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Can intravenous lidocaine definitely attenuate propofol requirement and improve outcomes among colonoscopic patients under intravenous sedation?

A double-blinded, randomized controlled trial

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Abstract

Background: Propofol-sparing effect of lidocaine has not been fully elucidated because propofol is usually mixed with many medications in anesthetic practice. Therefore, the study aimed to verify the additive effect of intravenous lidocaine to propofol without other sedative medications and control the depth of anesthesia using the bispectral index (BIS) during colonoscopy in a prospective, randomized, double-blinded controlled trial.

Methods: Sixty-eight patients scheduled and undergoing colonoscopy were randomly allocated to receive intravenous lidocaine (1.5 mg/kg then 4 mg/kg/h) (Group L) or a similar volume of normal saline (Group C) with propofol administration guided by BIS monitoring. The primary outcome was total propofol requirements between group comparisons. The secondary outcomes included the number of hypoxemic periods, hemodynamic changes, duration in returning of BIS > 85, sedation scores, pain scores, postoperative opioid requirement, and patient satisfaction between group comparisons.

Results: Intravenous lidocaine showed significantly reduced total propofol use (151.76 ± 50.78 mg vs 242.06 ± 50.86 mg, Group L vs Group C, respectively, $P < .001$). Duration in returning to BIS > 85, sedation scores, and patient satisfaction scores were significantly superior in Group L ($P < .05$). The number of hypoxemic episodes, changes of hemodynamic response, pain scores, and postoperative opioid requirement were similar in both groups. No adverse effects were detected in both groups.

Conclusion: Intravenous lidocaine produced a definitely effective reduced propofol requirement without other sedative agents and improved outcomes including patient satisfaction, duration in returning to BIS > 85, and sedation score during colonoscopy without adverse effects.

Abbreviations: BIS = bispectral index, GPES = global perceived effect scales, IQR = interquartile range, MAP = mean arterial pressure, PACU = postanesthetic care unit, VNRS = verbal numerical rating score scale.

Keywords: bispectral index, colonoscopy, lidocaine, monitoring, propofol

1. Introduction

Colonoscopy is one of the approved procedures endorsed to assess colorectal cancer following national guidelines and cost-effectiveness.[1,2] However, abdominal pain or discomfort is a common patient concern during procedures due to colonic traction or distension result in stimulating visceral nociceptive receptors in the colon.[3] Most of the patients could not tolerate colonoscopy with no sedation especially complex procedure such as biopsy, removal of foreign bodies, stricture management, or fistula management which determined a longer procedure time.[4] Therefore, intravenous sedation has accommodated a role for alleviating burdened symptoms.[5] In the past decade, many sedative medications such as midazolam or ketamine have been provided.[6] However, propofol has become popular for intravenous sedation in modern situations owing to short onset and duration.[5,7] Unfortunately, hypotension and bradycardia are common propofol adverse effects.[5,8] Therefore, the reducing dosage of propofol should produce better outcome. Related studies have combined propofol with other medications such as midazolam, ketamine, or dexmedetomidine to anticipate propofol sparing effects.[9–13]

Presently, lidocaine is one of the common medications combined with propofol and providing several benefits.[13–15]

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Trial Registration: Thai Clinical Trials Registry (TCTR20210517001).

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For instance, antinociceptive effects during surgical stimulation[16,17] reduced the colonic distension reflex,[3,4] diminished intraoperative volatile consumption,[18,19] and proved beneficial to postoperative pain, fatigue, bowel function, fentanyl-induced cough, and hospital stay regarding various procedures.[17,21–26] One related study showed adding intravenous lidocaine to propofol with ketamine significantly reduced the propofol requirement[13] in which ketamine has been reported for opioid sparing and antinociceptive effects from blocking N-Methyl-D-Aspartate receptors[27,28] resulting in impeding only lidocaine effects. Moreover, those effects did not control the depth of anesthesia using the bispectral index (BIS).[13] Consequently, this study aimed to validate synergistic effects of intravenous lidocaine to propofol infusion without other sedative medications and investigated adverse effects in controlling depth of anesthesia using the BIS during colonoscopy in a prospective randomized trial.

