

Original Article

Effect of Oral Midazolam in Pain Relief of Patients Need Nasogastric Tube Insertion: A Clinical Trial Study

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Received: 14-07-2019.
Accepted: 30-12-2019.
Published: 26-06-2020.

INTRODUCTION

Nasogastric tube (NGT) is one of the most common emergency procedures used to remove the stomach contents and reduce stomach and intestinal stomach pressure in cases such as intestinal obstruction, gastrointestinal bleeding, poisoning, and intubation.^[1] One of the main problems in NGT insertion is pain when passing through the tube from the nasal mucosa and the beginning of the throat, which leads to restlessness and resistance of the patient during tube insertion and its arbitrary removal. Patient pain control during this procedure is one of the important measures. Throat anesthesia is mentioned to resolve this problem. On

ABSTRACT

Objective: Due to the presence of pain during nasogastric tube (NGT) insertion and related complications and lack of positive clinical response of nasopharyngeal anesthesia with lidocaine and the related side effects and limitations in ketamine and intravenous midazolam, this study aims to determine the efficacy of oral midazolam in relieving pain in the patients requiring NGT insertion.

Methods: A randomized, triple-blind clinical trial was performed on the patients in the Emergency Department of Zanjan Valiasr and Mousavi Hospitals in Iran, who were nominated for NGT. In each group, 100 patients were examined. Two milligram syrups of midazolam and placebo were administered 20 min before the procedure. In two groups, the pain based on the Visual Analog Scale and satisfaction rate of patients during the NGT insertion were compared. The data were analyzed through the SPSS software version 16.0. **Findings:** There was no statistically significant difference in the demographic characteristics of two groups. Despite the effects of potential confounding variables, the cause of the referral and indication of NGT, as well as the use of midazolam syrup, had a significant relationship with the outcome, so that midazolam group experienced less pain. The mean and standard deviation of the examined outcomes (feeling of pain and satisfaction with NGT insertion) was statistically significantly different in the midazolam group as compared to the placebo group ($P = 0.001$). **Conclusion:** Midazolam was effective in decreasing pain and increasing the satisfaction of patients after NGT insertion. This manuscript is registered in Irc. com with code IRCT20110629006922N4.

KEYWORDS: Midazolam, nasogastric tube, pain, satisfaction

the other hand, impregnation of the NGT tip with the lidocaine gel does not give enough time for numbness, and on the other hand, it causes the patient to feel angry due to the bitterness and excitation of the pharynx.^[2]

Midazolam is a category of benzodiazepine medications that have a short start and short duration of action and is used for relaxation and short-acting anxiety. It has fast oral absorption and liver metabolism. The

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How to cite this article: Rouhi AJ, Zeraatchi A, Rahmani F, Rouhi AJ, Motamed N, Rastin A, et al. Effect of oral midazolam in pain relief of patients need nasogastric tube insertion: A clinical trial study. J Res Pharm Pract 2020;9:112-7.

Access this article online

Quick Response Code:



Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_19_80

usual dose is 0.1–0.025 mg and the peak is 1–2 h and half a lifetime of 1.5–3 h. The advantage of oral administration is easy titration and has no side effects.^[1,2] The drug is very safe. In intravenous (IV) drug administration, respiratory depression may occur in <10% of patients, mainly due to increased obstruction and resistance to upper airways due to decreased muscle tone. Often, the side effects of the drug are seen in the IV administration.^[1-3]

In sedative and antinociceptive procedures, in cases where the procedure involves low anxiety but with high anxiety, such as cerebrospinal fluid puncture or central venous insertion, IV midazolam, and venous propofol are recommended, and in cases where the procedure has little pain. It requires a localized or tranquilized anesthetic to a moderate extent (such as a reduction of the shoulder joint dislocation that injected lidocaine into the articular), IV midazolam is a safe and safe choice.^[4] In children, it can also be given orally in addition to the IV form.^[2]

Midazolam was able to increase pain tolerance and reduce the intensity of pain induced by puncture to a significant extent compared to the other three arms, but there was no difference in the intensity of fear.^[5]

Midazolam is a short-acting benzodiazepine with anxiolytic effect. Its oral administration has easy titration and fast absorption. The drug is very safe, and its oral administration has not been studied in relieve pain. Other medicines such as lidocaine, ketamine, and propofol had more limitations and side effects than midazolam. Therefore, we decided to evaluate the effect of oral midazolam on patients who require NGT insertion.^[3]

Due to the presence of pain during the introduction of NGT and its related complications in many patients receiving it and the lack of positive clinical response to thrombocytopenia with lidocaine as well as the related side effects and limitations in studies with IV ketamine and midazolam, we decided to investigate the effect of oral midazolam in relieving pain in patients requiring the ease of use for NGT.

