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ORIGINAL RESEARCH PERIOPERATIVE MEDICINE

Comparison of the effect of lidocaine and its combination with melatonin and the Valsalva maneuver on etomidate induced injection pain

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ABSTRACT

Background & Objective: Etomidate is commonly used in anesthesia practice because of its rapid recovery time, low incidence of apnea, and lower incidence of allergic reactions; but pain upon injection is one of the unfavorable complications of this drug, which can cause both physical and mental discomfort to the patients. It is imperative to use appropriate means to lower the pain at the injection site of etomidate in patients undergoing anesthesia. We conducted this study to compare the effects of lidocaine, lidocaine and the Valsalva maneuver, with a combination of lidocaine, melatonin and the Valsalva maneuver on decreasing the pain of etomidate injection.

Methodology: This clinical trial enrolled 135 patients. The patients were allocated into 3 groups, with one group receiving lidocaine (Group 1), the second group receiving lidocaine and the Valsalva maneuver (Group 2), and the last group receiving a combination of lidocaine, melatonin and the Valsalva maneuver. The pain resulting from injecting etomidate was evaluated based upon the Visual Analog Scale (VAS) score (with 1 being no pain and 10 the most severe imaginable pain). Data were compared and analyzed using proper statistical tests using SPSS version 23.

Results: The results of this study showed that the overall pain score in all of the groups after injection of etomidate did not show any significant difference. The mean VAS score in Group 1 was 0.27 ± 0.88, in Group 2 it was 0.16 ± 0.63, and in Group 3 0.04 ± 0.2. However, the difference between the groups was statistically not significant (P = 0.32).

Conclusion: The current study shows that the pain on injection of etomidate in the three groups of the study was reduced in a similar fashion; however, in the group which combined lidocaine, melatonin and the Valsalva maneuver, pain was the lowest, but the overall differences in score in the three groups were statistically not different.

Keywords: Etomidate, lidocaine, melatonin, Valsalva maneuver.

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1. INTRODUCTION

Etomidate is a short acting non-barbiturate anesthetic and hypnotic which can be used intravenously. Because of the low incidence of hemodynamic changes, etomidate is a suitable option for anesthesia induction in trauma, hypovolemic patients, and those with cardiovascular disorders.[1] Moreover, the likelihood of apnea after the use of etomidate is lower as compared to barbiturates and propofol. The risk of allergic reactions is less because of the lack of histamine release after drug

injection.[2] Additionally, brain protection, and fast recovery after single-dose injection, are other reasons to use etomidate for the induction of anesthesia.[3] However, some complications of this drug include adrenal suppression, nausea and vomiting, myoclonus, and pain upon injection. The transient pain during injection is one of the most common complaints of patients after the use of this drug.[2, 4, 5]

Various studies have evaluated the different methods for pain reduction after etomidate injection, which include using a formulation with lipids or using lidocaine before the injection of the drug.[6-7] The use of lidocaine before or in combination with etomidate has been proven effective in reducing pain.[8-9] Another effective method is the physiological use of the Valsalva maneuver (VM). The VM is an effective physiological method in reducing pain which is effective on both the physical and the mental aspects of pain after medical interventions.[10] The maneuver is performed by exhaling against a closed epiglottis, thereby increasing the intrathoracic and the intra-abdominal pressure thus stimulating the vagus nerve and suppressing the spinal pain receptors, which ultimately leads to the suppression of pain signals.[11] Based on the results of various studies, the VM has been effective in decreasing the pain upon injection of anesthetics such as propofol[12] and etomidate.[13]

One of the other medications effective in reducing pain is melatonin.[14-15] Melatonin is a hormone which is naturally secreted from the pineal body and to a lesser extent from other tissues of the body, with receptors in different parts of the body including the central nervous system.[16] Based on various studies, premedication with melatonin before anesthesia has shown a noticeable effect in decreasing anxiety and post-operative pain.[17, 18, 19]

We compared the effects of lidocaine, lidocaine plus the VM, and a combination of lidocaine, melatonin and the VM in decreasing the pain upon injection of etomidate in patients undergoing anesthesia.

