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Evaluation of lignocaine, dexmedetomidine, lignocaine-dexmedetomidine infusion on pain and quality of recovery for robotic abdominal hysterectomy: a prospective randomized controlled trial

Pudi Shivaji, Sanjay Agrawal, Ajay Kumar, Anupama Bahadur*

All India Institute of Medical Sciences, Obstetrics & Gynaecology, Department of Anaesthesiology and Critical Care, Rishikesh, India

*** Corresponding author.**
E-mail: sanjay.anaes@aiimsrishikesh.edu.in (S. Agrawal).
ORCID ID: 0000-0002-2806-1943

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Abstract

*Background***:** Acute postoperative pain is associated with poor quality of recovery after surgery. Perioperative use of intravenous lignocaine or dexmedetomidine have demonstrated better pain control, early return of bowel function, and effects on quality of recovery.

Methods: Ninety-six women planned for elective Robotic abdominal hysterectomy were randomized into four groups. Groups received lignocaine infusion (1.5 $mg.kg^{-1}$ loading, 2 $mg.kg^{-1}.h^{-1}$ infusion) (Group I), dexmedetomidine infusion (1 $\mu g.kg^{-1}$ loading, 0.6 $\mu g.kg^{-1}.h^{-1}$ infusion) (Group 2), lidocaine (1.5 $mg.kg^{-1}$ loading, 2 $mg.kg^{-1}.h^{-1}$ infusion), and dexmedetomidine infusions (1 $\mu g.kg^{-1}$ loading, 0.5 $\mu g.kg^{-1}.h^{-1}$ infusion) (Group 3),and normal saline 10 mL loading, 1 $mL.kg^{-1}.h^{-1}$ infusion) (Group 4). Primary outcome was visual analogue pain scores at 1, 2, 4, 12, and 24 hours after surgery. Secondary outcomes included postoperative fentanyl requirement, time of return of bowel sounds and flatus, QoR15 score on day 1, 2, and discharge.

*Results***:** The VAS was significantly lower in Groups 2 and 3 compared to Groups 1 and 4. Total postoperative fentanyl consumption in the first 24 hours was 256.25 ± 16.36

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mcg (Group 1), 177.71 ± 16.81 mcg (Group 2), 114.17 ± 16.19 mcg (Group 3), and 304.42 ± 31.26 mcg (Group 4), respectively. Time to return of bowel sounds and passage of flatus was significantly shorter in Groups 2 and 3 ($p < 0.01$). QoR15 scores after surgery were higher in Group 3 compared to Groups 1, 2, and 4, ($p < 0.01$) respectively.

*Conclusion***:** Combined infusion of lignocaine and dexmedetomidine significantly decreased postoperative pain, fentanyl consumption, and improved quality of recovery score after surgery in patients undergoing Robotic abdominal hysterectomy.

KEYWORDS

Quality of recovery score,

Robotic abdominal hysterectomy,

Postoperative pain,

Lignocaine,

Dexmedetomidine,

Lignocaine,

Dexmedetomidine

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Introduction

Postoperative pain is a normal physiological response to surgical trauma/manipulations/ traction of somatic or visceral structures. Inflammatory, visceral or neuropathic mechanism all contribute to post-operative pain.[1] In the era of fast-track surgeries the anesthesia technique needs to be modified to satisfy surgical needs and early discharge. Minimally invasive surgeries, early mobilization, and preference of short acting anesthetics along with multimodal analgesics postoperatively decrease hospital stay along with increased patient satisfaction.[2] Hysterectomy is a common gynecological surgical procedure done worldwide for a number of reasons. The surgical approaches have evolved with time from open abdominal hysterectomy to laparoscopic hysterectomy to robotic hysterectomy. The advantages for patients are decreased tissue damage, less inflammation and pain, thereby decreasing hospital stay and improving patient satisfaction.[3]

Perioperative use of infusions of lignocaine or dexmedetomidine influence postoperative pain and early home readiness. The advantage postulated is a consequence of opioid sparing effect as well as influence on the inflammatory response of post-surgical insult. Perioperative use of lignocaine or dexmedetomidine as a part of multimodal anesthesia is associated with decreased anesthetic usage as well as reducing postoperative pain.[4,5] Modification of inflammatory markers are one of the proposed mechanisms of their action to decrease pain.[6] Literature regarding perioperative use of combination of lignocaine and dexmedetomidine is sparse and needs further evaluation.

