Comparison of Dexmedetomidine versus Ketamine during Laparoscopic Cholecystectomy Regarding Intra-operative Vital signs and Post-operative pain

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Abstract

Background: laparoscopic cholecystectomy became a widespread procedure with less invasive technique for treatment of gallbladder diseases, So control of post-operative pain associated with it became a source for medical researches to find different drugs and modalities other than opioids usually used for these kinds of operations.

Objectives: This study aimed to compare ketamine and dexametomidine infusion as an adjuvant to general anesthesia methods for laparoscopic cholecystectomy patients for follow up post-operative pain and vital signs.

Patients and methods: This was a prospective clinical-trial conducted at Qena University Hospital in duration from April 2023 to April 2024, involved fifty adult patients divided into Group K (ketamine infusion) and Group D (dexametomidine infusion). General anesthesia was administered to both groups, intraoperative vital signs monitoring was performed, and postoperative pain was measured using the Visual Analogue Scale (VAS).

Results: There was significant decrease in group K when compared to group D regarding Follow up VAS score through the first day post-operative ($p < 0.05$).

Intra-Operative HR was significantly increased in group K when compared to group D through time from the start of the operation till end of operation ($p < 0.05$).

When comparing group K to group D, there was a substantial increase in Intra-Operative SBP 10 to 40 minutes after the procedure began ($p < 0.05$).

Conclusion: ketamine provided better pain control although with more elevation in HR and BP than dexametomidine infusion.

Keywords: Ketamine; Dexametomidine infusion; Opioid-Free Anesthesia; Laparoscopic Cholecystectomy.

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Introduction

The favored therapy for gallbladder diseases rapidly changed to laparoscopic cholecystectomy (LC) instead of open cholecystectomy **(El Nakeeb et al. ,2017**). The LC offer great advantages over open surgical procedures like decrease post-operative anxiety and discomfort and localized pain from large abdominal wounds, so shorter stay follow up in the hospital usually for one day instead of one week, also for the surgeon offer a wide over view for surgical field with few surgical pores for a small camera torchers, finally offer less rates of developing scares for cosmetic and patient satisfaction **(Calland et al. ,2001)** . A laparoscopic cholecystectomy (LC) may induce post-operative pain for a variety of reasons and the usual treatment used was opioids which contribute in some complication for some patients. For above reasons many researchers compered different modalities for decrease the post-operative pain and follow up vital signs associated with each modality.

A α2-adrenoceptor agonist, dexmedetomidine has sedative, anxiolytic, sympatholytic, and analgesic-sparing effects with only a slight respiratory function reduction. With an α2:α1 ratio of 1620:1, it is strong and extremely selective for α2-receptors **(Weerink et al. ,2017).**

Ketamine is a racemic combination of (S)- and (R)-ketamine, has been used in clinical settings. Ketamine has analgesic, anti-inflammatory, and antidepressant effects in addition to its dissociative anesthetic effects **(Zanos et al. ,2018).**

The aim of this prospective comparative study was to compare different drug adjuvants to general anesthesia of laparoscopic cholecystectomy in the form of Dexametomidine versus ketamine infusion as regarding post-operative analgesia effects and follow up intra-operative vital signs**.**

Patients and methods

This was a prospective clinical-trial conducted at Qena University Hospital in duration from April 2023 to April 2024. Fifty adult patients underwent general anesthesia for a laparoscopic cholecystectomy for the study. The patients were split into two groups: Group K, consisting of 25 patients, received ketamine infusion, whereas Group D, also consisting of 25 patients, received Dexamedatomdine infusion. A closed envelope was used for the randomization process.

The eligibility criteria for inclusion encompassed adult patients aged 18 to 60 years undergoing elective laparoscopic cholecystectomy under general anesthesia, categorized as ASA I or II according to American Society of Anesthesiologists physical status classification **(Daabiss ,2011)**. Exclusion criteria comprised hypersensitivity to study medications, history of alcohol or drug abuse, severe systemic diseases, recent opioid analgesic use, specific medication usage, cognitive impairment, and ASA III or IV classification.

Patient Preparation: Informed consent was obtained from all patients. Complete medical history, including personal, medical, surgical, and family history, was recorded. A thorough physical examination, including vital

signs (blood pressure, temperature, heart rate, respiratory rate), was conducted.

- Anesthesia Induction: Propofol 1% at 2 mg/kg and atracurium at 0.5 mg/kg were used as anesthetics. FiO2 = 1 was maintained by using isoflurane in oxygen to maintain anesthesia. To maintain neuromuscular block, atracurium besylate doses of 0.1 mg/kg were administered every 20 minutes (Bovianska 1997).
- After induction Dexmedetomidine (D) group received IV dexmedetomidine (1 micro.gram/kg loading), followed by (0.2 micro.gram/kg/h infusion. Ketamine (K) group received IV ketamine (0.35 mg/kg loading, followed by 1mg/kg/h infusion.

Anesthesia and Ventilation: Volume-controlled mechanical ventilation was used to ventilate patients after intubation.

Reversal of Neuromuscular Blockade: Neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg) were used to reverse neuromuscular blockade **(Ghoneim and El Beltagy ,2015).**

The study employed the Visual Analogue Scale (VAS) for postoperative pain assessment, as described by DeLoach et al. (1998). The VAS is a validated measure of pain intensity, ranging from 0 to 100 mm, where higher scores indicate greater pain intensity. Pain levels were categorized into four groups: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm), and severe pain (75-100 mm).

