

Comparative Study of Intranasal Midazolam Spray/ Oral Midazolam as Premedication in Paediatric Patients

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A B S T R A C T

Introduction: In present era need of premedication is there to alleviate anxiety of surgery and anaesthesia in child as well as parents. Study aimed to evaluate midazolam premedication through both intranasal & oral routes in children.

Material and methods: A Randomised Double blind comparative study was done in VS General Hospital & NHLM Medical college, Ahmedabad Gujarat India from August 2015 to December 2017. A total 60 patients belonging to ASA grade I&II, randomly divided in 2 groups of 30 patients in each group, aged 2 to 10 years undergoing elective surgery under general anaesthesia with duration of 30-75 min. Basal vitals were recorded by multipara monitor in preoperative room.

Results: Results were comparable in both groups. Desired sedation level was achieved earlier in INM group at 10, 20 min. At a 30 min in both groups desired sedation level achieved. In INM group 96.7% and in OM group 86.8% children were satisfactory separated. From parents. Mild Adverse effects in both groups were assessed, But no pharmacological or airway intervention required in any patients. At 30 min postoperatively all patients in each group achieved recovery score ≥ 9 .

Conclusion: Both group provides good premedication at 30 min after study drug but INM group provides cost effective premedication with few adverse effects.

Keywords: Premedication, Intranasal Midazolam, Oral Midazolam, Paediatric Patients

INTRODUCTION

"Sedation is the process of establishing a state of calm" The preoperative period is often an extremely traumatic time for the young child undergoing surgery. Up to 65% of all children undergoing anaesthesia and surgery develop intense anxiety and fear in the preoperative holding area and during induction of anaesthesia.¹ This anxiety can be attributed to separation from parents and uncertainty about the anaesthesia, surgery, and outcome of the procedure.²

Preoperative anxiety stimulates sympathetic, parasympathetic and endocrine system leading to an increase in heart rate, blood pressure and cardiac excitability. This all psychomotor and autonomic responses are due to anxiety activated human stress response leading to increase serum cortisol, epinephrine and their peripheral effectors, hypothalamic-pituitary-adrenal axis.^{3,4} Children are especially vulnerable to this problem, since their understanding is limited. Preoperative anxiety in unpremedicated children is two fold^{5,6}

The pre-operative interventions directed towards reduction of anxiety are grouped into psychological/non-pharmacological and pharmacological methods. Although the non-pharmacological means in the form of friendly visit by the anaesthesiologist to establish rapport with the

child, briefing about the procedure whenever feasible, helps to minimize the child's anxiety, pharmacological agents are often helpful to provide sedation and smooth induction. Sedative premedication are more effective in this regard.⁷ Hence all paediatric patients need to be premedicated in order to decrease preoperative anxiety.

Criteria for ideal premedication are to be available in preparation that is readily acceptable, reliable rapid onset, provide anxiolysis with mild sedative effects with sufficient duration, provide rapid recovery in form of alertness and early discharge. Midazolam is a potent short acting benzodiazepine, sedative, hypnotic has been used as a premedication for general anaesthesia in children to reduce preoperative anxiety.

Midazolam was first introduced as a pre mediant for children in 1980's, rapidly achieve widespread acceptance as a preferred pre medication before induction of anaesthesia.⁸ Currently Midazolam is a preferred pre medication more than 90% of the time. It can be administered via multiple routes:

It was also compared with ketamine premedication.¹⁰ The advantages of intranasal route includes, rich vascular plexus of nasal cavity providing rapid access to blood stream, avoiding gastro intestinal and hepatic first pass metabolism,

thus greater bioavailability, essentially painless, convenience of usage, disadvantages are negligible, such as burning sensation, respiratory depression.¹¹

The advantages of oral route being better patient compliance, convenience and simplicity of administration, disadvantages are slow onset of action, low oral bioavailability and delayed recovery.¹²

The purpose of this study was to compare intranasal and oral routes of administration to study the onset of action, and effectiveness as premedication and post operative recovery characteristics.

MATERIAL AND METHODS

After taking informed consent from the parents of the children undergoing the study, a total of 60 patients aged between 2-10 years, of either sex belonging to ASA Grade I & II posted for elective surgeries were selected. A prospective, randomised study was done by dividing them in two different groups.

