Mohamed et al. Ain-Shams Journal of Anesthesiology (2020) 12:69
https://doi.org/10.1186/s42077-020-00120-8

Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

Intraoperative clonidine vs lidocaine on hemodynamic response to laryngoscopic intubation and immune function in gynecological surgeries

Sawsan Gaber Mohamed[1*], Noha Mahmoud Hamdy[2] and Amira Abo Elnasr Awad[3]

Abstract

Background: This prospective randomised double-blind study was carried out on forty patients American Society of Anesthesiologists (ASA) physical status I–II , aged 40–60 years, scheduled for elective abdominal gynecological surgeries under general anesthesia after obtaining the approval of the local institutional ethical committee and oral consent of the patients. This study was conducted to evaluate the effects of perioperative intravenous clonidine versus lidocaine on hemodynamic stress response to laryngoscopic intubation, immune function, pain intensity, time to the first request for analgesia, and total dose of analgesic requirement in the first 24 h postoperatively in gynecological surgeries.

Results: Throughout the study, heart rate and mean arterial blood pressure were significantly lower in clonidine group (group C) compared to lidocaine group (group L). Postoperatively, the levels of IL-6 were significantly higher in (group L) compared to (group C). VAS pain scores were lower in the clonidine group in comparison to the lidocaine group. There was a higher total dose of analgesia in the lidocaine group when compared to the clonidine group.

Conclusions: Both clonidine and lidocaine can be used to attenuate the hemodynamic response; however, clonidine was better in the reduction of postoperative pain scores and the decrease in the production of pro-inflammatory cytokines.

Background

Laryngoscopy and endotracheal intubation are stressful stimuli, which lead to reflex sympathetic activity and the release of adrenaline and noradrenaline (Kranke et al. 2015).

Interleukin 6 (IL-6) is a pro-inflammatory molecule which increased in patients with surgery, trauma, burns, critical illness, and infections. Surgical stress, surgical approaches, and procedural complexities increased IL-6 serum levels which reflect the impact of the trauma and the extension of damaged tissue (Zelzer et al. 2009; Oliveira et al. 2015).

Various analgesic agents are effective in decreasing postoperative pain such as opioids; however, the use of opioids is usually associated with many undesirable side effects. Nonetheless, the use of analgesics before the pain stimulus or surgical trauma prevents harmful central nervous system responses and inflammation (Wick et al. 2017).

Lidocaine has analgesic, anti-hyperalgesic, and anti-inflammatory effects due to its ability to act as a sodium channel blockade and its inhibition of N-methyl-D-aspartate (NMDA) receptors. Intravenous lidocaine provides attenuation of pressor responses to laryngoscopic

* Correspondence: sawsan.saadawy@gmail.com; sawsan.saadawy@yahoo.com
[1]Intensive Care and Pain Management, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt
Full list of author information is available at the end of the article

intubation and has a favorable safety profile. Thus, the analgesia may persist even after plasma concentration reduction (Watt et al. 2015; Kaba et al. 2007).

Clonidine, an imidazoline derivative and a selective centrally acting α2 agonist, has potent antinociceptive properties, inducing dose-dependent sedation, analgesia, and anxiolysis without relevant respiratory depression. It produces a fall in the heart rate (HR) and blood pressure, which is associated with decreased systemic vascular resistance (SVR) and cardiac output, attenuating hemodynamic responses to laryngoscopy and decreasing anaesthesia requirements during surgery (Raval and Mehta 2002).

