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RESEARCH ARTICLE

Effectiveness and safety of Ketamine and Midazolam mixture for procedural sedation in children with mental disabilities: A randomized study of intranasal versus intramuscular route

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ABSTRACT

Background: Sedation outside the operating room is challenging especially for mentally disabled children. The intravenous sedation is an effective way of drug administration, but it is difficult to insert. The intramuscular route still has fear of injection. The intranasal route can be an effective, needleless, and painless approach for procedural sedation.

Methods: 40 children with a mental disability aged from 4–12 years classified as ASA class I and II were included after parents' approval for procedural sedation. They were divided into two groups; IN who received intranasal Midazolam 0.2 mg/kg and Ketamine 5 mg/kg and group IM who received the same dose intramuscularly. The heart rate, oxygen saturation and mean arterial blood pressure were recorded. We used the Pediatric Sedation State Scale to assess the level of sedation of children. Also, the satisfaction of the parents and complications were recorded.

Results: The onset of sedation showed no statistical difference between the two groups while the duration of sedation and the time of discharge from the post-anesthesia care unit were significantly higher in the IM group. The sedation score was statistically higher in the IM group at 10 minutes while in 20 and 30 minutes it showed no statistically significant difference with comparable sedation state. Parents of IN group showed a statistically significant higher level of satisfaction.

Conclusion: Midazolam and Ketamine mixture given through the nasal route with nasal atomization device is a needleless approach and as effective and safe as an intramuscular route for procedural sedation in mentally disabled children.

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KEYWORDS
Intranasal Midazolam; intranasal Ketamine; sedation score; parents' satisfaction

1. Introduction

Sedoanalgesia decreases the need for general anesthesia outside the operating room. The intravenous route is the standard way of sedation, but its use can be limited in uncooperative mentally disabled children. Active Physical restraint of these children causes emotional trauma for both parents and children. Children with mental developmental delays account for 2%–3% of the general population. Thirty to forty percent of these children may come to the anesthesiologist for various therapeutic and diagnostic procedures [1].

Oral sedation can be used in these patients but it has various disadvantages as delayed onset of action, bitter taste, postoperative nausea and vomiting [2,3], and the need for the addition of different types of flavored syrup or honey according to the preference of the patient. Some children may refuse to take such oral drugs up to spitting it. On the other hand, intramuscular sedation is an easy effective way of administration [4], and it is preferred due to its rapid onset of action and higher predictability of the duration, however, phobia of the pain of injections must be considered as a disadvantage in this vulnerable pediatric patient. The intranasal route is an important alternative route because it is a painless and needleless approach with rapid drug absorption from nasal mucosa reaching the cerebrospinal fluid and bypassing the first-pass metabolism in the liver [5].

The intranasal route has a comparable time of onset of action to the intravenous route, but higher doses are needed to offset incomplete absorption from the mucosa of the nose [6,7]. Using mucosal atomization devices solve this problem as they simply administer intranasal drugs up to 1ml in each nostril and provide smaller drug particle size of 30–100 microns leading to higher bioavailability, and higher patient satisfaction [7,8].

Intranasal midazolam for sedation of children was first described by Wilton et al [3]. Nasal midazolam dose can range from 0.1–0.5 mg/kg. Intranasal midazolam is an efficient sedative in mild to moderate irritable children, but for more challenging children, the addition of stronger sedative drug is advised [9].

Ketamine is commonly used as a premedication and recently can be used in children via the nasal route. It is used as a nasal spray in the management of adult cases

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with resistant depression. In literature, Variable doses and frequencies of intranasal ketamine are noticed with the single-dose ranged from 2 to 10 mg/kg [10].

In our institute, we give either oral Midazolam or intramuscular Ketamine followed by sevoflurane or propofol for pediatric procedural sedation. Nasal Midazolam Ketamine mixture has not been tried despite being a feasible choice with many possible advantages. A combination of ketamine and midazolam causes deeper sedation and the less dysphoric reaction of ketamine. We claim that the usage of the technique of nasal sedation is a good possibility that may promise to overcome the combative behavior of mentally retarded patients presented for medical procedures.

