CLINICAL INVESTIGATIONS

A Combination of Midazolam and Ketamine for Procedural Sedation and Analgesia in Adult Emergency Department Patients

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Abstract. **Objective:** To describe the clinical characteristics of a combination of midazolam and ketamine for procedural sedation and analgesia in adult emergency department (ED) patients. **Methods:** This was a prospective, observational trial, conducted in the ED of an urban level II trauma center. Patients ≥ 18 years of age requiring procedural sedation and analgesia were eligible, and enrolled patients received 0.07 mg/kg of intravenous midazolam followed by 2 mg/kg of intravenous ketamine. Vital signs were recorded at regular intervals. The adequacy of sedation, adverse effects, patient satisfaction, and time to reach discharge alertness were determined. Descriptive statistics were calculated using statistical analysis software. **Results:** Seventy-seven patients were enrolled. Three were excluded due to protocol violations, three due to lack of documentation, and one due to subcutaneous infiltration of ketamine, leaving 70 patients for analysis. The average age was 31 years, and 41 (59%) were female. Indications for procedural sedation and analgesia included abscess incision and drainage (66%), fracture/joint reduction (26%), and other (8%). The mean dose of midazolam was 5.6 ± 1.4 mg and the mean dose of ketamine was 159 ± 42 mg. The mean time to achieve discharge criteria was 64 ± 24 minutes. Five patients experienced mild emergence reactions, but there were no episodes of hallucinations, delirium, or other serious emergence reactions. Eighteen (25%) patients recalled dreaming while sedated; twelve (17%) were described as pleasant, two (3%) unpleasant, three (4%) both pleasant and unpleasant, and one (1%) neither pleasant nor unpleasant. There were four (6%) cases of respiratory compromise, two (3%) episodes of emesis, and one (1%) case of myoclonia. All of these were transient and did not result in a change in the patient's disposition. Only one (1%) patient indicated that she was not satisfied with the sedation regimen. **Conclusions:** The combination of midazolam and ketamine provides effective procedural sedation and analgesia in adult ED patients, and appears to be safe. **Key words:** procedural sedation; procedural analgesia; ketamine; midazolam. ACADEMIC EMERGENCY MEDICINE 2000; 7:228–235

OPIATES, benzodiazepines, and barbiturates, alone, or in combination, are among the most widely used agents for procedural sedation and analgesia.[1,2] Drugs such as fentanyl, midazolam, and methohexital, because they have a rapid onset and short duration of action, have been shown to be particularly useful for emergency department (ED) use.[3–10] Unfortunately, all of these agents may cause respiratory depression, particularly when given in combination, in large doses, or to patients with underlying respiratory diseases.[3,5–14]

Ketamine hydrochloride is a phencyclidine derivative that causes dissociation between the cortical and limbic systems, preventing the higher centers from perceiving visual, auditory, or painful stimuli. It possesses a rapid onset and short duration of action and produces profound sedation and analgesia. However, laryngeal reflexes are maintained and respiratory depression is rare.

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Received June 30, 1999; revisions received August 30, 1999, and October 19, 1999; accepted October 19, 1999. Presented at the SAEM annual meeting, Boston, MA, May 1999.
Dr. Chudnofsky has previously received grant support and honoraria from Roche Laboratories, makers of midazolam. No financial support was provided for the current study.
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These properties have made ketamine a very popular agent for procedural sedation and analgesia in pediatric ED patients.[15–19] Unfortunately, when given to adult patients, it frequently causes emergence anxiety, nightmares, hallucinations, and delirium.[1,2] These *emergence reactions* have limited the use of ketamine in adults.