Intra-operative monitoring involved recording vital signs as BP and HR and post-operative pain levels using the VAS at various time points: 0, 1, 2, 4, 6, 12, 18, and 24 hours postoperatively was recorded. Hemodynamic parameters such as heart rate (HR) and blood pressure (BP) were assessed every 10 minutes in the intra-operative period and also vital signs were assessed every 5 minutes in post-anesthesia care unit (PACU). Monitoring for complications related to the infusion of ketamine and dexmedetomidine was also conducted. Also rescue analgesia as ketorolac 30 mg given and recorded when needed.

The primary objective of the study was to evaluate patient response to ketamine and dexmedetomidine infusion, focusing on pain perception measured by the VAS. Secondary measures included the assessment of hemodynamic parameters and the observation of any complications associated with the infusion.

Ethical code of the study: SVU-MED-AIP029-1-23-4-618

Statistical analysis

Data was depicted through either the utilization of mean and standard deviation (qualitative data representation) or numerical values and percentages (quantitative data representation). Group comparisons were conducted using the Chi-Square test or Ficher exact test for quantitative data, the Mann-Whitney U test for continuous data that did not adhere to normal distribution, and the Student's t-test for continuous data that adhered to normal distribution. Statistical significance was established at a significance level of less than 0.05.

Results

As illustrated in (**Table.1)** Demographic data of included subjects in both groups, in Group K, 60% of the patients are female and 40% are male, while in Group D, 48% of the patients

are female and 52% are male. Similarly, in Group K, 40% of the patients are from rural areas and 60% are from urban areas, while in Group D, 44% are from rural areas and 56% are from urban areas as shown in **(Fig.1).**

Table 1. Demographic data of included subjects in both groups

Variables	Group K (N = 25)	Group D (N = 25)	P. Value
Age (Years)	37.28 ± 2.777	34.48 ± 8.466	0.123 [t]
Sex			
• **Female**	15 (60%)	12 (48%)	0.3946[X]
• **Male**	10 (40%)	13 (52%)	
Residence			
• **Rural**	10 (40%)	11 (44%)	0.77447[X]
• **Urban**	15 (60%)	14 (56%)	

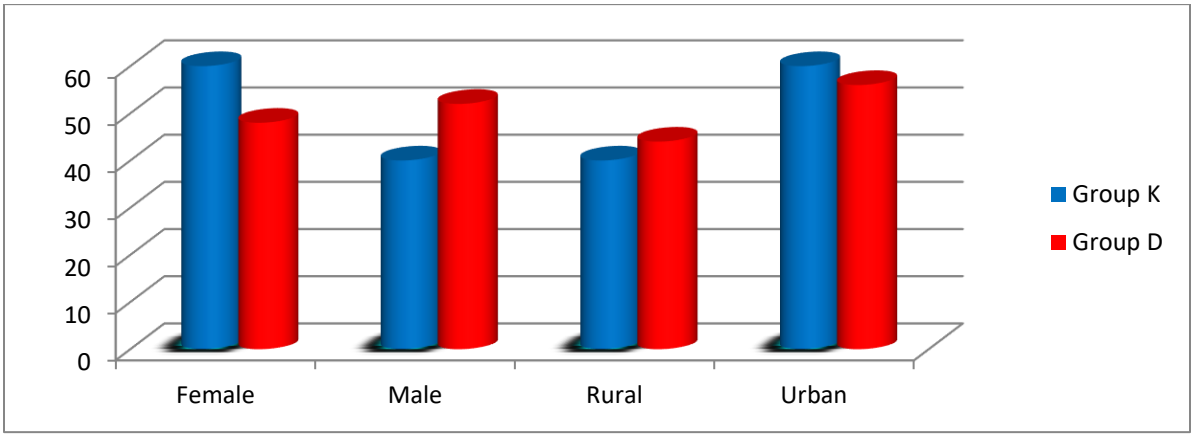

Fig.1. Sex distribution and residence in both study groups.

Also in **(Table.2)** Initial (Pre-Operative) assessment of included subjects in both groups show that there was no significant difference between both groups regarding initial assessment (Pre-Operative) . The mean systolic blood pressure in Group K is 127.96 mmHg and in Group D is 123.88 mmHg. The mean diastolic blood pressure in Group K is 75.48 mmHg and in Group D is 71.52 mmHg as shown in **(Fig.2).**

Table 2. Initial (Pre-Operative) assessment of included subjects in both groups

Variables	Group K (N = 25)	Group D (N = 25)	P. Value
ASA (I)	25 (100%)	25 (100%)	-
Blood Pressure			
• **Systolic (mmHg)**	127.96 ± 12.716	123.88 ± 11.896	0.123[t]
• **Diastolic (mmHg)**	75.48 ± 8.65	71.52 ± 10.662	0.156[t]
Temperature (ºC)	36.94 ± 0.1	36.97 ± 0.08	0.205[t]
HR (Beat/min.)	92.08 ± 4.47	89.04 ± 7.87	0.099[t]
RR (Cycle/min.)	14.56 ± 1.12	14.8 ± 0.91	0.411[t]
Operation Time (min)	72.8 ± 13.08	70 ± 9.57	0.392 [t]