The QoR-15 is a recently developed patient-reported, outcome measurement of postoperative quality of recovery.[7] It was developed from the larger QoR-40, which as extensively used and validated as a measurement of postoperative quality of recovery.[8] The QoR-15 had equivalent, psychometric properties compared to the QoR-40 but was more feasible to use.

With this background, we planned to study the effects of infusions of lignocaine, dexmedetomidine and the combination of lignocaine and dexmedetomidine on postoperative pain, analgesic requirement, and Quality of Recovery (QoR) in patients undergoing elective Robotic abdominal hysterectomy. We hypothesized that the

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combination of lignocaine and dexmedetomidine will provide better analgesia and improved QoR score compared to use of individual agents alone.

Methods

The study was conducted after obtaining Institutional Ethics committee approval of AllMS, Rishikesh and written informed consent of patients. The trial was registered with Clinical Trial Registry India (CTRI/REF/2019/09/021323). One hundred and twenty females with American Society of Anesthesiologists (ASA) physical status I and II, aged 30–65 years and scheduled for Robotic Total Abdominal Hysterectomy under general anesthesia were enrolled between October 2019 and March 2020. Patients with BMI > 35 $kg.m^{-2}$, allergy to study drugs, history of use of opioid, analgesics, psychotropic drugs (or) beta blockers, uncontrolled hypertension, A-V conduction block, history of sleep apnea were excluded from the study.

The patients were randomized to one of four groups utilizing the sealed envelope randomization method available at www.sealedenvelop.com. The numbers were maintained in sequentially numbered opaque envelopes for concealment until 1 hour before induction of anesthesia. On the day of surgery, the envelops were opened and as per group allotment and the drug infusions prepared. An anesthesia support staff prepared the drug infusion as per written instructions. The staff was not involved in the management of cases. Surgeon and patients were blind to the group allotment.

The patients received infusions of Lignocaine 1.5 $mg.kg^{-1}$ over 15 minutes followed by continuous infusion at 2 $mg.kg^{-1}.h^{-1}$ till end of surgery (Group 1), dexmedetomidine 1 $mcg.kg^{-1}$ over 15 minutes followed by continuous infusion at 0.6 $mcg.kg^{-1}.h^{-1}$ till end of surgery (Group 2), infusion of lignocaine 1.5 $mg.kg^{-1}$ and dexmedetomidine 1 $mcg.kg^{-1}$ over 15 minutes followed by infusions at 2 $mg.kg^{-1}.h^{-1}$ (lignocaine) and at 0.5 $mcg.kg^{-1}.h^{-1}$ (dexmedetomidine) until end of surgery (Group 3) and infusion of normal saline 10 mL over 15 minutes followed by infusion at1 $mL.kg^{-1}.h^{-1}$ till end of surgery (Group 4).

Preoperatively on the day before surgery, patient was explained the Visual Analogue Score (VAS) for pain assessment, QoR 15 score and use of the patient-controlled analgesia (PCA) pump. All eligible patients were kept nil per oral for solids for 8 hours and 2 hours for clear liquid and were premedicated with Tablet (Tab). Ranitidine 150 mg and Tab. Alprazolam 0.25 mg the night before, and 2 hours prior to surgery with sips of water.

On shifting the patient to the operation theatre after achieving intravenous cannulation of peripheral vein, patients were preloaded with 250 mL of Ringer's lactate. Standard ASA monitoring like ECG, noninvasive blood pressure (NIBP) and pulse oximetry (SPO2) were established. Bispectral index (BIS) (Covidien, Singapore) electrode was applied over the forehead and initial readings noted.

Anesthesia induction in all the groups was achieved with inj. fentanyl 2 mcg.kg^{-1}, inj. propofol 1–1.5 mg.kg^{-1} till loss of verbal commands, neuromuscular blockade achieved with inj. vecuronium 0.1 mg.kg^{-1} and intubation completed with an approriate sized cuffed endotracheal tube. Maintenance of anesthesia was achieved with 66% N2O in O2, infusion of test drug as per the group allotment, incremental concentration of isoflurane (MAC 08–1.0), intermittent boluses of inj. fentanyl 1 mcg.kg^{-1} (when heart rate > 20 beats from baseline) and inj. vecuronium 1 mg (as assessed by neuromuscular monitor (Drager Trident, Drager Medical system, Inc, Telford, PA, USA). Ventilation was adjusted to maintain end tidal carbon dioxide value between 35–37 mmHg. BIS maintained between 40–60. inj. paracetamol 1 g and inj. ondansetron 0.1 mg.kg^{-1} were administered 15 minutes before the end of the surgery. At the end of surgery, the respective infusions were stopped, with resumption of spontaneous effort and BIS between 80–100, achieving the TOF ratio0.9 neuromuscular blockade was reversed by administration of inj. neostigmine (0.05 mg.kg^{-1}) and inj. glycopyrollate (0.01 mg.kg^{-1}) and patient extubated and shifted to PACU.

