. Throughout a significant portion of the 20th century, pethidine was the preferred opioid among several doctors **[8].**

The analgesic action of tramadol has yet to be fully understood, but it is believed to work through modulation of serotonin and norepinephrine in addition to its mild agonist of the μ- opioid receptor **[9].**

The aim of this work had been to evaluate the postoperative analgesic impact of intra-incisional infiltration of meperidine added to bupivacaine versus tramadol added to bupivacaine in elective CS utilizing spinal anaesthesia.

PATIENTS AND METHODS

This randomised controlled double blinded research has been performed at Al-Azhar University Hospitals (Assiut) between March 2020 to April 2021, after Al-Azhar University Research Ethics Committee approval **(AZAST/Research/MSc/3-MARCH-2020).** Consent has been attained from the cases prior to the enrolment after detailed explanation of the surgical, anesthetic and analgesic techniques and their possible risks.

Patients who included in the study was consecutive American Society of Anaesthesiologists (ASA) class I- II full-term pregnant female, aged 20 to 35 years undergoing elective CS under spinal anesthesia.

Exclusion criteria were patients with allergy to any of the studied drugs, contraindication of spinal anesthesia, diabetes mellitus, existence of kidney or liver disorders, pre-eclampsia or pregnancy-induced hypertension, arrhythmia, bradycardia, A-V nodal block, Monoamine oxidase inhibitors, body mass index > 35kg/m^2 and abuse of any drugs included in study.

Eligible cases have been randomly allocated via an independent researcher to the Meperidine group, Tramadol group as well as bupivacaine group utilizing computer-generated codes based on the permuted block randomization technique with block size of four, and the separation of group were concealed in sequentially numbered, sealed opaque envelopes which have been opened only following attaining the consent. The cases and the anesthesiologists who were responsible for gathering the information in the operating room have been blinded to the separation of group.

Patients were randomly allocated to the following:
Meperidine (number = 30): patients received 50 mg meperidine with 50 mg bupivacaine diluted in 20 ml normal saline to reach 0.25% concentration to be injected subcutaneously around the incision.
Tramadol (number = 30): patients received 50 mg tramadol with 50 mg bupivacaine diluted in 20 ml normal saline to reach 0.25% concentration to be injected subcutaneously around the incision.
Bupivacaine (number = 30): patients received 50 mg bupivacaine diluted in 20 ml normal saline to reach 0.25% concentration to be injected subcutaneously around the incision.

Preoperative preparation:
In the last hospital visit before surgery, patients were directed to fast for six hours after solid light meals and two hours after clear fluids. All cases have been examined in the ward prior to attending the theater in addition of detailed history taking through the anesthesiologist who prepared the study solutions. standard follows-up (pulse oximetry, noninvasive blood pressure, five-lead electrocardiogram) using multichannel monitor (spacelab health care Xprezzon UK) have been utilized and intravenous access has been attained and 10ml/kg of Ringer acetate was given as a preload. The baseline blood pressure, HR and Spo2% have been determined in the preparation room prior to spinal anesthesia.
All patients obtained spinal anaesthesia at (L3-L4) in the sitting position with 25 mcg Fentanyl (Fentanyl-Janssen JANSSEN-pharmaceutical, USA) added to (1.7 - 2 ml) hyperbaric bupivacaine 0.5% (Sunybupivacaine 0.5% ampoule, sunny medical group, Egypt) (according to the pregnant height using 25-gauge needle (Quincke KDL® China) under complete aseptic conditions. Patients laid supine with left lateral tilt 15º. Sensory block was tested by pin prick test. The cesarean section was carried out, and throughout the skin closure phase, the patient remained on the operating table, the surgeon was given a blinded syringe (labeled A, B or C) containing one of the three solutions to be injected subcutaneously around the incision.

