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

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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...
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 anesthesia 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 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.

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          | 0.500⁴     | 0.619   |
| ASA                  |                        |                        |            |         |
| I                    | 16 (80.0%)             | 17 (85.0%)             | 0.173⁰     | 0.677   |
| II                   | 4 (20.0%)              | 3 (15.0%)              |            |         |
| Weight (kg)          | 88 ± 10.22             | 90 ± 23.21             | 0.353⁴     | 0.726   |
| Height (cm)          | 151.10 ± 10.13         | 149.22 ± 4.72          | 0.752⁴     | 0.456   |
| Surgical duration (min) | 79.4 ± 10.5          | 77.8 ± 17.3            | 0.354⁴     | 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

⁴Independent t test

⁰Chi-square test

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
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).
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 &mu;g/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 &mu;g/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 &mu;g/kg bolus and 0.9 &mu;g/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 valuea | 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 &le; 0.05 was considered significant
P value &ge; 0.05 was considered non-significant
P value &lt; 0.001 was considered highly significant
*aMann-Whitney test
Interquartile range (IQR) P value < 0.001 was considered highly significant.

Similarly, a study conducted by Herroeder et al. 2007 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

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**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 valuea | 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
*aMann-Whitney test
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.

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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. NWH 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.

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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 8950. 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.

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Abbreviations
ASA: American Society of Anesthesiologists; ECG: Electrocardiography; HR: Heart rate; MAP: Mean arterial pressure; NIBP: Noninvasive blood pressure; NMOA: 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

Nil

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Nil

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