So this study will evaluate the efficacy and safety of the administration of ketamine midazolam mixture through the intranasal route in comparison with the intramuscular route for procedural sedation in mentally disabled children outside the operating room.

2. Materials and methods

This study was a comparative prospective randomized study applied in our Anesthesia department-University Hospitals from March 2019 to November 2019. Once we got the approval of the Ethical Committee of Ain Shams University, we selected patients who referred from the pediatric outpatient clinic, the Radiology department, and/or after admission to the emergency room. Written consents following the ethical regulations were taken from the parents/guardians who were informed about the sedation protocol with no intended effort to get their approval. After Ain Shams University's ethical approval, the proposal has been registered in the ClinicalTrials.gov Identifier: NCT03860831.

We included in this study 40 children with mental disability due to autism, Down syndrome or cerebral palsy. They were classified according to the American Society of Anesthesiology (ASA) physical status into Classes I and II. Children aged 4 to 12 years. All were scheduled for short procedures (30 minutes or less) under sedation in remote areas as a dental clinic, burn unit, oncology department, MRI, CT, or who came to the emergency department for small wounds suturing or reduction of a fracture.

We excluded cases after parents' refusal, who showed cooperation and readiness for venous access insertion or patients with existing venous access. Also, children with known allergy to the drugs under study, liver or renal organ dysfunction, suspected difficult airway or difficult cannulation. Patients with congenital heart disease, severe respiratory illness, increased intracranial tension or intraocular pressure, severe trauma, significant nasal discharge or obstruction were also excluded from the study.

The selected patients were randomized and allocated using an automated method dividing them into two study groups. Fasting for at least six hours was fulfilled by all patients. It was not possible to blind the parents or the anesthesia team about the type of intervention. The surgeon and the nurse or the assistant who recorded the data of patients were blinded about the route of drug administration. Patients were divided into two groups:

Group IN received midazolam (0.2 mg/kg) in addition to ketamine (5 mg/kg) intranasally [8,9]. In cases that needed a small dose, an insulin syringe was used, then the drugs diluted with normal saline to reach 2ml. The calculated dose was divided inside the two nostrils equally using the intranasal mucosal LMA, MAD atomization device (Figure 1) with the help of the parents. Half of the dose in the form of midazolam (0.1 mg/kg) + ketamine (2.5 mg/kg) can be given again after 10 minutes in cases that showed no or unsatisfactory response.

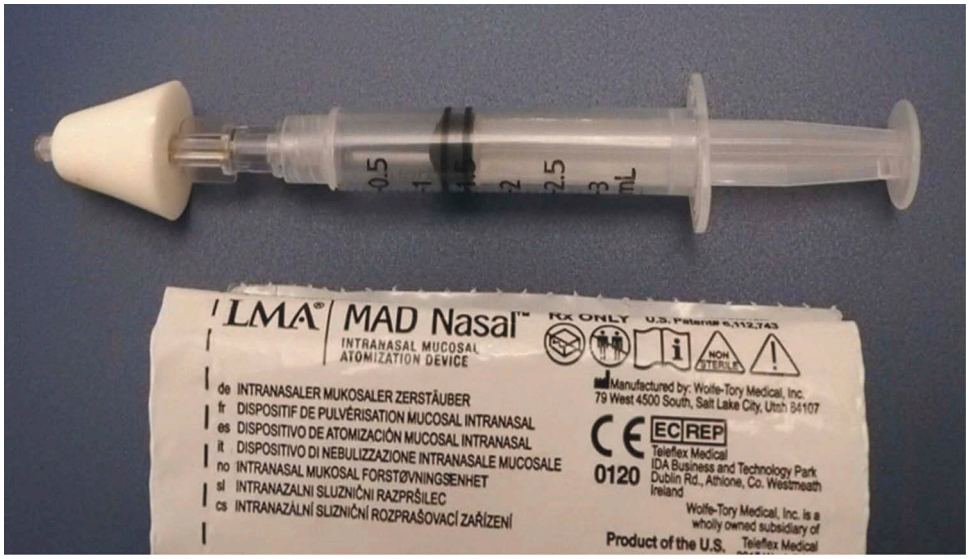

Figure 1. Intranasal LMA, MAD atomization device.