2. METHODOLOGY

This study was approved by the Ethics Committee of the Isfahan University of Medical Science (IR.MUI.MED.REC.1399.968). The trial has been registered on the IRCT website (IRCT20160307026950N31).

The study is a triple-blind clinical trial with a control group the study was performed on ASA I and II, aged between 18 and 65 y, patients undergoing general anesthesia using etomidate.

The patients who had sepsis or a history of any allergic reactions, renal function impairment, liver function impairment, a history of hypertension, or uncontrolled diabetes were not included in the study. Those who had any signs of allergies at the time of medicine injection or an inability to perform the VM were excluded from the study.

The number of cases for the study was calculated using the following equation;[12]

$$N = \frac{(Z\alpha + Z\beta)^2[P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

In which:

P_1 = 0.77, incidence of intermediate pain

P_2 = 0.44, incidence of intermediate pain

$Z\alpha$ = 1.96 (95%), for calculating accuracy

$Z\beta$ = 0.84 (80%), for calculating power

5% downfall of cases.

The number of required cases was calculated to be 45 patients in each group, means a total of 135 patients.

On the day before surgery, written consent was obtained from the patients and the methods for performing the VM and also answering the Visual Analogue Scale (VAS) were explained to the patients.

The patients were allocated into three groups using the random allocation software;

Group A: The patients received lidocaine 2% and placebo (omega3 pearl). For the purpose of blinding the study the VM device was used, but by removing the patient's finger from the hole, no pressure was applied.

Group B: The patients received lidocaine and placebo (omega3 pearl) plus the VM by blowing into the plastic tube for a minimum of 20 sec.

Group C: The patients received oral melatonin (Razak Company, Tehran, Iran) 1 hour prior to surgery and then received IV lidocaine and then performed the VM after 3 min.

Monitoring of vital signs included electrocardiogram, non-invasive blood pressure, pulse oximetry, and capnography. An 18G intravenous (IV) catheter was inserted into the dorsal surface of the hand for IV injections.

Inj etomidate was injected by an anesthetist technician who was not involved in the study; in the second and third group after performing the VM. All the patients immediately received 25% of the total calculated etomidate dosage in 5 sec as a bolus dose and then received the remainder after their specific intervention in each group. Afterwards infusion was stopped for 15 sec

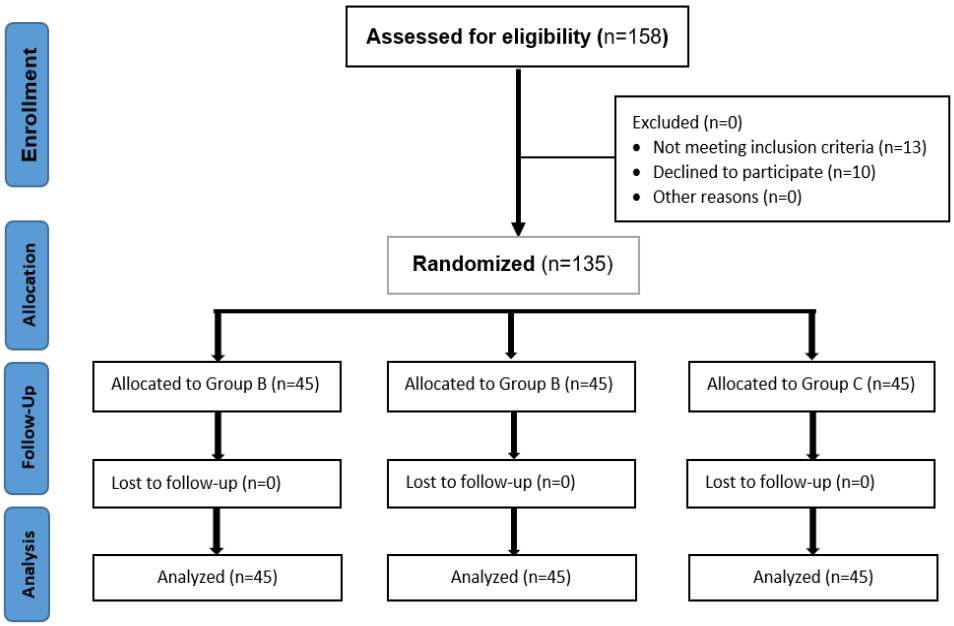

Figure 1: Study flow diagram

and pain scores were recorded 20 sec after etomidate injection.

