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ORIGINAL RESEARCH **ANESTHESIOLOGY**

Opioid free versus opioid based anesthesia in abdominal gynecological surgery: a prospective randomized controlled trial

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Abstract

Background & objective: Opioids have been in use by the anesthesiologists in almost all major surgical cases since ages, but these are not without side effects. During the recent past, opioid free anesthesia–a wonderful technique, has gained rapid popularity as it saves the patient from the side effects. Many drugs and drug combinations have been advocated. Ketamine–lidocaine combination produces central desensitization of the pain pathways, and an anti-inflammatory and anti-hyperalgesic effect in a synergistic manner. We compared opioid free versus opioid based anesthesia in abdominal gynecological surgery regarding analgesic efficacy and the side effects.

Methodology: After trial registration (PACTR202007844671903), 68 patients enrolled in this study were divided into two groups (34 each) according to the analgesics used. Under GA, Group O received loading dose of fentanyl 1 µg/kg followed by infusion at a rate of 1 µg/kg/h. Group OF received ketamine 0.5 mg/kg as a bolus, a loading dose of lidocaine 1.5 mg/kg followed by infusion 1.5 mg/kg/h. The primary outcome objective was postoperative pain assessed for 24 h using VAS score.

Results: The VAS score was significantly lower in Group OF during the first 4 postoperative hours; at immediate postoperative time–VAS^0 (p 0.001), after one hour–VAS^1 (p 0.001), 2h after–VAS^2 (p = 0.001), and 4 h after–VAS^4 (p = 0.001). Also, Group OF showed significantly lower recovery time (p = 0.001), higher RASS score (p = 0.001), less rescue analgesic consumption, no bowel dysfunction with stable peri-operative hemodynamics.

Conclusion: Opioid free anesthesia is a promising technique, using ketamine–lidocaine combination in abdominal gynecological surgeries enhanced patients recovery with better analgesia profile and stable hemodynamics.

Abbreviations: HR–heart rate; MABP–mean arterial blood pressure; NIBP–non–invasive blood pressure; NMDA–N-methyl D-aspartate; NSAIDs–non steroidal anti-inflammatory drugs; OFA–opioid free anesthesia; PACU–post anesthesia care unite; RASS–Richmond agitation sedation score; RR–respiratory rate; VAS–visual analogue score; VCV–volume controlled ventilation

Key words: Anesthesia; Anesthesia, Opioid free; Analgesia; VAS; Gynecological surgery; Lidocaine; Ketamine

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1. Introduction

Abdominal gynecological surgeries are frequent procedures and a balanced general anesthesia is considered to be the best technique.[1] Analgesia is a one of the three cornerstones of balanced anesthesia. Opioid have been used for since ages for pain control; however, 4.7–26.2% of the operated women continue to experience chronic postoperative pain.[1,2]

Opioids are not free of complications either; opioid use is associated with many side–effects such as tolerance,

hyperalgesia, postoperative ileus, constipation, urinary retention, respiratory depression, shivering, nausea and vomiting etc.; leading to a delayed patient recovery, delayed hospital discharge and unanticipated hospital stay complications and increase health service cost.[3]

Opioid free anesthesia (OFA) is a wonderful technique, first prescribed in plastic and bariatric surgeries and now being used for many other procedures including gynecological and oncological surgeries.[4, 5] OFA means no opioid use, either pre or intra-operatively, until patient is completely recovered. Analgesia is achieved by alternative techniques like loco–regional anesthesia or alternative drugs used in a multimodal manner.[6] In a study the use of sympatholytic drugs and non–opioid analgesics were used and showed stable intraoperative hemodynamics, reducing the need for further analgesics either during intraoperative or postoperative period.[7]