For group IM intramuscular midazolam (0.2 mg/kg) in addition to ketamine (5 mg/kg) was given in the gluteal region. Also, half of the dose midazolam (0.1 mg/kg) + ketamine (2.5mg/kg) can be repeated once by the same route after 10 minutes if the child showed little or no response.

Physical restraint was applied with the help of the parents during drug administration in the 2 groups if needed. Venous cannula was inserted when parents' separation was possible after drug administration in both groups.

Heart rate (HR), Oxygen saturation (Spo2), and mean arterial blood pressure (MBP) was continuously monitored and recorded every 5 min after parents' separation for 60 minutes. Local anesthesia was given in painful procedures if possible.

Sedation level after 10, 20 and 30 min were evaluated by the Pediatric Sedation State Scale (PSSS) [11] as follows:

- State 5: Movement impedes procedure and requires forceful immobilization.
- State 4: Movement requires gentle immobilization to maintain certain positioning
- State 3: Facial expression of pain.
- State 2: Quiet, not moving, no frown, no verbalization of complaint (ideal state).
- State 1: Deeply asleep with normal vital signs but requires airway monitoring.
- State 0: Deeply asleep with abnormal physiologic parameters that require acute intervention (e.g., O_2saturation <90%, hypotension or bradycardia).

Intravenous ketamine 0.5-1mg/kg was given if needed due to prolongation of the procedure. Respiratory events as airway obstruction and desaturation of less than 92% were treated by jaw thrust and oxygen supplementation, apnea or laryngeal spasm were managed with endotracheal intubation. Wheezing was recorded and properly managed with bronchodilators and steroids. Bradycardia less than 80 bpm or increased secretions was treated by atropine (0.01–0.02 mg/kg). Emergency cart and drugs were available for hemodynamic and respiratory instability.

After the end of the procedure, patients were transferred to the post-anesthesia care unit (PACU) under full noninvasive monitoring till recovery, then transferred to a nearby area for another 2 hours before home discharge.

After the recovery of the patients, parents were asked to rate their overall satisfaction by using a simple image of 5 points Likert scale [12] (Figure 2).

2.1. Primary outcome

effectiveness of sedation.

2.2. Secondary outcome

onset, duration of sedation, adverse effects, parents' satisfaction.

2.3. The endpoint of the study

if our technique failed to sedate the patients, general anesthesia by inhalational sevoflurane was used to perform the procedure.

3. Sample size justification

After setting, alpha error at 5% and power at 80% using the E power program, results from a pilot study showed that the mean recovery time for the nasal group was 20 minutes while for intramuscular it was 30 minutes with a common standard deviation of 40. Based on this the needed sample size is 20 cases per group.

4. The statistical analysis

We used a standard SPSS software package version 21 (Chicago, IL) for statistical analysis. The numerical data are presented as mean ± standard deviation (SD) and differences between groups were compared using the independent Student's *t*-test, data not normally distributed were compared using Mann-Whitney test and are presented as median (IQR) and categorical variables were analyzed using the χ2 test or Fisher

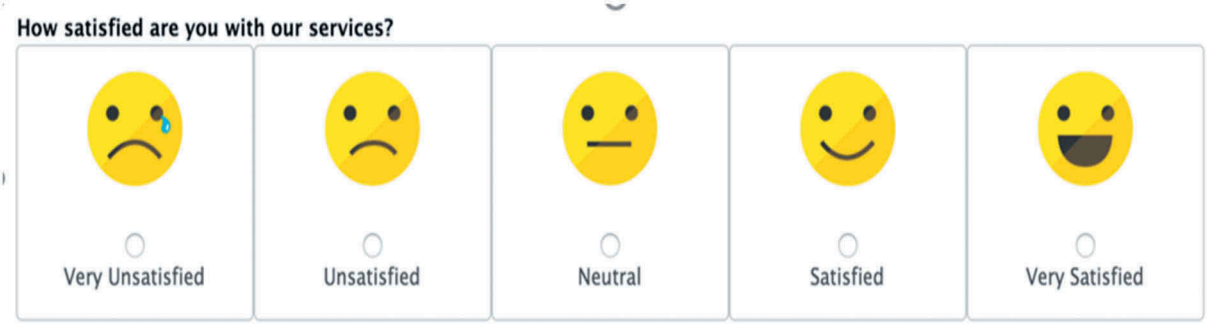

Figure 2. A simple image of 5 points Likert scale for parents' satisfaction.

exact test and are presented as number and percentage (%). All P values are two-sided. P < 0.05 is considered statistically significant.