Measurements:
Hemodynamic parameters included: HR (beats/ min) and non-invasive arterial blood pressure (mmHg), systolic arterial blood pressure (SBP) and diastolic arterial blood pressure (DBP) at 15, 30, 60 minutes and 3, 6, 9, 12, 15, 18, 21, 24 hours following arrival in recovery room. Pain measurements Visual analogue scale: The intensity of pain at rest and while coughing was evaluated using a visual analog scale (VAS) from 0 (no pain) to 10 (most pain conceivable) at recovery room at 3, 6, 9, 12, 15, 18, 21, 24 hours after arrival in the recovery room.
Need of additional intravenous opioids: If analgesia was deemed insufficient at any point (VAS was >3), an additional bolus of intravenous morphine (morphine sulphate 10 mg Misr, Egypt) 0.1 mg/kg was given and total doses and time of the first dose was recorded.
Sedation score had been monitored utilizing the following score: Score 1: Alert, 2: Occasionally drowsy, 3: Frequently drowsy, 4: Sleepy, easy to arouse and 5: Somnolent, difficult to arouse. Side effects like vomiting, nausea and allergy to any of the studied drugs.
The 1^{ry} endpoint in the present study was assess of the postoperative analgesic effect of intra-incisional infiltration of meperidine added to bupivacaine versus tramadol added to bupivacaine among individuals undergoing elective CS under spinal anaesthesia. Secondary endpoint includes need of intra -venous opioids, hemodynamic effect, sedation score, and side effects.

Sample size calculation:
This research based on research performed by **Jabalameli et al. [10]** Epi Info STATCALC has been utilized to estimate the size of the sample through based on the following assumptions: - ninety-five percent 2-sided confidence level, with a power of eighty percent & α error of five percent. The final maximum size of the sample determined from the Epi- Info output was 78. Consequently, the size of the sample has been elevated to 90 individuals to account for any dropout cases throughout monitor.

Statistical analysis:

Statistical analysis was done by SPSS version 28 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and standard deviation (SD) and contrasted among the three groups employing ANOVA (F) test with post hoc test (Tukey). Qualitative parameters had been displayed as frequencies and percentages (%) and had been analysed employing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

104 cases have been examined for eligibility; 9 cases have been excluded for not meeting the inclusion criteria and 5 cases refused to take apart in the work. 90 cases have been involved (30 cases in each group) and have been randomized to the groups of the research. All cases have been examined (30 in the meperidine group, 30 in the tramadol group and 30 in Bupivacaine group). **(Fig. 1)**

