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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Local wound infiltration with fentanyl vs ketamine after open abdominal hysterectomy: a prospective, randomized, double-blind study

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ABSTRACT

Background & Objective: Local wound infiltration with local anesthetics is known to be an efficacious analgesic modality with minimal side effect. We evaluated the comparative analgesic effect of fentanyl with ketamine as an additive to 0.25% bupivacaine for local wound infiltration during open abdominal hysterectomy.

Methodology: Ninety female patients with ASA class I or II, aged 20–60 y, who underwent elective open abdominal hysterectomy under spinal anesthesia, were allocated randomly to one of the three groups. Patients of Group C received 30 ml of 0.25% bupivacaine, Group F received 30 ml of 0.25% bupivacaine plus 2 ml of fentanyl (100 µg), and Group K received 30 ml of 0.25% bupivacaine plus 2 mg/kg ketamine. The time to first analgesic demand and the total analgesic consumption in the first 24 h postoperatively were noted. Postoperative sedation score was also noted in all patients.

Results: Total analgesic consumption in the first 24 h postoperatively was significantly less in both Group K and F, in comparison to Group C (P = 0.001); however, there was no statistically significant difference between Group K and Group F (P = 0.706). The first call for analgesia was significantly earlier in the Group K in comparison to Groups C and F (P = 0.001). The sedation score was higher in Group K than the other two groups (P > 0.001) .

Conclusion: Local wound infiltration with ketamine as an adjuvant to bupivacaine appears to be a promising analgesic modality in open abdominal hysterectomy surgery. It has comparable analgesic effect to fentanyl when added to bupivacaine in local wound infiltration with longer duration of analgesia and minimal sedative effects.

Key words: Analgesia; Fentanyl; Hysterectomy Ketamine

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1. INTRODUCTION

Open abdominal surgeries are associated with significant postoperative pain and morbidity, so an effective analgesic regimen is required to improve patient comfort and allow early mobilization.[1] Wound infiltration with local anesthetics is an efficacious analgesic modality with minimal side effects.[2] Opioids are widely used for intraoperative as well as postoperative pain management; and these act both on the central and spinal cord levels to produce an analgesic effect.[3]

Ketamine is an N-Methyl-D-Aspartate (NMDA) receptor antagonist, and inhibits pain transmission and suppresses allodynia and hyperalgesia at the spinal level and in the central nervous system.[4] We

hypothesized that adding ketamine would improve the postoperative analgesic efficacy of local wound infiltration compared to fentanyl, and evaluated the comparative analgesic efficacy of fentanyl and ketamine as an additive to bupivacaine in local wound infiltration during open abdominal hysterectomy.

2. METHODOLOGY

This prospective, randomized blinded control study was conducted at Menoufia University hospitals after getting the institutional ethics committee approval from the Menoufia University Hospital (IRB approval number; 4\ 2022 ANET1-2). Informed written consent was obtained from all eligible patients. The trial was registered at https://pactr.samrc.ac.za/Default.aspx (No. PACTR202203545530206) in February 2022. The report of the current trial was designed in concordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Ninety female patients with the ASA class I or II, aged between 20–60 y, undergoing elective open abdominal hysterectomy using Pfannenstiel incision under spinal anesthesia were enrolled in the study. Patients on opioid therapy, central nervous system depressants, or with physical dependence on opioids; those with hepatic, cardiac, or renal disease, lactation, diabetes mellitus, and/or bleeding disorder were not included. We also excluded patients refusing or having a contraindication for neuraxial blocks, respiratory depression, hypersensitivity to one of the drugs, and who refused to participate in the study.

All patients meeting the inclusion criteria were randomized into one of the three groups using a computerized software program (GraphPad software QuickCalcs, Inc.California, USA. website: http://www.graphpad.com/quickcalcs/ index. cfm). The allocation was masked for the participants, the clinical staff, the trial investigators, and the trial statistician who conducted the analyses. The drug preparation and administration were performed by an anesthesiologist who was not involved in the study.

All patients were premedicated with bromazepam 1.5 mg the night before surgery and 2 h before the call to the operating room. In the operating room, continuous electrocardiography, non-invasive blood pressure, and pulse oximetry were recorded. An 18-gauge cannula was inserted in a peripheral vein, and warmed lactated ringer was infused 10 ml/kg within 30 min, then run at 7 ml/kg/h. Premedication was given in the form of glycopyrrolate 0.004 mg/kg and inj. midazolam 0.03 mg/kg.

