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ORIGINAL

Comparing the efficacy in the intravenous and sublingual administration of midazolam for the sedation of patients during upper gastrointestinal endoscopy

Comparación de la eficacia en la administración intravenosa y sublingual de midazolam para la sedación de pacientes durante la endoscopia digestiva alta

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Abstract

Background: Upper gastrointestinal (GI) endoscopy is a common procedure for the diagnosis and treatment of upper digestive tract diseases. Relief of pain and discomfort during endoscopy is necessary. In our study, the sublingual administration and the injection of midazolam were compared in terms of their efficacy in the sedation of patients undergoing upper gastrointestinal endoscopy.
Methods: In this double-blind clinical trial, 80 patients were divided into two groups. The first and the second groups received 2.5 mg intravenous and 5 mg sublingual midazolam respectively. The patients were evaluated and compared using standard questionnaires in terms of sedation, pain/discomfort, and satisfaction. They were also monitored for blood pressure, heart rate and SPO2. The data were analyzed by the SPSS 16 software using Tukey's test and Spearman's correlation coefficient. The significance level was considered to be $P<0.05$.
Results: According to the results, there was a statistically significant difference between the two groups in terms of the mean Ramsay score after sublingual administration or injection. For the double dose in the sublingual group, this score was higher than that in the intravenous group. There was no statistically significant difference between the two groups in terms of pain and satisfaction. In both methods, the difference between the mean sedation scores was statistically significant before and after the treatment. The effect of each method was also significant on the improvement of the sedation score. There was no significant difference between the two groups in terms of systolic and diastolic blood pressures, heart rate and SPO2.
Conclusion: As it was concluded, double dose of sublingual midazolam has a statistically greater effect on sedation than intravenous administration. The effects of the two methods on oxygen saturation, heart rate and blood pressure are statistically similar.

Key words: Upper endoscopy, Midazolam, Sublingual, intravenous, Sedation, Pain.

Resumen

Antecedentes: La endoscopia del tracto gastrointestinal superior (GI) es un procedimiento común para el diagnóstico y tratamiento de las enfermedades del tracto digestivo superior. Es necesario aliviar el dolor y las molestias durante la endoscopia. En nuestro estudio, se comparó la administración sublingual y la inyección de midazolam en cuanto a su eficacia en la sedación de pacientes sometidos a endoscopia gastrointestinal superior.
Métodos: En este ensayo clínico doble ciego, 80 pacientes fueron divididos en dos grupos. El primer y el segundo grupo recibieron 2,5 mg de midazolam intravenoso y 5 mg de midazolam sublingual, respectivamente. Los pacientes fueron evaluados y comparados mediante cuestionarios estándar en términos de sedación, dolor/malestar y satisfacción. También se controlaron la presión arterial, la frecuencia cardíaca y la SPO2. Los datos se analizaron con el programa informático SPSS 16 utilizando la prueba de Tukey y el coeficiente de correlación de Spearman. El nivel de significación se consideró $P<0,05$.
Resultados: Según los resultados, hubo una diferencia estadísticamente significativa entre los dos grupos en cuanto a la puntuación media de Ramsay tras la administración sublingual o la inyección. En el caso de la dosis doble en el grupo sublingual, esta puntuación fue superior a la del grupo intravenoso. No hubo diferencias estadísticamente significativas entre los dos grupos en términos de dolor y satisfacción. En ambos métodos, la diferencia entre las puntuaciones medias de sedación fue estadísticamente significativa antes y después del tratamiento. El efecto de cada método también fue significativo en la mejora de la puntuación de sedación. No hubo diferencias significativas entre los dos grupos en cuanto a la presión arterial sistólica y diastólica, la frecuencia cardíaca y la SPO2.
Conclusiones: Como se concluyó, la doble dosis de midazolam sublingual tiene un efecto estadísticamente mayor sobre la sedación que la administración intravenosa. Los efectos de los dos métodos sobre la saturación de oxígeno, la frecuencia cardíaca y la presión arterial son estadísticamente similares.

Palabras clave: Endoscopia superior, Midazolam, Sublingual, Intravenoso, Sedación, Dolor.