Methods

This prospective randomised double-blind study was carried out on forty patients American Society of Anesthesiologists (ASA) physical status I–II , aged 40–60 years, scheduled for elective abdominal gynecological surgeries under general anesthesia after obtaining the approval of the local institutional ethical committee and informed oral consent of the patients. The patients were randomly assigned into two groups: 20 patients each, the clonidine group (group C) and the lidocaine group (group L), by computer-generated randomised numbers. The study period lasted from July 2018 to September 2019. The exclusion criteria included patients who had cardiovascular abnormalities and hepatic and renal disorders and history of allergy to the studied drugs, analgesia, or steroid usage in the previous 48 h, previous medication with immunosuppressive drugs and alcohol or drug abuse. All patients were checked 24 h before surgery to fulfil the inclusion criteria of the study through a detailed history and clinical examination. After reviewing the results of routine investigations, the study design was explained to the patients involving the use of a visual analog scale for pain assessment (where 0 = represent no pain and 10 = represent the worst pain).

On arrival at the operating theatre, a peripheral intravenous line was inserted with 18 G intravenous cannula, and all the patients were monitored using standard monitoring devices, including electrocardiography, non-invasive blood pressure measurement (NIBP), and pulse oximetry.

Patients in the clonidine group (C) received intravenous bolus of clonidine (2 μg/kg), prepared in a 10-ml syringe and diluted to 10 mL saline, 5 min before the induction of anesthesia, followed by continuous infusion at a rate of 1 μg/kg/h prepared in a 50-ml syringe (Ratiopharm, Germany). The infusion was continued during the operation and till the end of surgery. Patients in the lidocaine group (L) received an intravenous bolus injection of lidocaine 2% (1.5 mg/kg), prepared in a 10-mL syringe and diluted to10 mL saline, 5 min before the induction of anesthesia, followed by continuous intravenous infusion at the rate of 2 mg/kg/h, prepared in a 50-mL syringe (Al-Debeiky Pharmaceutical Industries, Egypt). The infusion was continued during the operation and till the end of surgery. Drugs were prepared in identical syringes before operation by an anesthesiologist (anesthesia resident) who had no rule in the study, the intraoperative monitoring was done by an anesthesiologist who administered the drug, but was unaware of the content of the syringes.

After preoxygenation, general anesthesia was induced with fentanyl (1 μg/kg) and propofol (1.5 mg/kg), while rocuronium (0.6 mg/kg) was used for intubation and muscle relaxation as intubation was performed with an endotracheal tube. Maintenance of anesthesia was achieved with a mixture of oxygen in air (1:1), isoflurane at 1–2% minimum alveolar anesthetic concentration (MAC), and intermittent boluses of rocuronium (0.1 mg/kg) was given, if required. Ventilation was controlled to maintain end-tidal carbon dioxide (EtCO2) of between 35 and 40 mmHg. Intraoperative fluid administration was 6–8 mL/kg/h of a ringer solution and if bradycardia (HR < 50 beats/min) occurred, it was treated with an injection of atropine (0.5 mg IV bolus). Hypotension, i.e., a mean arterial pressure (MAP) of less than 60 mmHg, was managed with ephedrine (3 mg IV bolus) and repeated after three minutes if required.

At the end of the surgery, patients were allowed to recover spontaneously and isoflurane and the intravenous lidocaine or clonidine infusion were discontinued. A combination of atropine (0.01 mg/kg) and neostigmine (0.05–0.08 mg/kg) was administered to reverse neuromuscular blockade and patients were extubated fully awake when all the extubation criteria were fulfilled in the operating room, then patients in both groups were transferred to the post-anesthesia care unit (PACU).

The following variables were recorded in both groups:

- Hemodynamic variables: HR (beat/min) and MAP (mmHg) were recorded on arrival to the operating room (baseline); after the infusion of both drugs (before intubation); 3 and 5 min after intubation, then every 10 min till the end of the surgery; after stopping the infusion after extubation; and on arrival to the PACU.
- Venous blood samples: samples were collected in EDTA tubes and centrifuged within 30 min of collection and the plasma was stored at − 70 °C until analysis. Serum concentrations of IL-6 were assessed with enzyme-linked immunosorbent assay (ELISA) kits specifically for human IL-6, (Research & Diagnostic Systems, Minneapolis, MN, USA). Samples were collected on the morning of the surgery and 4 and 24 h postoperative to measure

cytokine production of IL-6. The IL-6 threshold laboratory value in this study was greater than 10 pg/mL.