5. Results

The present work was conducted on 40 children with mental disabilities undergoing procedural sedation. They were divided into two groups; Group IN received intra-nasal Midazolam 0.2 mg/kg + Ketamine 5 mg/kg while group IM received the same dose of Midazolam and Ketamine yet with IM injection (Figure 3).

Patients' characteristics were similar in both groups with no statistical significance (Table 1)

Four children representing 20% of the IN group required a second dose after 10 minutes to reach the desired level of sedation. However, in the IM group, one case representing 5% needed the second injection.

Regarding the type of procedures done to our patients, we found no statistical difference between the two groups. In dental procedures, continuous suction and rubber dam were used to avoid aspiration (Table 2).

Comparing the changes in heart rate, mean arterial blood pressure, respiratory rate and oxygen saturation, differences among both groups were statistically not significant (Table 3) (Figure 4).

Concerning the onset of sedation, there was no statistical difference between the two groups while there was a statistically prolonged sedation in the IM group. Time to discharge from the PACU showed a statistically significant difference between the two groups where the IN group was discharged earlier than the IM group as noted in Table 4.

Concerning the sedation score, patients in the IM group achieved a higher sedation state at 10 minutes than the patients in the IN group and comparable sedation state at 20 and 30 minutes (Table 5) (Figure 5).

Prolonged recovery time recorded the higher complication incidence being recorded in 3 cases with all following IM group. Overall, we found no statistically significant difference between the IN and IM groups regarding the rate and types of complications (Table 6). Regarding parents' satisfaction; group IN showed higher significance regarding the very satisfied scale with p-value 0.041 (Table 7).

6. Discussion

In literature, there is a huge variation in both locally and internationally usage of sedative drugs and their route of administration for procedural sedation in children [13–15]. Most of the anesthesiologists prefer intravenous