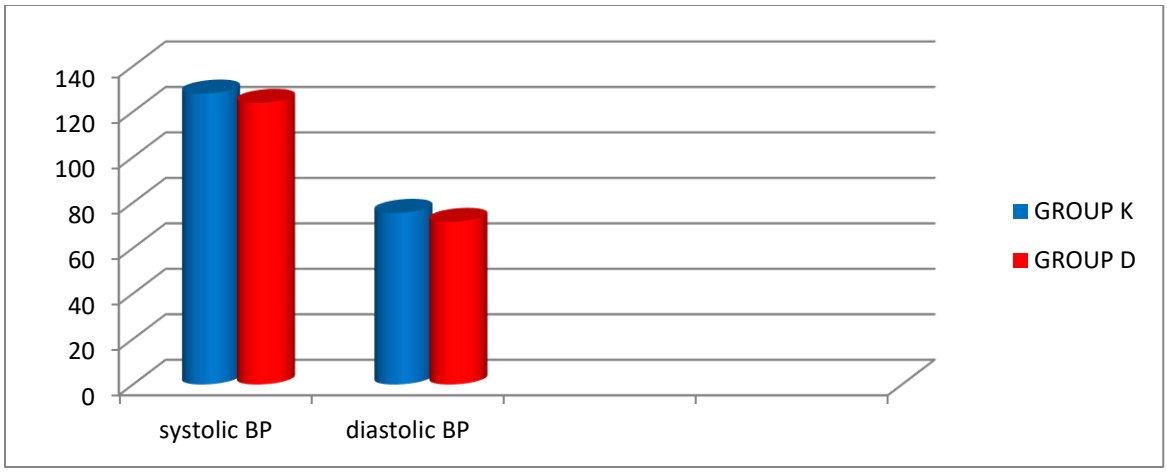

Fig.2. Pre-operative blood pressure assessment in both study groups.

Intra-Operative HR was significantly increased in group K when compared to group D through time from the start of the operation till end of operation. **(Fig.3).**shows HR values for both groups fluctuate over time, but overall Group K tends to have slightly higher HR values than Group D.

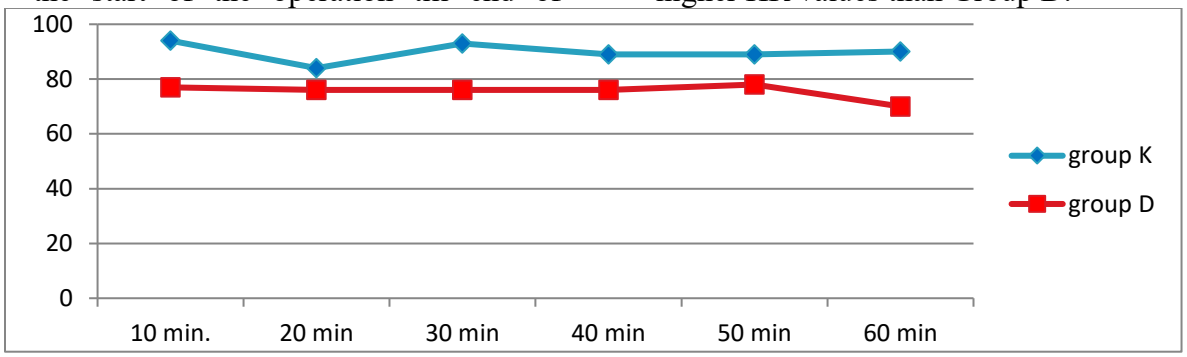

Fig.3. Intra-Operative HR of included subjects in both groups.

Intra-Operative SBP: There was significant increase in 10 to 40 minutes from the start of the operation in group K when compared to group D. From 50 minutes and so on there was no significant difference between the two study groups. The **(Fig.4)**shows Mean Intra-operative systolic BP values for both groups fluctuate over time. Group K generally has higher systolic BP values than Group D, although the difference is not always significant. For example, at 50 minutes, Group K has a systolic BP value of 120.88 compared to 119.54 for Group D with p value < 0.05 and that for the end of operation no significant difference .

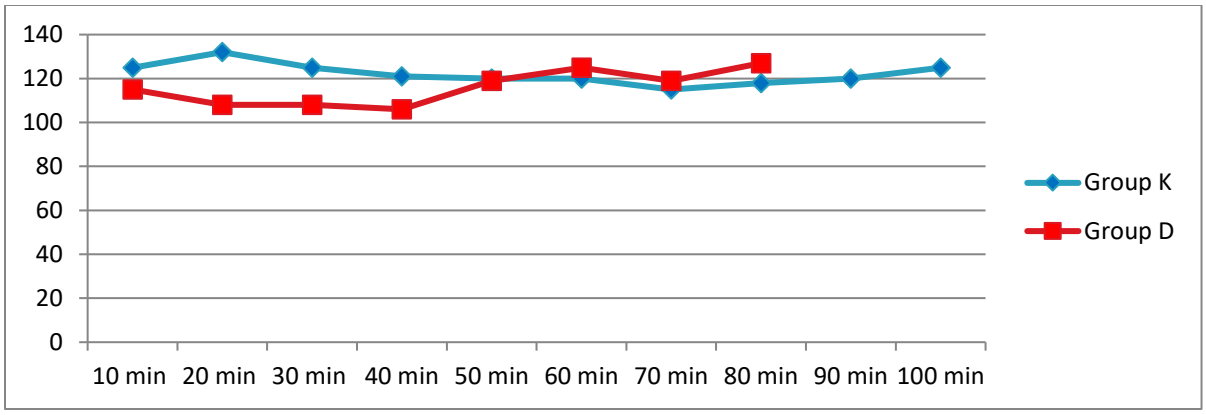

Fig.4. Intra-Operative SBP of included subjects in both groups.