- Post-operative pain intensity measured using a visual analog scale (VAS): a patient with a VAS score of greater than 4 was managed with an intramuscular injection of diclofenac sodium (75 mg) and further subsequent doses of diclofenac were allowed if needed, without exceeding a total dose of 225 mg every 24 h.
- The first request for analgesia and total doses of analgesic requirement during the first 24 h after surgery was recorded.

Outcomes

The primary aim of the study was to evaluate the hemodynamic changes to endotracheal intubation (HR and MAP).

Secondary aims were to observe postoperative pro-inflammatory changes (in levels of IL-6), scores along the VAS, time for the first request for analgesia and the total doses of analgesic requirement.

Sample size

MedCalc® version 12.3.0.0 program "Ostend, Belgium" was used for calculations of sample size, statistical calculator based on 95% confidence interval and power of the study 80% with α error 5%, According to a previous study (Roy et al. 2014), showed that the significant higher mean in group B received lignocaine compared to group A received clonidine according to heart rate at induction (90.3 ± 7.9 compared to 105.4 ± 8.9), respectively, also systolic blood pressure at induction (124.9 ± 5.9 compared to 147.9± 22.7), respectively, as well as diastolic blood pressure at induction (78.92 ± 4.009 compared to 91.88 ± 3.931), respectively. So it can be relied upon in this study, based on this assumption, the sample size was calculated according to these values produced a minimal samples size of 40 cases were enough to find such a difference, subdivided into two groups.

Statistical analysis

Data were statistically described in terms of mean and standard deviation (SD) and range of frequencies (number of cases) and percentages when appropriate. A comparison of numerical variables between the study groups was done using the Student's *t* test for independent samples with parametric distribution and Mann-Whitney test for non-parametric distribution. For comparing categorical data, chi-square test was performed. *P* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) version 22 for Microsoft Windows.

Results

There was no statistically significant difference between clonidine and lidocaine groups with regard to demographic variables (age, ASA, weight, height, and duration of operation) (Table 1).

There was a statistically significant lower HR in the clonidine group when compared with the lidocaine

Table 1 Demographic data in both groups

	Lidocaine group *N* = 20	Clonidine group *N* = 20	Test value	*P* value
Age (years)	38.22 ± 11.22	39.95 ± 10.65	0.500[a]	0.619
ASA				
I	16 (80.0%)	17 (85.0%)	0.173[b]	0.677
II	4 (20.0%)	3 (15.0%)		
Weight (kg)	88 ± 10.22	90 ± 23.21	0.353[a]	0.726
Height (cm)	151.10 ± 10.13	149.22 ± 4.72	0.752[a]	0.456
Surgical duration (min)	79.4 ± 10.5	77.8 ± 17.3	0.354[a]	0.725
Type of operation				
Hysterectomy (abdominal or vaginal)	15 (75.0%)	14 (70.0%)	0.868	0.648
Repair of vaginal prolapse and cysto-rectocele	3 (15.0%)	5 (25.0%)		
Ovarian cystectomy	2 (10.0%)	1 (5.0%)		

Data are expressed as mean ± SD or *n* (%)
p value ≥ 0.05 is considered non-significant
ASA American Society of Anesthesiologists
[a]Independent *t* test
[b]Chi-square test