Introduction

Upper gastrointestinal endoscopy is a commonly used diagnostic and therapeutic procedure whose application requires sedative drugs to reduce patients' anxiety, pain and discomfort. Findings have shown that the use of sedatives increases patients' satisfaction and decreases their discomfort during the GI endoscopy procedure[1]. The intravenous administration of benzodiazepines, with midazolam included, is a common sedation method for upper GI endoscopy candidates[2]. Since the intravenous administration of sedatives requires accurate monitoring and trained personnel and has serious complications such as respiratory depression and apnea (10), oral, sublingual or intranasal administration can be an alternative with fewer side effects[2]. Research has shown that the sublingual administration of midazolam is effective for the sedation of children and adults[3,4]. So far, little research has been conducted on the sublingual administration of midazolam. The present study, therefore, seeks to compare intravenous and sublingual administrations of midazolam for the sedation of adult candidates during upper GI endoscopy.

Patients and methods

The present study is a double-blind RCT (randomized clinical trial) conducted on 80 adult candidates for the diagnostic endoscopy of the GI tract. Once it was approved by the university ethics committee, the research population was selected among the patients of ASA (American Social Anesthesiology), classes I and II, who were in the range of 15-55 years of age. They served as the first-time candidates for the diagnostic endoscopy of the upper GI tract.

The main inclusion criteria were shortlisted as the age range of 15-55 years, ASA classes I and II, and first-time candidacy for upper GI endoscopy. The exclusion criteria were defined as follows:

- Addiction to drugs, alcohol, sedatives and psychotropic drugs
- Psychotics undergoing medical treatment
- Severe systematic diseases (e.g. cardiac, pulmonary, hepatic and renal diseases)
- History of sedatives use within at least the past month
- Pregnancy and breastfeeding

Once the study was approved by the medical ethics committee, 80 patients (40 per group) were selected to participate in the study conducted in the endoscopy ward of Shahid Sadouqhi Hospital of Yazd. Also, informed consent was taken from them individually. All the patients underwent hemodynamic monitoring (for average systolic and diastolic blood pressure and HR) and SPO2, and an IV access was prescribed for them. They were randomly assigned to two groups of 40. The grouping was based on a random number table in the Random Allocation Software. The first group received 2.5 mg of midazolam (from Exir Co.) as an IV bolus injection, and the second group had the sublingual administration of 5 mg of midazolam (from the same company). Both received a placebo as well. There was a sublingual placebo for the first group and IV normal saline for the second one. It was a double-blind study during which neither the researcher nor the patients were informed of the administration of drugs. This was based on the standards of the consort statement. Intermittent doses of intravenous midazolam 1 mg were administered if the sedation was insufficient and the endoscopy was intolerable for the patients. This continued until an optimal sedative score was reached. The results were then recorded in a questionnaire.

The patients' sedation level was assessed based on the Ramsay Score. The pain/discomfort score (0-10) and the satisfaction score (0-10) were both recorded for each candidate. Such therapeutic measures as the administration of intravenous fluids and injection of IV ephedrine 5 mg were performed as the systolic blood pressure dropped by 20% to 90% and more. In the case of SPO2 decrease by 90%, the patients received pure oxygen through a nasal mask and were brought back to consciousness. All the reports on these procedures were recorded in the questionnaire.

Data analysis

Numerical indices (mean ± SD) and frequency tables (percentages) were used for the data illustration in SPSS 16.0, the former for quantitative variables and the latter for qualitative variables. The data were analyzed using ANOVA, Tukey's multiple comparison and T-Test. Probability values less than 0.05 were considered significant.

Results

A total number of 80 patients participated in the study. They were assigned to two groups of 40, and their demographic data, including age and gender, were recorded. As presented in **table I**, the results of the chi-square test refer to no significant difference between the two groups in terms of demography, namely age and gender.

Table I: Comparison of the demographic data of the tested groups.

