Ketamine With and Without Midazolam for Emergency Department Sedation in Adults: A Randomized Controlled Trial

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Study objective: We assess whether midazolam reduces recovery agitation after ketamine administration in adult emergency department (ED) patients and also compared the incidence of adverse events (recovery agitation, respiratory, and nausea/vomiting) by the intravenous (IV) versus intramuscular (IM) route.

Methods: This prospective, double-blind, placebo−controlled, 2×2 factorial trial randomized consecutive ED patients aged 18 to 50 years to 4 groups: receiving either 0.03 mg/kg IV midazolam or placebo, and with ketamine administered either 1.5 mg/kg IV or 4 mg/kg IM. Adverse events and sedation characteristics were recorded.

Results: Of the 182 subjects, recovery agitation was less common in the midazolam cohorts (8% versus 25%; difference 17%; 95% confidence interval [CI] 6% to 28%; number needed to treat 6). When IV versus IM routes were compared, the incidences of adverse events were similar (recovery agitation 13% versus 17%, difference 4%, 95% CI −8% to 16%; respiratory events 0% versus 0%, difference 0%, 95% CI −2% to 2%; nausea/vomiting 28% versus 34%, difference 6%, 95% CI −8% to 20%).

Conclusion: Coadministered midazolam significantly reduces the incidence of recovery agitation after ketamine procedural sedation and analgesia in ED adults (number needed to treat 6). Adverse events occur at similar frequency by the IV or IM routes. [Ann Emerg Med. 2011;57:109-114.]

Please see page 110 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Procedural sedation and analgesia is a technique of administering sedatives (midazolam, propofol, etomidate) or dissociative agents (ketamine) with or without opioid analgesics (fentanyl, morphine, meperidine) to induce a state that allows the patient to tolerate unpleasant procedures while maintaining cardiorespiratory function.[1] Ketamine, first described in 1965, has been administered extensively for procedural sedation and analgesia in children and is a safe and effective sedative analgesic for painful procedures not only in the emergency department (ED) but also in the out-of-hospital setting.[2-5] The widespread acceptance of ketamine as an agent for procedural sedation and analgesia in adult ED patients may be limited by physician apprehension about dreaming and hallucinations during recovery, and unpleasant reactions and nightmares, collectively referred to as recovery agitation.

Importance

Many practitioners believe recovery agitation can be minimized by coadministration of midazolam with ketamine.[6] Although this method does not appear to be true in children, it might still apply in adults.[7,8] If this were true, it would make clinicians less reluctant to administer ketamine to adults.

Goal of This Investigation

We had 2 main objectives: (1) compare the incidence of recovery agitation in adults receiving ketamine with and without midazolam, and (2) compare the incidence of adverse events, categorized as respiratory, nausea/vomiting, and recovery agitation between groups receiving intravenous (IV) and intramuscular (IM) ketamine. Secondary objectives were to compare the effect of midazolam on sedation times and on provider and patient satisfaction scores.

Editor's Capsule Summary

What is already known on this topic

Emergency physicians are often reluctant to sedate adults with ketamine, fearing unpleasant hallucinatory recovery reactions.

What question this study addressed

Does coadministered midazolam decrease recovery agitation after emergency department (ED) ketamine sedation in adults?

What this study adds to our knowledge

In this study of 182 subjects, coadministered midazolam decreased the incidence of recovery agitation of any severity by 17% (number needed to treat to benefit=6).

How this is relevant to clinical practice

Coadministered midazolam reduces the incidence of recovery agitation after ED ketamine sedation in adults, although this study does not clarify how many of the prevented occurrences were clinically important.

MATERIALS AND METHODS

Study Design and Setting

We performed a prospective, randomized, double-blind, placebo−controlled, 2×2 factorial[9] trial in the ED of a university medical center from June 2003 until December 2004 (annual census 45,000). The study was approved by the hospital ethics committee, and written informed consent was obtained from each patient.