METHODS

This study was a randomized, blinded triplicate clinical trial conducted in the Emergency Ward of Valiasr Hospital and Mousavi Hospital in Zanjan city of Iran from March 2018 to May 2019. The total sample size was 200 patients (100 patients per each group). Patients were divided into two-person blocks based on Random Software Allocation Software (RAS) (Global Info Solutions & Services (GISS) is a technology company headquartered in Bangalore, India) and then two

case groups (midazolam receiving group) and control group (placebo group) were defined in the software.

The inclusion criteria included patients aged 18–60 years who were admitted to the emergency department for the treatment or diagnostic purposes under the NGT insertion procedure. The exclusion criteria included pregnancy, lactation, chronic obstructive pulmonary disease, loss of consciousness (content and level), nausea and vomiting, benzodiazepine susceptibility, weighing <40 kg, and obese (Body mass index [BMI] >30), other contraindications for benzodiazepine administration (e.g., recent consumption of benzodiazepines and epithets), and dissatisfaction with the study.

Participants were randomly divided into two groups based on RAS software. Prepared syrups were dosed with midazolam and placebo administered to the person responsible for the NGT and administered orally for 20 min before the procedure with a mild stenting dose (2 mg). Then, the procedure was based on the standard protocol. It should be noted that containers containing drugs and placebo were precoded so that the relevant assistant, patient, and NGT employ the contents of the dishes. Moreover, the placebo was used in terms of color, odor, and appearance of the drug. The injectable solution of midazolam hydrochloride (Ampule 15 mg/3 ml Midamax, Tehran Chimi, Iran) was introduced in Syrup Bp (66.7% sucrose and 33.3% water as solvent) and flavored with orange extract to prepare oral solution of midazolam 2 mg/ml.

The compound was prepared in pH = 3.5 by the responsible pharmacist with shelf life of 14 days. Adjustment to a pH of about 3.5 ensured that the drug remains stable in solution.

Eventually, in two main groups (based on the Visual Analog Scale rating from 1 to 10), the reminder of the insertion time and patient satisfaction (based on patients explanation, rating from 1 to 10) during the NGT insertion was compared based on the patient statement. If there was previous experience with NGT, the patient was also asked about the comparison with the previous one.

The primary outcome variable in this study was the patient's pain rate and the secondary outcome of the patient's satisfaction from the procedure. The analysis strategy was as per the protocol in this study.

The data of all patients, including age, sex, BMI, vital signs, current condition, NGT, NGT size, and previous history of NGT insertion, were recorded.

The data were analyzed using the SPSS version 16.0 SPSS (Headquarters: Armonk, New York, U.S.). At

first, the normal distribution of the data was investigated using the Kolmogorov–Smirnov test. In descriptive statistics, mean \pm standard deviation was used to report the quantitative variables and the frequency (based on percent) to report the nominal variables. To compare the two groups in terms of qualitative (nominal) and quantitative variables, the Chi-square test and independent sample *t*-test were applied, respectively. $P < 0.05$ was considered statistically significant in all cases.

This manuscript is registered in IRCT.com with code IRCT20110629006922N4.

RESULTS

In this clinical trial, 200 patients were studied. These patients were selected from among those who had the medical indication for NGT insertion.

The results did not show statistically significant differences in the baseline characteristics of the two groups in the study. Table 1 shows the mean and SD of baseline characteristics (including quantitative and continuous variables) in the two groups treated with midazolam and placebo.

Among the variables studied, only the distribution of the cause of referral and the indication of NGT showed

significant differences between the two groups. Table 2 shows the baseline characteristics of the participants in the two groups treated with midazolam and placebo.

According to the results of the study, pain and satisfaction in the two groups showed a significant difference. Hence, that the group receiving midazolam had less pain and satisfaction than the placebo group. Table 3 shows the mean and SD of the outcomes of the study in the two treatment groups.

Table 4 shows the multiple linear regression results, in which the amount of pain as a consequence, midazolam syrup as a predictive variable, and the reason for the referral and indication of NGT were considered as confounding variables. According to the results of the study, despite removing the potential effects of confounding variables, including the cause of the referral and indication of NGT, use of midazolam syrup had a significant relationship with the outcome, so that the patients with midazolam experienced less pain.

Table 5 reports the multiple linear regression results, in which satisfaction as a result, midazolam syrup as a predictive variable, and the reason for the referral and indication of NGT were considered confounding variables. According to the results of the study, despite removing the potential effects of confounding variables, including the cause of the referral and indication of NGT, the use of midazolam syrup had a significant relationship with the outcome, so that the users of midazolam were more satisfied.