Variable		IV	SL	P-value
Gender	*Male*	18	17	0.822
	Female	22	23	
Age		41.6	39.3	0.534

Table II and **figure 1** summarize the comparative results of the Ramsay Score evaluation for the sedation monitoring, mean pain score and satisfaction level of the patients. As it can be seen, the two groups had a statistically significant difference in the mean value of

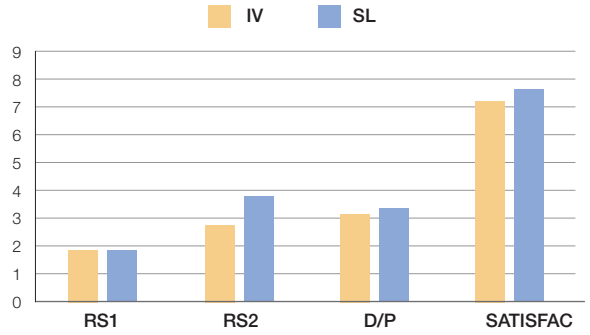
their Ramsay scores after injection; the sublingual group scored a higher value than the intravenous group. This finding along with the t-test results and the p-values indicated that the major difference only belonged to the RS2 mean scores of the methods of administration. In other words, the two groups were not significantly different in terms of pain and satisfaction levels.

Table II: Comparison of the mean values of the intended variables (i.e, sedation, pain and satisfaction scores) in each group.

		Mean	P-value
RS1	IV SL	1.88 1.88	1
RS2	IV SL	2.78 3.88	0.001
D/P	IV SL	3.15 3.40	0.573
SATISFAC	IV SL	7.3 7.7	0.304

RS1 = Ramsay Score before midazolam, RS2 = Ramsay Score after midazolam, D/P=Discomfort/Pain, Satisfac = Satisfaction

Figure 1: Comparison of the mean values of the intended variables (i.e. sedation, pain and satisfaction scores) in each group.



The variation of the mean sedation scores of each group was measured and compared before and after intervention, as presented in **table III**. Based on the results, there was a statistically significant difference between the mean scores of sedation before and after injection in each administration group, implying that both administration methods had a significant impact on the improvement of the sedation scores.

Table III: Comparison of the mean scores of sedation before and after intervention in each group.

Variable		Mean	Mean difference (before and after)	P-value
IV	Before After	1.88 2.78	0.9	0.001
SL	Before After	1.88 3.88	2	0.001

The groups were also compared in terms of the frequency distribution of the administration side effects, such as respiratory depression, hypotension and bradycardia. The results are summarized in **tables IV**, **V, VI** and **VII**. As suggested comparatively, the SBP, DBP, PR, and SPO2 trends brought about no significant change in those groups over time.

Table IV: Determining the mean value of the systolic blood pressure in each group.

Systolic blood pressure (SBP)		Mean ± SD
SBP1	IV SL	117.5 117.37
SBP2	IV SL	117.5 117.37
SBP3	IV SL	117.5 117.37
SBP4	IV SL	117.5 117.37
SBP5	IV SL	117.5 117.37

SBP1= before drug prescription, SBP2= 10 min after drug prescription, SBP3= 20 min after drug prescription, SBP4= during endoscopy (30 min after drug prescription), SBP5= during discharge (one hour after drug prescription)

Table V: Determining the mean value of the diastolic blood pressure in each group.

Diastolic Blood Pressure (DBP)		Mean ± SD
DBP1	IV SL	78.25 79.38
DBP2	IV SL	78.38 79.38
DBP3	IV SL	78.38 79.38
DBP4	IV SL	78.38 79.38
DBP5	IV SL	78.48 79.38

DBP1= before drug prescription, DBP2= 10 min after drug prescription, DBP3= 20 min after drug prescription, DBP4= during endoscopy (30 min after drug prescription), DBP5= during discharge (one hour after drug prescription)

Table VI: Determining the mean value of the heart rate in each group.

Heart rate (PR)		Mean ± SD
PR1	IV SL	78.83 80.40
PR2	IV SL	76.93 79.45
PR3	IV SL	78.98 79.50
PR4	IV SL	48.88 82.87
PR5	IV SL	79.95 80.93

PR1= before drug prescription, PR2= 10 min after drug prescription, PR3= 20 min after drug prescription, PR4= during endoscopy (30 min after drug prescription), PR5= during discharge (one hour after drug prescription)

Table VII: Determining the mean value of the peripheral oxygen saturation in each group.