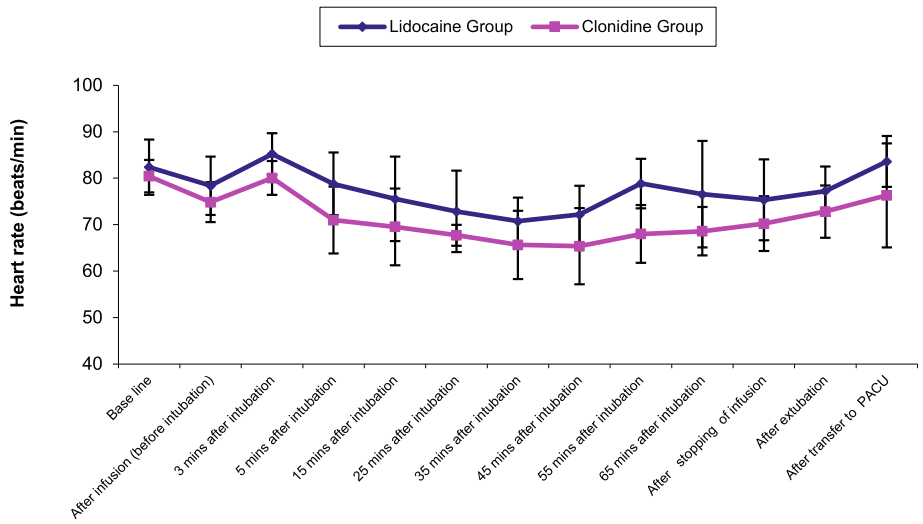

Fig. 1 Heart rate (HR) changes in both groups. Lines are mean values and error bars are SD

group after drug infusion and throughout the study (Fig. 1).

There was also a statistically significant lower MAP in the clonidine group in comparison to the lidocaine group after drug infusion and throughout the study (Fig. 2).

The level of IL-6 in the preoperative period showed no statistically significant difference between both groups, but the levels of IL-6 at 4 and 24 h postoperative were significantly lower in the clonidine group when compared with the lidocaine group (Fig. 3).

The mean values of postoperative VAS pain scores were lower in the clonidine group in comparison to the lidocaine group, which was significant at the PACU stage and in the first 4 h postoperative. However, the differences between both the groups were statistically insignificant at 8, 12, and 24 h after the operation (Table 2).

There was a significant increase in the time taken for the first request for postoperative analgesia and a significant decrease in the total dose of analgesic in the clonidine group when compared to the lidocaine group (Table 3).

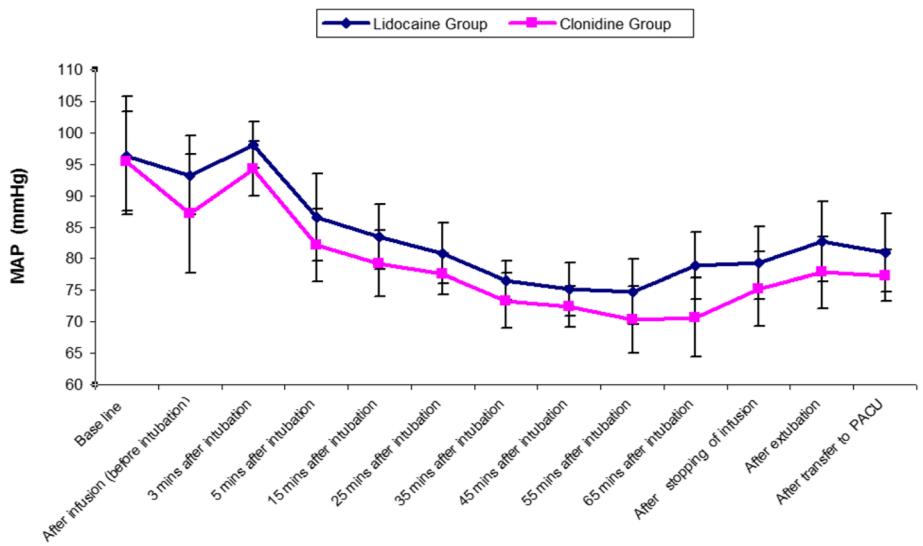

Fig. 2 Mean blood pressure (MAP) changes in both groups. Lines are mean values and error bars are SD