Selection of Participants

We attempted to enroll consecutive patients selected for ketamine administration who were between the ages of 18 and 50 years and in good health or with only mild systemic disease (American Society of Anesthesiologists grades I or II). We excluded patients with significant cardiovascular disease, central nervous system lesions or injuries, psychiatric disorders, pregnancy, ocular pathology, thyroid disease, acute pulmonary infections, conditions requiring stimulation of the posterior pharynx, and who had ingested solid food in the previous 4 hours or clear liquids in the previous 2 hours.[10,11]

Interventions

The treatment allocation sequence was determined from a computer-generated, random-number table and kept in a secure shelf in the ED, separate from patient care areas. After consent, an attending emergency physician accessed the randomization tool and placed the patient's name in the next open slot on the table. In this manner, patients were randomized to the 4 groups shown in the Figure.

Each day, sets of 3 prefilled syringes were prepared for each of the 4 patient groups, taped together by the hospital pharmacist, numbered by a research attending emergency physician not actively involved in any part of the study, and stored in a moisture- and temperature-controlled locked drawer. Only the research attending physician had a key to this drawer and knew the randomization numbers. Prefilled syringes were destroyed if their contents were outdated in the next 24 hours.

Syringes were labeled with black "IM" for IM ketamine or placebo, red "IV" for IV ketamine or placebo, and blue "IV" for IV midazolam or placebo. All agents used were colorless and clear. Standard racemic ketamine (Ketalar 50 mg/mL vial; Pfizer Pharmaceuticals, New York, NY) was used in the study. The red-labeled syringe contained 3 mL (150 mg) ketamine and 7 mL normal saline solution or 10 mL placebo, the black-labeled syringe contained 8 mL (400 mg) ketamine and 2 mL normal saline solution or 10 mL placebo, and the blue-labeled syringe contained 3 mL (3 mg) midazolam and 7 mL normal saline solution or 10 mL placebo. Every patient had an 18-gauge IV line placed. All 3 syringes (1 IM and 2 IV) were administered to each patient with a dose of 0.1 mL/kg in the order of blue, red, and black. Thus, every patient received ketamine either 1.5 mg/kg IV or 4 mg/kg IM, with or without 0.03 mg/kg midazolam. This approach ensured that both the patient and the physician were blinded about which drug was being administered by which route. The contents of the blue and red syringes were injected during a minimum of 2 minutes. After the patient reached the Ramsay Sedation Scale score of at least 4, the procedure was initiated by a physician other than the one supervising the procedural sedation and analgesia. If the patient did not reach the desired Ramsay Sedation Scale score in the first 5 minutes, an additional 0.025 mL/kg of drug from the black and red syringes was administered IM and IV. If the patient still did not reach a Ramsay Sedation Scale of at least 4, he or she was excluded from the study.

Methods of Measurement and Data Collection and Processing

Demographic features, type of procedure, Ramsay Sedation Scale score, vital signs, duration of procedure and sedation time, and presence of adverse events were recorded on a standardized data collection instrument (Appendix E1, available online at http://www.annemergmed.com) by pretrained treating physicians or nurses.

Respiratory adverse events were defined as oxygen desaturation (pulse oximetry ≤90%), apnea (a minimum 20-second transient cessation of breathing), or laryngospasm. The presence or absence of nausea and vomiting was recorded. We defined recovery agitation as any moaning, screaming, cursing, unpleasant dreams, or unpleasant hallucinations, regardless of severity. Pleasant hallucinations were not counted as adverse events.