Peripheral oxygen saturation		Mean ± SD
SPO1	IV SL	96.23 96.00
SPO2	IV SL	96.18 95.98
SPO3	IV SL	96.15 96.00
SPO4	IV SL	96.05 95.95
SPO5	IV SL	96.13 95.98

SPO1= before drug prescription, SPO2= 10 min after drug prescription, SPO3= 20 min after drug prescription, SPO4= during endoscopy (30 min after drug prescription), SPO5= during discharge (one hour after drug prescription)

Discussion

This study was conducted to comparatively investigate the effects of intravenous injection and sublingual administration of midazolam on the sedation of first-time upper-GI endoscopic patients. In this regard, the sublingual administration of midazolam had no complications during the diagnostic endoscopy of the upper GI tract.

Having better anti-anxiety and hypnotic effects, intravenous midazolam is more commonly administered for sedation during upper GI endoscopy[5,6].

Rafiei et al. compared the impacts of IV (.05-.1 mg/kg) and oral (.5 ml/kg) administrations of midazolam on 61 patients who underwent upper GI endoscopy. They found no statistically significant difference between the two administration methods in terms of sedation scores and satisfaction. As for SPO2, the oral method had a lower mean score than the intravenous one[7]. In our study, there was also no significant evidence of difference in satisfaction with intravenous and sublingual methods. The sedation mean score, nevertheless, was higher in the sublingual group. Moreover, no group showed significant superiority in its SPO2 mean values; the decrease in the mean score of SPO2 was considerable in neither group.

Shafa et al. compared the effects of the intravenous administration of dexmedetomidine and midazolam on the quality of sedation during the diagnostic endoscopy of the upper GI tract in 72 children. Based on the results, the recipients of midazolam experienced a higher level of sedation than those that took dexmedetomidine during endoscopy, accentuating the better impact of IV midazolam than dexmedetomidine[8]. In our study, unlike the intravenous drug reception, the sublingual method had a statistically better impact on the patients' sedation level (sublingual 5 mg versus intravenous 2.5 mg).

Khodadad et al. studied the effect of oral (.25-.5 mg/kg) versus IV (.1-.3 mg/kg) midazolam on the sedation of 199 children during upper GI endoscopy. They found that the average duration of sedation was significantly higher in the oral group than in the intravenous recipients. Thus, those in the oral group were significantly more satisfied than the IV group patients. Neither of the oral and IV methods, however, resulted in deep sedation in any of the patients[9]. Consistent with the findings of Khodadad et al., our study reached a statistically significant difference between the sedation levels of the sublingual and intravenous groups; the sublingual recipients had better sedation than the IV patients. These two studies, thus, both confirmed the priority of oral and sublingual methods over intravenous administration.

Gupta et al. compared the sedating impacts of oral and sublingual midazolam. Their findings were suggestive of higher sedation in sublingual administration, but the difference was not statistically significant. Of course, Gupta's study was not performed on patients under endoscopic diagnosis[10]. In line with that investigation, our study showed that sublingual administration could more effectively sedate patients than the intravenous method. It was, however, different from Gupta's study in two ways, namely the type of disease and the type of drug administration; we had a sublingual/intravenous dichotomy, while Gupta et al. focused on the sublingual/oral differentiation.

Roseman et al. conducted another comparative study on the sedation effects of sublingual and intravenous midazolam. Their participants were candidates for elective surgery. A majority of the intravenously-treated patients scored RS2 (Ramsay Score) after 10 minutes of sedation, while the sublingual patients reached RS1-2 after 10 to 20 minutes and RS2-3 after 30 minutes of administration[11]. The sublingual sedation in our study was consistent with that in the research by Roseman et al. This is to say that, in both studies, the Ramsay scores (i.e. sedation levels) before and after the drug administration were significantly different. According to the initial experiments in our study, the sublingual effect constitutes over 50% of intravenous methods. That is, a double dose of sublingual midazolam would result in higher sedation than that created by the intravenous method. This may contribute to the absorption of more than 50% of the drug in the sublingual method. This finding may open a new horizon to researchers for the further investigation of sublingual absorption. In this regard, it is recommended to use a lower dose of sublingual midazolam.

As numerous studies have reported, sublingual administration is not commonly practiced probably due to the bitter taste of the drug. In this respect, the pharmaceutical industry is expected to find a way to improve the taste of midazolam in the future.

Several pieces of research have compared the effects of different midazolam administration methods[12-14]. The results of comparing the sublingual and orogastric routes of midazolam administration have indicated that the plasma level increases after sublingual administration, as compared to the orogastric route[10].

