Application of intravenous lidocaine in patients undergoing operative hysteroscopy: a randomized, double-blind, controlled study

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Research Article

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Abstract

Background: The role of intraoperative intravenous lidocaine infusion has been previously evaluated for pain relief, inflammatory response, and post-operative recovery, including in endoscopic surgery. The present study is a randomized double-blinded trial in which we evaluated whether intravenous lidocaine infusion would reduce postoperative pain, propofol requirement and remifentanil consumption in patients undergoing hysteroscopy surgery.

Methods: Eighty-five patients scheduled to undergo elective operative hysteroscopy surgery under general anesthesia were randomized into two groups. Group L included patients who received an intravenous lidocaine bolus 1.5mg/kg over 3 min followed by a continuous infusion at the rate of 2 mg/kg/h until surgery completed, and Group C received 0.9% normal saline solution at an equivalent rate. The depth of anesthesia was monitored using the Narcotrend, which was based on measurement of the patient's cerebral electrical activity. Primary outcome of the study was postoperative hypogastric pain evaluating by visual analogue scale (VAS). Secondary outcomes include propofol requirement and remifentanil requirement.

Results: VAS score of Group L was significantly lower than Group C at postoperative 0.5 h, 4 h, respectively ($P < 0.05$), while no obvious difference was found at postoperative 24 h. There was no difference between groups in propofol requirement, but Group L required less dosage of remifentanil than Group C ($P < 0.05$). Moreover, the incidence of throat pain was significantly lower in Group L. No adverse events associated with lidocaine was discovered.

Conclusions: Administration of intravenous lidocaine infusion as an adjuvant alleviated short-term postoperative hypogastric pain and throat pain, and reduced remifentanil requirement in patients undergoing operative hysteroscopy surgery.

Trial registration: Chinese Clinical Trial Registry (chictr.org.cn) with registration number ChiCTR1800016857.

Keywords: Lidocaine, hysteroscopic surgery, remifentanil, propofol

Introduction

Operative hysteroscopy is usually done under general anesthesia (GA) in our hospital, which offer advantages to physicians and patients. For physicians, GA will help them reduce potential difficulty of uterine access compared with local anesthesia. For patients, GA will reduce the experience of pain during operative hysteroscopy procedures[1]. The main cause of pain is that local anesthesia cannot block completely innervation of the uterus[2-3]. However, postoperative pain, delayed recovery, and anaphylactic reactions may complicate GA and increase the operative risk.

Intraoperative lidocaine infusion has become widely accepted as an adjuvant of GA, and it has been associated with opioid-sparing, pain relief, reduced post-operative nausea and vomiting and enhanced recovery. Recently, intravenous lidocaine infusion has been shown to reduce postoperative pain and opioid requirement among patients undergoing endoscopic submucosal dissection (ESD)[4]. Similar to ESD, operative hysteroscopy is also an endoscopic surgical procedure of natural lumens. To the best of our knowledge, data on the efficacy of intravenous lidocaine in operative hysteroscopy is sparse.

We hypothesized that the administration of intravenous lidocaine reduces postoperative pain, propofol requirement and remifentanil requirement in patients undergoing operative hysteroscopy.

Methods

Study population

The study protocol was approved by the hospital ethics committee of Renmin Hospital of Wuhan University and was registered at http://www.chictr.org.cn (registration number: ChiCTR1800016857). Written informed consent was obtained from 85 patients classified American Society of Anesthesiologists (ASA) I-II undergoing operative hysteroscopy. Patients were excluded if they met one of the following criteria: less than 18 years old, hypersensitivity to lidocaine, only performing diagnostic hysteroscopy, chronic abuse of opioid or nonsteroidal anti-inflammatory drug, chronic pain, misunderstanding of oral information about the study, other severe systemic diseases, or serious surgical complications.

Study group

Patients were categorized into two study groups using a random number table method by an independent anesthetist (IA) not involved in the treatment or follow-up of patients. The study drugs were prepared in syringes of identical appearance by the same IA as follows: 20-mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the bolus) and 50-mL syringe contained 1% lidocaine solution or 0.9% normal saline solution (for the continuous infusion). The treatment and follow-up anesthetist were all blinded to patient assignment until analysis completion. When the patient has abnormal conditions (such as serious complications) during the trial, and needs to cease blinding, the IA will cease blinding.

