Original Article

Comparison the Effects of Ephedrine and Lidocaine in Treatment of Intraoperative Hiccups in Gynecologic Surgery under Sedation

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Abstract

Background: This study aimed to evaluate and compare the therapeutic effects of ephedrine and lidocaine in treatment of intraoperative hiccups in gynecologic surgery under sedation. **Materials and Methods:** This randomized clinical trial in Isfahan was done on fifty female patients referring to Shahid Beheshti Hospital who needed to have sedation for medical interventions and they afflicted hiccups during surgery or sedation. Patients divided into two groups of 25 randomly assigned to one of the two groups of ephedrine or lidocaine. Ephedrine group received 5 mg/kg of medicine, while the lidocaine group was under treatment with 1 mg/kg lidocaine. Patients were monitored about systolic and diastolic blood pressure, MAP, heart rate, duration of hiccup, frequency of betterment, duration of intervention, and recovery at 15-min intervals of surgery and recovery. **Results:** Hiccups were resolved in 14 cases (56%) in the lidocaine group, while the improvement of such problem was achieved in 24 cases (96%) in ephedrine group ($P < 0.001$), so that the two groups did not have any significant difference in terms of the time of onset but the stop time of hiccups (relative to its start time) in the ephedrine group with the mean value of (2.40 ± 1.16) was significantly lower than the lidocaine group with the mean of 19.64 ± 22.76 min ($P = 0.014$). In addition, no complications were observed in the two groups. **Conclusion:** Ephedrine has been more successful than lidocaine as a stimulant in controlling hiccups, and it has been able to suppress hiccups in a higher percentage of patients at a shorter time.

Keywords: *Ephedrine, gynecologic surgery, intraoperative hiccups, lidocaine*

Introduction

Hiccup is a spontaneous and involuntary state that most people experience it and it is generally resolved spontaneously without any complications. Hiccup is intermittent, involuntary, and spasmodic contraction of the diaphragm and intercostal muscle. Sudden contraction begins with a sudden inhalation and ends by closing the glottis resulting in production of hiccup's sound.[1,2]

The cause of hiccups is still unclear, and there are many potential causes for hiccups, many of which are associated with the gastrointestinal tract, and include the stimulation of the vagus and phrenic nerves. Other causes consist of central nervous system disorders, metabolic and mental disorders, and medications. Additional metabolic reasons of hiccups include hypokalemia, hypocalcemia, dyspnea, and uremia. Concurrently, certain drugs, such as steroids, benzodiazepines, narcotics, and antidopaminergic drugs which are used to treat hiccups, can cause hiccups.[3,4]

This is due to the complexity of the origin of hiccups, the possibility of the involvement of dopamine and serotonin routes, calcium channel, and aminobutyric acid in the brain stem and medulla.[5,6] Several drug agents have been reported to be effective in treating stable and chronic hiccups. Most of these factors directly affect the receptors of dopamine and gamma-aminobutyric acid. In the 1950s, the efficacy of chlorpromazine in the discontinuation of chronic hiccups has been represented in two studies. Recently, it has been used orally for treating hiccups, although its effectiveness has not been shown.[7,8]

In clinical trials and review of conducted affairs, the use of metoclopramide and baclofen in the treatment of hiccups has been approved. In other cases, gabapentin has been shown to be effective in treating this disease. Other nonpharmacological

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treatments have been reviewed in several studies, some of which have revealed the effect of acupuncture in cessation of hiccups patients with such disease. Other studied therapies include positive pressure ventilation, hypnosis, and surgical procedures.[9,10]

Among the cases, where hiccups occur in patients can be referred to stimulation of the vagus nerve endings inside the abdomen especially, when it is triggered by the manipulation during some surgery. Postoperative hiccups also occur at different times in various surgical procedures; it is more likely to happen in gastrointestinal surgeries. Furthermore, the use of anesthetic drugs in surgery is associated with the incidence of hiccups. Anesthesia with propofol as well as epidural anesthesia with bupivacaine have caused the incidence of hiccups, but it is still not clear whether an occurrence of hiccups is due to surgery or anesthetic agents.[11-13] Among other cases which lead to hiccups, it can be noted to the time of sedation.

If the hiccup occurs due to insufficient depth of anesthesia or inadequate relaxation, treatment is determined, but sometimes hiccups occur despite the adequate depth of anesthesia as well as satisfactory relaxation.[14,15] To control and treat hiccups in anesthesia and sedation, it seems that deflating the stomach if it is dilated or stimulation of the mead pharynx behind the uvula are appropriate methods. Lidocaine and ephedrine can be mentioned among the drugs used in these patients. Treatment with intravenous lidocaine at a dose of 1 mg/kg has resulted in stopping hiccups following anesthesia induction.