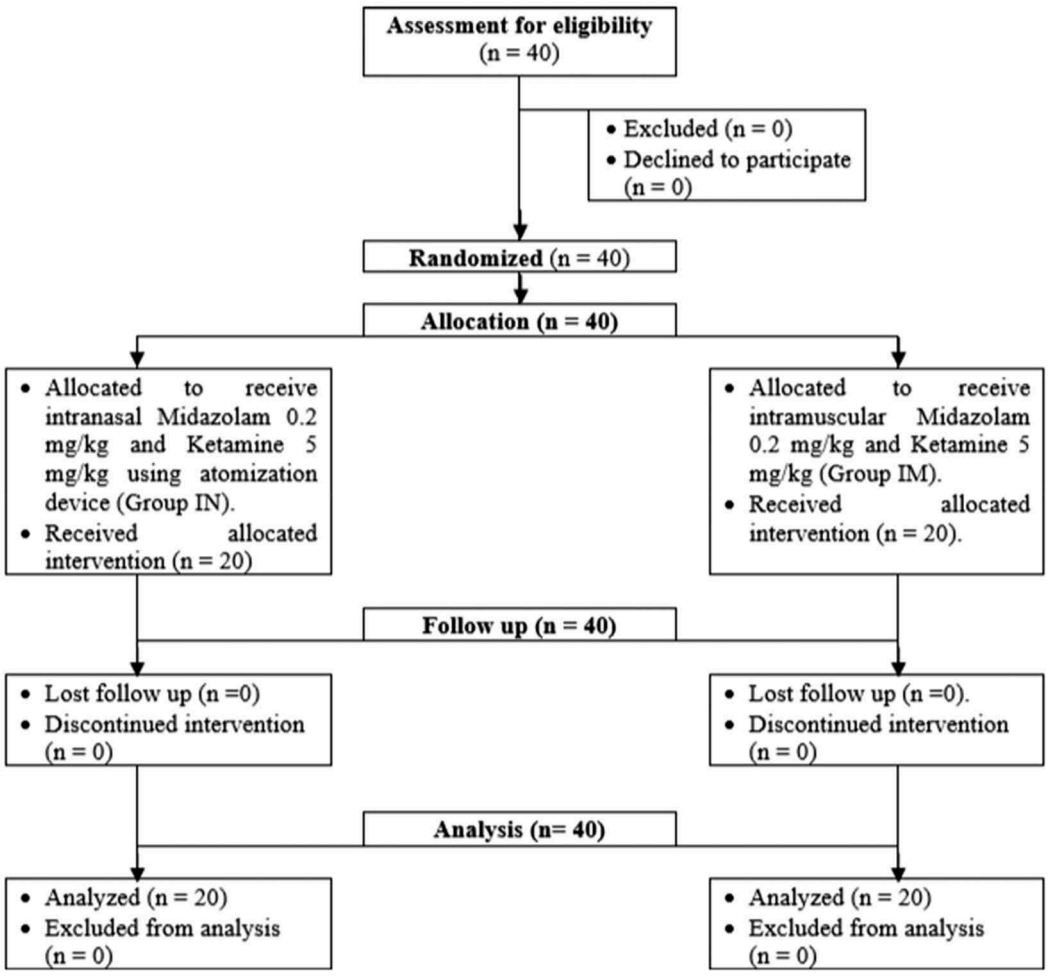

Figure 3. Consort flow chart.

Table 1. Demographic data of the patients.

Variables	Group IN (n = 20)	Group IM (n = 20)	p-value
Age (years)	7.3 + 2.54	6.24 + 3.06	0.235
Weight (kg)	23.1 + 5.49	21.76 + 6.52	0.482
ASA (I/II)	10/10	12/8	0.524
Sex (M/F)	11/9	12/8	0.538

Age and weight data are presented as mean ±SD.
P > 0.05 is considered statistically non-significant.

Table 2. Types of procedures in both groups.

Procedure	IN group	IM group
Dental	5	6
MRI and CT	5	5
Suturing	1	1
Burn dressing	2	1
Fundus examination	1	2
Lumbar aspiration	0	1
Fracture reduction	1	2
Audiometry	2	1
Upper GIT endoscope	1	0
Pediatric ECHO	2	1
Total	20	20

Table 3. Mean ± S.D of vital data for the two groups.

Vital Data	Group IN (n = 20)	Group IM (n = 20)	p-value
MAP (mmHg)	94.85 ± 5.22	94.5 ± 4.32	0.779
HR (bpm)	102.85 ± 5.49	101.7 ± 6.2	0.52
RR (n/min)	21.4 ± 1	21.35 ± 1	0.858
SpO_2 (%)	97.1 ± 1.41	97.3 ± 1.71	0.71

P > 0.05 is considered statistically non-significant.

Table 4. Onset and duration of sedation.

	Group IN (n = 20)	Group IM (n = 20)	P-value
The onset of sedation (min)	8.6 ± 3.69	7.24 ± 1.8	0.139
Duration of sedation (min)	35.1 ± 4.81	46.29 ± 6.94	< 0.001*
Time to discharge from PACU (min)	70.35 ± 10.18	93.5 ± 11	< 0.001*

Data are presented as mean ±SD.
P > 0.05 is considered statistically non-significant.

route due to the possibility to titrate the dose and to predict the drug action [14], but Children with mental disabilities who already suffer from their injury and illness, should be protected from more discomfort and iatrogenic pain caused by intravenous access insertion [16]. Iatrogenic needle phobia in handicapped children is usually due to prior exposure for vaccinations, previous medical interventions, or repeated procedures in chronic cases. Those patients should have adequate sedation and analgesia to avoid emotional factors that can increase their perception of pain [17].

Many studies evaluated intranasal sedation as pre-operative premedication in normal healthy children [7,18] but to our knowledge, no study compared intra-nasal route versus intramuscular route for procedural sedation in combative mentally disabled children.