Interventions

Patients in the lidocaine group (Group L) received intravenous lidocaine as a bolus dose of 1.5 mg/kg over 3 minutes before anesthesia induction, followed by a continuous infusion at a rate of 2 mg/kg/h until the end of the surgery. Patients in the control group (Group C) received 0.9% normal saline solution

at an equivalent rate. All patients received the same anesthetic protocol without premedication. Standard monitoring consisted of five-lead electrocardiography, oxygen saturation, noninvasive blood pressure and Narcotrend (NT) monitoring. Anesthesia was induced with propofol 2.5 mg/kg, then remifentanil 1.5 μg/kg within one minute followed by placing the laryngeal mask (Lubricated with sterile paraffin oil). Patients were given mechanical ventilation or convert to assisted ventilation when patients resumed spontaneous breathing. Anesthesia was maintained with continuous remifentanil and propofol infusion. Remifentanil was adjusted at a rate of 5-10μg/kg/h, and propofol was adjusted the rate according to the following Narcotrend Index (NTI) target values: during maintenance in a range of 37-64; 5 min before the end of surgery in a range of 65-79. In case of intraoperative patient movement, additional remifentanil (1 μg/kg) was injected immediately.

Outcomes and adverse events observation

Mean blood pressure (MBP), heart rate (HR) and NTI were collected at 6 separate time points: before intravenous lidocaine (T0), before anesthesia induction (T1), 5 and 10 min after surgery (T2 and T3), the end of surgery (T4), the time to remove the laryngeal mask (T5). The total administered doses of remifentanil and propofol were recorded. Postoperative hypogastric pain at rest was evaluated at 0.5 h (T6), 4 h (T7), and 24 h (T8) after surgery by visual analogue scale (VAS, 0 = no pain, 10 = unbearable pain). In case of VAS ≥ 6, 50 mg intravenous flurbiprofen was injected. The incidence of throat pain was assessed using VAS within 24 hours after surgery (any VAS ≥ 2 considered to be sore throat). The incidence of postoperative nausea or vomiting was also recorded up to 24 hours after the procedure.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 6 (GraphPad Software Inc.). Quantitative variables were expressed as mean ± standard deviation (SD); Categorical variables were presented as count (%). The unpaired *t* test and Fisher's exact test were used for statistical analysis. *P* values less than 0.05 was considered to represent a statistically significant difference.

Results

The study flowchart was shown in Figure 1. Of 98 patients assessed for eligibility, 85 patients were enrolled and randomly assigned to the study groups. Five patients (2 in Group L and 3 in Group C) were eliminated from the analysis for only performing diagnostic hysteroscopy or uterine perforation. Patient characteristics and surgery time were similar between the groups (Table 1). For MAP, HR and NTI at the corresponding time points, no significant difference was found between the groups (Figure 2).

Data related to drug administration, VAS and events after surgery were presented in Table 2. The total administered dose of propofol was lower in Group L, but this result was not significant ($P = 0.192$). The total administered dose of remifentanil was 13% lower in Group L than in Group C (236.40 ± 40.78 vs. 270.50 ± 47.38 μg, mean ± SD; $P < 0.001$). No significant difference was identified in VAS of 24 h (T8; $P = 0.111$), but there was significant difference in postoperative 0.5 h and 4 h (T6 and T7) between groups, respectively ($P < 0.05$). No patient was given flurbiprofen after surgery. Plasma levels of lidocaine were not analyzed, but we counted the total dosage of lidocaine each patient in Group L (133.02 ± 22.11 mg), and no patient receiving lidocaine reported subjective symptoms of local anesthetic systemic toxicity. Fewer patients in Group L complained of throat pain (22.5% vs. 47.5%, $P = 0.034$). Both groups did not differ with respect to the incidence of nausea or vomiting ($P > 0.05$).

Discussion

In this randomized, double-blind, placebo-controlled trial, intravenous lidocaine administered as a bolus of 1.5 mg/kg and then as a continuous infusion of 2 mg/kg/h during operative hysteroscopy reduced the severity of earlier postoperative hypogastric pain as well as the incidence of throat pain. Moreover, lidocaine administration reduced the remifentanil requirement during operative hysteroscopy.