Procedure duration was defined as the time from commencement of specific procedure-related actions until the physicians performing the interventions stated to the individual supervising procedural sedation and analgesia that they were finished. Sedation time was defined as the time from administration of the first syringe until the following discharge

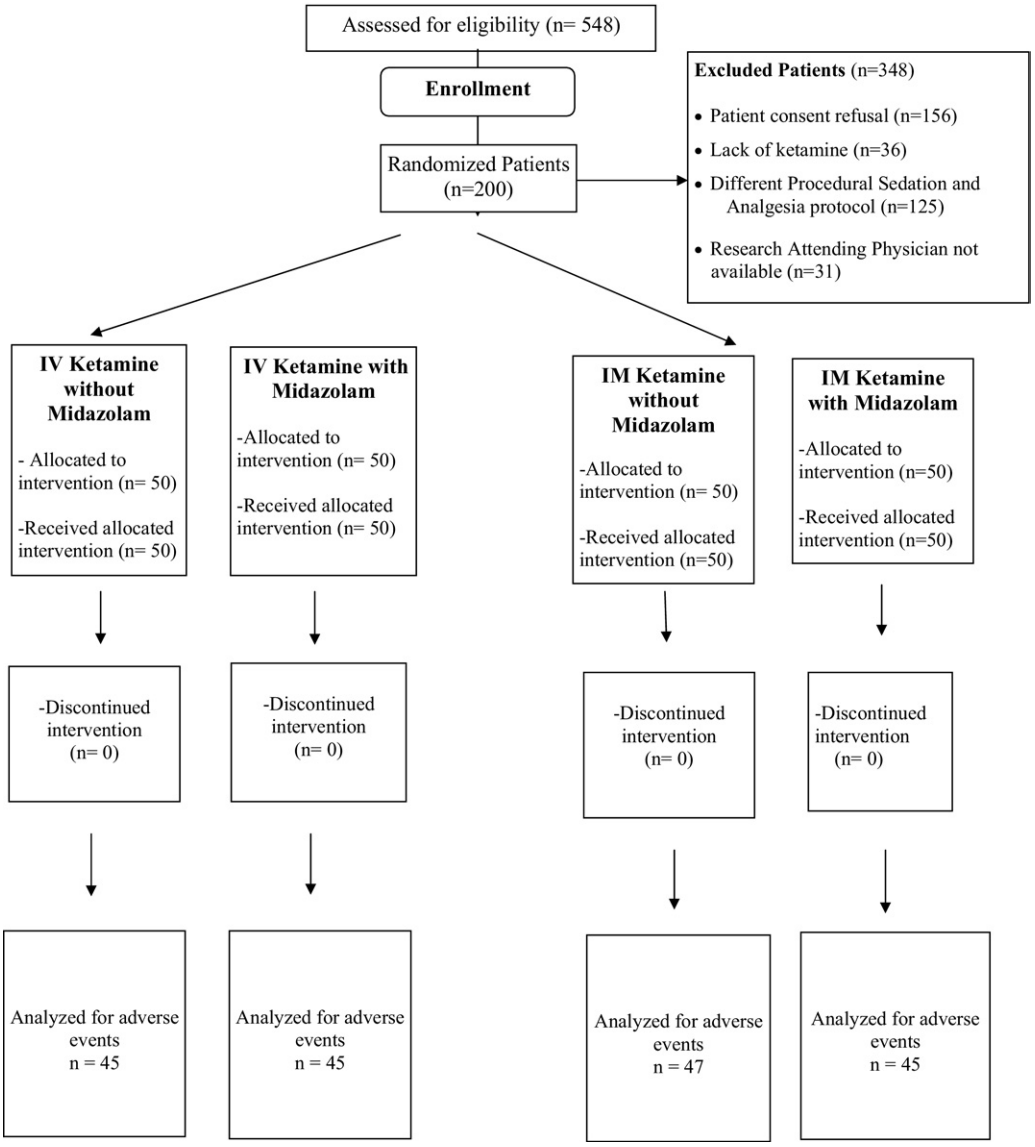

Figure. The CONSORT flowchart.

criteria were met: (1) a patent airway exists with normal (>95% saturation on room air) patient oxygenation; (2) the patient is awake or easily aroused with minimal tactile or vocal stimulation; and (3) the patient's level of alertness has returned to baseline, as assessed by physician judgment, or the patient has the Ramsay Sedation Scale score of less than or equal to 2.