Under aseptic conditions, subarachnoid block was given at L3–4 or L4–5 interspaces in midline approach, in the sitting position. Injection of 3–3.5 ml of hyperbaric bupivacaine (Marcaine® Spinal Heavy 0.5%; manufactured by Sunny Pharmaceutical, Cairo-Egypt) over 60 sec, using a 25G Quincke spinal needle (Spinocain®, B. Braun Melsungen, Germany) to achieve a desirable level of anesthesia, according the patient height and weight. After completion of the subarachnoid block, the injection site was covered with sterile gauze, the patient was positioned supine with left lateral tilt, and a urinary catheter was inserted. Surgery was allowed to proceed when complete sensory block at T4 dermatome was assessed by pinprick and grade four motor block was achieved. If the sensory and motor blockade was not complete, the procedure was aborted and the patient was excluded from the trial and, surgery continued under general anesthesia.

Hypotension (MAP < 20% from baseline) was treated with intravenous infusion of crystalloid solution and/or ephedrine 6 mg IV in incremental doses. Bradycardia (HR < 50 beats/min) was treated with atropine 0.01 mg/kg IV boluses.

After the closure of the abdominal sheath and muscle layer and before the skin closure, Group C (control group) patients received 30 ml of 0.25% bupivacaine in the incision line; while Group F (fentanyl group) received 30 ml of bupivacaine 0.25% plus fentanyl 100 µg, and Group K (ketamine group) received 30 ml of bupivacaine 0.25% with ketamine 2 mg/kg.

The medications used in the study were administered by the obstetrician who was blinded to the study drug in subcutaneous tissue and the overlaying skin of the surgical wound edges. The skin was closed and the patients were transferred to post-anesthesia care unit (PACU). A blinded observer (anesthesia resident) assessed the pain scores and consumption of analgesics during the first 24 h postoperatively.

In the postoperative period, the patients were evaluated for pain using the visual analogue scale (VAS) on arrival to the PACU (0), then at 2, 4, 6, 8, 10, 12, 18 and 24 h at rest and on coughing. Acetaminophen 1 gm was infused every 8 h on the first postoperative day, as part of a multimodal postoperative analgesia regimen. If the visual analogue scale was ≥ 4, ketorolac 30 mg was given. If the VAS remained ≥ 4 after 10 min, pethidine 50 mg IM was given.

The patients were evaluated for sedation by the sedation score [awake, alert = 0, quietly awake = 1, sleepy but arousable easily = 2, deeply asleep = 3].[5]

The study drugs side effects such as hypotension, bradycardia, nausea, vomiting, or psychological complications were observed for 24 h postoperatively.

Table 1: Demographic data of the studied groups (N = 90).

Studied variables	Group C (N = 30)	Group F (N = 30)	Group K (N = 30)	Test of sig	P value
Age / years					
Mean ± SD	40.5 ± 14.4	39.9 ± 13.9	41.3 ± 13.5	K	0.906
Median (IQR)	41.0 (27.5–56.2)	37.0 (27.7−55.5)	40.0 (29.7–54.5)	0.198	
BMI (kg/m^2)					
Mean ± SD	25.8 ± 0.98	25.7 ± 0.96	25.9 ± 0.91	F	0.809
Median (IQR)	25.8 (24.9−26.6)	25.7 (24.8–26.4)	26.0 (25.1–26.5)	0.212	
ASA N (%)					
I	15 (50.0)	16 (53.3)	16 (53.3)	χ^2	0.956
II	15 (50.0)	14 (46.7)	14 (46.7)	0.089	
Duration of surgery (min)					
Mean ± SD	90.5 ± 12.7	89.5 ± 12.1	90.0 ± 12.4	K	0.952
Median (IQR)	90.0 (75.0–105.0)	90.0 (75.0–105.0)	90.0 (75.0–105.0)	0.099	

K: Kruskal Wallis test, F: ANOVA test, χ2: Chi-square test

The patient satisfaction was evaluated in the first 24 h postoperatively by patient satisfaction score (PSS) [Excellent = 4, Good = 3, Moderate = 2, Poor = 1].[6]

The primary outcome was the cumulative analgesics consumption in the first 24 h postoperatively. The VAS recorded at rest and on coughing, the first demand of analgesia, the side effects of the studied drugs, sedation score, and the patient satisfaction were the secondary outcomes.

Statistical analysis

Based on the results of a previous study[2], a minimum sample size of 25 participants in each group was required to provide statistical significance, with setting power at 80% and confidence level at 95% and using PASS 11th. To avoid patient dropout the investigators recruited 90 participants, 30 for each group.

The data were analyzed statistically with Statistical Package of Social Science [SPSS] version 20 [SPSS, Inc, Chicago, Illinois, USA]. The quantitative data are presented as mean, standard deviation (SD), range, while the qualitative data are presented as numbers and percentages. Data distribution was evaluated by the Shapiro test of normality**.** The relation between two

Table 2: Analgesic data of the studied groups (N=90).