Group allocation:

Execution of Randomised group was by sequential numbered sealed opaque envelope. Envelope was opened just before premedication in preoperative room.

INM: Children received 0.2 mg/kg of midazolam through atomizer in half divided dose in each nostril.

OM: Children received 0.5 mg/kg of oral midazolam preservative free from the ampule (concentration of the drug was 5mg/ml) and mixed with equal amount of freshly prepared sugar syrup.

Inclusion criteria: Patients aged between 2-10 years, Patients of either sex, Patients with ASA Grade I & II, Surgeries lasting up to 30-75 mins.

Exclusion Criteria: Patients with Rhino Pharyngitis. Patients with nasal pathology. Patients with H/o allergy to the study drug. Patients on sedative medication, Surgeries less than 30 mins and more than 75 mins, Patients on treatment with theophylline, H₂ receptor antagonists, Patients with history of prematurity or chronic illness, Patients with H/o developmental delay, Patients with cardio-respiratory disorders, Patients with Hepatic and Renal disease, Patients with ASA Grade III & above.

Sample size calculation: We did pilot study of 5 patients in each group. Reviewed literature of Previous studies suggests difference of mean sedation score of 1.2 out of 5 (24% incidence of sedation) between intranasal & oral midazolam, to have at least 80% power & alpha error of 0.05, & Beta error of 0.2 sample size of 24 in each group was calculated. we have enrolled 30 patient in each group (Total 60 patients). Study was Double blind as one anaesthetist prepared premedication according to group allocation, & give it to patient, other blinded a anaesthetist take observations in preoperative room and in operation theatre & conduct a anaesthesia.

Method of premedication

A Preoperative visit was made on the day prior to elective surgery. A thorough general physical examination was done

& potential intravenous cannulation sites were noted. All routine investigations were done. Parents explained about the concerned technique & informed consent taken. No sedative premedication ordered on the day prior to surgery. Parents were also instructed to keep the children fasting for 6 hours for solid food and 4 hours for liquids.

In the Preoperative room: On the morning of surgery, Children were shifted along with one of the parents to the Preoperative room. Baseline HR, SBP, DBP, SPO₂, RR, Temperature was recorded using Multichannel monitor before administration of the drug. (provision for oxygenation, resuscitation kept ready in preoperative room.)

Position of patient: With the children sat on the parents lap with facing forward while their arm were gently restrained by one parental hand and other hand used to tilt the forehead back 15 degree. (In each group)

Group INM: Received intranasal midazolam through atomiser spray 0.2mg/kg divided in half dose administered in each nostril. (5mg/ml, each spray delivered 0.1ml or 0.5mg)

Group OM: Received preservative free oral midazolam from midazolam ampule containing 5mg/ml and dose of 0.5mg/kg was given with equal amount of freshly prepared sugar syrup.

After administration of premedication patients were observed for following adverse effects: Watering of eyes, Bad taste, Nasal congestion/Nasopharyngeal irritation., Nausea & vomiting, Sneezing, Dizziness. For Nausea, vomiting inj. ondasetron kept ready, interval of 5 min after administration of the drug to parent separation the HR, SBP, DBP, RR, SPO₂ and Degree of sedation were noted.

Five point sedation score¹¹

Sedation level	Criteria	Score
Agitated	Patient clinging to parents and/ or crying	1
Alert	Patient is aware but not clinging to parent but not cry	2
Calm	Sitting or lying comfortably with spontaneous eye opening	3
Drowsy	Sitting or lying comfortably with eyes closed but respond to stimulation	4
Asleep	Eyes closed, arousable but does not respond to minor stimulation	5

AT 20 MIN, children were separated from the parents & shifted to the Operation theatre. HR, SBP, DBP, SPO₂, RR, Sedation Level and Reaction to separation from parents were assessed by parental separation score 47.

Parental separation score¹⁵

Behaviour of the child	Criteria	Score
Excellent	Patient unafraid, Cooperative or asleep	1
Good	Slight fear/crying, quite with reassurance	2
Fair	Moderate fear and crying not quite with reassurance	3
Poor	Crying, need for restraint	4

At 30 Min after premedication, appropriate monitors were connected (precordial stethoscope, electrocardiogram, NIBP, pulse oxymeter). IV Canulation attempted & reaction to Venepuncture was assessed by the Response to venepuncture. Response to venepuncture¹⁶

Reaction to venepuncture	Criteria
Satisfactory demeanour	If the child showed no response or winced or whimpered
Unsatisfactory demeanour	If the child cried or behaved in a violent manner.