Patients received monitoring, including blood pressure, pulse rate, respiratory rate, pulse oximetry, and Ramsay Sedation Scale scores.[12,13] Measurements were documented at baseline, during the procedure (recorded every 5 minutes), and postprocedure (recorded every 10 minutes) until sedation completion. Airway management equipment and flumazenil were always available at the bedside.

After completion of the sedation process, patients, physicians, and nurses were queried about their level of satisfaction, from 1 (least satisfied) to 5 (most satisfied), with a Likert scale. The responses were categorized as satisfied (Likert scale score of 4 or 5) and not satisfied (score of 1, 2, or 3).

Outcome Measures

The 2 main study outcomes were comparisons of the incidence of recovery agitation in groups receiving midazolam or placebo and the incidences of adverse event types in groups receiving IV versus IM ketamine. Secondary outcomes were the effect of midazolam versus placebo on sedation times and satisfaction scores.

Primary Data Analysis

We analyzed our data descriptively with MedCalc (version 11.0.0.4, MedCalc Software, Mariakerke, Belgium). Assuming a baseline recovery agitation incidence of 20%, we calculated that 76 patients were needed in both of the combined groups to

Table 1. Characteristics and procedures for study subjects by treatment group.

Characteristic	IV Ketamine Without Midazolam, n=50	IV Ketamine With Midazolam, n=50	IM Ketamine Without Midazolam, n=50	IM Ketamine With Midazolam, n=50
Age, y, median (IQR)	35 (24–40)	29 (25–38)	27 (22–33)	31 (22.5–37)
Sex, male/female (%)	35/15 (70/30)	37/13 (74/26)	33/17 (66/34)	36/14 (72/28)
Duration of procedure, min, median (IQR)	13 (10–18)	13.5 (8–17)	14 (13–21.5)	15 (11.5–18)
Procedures				
Fracture reduction	18	21	25	21
Burn wound care	6	5	6	5
Dislocation reduction	4	4	6	7
Abscess incision	4	4	2	6
Laceration repair	5	2	5	3
Foreign body removal	4	2	4	3
Lumber puncture	1	1	1	3
Tube thoracostomy	2	0	1	0
Thrombosed hemorrhoidectomy	0	0	0	1

y, years;*IQR*, interquartile range; *min*, minutes.

Table 2. Outcome events in each group.

Outcomes	IV Ketamine Without Midazolam, n=45, No. (%)	IV Ketamine With Midazolam, n=45, No. (%)	IM Ketamine Without Midazolam, n=47, No. (%)	IM Ketamine With Midazolam, n=45, No. (%)
Recovery agitation	10 (22)	3 (7)	13 (28)	4 (9)
Nausea	8 (18)	9 (20)	12 (26)	10 (22)
Vomiting	4 (9)	4 (9)	6 (13)	3 (7)
Laryngospasm	0	0	0	0
Oxygen desaturation	0	0	0	0
Apnea	0	0	0	0
Sedation time, min, median (IQR)	24 (22–31)	24 (19–34)	36 (29–58)	49 (35–62.5)

detect a difference of 15% with 80% power and 2-tailed .05 α. P=.05 was accepted as significant.

RESULTS

Patient participation is shown in the Figure. Of 200 subjects originally enrolled, 182 ultimately had data collected on adverse outcomes. All subjects achieved adequate sedation in the first 5 minutes (Ramsay Sedation Scale score of at least 4), and so none were excluded on this basis or required additional medication. Clinical characteristics were similar between groups (Table 1).

The number of patients missing data elements were as follows: demographic information (11), vital signs (10), history (4), Ramsay Sedation Scale score (6), and adverse events (18). This left 151 patients available for analysis of midazolam's effect on sedation times and satisfaction scores. No patient received any intervention triggered by the measurement of any vital sign or a change in its value.

The breakdown of individual adverse events is shown in Table 2. We observed significantly less recovery agitation in both midazolam cohorts relative to placebo (Table 3), and the estimated number needed to treat according to this 17% absolute reduction is 6. There was no difference in the incidence of any adverse event between the IV and IM ketamine groups.