The hemodynamic parameters, and any drop in SpO_2 before the VM, were recorded 1 and 2 min after etomidate injection, 5 and 10 min after anesthesia induction and every 15 min thereafter until the end of anesthesia. Anesthesia was induced one minute after the VM by injecting 0.3 mg/kg of etomidate plus 2 µg/kg of fentanyl. Subsequently, endotracheal intubation was performed. General anesthesia was maintained using isoflurane and fentanyl. After surgery the parameters were assessed upon entry into post-anesthesia care unit (PACU) and every 15 min thereafter until discharge from the recovery room. Nausea and vomiting were recorded.

3. RESULTS

Table 1 shows the comparison of the demographics of the participants in the study. In the study, 88 (65.2%) patients were male and 47 (34.8%) were female. There was no difference in terms of gender between the three groups (P = 0.65) (Figure 2).

The mean age for all participants was 38.59 ± 13.66 y. with the range being 18 to 65 y. The mean age in females was 41.23 ± 14.41 y and in the males, it was 37.18 ± 13.11 y (P = 0.12). There was no significant difference regarding the age of the patients in the three study groups (P = 0.15).

The results of the present study show that 20 sec after injection, the pain score based on the VAS system had a descending trend from the Group A towards the Group B and the Group C. However, the results showed that the changes in the pain score in terms of the time in the three groups did not show any significant difference (P = 0.26). Additionally, there was no significant difference in the pain score from the time of injection to 20 sec after injection in the three groups. Figure 2 shows the mean of the pain scores in the three study groups.

Table 1: Demographic characteristics of the participants

Variable		Total	Group A	Group B	Group C	P-value
**Gender	Female	47 (34.8)	18 (40)	15 (33.3)	14 (31.1)	0.65[&]
	Male	88 (65.2)	27 (60)	30 (66.7)	31 (68.9)	
*Age (y)		38.59 ± 13.66	37.53 ± 12.90	37.73 ± 13.26	41.46 ± 14.77	0.57[&&]
*BMI (kg/m^2)		24.76 ± 3.24	24.33 ± 3.35	25.21 ± 2.8	24.73 ± 3.51	0.44[&&]

*[&&]T-Test; [&]Chi square; *Quantitative variable was expressed as mean ± SD. ** Qualitative variables were expressed in n (%). Chi-square test was used to compare the results. P < 0.05 is significant*

Table 2: Comparison of the VAS pain scores in the three study groups

Time	Group A	Group B	Group C	P-value*
Before injection	0	0	0	-
20 sec after injection	2.7 ± 0.88	1.6 ± 0.63	1.4 ± 0.20	***0.32**
P-value**	0.05	0.109	0.16	****0.26**