Patients were premedicated with INJ.Glycopyrrolate 0.004mg/kg and Inj Paracetamol 15mg/kg IV.

Patients were preoxygenated by 100% O₂ with mask. Based on the body weight, children < 20kg paediatric circuit consisting of Jackson Ree's modification of Ayre's T – piece and children > 20 kg, Bain's circuit was used with appropriate fresh gas flows response to Mask Placement was assessed by Mask placement score.

Mask placement score

Behavior of the child	Criteria	Score
Agitated	Refuses mask	1
Alert	Refuses, but accepts after persuasion	2
Calm	Mask acceptance with level 3 of sedation	3
Drowsy	Mask acceptance with level 4 of sedation	4
Asleep	Mask acceptance with level 5 of sedation	5

Patients were induced with injection Thiopentone (2.5%) 6mg/kg and injection Atracurium 0.5mg/kg. patients were intubated with appropriate size of endotracheal tube. Anaesthesia was maintained with O₂+N₂O+Sevoflurane (0.5%-0.8%) and inj.Atracurium 0.1mg/kg as when required. Patients were ventilated with the help of pressure controlled mode of ventilator of Drager work station.

EtCO₂ was maintained in the range of 25-35 cm of H₂O in each patients. Per operative IV fluids was administered as per Hager's formula At the end of surgery, all the inhalational anaesthetic agents were discontinued and 100% O₂ administered. Residual effect of relaxants were reversed with Inj, Neostigmine 0.05mg/kg & Inj.Glycopyrrolate 0.008mg/kg, Extubation was done after thorough suctioning of the oral cavity and return of protective reflexes. Time interval from reversal to the extubation was noted. Duration of

surgery was taken from time of intubation to the time of last skin stitch. Post operative recovery was assessed by THE Modified Alderte Score.

The modified alderte score

Parameter	criteria	score
Circulation	BP+50mmHg pre op	0
	BP+20-50mmHg pre op	1
	Bp+ 20 mm of Hg	2
O2 saturation	Saturation < 90% even with supplemental O ₂	0
	Needs O ₂ inhalation to maintain O ₂ saturation > 90%	1
	Maintain > 92% on room air	2
Respiration	Apnoeic Dyspnea /	0
	Shallow breathing	1
	Able to take deep breath and cough	2
consciousness	Nonresponding	0
	Arousal on calling	1
	Fully Awake	2
Activity	Able to move no extremities voluntarily or on command	0
	Able to move 2 extremities voluntarily or on command	1
	Able to move 4 extremities voluntarily or on command	2

This score was assessed after extubation at 10 min interval up to 30 min and after achieving satisfactory score of 8-10. patients were shifted to post operative ward.

In postoperative ward

All the patient's vitals (HR, SBP, DBP, SPO₂, RR) were monitored up to 24 hours. Postoperatively analgesia was given to all the patients in form of suppository of diclofenac sodium 1.5mg/kg for pain relief. All the children were observed for 24 hours for any adverse effects.

STATISTICAL ANALYSIS

Data were recorded in MS Excel spreadsheet and analysed by SPSS SOFTWARE 16 (IBM, Armonk, NY, USA).

Data having numerical values were analysed by unpaired Student's T test.

Categorical variables were analysed by Chi Square test .

Parameters	Group INM (n=30)	Group OM (n=30)	P value	Inference
Age (years)	5.86±2.73	5.96±2.65	>0.05	NS
Sex (male/Female)	21/9	19/11	>0.05	NS
Weight(kg) Mean+/- SD	16.66±4.94	17.5±5.00	>0.05	NS
ASA grade (1/2)	22/8	23/7	>0.05	NS
Duration of surgery(min) Mean+/-SD	60.33±11.66	58.6±9.68	>0.05	NS

Table-1: Demographic profile

RESULTS

Baseline vitals

Table 1 shows comparable Demographic parameters in each group.(p>0.05)

Vitals of patients after premedication: Same parameters observed in preoperative room at 5 min interval upto 30 mins. HR was decreased after 5 min, but it was not more than 30%.so no pharmacological intervention required. (P>0.05) RR was decreased gradually in each group but not less than 12/min& Spo2 maintained.No airway intervention required. (P>0.05) (table-2).