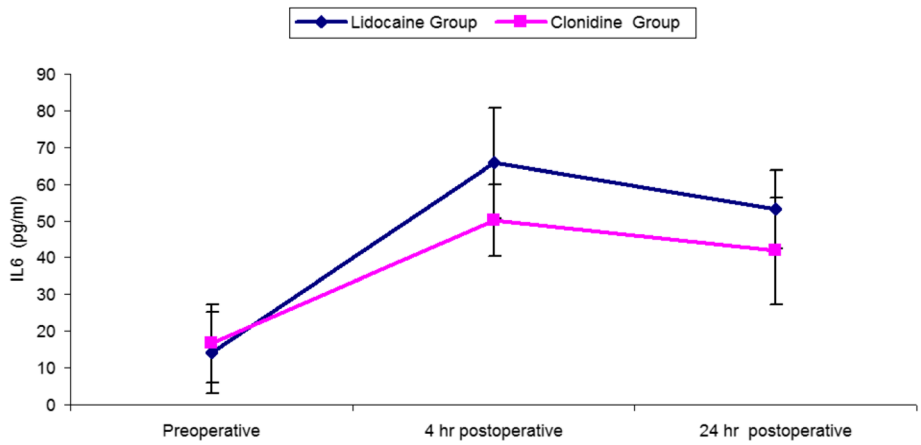

Fig. 3 Interleukin 6 (IL-6) level changes in both groups. Lines are mean values and error bars are SD

Discussion

The study conducted and revealed that the HR and MAP were significantly lower in the clonidine group in comparison to the lidocaine group. The levels of IL-6 at 4 and 24 h postoperatively were also significantly higher in the lidocaine group.

The VAS pain scores were lower in the clonidine group, in the first 24 h, in comparison to the lidocaine group, which was significant at PACU and the first 4 h postoperatively. Also, clonidine reduced postoperative analgesic requirements during the first 24 h.

Similar to the present study, Marulasiddappa and Nethra 2017 used clonidine (2 μg/kg, intravenous before induction) and compared it with lidocaine (1.5 mg/kg) during operations of neurosurgery. The attenuation of stress responses and maintenance of the hemodynamic stability were significantly higher in the clonidine group at baseline, after induction and at 1, 2, 3, 5, 10, and 15 min after intubation compared to the lidocaine group.

Another study comparing lidocaine and oral clonidine was done by Chatterjee et al. 2015 who found that oral clonidine (4 μg/kg, 3 min before intubation) is a better attenuating agent than intravenous lidocaine (2 mg/kg, 3 min before intubation). However, this study is not similar to the present study in regards to dosage and the route of administration, but had a similar final conclusion.

Coinciding with the current study, Roy et al. 2014 used clonidine (2.25 μg/kg bolus and 0.9 μg/kg/h infusion) and compared it with lidocaine (1.5 mg/kg bolus and 0.6 mg/kg/h infusion) during laparoscopic hysterectomy. The attenuation of HR, systolic, and diastolic blood pressure were significantly higher in clonidine group, during tracheal intubation at 1 min, 3 min, 10 min, 30 min, 60 min, and 90 min, as compared to the lidocaine group .

A study conducted by Mohammadi et al. 2016 who studied the effect of adding oral clonidine (0.2 mg, 90 min before induction) compared to intravenous lidocaine (1.5 mg/kg, before induction) and added fentanyl to both group before induction (3 mcg/kg). They reported that both groups were equally effective in decreasing hemodynamic stress responses to tracheal intubation in controlled hypertensive patients, although the difference was statistically insignificant. Their results

Table 2 Changes in VAS scores in both groups

VAS	Lidocaine group *N* = 20	Clonidine group *N* = 20	Test value[a]	*P* value
At PACU (1 h)	3.00 ± 1.62	2.01 ± 1.08	2.274	0.029
4 h postoperative	4.60 ± 1.64	3.27 ± 1.66	2.549	0.015
8 h postoperative	3.40 ± 0.72	3.20 ± 1.12	0.672	0.506
12 h postoperative	2.73 ± 1.72	2.00 ± 0.37	1.856	0.071
24 h postoperative	1.93 ± 0.35	1.71 ± 0.40	1.851	0.072