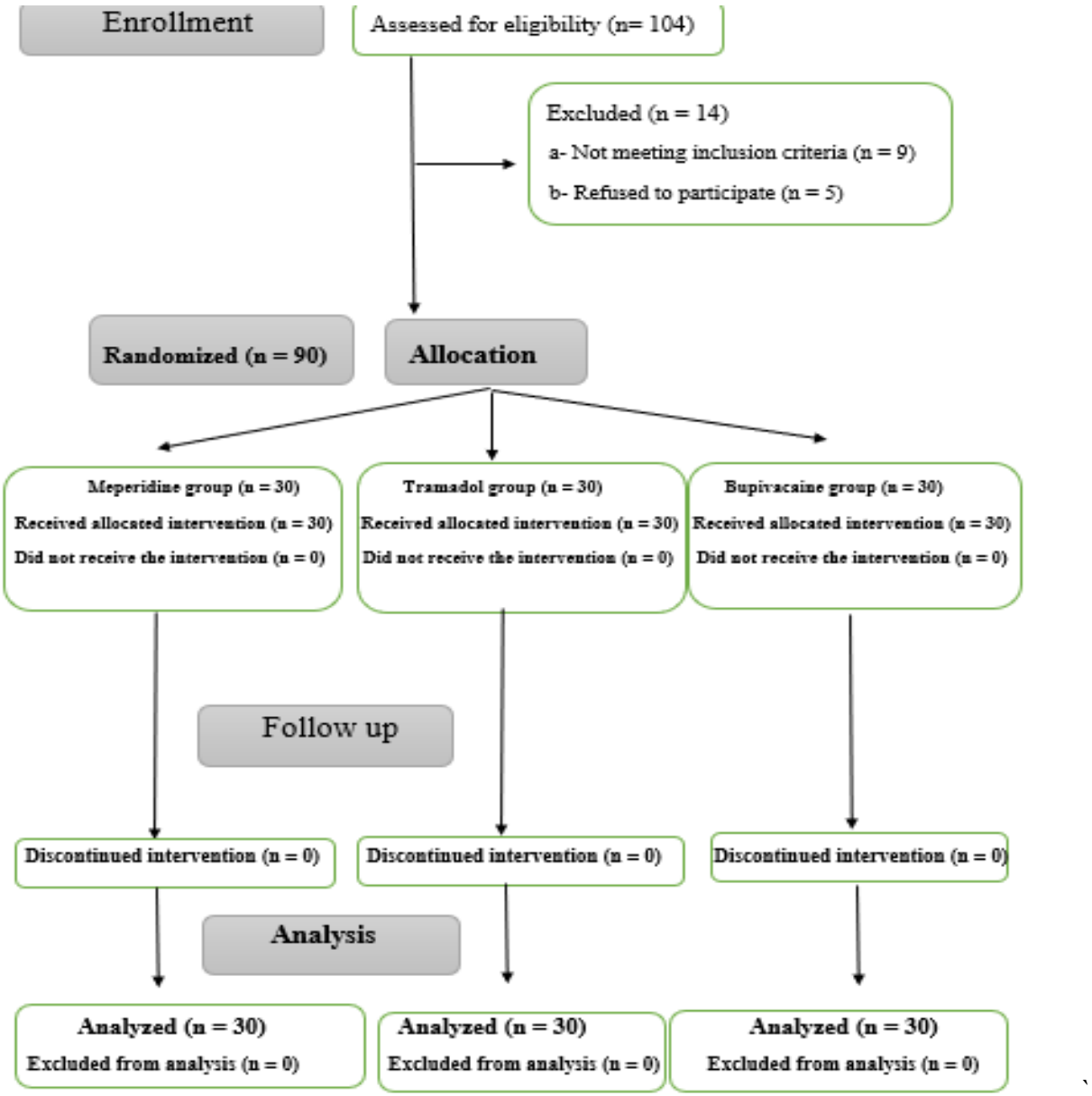

Fig. (1): consort flow chart

Demographic data was insignificantly different between the studied patients. (**Table 1)**

Table (1): Demographic data of the studied groups (Age – Weight – BMI -Operation time)

	Meperidine group (n=30)	Tramadol group (n=30)	Bupivacaine group (n=30)	Test	P
Age (years)	28.36±3.71	28.52±3.29	27.53±3.81	F =0.537	0.573
Weight (kg)	81.92±6.53	81.88±6.17	79.02±7.39	F =0.602	0.514
BMI (Kg/ m^2)	28.20±1.42	29.24±1.81	27.21±1.53	F =0.812	0.791
Operation time (min)	43.37±3.69	44.79±2.59	45.31±3.39	F =0.792	0.817

Data is presented as mean ± SD. BMI: body mass index

Heart rate (HR), systolic blood pressure (SBP), Diastolic blood pressure (DBP) among three studied groups (intraoperatively and in the recovery room) were insignificantly different. **(Fig. 2).**