Regarding Intra-Operative DBP, There is no significant difference between the two groups except at 30 minutes and 70 minutes mean DBP significantly higher in group K group. **(Fig.5)** Mean DBP values for both groups fluctuate over time. Group K generally has higher mean DBP values than Group D, although the difference is not always significant. For example, at 30 minutes and 60 min, Group K has a mean DBP value of 81.64 and 70.08 respectively compared to Group D.

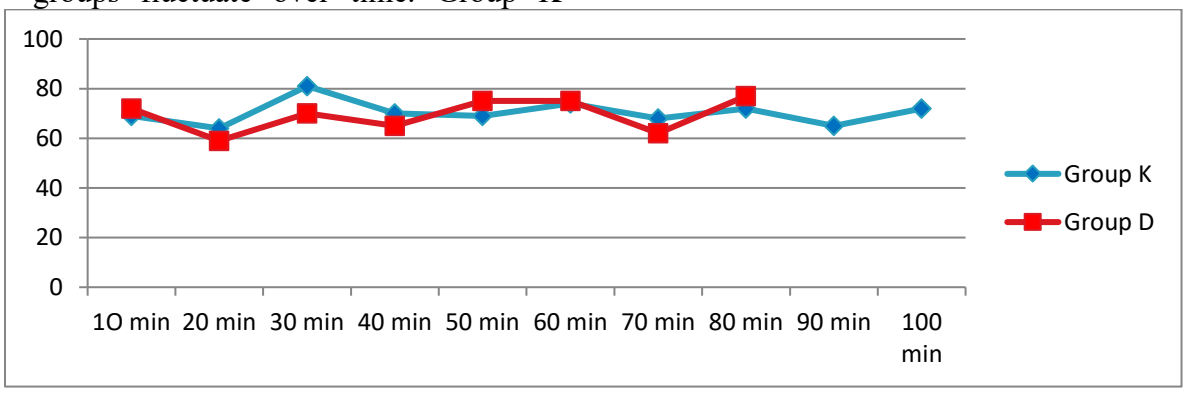

Fig.5. Intra-Operative DBP of included subjects in both groups.

In PACU – HR There was significant increase through first hour post-operative in group K when compared to group D. The data in the **(Fig.6)** suggests that the mean HR values for both groups decrease over time in the PACU. Group K generally has higher mean HR values than Group D. At 5 minutes, Group K has a mean HR value of 96.96 compared to 86.40 for Group D with p value <0.05 and that for all the time of PACU period.

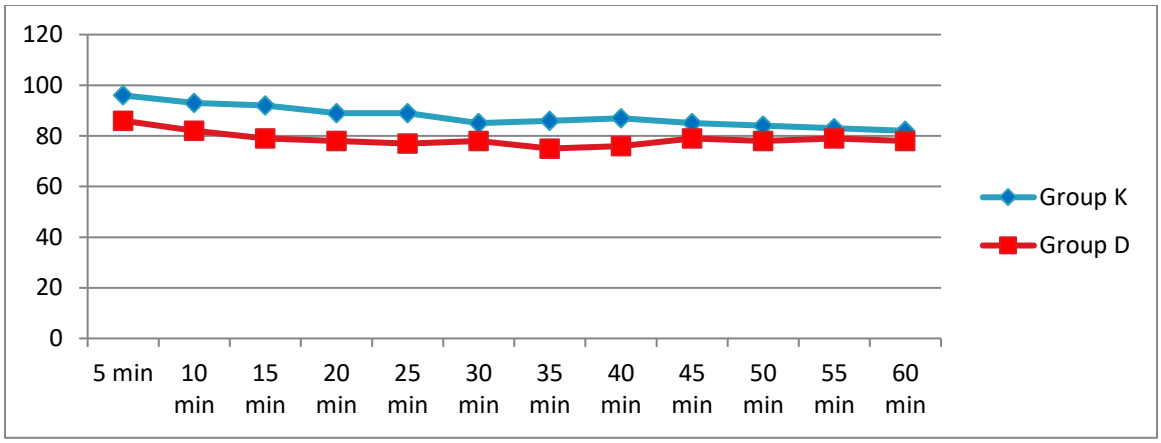

Fig.6. PACU – HR of included subjects in both groups.

Regarding PACU - SBP There was significant increase in group K when compared to group D through first hour post-operative.

(Fig.7) shows Group k had high mean PACU - SBP values for example, at 5 min mean BP with Group k 134.40 compared to 112.56 for group D and that for the rest of PACU period. The data analysis revealed significant findings in several parameters between groups K (ketamine) and D (dexmedetomidine) during the postoperative period.