A number of agents, including diazepam, lorazepam, fentanyl, droperidol, and others, have been used with varying success to reduce or prevent emergence reactions associated with ketamine use.[20–27] Diazepam and lorazepam have been the most successful, but their use may prolong recovery time, making them less desirable in the ED setting.[22–27] Midazolam has also been used in this regard, but data are limited. Despite this paucity of data, available literature does suggest that compared with ketamine alone[28] or a combination of diazepam and ketamine,[29,30] midazolam results in fewer emergence reactions and a shorter time to complete recovery. This suggests that a combination of midazolam and ketamine would be ideal for procedural sedation and analgesia in adult ED patients. However, to our knowledge, there have been no studies to confirm this. Therefore, we performed a preliminary study to describe the clinical characteristics of a combination of midazolam and ketamine for procedural sedation and analgesia in adult ED patients.

METHODS

Study Design. This was a prospective, observational study conducted at an urban level II trauma center that serves as a primary teaching site for an emergency medicine residency. Written informed consent was obtained from all subjects and the study was approved by the hospital's institutional review board.

Study Setting and Population. Patients ≥ 18 years of age who required ED procedural sedation and analgesia, regardless of the time of their last meal, were eligible for inclusion in the study. Exclusion criteria are listed in Table 1.

Study Protocol. Following initiation of noninvasive monitoring and supplemental oxygen, patients received 0.07 mg/kg of intravenous (IV) midazolam. We chose 0.07 mg/kg based on previous study by Cartwright and Pingel.[29] After a 2-minute observation period, patients were given 2 mg/kg of IV ketamine over 2 minutes. This dose of ketamine was chosen in order to consistently obtain the dissociative state without the need for titration, which could result in differing doses among study patients. The painful procedure was begun immediately after completing ketamine administration.

TABLE 1. Exclusion Criteria

- Acute or chronic pulmonary infection or disease
- Angina, congestive heart failure, aneurysm, or uncontrolled hypertension
- Brain injury associated with altered mental status or focal neurologic deficit
- CNS mass lesion, hydrocephalus, or other conditions associated with intracranial hypertension
- Glaucoma or acute globe injury
- Thyroid disorder or medication
- Porphyria
- Pregnancy or lactation
- Allergy to any of the study medications
- Inability to give informed consent or complete study procedures
- The use of procedural sedation could compromise patient safety

Measures. Vital signs, which included blood pressure, heart rate, respiratory rate, and oxygen saturation, were recorded at baseline, and every 5 minutes during the procedure. All patients had continuous monitoring of electrocardiography and oxygen saturation throughout the study. Following completion of the procedure, vital signs were recorded every 10 minutes until the patient returned to his or her baseline level of alertness. Abnormal vital signs occurring between recording intervals were documented on the data collection instrument. An alertness scale previously used, but not validated by the authors, was used to verify return to baseline alertness and suitability for discharge (Table 2).[31] The time to achieve discharge alertness was defined as the time from the start of ketamine administration until return to baseline alertness.

Respiratory therapists experienced in ED procedural sedation and analgesia underwent a one-hour training session during which they received instruction on the study protocol, alertness scale, and recognition of emergence reactions. A respiratory therapist was assigned to monitor each patient and was responsible for recording vital signs and concurrently documenting the presence of adverse effects, including respiratory depression, emesis, myoclonus, and emergence anxiety, euphoria, hallucinations, and/or delirium on a standardized data collection instrument. Respiratory therapists were chosen to complete the data collection instrument because in our ED, a respiratory therapist is required to monitor all patients receiving procedural sedation and analgesia. This policy has resulted in our respiratory therapists' gaining a great deal of experience with procedural sedation and analgesia. Despite this experience, if an adverse effect occurred during recovery (i.e., after the study group physician had left the exam room), the study group physician was asked to return to the patient's room to corroborate the presence of