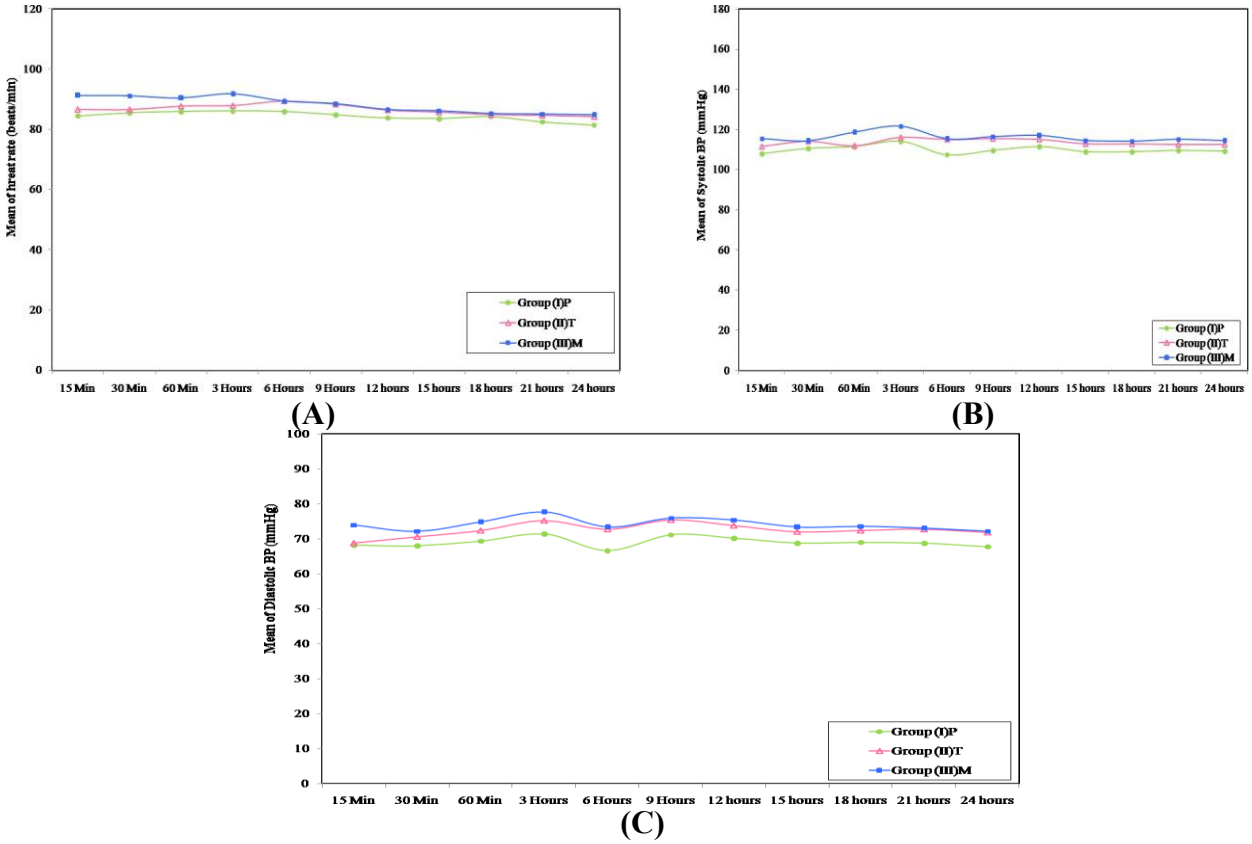

Fig. (2): Comparison between three studied groups according to (A) heart rate, (B) systolic blood pressure and (C) diastolic blood pressure.

VAS at rest and cough at 21 and 24 hours following arrival in recovery room was insignificantly different between the studied groups. VAS at rest and cough had been substantially decreased in meperidine group contrasted to tramadol group at 3, 6, 9, 12, 15 and 18 hours ($P<0.05$). VAS at rest and cough had been substantially decreased in meperidine group than bupivacaine group at 3, 6, 9, 12, 15, 18 hours ($P\leq0.001$). VAS at rest and cough had been substantially decreased in tramadol group contrasted to bupivacaine group at 3, 6, 9, 12, 15 and 18 hours ($P<0.05$). (**Table 2).**

Table (2): Comparison between three studied groups according to VAS at rest and cough (0 - 10)

	3 Hours	6 Hours	9 Hours	12 hours	15 hours	18 hours	21 hours	24 hours
VAS at rest								
Meperidine Group	0.35±0.58	0.61±0.67	0.85±0.54	1.22±0.66	1.59±0.68	1.81±0.62	1.98±0.83	1.79±0.71
Tramadol Group	1.0±0.66	1.46±0.76	1.78±0.57	2.01±0.52	2.24±0.74	2.19±0.46	2.0±0.69	1.89±0.69
Bupivacaine Group	1.47±0.64	1.97±0.67	2.27±0.65	2.47±0.78	2.63±0.84	2.59±0.83	2.17±0.41	1.95±0.53
KW	28.334*	32.969*	46.434*	34.561*	24.816*	16.960*	1.445	2.165
P	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	0.495	0.341
P1	**0.001***	**<0.001***	**<0.001***	**<0.001***	**0.001***	**0.010***	0.784	0.441
P2	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	0.243	0.136
P3	**0.015***	**0.013***	**0.002***	**0.021***	**0.040***	**0.043***	0.323	0.517
VAS at cough								
Meperidine Group	1.35±0.67	1.61±0.55	1.87±0.54	2.20±0.64	2.57±0.57	2.79±0.60	2.97±0.83	2.79±0.71
Tramadol Group	2.01±0.64	2.47±0.68	2.77±0.53	3.0±0.54	3.22±0.67	3.17±0.46	3.0±0.64	2.87±0.68
Bupivacaine Group	2.51±0.67	2.97±0.66	3.27±0.61	3.58±0.77	3.71±0.82	3.63±0.83	3.13±0.42	2.99±0.51
KW	28.334*	32.969*	46.434*	34.561*	24.816*	16.960*	1.445	2.165
P	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	0.495	0.341
P1	**0.001***	**<0.001***	**<0.001***	**<0.001***	**0.001***	**0.010***	0.784	0.441
P2	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	0.243	0.136
P3	**0.015***	**0.013***	**0.002***	**0.021***	**0.040***	**0.043***	0.323	0.517