All the patients received post-operative analgesia with fentanyl (5 µg.mL^{-1}) through IV PCA pump (B Braun Perfusor Space Pump). A total dose of fentanyl as 1.5 µg.kg^{-1}.h^{-1} was utilized, 40% of the calculated dose as continuous infusion and the remaining 60% divided into three equal doses with a lockout interval of 20 minutes. Pain with VAS > 6, an additional 25 mcg of fentanyl administered. The patients were discharged to the ward on achieving Aldrete score of ≥ 9. Postoperative analgesia for the next 24 hours was managed by PCA with fentanyl. Postoperative pain at rest was assessed at time intervals of 1, 2, 4, 12, and 24 hours postoperatively. Total fentanyl requirements in the first 24 hours were recorded. Return of bowel function was assessed by enquiring about time of passage of flatus after surgery and auscultation for bowel sounds. Patients were monitored for nausea, vomiting, itching, bradycardia, hypotension, and any other complications. A 15-point Quality of Recovery score QoR-15 was utilized for assessment on postoperative day 1, 2, and on day of discharge to assess the quality of recovery and total score calculated for each patient.

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A power analysis based on a previous study[9,10] revealed that a total sample size of 24 patients in each group was required to achieve a power of 80% and α error of 0.05 for detection of difference in VAS pain score of 1.3. Taking into account a dropout rate of 5% estimated from initial pilot observations, we aimed to include at least 120 patients in our study (30 patients in each group).

Data obtained was analyzed statistically using IBM Statistical Package for Social Sciences (SPSS) for Windows version 26 (IBM Corp., Armonk, NY). For categorical variables, the difference in proportions was assessed using the chi square test. For continuous variables, mean difference between two independent group was tested using the independent *t*-test while for more than three groups One-way Analysis of Variance (ANOVA) test was used. To check the homogeneity of variances, which is one of the assumptions in ANOVA, Levine's test used. For all variables which had a significant *p*-value of < 0.05 on ANOVA, a post hoc test was applied. For quantitative outcomes, the oneway ANOVA test was used to compare the four groups. Data are expressed as numbers, percentage, mean ± standard deviation (SD), median ± IQR and $p < 0.05$ considered as statistically significant.

Results

Ninety-six patients were recruited and randomized, and all the patients completed the study (Fig. 1). Due to inability to procure instruments for robotic surgery and COVID-19 travel restrictions, only 96 patients could be recruited

The patients were similar in their demographic profile (Table 1).

The VAS at rest were significantly lower in Groups 3 and 2 compared to Groups 1 and 4 (Table 2), and remained so during all times of observation. On comparing VAS between groups 1 and 4, a difference was observed during the first and second hour, however the difference was negligible at 4 hours and beyond. (Table 2)

Total postoperative fentanyl consumption during the first 24 hours via PCA was 256.25±16.36 mcg (95% CI: 249.34, 263.16) in Group 1, 177.71±16.81 mcg (95% CI: 170.61, 184.81) in Group 2, 114.17±16.19 mcg (95% CI: 107.36, 120.98) in Group 3 and 304.42±31.26 mcg (95% CI: 291.21, 317.62) in Group 4, respectively. The requirement was significantly reduced in Group 3 compared to the other three groups ($p < 0.001$). Post-operative fentanyl requirement was also reduced in-groups 1 and 2, compared to Group 4 ($p < 0.001$).

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Time to return of bowel function was slowest in Group 4 (34.58 ± 1.84 hours) compared to all other Groups ($p < 0.001$). Return of bowel function was significantly early in group 3 compared to groups 1 and 2 respectively ($p < 0.001$). (Table 3)

The average QoR 15 score preoperatively in all groups was almost equal. There was no statistically significant difference among the four groups ($p = 0.55$). On day 1, improved QoR 15 scores were observed in Group 3 compared to Groups 1, 2, and 4. There is no difference between Groups 1 and Group 4. A statistically significant difference was noted between the four groups in terms of QoR 15 score on Day 1 (*p*-value 0.001). On Day 2 QoR 15 score was high in the group 3 compared to other groups. A statistically significant difference was noted between the four groups in terms of QoR 15 score on Day 2 (*p*-value 0.001). On discharge day, the QoR 15 score in all groups was equal and almost reached to pre-operative QoR 15 score values (Table 4).