P value of ≤ 0.05 was considered significant
P value ≥ 0.05 was considered non-significant
P value < 0.001 was considered highly significant
[a]Mann-Whitney test

Table 3 Time to the first request for postoperative analgesia and total dose of analgesic in the first 24 hours in both groups

	Lidocaine group $N = 20$	Clonidine group $N = 20$	Test value[a]	*P* value
First request for analgesia (min)	63.6 ± 18.7	75.8 ± 16.7	$t = 2.176$	0.036
Diclofenac sodium (mg)/24 h	150 (0)	75 (0)	$z = 6.382$	< 0.001
By median IQR	[75–150]	[75–150]		

P value ≤ 0.05 was considered significant
P value < 0.001 was considered highly significant
IQR Interquartile range
[a]Mann-Whitney test

differed from the current study. However, this difference may be due to different drug doses and the route of drug administration.

In contrast to the present study, Gupta et al. 2018 studied three groups: clonidine group received intravenous clonidine (2 μg/kg, 30 min before laryngoscopic intubation); lidocaine group received intravenous lidocaine (1.5 mg/kg, 90 s before the intubation); and control group received normal saline (NS). They evaluated systolic blood pressure (SBP), diastolic (DBP), MAP, and HR measured at the baseline, pre-induction and at 3, 5, and 10 min. The rise in BP and HR from the baseline to one minute after intubation was significantly less in both lidocaine and clonidine groups as compared to the control group; however, the lidocaine group maintained hemodynamic around the baseline better than the clonidine group. Their results were different from the current study as they used clonidine as an intravenous bolus only and they recorded data at different time points.

Supporting the current study as regarding to the changes in the level of IL-6, research conducted by Kim and Hahn 2000 on the effect of 2.5 mg/kg clonidine administered orally 90 min before the operation in one group while another group received normal saline. It was found that levels of IL-6 increased in patients of both groups in response to the stress of surgery. When IL-6 levels were compared between the two groups, they were significantly lower in the clonidine group than in the control group when measured three hours after the start of the surgery.

In agreement with the current study, Marret et al. 2008 performed a meta-analysis which compared continuous infusion of lidocaine during and after abdominal surgery with saline and reported that lidocaine infusion attenuated postoperative production of pro-inflammatory cytokines.

Similarly, a study conducted by Herroeder et al. 2007 examined the effect of a lidocaine infusion in the inflammatory response after colorectal surgery. IL-6 was measured before, at the end of the surgery, 2 h and 3 days postoperatively and it was reported that lidocaine significantly attenuated the inflammatory response. Also, a study conducted by Kuo et al. 2006 compared intravenous lidocaine and normal saline in cancer colon surgeries, and IL-6 was measured before, at the end of surgery and 12 and 24 h postoperative. They reported that intravenous lidocaine resulted in less IL-6 production than the saline administration.

Another observation in the current study was that postoperative VAS pain scores which was lower in the clonidine group in the first 24 h in comparison to the lidocaine group, which were significant at PACU and in the first four postoperative hours. These findings coincide with the results of a study conducted by Singh and Arora 2011 which showed that there was a significant reduction in postoperative analgesic requirement and the time for the first dose of analgesic was prolonged for patients in the clonidine group, who were administered oral clonidine (150 μg, 60 to 90 min before induction of anesthesia), when compared with the control group. The average requirement of diclofenac sodium within 24 h was higher in the control group in comparison to the clonidine group.

However, in the study of Grady et al. 2012 who studied the effects of perioperative lidocaine infusion and ketamine on postoperative pain in patients undergoing abdominal gynecologic procedures, different observations were noted. It was demonstrated that postoperative VAS scores were not different between the lidocaine or ketamine groups. The discrepancies between studies may be related to the different types of surgery, time onset of infusion, and the duration of drugs.