Data is presented as mean ± SD. * Significant P value<0.05. KW: Kruskal Wallis test. P1: p value for comparing between meperidine Group and tramadol Group, P2: p value for comparing between meperidine Group and bupivacaine Group, P3: p value for comparing between tramadol Group and bupivacaine Group. VAS: visual analogous scale.

The time of first dosage of morphine given postoperatively was earlier in Bupivacaine group contrasted to tramadol group than meperidine group (P<0.05). The time to first analgesia request was significantly earlier in bupivacaine group in comparison to meperidine group (P≤0.001) and it was significantly earlier in bupivacaine group in comparison to tramadol group (P=0.002). The amount of morphine given postoperative had been substantially decreased in meperidine group and tramadol group than bupivacaine group (P≤0.001). Sedation score had been insignificantly varied among the studied groups. (**Table 3).**

Table (3): Time and amount of need of intravenous opioids and sedation score in the studied groups.

	Meperidine Group (n=30)	Tramadol Group (n=30)	Bupivacaine Group (n=30)	Test	P
Time of Morphine Given	18.87±4.81	15.73±5.59	11.32±3.77		
	P1=0.097, **P2<0.001*, P3=0.002***			KW=18.921	**<0.001***
Amount of Morphine Given (mg)	2.54±3.16	4.23±3.44	9.73±3.43	KW=31.789	**<0.001***
	P1=0.087, **P2<0.001*, P3<0.001***				
Sedation score	1.77±0.77	1.43±0.67	1.37±0.53	KW=4.027	0.134
	P1=0.124, P2=0.063, P3=0.845				
Alert	14 (46%)	19 (63%)	19 (63%)		
Occasionally drowsy	10 (34%)	8 (27%)	11 (37%)		
Frequently drowsy	6 (20%)	3 (10%)	0 (0%)	MC=6.581	0.146
Sleepy, easy to arouse	0 (0%)	0 (0%)	0(0%)		
Somnolent, difficult to arouse	0 (0%)	0 (0%)	0 (0%)		
	P1=0.291, P2=0.057, P3=0.443				

Data is presented as mean ± SD or frequency (%). * Significant P value<0.05. KW: Kruskal Wallis test, MC: Carlo test Monte. P1: p value for comparing between meperidine Group and tramadol Group, P2: p value for comparing between meperidine Group and bupivacaine Group, P3: p value for comparing between tramadol Group and bupivacaine Group.

Side effects were insignificantly different between the studied groups. (**Table 4)**

Table (4): Side effects among the studied groups

	Nausea	Vomiting	Allergy to the drug
Meperidine Group	6 (20%)	3 (10%)	0(0%)
Tramadol Group	6 (20%)	4 (14%)	0(0%)
Bupivacaine Group	9 (30%)	5 (17%)	0(0%)
X2	1.700	1.107	1.843
P	0.481	^{MC}P =0.865	^{MC}P =1.000

Data is presented as frequency (%).X^2: Chi square test, MC: Carlo test Monte.

DISCUSSION

Caesarean sections both elective or emergency surgeries were done under anesthesia. General or Spinal anesthesia can be used. Spinal anesthesia is one of the widely used techniques for Caesarean sections **[11].** Among various anesthesia techniques used, multimodal analgesia is effective for postoperative pain relief. Wound infiltration with local anesthetics reduces dosage of analgesia **[12].** Demographic data - age distribution, Weight, BMI and operation time showed no significant difference. hemodynamic variables were also comparable between the three groups at all time intervals either intraoperatively or after arrival in recovery room. Although intravenous meperidine had atropine like action but the use of subcutaneous meperidine and bupivacaine in meperidine group in this study didn't show any increase in heart rate. **Jabalameli et al. [10]** found no significant difference in hemodynamic changes when evaluating preemptive subcutaneous pethidine for post-operative pain after cesarean section.