There is limited information on the effect of ephedrine for reducing hiccups in which suppression of hiccups 15 s after an injection of 5 mg ephedrine has been indicated. Although the mechanism of ephedrine's effect on hiccup suppression is not known, it is possible that the effects of bronchodilator and nocturnal decongestants of ephedrine or being central stimulant are the probable causes of hiccup suppression.

However, due to the availability and common use of this medication in the operating room and that the drug is safe in low doses in anesthetics and sedation; it can be used as a standard treatment in such patients if there is sufficient evidence that the medicine is effective. Therefore, given that there is not enough information about the effect of ephedrine on suppressing hiccup after sedation and due to the matter that there is also no clear indication for treating hiccups under the mentioned conditions.

The present study was designed as a clinical trial, with the aim of evaluating the therapeutic effect of ephedrine in comparison with lidocaine in hiccup suppression after sedation in patients at Isfahan, Shahid Beheshti Hospital in 2016.

Materials and Methods

The current study was conducted as a randomized clinical trial in Isfahan, Iran. The study population included female patients referring to Shahid Beheshti Hospital in Isfahan, who needed to have sedation for medical interventions and they afflicted hiccups during surgery or sedation.

Inclusion criteria consist of age between 20 and 50 years, occurrence of hiccups during surgery or sedation, patients with Grade 1 ASA having normal heart function, having normal blood pressure below 120/80 mmHg, no history of palpitations, tachycardia or any kind of arrhythmia, lack of cancer, lack of being afflicted with neurological disorders, written consent to be free, and informed to participate in the study.

In case of pregnancy, sensitivity to the medications studied, history of heart disease, history of a cerebral aneurysm, hypertension above 120/80 mmHg, change in method of anesthesia, and patient"s desire to withdraw from the study, they were excluded.

Sampling method is simple was nonrandom. Moreover, the sample size was calculated based on the formula and related parameters (power: 1.96 and significance level: 0.05) as well as considering the limitations of the study which was obtained to be a total of 48 patients. In this study, fifty patients were examined in two groups including 25 individuals. Patients eligible for being included in the study were justified about the objectives of the plan and they entered the study with the written consent of the company based on the order of their referrals.

Throughout the medical intervention, if hiccup occurred for patients during surgery or sedation, they were randomly situated in one of two ephedrine or lidocaine intervention groups by randomized allocation software and immediately, the medicine was injected to them. In the absence of hiccups, patients were excluded from the study.

The ephedrine group included 25 patients, who were under treatment with 5 mg/kg ephedrine, while the lidocaine group consisted of 25 patients, and who were under treatment with 1 mg/kg lidocaine. Patients were monitored during medical intervention and also in recovery, the studied variables were evaluated every 15 min.

To comply with blindness in the present research, patients were not aware of being in the treatment groups. Furthermore, collection and evaluation of information were done by contributing colleagues who did not know anything about the grouping of patients.

In case, hiccups were not suppressed with the studied medicines, 1 mg/kg of propofol was used which can be repeated up to three doses. In the absence of response to propofol, largactil was used.

Measured variables in this study included age in terms of year, the status of smoking, the type of medical

intervention, systolic and diastolic blood pressure during surgery and recovery, MAP during surgery and recovery, heart rate during surgery and recovery, duration of hiccup, the improvement frequency, and duration of intervention and recovery.

Data were analyzed by SPSS 23 (SPSS Inc., Chicago, Ill., USA) software after being collected. Quantitative variables were presented based on the mean ± standard deviation or median [interquartile domain] and qualitative variables were exhibited as numbers (percentages). Data were analyzed using independent *t*-test and Chi-square and as it is needed, Mann–Whitney and Fisher's exact tests were used.

Results

The current study was performed on 50 female patients undergoing gynecology surgery in two groups including those receiving lidocaine (n = 25) with the mean age of 37.32 ± 7.25 years and ephedrine recipient group (n = 25) with the mean age of 37.36 ± 10.51 years. The two groups were similar in terms of age, weight, height, body mass index, duration of sedation, and recovery time ($P > 0.05$) [Table 1].

On the other hand, at the beginning of the study, the two groups were consistent in terms of systolic and diastolic blood pressure, heart rate, and oxygen saturation percentages. There was no significant difference between the two groups statistically.

In contrast, with the passage of time in the 30th min during surgery on arrival to recovery, systolic and diastolic blood pressure in the ephedrine group was significantly higher than the lidocaine group ($P < 0.05$). Furthermore, the heart rate of patients at the time of entering the recovery and 15 min later at recovery was lower in the ephedrine group than in the lidocaine group ($P < 0.05$). The two groups did not differ in terms of SPO_2 percentages at any time.