** Compare groups; ** Comparison between 2 times; Data given as Mean ± SD*

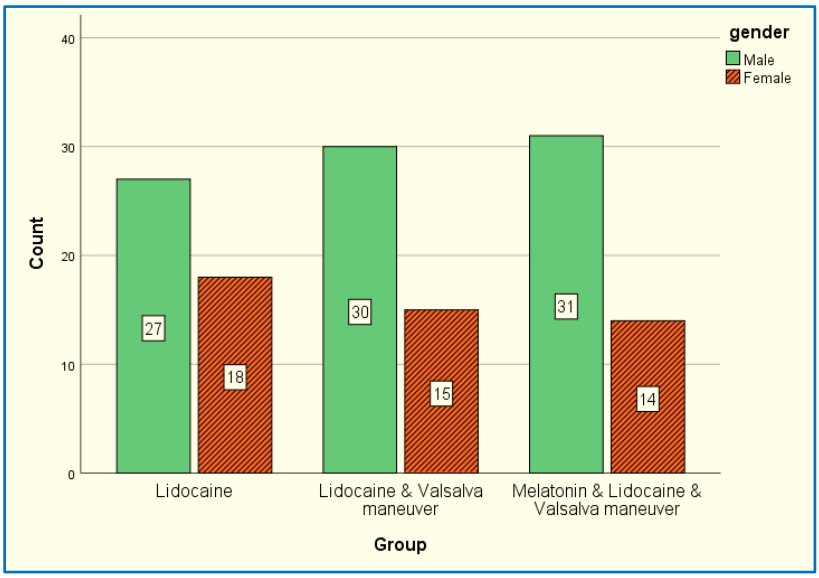

Figure 2: Gender distribution in the three study groups

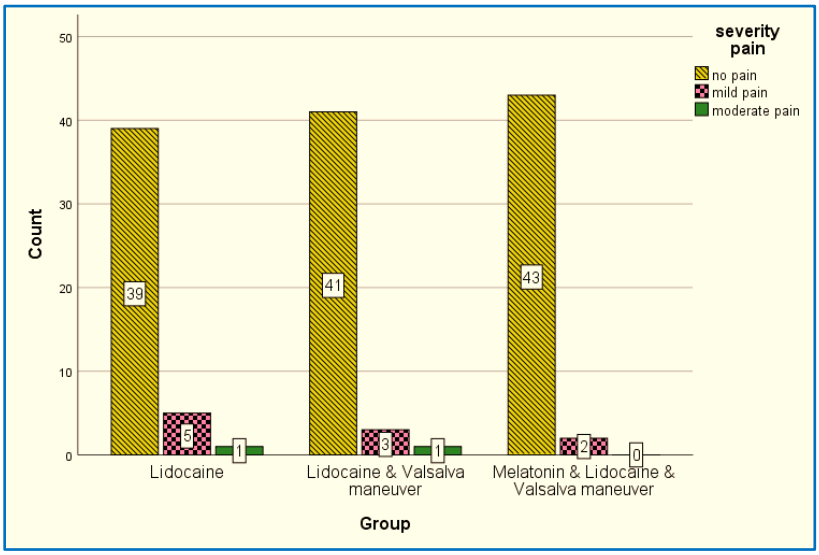

Figure 3: Severity of pain in the 3 groups

Overall, 39 (86.7%) patients in Group A, 41 (91.1%) patients in Group B, and 43 (95.6%) patients in the Group C, did not report any pain (Figure 3). The results showed that there was no significant difference in the severity of pain in the three study groups (P = 0.62).

Table 3 shows the changes in blood pressure measured eight times in the three groups. The results of this

research showed that the changes in systolic blood pressure based on time in the 3 groups had no significant difference (P = 0.58). Nevertheless, the changes in systolic blood pressure based on time in the Group A and the Group C showed significant difference but the difference in Group B was not significant. Additionally, the changes in the diastolic blood pressure and MAP based on time were not significantly different in the three groups. This is despite the fact that the changes in diastolic blood pressure and MAP in the Group C were significantly different but these changes were not significantly different in the Group A or Group B.

The results of the present study also demonstrate that the changes in heart rate (HR) during time were not significantly different in the three groups (P = 0. 49). In addition, the changes in HR were significantly different in group three but not in the other two clinical groups (Table 3).

Moreover, based on Table 3, the changes in arterial blood saturation (SpO_2) in the 3 groups during time did not show any significant differences (P = 0.82). On the other hand, the changes in SpO_2 during time in the Group A and the Group C were significantly different but these changes were not different in the Group B. It should be mentioned that in none of the patients had any drop in oxygen saturation during any of the time periods.