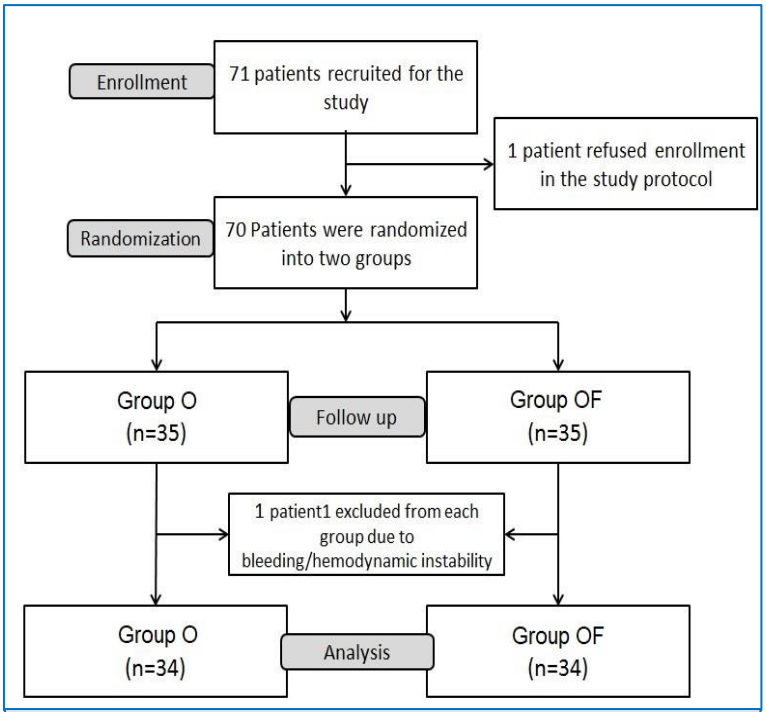

Figure 1: CONSORT diagram

Other drugs described include dexmedetomidine, acetaminophen, pregabalin, gabapentin, and NSAIDs etc. Ketamine is a short acting anesthetic drug that has analgesic properties at sub-anesthetic doses. It acts as an N-methyl D-aspartate (NMDA) receptor antagonist and has anti-inflammatory and anti-hyperalgesia properties.[8]

Lidocaine has been extensively used as an intravenous anesthetic and for pain relief. The mechanism of action of lidocaine involves its binding to sodium channels and its interaction with the general anesthetic agents resulting in a synergistic effect. It also has anti-inflammatory action and it prevents central hyperalgesia.[9] Lidocaine and ketamine, both moderate the inflammatory response to surgery.[10]

We hypothesized that an OFA protocol employing lidocaine plus ketamine will have equivalent analgesic efficacy, but with better hemodynamic stability and reduced postoperative complications as compared to the use of fentanyl in gynecological surgery.

2. Methodology

This prospective randomized double blinded study was conducted in Mansoura University Hospital. Formal approval of the institutional research board (R.20.06.912) at July 5-2020 was obtained. The study was registered with Pan African Clinical Trial Registry (No. PACTR202007844671903) dated July 17, 2020. Informed consent was obtained from all patients, ASA I or II, aged 18-65 y, and scheduled for abdominal gynecological surgery. Patient refusal to participate in the study or known allergy to the study drugs, addiction, psychological troubles, major cardiopulmonary disorders, altered kidney, liver, thyroid functions or complicated surgery were excluded from the study. 71 patients were included in this study, one patient refused to participate, 2 patients excluded due to severe bleeding and hemodynamic instability, the remaining 68 were divided into 2 equal groups of 34 patients each (Figure 1).

The candidates were randomly divided into two groups, using closed envelope technique in blocks of 10; OFA (Group OF) (n = 34), and opioid based (O Group) (n = 34).

All cases were subjected to routine preanesthesia assessment according to the institutional policy, including detailed history and clinical examination, ECG, echocardiography, complete blood count, liver function tests, renal function tests, thyroid function tests and coagulation profile. In the operative suite, patients were connected to a multi-parameter monitor (Datex B850, General Electric, USA) for monitoring ECG, NIBP, and oxygen saturation. An 18G venous catheter was inserted in the right arm. Premedication included pantoprazole (Zurcal®, AUG pharma, Spain), dexamethasone 8 mg and midazolam (Midathetic®, Amoun Pharmaceuticals, Egypt) 3 mg. At the operating room patients were connected to anesthesia monitor for monitoring of ECG, NIBP, and end tidal CO_2 and oxygen saturation.