In addition, the clinical status of patients also in the last follow-up (45th min of recovery) revealed that both groups had no significant difference in terms of blood pressure level and heart rate as well as no significant difference ($P > 0.05$). On the other hand, from the beginning of the surgery to the last minute of the recovery in each of the two groups, we encountered changes in clinical factors that eventually returned to normal ($P < 0.05$) [Table 2].

Table 1: Basic and surgical information of patients in two studied groups

Characteristic	Lidocaine (n=25)	Ephedrine (n=25)	P
Age (year)	37.32±7.25	37.36±10.51	0.831
Weight (kg)	67.56±7.03	70.96±12.41	0.464
Height (cm)	160.56±8.22	162.01±10.18	0.582
BMI	26.17±12.43	26.67±11.23	0.882
Duration of sedation (min)	25.80±5.14	19.40±5.65	0.123
Duration of recovery (min)	38.20±7.48	38.60±8.23	0.968

BMI: Body mass index

Eventually, the results of evaluation of hiccup status and complications in patients indicated that problem of hiccups was resolved in 14 cases (56%) in the lidocaine group, while the betterment of such unwelcome matter was achieved in 24 cases (96%) in ephedrine group ($P < 0.001$), so that the two groups did not have any significant difference in terms of the time of onset of hiccups; but the stop time of hiccups (relative to its start time) in the ephedrine group with the mean value of (2.40 ± 1.16) was significantly lower than the lidocaine group at an average of 19.64 ± 22.76 min (P = 0.014). In addition, no complications were observed in the two groups [Table 3].

Discussion

Hiccup, the medical term for which is singlets, is a pervasive disorder that transcends all ages and cultures.[16] Despite its prevalence, the pathophysiology behind this phenomenon remains an enigma. In most cases, hiccup is merely an annoyance, but in severe cases, the consequences of postoperative hiccup can be dramatic, leading to increased postsurgical pain, exhaustion, arrhythmias, and wound dehiscence.[17] Literally, hundreds of invasive, pharmacologic, and nonpharmacologic "alternative" treatments have been described for a hiccup. Various drugs such as ketamine 25 mg IV, ephedrine 5 mg IV, atropine 0.5 mg IV, and dexmedetomidine 50 g IV over 10 min have been used to manage intraoperative hiccups.[18]

The aim of this study was to evaluate the therapeutic effect of ephedrine in comparison with lidocaine in hiccup suppression after sedation in patients undergoing gynecologic surgeries.

According to the results of the current study, the two groups were similar in terms of underlying and clinical factors at the time of entering the study, so that there was no difference in blood pressure, heart rate, and SPO_2. Systolic and diastolic blood pressure only 30 min after surgery and at the time of recovery, in the lidocaine group was significantly lower than the ephedrine group. Moreover, the heart rate of patients was also significantly higher in the lidocaine recipient group than ephedrine group at the time of entrance to recovery and 15 min later. But in other times, and finally in the last follow-up carried out in the recovery, the clinical status of the patients was evaluated to be the same in two groups.

Therefore, looking at the patient's clinical condition, it can be seen that during the 1st min of surgery, the level of the blood pressure and SPO2 as well as heart rate has been reduced over time. Then, the uptrend of mentioned parameters started in the final minutes of operation, thus at

Table 2: Determining and comparing the clinical factors of patients during operation and recovery among the two studied groups

Characteristic	Groups	During operation			Recovery				P_1
		0 min	15 min	30 min	0 min	15 min	30 min	45 min	
SBP	Lidocaine	117.00±16.71	112.88±13.35	112.70±7.06	113.32±11.48	119.88±8.94	121.23±8.25	123.31±6.51	0.019
	Ephedrine	118.44±10.00	117.88±11.65	118.00±9.47	121.20±14.20	122.68±13.85	125.84±13.49	127.25±9.60	<0.001
P_2		0.713	0.164	0.029	0.0.036	0.399	0.847	0.095	
DBP	Lidocaine	70.52±10.09	69.20±12.51	67.45±6.10	66.96±5.22	73.52±6.09	70.18±6.74	73.08±4.80	0.028
	Ephedrine	72.80±5.77	71.60±9.15	70.78±1.64	73.24±11.65	73.82±10.11	74.44±9.77	75.00±4.37	0.002
P_2		0.332	0.442	0.011	0.017	0.899	0.079	0.145	
HR	Lidocaine	83.16±13.40	83.92±9.70	83.05±3.84	85.80±8.79	86.68±7.05	88.00±8.92	89.08±6.23	0.001
	Ephedrine	87.36±12.51	84.96±12.22	83.44±6.13	79.20±10.48	83.56±9.06	85.68±4.01	88.42±2.27	<0.001
P_2		0.257	0.740	0.788	0.019	0.023	0.241	0.621	
SPO_2	Lidocaine	98.80±1.08	96.24±1.48	96.80±1.91	97.92±1.82	98.59±1.50	98.38±1.32	98.60±1.09	<0.001
	Ephedrine	98.96±1.02	96.28±1.06	96.84±1.06	97.80±1.35	97.80±1.35	98.83±0.83	99.11±1.05	<0.001
P_2		0.593	0.913	0.927	0.792	0.056	0.155	0.098	