Score of 1,2 is unsatisfactory,3,4,5 is satisfactory.In group INM patients were sedated early (p<0.001) at 15 minutes .but at 30 min of premedication both groups were sedated (p>0.05) (table-3,4a). Table 4b shows that at 5, 10, 15 min Mean sedation score was more in INM group. But

afterwards it was comparable in both groups.

Table-5 shows that in INM group 29/30,& in OM group 26/30 patients separated from parents with excellent and good score. Table 6 shows comparable response to venepuncture in both groups.

Table-7 shows that satisfactory response (more than or=3) was achieved in 27/30 patients in each group.3 patients in each group were alert.

Table-8 shows in INM group satisfactory score ≥9 achieved early then Group OM but at 30 min postoperatively both groups were having score ≥9.

Postoperative patients vitals were monitored periodically for 24 hours, at 10 min interval for 30 mins, then 30 min upto 120 mins, & then at 4,6,12,24 hours. All patients were conscious, co-operative, having stable haemodynamics, without any adverse effects.

Cost of mean midazolam in each group was calculated as

Parameters Mean+/-SD	Group INM (n=30)	Group OM (n=30)	Pvalue	Inference
HR	134.16±8.97	131.4±9.52	>0.05	NS
SBP	104.73±8.93	103.33±7.72	>0.05	NS
DBP	67.86±6.45	64.4±6.93	>0.05	NS
Spo2	98.93±0.90	99.1±0.71	>0.05	NS
RR	22.8±3.69	25.7±3.37	>0.05	NS

Table-2: Vital parameters

Adverse effects	Gr. INM (n=30)	Gr. OM (n=30)
Watering of eyes	1(3.3%)	0
Bad taste	0	0
Nasal congestion/irritation	2(6.6%)	0
Nausea/vomiting	0	3(10%)
Sneezing	1(3.3%)	0
Dizziness	0	0

Table-3:

score	Group INM (n=30)						Group OM (n=30)						P value	Inference
	Time in minutes in both groups													
	basal	5	10	15	20	30	basal	5	10	15	20	30		
1	16	00	00	00	00	00	18	08	00	00	00	00	0.51	NS
2	14	15	02	00	00	00	12	22	21	06	00	00	0.04	S
3	00	14	11	05	02	00	00	00	09	17	12	05	<0.001	HS
4	00	01	12	17	14	10	00	00	00	07	13	16	0.037	S
5	00	00	05	08	14	20	00	00	00	00	05	09	0.79	NS

Table-4(a): Sedation level by 5 point sedation score

Time	Gr INM (n=30)	Gr. OM (n=30)	P value	Inference
Baseline	1.47±0.51	1.40±0.50	>0.05	NS
5min	2.53±0.57	1.73±0.45	<0.05	S
10 min	3.67±0.84	2.30±0.47	<0.05	S
15 min	4.10±0.66	3.03±0.67	<0.05	S
20 min	4.37±0.61	3.77±0.73	>0.05	NS
30 min	4.67±0.48	4.13±0.68	>0.05	NS

Table-4(b): Mean sedation score

Score	Gr. INM (n=30)	Gr. OM (n=30)
Excellent	22	12
Good	07	14
Fair	01	04

Table-5: Parent separation score

Response	Gr. INM (n=30)	Gr. OM (n=30)
Satisfactory	26	25
Unsatisfactory	04	05

Table-6: Response to venepuncture

Response	Group INM (n=30)	Group OM (n=30)
Agitated(1)	00	00
Alert(2)	03	03
Calm(3)	02	02
Drowsy(4)	10	20
Asleep(5)	15	05
Mean response(mean±SD)	4.23±0.97	3.97±0.80

Table-7: Response to mask placement

score	Group				-			
	0 min	10 min	20 min	30 min	0 min	10 min	20 min	30 min
6	00	00	00	00	03	00	00	00
7	11	03	00	00	20	12	04	00
8	19	20	07	00	07	18	18	00
9	00	07	14	03	00	00	08	15
10	00	00	09	27	00	00	00	15
Mean Score	7.60	8.13	9.06	9.90	7.13	7.60	8.13	9.5