Anesthesia was induced using propofol 1-2 mg/kg (Diprivan®, Fresenius KABI.), fentanyl 1 µg/kg (Fentanyl Hameln®, Hameln pharmaceuticals, Germany) as loading dose followed by infusion 1 µg/kg/h and Atracurium 0.6 mg/kg (Atrabesylate®, Egypharm, Egypt) in Group O. In Group OF patients anesthesia was induced using propofol 1-2 mg/kg (Diprivan, Fresenius KABI.), 0.5 mg/kg ketamine (Ketalar®, Pfizer, Egypt) as bolus dose only, 1.5 mg/kg lidocaine (Debocaine®, Elnasr Debekiy, Egypt) as loading dose followed by infusion of lidocaine 1.5 mg/kg/h. Atracurium 0.6 mg/kg (Atrabesylate®, Egypharm, Egypt) was used as muscle relaxant. The case anesthesiologist was blinded as drug preparation was done by another trained anesthesiologist according to randomization number received with the patients in a closed envelope. An independent anesthesiologist prepared drugs for loading and for continuous infusions in covered syringes labelled by randomization number. As patients in Group OF, two study drugs were used as loading during anesthesia induction, patients in Group O received saline as placebo during anesthesia induction in a second covered syringe with same volume.

A proper sized endotracheal tube was inserted and fixed in place after confirmation of correct positioning. Patients were ventilated with (GE Datex-Ohmeda Aisys (USA) ventilator) using volume controlled ventilation (VCV) mode to keep $EtCO_2$ at 35 ± 2 mmHg. Anesthesia was maintained with sevoflurane (Sevorane®, Abbott, Egypt) 1-2% in 40% oxygen air gas mixture. Atracurium was supplemented as required. Fentanyl or lidocaine infusion was continued according to study group as described before, 1 gm of paracetamol (Perfalgan®, Bristol Mayers Squibb) was infused in both groups as a part of multimodal analgesia technique before skin incision. Another 18 or 20 G IV line was inserted to infuse ringer acetate at 4 ml/kg/h and other fluids or blood product as needed during surgery. Suitable sized urinary catheter was inserted before starting surgery. Surgery started with Pfannenstiel incision. Intra operative hemodynamic monitoring and management were done. After completion of the surgical procedure, infusion of study drugs were stopped 10 min before the end of anesthesia. Muscle relaxation was reversed with neostigmine 0.05 mg/kg + atropine 0.02 mg/kg. Fully awake extubation was done after meeting the extubation criteria. Recovery time was noted (time from turning off inhalational anesthetics till awake extubation).

Postoperatively, in the PACU, patients were observed for hemodynamics, sedation score using RASS, pain assessment by VAS, the incidence of respiratory depression (RR < 10/min) for one hour. In the surgical ward, patients received paracetamol 1 g every 8 h, ringer acetate 4 ml/kg/h till starting oral intake. Rescue analgesia based on pethidine 0.5 mg/kg IV when VAS > 4. Data recorded by trained nurses included VAS, HR, MABP, SpO_2 at 1 h, 2 h, 4 h, 6 h, 12 h, 24 h, postoperatively, total pethidine intake, the incidence of nausea / vomiting, ileus and constipation within first 24 h.

Statistical analysis:

For sample size calculation, a pilot study of 5 patients scheduled for gynecological surgeries was deigned. The mean VAS in the first postoperative hour was calculated (6 ± 1.4). A reduction of VAS score by 20% was considered an accepted effect size to detect statistical difference between the two groups. G*power software version 3.1.9.4 was used and a total sample size of 62 in the two groups was sufficient to achieve a study power of 0.95 with a beta error of 0.05. To make up for the drops out 6 (10%) cases were added making a total of 68 Patients. Cases in the pilot study were not included in the study groups. Perioperative data were tabulated and analyzed using IBM SPSS software version 22. Continuous data were presented as mean ± SD or median (IQR) according to the normality of distribution. Nominal and categorical data are presented as numbers and percentages. Independent sample T test, Mann-Whitney test, chi square test or Kruskal Wallis test was utilized to detect statistical differences between the studied groups. A $p < 0.05$ was considered significant.

3. Results

Perioperative characteristics of the patients are presenting in (Table 1) with no significant difference among studied groups.

Operative hemodynamic data of the patients (HR, MABP) are presented in Figure 2, with no significant difference among the studied groups.

Postoperative characteristics are presented in Table 2, with significant difference among studied groups regarding: recovery time, RASS scores, analgesic request, number of analgesic requests, total pethidine dose, time to analgesic request, with no significant difference among studied groups regarding mean postoperative HR and MABP.

Comparative postoperative VAS scores are presented in Figure 3, with significant difference among studied groups at all times.

Comparative frequencies of postoperative complications are presented in Table 3, with significant difference among studied groups as regarding PONV, ileus, and constipation. There was no significant difference among studied groups as regards to postoperative respiratory depression.