Table 1: Mean and standard deviation of quantitative variables of baseline demographic characteristics in two groups (n=200)

Demographic parameters	Mean \pm SD		P*
	Midazolam group	Placebo group	
Age (years)	42.05 \pm 14.52	42.30 \pm 12.12	0.700
Weight (kg)	74.27 \pm 8.41	74.64 \pm 8.14	0.752
Height (cm)	165.76 \pm 7.00	165.51 \pm 5.90	0.785
BMI (kg/m ²)	27.06 \pm 2.92	27.27 \pm 2.91	0.607

*Independent *t*-test was applied BMI. BMI=Body mass index, SD=Standard deviation

DISCUSSION

The aim of this study was to evaluate the effect of midazolam on pain and satisfaction of patients receiving NGT. Accordingly, 200 patients were treated with midazolam syrup and placebo syrup in two groups of 100 patients. Our results showed that midazolam was

Table 2: Mean and standard deviation of qualitative variables of baseline demographic characteristics in two groups (n=200)

Variable	Condition	Frequency (percentage)		P
		Midazolam group	Placebo group	
Sex	Male	53 (53)	49 (49)	0.671*
	Female	47 (47)	51 (51)	
NGT indication	GI decompression	10 (10)	14 (14)	0.001**
	GI bleeding	12 (12)	0 (0)	
	Gastric washing	52 (52)	59 (59)	
	Persistent epigastric pain	14 (14)	11 (11)	
	Acute cholecystitis	12 (12)	10 (10)	
	Acute pancreatitis	0 (0)	6 (6)	
Time reminder of NGT insertion	No	4 (4)	6 (6)	0.748*
	Yes	96 (96)	94 (94)	

*Chi-square test was applied, **Fisher's exact test was applied. GI=Gastrointestinal, NGT=Nasogastric tube

Table 3: Mean and standard deviation of the outcomes of two groups of the study (n=200)

Outcome	Mean±SD		P*
	Midazolam group	Placebo group	
Pain	4.08±1.12	5.9±0.96	0.001
Satisfaction	6.07±1.2	4.55±1.02	0.001

*Independent *t*-test was applied. SD=Standard deviation

Table 4: The results of multiple linear regression on the amount of pain as outcome (n=200)

Variable	Standardized β factor	Nonstandardized β factor	T-test	P
Cause of referral	-0.072	-0.031	-1.270	0.206
NGT indication	0.127	0.129	2.24	0.026
Midazolam syrup	0.651	1.804	12.22	0/001

NGT=Nasogastric tube

Table 5: The results of multiple linear regression on the satisfaction rate as the outcome (n=200)

Variable	Standardized β factor	Nonstandardized β factor	T-test	P
Cause of referral	0.261	0.114	4.46	0.001
NGT indication	-0.312	-0.316	-5.32	0.001
Midazolam syrup	0.536	-1.49	-9.74	0.001

NGT=Nasogastric tube

able to reduce the amount of pain versus placebo, and satisfaction was higher in the midazolam group than the placebo group. When results were modulated in terms of potential confounding variables, such as the NGT indication and the cause of referral in multivariate models, the results also showed a greater effect of midazolam as compared to placebo.

Manning, in confirmation of our results, showed the effect of midazolam in pain relief after NGT insertion in emergency patients our study, midazolam was administered intravenously. Due to the different routes of administration of midazolam (injectable and oral in two studies), the results cannot be accurately compared. However, we observed similar results with their study, due to the sedative effect of this drug.^[6]

Conway *et al.*, in their systematic review study, failed to demonstrate that sufficient evidence for the efficacy of midazolam as a sedative drug before medical intervention is more effective or less effective than placebo. On the other hand, evidence suggests that midazolam provides less sedation than chloral hydrate in children who are subjected to noninvasive diagnostic medical procedures.

Midazolam made them drowsy, reduced anxiety, and made it easier to perform a procedure. However, the effect of pain in this study was not evaluated. Due to the different methods of administering midazolam in various studies analyzed by them, the results of this study are not comparable to our study. Our review has also been done on adult patients, but Conway analyzes the studies on children and adults.^[7]

Jeon *et al.*'s study was a randomized, single-blind study, with a total of 128 women were allocated to the midazolam premedication group and control group (64 patients in each group). They showed that midazolam is not effective in reducing anxiety before surgery. However, midazolam in this study increases the effect of sedation of anesthetic drugs and reduces the duration of anesthetic induction. Furthermore, midazolam helps to maintain hemodynamic stability by reducing stress response during induction of anesthesia. Unlike our results, this study did not have an analgesic effect after surgery. However, the study's authors emphasized that midazolam may have analgesic effects during the induction of anesthesia, which can be interpreted in light of our results. The inability of midazolam after surgery can be influenced by the duration of midazolam administration before and after the patient's recovery. While in our study, there was only a 20-min interval between midazolam administrations before the introduction of NGT. In surgery, this period can be much longer, while the analgesic effects of this drug were demonstrated in Jeon *et al.* During anesthesia induction, as we know, midazolam is known as a short-acting sedative.^[8] The difference between the results of this study could be due to the differences in the study groups. Hence, that in the study of Geon, the research was done on the woman before surgery, but our examination included both sexes before the insertion of the tube.