Table 3. Changes in the mean arterial pressure, heart rate, arterial oxygen saturation in the three study groups during times 1 to 8

Variable	Time of assessment	Group A	Group B	Group C	P-value*
Mean Arterial Pressure (mmHg)	Before injection	96.02 ± 11.88	98.53 ± 10.56	94.22 ± 7.23	0.13
	5 min after injection	98.37 ± 6.68	98.28 ± 12.25	97.51 ± 15.58	0.38
	10 min after injection	98.37 ± 6.68	98.57 ± 8.46	94.60 ± 15.34	0.85
	15 min after injection	99.42 ± 6.13	98.82 ± 8.68	98.48 ± 17.83	0.93
	First 15 min during the operation	100.0 ± 4.65	99.88 ± 9.85	100.97 ± 16.28	0.88
	Sec 15 min during the operation	100.4 ± 4.67	90.04 ± 9.88	94.19 ± 11.22	0.33
	Third 15 min during the operation	98.68 ± 5.44	98.02 ± 8.50	97.60 ± 12.06	0.88
	Fourth 15 min during the operation	100.5 ± 6.21	96.96 ± 8.15	93.23 ± 12.77	0.089
	Comparison of the 1st to 8th time (P-value)	**0.023**	**0.90**	**P < 0.0001**	**P = 0.801**
Heart Rate (BPM)	Before injection	85.42 ± 14.64	84.06 ± 9.21	80.71 ± 8.85	0.13
	5 min after injection	85.11 ± 12.59	84.71 ± 87.13	87.13 ± 12.33	0.38
	10 min after injection	83.88 ± 11.79	82.73 ± 8.29	84.92 ± 6.01	0.85
	15 min after injection	83.6 ± 9.12	82.93 ± 7.98	83.85 ± 6.85	0.93
	First 15 min during the operation	84.35 ± 9.58	81.9 ± 6.97	84.14 ± 5.28	0.88
	Sec 15 min during the operation	82.85 ± 9.8	80.51 ± 5.95	85.45 ± 6.72	0.33
	Third 15 min during the operation	81.84 ± 8.18	80.12 ± 4.09	85.35 ± 7.72	0.88
	Fourth 15 min during the operation	82.76 ± 6.36	80.24 ± 5.57	83.92 ± 6.35	0.089
	Comparison of the 1st to 8th time (P)	**0.27**	**0.027**	**0.053**	**0.479**
Percentage of blood oxygen saturation	Before injection	93.59 ± 4.74	94.53 ± 1.35	95.17 ± 1.61	0.044
	5 min after injection	98.88 ± 0.49	99.22 ± 0.26	98.55 ± 1.05	0.005
	10 min after injection	99.18 ± 0.54	99.26 ± 0.53	99.51 ± 0.5	0.011
	15 min after injection	99.27 ± 0.58	99.28 ± 0.45	99.48 ± 0.54	0.106
	First 15 min during the operation	99.25 ± 0.57	97.26 ± 13.46	99.42 ± 0.62	0.35
	Sec15 min during the operation	99.17 ± 0.5	99.28 ± 0.45	99.39 ± 0.58	0.15
	Third 15min during the operation	99.21 ± 0.48	99.27 ± 0.45	99.52 ± 0.5	0.016
	Fourth 15min during the operation	99.19 ± 0.51	99.21 ± 0.41	92.57 ± 26.64	0.14
	Comparison of the 1st to 8th time (P)	**P < 0.0001**	**P < 0.0001**	**0.39**	**0.82**

**t-test; Data presented as Mean ± SD*

P < 0.05 considered as significant.

Table 5: Comparison of the incidence of nausea and vomiting in the three groups

Variable	Group A	Group B	Group C	P-value
Nausea	5 (11.1)	5 (11.1)	6 (13.3)	0.93
Vomiting	2(4.4)	2 (4.4)	1 (2.2)	0.80

Data presented as n (%)

P<.05 considered as significant.

Table 4 depicts the distribution of frequency of tachycardia in the patients at various recording times. This table shows that at the time before injection, the incidence of tachycardia in the Group A was significantly higher than the other two groups (P = 0.024). On the other hand, at the time of 10 min after the injection of the medication, tachycardia was significantly higher in Group C than the other two groups (P = 0.013).

Additionally, the results of the study showed that the incidence of nausea and vomiting was not significantly different in the 3 groups (Table 5)

4. DISCUSSION

Based on the efficacy and rapid recovery time of etomidate and also its lower rate of complication, such as apnea, and allergic reactions, this medication is one of the most widely used medicines in anesthesia. However, the pain on injection of etomidate is an unwanted complication which causes both physical and mental discomfort for some patients. Therefore, the reduction of pain in patients undergoing anesthesia with etomidate is of utmost importance. Previously, there have been different methods proposed for decreasing this pain.