Lidocaine infused intravenously has shown effectiveness in controlling postoperative pain[5]. The analgesic mechanisms of intravenous lidocaine are multifactorial, including a sodium channel blockade, a reduction in spinal cord sensitivity and a synergic effect with the general anesthetic agents[6]. The analgesic efficacy of intravenous lidocaine has been observed mostly in abdominal surgeries, including colectomy[7], gastrectomy[8], and cholecystectomy[9]. Moreover, Kim et al. confirmed the postoperative analgesic effects of intravenous lidocaine after ESD[4], a kind of endoscopic surgical procedure of natural lumens, which is similar to operative hysteroscopy. In this same study, it was speculated the analgesic effects of lidocaine were mainly for visceral pain[4]. Therefore, we hypothesized that intravenous lidocaine would be beneficial for controlling visceral pain from operative hysteroscopy. In our study, administration of intravenous lidocaine resulted in reduction of earlier postoperative hypogastric pain intensity and less remifentanil consumption during operative hysteroscopy, which was consistent with a previous report that lidocaine infused intravenously had an impact on pain scores in the early postoperative phase[10]. It was confirmed that the half-life of lidocaine was only 1.5-2 hours after bolus injection or infusion lasting less than 12 hours[11]. This may contribute to the reason why analgesic effect was noted at earlier postoperative but not at 24 hours in our results.

The NTI determined by the Narcotrend monitoring system is a dimensionless continuous variable scored from 0 to 100 that reflects the depth of anaesthesia. Based on the NTI, the depth of anaesthesia is from stage A (awake) to stage F (very deep anesthesia), with stage D (37-64) indicating the routine depth of anaesthesia for surgery. Previous studies reported that intravenous lidocaine had a propofol sparing effect during GA [12-13]. In this study we ensured that each patient was at a consistent anesthetic depth

by Narcotrend monitor. The results of this study indicated that intravenous use of lidocaine could reduce the amount of propofol, but there was no significant difference. The reason may be short hysteroscopic procedure time, resulting in insufficient observation time.

Remifentanil is the drug of choice for endoscopy because of its rapid onset and offset of action, and minimal adverse effects on cardiovascular and respiratory parameters[14]. To observe postoperative earlier analgesic effect of intravenous lidocaine, another advantage of remifentanil is the ability to avoid interference of using other opioid drugs. Administration of intravenous lidocaine was shown to have an opioid sparing effect during GA, including fentanyl[15], sufentanil[16] and morphine[17]. Recent studies showed that a remifentanil sparing effect of intravenous lidocaine in the intraoperative period was found[18], which was consistent with our findings. However, another study reported that perioperative intravenous lidocaine infusion had no significant effect on remifentanil requirement during hypotensive anesthesia for elective transsphenoidal endoscopic hypophyseal adenoma excision procedure [19]. This difference was likely due to the distinct types of surgery performed and different anesthesia management regime.

We used the laryngeal mask for mechanical ventilation to assure the respiratory safety of patients in this study. On the other hand, the placement of the laryngeal mask also provided another way for us to observe the analgesic effect of lidocaine. Administration of intravenous lidocaine reduced the incidence of throat pain caused by placing the laryngeal mask from 47.5% to 22.5% in this study. Our observations were in line with several studies that administration of IV lidocaine was effective in reducing throat pain after endoscopic submucosal dissection[4] and postoperative sore throat caused by tracheal intubation[20]. As sore throat was the source of discomfort after minor surgery, efforts to reduce throat pain with drugs should be taken. We did not observe any significant difference in the incidence of postoperative nausea or vomiting, which is consistent with previous report[21-22].

There are some limitations in our study. We have not measured the plasma levels of lidocaine in our patients because this service is not available in our institution. However, the protocol of administering a loading dose followed by a continuous IV infusion of lidocaine during GA has been used in several previous investigations. This dose was reported to be well below the toxic level[23-24]. Another limitation is the small number of patients. Hence, a larger-scale trial is needed to further validate our results.

In conclusion, Intravenous lidocaine infusion for operative hysteroscopy alleviated earlier postoperative hypogastric pain and throat pain, and decreased remifentanil consumption.