4. Discussion

Table 1: Perioperative characteristics in the two studied groups.

Parameter	Group O (n = 34)	Group OF (n = 34)	P
Age (y)	48 ± 10	45 ± 13	*0.31*
BMI (kg/m^2)	27 ± 3.5	26 ± 3.7	*0.76*
Operative time (min)	111 ± 21	106 ± 20	0.38
Type of surgery			
Hysterectomy	22	21	
Laparotomy	9	2	
Ovarian surgery	1	6	
Myomectomy	2	5	

*BMI: body mass index. *p < 0.05 considered significant Data presented as mean ± SD and absolute numbers.*

Table 2: Postoperative characteristics in the two studied groups. Data are presented as mean ± SD and median (IQR).

Postoperative data	Group O (n = 34)	Group OF (n = 34)	P
Analgesic requests (n)%	34 (100%)	26 (76%)	0.002*
No. of analgesic requests	3.7 ± 1.2	0.9 ± 0.6	0.001*
Total pethidine dose (mg)	133 ± 35	58 ± 14	0.001*
Time to analgesic request (min)	0 (60)	60 (120)	0.003*
Recovery time (min)	10.7 ± 1.2	4.6 ± 1	0.001*
RASS score on recovery	-1 (1)	0 (0.25)	0.001*
Mean postoperative HR	80 ± 15	79 ± 7	0.86
Mean postoperative MABP	91 ± 4	90 ± 7	0.42

**p-value is considered significant if less than 0.05*
RASS: Richmond agitation sedation score, HR: heart rate (beats per min), MABP: mean arterial blood pressure (mmHg)

Table 3: Postoperative complications in the two groups. Data are presented as number (%).

Postoperative data	Group O (n = 34)	Group OF (n = 34)	p-value
Constipation	10 (29)	3 (9)	0.03*
Ileus	8 (24)	1 (3)	0.01*
PONV	16 (47)	4 (11)	0.001*
Respiratory depression	5 (15)	1 (3)	0.099

PONV: postoperative nausea and vomiting
**p value is significant if less than 0.05*

In this trial, we observed that the patients receiving OFA protocol had lower VAS scores during the first 4 hours postoperatively, lesser recovery time, better RASS score, less rescue analgesia consumption, less gastro intestinal symptoms in form of nausea, vomiting, ileus and constipation.

Analgesia is a one of the three general anesthesia components beside amnesia and hypnosis. For long times opioids have been used, but opioids have many side effects.

OFA is a new promising technique aimed at avoiding perioperative use of opioids, hence reducing the co-morbidities. Many drugs have been prescribed in many previous trials, such as dexmedetomidine, pregabalin, gabapentin and acetaminophen. We used ketamine and lidocaine combination. Ketamine is a NMDA-receptor antagonist with long acting, potent analgesic effects as it modulate opiate receptor.[11] Ketamine produces central desensitization of pain pathways, reducing central hyperalgesia specially when used preemptively as we did.[12] Moreover, many studies described value of ketamine use in reduction of chronic postsurgical pain.[13] Lidocaine is a sodium channel blocker, having potent anti-inflammatory and anti-hyeralgesic effects.[9] Both act in synergistic manner to reduce central pain perception and modulate inflammatory response to surgery.[10,14]

Regarding analgesic profile of our results, VAS score was adopted as the primary outcome objective. We found that VAS scores in Group OFA patients were lower at 0, 1, 2, 4, and 6 hours postoperatively. In addition, rescue analgesia consumption were significantly different between both groups. Regarding number of analgesic request, total dose of pethidine intake within first 24 hours, time to first pethidine intake were lower in Group OFA. This may be attributed to previously described actions of used