Satisfaction scores were similar among physicians and nurses for the 4 patient cohorts (Table 4). However, patients significantly favored the midazolam groups.

The duration of sedation was significantly longer with the IM route compared with IV but was not similarly affected by midazolam (Table 3).

LIMITATIONS

We studied only adults between the ages of 18 and 50 years, and thus our data cannot apply to elderly patients who are perhaps more likely to experience the sympathomimetic effects of ketamine.

Although every attempt was made to conceal drug allocation, blinding may not have been complete. Given the rapid onset of IV ketamine and midazolam, it might be possible to determine active agent versus placebo during administration; however, our study design should have minimized this likelihood.

Another limitation is that investigators recorded any perceived recovery agitation as positive regardless of severity. Minor transient restlessness or a single soft moan may have thus been coded as positive, and thus not all of the 17% absolute reduction observed in recovery agitation may be clinically important. Nonetheless, this approach was consistent across all groups, and the overall incidence for

Table 3. Analysis of adverse events and sedation times after combining groups according to the administration of midazolam and route of ketamine administration.

Outcomes	Midazolam Groups, n=90	Nonmidazolam Groups, n=92	Difference in Percentage or Median (95% CI)	IV Ketamine Groups, n=90	IM Ketamine Groups, n=92	Difference in Percentage or Median (95% CI)
Recovery agitation, No. (%) [95% CI]	7 (8) [3 to 15]	23 (25) [16 to 38]	17 (6 to 28)	13 (14) [8 to 25]	17 (18) [11 to 30]	4 (−8 to 16)
Respiratory adverse events, No. (%) [95% CI]	0 (0) [0 to 4]	0 (0) [0 to 3]	0 (0) (−2 to 2)	0 (0) [0 to 4]	0 (0) [0 to 3]	0 (0) (−2 to 2)
Gastrointestinal adverse events, No. (%) [95% CI]	26 (29) [19 to 34]	30 (33) [22 to 47]	4 (−10 to 18)	25 (28) [18 to 41]	31 (34) [23 to 48]	6 (−8 to 20)
Sedation time, min, median (IQR)	35 (24 to 49)*	29 (24 to 37)†	6 (−2 to 8)	24 (19 to 32)‡	43 (30 to 58)§	19 (11 to 22)

*For midazolam groups used in sedation time calculations, n=74.
†For nonmidazolam groups used in sedation time calculations, n=77.
‡For IV ketamine groups used in sedation time calculations, n=76.
§For IM ketamine groups used in sedation time calculations, n=75.

Table 4. Satisfaction rates of physicians, nurses, and patients in individual and combined groups.

Variables	IV Ketamine Without Midazolam, n=45, No. (%)	IV Ketamine With Midazolam, n=45, No. (%)	IM Ketamine Without Midazolam, n=47, No. (%)	IM Ketamine With Midazolam, n=45, No. (%)	Midazolam Groups, n=90, No. (%)	Non-midazolam Groups, n=92, No. (%)	Difference in Combined Groups, % (95% CI)
Physicians	29 (76)	30 (79)	25 (64)	29 (81)	59 (80)	54 (70)	10 (−5 to 24)
Nurses	29 (76)	30 (79)	25 (64)	29 (81)	59 (80)	54 (70)	10 (−5 to 24)
Patients	21 (55)	26 (68)	16 (41)	25 (69)	51 (69)	37 (48)	21 (4 to 36)

recovery agitation observed in our study (16%) is consistent with that observed in other reports.

DISCUSSION

In this large prospective, randomized, double-blind, placebo-controlled trial, we found that the addition of midazolam to ketamine in ED adults can significantly reduce the incidence of recovery agitation, with the number needed to treat estimated at 6. We believe that this is clinically important and that clinicians formerly reluctant to administer ketamine to adults can now do so with greater confidence by coadministering midazolam. Adding this benzodiazepine improved patient satisfaction and did not significantly prolong sedation time or increase the incidence of other adverse events.

We observed no statistically significant difference in adverse events between IM and IV routes, and thus it appears that physicians can select an administration technique according to other factors.