Complications observed in the perioperative period were hypotension in 23 patients (Group 2) and 24 patients (Group 3). Bradycardia observed in 24 patients (Group 2) and 24 patients (Group 3). None of the patients required treatment with atropine or mephenteramine. Sedation after extubation was observed in 24 patients each in Groups 2 and 3 respectively. Complications like nausea, vomiting, pruritus and hypoxia were not noted in any of the groups during in the postoperative period.

Discussion

We found that combined infusion of lignocaine and dexmedetomidine provided better recovery with improved postoperative analgesia and better quality of recovery score compared to use of lignocaine or dexmedetomidine infusion alone.

Several studies have reported that lignocaine infusion improved postoperative analgesia, reduced postoperative opioid requirement, accelerated postoperative recovery of bowel function and enhanced early rehabilitation in patients undergoing major abdominal surgery.[11-16]

Our results are similar to the above-mentioned studies. We observed reduced VAS at different point of observations, reduced postoperative fentanyl consumption, early return of bowel function and improved Quality of Recovery 15 score on Day 1 and Day 2 when compared to control group.

Herroeder et al.[17] found that lidocaine infusion significantly accelerated return of bowel function and shortened length of hospital stay by one day compared to control group. But no difference was observed in daily pain ratings between the lignocaine and

control group for patients undergoing colorectal surgeries. Herzog et al.[18] in their study observed no beneficial effects on postoperative pain, opioid sparing, bowel function return, and hospital stay after robot-assisted colorectal surgeries in patients administered intravenous lignocaine. The causes of contradictory results may be related to dose, anesthetic time, anesthetic drugs, type of surgery, surgeon experience and duration of lidocaine infusion during the perioperative period We observed that bowel function returned faster in patients receiving lignocaine infusion in the perioperative period.

Use of Alpha-2 adrenoreceptor agonists as anesthetic adjuvants in the perioperative period is increasing due to their beneficial pharmacological effects. Their use provides hemodynamic stability, decreases stress response to surgery by its central sympatholytic action and reduces anesthetic and opioid requirements.[19,20]

Bakhamees et al.[21] demonstrated that intravenous dexmedetomidine (0.8 $mcg.kg^{-1}$ bolus, 0.4 $mcg.kg^{-1}.h^{-1}$) decreased the total requirement of fentanyl and propofol requirement for maintenance of anesthesia compared to placebo ($p < 0.05$). In the postoperative period, dexmedetomidine decreased pain scores and PCA morphine use significantly and showed better recovery profile as compared to placebo group. Similar results were also demonstrated by Gurbet et al.[22] Our results were consistent with the above studies

Xu et al.[9] were the first to have used the mixture of dexmedetomidine and lignocaine for patients undergoing abdominal hysterectomy and demonstrated the effectiveness of combination compared to either lignocaine or dexmedetomidine infusion alone. Our results were similar to the study of Xu et al. in terms of reduced VAS, decreased postoperative fentanyl requirement, early bowel motility and improved quality of recovery score.

QoR is a global measure of recovery where different aspects of recovery are quantified on a Linkert scale. QoR 15 is an abridged version of QoR 40 scale first used by Myles et al.[23,24] QoR 15 measures the recovery on scale ranging from 0 to 150 with higher the score, better the recovery. Minimal clinical important difference of 8 has been accepted to be significant.

Klief et al. classified the recovery of patient based on QoR 15 score as poor, moderate, good and excellent with corresponding values of 0–89, 90–121, 122–135, 136–150 respectively.[25] Our study demonstrated better perception of psychological benefits along with decreased pain with lignocaine, dexmedetomidine or their

combination. Scores on days 1 and 2 were significantly better with dexmedetomidine+lignocaine infusion > dexmedetomidine infusion > lignocaine infusion > control. The pharmacological effects of the drugs as well as their effects on inflammation, analgesic requirement and nausea vomiting may have been responsible for these effects. In a study of use of perioperative lignocaine infusion and early QoR Wang et al. demonstrated a better QoR 40 score on day 1 and 2 in patients receiving lignocaine infusion.[26] Similar results were also observed by Koshyari et al.[27] Similarly in a meta-analysis of use of dexmedetomidine and QoR, Miao et al.[28] concluded that dexmedetomidine as anesthetic adjuvant is associated with enhanced recovery without significant risk of adverse effects.