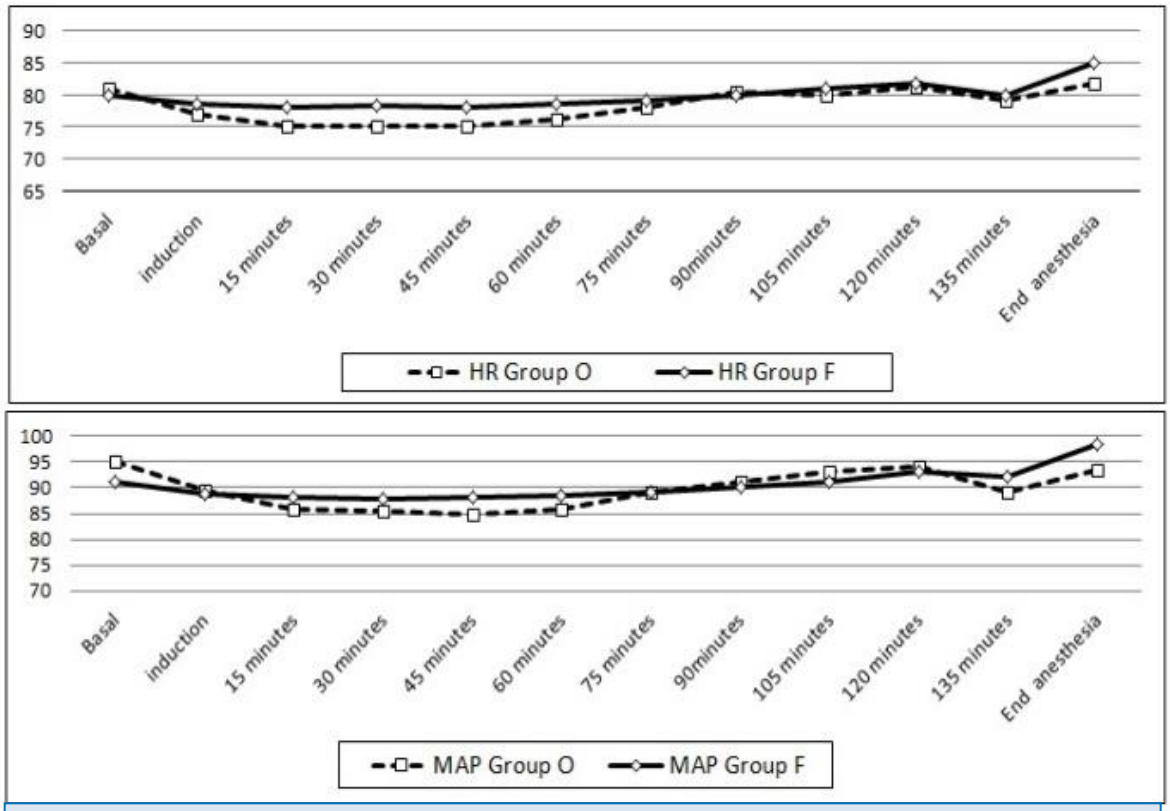

Figure 2: Comparative operative hemodynamic data; Heart rate above and Mean arterial pressure below

drugs. Also, ketamine have opioid sparing effect leading to reduction of rescue analgesia consumption in Group OFA.

Our results match with those of Soffian et al., who used ketamine–lidocaine combination in OFA technique for spine surgery. Their results showed improved analgesic profile assessed by numerical rating scale with significant reduction in rescue analgesia intake (morphine consumption).[14] Guinot et al. used the same technique in cardiac surgery, but found no significant difference in pain scores in the first 48 hours postoperatively; however, morphine consumption as rescue analgesia was significantly less in Group OFA.[15]

Mulier et al. used the same technique with adding dexmedetomidine in laparoscopic bariatric patients, and showed better VAS scores in Group OFA. Also, Toleska et al. reported different drugs like ketamine, lidocaine and dexmedetomidine used separately, or in different combinations with good results regarding postoperative pain control and analgesic consumption.[4]