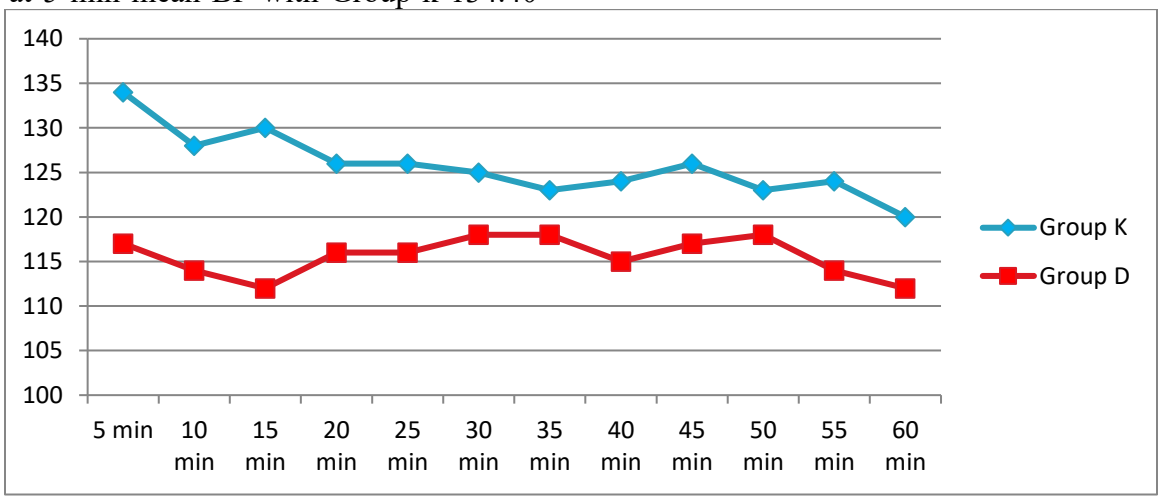

Fig.7. PACU – SBP of included subjects in both groups.

Diastolic Blood Pressure (DBP): There was a notable increase in DBP in group K compared to group D during the first hour postoperatively, except at 50 and 60 minutes where no significant difference was observed as illustrated in **(Fig.8).**Overall, group K exhibited higher mean DBP values compared to group D across all time points, except at 30 and 55 minutes.

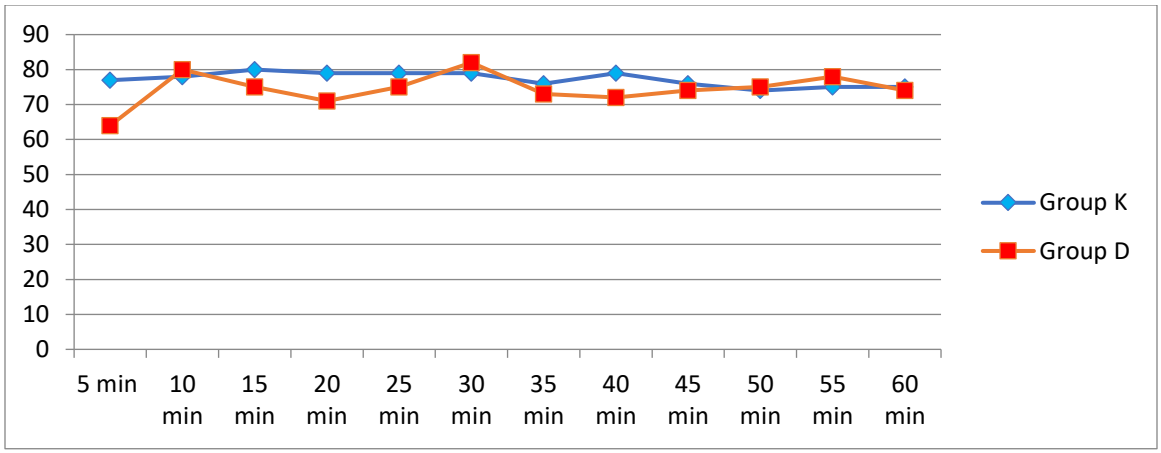

Fig.8. PACU – DBP of included subjects in both groups

Visual Analogue Scale (VAS) Score: Group K demonstrated a significant decrease in VAS scores compared to group D throughout the first day postoperatively. Specifically, group K consistently exhibited lower mean VAS scores than group D across all time points, with the most noticeable difference observed at 6 hours, where group D had a higher score compared to group K as illustrated in **(Fig.9).**

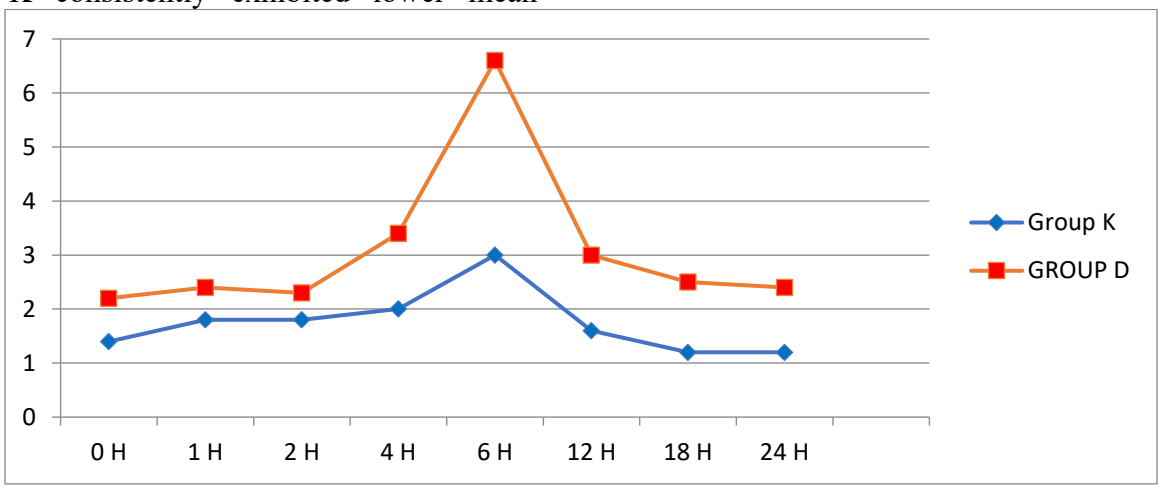

Fig.9. Follow up VAS score of included subjects in both groups.