TABLE 2. Alertness Scale*

Category	Scoring Criteria
Responsiveness	3—Completely responsive 2—Lethargic but responds to name 1—Responds only after prodding 0—No response to prodding
Speech	3—Normal 2—Slurring or slowing, but understandable 1—Few recognizable words, not understandable 0—Unable to speak
Eyes	3—No ptosis; focuses and follows readily 2—Glassy eyed or ptosis < 1/2 eye, focuses and follows 1—Marked ptosis (≥1/2 eye), does not focus or follow 0—Eyes do not open to command
Coordination	3—Accurate in 5 of 5 attempts at finger-to-nose 2—Accurate in 3–4 of 5 attempts at finger-to-nose 1—Accurate in 1–2 of 5 attempts at finger-to-nose 0—Unable to perform or attempt finger-to-nose

*This scale has been previously used (Chudnofsky CR, for the Emergency Medicine Conscious Sedation Study Group. Safety and efficacy of flumazenil in reversing conscious sedation in the emergency department. Acad Emerg Med. 1997; 4:944–9) but not validated.

TABLE 3. Definitions of Emergence Reactions*

Rating	Duration	Patient Distress	Treatment	Disposition
Mild	≤30 min	Minimal	None	Unchanged
Moderate	1–2 hr	Moderate	Yes	Unchanged
Severe	>2 hr	Severe	Yes	Changed

*The severity of an emergence reaction was based on the single highest (most severe) category reached [e.g., a reaction lasting 40 minutes (moderate rating) that caused only minimal patient distress (mild rating), but that required treatment (severe), was considered a *severe* reaction].

any adverse effect identified by the respiratory therapist. In addition, both the physicians the and the respiratory therapists were encouraged to describe any other findings and behavior that could be considered an emergence reaction. For purposes of this study, hallucinations and delirium were defined as severe emergence reactions regardless of their intensity. Anxiety, euphoria, and other reactions were rated as mild, moderate, or severe (Table 3). All adverse effects were recorded at the time they occurred, but emergence reactions were rated retrospectively based on documentation obtained from the data collection instrument, nursing notes, and physician reports. Treatment of adverse effects was left to the discretion of the study group physician caring for that patient. Prior to discharge, the patients were asked whether they had experienced any dreams while they were sedated, and if so, whether they were pleasant, unpleasant, both, or neither. They were not asked to describe their dreams in any further detail. Finally, the patients were asked whether they would choose the same drugs to sedate them if they required a painful procedure in the future. A specific alternative was not suggested.

Data Analysis. Descriptive statistics were calculated using statistical analysis software (Microsoft Excel, Redmond, WA, 1997). Means are reported ± standard deviation (SD).

RESULTS

A total of 77 patients were enrolled in the study. Three patients were excluded due to protocol violations, three due to lack of documentation, and one due to subcutaneous infiltration of ketamine, leaving 70 patients for analysis. None of the excluded patients experienced any adverse effects.

The average age was 31 years (median 28.5 years; range 18–68 years); 41 (59%) were female. Abscess incision and drainage was the most common indication for procedural sedation and analgesia (66%), followed by bone and joint reduction (26%) (Table 4). The mean dose of midazolam was 5.6 ± 1.4 mg and the mean dose of ketamine was 159.1 ± 42 mg. The mean time to achieve discharge alertness was 63.4 ± 23.4 minutes (median 59 minutes; range 20–130 minutes). No patient required a second dose of ketamine.

The average alertness score following drug administration was 0.7, indicating excellent sedation. There were five mild emergence reactions; two (3%) cases of emergence anxiety, two (3%) cases of euphoria, and one (1%) episode when the patient called out during recovery. The latter was considered a mild reaction since the patient did not remember the event and she was perceived by study personnel to be in minimal distress. There were no episodes of hallucinations, delirium, or other serious emergence reactions.

TABLE 4. Indications for Procedural Sedation and Analgesia

Indication	Number (%)
Abscess incision and drainage	46 (66%)
Fracture/joint reduction	18 (26%)
Chest tube insertion	2 (3%)
Foreign body removal	1 (1%)
Wound care	1 (1%)
Lumbar puncture	1 (1%)
Hemorrhoid thrombectomy	1 (1%)

Eighteen (25%) patients remembered dreaming while sedated. Twelve (17%) described their dreams as pleasant, two (3%) as unpleasant, three (4%) as both pleasant and unpleasant, and one (1%) as neither pleasant nor unpleasant.