2. Methods

This prospective, randomized, double blind, placebo-controlled study was conducted at Phramongkutklao Hospital and College of Medicine. All patients were enrolled and provided informed consent from July 2021 to December 2021. The study protocol was approved by the Institutional Review Board of the Royal Thai Army Medical Ethics Committee and registered with the Thai Clinical Trials Registry (TCTR20210517001).

2.1. Participants

Sixty-eight patients were scheduled for colonoscopy under intravenous sedation. The inclusion criteria involved patients aged 20 to 80 years with the American Society of Anesthesiologists physical status I-III. Patients were excluded when they exhibited severe cardiovascular and pulmonary diseases, liver or renal insufficiency, mental disorders, language barrier, history of colectomy, or history of being allergic to lidocaine.

2.2. Randomization and blinding

All participants were categorized in two blinded groups using a block of four, computer-generated, randomized table, and concealed envelopes. The first independent anesthesiologist opened sequential numbers and prepared syringes in normal saline (Group C) and lidocaine (Group L). The second blinded anesthesiologist provided intravenous sedation as the study protocol and all outcomes were assessed and recorded using a third anesthesiologist blinded to the study. All participants were blinded to receive either Group C or L.

2.3. Procedures

Colonoscopy was performed as a 1-day surgery under intravenous sedation. An intravenous isotonic balanced solution was administered on arrival at the preoperative unit. Pulse oximetry, mean arterial pressure (MAP), electrocardiography, and the BIS were monitored upon arrival in the operating theater at baseline and then every 5 minutes during the operation. All patients were assigned in the left lateral position and provided oxygen supplement under partial rebreathing mask with oxygen flow at 6 L/min before intravenous sedation. The lidocaine dosage protocol was established from related studies[13,14] in which 1.5 mg/kg of lidocaine intravenous was injected over 10 seconds before intravenous sedation followed by 4 mg/kg/h of lidocaine infusion throughout the intraoperative period in Group L. Patients in Group C imitated the bolus and intravenous infusion of normal saline with similar dosage and infusion rates as Group L. Intravenous 1.2 mcg/kg of fentanyl was administrated for analgesia premedication and then intravenous sedation was titrated with 0.5 mg/kg of propofol until the BIS value was less than 65. The depth of anesthesia was controlled at a range of BIS level from 55 to 65. The bolus dose of propofol, 20 to 30 mg, was titrated when BIS level increased more than 65. All anesthetic medications were discontinued after completing procedures and patients were transferred to the postanesthetic care unit (PACU) after recovering full consciousness and BIS > 85.

2.4. Outcome measures

The primary outcome was a comparison of total dosage of intravenous propofol between groups. The secondary outcomes were a comparison of hemodynamic variations, episodes of oxygen desaturation (defined as pulse oximetry less than 92%), the duration of full consciousness and prompt response to the PACU (defined as able to follow commands and BIS > 85). The sedative level was evaluated on arrival at the PACU based on the Ramsay sedation scale (1: anxious, agitated, or restless; 2: cooperative, oriented, and tranquil; 3: responds to commands but is asleep; 4: brisk response to glabellar tap or loud noise; 5: a sluggish response to light glabellar tap or loud noise, and 6: no response). Patient satisfaction was assessed at 1 hour post-colonoscopy using global perceived effect scales (GPES) on a 7-point scale (question: how would you rate your satisfaction with this anesthetic procedure? grade 1: very dissatisfied, 2: somewhat dissatisfied, 3: slightly dissatisfied, 4: neither satisfied nor dissatisfied, 5: slightly satisfied, 6: somewhat satisfied, and 7: very satisfied).[29] Average verbal numerical rating score scale (VNRS; 0–10) and opioid requirement while in the PACU, adverse effects of lidocaine such as drowsiness, lightheadedness, metallic taste, visual disturbances or perioral numbness,[29] and surgical complications were compared between groups.

2.5. Statistical analyses

The sample size was calculated based on the related study of Forster et al,[13] showing averaged total dosage of propofol in the lidocaine group was 58 mg ± 47, whereas average total dosage of propofol in the placebo group was 121 mg ± 109. The result implied 28 patients were required for each group to reach a significance level of 0.05; the power of study was set at 80%, and we added 20% for loss to follow-up. The final number of participants totaled at least 34 per group. Descriptive statistics for continuous variables, presented as mean and standard deviation, was performed using the independent *t* test. Categorical variables were assessed using the chi-square test. The duration of recovering full consciousness was shown as median and interquartile range (IQR) and compared using the Mann–Whitney test. All data were analyzed using SPSS, Version 26.0 (IBM Corp. Released 2011, IBM SPSS for Windows, Armonk, NY). A P value < .05 was considered statistically significant.