Rescue Analgesia: Group D required rescue analgesia ketorolac 30 mg in eight cases, whereas no cases in group K needed rescue analgesia. The difference in the requirement for rescue analgesia between the two groups was significant, indicating better pain control in group K.

Heart Rate (HR): Group K showed a significant increase in HR compared to group D during most of the first day postoperatively. Although the difference in HR between the two groups reduced over time, group K consistently exhibited higher HR values compared to group D at all-time points as illustrated in **(Fig.10).**

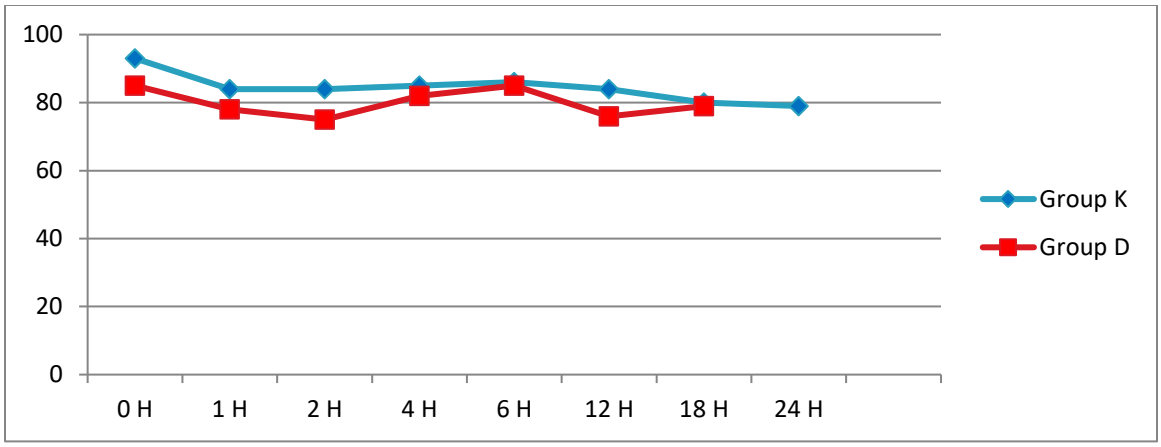

Fig.10. Follow up HR of included subjects in both groups.

Systolic Blood Pressure (SBP): Group K exhibited a significant increase in SBP compared to group D during most of the first 12 hours postoperatively. However, no significant difference was observed between the two groups at 6, 18, and 24 hours postoperatively. Throughout the follow-up period, both groups showed comparable mean SBP values, with slight fluctuations but no significant difference between the groups by 24 hours as illustrated in **(Fig.11).**

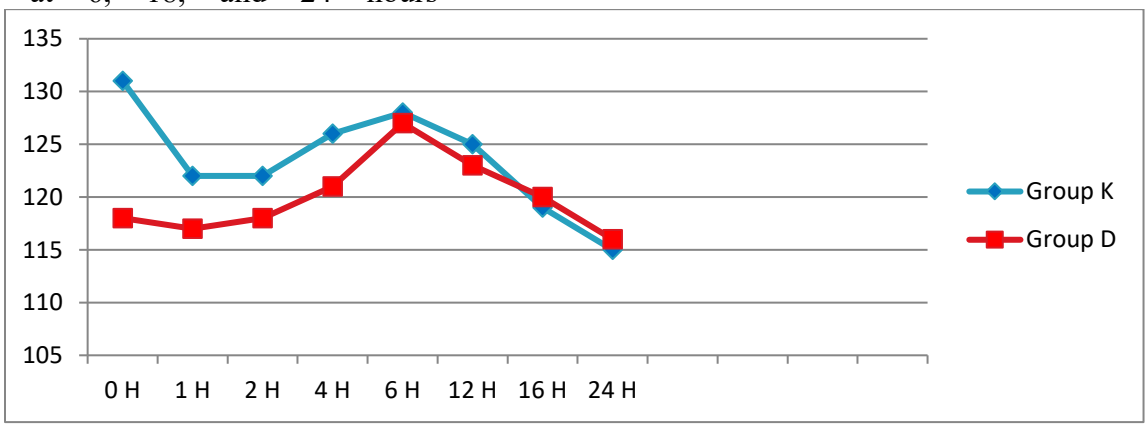

Fig. 11. Follow up SBP of included subjects in both groups.

Trends in Diastolic Blood Pressure: Initially, there was a significant difference in DBP between the two groups during the first 2 hours, with group K having higher DBP. However, after 2 hours, there was no significant difference between the groups, and DBP values became closer in both groups throughout the remainder of the operation as illustrated in **(Fig.12).** These findings suggest that ketamine infusion may lead to higher DBP, lower VAS scores, reduced need for rescue analgesia, and higher HR and SBP compared to dexmedetomidine infusion during the early postoperative period. However, further research is needed to fully understand the clinical implications of these differences.

Lastly, there was no recorded complication in both groups.