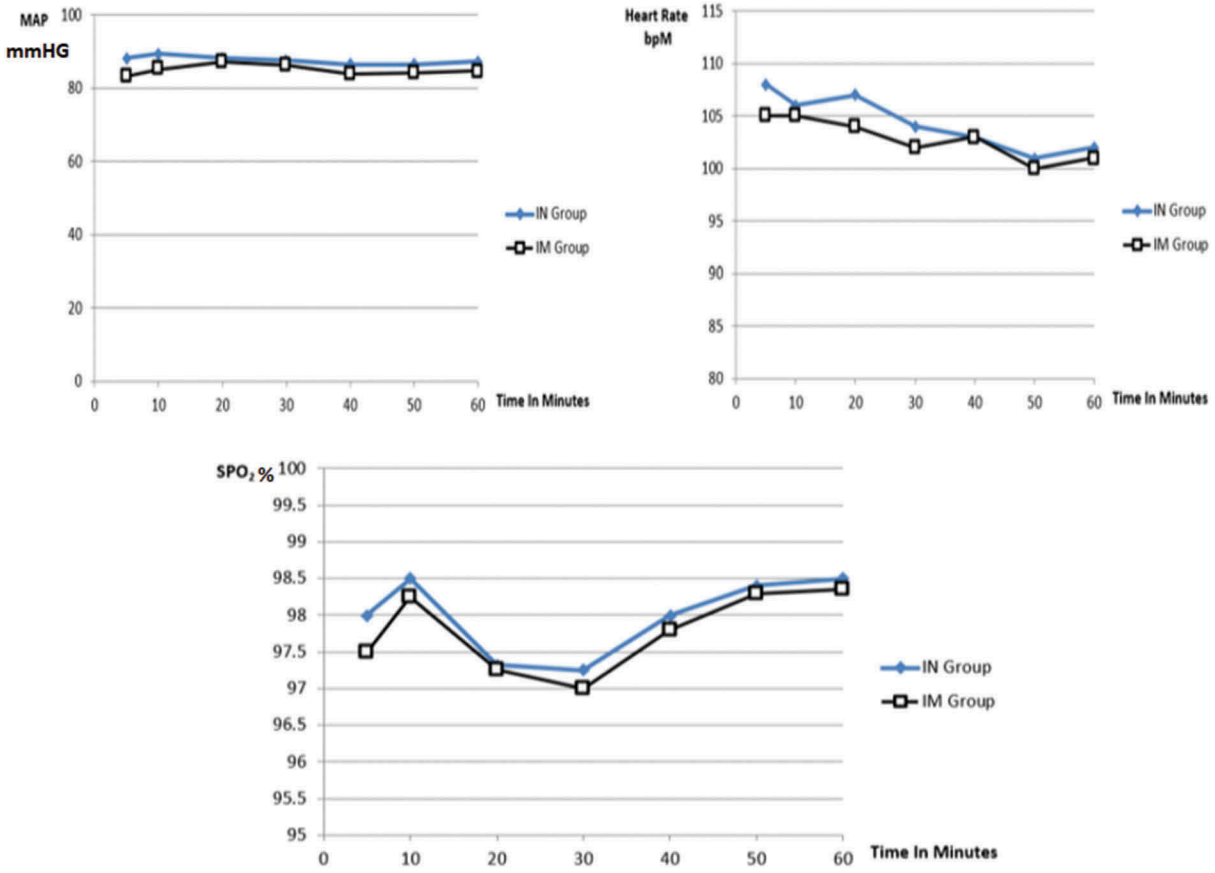

Figure 4. Mean arterial blood pressure (MAP), Mean heart rate, and oxygen saturation for the two groups during study time.

Table 5. Sedation score.

Time	Group IN (n = 20)	Group IM (n = 20)	p-value
10 min.	3 (3–4)	2 (2–3)	< 0.001
20 min.	2 (1–2)	1 (1–2)	0.268
30 min.	1 (1–2)	1 (1–2)	0.433

Data are presented as median (IQR).
P > 0.05 is considered statistically non-significant.