Comparing sublingual and oral methods, Fuji et al. found that the sublingual method had higher bioavailability than the oral one, which was due to the elimination of the hepatic first pass effect in the oral method[15].

According to Odu et al., there was no significant difference between sublingual and intravenous administrations in terms of pharmacokinetic parameters[16]. In general, sublingual administration is apparently preferred to other methods for its kinetic parameters. Similarly, the present

study has provided evidence for the supremacy of a double dose in the sublingual method over intravenous administration; the former has proved to have a better impact on the sedation scores of endoscopic patients.

As Odu et al. confirmed, the sublingual intake of midazolam is highly preferred to other ways of taking the drug due its lower stress, painlessness and higher bioavailability. Besides, sublingual administration involves considerable absorption. Odu et al. did not observe any statistically significant difference between the kinetic parameters of the two groups of recipients[16].

Based on the results of the present research, neither of the methods of drug administration has a significant impact on the SPO2 level, which means they cannot significantly affect the respiratory status of patients. This finding is confirmed by numerous similar studies.

Nejati at al. investigated the effect of midazolam on SPO2 in upper GI endoscopy. They found that midazolam administration would not change SPO2 levels. It is worth noting that they only injected midazolam intravenously[17]. Likewise, in our study, neither the sublingual method nor the intravenous one could significantly change the SPO2 levels.

In their pre-endoscopic intravenous injection of midazolam, Dhariwal et al. found the patients' SPO2 levels to be 94.9%, 92.8% and 91.2% before endoscopy, after sedation and during endoscopy respectively[18]. These three levels had no significant difference, which is in line with the results of our study.

According to the findings of our study, neither way of administrating midazolam had a significant effect on blood pressure and heart rate. Liacouras et al. evaluated 123 upper GI endoscopic patients after a midazolam injection (0.5 mg/kg, maximum 20 mg). They found that the heart rate, blood pressure and SPO2 level of the patients were not significantly different before and after the drug administration, which is consistent with the findings of our study[19]. In other words, neither administration method could significantly affect the heart rate, blood pressure and SPO2 level.

Kumar et al. found that, although patients with no important underlying diseases are less likely to be at the risk of SPO2 reduction during upper GI endoscopy, continuous monitoring of their oxygen saturation is recommended[20].

Karl et al. compared the effects of pre-endoscopic midazolam injections on the change of oxygen saturation in 60 patients. The results indicated the reduction of SPO2 to less than 90% in only five patients (8.3%). They concluded that the intravenous administration of low-dose midazolam is a safe method for an endoscopy procedure[21]. In a similar approach practiced in our study, no evidence has been found for SPO2 reduction to less than 95%, implying that both intravenous and sublingual administrations of midazolam are safe in terms of SPO2, as it was in Karl's study.

Due to its short half-life, the drug cannot have any significant effect on the stability of the cardiovascular system and the respiratory center. It is, thus, considered as an effective sedative drug for endoscopy procedures. In contrast, other sedative drugs such as diazepam are associated with more complications because their half-life is much longer. Midazolam proved to have no significant impact on the heart rate and the respiratory system of the patients in our study. This drug is highly preferred over other sedatives for its shorter half-life and higher clearance[22,23].

A double dose of sublingual midazolam is of a higher sedative effect than intravenously injected midazolam. The absorption of sublingual midazolam is, indeed, more than 50%. Therefore, it is recommended to compare the lower doses of sublingual and injected types of midazolam.

Conclusion

The results of this study showed that a double dose of sublingual midazolam is significantly more effective than intravenous administration for the sedation of patients during endoscopy. However, the patients' satisfaction level was not significantly different in the sublingual and intravenous groups. Finally, the two groups had no significant difference in terms of such complications as respiratory depression, hypotension and heart rate change.

Ethical consideration

The study was approved by Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (AIR.SSU.MEDICINE.REC.1397.185). This study was also registered in Iranian Registry of Clinical Trials (IRCT20100102002963N36).

Abbreviations

GI: Gastrointestinal
SPO2: Oxygen Saturation
RS2: Ramsay Score
HR: Heart Rate

Conflict of Interest

The authors declare that there is no conflict of interest in the publication of this paper

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