Abbreviations

ASA = American Society of Anesthesiologists, ESD = endoscopic submucosal dissection, GA = general anesthesia, HR = heart rate, IA = independent anesthetist, MBP = mean blood pressure, NT = Narcotrend, NTI = Narcotrend Index, SD = standard deviation

Declarations

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Availability of data and materials

All data and material are kept by the corresponding author and are available in paper for any further question.

Author contributions

Huaxin Wang and Liying Zhan designed this study together. Huaxin Wang, Xuan Peng and Liying Zhan performed the statistical analysis and drafted the protocol. Huaxin Wang and Liying Zhan was responsible for the writing revision.

Data curation: Huaxin Wang, Liying Zhan.

Formal analysis: Huaxin Wang, Xuan Peng, Liying Zhan.

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Writing – review and editing: Xuan Peng, Liying Zhan.

Ethics approval and consent to participate

The study protocol was approved by the hospital ethics committee of Renmin Hospital of Wuhan University. Written informed consent was obtained from all patients.

Consent for publication

Not Applicable.

Declaration of conflicting interest

The authors have no conflicts of interest to disclose.

References

1. Munro M. G., Brooks P. G. Use of local anesthesia for office diagnostic and operative hysteroscopy. J Minim Invasive Gynecol. 2010. 17(6). 709-718
2. Chudnoff S., Einstein M., Levie M. Paracervical block efficacy in office hysteroscopic sterilization: a randomized controlled trial. Obstet Gynecol. 2010. 115(1). 26-34
3. Tangsiriwatthana T., Sangkomkamhang U. S., Lumbiganon P., Laopaiboon M. Paracervical local anaesthesia for cervical dilatation and uterine intervention. Cochrane Database Syst Rev. 2013. (9). D5056
4. Kim J. E., Choi J. B., Koo B. N., Jeong H. W., Lee B. H., Kim S. Y. Efficacy of Intravenous Lidocaine During Endoscopic Submucosal Dissection for Gastric Neoplasm: A Randomized, Double-Blind, Controlled Study. Medicine (Baltimore). 2016. 95(18). e3593
5. Estebe J. P. Intravenous lidocaine. Best Pract Res Clin Anaesthesiol. 2017. 31(4). 513-521
6. Lauretti G. R. Mechanisms of analgesia of intravenous lidocaine. Rev Bras Anestesiol. 2008. 58(3). 280-286
7. Lee M. W., Or D. Y., Tsang A. C., Ng D. C., Chen P. P., Cheung M. H., Li R. S., Leong H. T. Intravenous lignocaine infusion facilitates acute rehabilitation after laparoscopic colectomy in the Chinese patients. Hong Kong Med J. 2017. 23(5). 441-445
8. Yon J. H., Choi G. J., Kang H., Park J. M., Yang H. S. Intraoperative systemic lidocaine for pre-emptive analgesics in subtotal gastrectomy: a prospective, randomized, double-blind, placebo-controlled study. Can J Surg. 2014. 57(3). 175-182
9. Zhao J. B., Li Y. L., Wang Y. M., Teng J. L., Xia D. Y., Zhao J. S., Li F. L. Intravenous lidocaine infusion for pain control after laparoscopic cholecystectomy: A meta-analysis of randomized controlled trials. Medicine (Baltimore). 2018. 97(5). e9771
10. Kranke P., Jokinen J., Pace N. L., Schnabel A., Hollmann M. W., Hahnenkamp K., Eberhart L. H., Poepping D. M., Weibel S. Continuous intravenous perioperative lidocaine infusion for postoperative