3. Results

Seventy patients were primarily enrolled and two patients were excluded due to uncontrolled hypertension on the day of colonoscopy (Fig. 1). In all, 68 patients completed this study. No significant differences were observed between the 2 groups ($P > .05$), regarding baseline characteristics including sex, age, BMI, American Society of Anesthesiologists classification, VNRS, colonoscopic time, and MAP as shown in Table 1.

The study found the average initial dosage of propofol in Group L (46.32 ± 11.37 mg) was significantly lower than that in Group C (66.91 ± 7.98 mg), $P < .001$. The mean supplemental dose of propofol was significantly reduced in Group L (105.44 ± 43.7 mg vs 175.15 ± 46.65 mg in Group L vs Group C, respectively, $P < .001$). Moreover, the study showed a significantly reduced average total propofol requirement in Group L

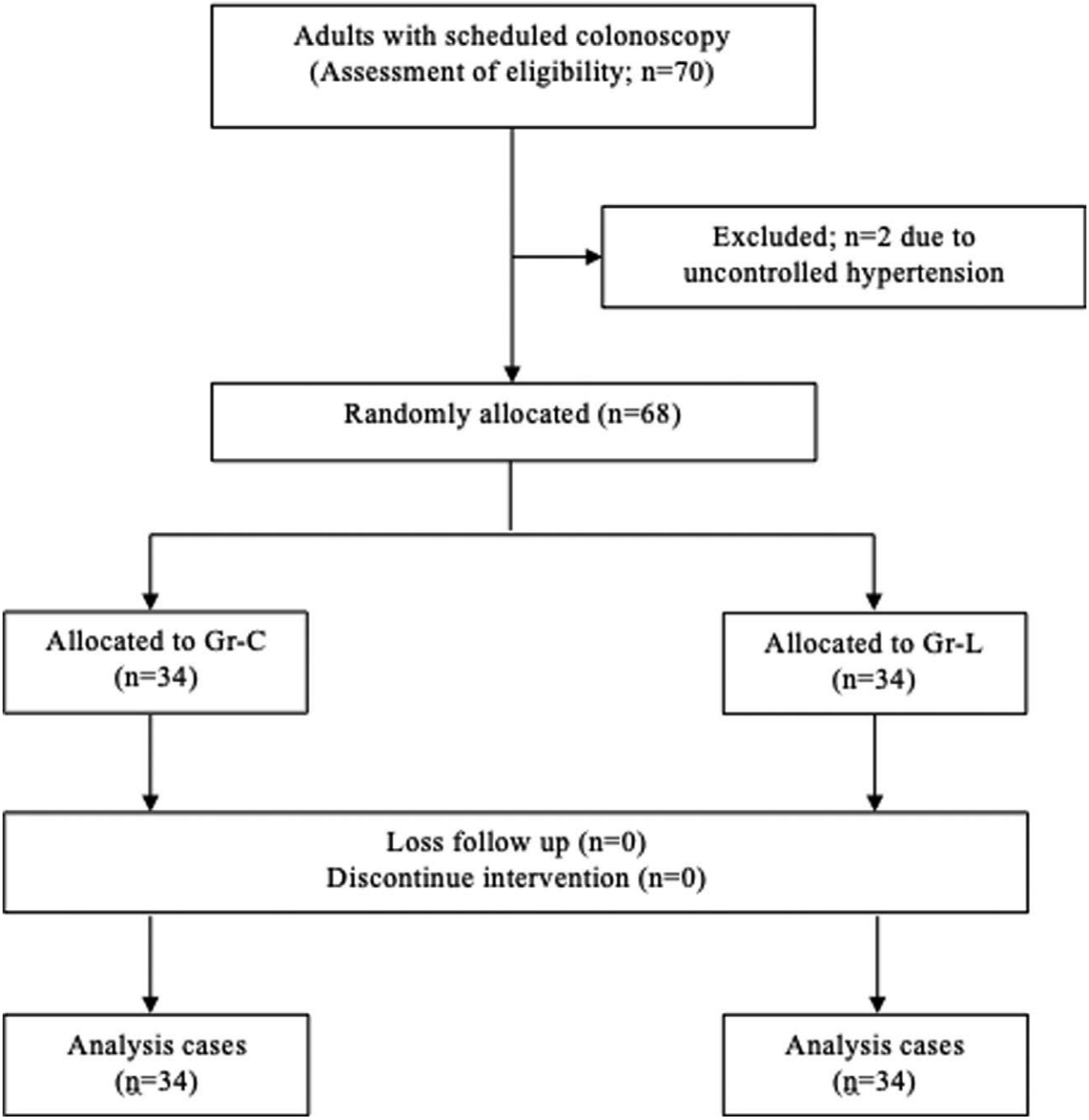

Figure 1. Procedure flowchart. Groups are defined in method under sample size calculation and randomization.

(151.76 ± 50.78 mg) compared to Group C (242.06 ± 50.86 mg), $P < .001$ (Table 2).

MAP decreased from baseline after anesthetic induction in both groups. Group C showed a greater decrease of MAP than Group L throughout colonoscopic times. However, no significant difference was found between group comparisons ($P > .05$) (Table 3). No significant difference was displayed in average total intravenous fluid replacement between group comparisons (433.53 ± 124.78 mL vs 382.06 ± 134 mL in Group L vs Group C, respectively, $P = .106$). However, Group L showed significantly less ephedrine administration than Group C (0.88 ± 2.16 mg vs 3.26 ± 5.34 mg in Group L vs Group C, respectively $P = .02$ (Table 2).