Hemodynamic effects like hypotension and bradycardia are observed in patients receiving dexmedetomidine. These effects are attributable to inhibition of the central sympathetic outflow overriding the direct stimulating effect as well as stimulation of the presynaptic α2-adrenoceptor, leading to a decreased norepinephrine release. Postoperative bradycardia may occur in as high as 40% healthy patients who were administered dexmedetomidine. The effect is temporary and can be managed with administration of atropine or ephedrine and volume infusions. Increased sedation was observed in our group postoperatively. This maybe an effect of dexmedetomidine as well as fentanyl infusion used for postoperative analgesia

The limitations of the study were small sample size, single centric as well as use in robotic surgeries, which are associated with less pain. Studies in larger populations and varied surgeries may give data on utility of dexmedetomidine-lignocaine combination for use in opioid free anesthesia technique.

In conclusion, we state that the dexmedetomidine–lignocaine combination provides a number of advantages to patients in terms of reduced pain, patient's perception of quality of recovery. These benefits are superior to the use of either agent separately.

Conflicts of interest

The authors declare no conflicts of interest.

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Figure 1 CONSORT flow diagram for this study.

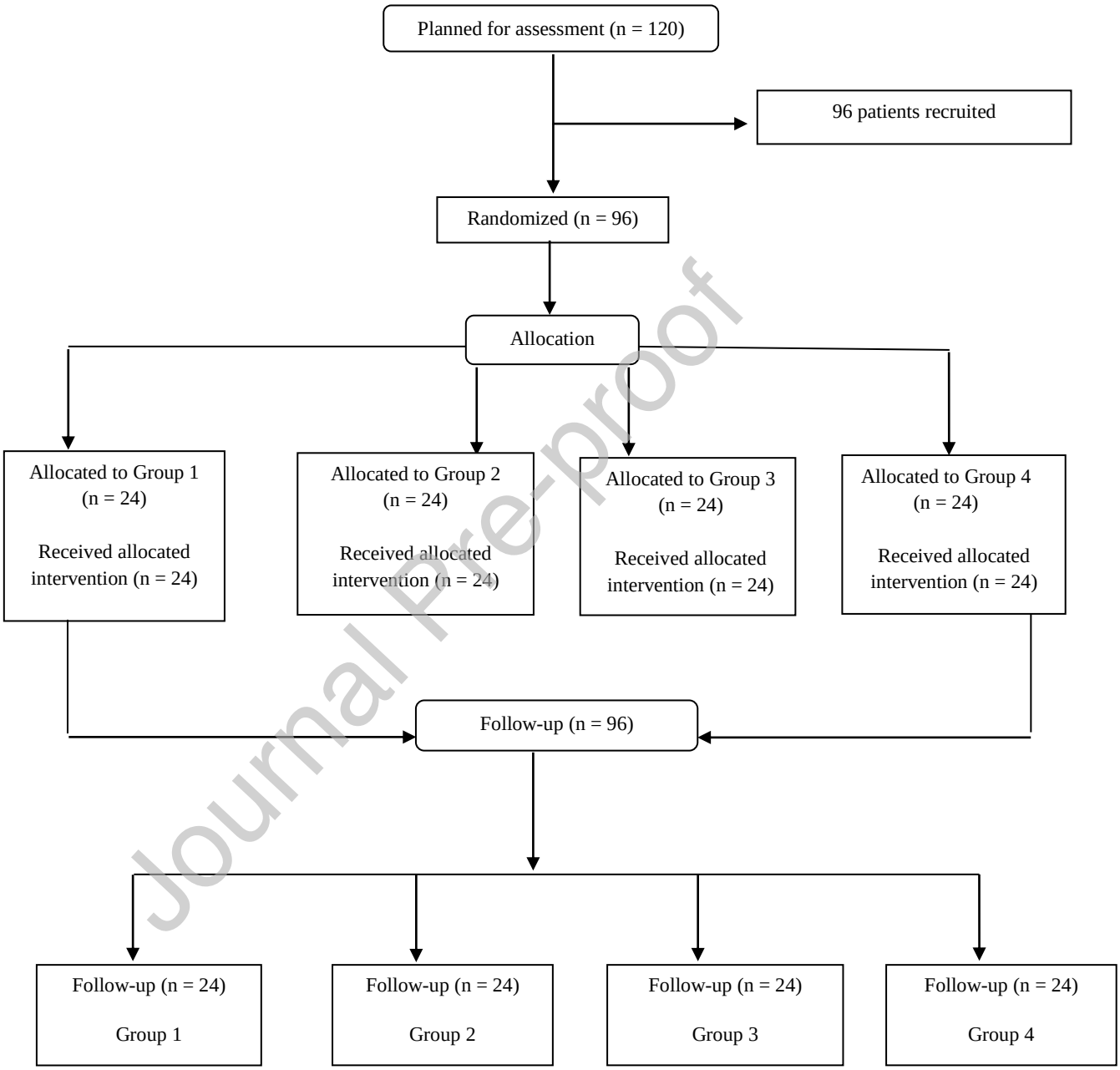

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Table 1 Demographic profile of the study populations.