Seven (10%) patients suffered adverse effects other than emergence reactions. These included four (6%) cases of respiratory compromise (Table 5), two (3%) episodes of emesis, and one (1%) case of myoclonus, which did not interfere with reduction of the patient's locked knee, and resolved prior to the patient's regaining consciousness.

Baseline and peak blood pressures and heart rates are illustrated in Table 6. Ketamine resulted in a significant rise in systolic and diastolic blood pressures and heart rates (Table 6). However, individual responses were variable, with some patients experiencing no change or even a slight drop in blood pressure at some recording intervals. All changes in blood pressure and heart rate were transient, and did not necessitate intervention. No patient suffered any sequelae or required a change in disposition because of hypertension or tachycardia.

Only one patient (1%) indicated that she would not choose the same sedation regimen again if she had to undergo a painful procedure in the future. This patient stated that she did not like the feeling of being sedated in general, but had no complaint specific to the use of midazolam and ketamine. Interestingly, this patient did not experience an emergence reaction or other adverse effects.

DISCUSSION

To our knowledge, this study represents the largest case series of IV midazolam and ketamine for procedural sedation and analgesia in adult ED patients. Our results are similar to those demonstrated in other outpatient settings. For example, White found that a combination of midazolam and ketamine virtually eliminated emergence reactions in healthy non-premedicated patients requiring emergency surgery.[28] In a study comparing midazolam–ketamine and diazepam–ketamine in healthy women undergoing short gynecologic procedures, Cartwright and Pingel demonstrated a significantly lower incidence of unpleasant dreams in those patients who received midazolam–ketamine.[29] Similarly, Toft and Romer found that midazolam–ketamine resulted in a significantly lower incidence of emergence reactions and significantly shorter recovery times than diazepam–ketamine in patients undergoing endoscopic examinations.[30] A control group was not used in our study; therefore, it is impossible to make any comparisons regarding the time to recovery. However, the patients

TABLE 5. Adverse Respiratory Effects

	Age (yr)/ Sex	Weight (kg)	Midazolam Dose (mg)	Ketamine Dose (mg)	Adverse Effect	Lowest O_2 Sat* (%)	Duration (sec)	Comments†
Patient 1	59/Female	97.3	6.8	195	Apnea	98	30	Apnea occurred 4 minutes after midazolam administration. The patient's head was repositioned and she was stimulated with return of spontaneous respiration.
Patient 2	38/Female	104.5	7.3	209	Apnea	87	60	Apnea occurred 6 minutes after midazolam administration (4 minutes after ketamine administration). An oral airway was inserted and ventilation was assisted with a bag–valve–mask (BVM) for approximately 1 minute.
Patient 3	18/Male	109.0	7.6	218	Apnea	65	120	Apnea occurred 3 minutes after midazolam administration (1 minute after ketamine administration). Ventilation was assisted with a BVM for approximately 2 minutes.
Patient 4	25/Female	99.6	7.0	200	Laryngospasm	88	60	Laryngospasm occurred following a harsh cough, approximately 14 minutes after administration of ketamine. An oral airway was inserted and ventilation was assisted with a BVM until the laryngospasm resolved, approximately 1 minute later.

*Lowest oxygen saturation reached at any time during the procedure.
†Treatment was left to the discretion of the attending emergency physician.