One patient in Group L and 5 patients in Group C reported only mild pain (VNRS = 1). However, no difference was found between group comparisons, $P > .99$. Only 2 patients (5.9%) in Group L and 4 patients (11.8%) in Group C experienced oxygen desaturation below 92% but without statistical difference as observed between the two groups, $P = .393$. Group L showed significantly rapid return to BIS > 85 than Group C (1 minute IQR (1, 2) vs 2 minutes IQR (1, 3) in Group L vs group C, respectively, $P = .001$) (Table 2).

Moreover, Group L showed a significantly greater percentage of patients who were more cooperative than Group C regarding Ramsay score ($P < .001$). In all, 32 patients (94.1%) in Group L and 14 patients (41.2%) in Group C had Ramsay score = 2. Altogether, 2 patients (5.9%) in Group L and 17 patients (50%) in Group C had Ramsay score = 3, and only 3 patients in Group C had Ramsay score = 4 (Table 4). However, Ramsey sedation scores of 1, 5, or 6 were not found in both groups. Furthermore, patients in Group L showed significantly higher satisfaction levels than patients in Group C regarding GPES scores (GPES = 7; very satisfied: 29 (85.3%) vs 18 (52.9%) and GPES = 6; somewhat satisfied; 5 (14.7%) vs 16 (47.1%) in group L vs. C, respectively, $P < .004$) (Fig. 2). GPES scores less than 5 or dissatisfaction was not found in both

Table 1

Patient characteristics at baseline.

Characteristics	Group C n = 34(%)	Group L n = 34(%)	*P* value
Sex, n (%)			
Male	18 (52.9%)	16 (47.1%)	.628
Female	16 (47.1%)	18 (52.9%)	
Age (yr)	63.56 (11.82)	63.88 (11.24)	.908
Body weight (kg)	64.18 (11.78)	61.32 (10.79)	.302
Height (cm)	165.65 (7.68)	165.03 (6.63)	.724
BMI (kg/cm^2)	23.23 (3)	22.48 (3.46)	.341
ASA			
Class I	6 (17.6%)	6 (17.6%)	1.000
Class II	28 (82.4%)	28 (82.4%)	
Colonoscopy time (min)	26.91 (8.44)	29.56 (10.54)	.257
Baseline MAP (mm Hg)	93 (9.62)	94.681 (0.29)	.490

All values are reported as mean (standard deviation) unless specified otherwise.
ASA = American Society of Anesthesiologists, BMI = body mass index, MAP = mean arterial pressure.

Table 2

Intraoperative results between groups comparison.