pain and recovery. Cochrane Database Syst Rev. 2015. 7. D9642

11. de Oliveira C. M., Issy A. M., Sakata R. K. Intraoperative intravenous lidocaine. Rev Bras Anestesiol. 2010. 60(3). 325-333
12. Xu S. Q., Li Y. H., Wang S. B., Hu S. H., Ju X., Xiao J. B. Effects of intravenous lidocaine, dexmedetomidine and their combination on postoperative pain and bowel function recovery after abdominal hysterectomy. Minerva Anestesiol. 2017. 83(7). 685-694
13. Cui W., Li Y., Li S., Wang R., Li J. Systemic administration of lidocaine reduces morphine requirements and postoperative pain of patients undergoing thoracic surgery after propofol-remifentanil-based anaesthesia. Eur J Anaesthesiol. 2010. 27(1). 41-46
14. Stroumpos C., Manolaraki M., Paspatis G. A. Remifentanil, a different opioid: potential clinical applications and safety aspects. Expert Opin Drug Saf. 2010. 9(2). 355-364
15. Ho MLJ, Kerr S. J., Stevens J. Intravenous lidocaine infusions for 48 hours in open colorectal surgery: a prospective, randomized, double-blinded, placebo-controlled trial. Korean J Anesthesiol. 2018. 71(1). 57-65
16. Sloan T. B., Mongan P., Lyda C., Koht A. Lidocaine infusion adjunct to total intravenous anesthesia reduces the total dose of propofol during intraoperative neurophysiological monitoring. J Clin Monit Comput. 2014. 28(2). 139-147
17. Ibrahim A., Aly M., Farrag W. Effect of intravenous lidocaine infusion on long-term postoperative pain after spinal fusion surgery. Medicine (Baltimore). 2018. 97(13). e229
18. Nakhli M. S., Kahloul M., Guizani T., Zedini C., Chaouch A., Naija W. Intravenous lidocaine as adjuvant to general anesthesia in renal surgery. Libyan J Med. 2018. 13(1). 1433418
19. Uzun S., Yuce Y., Erden A., Aypar U. Impact of perioperative lidocaine infusion and bis monitorization on remifentanil dosage in hypotensive anesthesia. Eur Rev Med Pharmacol Sci. 2014. 18(4). 559-565
20. Tanaka Y., Nakayama T., Nishimori M., Tsujimura Y., Kawaguchi M., Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015. 7. D4081
21. Gholipour Baradari A., Firouzian A., Hasanzadeh Kiabi F., Emami Zeydi A., Khademloo M., Nazari Z., Sanagou M., Ghobadi M., Fooladi E. Bolus administration of intravenous lidocaine reduces pain after an elective caesarean section: Findings from a randomised, double-blind, placebo-controlled trial. J Obstet Gynaecol. 2017. 37(5). 566-570
22. Farag E., Ghobrial M., Sessler D. I., Dalton J. E., Liu J., Lee J. H., Zaky S., Benzel E., Bingaman W., Kurz A. Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiology. 2013. 119(4). 932-940
23. Kaba A., Laurent S. R., Detroz B. J., Sessler D. I., Durieux M. E., Lamy M. L., Joris J. L. Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology. 2007. 106(1). 11-18, 5-6
24. Bazin P., Padley J., Ho M., Stevens J., Ben-Menachem E. The effect of intravenous lidocaine infusion on bispectral index during major abdominal surgery. J Clin Monit Comput. 2017.

Tables

Table 1 Baseline characteristics.

	Group L (n=40)	Group C (n=40)	Statistics (unpaired *t* test or Fisher's exact)	*p*-Value
Age (years)	31.38 ± 7.37	32.85 ± 7.73	t=0.837	0.385
Weight (kg)	53.20± 8.02	55.10 ± 10.61	t=0.904	0.369
Height (cm)	167.00 ± 7.90	168.10± 8.50	t=0.814	0.418
ASA physical status, n (%)				0.642
	24 (60%)	27 (67.5%)		
	16 (40%)	13 (32.5%)		
Duration of surgery (min)	29.83 ± 9.53	27.45 ± 7.46	t=1.241	0.218

Values are shown as mean ± SD or number of patients (proportion). ASA = American Society of Anesthesiologists.

Table 2 Perioperative data.

	Group L (n=40)	Group C (n=40)	Statistics (unpaired *t* test or Fisher's exact)	*p*-Value
Total propofol (mg)	237.20 ± 49.30	251.90 ± 50.45	t=1.316	0.192
Total remifentanil (μg)	236.40 ± 40.78	270.50 ± 47.38	t=3.452	< 0.001
VAS				
T6	1.83 ± 1.24	2.43 ± 1.10	t=2.285	0.025
T7	1.98 ± 0.95	2.63 ± 1.23	t=2.643	0.010
T8	0.90 ± 0.81	1.20 ± 0.85	t=1.612	0.111
Throat pain, n (%)	9 (22.5%)	19 (47.5%)		0.034
Nausea or vomiting, n (%)	4 (10%)	9 (22.5%)		0.225

Values are presented as mean ± SD or number of patients (proportion). VAS = visual analogue scale (0 = no pain, 10 = unbearable pain). T6 = 0.5 h after surgery, T7 = 4 h after surgery, T8 = 24 h after surgery.