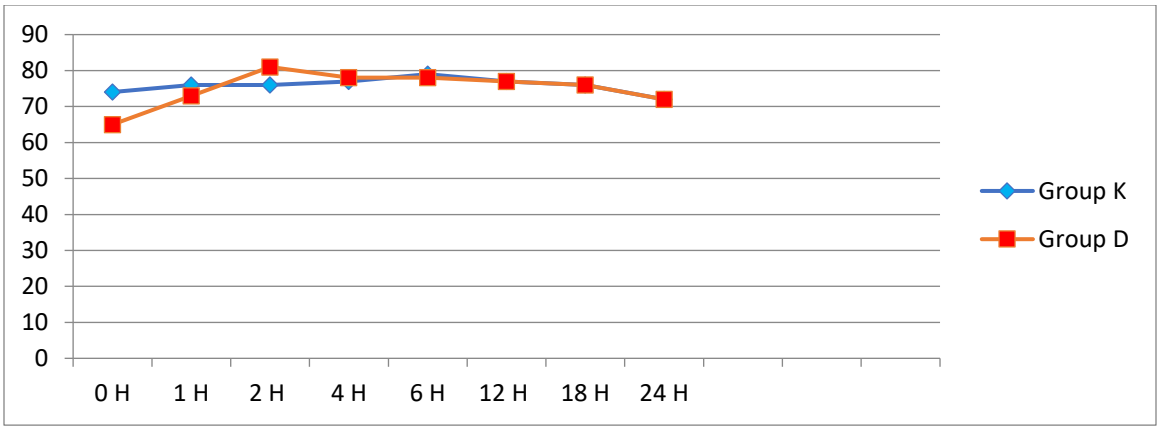

Fig.12. Follow up DBP of included subjects in both groups.

Discussion

For symptomatic cholelithiasis, laparoscopic cholecystectomy is regarded as the most common method of treatment (Barkun et al. 1995). Compared to open surgery, laparoscopic surgery has shown benefits such as shorter recovery times, smaller incisions, shorter postoperative ileus, less blood loss, shorter hospital stays, quicker healing, and an earlier return to preoperative activities and job **(Buanes and Mjåland ,1996).** In actuality, one of the main benefits of laparoscopy over open surgery is less pain following operation. Postoperative pain, however, has not entirely subsided and remains significant **(Boddy, Mehta, and Rhodes ,2006)**. After a laparoscopic cholecystectomy, pain is the main cause of extended hospital stays and can raise morbidity (Bisgaard, Kehlet, and Rosenberg 2001). Patients commonly report discomfort from port site incisions and back and shoulder discomfort. Between 12 and 60 percent of individuals experience shoulder and sub diaphragmatic pain **(Alkhamesi et al. ,2007)**

Previously, the use of opioid analgesics was restricted to post-operative pain management. On the other hand, using opioids has been associated with a number of negative side effects, including constipation, nausea, vomiting, and respiratory depression. Furthermore, prolonged use of opioids can lead to the emergence of addictive behaviors and dependency **(Beloeil ,2019)**.

Consequently, there is an increasing concept towards the advancement of anesthetic procedures that do not include the use of opioids, with the aim of effectively addressing postoperative pain in individuals undergoing laparoscopic cholecystectomy **(Beloeil ,2019).**

Previous study data has demonstrated that dexamametomidine and ketamine infusion are effective in lowering postoperative pain and narcotic usage after a variety of surgical procedures. However, there is little information in the literature about these techniques' efficacy for laparoscopic cholecystectomy patients **(Khalil et al. ,2023) (Garg et al. ,2016) (Jelodar et al. ,2023).**

Ketamine is a phencyclidine derivative that was developed in the 1960s as an anaesthetic agent. Being a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist is one of ketamine's most significant pharmacological characteristics **(Mion and Villevieille ,2013)**. It is thought that NMDA receptor antagonism in the brain and spinal cord is the primary cause of ketamine's analgesic activity at subanaesthetic doses. In terms of pain, the NMDA receptor plays a role in opioid tolerance, central sensitization, and

pain signal amplification **(Trujillo and Akil ,1991)** .

A highly selective α-2 agonist, dexmedetomidine, may become a more crucial adjunct to take into account when using a multimodal strategy to postoperative pain management. Dextmedetomidine has potent anxiolytic effects along with analgesic qualities that spare opioids. While the precise process of antinociception remains unclear, it is believed to arise from the activation of α-2 receptors in the central nervous system and spinal cord **(Patch III et al. ,2017).**

The study included 50 adult patients undergoing laparoscopic cholecystectomy under general anesthesia. The patients were divided into two groups: Group K, consisting of 25 patients who received ketamine, and Group D, consisting of 25 patients who received dexametomidine infusion.

The primary objective of the study was to assess the efficacy of opioid-free anesthesia methods, specifically ketamine and dexmedetomidine infusion, in patients undergoing laparoscopic cholecystectomy. This prospective comparative clinical randomized study was conducted at the Anesthesia, Intensive Care Unit, and Pain Management Department of Qena University Hospital and included fifty adult patients undergoing laparoscopic cholecystectomy under general anesthesia. The patients were divided into two groups: Group K, comprising 25 patients who received ketamine infusion, and Group D, comprising 25 patients who received dexmedetomidine infusion.

The main results were as follows: As our primary aim for this research to compare post-operative analgesia effects of ketamine and dexametomidine infusion we tracked the patient needs for post-operative pain killer and degree of pain associated through the number of dose administrated as a rescue analgesia with Non-Steroidal-anti-inflammatory drugs like 30 mg ketorolac and the VAS score for one hour at PACU and for 24 hour at ward.

We found that regarding rescue analgesia, ketamine group had no rescue analgesia required throughout the study period, while dexametomidine infusion group had 8 (32%) patients who required rescue analgesia. This difference was statistically significant with a p-value = 0.004. Regarding the dose of rescue analgesia administered in Group D, no rescue analgesia was given at 0, 1, 2, and 4 hours postoperatively, but at 6 hours, the mean dose was 9.60 ± 14.28 . No rescue analgesia was required at 12, 18, and 24 hours postoperatively in Group D. Ketamine is likely more effective than dexametoidine infusion in reducing the need for rescue analgesia due to its targeted impact reducing pain perception therefore decrease the need for rescue analgesia.