These findings were also consistent with those obtained by Krishna Murthy and Vinay Kumar 2018 and Moslemi et al. 2018 who investigated the perioperative intravenous injection of lidocaine (1.5 mg/kg prior induction) followed by a 1.5–2 mg/kg/h infusion until the end of surgery, in comparison to normal saline, and it was reported that perioperative lidocaine improves the pain intensity and reduced postoperative consumption of analgesia.

Finally, in contrast to the current study, Martin et al. 2008 who studied the effects of lidocaine infusion during total hip arthroplasty surgeries starting with bolus dose

of intravenous 1.5 mg/kg lidocaine over 30 min before surgical incision then followed by continuous infusion of 1.5 mg/kg/h and infusion was continued for 1 h after the termination of surgery and was compared lidocaine group with control group receiving saline. The two groups had no significant differences considering their morphine requirements and did not have different in pain scores postoperatively.

Their results were different from the current study as they used lidocaine compared with control group and they recorded data at different time points and also may be due to different type of operation.

Conclusion

Both clonidine and lidocaine can be used safely in the attenuation of the hemodynamic response of laryngoscopy, but clonidine is more effective in reducing pain intensity, meeting analgesic requirements and decreasing the production of proinflammatory cytokines after gynecological surgery.

Abbreviations

ASA: American Society of Anesthesiologists; ECG: Electrocardiography; HR: Heart rate; MAP: Mean arterial pressure; NIBP: Noninvasive blood pressure; NMDA: N-methyl-D-aspartate; SVR: Systemic vascular resistance; I.V: Intravenous; MAC: Minimum alveolar anesthetic concentration; EtCO2: End-tidal carbon dioxide; PACU: Post-anesthesia care unit; ELISA: Enzyme-linked immunosorbent assay; VAS: Visual analog scale; SD: Mean standard deviation; IL-6 : Interleukin 6; LA: Local anesthetic

Acknowledgements

The authors would like to acknowledge the cooperation of all participants, operative rooms' nurses, and all our residents of anesthesia of the Faculty of Medicine for Girls, Al-Azhar University.

Authors' contributions

SGM and AAA contributed to the conception and design of the study. Both organized the data collection, reviewed, and greatly contributed to the interpretation of results. NMH performed the laboratory analysis and collection of data. All authors checked the statistical analysis and critically reviewed its comprehensive content, and finally approved the version to be submitted for publication.

Funding

Nil

Availability of data and materials

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

Ethics approval and consent to participate

The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine for Girls, Cairo, Al-Azhar University (FMGIRB) under registration number N0 RHD. IRB 20/910/80. Informed oral consent was obtained from all participants. Consent of patients were verbal consent in the front of witnesses (resident of anesthesia and relative of patients). (Patients agree to participate but do not want to sign the written consent form, some of these patients found it difficult to sign their name).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Intensive Care and Pain Management, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. [2]Clinical Pathology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt. [3]Intensive Care and pain managements, Faculty of Medicine for girl, Al-Azhar University, Cairo, Egypt.

Received: 31 October 2019 Accepted: 10 November 2020
Published online: 03 December 2020

References

Chatterjee A, Samaddar DP, Srividhya DS, Sahay N (2015) A comparative study of IV lidocainevs. oral clonidine for attenuation of hemodynamic response to laryngoscopy and endotracheal intubation. Indian J Clin Anaesth 2:41–47

Grady MV, Mascha E, Sessler DI, Kurz A (2012) The effect of perioperative intravenous lidocaine and ketamine on recovery after abdominal hysterectomy. Anesth Analg 115(5):1078–1084

Gupta A, Joseph A, Mahajan HK, Chauhan PR, Sarkar A, Dhanerwa R, Chaubey D (2018) Evaluation of Clonidine and lidocaine for Attenuation of Haemodynamic Response to Laryngoscopy and Intubation: A Randomised Controlled Trial. J Clin Diagn Res 12(2):17–20.