According to Salem *et al.*'s study, the comparison of the efficacy and safety of midazolam syrup versus orally administered IV midazolam (PO midazolam) in noncooperative children in dental treatments was investigated, and the result was a positive effect on safe sedation in noncooperative children. Acceptable behavior was observed in 90.9% of syrup groups and 86.4% of PO group. The ratings of sleep, crying, and movement domains were not significantly different between groups. Physiological parameters remained in the normal range without any significant difference between the groups, and no adverse effect was observed.^[9] Despite the different research background in dentistry and pediatrics, this adult study and the NGT treatment process were inspired by the positive

effects of midazolam. This similarity can be due to the effects of sedative midazolam. We also showed that patients receiving midazolam had more satisfaction than placebo. This is foreseeable. As tolerating the pain and reducing the anxiety caused by midazolam, less can lead to the satisfaction of patients. However, with regard to the antianxiety effects of midazolam, there were no consistent results.

Soliman was studied on 647 intensive care physicians from 16 Western European countries. Midazolam was used as a sedative by 63% of respondents and propofol by 35%. Midazolam is preferred over propofol in France, Germany, the Netherlands, Norway, and Austria. For analgesia, the most commonly used drugs included morphine (33%), fentanyl (33%), and sufentanil (24%). Multivariate analysis showed that the combination of midazolam and fentanyl was most often used in France; propofol with morphine in Sweden, the UK and Ireland, and Switzerland; midazolam with morphine in Norway; and propofol with sufentanil in Belgium and Luxemburg, Germany, and Italy. The use of a sedation scale varied from 72% in the UK and Ireland to 18% in Austria. This study demonstrates substantial international differences in sedative and analgesic practices in Western European ICUs.^[10] Our results showed that midazolam was able to reduce the amount of pain versus placebo, and satisfaction was higher in the midazolam group. Mean and SD of the pain elimination outcomes of midazolam and placebo recipients were 4.08 ± 1.12 and 5.9 ± 0.96 , respectively. Mean and SD of the satisfaction of midazolam and placebo recipients were 6.07 ± 1.2 and 4.55 ± 1.02 , respectively. This similarity with soliman can be due to the sedative and analgesic effects of midazolam, but in our study, we only used oral midazolam for the patient and other drugs do not be used. Thus, the number and route of drug usage were not similar; therefore, the percentages of two studies were different.

We showed in this study that midazolam is an effective drug for reducing pain following the introduction of NGT. Meanwhile, this drug has increased the satisfaction of patients versus placebo. We also showed that this effect is independent of the indication of the NGT embedding or the causes of the visit. In addition, this study has a good sample size that has led to the randomization of patients with many confounding variables in the two groups. In addition, the study was of sufficient power to discover the difference between the two groups. Of particular note in this study is the investigation of satisfaction of the patients with NGT insertion after the administration of midazolam, which has not been studied in other similar studies.

Among the limitations of this study were the stringent exit criteria that were considered for inclusion in the study, which results in generalizability results for all those who need NGT have not. Although we conducted the study with a sufficient sample size. However, the multicentricity of the study will result in more generalized results. Meanwhile, in this study, as far as the study guides are concerned, we first evaluated patients' satisfaction with the evaluation of the effect of this drug on pain, although this could be a sign of the strength of this study. However, we could not compare the results of our study with the other studies. In addition, other studies on the effect of this drug on satisfaction in different populations are needed. One of the other limitations of this study is the lack of safety assessment of this drug in terms of side effects. Study guides recommended that studies be conducted in this area. Meanwhile, we compared this drug to a placebo. If comparisons with other drugs in this area and cost comparison, the efficacy of similar drugs with midazolam could be helpful in clinical decision-making.

In our study, midazolam was effective in decreasing pain and increasing the satisfaction of patients after NGT insertion. In order to provide more evidence, guidance is needed on the use of this drug in patients requiring NGT.

AUTHORS' CONTRIBUTION

All authors contributed to the concept of this research, study design, data gathering, analysis or interpretation, and revised the drafted manuscript and approved its final version. They are also accountable about the content of this manuscript and guarantee the integrity of the research.

Acknowledgments

The authors would like to thank the emergency interns and residents for their participation in the survey who supported my work in this way and helped me get results of better quality.

Financial support and sponsorship

This study was financially supported by the Research Deputy of Zanjan University of Medical Sciences, Zanjan, Iran.

Conflicts of interest

There are no conflicts of interest.

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