Table-8: Postoperative recovery score(Alderte score)

	Gr. INM (n=30)	Gr. OM (n=30)
Dose of Midazolam	0.2mg/kg	0.5mg/kg
Mean weight of patients	16.66kg	17.5 kg
Mean dose of Midazolam	3.3 mg	8.7 mg
Cost of mean Midazolam	31.68Rs	47.85Rs

Table-9: Cost of sedation

midazolam spray atomizer used in study costs 240 Rs for 5ml of 25 mg & preservative free midazolam injection of 1ml of 5mg/ml costs 27.50 Rs. so INM group is cost effective (table-9).

DISCUSSION

Pre anaesthetic medication in paediatric patient should aim to relieve anxiety due to unfamiliar persons, strange operation theatre atmosphere. However ideal pre medication should provide proper sedation, easy parent child separation, facilitated ease of induction in form of satisfactory venepuncture, mask acceptance, with minimum adverse effect and satisfactory recovery profile.¹²⁻¹⁹

Numerous pre medicants used for same. We evaluate Midazolam as pre medicant for children through 2 different routes:-Intranasal and Oral.^{20,21}

Oral midazolam in the dose of 0.5 mg/kg is a safe and

effective mode of premedication than that of 0.75 mg/kg and 1 mg/kg which gives no additional benefit, may cause more side effects.²² Connor et al & Lam et al used midazolam for premedication through various routes²³⁻²⁹

Intranasal midazolam has been used in the doses of 0.2, and 0.3 mg/kg, but found no additional benefits from higher dosage and recommended the lower dose of midazolam 0.2 mg/kg.^{9,13} Similarly in other studies, intranasal midazolam spray was used in the dose of 0.2 mg/kg^{22,23} while a mucosal atomizer device was used to administer midazolam intranasally in the dose of 0.2 mg/kg.¹⁶ Concentrated, atomized midazolam spray ensures accurate drug delivery 30-100 micron droplets, covers larger nasal mucosal area and increases bioavailability maximally.^{22,28,29} We used oral midazolam in freshly prepared sugar syrup in the dose of 0.5 mg/kg and intranasal Midazolam atomized spray in the dose of 0.2 mg/kg.

Demographic data

As per table 1 there was no significant difference in demographic parameters like Age, Sex, Weight, Duration of surgery, ASA grade.

Baseline vital parameters

As per table 2 Baseline vitals were comparable in each group. Earlier assessors used a 3-, 4- or 5-point sedation

scales to assign sedation score.^{9,22,24} In our study, 5-point sedation scale was used to measure sedation. Before giving Midazolam (Basal values) children in INM and OM group were agitated and alert (score 1, 2). Desirable sedation level was considered at a score ≥ 3 .

After 5 mins of pre medication, in INM group 15/30 children (50%) had score ≥ 3 and in OM group no children have sedation score ≥ 3 . After 10 mins of pre medication, in INM group 28/30 children (93.4%) and in OM group 9/30 children (30%) had desirable sedation level (score ≥ 3). Quicker effect in INM group was due to olfactory mucosal absorption of medications directly into the cerebral spinal fluid and brain.

In the study of Wilton et al²⁷, states that significant changes in sedation level were founded as early at 5 min after INM. Our finding co relate with the study of WILTON et al. After 15 min of pre medication, in INM group 30/30 (100%) and in OM group 24/30 (80%) children had desirable sedation level. After 20 min of pre medication, in both groups all children had desirable sedation level. According to the study of Kain et al¹², significant anxiolytic and sedative effect of oral Midazolam were observed at 15+4 min of administration. Findings of 15 and 20 min after drug in OM group were co relate with the study of Kain et al.¹²

According to the study of Kogan A et al¹⁴ and Knoester et al¹³ demonstrable high plasma concentration of INM was at 14+5 min and maximum sedation and anxiolysis at 20 min in INM group and at 30 min in OM group. Our results co relate with above studies

After 30 min of pre medication, in INM group 30/30 (100%) and in OM group 25/30 (84.85%) children achieved deep sedation level of score 4/5.

Parental separation

Most important criteria of satisfactory pre medication is its ability to facilitate the separation of the child from parents. Kogan et al¹⁴ found maximum sedation and anxiolysis at 20 min in intranasal group while at 30 min for the oral group. To avoid bias and incongruence with the earlier studies, we observed children for sedation level for 20 min and then separated them from their parents.