Herroeder S, Pecher S, Schönherr ME, Kaulitz G, Hahnenkamp K, Friess H, Bauer H (2007) Systemic lidocaine shortens the length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg 246(2):192

Kaba A, Laurent SR, Detroz BJ, Sessler DI, Durieux ME, Lamy ML, Joris JL (2007) Intravenous lidocaine infusion facilitates acute rehabilitation after laparoscopic colectomy. Anesthesiology 106(1):11–18

Kim MH, Hahn TH (2000) The effect of clonidine pretreatment on the perioperative proinflammatory cytokines, cortisol, and ACTH responses in patients undergoing total abdominal hysterectomy. Anesth Analg 90(6): 1441–1444

Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW, Hahnenkamp K, Weibel S (2015) Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev 7. https://doi.org/10.1002/14651858.CD009642.pub2

Krishna Murthy TK, Vinay Kumar PV (2018) Effect of perioperative intravenous lidocaineinfusion on haemodynamic responses and postoperative analgesia in laparoscopic cholecystectomy surgeries. Anesth Pain Med 8(2):e63490

Kuo CP, Jao SW, Chen KM, Wong CS, Yeh CC, Sheen MJ, Wu CT (2006) Comparison of the effects of thoracic epidural analgesia and iv infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery. Br J Anaesth 97(5):640–646

Marret E, Rolin M, Beaussier M, Bonnet F (2008) A meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. Br J Surg 95(11):1331–1338

Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, Fletcher D (2008) Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. Anesthesiology 109(1):118–123

Marulasiddappa V, Nethra HN (2017) A comparative study of clonidine and lidocainefor attenuating pressor responses to laryngoscopy and endotracheal intubation in neurosurgical cases. Anesth Essays Res 11(2):401

Mohammadi SS, Maziar A, Saliminia A (2016) Comparing clonidine and lidocaine on the attenuation of hemodynamic responses to laryngoscopy and tracheal intubation in controlled hypertensive patients: a randomized, double-blinded clinical trial. Anesth Pain Med 6(2):e34271

Moslemi F, Rasooli S, Dehdilani M, Sadeghi-Bazargani H, Dehdilani M (2018) The Effect of Intravenous Infusion of Lidocaine to Control Postoperative Pain After Gynecologic Laparoscopic Surgery: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial. Iran Red Crescent Med J 20(7):1–9

Oliveira CMBD, Sakata RK, Slullitel A, Salomão R, Lanchote VL, Issy AM (2015) Effect of intraoperative intravenous lidocaine on pain and plasma interleukin-6 in patients undergoing hysterectomy. Rev Bras Anestesiol 65(2):92–98

Raval DL, Mehta MK (2002) Oral clonidine pre medication in attenuation of haemodynamic response to laryngoscopy and intubation. Indian J Anaesth 46(2):124

Roy S, Chaudhuri A, Saha D, Maulik SG, Bandopadhyay AK (2014) Comparative study of clonidine versus lidocainefor attenuation of hemodynamic responses during laparoscopic hysterectomy. J Basic Clin Reprod Sci 3(1):38–43

Singh S, Arora K (2011) Effect of oral clonidine premedication on perioperative haemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Indian J Anaesth 55(1):26
Watt DG, Horgan PG, McMillan DC (2015) Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. Surgery 157(2):362–380
Wick EC, Grant MC, Wu CL (2017) Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg 152(7):691–697
Zelzer S, Aigner RM, Khoschsorur G, Hofer HP, Schaur RJ, Foldes-Papp Z (2009) Comparative study of the immunological marker IL-6 and the non-immunological marker PCT in surgery patients with infections and multiple trauma. Open Pathol J 3:124–30.

Publisher's Note