In the current study, the pain on injection of etomidate in the three groups did not show a significant increase compared to the time before injection, which was free of pain. This means that lidocaine alone, and in combination with the VM and also in combination with melatonin and the VM had high efficiency in reducing the pain on injection of etomidate. This finding was in accordance with other studies in this regard which are reviewed below.

Nazemroaya et al. postulated that a combination of lidocaine and the VM decreased the pain on injection of etomidate.[13] Also, in a study performed by Pourmahdi et al., it was shown that lidocaine significantly decreased the pain on injection of etomidate, compared to a control group.[9] In other studies, the effectiveness of this medication on decreasing the pain on injection of propofol was proven.[22-24, 25]

VM has many benefits being economical, without any side effects, pain-free and popular among patients. Therefore, using this method simultaneously with other proven medications or techniques can be a suitable option in decreasing the pain on injection of etomidate.[13,26] Additionally, performing the VM has been shown to be effective in reducing the dose-dependent complications of other drugs.[26] In the current study, the pain intensity in the combination group of lidocaine and the VM was less than the lidocaine alone group, but this difference was not statistically significant.

In a study done by Kumar et al., it was found that VM added to other proven methods of pain reduction, can ensure that the injection pain of propofol is reduced.[26] This method was also used to control pain in other medical procedures. For example, in a study on the efficacy of two methods of performing the VM and ice-pack massage on reducing the pain of needle insertion into an AVF (arterio-venous fistula) were reported. They concluded that the VM decreased pain more effectively than ice-pack massage.[27] Babaie et al. showed that the VM was an alternative drug-free method that reduced the pain of IV catheterization without causing any hemodynamic changes.[28]

Although in this study the efficacy of the three groups in reducing pain was not shown to be statistically significant, but the combination of lidocaine and melatonin with the VM was shown to have the highest efficacy and lowest amount of pain. Such that, none of the patients in this group showed any levels of intermediate pain with only two of 95% of the patients experiencing no pain at all. This finding confirms the beneficial effect of melatonin in decreasing the injection pain. Other studies have also shown the beneficial effect of melatonin in reducing pain. For example, a study performed by Mowafi et al., showed that administering melatonin prior to IVRA was a beneficial procedure, since it reduced patient anxiety, pain of tying a tourniquet, and pain after surgery.[29]

The findings of Caumo et al. signified the fact that melatonin administration before surgery had anxiolytic and analgesic effects (especially in the 24-hour period after surgery). Moreover, the re-establishment of the circadian rhythm was improved.[30] A review study by Danilova and Kurganova showed that on the one hand, the circadian rhythm restoration due to melatonin caused an improvement in sleep pattern and on the other hand, it provided analgesic effects on chronic pain by both effecting the melatonin receptors and other neurotransmitters.[3]

5. CONCLUSION

Based on the results of the current study, it is confirmed that the pain on injection of etomidate can be reduced by either injecting lidocaine IV, or use of melatonin or VM performed by the patient prior to the etomidate injection; however, combined use of lidocaine, melatonin and the Valsalva maneuver will reduce the pain to the lowest, but the overall differences in VAS scores in the three groups were statistically not different. The efficacy of melatonin oi pain on injection of etomidate was shown for the first time.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

BN: Study concept, analysis, and design, interpretation of the data, critical revision of the manuscript for important