Ketamine sedation and analgesia differs from that of other agents in that it lacks the characteristic dose-response continuum to progressive titration. At doses below a certain threshold, ketamine produces analgesia and sedation. However, once a critical dosage threshold (1 to 1.5 mg/kg IV or 3 to 4 mg/kg IM) is achieved, the characteristic dissociative state abruptly appears. This dissociation has no observable levels of depth and is not consistent with formal definitions of moderate sedation, deep sedation, or general anesthesia. Therefore, it must be considered from a different perspective than agents that exhibit the classic sedation continuum.[14] In this study, patients reached the median Ramsay Sedation Scale score of 4.5 to 5 (defined as dissociation by the authors for the purposes of this investigation) by the fifth minute after ketamine administration, regardless of route. As expected, sedation time was longer in the IM groups compared with the IV groups but was not significantly affected by midazolam.

Although we found no significant differences in satisfaction scores for physicians or nurses, subjects receiving midazolam reported a 21% higher satisfaction rate with the overall experience compared with those receiving placebo. Whether this enhanced experience results from the reduction in recovery agitation or other factors is not clear, given the study design. However, improving patient satisfaction regardless of the mechanism is an important outcome.

Other adult studies of ketamine and midazolam exist but are not controlled trials like ours. Strayer and Nelson[15] published a comprehensive review of the adult ketamine literature and found 87 studies applicable to emergency medicine. These studies found a cumulative 10% to 20% incidence of recovery agitation in mostly nonpremedicated patients. Among these 87 studies, none contained a control group to correctly compare the effectiveness of midazolam on adverse events. Tolksdorf et al[16] randomized 90 patients into 3 groups of 30 patients each. Group 2 received IV midazolam 5 mg (approximately 0.05 to 0.1 mg/kg) with IV ketamine 0.5 to 1 mg/kg, and group 3 received IV midazolam 7.5 mg (approximately 0.07 to 0.1 mg/kg) with IV ketamine 2 to 3 mg/kg. Only 1 patient in group 2 complained of unpleasant dreams. Chudnofsky et al[17] administered 2 mg/kg IV ketamine with concurrent 0.07 mg/kg IV midazolam to 77 ED adults to

facilitate painful procedures. They reported 5 patients (7%) with mild recovery agitation. These results compare favorably with the findings reported in this article from the IV ketamine and midazolam group, where recovery agitation occurred in 7% of patients.

In summary, our data suggest that the use of midazolam in combination with either IM or IV ketamine can significantly reduce the incidence of recovery agitation in adult ED patients. There appears to be no difference in the incidence of any adverse events with either route (IM versus IV) of ketamine administration. However, the IM route is associated with prolonged sedation times. The use of midazolam did not significantly prolong sedation times and was associated with greater patient satisfaction.