Studied variables	Group C (N = 30)	Group F (N = 30)	Group K (N = 30)	Test of sig	P value	
First call of analgesia (h)						
Mean ± SD	4.10 ± 0.80	8.50 ± 0.82	9.73 ± 0.73	K	**0.001****	**P1:0.001****
Median (IQR)	4.00 (3.00–5.00)	8.50 (8.00–9.00)	10.0 (9.00–10.0)	71.3		**P2:0.001****
						P3:0.001**
Ketorolac (mg) use						
Mean ± SD	78.0 ± 14.9	56.0 ± 20.4	54.0 ± 19.9	K	**0.001****	**P1:0.001****
Median (IQR)	90.0 (60.0–90.0)	60.0 (30.0–90.0)	60.0 (30.0–90.0)	23.4		**P2:0.001****
						P3:0.706
Pethidine use	N (%)	N (%)	N (%)	χ^2	**0.001****	
	7 (23.3)	0 (0.00)	0 (0.00)	15.1		

**Significant **High significant K: Kruskal Wallis test χ2: Chi-square test N: Number % percentage*

P1: Comparison between group C and group F. P2: Comparison between group C and group K. P3: Comparison between group K and group F.

qualitative variables were studied by the Chi-square test (χ^2). The comparison between normally distributed three groups and having quantitative variables was done using ANOVA (F) test. If the three groups were not normally distributed and having quantitative variables, the comparison was done using Kruskal Wallis (K). A post hoc test was done by using the Bonferroni test. P < 0.05 was considered statistically significant.

3. RESULTS

A total of 90 patients were allocated into three groups with thirty patients in one group out of 95 patients who were assessed for eligibility. The study groups were and/or surgery duration (P > 0.05) (Table 1).

The cumulative analgesic consumption in the first 24 statistically equivalent regarding demographic data postoperative hours was significantly less in both Group K and Group F in comparison to Group C (P = 0.001); however, the difference was statistically not significant between Group K and Group F (P = 0.706) and both Group K and Group F did not receive pethidine. The first demand of analgesia was significantly earlier in Group K, followed by Group F, and then Group C (P = 0.001) (Table 2).

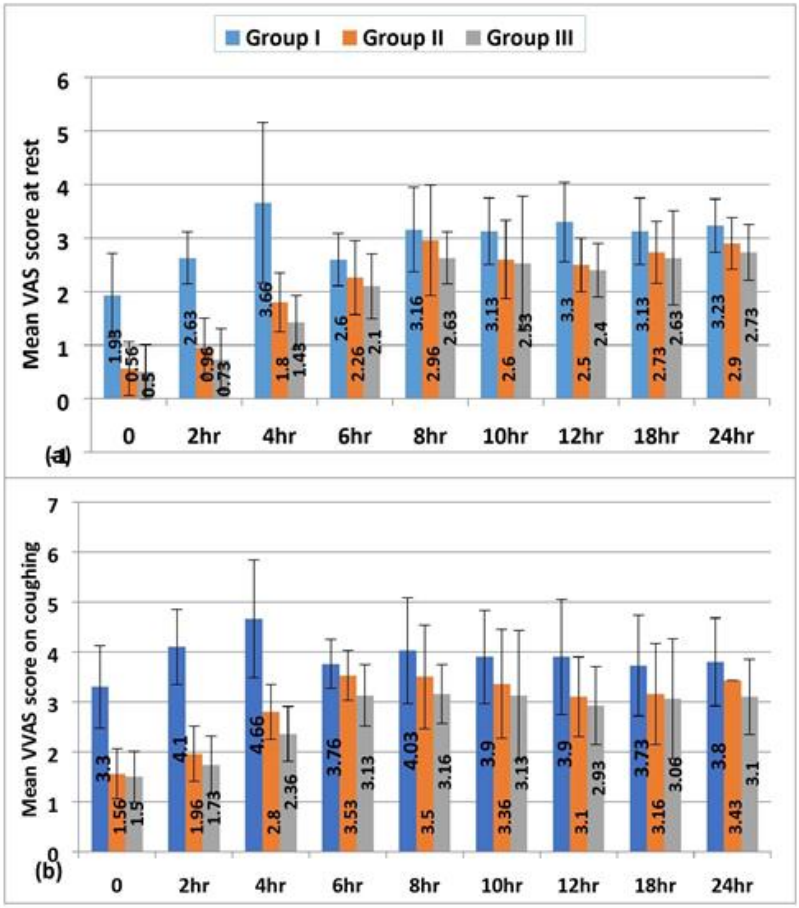

Figure 1: Mean VAS among the studied groups, (a) at rest, (b) on coughing.

Statistically significant lower VAS scores were observed at all times of measurement during rest in both Group K and Group F compared to Group C. (P < 0.001 and 0.035). Likewise, on coughing, VAS was significantly less in both K and F groups at all times of measurement in comparison to Group C (P < 0.001,

Table 3: Sedation score and satisfaction among the studied groups (N=90).