	Group C n = 34(%)	Group L n = 34(%)	*P* value
Initial propofol (mg)	66.91 (7.98)	46.32 (11.37)	<.001*
Supplemental propofol (mg)	175.15 (46.55)	105.44 (43.7)	<.001*
Total propofol (mg)	242.06 (50.86)	151.76 (50.78)	<.001*
Total fluid replacement (mL)	382.06 (134)	433.53 (124.78)	.106
Ephedrine(mg)	3.26 (5.34)	0.88 (2.16)	.020*
Hypoxemia (n,%)	4 (11.8%)	2 (5.9%)	.393
Duration of BIS > 85 min, median (IQR)	2 (1, 3)	1 (1, 2)	.001*

All values are reported as mean (standard deviation) unless specified otherwise.
BIS = bispectral index, IQR = interquartile range.

Table 3

Intraoperative mean arterial pressure between groups comparison.

MAP at each time points	Group C n = 34(%)		Group L n = 34(%)		*P* value
	Mean (SD)	Change (95% CI)	Mean (SD)	Change (95% CI)	
Baseline	93 (9.62)	Reference	94.68 (10.29)	Reference	1
5 min	72.76 (8.95)	–20.24 (–24.41, –16.06)	78.38 (11.44)	–16.29 (–21.08, –11.51)	.224
15 min	73.26 (7.31)	–19.74 (–23.91, –15.56)	77.32 (8.81)	–17.35 (–22.13, –12.57)	.462
The end	76.74 (9.62)	–16.26 (–20.44, –12.09)	79.68 (10.13)	–15 (–19.78, –10.22)	.696

CI = confidence interval, MAP = mean arterial pressure, SD = standard deviation.

Table 4

Ramsay sedation score in PACU between groups comparison.

Ramsay sedation score in PACU	Group C n = 34(%)	Group L n = 34(%)	*P* value
2	14 (41.2%)	32 (94.1%)	<.001*
3	17 (50%)	2 (5.9%)	
4	3 (8.8%)	0 (0%)	

2 = co-operative, oriented, and tranquil, 3 = responds to commands but is asleep, 4 = brisk response to glabellar tap or loud noise, PACU = postanesthetic care unit.

groups. Moreover, no patient reported pain or required pain medication after procedure.

In addition, no serious side effects including neurologic or cardiogenic events and surgical complications were reported during the course of the study.

4. Discussion

This constituted the first prospective study to demonstrate the additive effects of lidocaine plus propofol without other sedative medications and controlled depth of anesthesia using the BIS, which prior studies referred BIS values between 40 and 60 represent adequate general anesthesia and the range of BIS values between 60 and 80 show optimal intravenous sedation including colonoscopy.[30,31] However, the target of 60 to 80 is huge wide range and this should impact the standard deviation of the propofol consumption. Therefore, the study used such narrow wide range of 55 to 65, which precisely controlled depth of anesthesia.

A significant reduction was found in both initial, supplement, and total dose of propofol in Group L according to the mechanism of lidocaine demonstrating inhibition of voltage-gated sodium channels and deactivating of excitatory neurons resulting in an antinociceptive effect.[13,17,32]

The study found an almost 38% reduction of total propofol in Group L while Forster et al showed a 50% reduction of the propofol requirement which might have resulted from a study combining propofol with ketamine and monitored depth of anesthesia by clinical observation separately.[13] Ketamine produced an antinociceptive effect from N-Methyl-D-Aspartate antagonists and has been proved to exhibit propofol sparing effects,[27,28] resulting in hindering of actual lidocaine effects. Moreover, a related study showed lidocaine had significantly reduced supplemented dosage of propofol similar to this study but without a significant decrease in the total dosage of propofol among elderly patients.[14] This might have stemmed from aged subjects presenting fewer anesthetic requirements during the maintenance period, very short colonoscopy time (12–13 minutes), and inspected depth of anesthesia using clinical observation separately without BIS monitoring.[14]

However, the study did not only perform diagnosis but also procedure of biopsy, removal of foreign bodies, stricture management or fistula management, which determined a longer procedure time of almost 30 minutes and controlled depth of anesthesia using the BIS, which could have precisely described propofol consumption between both groups.

The study showed lower ephedrine use in Group L corresponding to lower propofol requirement when combined with lidocaine. However, no significant difference was found in MAP between groups throughout the colonoscopic time similar to a related study,[14] which might have stemmed from the optimum fluid and ephedrine replacement in both groups.