HDP: drafting of the manuscript, intellectual content

11. REFERENCES

1. Bordo D, Chan SB, Shin P. Patient satisfaction and return to daily activities using etomidate procedural sedation for orthopedic injuries. West J Emerg Med. 2008;9(2):86. [PubMed]
2. Forman SA, Warner DS. Clinical and molecular pharmacology of etomidate. J Am Soc Anesthesiol. 2011;114(3):695-707. [PubMed] DOI: 10.1097/ALN.0b013e3181ff72b5
3. Nooraee N, Fathi M, Edalat L, Behnaz F, Mohajerani SA, Dabbagh A. Effect of Vitamin C on serum cortisol reduction after etomidate induction of anesthesia. J Cell Mol Anesth. 2015;1(1):28-33. DOI: 10.22037/jcma.v1i1.10149
4. Valk BI, Struys MM. Etomidate and its analogs: A review of pharmacokinetics and pharmacodynamics. Clin Pharmacokinet. 2021;60(10):1253-69. [PubMed] DOI: 10.1007/s40262-021-01038-6
5. Godwin SA, Caro DA, Wolf SJ, Jagoda AS, Charles R, Marett BE, et al. Clinical policy: procedural sedation and analgesia in the emergency department. Ann Emerg Med. 2005;45(2):177-96. [PubMed] DOI: 10.1016/j.annemergmed.2004.11.002
6. Doenicke A, Roizen M, Hoernecke R, Lorenz W, Ostwald P. Solvent for etomidate may cause pain and adverse effects. Br J Anaesth. 1999;83(3):464-6. [PubMed] DOI: 10.1093/bja/83.3.464
7. Azimaraghi O, Aghajani Y, Molaghadimi M, Khosravi M, Eslami K, Ghadimi F, et al. Ondansetron reducing pain on injection of etomidate: A controlled randomized study. Rev Bras Anestesiol. 2014;64:169-72. [PubMed] DOI: 10.1016/j.bjane.2013.06.013
8. Brock MF, Grace BE, Morley B, Hillegass G, Houle TT, Groban L. Does lidocaine more effectively prevent pain upon induction with propofol or etomidate when given preemptively than when mixed with the drug? J Clin Anesth. 2010;22(7):505-9. [PubMed] DOI: 10.1016/j.jclinane.2009.11.004
9. Pourmehdi Z, Soltanzadeh M, Soltani F, Leilatan J. Comparing the efficacy of Lidocaine versus Magnesium sulfate on pain associated with intravenous administration of Etomidate. J Iranian Soc Anaesthesiol Intensive Care. 2015;37(2):112-9. [FreeFullText]
10. Mohammadi SS, Pajand AG, Shoeibi G. Efficacy of the valsalva maneuver on needle projection pain and hemodynamic responses during spinal puncture. Int J Med Sci. 2011;8(2):156. [PubMed] DOI: 10.7150/ijms.8.156
11. Kirchner A, Stefan H, Bastian K, Birklein F. Vagus nerve stimulation suppresses pain but has limited effects on neurogenic inflammation in humans. Eur J Pain. 2006;10(5):449-55. [PubMed] DOI: 10.1016/j.ejpain.2005.06.005
12. Agarwal A, Sinha PK, Tandon M, Dhiraaj S, Singh U. Evaluating the efficacy of the valsalva maneuver on venous cannulation pain: a prospective, randomized study. Anesth Analg. 2005;101(4):1230-2. [PubMed] DOI: 10.1213/01.ane.0000167270.15047.49
13. Nazemroaya B, Aghadavodi O, Honarmand A, Ahmadian S. A comparative study of Valsalva maneuver, lidocaine, and Valsalva maneuvers with administration of lidocaine to reduce the pain associated with administration of etomidate during general anesthesia. Anesth Pain Med. 2021;11(3). [PubMed] DOI: 10.5812/aapm.113408
14. Kuthati Y, Lin SH, Chen J, Wong CS. Melatonin and their analogs as a potential use in the management of neuropathic pain. J Formos Med Assoc. 2019;118(8):1177-86. [PubMed] DOI: 10.1016/j.jfma.2018.09.017
15. Gelfand AA, Ross AC, Irwin SL, Greene KA, Qubty WF, Allen IE. Melatonin for acute treatment of migraine in children and adolescents: A pilot randomized trial. Headache. 2020;60(8):1712-21. [PubMed] DOI: 10.1111/head.13934
16. Chen WW, Zhang X, Huang WJ. Pain control by melatonin: physiological and pharmacological effects. Exp Ther Med. 2016;12(4):1963-8. [PubMed] DOI: 10.3892/etm.2016.3565
17. Maitra S, Baidya DK, Khanna P. Melatonin in perioperative medicine: current perspective. Saudi J Anaesth. 2013;7(3):315. [PubMed] DOI: 10.4103/1658-354X.115316
18. Gitto E, Romeo C, Reiter R, Impellizzeri P, Pesce S, Basile M, et al. Melatonin reduces oxidative stress in surgical neonates. J Pediatr Surg. 2004;39(2):184-9. [PubMed] DOI: 10.1016/j.jpedsurg.2003.10.003
19. Lotfy M, Ayaad M. Preoperative oral melatonin can reduce preoperative anxiety and postoperative analgesia in a dose-dependent manner. Ain Shams J Anesthesiol. 2021;13(1). DOI: 10.1186/s42077-021-00146-6
20. Crichton N. Visual analogue scale (VAS). J Clin Nurs. 2001;10(5):706-6. [FreeFullText]