After 20 min of pre medication, in group INM 29/30 (96.7%) and in group OM 26/30 (86.8%) children were satisfactory separated from their parents with a score 1/2 (excellent/good). This data was due to faster pharmacodynamic effect of INM due to high bioavailability.

In studies of Bhakta et al¹⁹, Kain et al¹² reported satisfactory separation with INM was 91% & 80% and with OM was 78%, & 70%.

Post premedication vitals

Mild gradual decrease in the HR was due to the satisfactory sedation as patient become calm. There was no pharmacological intervention required.

Mild respiratory depression was there but no airway intervention was required in any patient. So, vigorous haemodynamic and respiratory monitoring is needed in each patient. That was done in our study with multipara monitor.^{24,25,26}

In studies of Kogan et al¹⁴ Lee -Kim et al¹⁷ Mc millan et al¹⁵

observed that vital signs remain stable with pre medication before surgery.

Adverse effects

In our study, in INM group nasal irritation/ congestion was observed in 2/30 (6.6%), sneezing in 1/30 (3.3%) and watering of eye in 1/30 (3.3%) of patients. In studies of BHAKTA et al¹⁹ and LUGO et al²⁰, nasal irritation was in 20/31, nasal discomfort in 17/38 patients. In our study, in OM group nausea and vomiting observed in 3/30 (10%) of patients that is co relating with study of PV desmukh et al.¹¹ No other side effects were observed.

Mask placement response

For pre oxygenation of the patient when 100% O₂ was applied through mask in both group's patients, response to mask placement was desirable.^{3,4,5} In INM group and OM group 27/30 (90%) patients had satisfactory response. However mean response to mask placement was more in INM group (4.23+0.97) as compare to the OM group (3.90+0.80).

In study of PV desmukh et al¹¹ response to mask placement was measured for gaseous induction. Mc millan et al¹⁵, showed that in OM group 80-90% had satisfactory mask acceptance. Bhakta et al¹⁹, showed that in INM group satisfactory mask placement was in 60% and 80% respectively. Kogan et al¹⁴ and Conorr et al²⁸, showed that 75% of patients have satisfactory response to mask placement in both INM and OM group.

Intra operative vitals: Intra operative vitals were comparable and stable in both the groups. (P>0.05)

Kogan et al¹⁴ and Lee - kim et al¹⁷, showed that intra operative vitals were stable in INM group. Mc millan et al¹⁵, found that stable intra operative haemodynamics after oral Midazolam.

Time interval from reversal to extubation: Reversal extubation time interval in INM group was 9.43 +1.14 min and in OM group 9.33 + 1.09 min.

Brosius et al⁷, his study suggest that midazolam pre medication in children does not affect recovery time (Reversal extubation time). Our study co relate with study of Brosius et al.⁷

Post operative recovery score

In our study, mean recovery score of INM/OM at 10 min was (8.13/7.60), at 20 min (9.06/8.13), at 30 min (9.9/9.5)

In INM group more children attained score more than 8 at 10 min and 20 min as compare to OM group. At 30 min in both group recovery score was comparable. (P>0.05)

In study of PV deshmukh et al¹¹ mean recovery score in INM/OM group at 10 min was (8.5/8.8), at 20 min (9.2/9.6) and at 30 min (10/10). Data at 30 min co relate with our study. BHAKTA et al¹⁹, shows that mean recovery score in INM group was 7.2 at 10 min, 8.9 at 20 min and 10 at 30 min which is co relate with INM group of our study.

Cost of sedation:- We have calculated mean cost of sedation in each group. In INM group it was 33 Rs. where as in OM group it was 47.85 Rs. It was due to the less dose required in INM group.

Limitations

1. There was no control group in our study as we wanted to pre medicate each child.
2. There was unavailability of BIS parameter through out

of study in pre operative room, in operation theatre and in post operative ward

CONCLUSION

In Nutshell, we conclude that INM atomizer spray & OM provides satisfactory sedation, parental separation, stable Haemodynamic & respiratory parameters over a period of study time without delay in extubation with Satisfactory recovery profile. INM provides cost effective faster onset but with more adverse effects than OM.

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