Figures

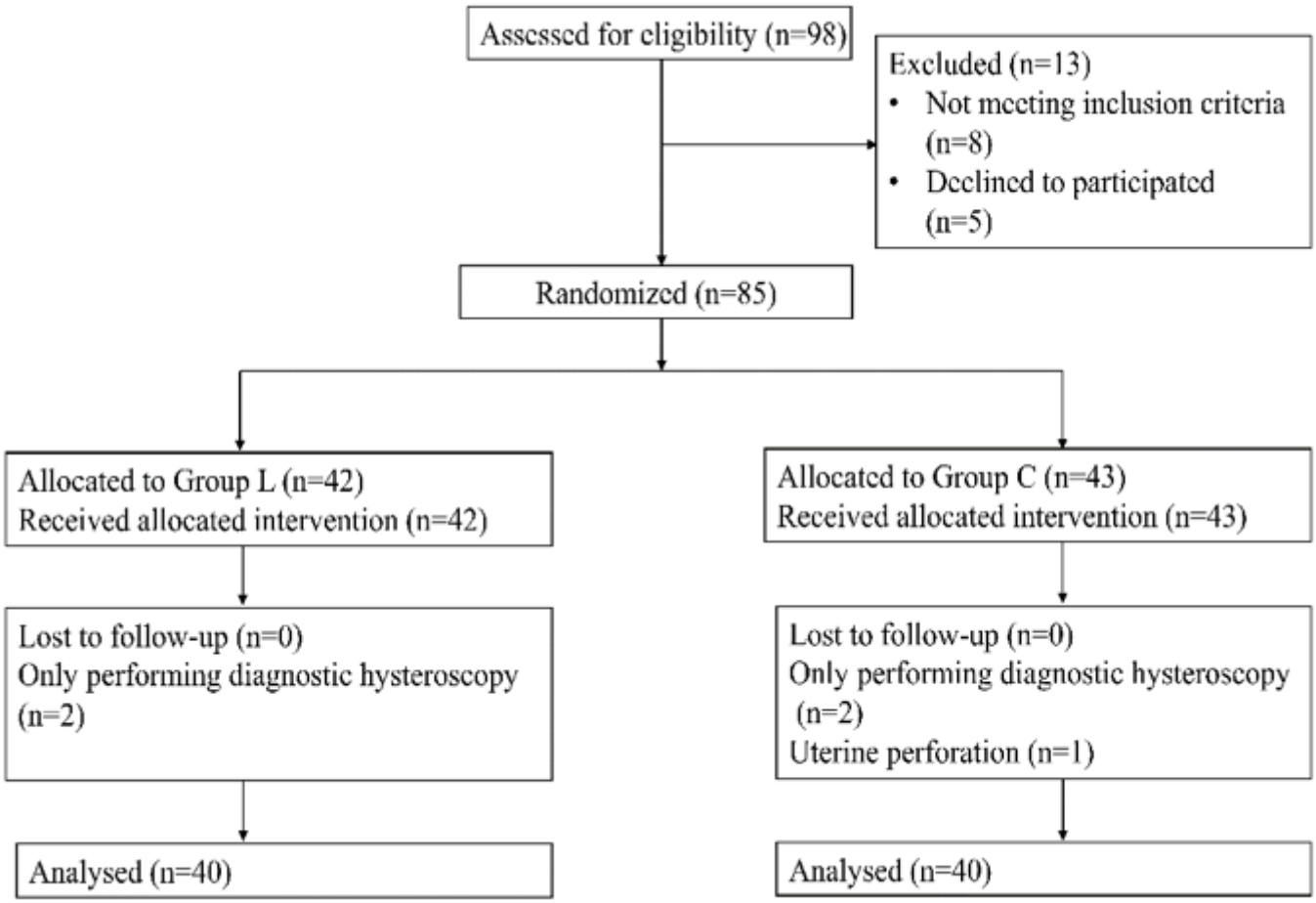

Figure 1

Flow diagram of patient recruitment.