21. Safavi M, Honarmand A, Sahaf AS, Sahaf SM, Attari M, Payandeh M, et al. Magnesium sulfate versus lidocaine pretreatment for prevention of pain on etomidate injection: A randomized, double-blinded placebo controlled trial. J Res Pharm Pract. 2015;4(1):4. [PubMed] DOI: 10.4103/2279-042X.150044
22. Hong J-M, Lee HJ, Cho AR, Baik JS, Lee DW, Ji YT, et al. Pretreatment with 5% lidocaine patch reduces cannula-induced and propofol-induced pain: a randomized, double-blind, placebo-controlled study. Korean J Anesthesiol. 2016;69(5):468. [PubMed] DOI: 10.4097/kjae.2016.69.5.468
23. Jarineshin H, Melekshoar M. Effect of intravenous injection of hydrocortisone and lidocaine 2% on pain after propofol injection: a double-blind randomized clinical trial. *Pars J Medl Sci*. 2022;17(3):43-9. DOI: 10.52547/jmj.17.3.43
24. Lang BC, Yang CS, Zhang LL, Zhang WS, Fu YZ. Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol in pediatric patients: a PRISMA-compliant meta-analysis of randomized controlled trials. Medicine. 2017;96(11). [PubMed] DOI: 10.1097/MD.0000000000006320
25. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ. 2011;342. [PubMed] DOI: 10.1136/bmj.d1110
26. Kumar S, Khuba S, Agarwal A, Gautam S, Yadav M, Dixit A. Evaluation of efficacy of Valsalva maneuver for attenuating propofol injection pain: a prospective, randomized, single-blind, placebo-controlled study. Korean J Anesthesiol. 2018;71(6):453. [PubMed] DOI: 10.4097/kja.d.18.00017
27. Davtalab E, Naji S, Shahidi S. Comparing the effects of valsalva maneuver and ice massage at Hoku point methods on pain intensity within the needle insertion to the arteriovenous fistula (AVF) for patients undergoing hemodialysis in selected hospitals in Isfahan in 2015. Int J Med Res Health Sci. 2016;5(5):101-7. [FreeFullText]
28. Babaei M, Jalali R, Jalali A, Rezaaei M. The effect of Valsalva maneuver on pain intensity and hemodynamic changes during intravenous (IV) cannulation. Iran J Nurs. 2017;30(108):52-9. [FreeFullText]
29. Mowafi HA, Ismail SA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. Anesth Analg. 2008;107(4):1422-6. [PubMed] DOI: 10.1213/ane.0b013e318181f689
30. Caumo W, Torres F, Moreira NL, Auzani JA, Monteiro CA, Londero G, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. Anesth Analg. 2007;105(5):1263-71. [PubMed] DOI: 10.1213/01.ane.0000282834.78456.90
31. Danilov A, Kurganova J. Melatonin in chronic pain syndromes. Pain Ther. 2016;5(1):1-17. [PubMed] DOI: 10.1007/s40122-016-0049-y
32. Song GH, Leng PH, Gwee KA, Moochhala SM, Ho KY. Melatonin improves abdominal pain in irritable bowel syndrome patients who have sleep disturbances: a randomised, double-blind, placebo-controlled study. Gut. 2005;54(10):1402-7. [PubMed] DOI: 10.1136/gut.2004.062034