In this study the impact of the addition of meperidine or tramadol to subcutaneous bupivacaine resulted in superior analgesia when compared to subcutaneous bupivacaine alone in cesarean

section, where the meperidine group receiving subcutaneous meperidine and bupivacaine was the best as regards postoperative analgesia followed by tramadol group receiving subcutaneous tramadol and bupivacaine, and the lowest level of analgesia was found in bupivacaine group alone.
On comparing VAS at rest and on cough between the three studied groups, it was zero at 60 minutes after arrival in recovery room; this could be due to the effect of spinal anesthesia. At 3, 6, 9, 12, 15, 18 hours postoperatively, this study showed that the mean value of the VAS had been substantially decreased in meperidine group and tramadol group than in bupivacaine group. **Armstrong et al. [13]** found that pethidine had a local anesthetic effect on peripheral nerves in vivo when added to prilocaine, while **Acalovschi et al. [14]** found that tramadol improves the onset and duration of intravenous regional anesthesia when added to lidocaine.
As regards the time of first dose of morphine given postoperatively, it was earlier in bupivacaine group contrasted to tramadol group than meperidine group, also the amount of morphine given postoperatively had been substantially decreased in meperidine group and tramadol group than bupivacaine group receiving bupivacaine alone. This was similarly noted by **Onutu et al. [15]** where the mean value of 24-hour total morphine consumption was significantly lower in groups receiving pethidine wound infiltration as compared with the group receiving intramuscular pethidine. **Khajavy et al. [16]** discovered that subcutaneous wound infiltration of tramadol after pyelolithotomy decreases postoperative opioid use in comparison to intravenous delivery.
Bupivacaine wound instillation resulted in suboptimal analgesia after CS **[17].**
Tissue reaction to surgical damage triggers inflammation, nociception, and hyperalgesia. This research indicated that **Trotter et al. [18]** found that subcutaneous wound infiltration with bupivacaine 0.5% didn't reduce morphine needs on the first postoperative day following lower segment CS.
In this research, the sedation scores across the three groups shown no significant difference. One study of **Jabalameli et al. [19]** noticed no difference in sedation scores in all times between groups receiving either tramadol or normal saline. Another study of **Marzida [20]** found that women receiving subcutaneous pethidine 1mg/kg every 8 hours were much more sedated than those receiving oral diclofenac this may be due to higher pethidine dose given than this study.
As regards the side effects, their occurrence was of no significant value in all the groups in this study. Although nausea and vomiting have been major side effects of opioid used for postoperative analgesia, 30% (9 patients) of the patients suffered from nausea and 17% (5 patients) suffered from vomiting in bupivacaine group receiving subcutaneous bupivacaine during the study because this group received higher amount of morphine postoperatively. Vomiting or nausea had been treated with metoclopramide 0.15 mg/kg as necessary. in agreement with this study, **Altunkaya et al. [21]** administered 2 mg/kg of subcutaneous tramadol, resulting in nausea in just one of the twenty patients evaluated during a 24-hour postoperative period after lipoma removal. **Khajavy et al. [16]** discovered that subcutaneous tramadol wound infiltration results in reduced symptoms of vomiting and nausea compared to intravenous treatment.
Limitations of the study included that the sample size had been relatively small. So, we recommend that the addition of meperidine or tramadol to intraincisional bupivacaine needs to be considered as a routine for postoperative pain management in the cesarean section. Opioid local wound infiltration can be a good alternative to the use of systemic analgesics after cesarean section where it decreases intravenous opioid consumption. Further studies on different doses of intraincisional meperidine or tramadol should be promoted to reach the optimum dose for their use in local wound infiltration.
At the end, addition of intraincisional meperidine or tramadol to bupivacaine caused adequate and prolonged analgesia. Meperidine when added to intraincisional bupivacaine provides significant analgesia better than intraincisional bupivacaine alone as lasting for a relatively long time.

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Conflict of Interest: Nil

Author contributions

All authors participated in the conception and design of the work. Material preparation and data acquisition were conducted by [Medhat H Allam, Mohamed M Abo El enain]. Data analysis and interpretation were done by [Mahmoud A Abdel Salam, and Mohamed A Abu Hatab]. The first draft of the manuscript was written by [Mahmoud A Abdel Salam, and Mohamed A Abu Hatab] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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