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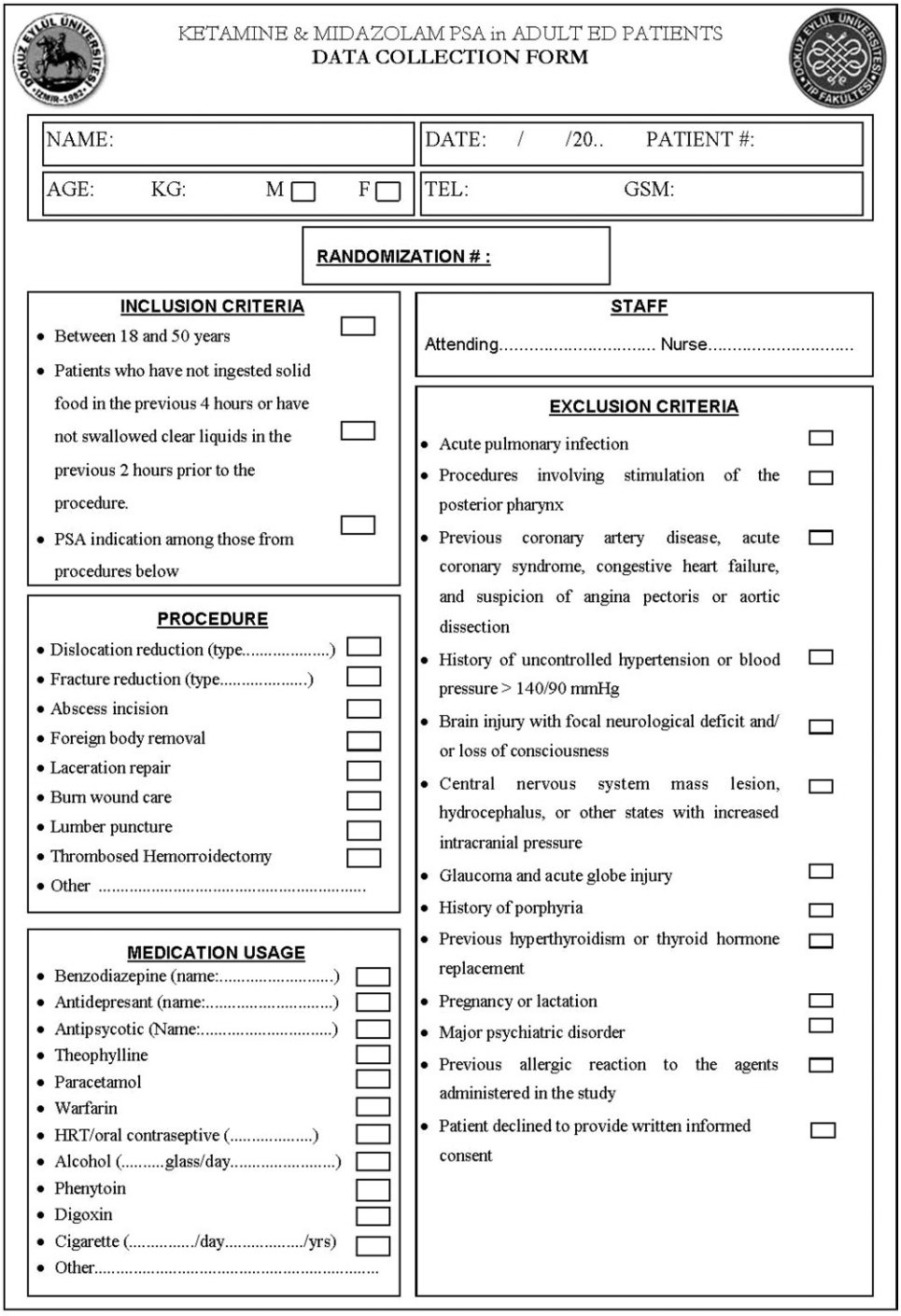
APPENDIX E1. Data collection form.



KETAMINE & MIDAZOLAM PSA in ADULT ED PATIENTS
DATA COLLECTION FORM

NAME:	DATE: / /20.. PATIENT #:
AGE: KG: M ☐ F ☐	TEL: GSM:

RANDOMIZATION # :

INCLUSION CRITERIA

- Between 18 and 50 years ☐
- Patients who have not ingested solid food in the previous 4 hours or have not swallowed clear liquids in the previous 2 hours prior to the procedure. ☐
- PSA indication among those from procedures below ☐

PROCEDURE

- Dislocation reduction (type.....) ☐
- Fracture reduction (type.....) ☐
- Abscess incision ☐
- Foreign body removal ☐
- Laceration repair ☐
- Burn wound care ☐
- Lumber puncture ☐
- Thrombosed Hemorroidectomy ☐
- Other .....

MEDICATION USAGE

- Benzodiazepine (name:.....) ☐
- Antidepresant (name:.....) ☐
- Antipsycotic (Name:.....) ☐
- Theophylline ☐
- Paracetamol ☐
- Warfarin ☐
- HRT/oral contraseptive (.....) ☐
- Alcohol (.....glass/day.....) ☐
- Phenytoin ☐
- Digoxin ☐
- Cigarette (...../day...../yrs) ☐
- Other.....