TABLE 6. Baseline and Peak Blood Pressures and Heart Rates*

Blood Pressure (mm Hg)	Subjects (n = 70)	Heart Rate (beats/min)	Subjects (n = 70)
Baseline		Baseline	84 (±16)
Mean SBP (±SD)	134 (±21)	Mean (±SD)	83
Median SBP	131	Median	52–126
Range SBP	100–218	Range	
Mean DBP (±SD)	78 (±13)		
Median DBP	77	Range	105 (±17)
Range DBP	52–109	Mean (±SD)	105
		Median	57–151
		Range	
Peak		Difference in means†	
Mean SBP (±SD)	159 (±21)	Heart rate (±SD)	21 (±15)
Median SBP	159	95% CI	17, 25
Range SBP	119–219		
Mean DBP (±SD)	97 (±14)		
Median DBP	95		
Range DBP	59–138		
Differences in means†			
SBP (±SD)	26 (±15)		
95% CI	22, 30		
DBP (±SD)	19 (±12)		
95% CI	16, 22		

*SBP = systolic blood pressure; DBP = diastolic blood pressure; SD = standard deviation; CI = confidence interval.
†For calculation of the differences in means for blood pressure and heart rate following administration of ketamine, a fall in blood pressure or heart rate was calculated as a "0" difference.

were back to baseline alertness and ready for discharge in an average of 64 minutes. This compares favorably with the use of intramuscular ketamine in nonpremedicated pediatric patients, as well as with other regimens used for procedural sedation and analgesia in adult ED patients.[7,8,10,17–19,31]

While there were no cases of emergence hallucinations, delirium, or other severe emergence reactions, 18 patients recalled dreaming while sedated. Of these, five patients described their dreams as being unpleasant (two unpleasant, three both pleasant and unpleasant). While at first these numbers may seem high, the occurrence of dreaming associated with ketamine use in our study is very similar to the frequency of dreaming associated with a variety of other agents.[32–35] More important, all of the patients in our study who experienced dreams stated that they would choose the same drugs to sedate them should they require a painful procedure in the future. This suggests that dreaming, regardless of content, did not interfere with patient satisfaction.

It may appear that midazolam, because of its potential to cause respiratory depression, diminishes the utility of ketamine. However, the risk of respiratory depression with midazolam is dose-dependent, and greater when it is coadministered with other respiratory or central nervous system depressants.[5,6,11–14] When administered as a *small*, single dose in conjunction with ketamine, midazolam should pose little risk to respiratory function. In our study, three (4%) patients experienced transient apnea. Each of these patients weighed in excess of 97 kg and received a correspondingly *large* dose of midazolam (Table 5). It is likely that this large dose of midazolam was responsible for the transient respiratory depression observed in these patients. Thus, although not established in a controlled study, it would seem prudent to base the dose of midazolam on ideal body weight when administering it to obese individuals. Furthermore, we chose 0.07 mg/kg of midazolam based on a previous study by Cartwright and Pingel.[29] While this dose falls within the recommended dosing range of midazolam (0.05–0.1 mg/kg),[1] it is likely that lower doses would also be effective in reducing or eliminating emergence reactions, with a smaller attendant risk of respiratory depression. Thus, to further maximize safety, future studies should be aimed at identifying the lowest dose of midazolam required to reduce or eliminate emergence reactions.

Ketamine inhibits the re-uptake of catecholamines, resulting in mild to moderate increases in blood pressure, heart rate, and cardiac output.[36,37] The hypertensive response is more pronounced in adults, and with IV use. Fortunately, stimulation of the cardiovascular system may be blunted with concurrent administration of a benzodiazepine.[36] In our study, ketamine did result in a transient

increase in systolic and diastolic blood pressures and heart rate (Table 6). However, this was well tolerated as no patient required treatment for hypertension or experienced any cardiovascular or central nervous system sequelae. It should also be noted that while uncontrolled hypertension was considered an exclusion criterion, the definition of uncontrolled hypertension was not specified in the study protocol, leaving the decision of study eligibility of hypertensive patients to the discretion of the treating physician. One patient with an elevated blood pressure (218/91 mm Hg) that could be considered by some clinicians to represent uncontrolled hypertension was enrolled in the study. Following administration of midazolam and ketamine, this patient's blood pressure actually decreased (164/94 mm Hg), and remained at this level for the duration of the study. Despite this patient's good outcome, ketamine generally results in a rise in both systolic and diastolic blood pressures and should be avoided in patients with uncontrolled hypertension.