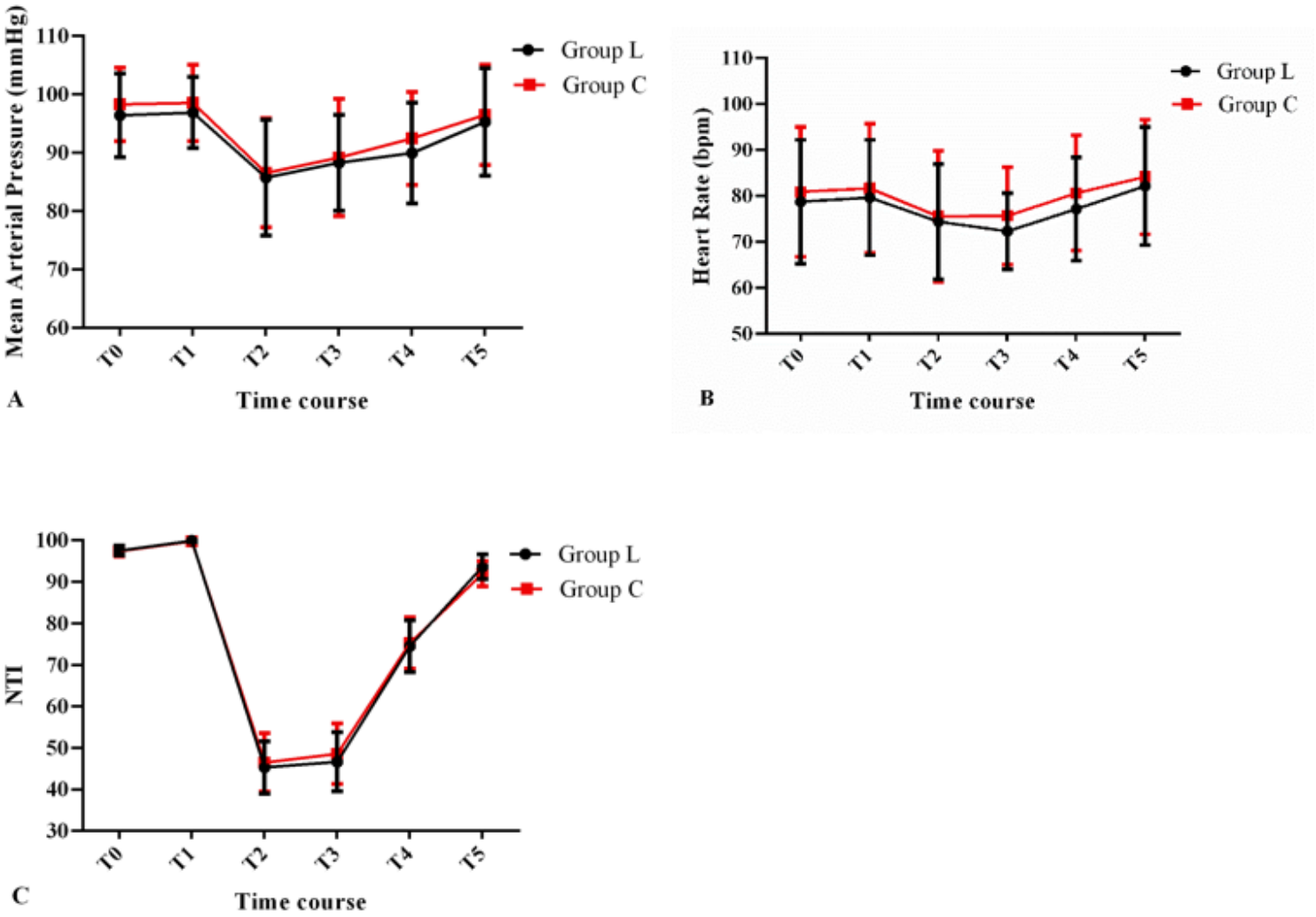

Figure 2

Changes in (A) mean blood pressure, (B) heart rate and (C) NTI. T0 = before intravenous lidocaine, T1 = before anesthesia induction, T2 = 5 min after surgery, T3 = 10 minutes after surgery, T4= the end of the surgery, T5 = the time to remove the laryngeal mask. NTI = Narcotrend Index. Data are expressed as mean ± SD.