P_1: Significant level of comparison mean of variables over time in each group, P_2: Significant level of comparison mean of variables between two groups. SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate

Table 3: Determining and comparing the status of hiccup suppression and incidence rate of complications in the two groups

Outcomes	Lidocaine (*n*=25)	Ephedrine (*n*=25)	*P*
Onset of the hiccup (min)	13.76±20.21	17.89±20.62	0.479
Time of the stopping hiccup (min)	19.64±22.76	2.40±1.16	0.014
Improvement hiccup (%)	14 (56)	24 (96)	<0.001
Side effect (%)	0	0	

the end of the 45th min in the recovery, those rates reached normal clinical condition and no significant difference was observed between the two groups.

Several articles describe the successful treatment of hiccups by intravenous or nebulized lidocaine, but as we know, there is no study to compare the effects of this medication with ephedrine.[18,19]

In an animal study, Oshima *et al*. found that mechanical stimulation of the dorsal epipharynx of anesthetized cats elicited a hiccup-like response, whereas chemical stimulation with gastric juice or mechanical stimulation of other parts of the upper airway failed to elicit the reflex. This response was dependent on the phase of the respiratory cycle, being suppressed during expiration and inhibited by CO_2 and chlorpromazine.[20]

One of the primary uses of lidocaine in medicine is as a local anesthetic where its ability to block sodium channels enables it to completely abolish nerve conduction. However, even in subanesthetic doses, lidocaine possesses membrane-stabilizing properties that diminish neuronal excitability and reduce ectopic discharges. It seems logical, therefore, that lidocaine might also prove beneficial in the treatment of certain patients with hiccup, particularly those in whom a neurogenic etiology is postulated.

Previously, two reports have shown intravenous lidocaine to be effective in the treatment of a hiccup, though in slightly different contexts. The first of these revealed a decreased incidence of methohexital-induced hiccups during general anesthesia, when patients were pretreated with intravenous lidocaine. The other was a report of a patient, whose hiccup resolved after a lidocaine bolus followed by a continuous infusion. Interestingly, in two case reports, a combination regimen of intravenous lidocaine and carbamazepine was necessary for sufficient symptom control,[21,22] paralleling our experience with ephedrine and lidocaine. The underlying mechanism by which lidocaine may stop hiccups remains unclear. Since IV lidocaine blocks calcium channels and stabilizes membrane potential, as well as it blocks sodium channels in sensory neurons and thereby decreases neuronal excitability and ectopic discharges, some authors argue that this may be the decisive mechanism.[23,24]

Recently, Koteswara *et al*. in a case report noted that dexmedetomidine a selective alpha-2 adrenergic receptor agonist abolished hiccup in a similar condition, implying that sympatholytic may have a role in suppressing intraoperative hiccup. They proposed the use of dexmedetomidine instead of atropine or ephedrine which have been reported to abolish perioperative hiccups but may cause unacceptable increases in heart rate and blood pressure.[25] However, dexmedetomidine is not readily available in many centers including ours.

Metoclopramide is readily available and has also been successfully used to terminate intraoperative hiccups following laryngeal mask airway (LMA) insertion after anesthesia has been induced with propofol.[26] It may also be effective in abolishing hiccups occurring after removal of LMA in postoperative patients, in whom anesthesia was induced with propofol. In these case reports on hiccups related to LMA insertion or removal after induction of anesthesia with propofol, it is uncertain whether some cases of perioperative hiccups are the direct effect of surgery.[27]

In addition, the most important outcome of the present study was the effect of the two medicines on the suppression of hiccups in patients. According to the results, hiccups were suppressed in 56% of lidocaine recipients and 96% of patients who received ephedrine.

A more detailed review of the result showed that although the two groups did not differ from the onset of hiccups, the time to stop hiccups in the ephedrine group relative to its start time was much lower than the lidocaine group. It has been reported in a study that the incidence of hiccups in patients undergoing sedation during endoscopy was more likely than others.

In this study, hiccups have been conveyed in 20% of patients who underwent endoscopy with sedation, while the occurrence of hiccups has been reported in only 5% of patients who experienced endoscopy without sedation.

Conclusion

According to the results of the current study, the two medicines including lidocaine and ephedrine are used to control the patient's clinical condition and to avoid side effects, but ephedrine has been more successful than lidocaine as a stimulant in controlling hiccups, and it has been able to suppress hiccups in a higher percentage of patients at shorter time.

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Conflicts of interest

There are no conflicts of interest.

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