Studied variables	Group C (N = 30)	Group F (N = 30)	Group K (N = 30)	χ2	P value
Sedation score					
0	13 (43.3)	5 (16.7)	3 (10.0)	30.3	**< 0.001****
1	17 (56.7)	19 (63.3)	10 (33.3)		
2	0 (0.00)	6 (20.0)	17 (56.7)		
Satisfaction score					
1	3 (10.0)	0 (0.00)	0 (0.00)	17.7	**0.007****
2	16 (53.3)	7 (23.3)	6 (20.0)		
3	7 (23.3)	14 (46.7)	14 (46.7)		
4	4 (13.3)	9 (30.0)	10 (33.3)		

*Data presented as n (%); **Highly significant, χ^2: Chi-square test*

0.011) (Figure 1).

The sedation score was significantly higher in Group K when compared to both F and C groups ($P < 0.001$). Also, patient satisfaction was higher in both Group K and Group F in comparison to Group C ($P = 0.007$) (Table 3).

4. DISCUSSION

This study demonstrated that using either ketamine or fentanyl as an adjuvant to bupivacaine in local wound infiltration for patients who underwent open abdominal hysterectomy reduced postoperative analgesic consumption and provided good postoperative VAS scores. However, ketamine was associated with superior analgesia without any obvious side effects.

Opioids have both central and peripheral antinociception action. Fentanyl has the phenol peperidine group which makes it the best drug regarding the peripheral analgesic effect in comparison to morphine or meperidine. So, it has a local anesthetic

effect on the nerves in addition to its less histamine releasing property.[7] Several opioid-sparing analgesic modalities are required to reduce postoperative opioid related side effect.[8] Ketamine and dexmedetomidine are just two pf the many tried by the anesthetists.

Ketamine is a non-competitive NMDA antagonist that inhibits glutamate-induced NMDA receptor activation on primary afferent nerve endings in the skin, which reduces peripheral input of pain into the spinal cord and the dorsal horn central sensitization.[9] In addition, its local effect can be due to the blockage of transmission of both sodium and potassium in the peripheral nerves.[10] Stubhaug et al. demonstrated that the acute postoperative pain can be decreased through the inhibition of C-fiber activity.[11]

In our study, ketamine was comparable to fentanyl regarding the reduction of postoperative analgesic consumption, and improving the analgesic quality when added to bupivacaine for local wound infiltration; and it was associated with prolonged time to the first call of analgesia which may be due to the local wound infiltration with 2 mg/kg ketamine acts as a drug reservoir which provides a longer duration of analgesia due to its slow absorption.[12] In agreement with our study, Tuchscherer et al.[13] reported that subcutaneous infiltration of 2 mg/kg ketamine improves the postoperative analgesic quality after cholecystectomy. Also, Safavi et al. infiltrated 2 mg/kg ketamine subcutaneously and confirmed the adequate postoperative analgesic effect of ketamine for patients who underwent cholecystectomy and explained these results by the local effects by ketamine.[12]

In our study, the use of ketamine produced adequate sedation scores without any episodes of respiratory depression. This is due to inhibition of the cerebral cortex and simultaneous stimulation of the limbic system which dissociate the central nervous system from external stimuli.[14] Surprisingly enough, this feature was reported by most of our patients to be the most satisfying point. They reported that they wished not to be vigilant during the recovery period. The sedative effect of ketamine was agreed upon by Rahman et al., who reported that infiltration of the surgical wound with ketamine reduces the postoperative pain with minimal sedation.[15] The patient's satisfaction was statistically and clinically improved in both ketamine and fentanyl groups which can be credited to the improvement in the postoperative analgesic quality.

The strength of this study is being an RCT, and comparing, for the first time, the fentanyl and ketamine analgesic efficacy when used as an adjuvant to bupivacaine in local wound infiltration. It offers a cost-effective management protocol for postoperative analgesia after open abdominal hysterectomy, which could be of great benefit in resource-limited areas. The study is, however, limited by the relatively small sample size. Larger multi-centric studies are recommended to attain a firm conclusion.

5. CONCLUSION

The local wound infiltration with ketamine as an adjuvant to bupivacaine is proposed as a safe and effective analgesic method in comparison to fentanyl. Also, ketamine is superior in being inexpensive, widely available, noninvasive, and having opioid- sparing analgesic effect.

6. Data availability

The numerical data generated during this research is available with the authors.

7. Acknowledgement

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8. Conflict of interest

The authors declare that there was no conflict of interest, and no external or industry funding was involved.

9. Authors' contribution

NA: Created the study hypothesis, contributed to study design, data collection and manuscript editing.

WM: Contributed the study design, data interpretation and manuscript editing.

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