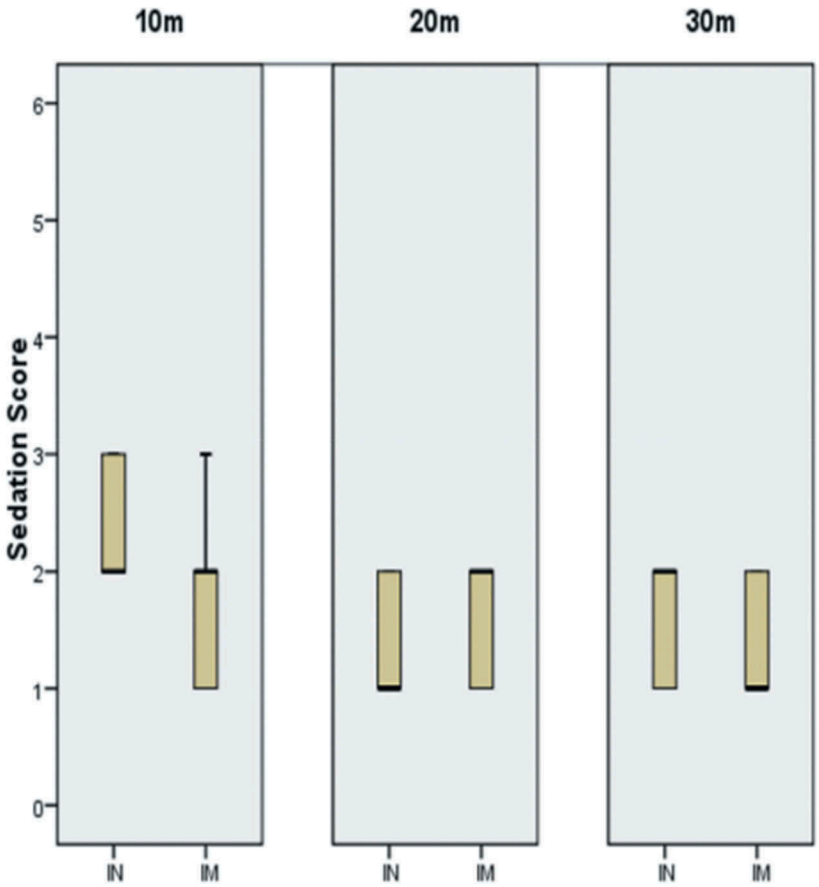

Figure 5. The sedation score at 10, 20 and 30 minutes in both groups. The middle black solid line represents the median sedation score, the upper and lower margins of each box represent IQR, the upper margin of the box is the maximum value.

Table 6. The rate of complications in the study groups.

Type of complication	IN group	IM group	p-value
Laryngospasm	0	0	1
Cough	1	0	1
Increase secretion	1	2	1
Vomiting	1	0	1
Emergence reaction	1	0	1
Prolonged recovery time	1	3	0.605
Lethargy	0	1	1

Table 7. Parents' overall satisfaction.

	Group IN	Group IM	p-value
Very unsatisfied	0 (0%)	2 (10%)	0.487
Unsatisfied	1 (5%)	4 (20%)	0.342
Neutral	4 (20%)	6 (30%)	0.716
Satisfied	5 (25%)	5 (25%)	1
Very satisfied	10 (50%)	3 (15%)	0.041

Data are presented as numbers and percentages.
P > 0.05 is considered statistically non-significant.

This study showed that a mixture of midazolam and ketamine were given through the nasal route with nasal atomization device was effective as an intramuscular route for procedural sedation in children with mental disabilities due to autism, Down syndrome and cerebral palsy. This intranasal mixture was well tolerated without major side effects.