STAFF

Attending..... Nurse.....

EXCLUSION CRITERIA

- Acute pulmonary infection ☐
- Procedures involving stimulation of the posterior pharynx ☐
- Previous coronary artery disease, acute coronary syndrome, congestive heart failure, and suspicion of angina pectoris or aortic dissection ☐
- History of uncontrolled hypertension or blood pressure > 140/90 mmHg ☐
- Brain injury with focal neurological deficit and/or loss of consciousness ☐
- Central nervous system mass lesion, hydrocephalus, or other states with increased intracranial pressure ☐
- Glaucoma and acute globe injury ☐
- History of porphyria ☐
- Previous hyperthyroidism or thyroid hormone replacement ☐
- Pregnancy or lactation ☐
- Major psychiatric disorder ☐
- Previous allergic reaction to the agents administered in the study ☐
- Patient declined to provide written informed consent ☐

PRE-PROCEDURE

Apply the syringes according to the color sequences below. IVs have to be applied by slow bolus exactly in 2 mins .

1. BLUE **IV**..... kg X **0.1 mL** = ☐ **mL**

2. RED **IV**..... kg X **0.1 mL** = ☐ **mL**

3. BLACK **IM** ..... kg X **0.1 mL**= ☐ **mL**

Additional dose protocol

4. RED **IV**.....kg X **0.025 mL** = ☐ **mL**

5. BLACK **IM** .....kg X **0.025 mL**= ☐ **mL**

RAMSAY SEDATION SCALE (RSS)

1 Point: Anxious and agitated or restless, or both

2 Points: Cooperative, oriented and tranquil

3 Points: Responds to commands only

4 Points:Brisk response to light glabellar tap or loud auditory stimulus

5 Points: Sluggish response to light glabellar tap or loud auditory stimulus

6 Points: No response

	RSS SCORE	Score if add. dose applied
TIME 0	☐	
5th MIN SCORE	☐	☐
15th MIN SCORE	☐	☐
DISCHARGE SCORE	☐	☐

NOTE: To start any procedure RSS has to be ≥ 4 at the 5th min. after the first syringe was applied. If the patient has not reached to this RSS, apply the additional dose protocol. 5 minutes after the additional dose is given, if the patient's RSS is still < 4, exclude the patient from the study and use another agent for PSA

EVERY 5 mins WHILE PROCEDURE CONTINUES

SEDATION ONSET : ☐☐

	SBP	DBP	HR	RR	SpO2
5	☐	☐	☐	☐	☐
10	☐	☐	☐	☐	☐
15	☐	☐	☐	☐	☐
20	☐	☐	☐	☐	☐
25	☐	☐	☐	☐	☐

EVERY 10 mins AFTER PROCEDURE UNTIL RECOVERY

END OF PROCEDURE : ☐☐

	SBP	DBP	HR	RR	SpO2
10	☐	☐	☐	☐	☐
20	☐	☐	☐	☐	☐
30	☐	☐	☐	☐	☐
40	☐	☐	☐	☐	☐
50	☐	☐	☐	☐	☐

END OF SEDATION : ☐☐ **DISCHARGE TIME:** ☐☐

ADVERSE EVENT (S) ? **YES** ☐ **NO** ☐

NAUSEA ☐ VOMITING ☐ LARYNGOSPASM ☐ REC. AGITATION ☐ OTHER : …….....

HALLUCINATION : a) FRIGTHENING ☐ b) PLEASANT ☐ .....

Have you been satisfied with the medication(s) and the sedation procedure?

	Extremely satisfied	*Very satisfied*	*Neither satisfied nor dissatisfied*	*Dissatisfied*	*Very dissatisfied*
PHYSICIAN SATISFACTION :					
NURSE SATISFACTION :					
PATIENT SATISFACTION :					

ANY PHARMACOLOGICAL AGENT(S) OTHER THAN THE STUDY MEDICATIONS

1- ..... DOSE:.....

2- ..... DOSE:.....