And regarding VAS score, there was significant decrease in group K when compared to group D through the first day post-operative. The calculated mean for the score for each group was marked at 6 hours, where Group D had a higher score of 6.6 compared with 3.12 for group K.

Our data support the superiority of ketamine infusion over dexametomidine as adjuvant analgesia with the general anesthesia in the laparoscopic cholecystectomy but also both decrease the need of number of analgesia required in general and decrease the opioid consumption especially.

Our research finding was consistent with other researches like **(Gorlin, Rosenfeld, and Ramakrishna ,2016)** that reported that In a variety of surgical procedures, sub-anesthetic dose of ketamine decreases perioperative opioid intake and improves pain scores with a low risk of adverse effects.

Radvansky et al. ,2015 also reported that for postoperative pain management, an intravenous bolus of ketamine administered before incision and a continuous infusion seem to be the most successful treatment modality. Patients may experience a lower chance of chronic postoperative pain in the months that follow if the infusion is administered over a longer period of time (48 hours) for more invasive and frequently painful operations.

Li et al. ,2021 reported that a continuous intraoperative infusion of dexmedetomidine has been shown to decrease stress, postoperative pain, analgesic medication use, and the incidence of neuropathic and post-chronic pain in patients recovering from thoracotomy.

Garg et al. ,2016 repored that both dexmedetomidine and low-dose ketamine infusions offer effective postoperative analgesia with little adverse effects. Following spine surgery, patients can safely and efficiently utilize either of the tested analgesic regimens to relieve postoperative pain.

Regarding the secondary aim in our research for follow up vital signs and hemodynamics intra and post-operative the main results that we found that mean Intra-operative systolic BP values for both groups fluctuate over time. But group K generally has higher systolic BP values than Group D, although the difference is not always significant. The difference was significant increase in Intra-Operative SBP from the start of the operation in group K when compared to group till 50 minutes and so on there was no significant difference between the two study groups.

According to Intra-Operative HR it was significantly increased in group K when compared to group D through time from the start of the operation till end of operation. Also for PACU period there was significant increase in PACU – HR and PACU - SBP through first hour post-operative in group k than group D.

We believe that the findings found support the action of ketamine and its pharmacodynamics on cardiovascular system as it induces a hyperadrenergic state (release of norepinephrine, dopamine, and serotonin) by stimulating noradrenergic neurons and inhibiting catecholamine absorption. Norepinephrine uptake inhibition is stereospecific; the R (−) isomer only blocks neuronal uptake, whereas the S (+) isomer also blocks extra-neuronal uptake. Extended synaptic activity results in a greater release of norepinephrine into the bloodstream **(Kohrs and Durieux ,1998)**. This explains the slightly elevated BP and HR intra operative and in PACU period associated with Ketamine group.

The effect of dexametomidine on hemodynamics can be attributed to the inhibition of catecholamine release by presynaptic α2-adrenoreceptors, which in turn causes enhanced vagal activity and a hypotensive phase, as documented by **Ehrenberg et al. ,2000.** After the first dose, mean arterial blood pressure dropped by an average of 13-27% compared to baseline and was steady for a considerable amount of time (**Bloor et al. ,1992**). Numerous studies have demonstrated a persistent, dose-dependent 60–80% decrease in circulating plasma catecholamines, which is in line with the long-lasting sympatholytic effects of dexmedetomidine **(Ebert et al. ,2000; Bloor et al. ,1992).**

This was consistent with our research findings that HR values overall in Group D tends to have lower HR values than Group K with statistically significant difference for lower values of HR in Group D.

In the current study, there were no postoperative complications observed in either Group K (ketamine group) or Group D (dexametomidine group) indicating that

both interventions are safe to use in patients undergoing laparoscopic cholecystectomy.

We recommend use of ketamine than dexametomidine as an adjuvant to general anesthesia of laparoscopic cholecystectomy for analgesic purpose and we recommend f urther studies with larger sample sizes conducted across multiple centers and trying different doses of the two drugs for example 0.5 mg\kg\hr for ketamine, are needed to confirm our findings and ensure their applicability to a wider patient population.

Conclusion

In conclusion, both ketamine and dexametomidine infusion are effective pain relievers and recovery aids for patients following laparoscopic cholecystectomy. Our study indicated that dexametomidine was related with lower heart rate and blood pressure values during and after the surgery, while ketamine offered better overall pain control and had a reduced incidence of patients requiring rescue analgesia. Importantly, neither intervention was associated with any postoperative problems, implying that they are both safe for use in laparoscopic cholecystectomy patients. Individual patient variables and surgeon preferences may influence method selection, and additional research may be required to better understand the possible benefits and challenges of each intervention.

List of abbreviation

Abb	Full Term
LC	laparoscopic cholecystectomy
NSAIDS	non-steroidal anti-inflammatory drugs
CO2	Carbon dioxide
ETCO2	end-tidal carbon dioxide
FIO2	percentage of inspired oxygen
RCTs	Randomized controlled trials
Cmax	Maximum concentration
NMDA	N-Methyl-D-Aspartate
GABA	γ-aminobutyrique acid
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
PACU	Post anesthesia care unit
VAS	visual analogue scale
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
HR	Heart rate

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