Parameters	**Group 1**	**Group 2**	**Group 3**	**Group 4**	***p*-value**
Age (years)	46.42 ± 5.73	45.79 ± 5.54	45.79 ± 5.54	46.63 ± 5.19	0.47
Weight (kg)	61.96 ± 5.396	62.88 ± 8.02	61.46 ± 3.37	61.75 ± 7.49	0.88
Height (cm)	158.88 ± 5.17	160.38 ± 3.77	159.50 ± 3.79	160.63 ± 3.82	0.44

BMI ($kg.m^{-2}$)	24.57 ± 2.18	24.44 ± 2.84	24.17 ± 1.38	23.93 ± 2.81	0.79
ASA I/II	10/14	15/9	16/8	15/9	0.287

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control; ASA, American Society of Anesthesiologists physical status.

Table 2 Pain assessed by VAS at rest after the surgery.

Parameters	**Group 1 (n = 24)**	**Group 2 (n = 24)**	**Group 3 (n = 24)**	**Group 4 (n = 24)**	***p*-value**
VAS at 1st Hr	5.0 ± 1.0	4.0 ± 0.0[a]	3.0 ± 0.0[a,b]	6.0 ± 1.0[a,b,c]	0.00
VAS at 2nd Hr	4.0 ± 0.0	3.0 ± 0.0[a,b]	2.0 ± 0.0[a,b,c]	4.50 ± 1.0[a]	0.00
VAS at 4th Hr	3.0 ± 1.0	2.0 ± 1.0[a,b]	1.0 ± 1.0[a,b,c]	3.50 ± 1.0	0.00
VAS at 12th Hr	2.0 ± 0.75	1.0 ± 1.0[a,b]	1.0 ± 0.0[a,b,c]	2.0 ± 1.0	0.00
VAS at 24th Hr	1.0 ± 1.0	1.0 ± 0.0[a,b]	0.0 ± 0.0[a,b,c]	1.0 ± 1.0	0.00

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.

[a] Group 1 vs. Groups 2, 3, 4.

[b] Group2 vs. Groups 3, 4.

[c] Group 3 vs. Group 4.

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Table 3 Resumption of Bowel function recovery among the groups.

Parameter	**Group 1 (n = 24)**	**Group 2 (n = 24)**	**Group 3 (n = 24)**	**Group 4 (n = 24)**	***p*-value**
Bowel function recovery (h)	30.38 ± 1.66[a]	26.15 ± 0.74[a,b]	22.65 ± 0.78[a,b,c]	34.58 ± 1.84	0.00

Data are presented as mean ± standard deviation.

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.

[a] Group 1 vs. Groups 2, 3, 4.

[b] Group 2 vs. Groups 3, 4.

[c] Group 3 vs. Group 4.

Table 4 Comparision of QoR 15 score among the groups.

Parameters	**Group 1 (n = 24)**	**Group 2 (n = 24)**	**Group 3 (n = 24)**	**Group 4 (n = 24)**	***p*-value**
QoR 15 preop	144 ± 3.0	144 ± 3.0	145 ± 3.0	144.5 ± 2.0	0.76
QoR 15 Day1	98.0 ± 3.0	107.5 ± 5.0[a,b]	126.0 ± 4.0[a,b,c]	87.0 ± 6.0	0.001
QoR 15 Day 2	122.5 ± 7.0	130.5 ± 4.0[a]	139.0 ± 2.0[a,b,c]	109.5 ± 6.0[a,b]	0.001
QoR 15 Discharge Day	143.0 ± 2.0	143.5 ± 2.0	145.0 ± 2.0	142.0 ± 3.0	0.65

Group 1, Lignocaine; Group 2, dexmedetomidine; Group 3, lignocaine + Dexmedetomidine; Group 4, control.

[a] Group 1 vs. Groups 2, 3, 4.

[b] Group 2 vs Groups 3, 4.

[c] Group 3 vs. Group 4.

Journal Pre-proof