The onset of sedation in our study was 8.6 + 3.69 minutes in the intranasal group and 7.24 + 1.8 minutes in the intramuscular group. We suspected that the intranasal route will be faster in onset but the results showed that the difference was statistically insignificant this is maybe because parts of the drugs have been swallowed or coughed in spite of using the nasal atomization device due to the use of physical strain in highly uncooperative patients. Khatavkar and Bakhshi's study [19] showed comparable results as the onset time of sedation was 10.16 ± 3.50 min. they gave nasal midazolam 0.15 mg/kg + ketamine 1 mg/kg as drops for premedication in children undergoing major surgeries. Taking into consideration that our onset was faster due to the

higher dose used to produce procedural sedation and analgesia, not for premedication. In contrast, Buonsenso et al [20] studied the effect of intranasal midazolam 0.5mg/kg in combination with 2mg/kg ketamine in children undergoing gastric aspirates for suspected tuberculosis found that the mean of the onset time of sedation was 22.9 minutes. This difference could be due to the higher ketamine dose we used in comparison to their dose.

Also, Saeed Majidinejad et al [21] found that adequate sedation through oral route was achieved in 32.87 ± 10.18 minutes after receiving 0.2 mg/kg midazolam and 5 mg/kg ketamine in 33 children scheduled for brain CT.

We used LMA mucosal atomization device as recommended by Pandey et al [22] instead of nasal dropper or syringe used by Gyanesh P et al [23] because atomization devices minimize drug volume and maximize drug concentration, which increases the bioavailability of the drugs.

In Pandey et al study [22] thirty-four uncooperative children received intranasal ketamine 6mg/kg either as drops or atomized nasal spray in two different dental visits. There was a statistically significant difference regarding the onset of sedation between the two methods of administration as the onset of action was more rapid with a mean duration of 5.13 minutes in the atomized group.

A comparison of the level of sedation between different studies is difficult due to the implementation of multiple scores of pediatric sedation. In spite of that, we claim that higher levels of sedation were achieved in our study in comparison with Khatavkar and Bakhsh [19] who used a sedation scale adapted from Wilton and Colleagues [3]. We used Pediatric Sedation State Scale (PSSS) [11] and the results showed that the IM group achieved a higher score of sedation at 10 min point than the IN group and the same level of sedation at 20 and 30 min.

Intramuscular midazolam, ketamine, and glycopyrrolate for pediatric sedation in the emergency department were investigated by JOHN W et al [24]. The discharge time from the recovery area averaged 76 minutes which is less than our average time of discharge time in the IM group 93 min. this is related to the difference of doses and type of our patients and their response to these sedative drugs. The average discharge time in the IN group was 70 minutes which is significantly shorter than the IM group. Our results as regards the IN group are very close to Buonsenso et al [20] who had an average duration of sedation 71.5 minutes in the intranasal group.

Regarding complications or vital data changes, our results are in line with the findings of the previous studies [22–24]. There were no major side effects. Also, children's pulse rate, mean arterial blood pressure, respiratory rate, and oxygen saturation levels did not change significantly throughout the sedation period.

As regards the parents' satisfaction, both groups were almost similar with a higher incidence of a very satisfied scale in the IN group using Likert scale and this is almost similar to Malia L., et al [25] who also used Likert scale for assessment of parents' satisfaction while using intranasal midazolam during an emergency. We used this simple scoring system due to the presence of illiterate parents and the difficult circumstances they were in with handling these children. More sophisticated questionnaires are available but would have been difficult to be completed by the parents

7. Conclusion

Intranasal Midazolam and Ketamine mixture given through the nasal route with nasal atomization device showed a similar effect as the intramuscular route for procedural sedation. It also shortens the time needed for discharge with no difference in the incidence of complications. So, It is considered an adequate alternative in children with mental disabilities.

8. Limitation of the study

Many evaluators assessed the depth of sedation and behavior parameters so interobserver reliability could not be tested, this is due to the distribution of this number of patients over different departments.

Randomization was done but we didn't stratify procedures to painful/non-painful procedures.

We didn't also follow up with the patients' late recovery after home discharge.

9. Recommendations

Multicenter research is needed to study a Larger population with other mental disabilities. studying other sedatives and different doses may also support our results.

Competing interests

The authors declare that they have no competing interests and no conflict of interest.

Declaration of interest

We agree that all copyright ownership is transferable to the Egyptian Journal of Anesthesia when the manuscript is accepted for publication in EJA.

We certify that the submitted article will not constitute "Redundant Publication".

This study is not previously published nor submitted elsewhere and the methods employed respect the Helsinki Declaration of 1975, as revised in 1983.

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