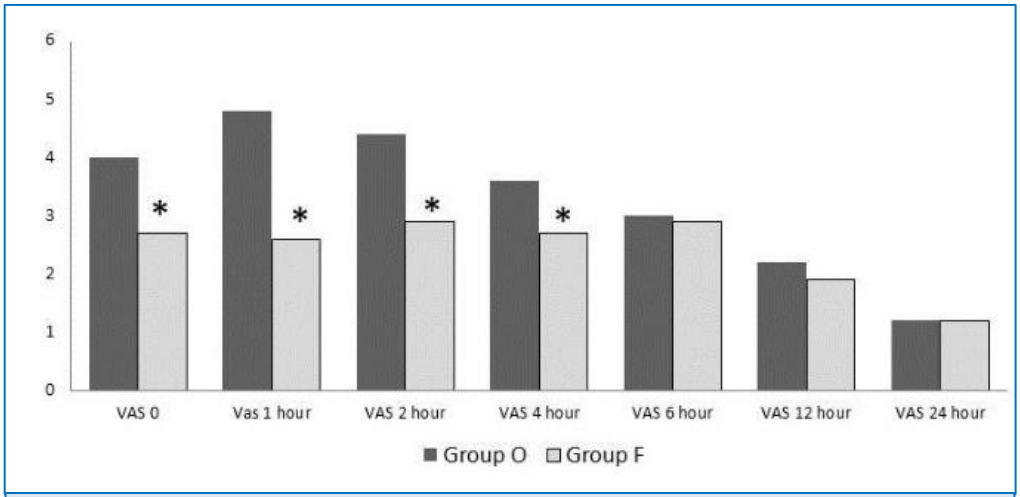

Figure 3: Comparative postoperative VAS score for 24 h

Dexmedetomidine activates alfa-2-adranoceptores leading to

inhibition of release of substance P from the dorsal horn, which leads to a reduction on the nociceptive inputs.[16] Many researchers used dexmedetomidine in laparoscopic procedures as a part of OFA protocol, all of them confirmed superiority of OFA protocols as regarding postoperative pain and reduced rescue analgesic intake.[17,18,19,20]

Grape et al. and Singh et al. in their meta-analysis comprising of 1309 patients, confirmed the superiority of OFA with dexmedetomidine over opioid based anesthesia regarding postoperative pain assessment and postoperative analgesia requirement.[21, 22]

Our results showing significant difference between studied groups regarding recovery time and RASS sedation score. These results match with many of the earlier studies, all of which confirmed better and rapid recovery in OFA patients.[23,4,15] Ahmed et al. compared fentanyl vs. ketamine–dexmedetomidine combination in laparoscopic cholecystectomy and presented significant difference in sedation score post–recovery ($p = 0.024$) among studied groups.[24] However, other researchers showed no significant difference in recovery time among studied groups.[14,17] The Soffian study used small sample size including 36 patients only, while in Hakim study the surgical procedures were laparoscopic gynecological surgery, which are considered ambulatory minimally invasive surgery; hence, the requirement for anesthesia and analgesia was minimal, with minimal side effect observed.

Regarding GIT symptoms, frequency of PONV, ileus and constipation was significantly reduced in the Group OFA of our study. The incidence of PONV has multiple risk factors including type of surgery, character of the patients, anesthetic technique, drugs used and recovery. Abdominal gynecological surgery, general anesthesia, opioid use and prolonged recovery have been associated with higher incidence of PONV. So, omitting the opioids and the resultant rapid recovery, may be associated with better results.[25] Gorlin et al. noted that sub-anesthetic dose of ketamine was associated with a statistically significant reduction in nausea and vomiting, possibly secondary to its opioid-sparing effects.[13] Many researchers concluded that OFA reduced the risk of PONV.[2, 21,22] However, Mulier et al. had doubts about the high incidence of PONV, weather it was related to the opioids or a lack of prophylaxis by antiemetics.[4]

As regarding ileus, probable mechanisms include disruption of the sympathetic and parasympathetic pathways to the gastrointestinal tract, inflammatory changes mediated over multiple pathways, and the use of opioids for the management of postoperative pain. Merret et al.,[19] in their meta-analysis published 2008 found that lidocaine infusion shortened postoperative ileus.

According to our results, constipation was more frequent in the opioid group. Opioids reduce gastric motility, delay gastric emptying, delaying absorption of medications and increasing absorption of fluid. Most patients with opioid induced constipation complain of straining and incomplete emptying of the rectum during defecation. Opioids also increase anal sphincter tone impairing the defecation reflex. Moreover, opioids have been found to decrease emptying of pancreatic juice and bile leading to delayed digestion.[23,25]

5. Limitations

A limitation in this study was the over–weight patients, who may not represent general population, heterogeneity of abdominal gynecological surgery, lack of patient follow up more than 24 h, especially for bowel function and hospital stay and finally pain assessment by VAS score only while stress markers may have been more specific and reliable.

6. Conclusion

Opioid free anesthesia by using ketamine–lidocaine combination in abdominal gynecological surgery patients improved analgesic profile, reduced rescue analgesia consumption and enhanced bowel function postoperatively, while we could not exhibit effect on patients' hemodynamics.

7. Acknowledgements

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8. Authors' contribution

MAA: Main author, study design, data collection, manuscript writing

AKA: Data collection, manuscript reviewing, statistical analysis

9. Conflict of interest

We declare that we have no financial or personal interests, which may have influenced us in writing this paper inappropriately.

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