Moreover, the study showed lower incidence of episodes of hypoxemia in both groups (5.9% in Group L and 11.8% in Group C) compared to 25% of patients from a related study[13] because all patients were provided partial rebreathing masks with a reservoir bag and BIS monitoring while Foster et al[13] demonstrated only oxygen cannula without BIS monitoring.

The number of patients in Group L reporting pain in the recovery period was less than patients in Group C similar to Forster et al.[13] None of the patients requested pain medication during the recovery period that might have stemmed from mild pain (VNRS = 1), no long procedure, adequate analgesic premedication, and gentle application of the colonoscopy probe supervised by an experienced surgeon.

Furthermore, the patients in Group L showed significantly more cooperation and satisfaction than Group C similar to related studies showing lidocaine produced a propofol sparing

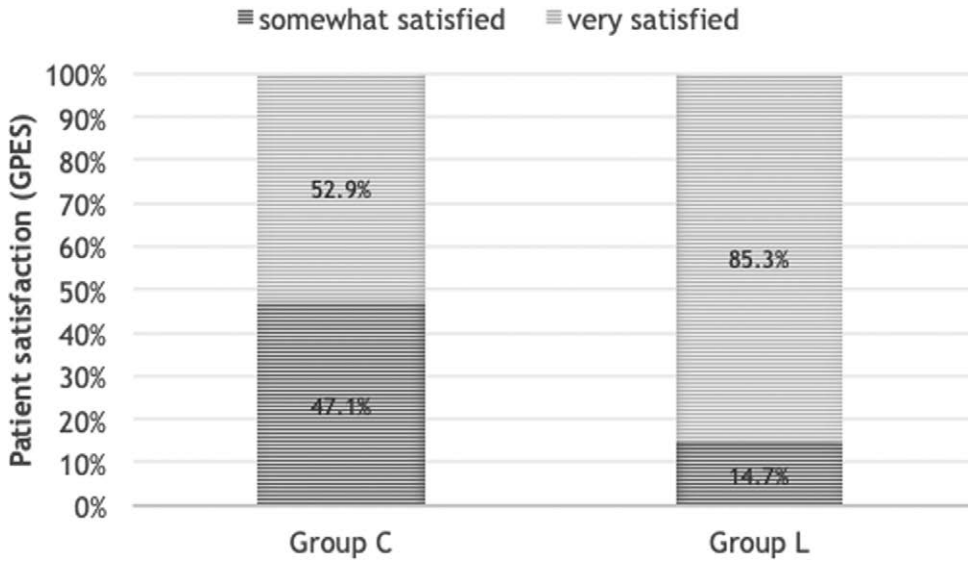

Figure 2. Patient satisfaction, which assessed at 1 hour post-colonoscopy by global perceived effects on a 7-point scale (GPES).

effect, reduced postoperative fatigue, and improved the quality of recovery after surgery.[13,18,22,33] Therefore, anesthesiologist and endoscopist can adapt this synergistic effect to normal practice without BIS monitoring.

4.1. Limitations

Firstly, the study did not demonstrate plasma lidocaine concentration. Therefore, it could not be established that concentrations were preserved within the therapeutic range. However, the usual dosage of lidocaine was similar to related studies,[13,14] and none of the patients presented adverse effects. Secondly, electronic recording of BIS values was not available which these values are not recorded in the study, in which BIS values fluctuated throughout the procedure. The study found decreasing BIS values less than 40 in the initial phase of induction that might have resulted from excessive initial dose of propofol and some patients awoke earlier regardless of exhibiting a BIS < 85 nearly at the end of anesthetic time. Consequently, the attending anesthesiologist must augment a tremendous dose of propofol. However, BIS values were controlled ranging from 55 to 65 overall. Thirdly, the study provided partial rebreathing mask might be resulted in lower incidence of episodes of hypoxemia although most of intravenous sedation can performed by nasal cannula. Finally, colonoscopy was not provided by only one endoscopist, which might have affected the procedural stimuli, operative times, and propofol requirement. However, an experienced surgeon supervised all procedures.

5. Conclusion

Intravenous lidocaine produced a definitely effective reduced propofol requirement without other sedative agents and improved outcomes including patient satisfaction, duration in returning to BIS > 85, and sedation score during colonoscopy without adverse effects.

Author contributions

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