We also cannot comment on the use of ketamine in adult ED patients with ischemic heart disease or congestive heart failure since these were exclusions to enrollment in the study. However, there was no maximum age beyond which patients could not be enrolled in the study. Therefore, it is possible that one or more of the eight patients over the age of 45 (or even those under the age of 45) may have had occult coronary artery disease. While this possibility may be a concern to some practitioners, it should be pointed out that early studies of benzodiazepine–ketamine anesthesia administered to cardiac surgical patients demonstrated cardiovascular stability.[38,39] Hence, we believed that the combination of midazolam and ketamine would be safe in patients over the age of 40 without a previous history of ischemic heart disease. Interestingly, no patient in the study developed ischemia or heart failure.

One patient (1%) in our study developed transient laryngospasm. Laryngospasm associated with the use of ketamine is rare, and thought to be secondary to stimulation of hypersensitized laryngeal reflexes.[40] Age less that 3 months and active respiratory infection appear to be important factors in the development of laryngospasm, and therefore are considered contraindications to the use of ketamine. However, in a pooled-data analysis of more than 11,589 pediatric ketamine administrations, laryngospasm necessitating intubation occurred in only two cases (0.017%).[40] Prior to discharge, our patient was again questioned regarding the presence of any respiratory problems. At that time, she indicated that she had recently had an upper respiratory infection, and was still bothered by a lingering cough. She did not provide that information prior to enrollment in the study. This underscores the need to obtain a complete history, particularly the presence of respiratory symptoms, prior to ketamine use.

The incidence of vomiting associated with the use of ketamine is approximately 8%.[40] Fortunately, the risk of aspiration is very low because ketamine preserves protective airway reflexes, and vomiting almost always occurs late in the recovery phase, after the patient has regained consciousness.[40] Two patients (3%) in our study experienced nausea and vomiting. Both patients were awake and alert at the time they vomited. Neither experienced aspiration or other sequelae. Furthermore, despite their emesis, both patients stated that they would choose the same drugs to sedate them should they require a painful procedure in the future.

Ketamine may cause skeletal muscle hypertonicity and random nonpurposeful movements of the head and extremities. However, these effects are usually mild and seldom interfere with performance of procedures.[40,41] One patient (1%) in our study developed myoclonia shortly after receiving ketamine. This did not interfere with the procedure and resolved spontaneously without intervention.

Ketamine may also cause an increase in intracranial pressure; thus, it is contraindicated in those patients with intracranial hypertension.[40] One patient with a presumptive diagnosis of meningitis was enrolled in the study. This patient had a normal neurologic and funduscopic examination. Thus the treating physician thought the patient could safely undergo a lumbar puncture without the need for a cranial computed tomography, and therefore could also be safely enrolled in the study. Despite this, the use of ketamine is not recommended in patients who have the potential for increased intracranial pressure.

Limitations and Future Questions

The major limitation of our study was lack of a control group. However, ketamine's effectiveness as an anesthetic agent is well known,[36,37] and the use of midazolam to reduce or eliminate emergence reactions has been reported in other settings.[28–30] Nevertheless, the combination had not previously been described in an adult ED population. Hence, we believed that a preliminary study to describe the clinical characteristics of midazolam and ketamine in adult ED patients was necessary before the combination was compared with other ED sedation and analgesic regimens. Furthermore, the occurrence of emergence reactions in up to 50% of adults receiving ketamine has also been well established.[37,40] Thus, we believed that the use of a

control group that did not receive midazolam would be unethical. Finally, performing painful procedures such as abscess incision and drainage and fracture or joint reduction using a placebo control group would be unacceptable under any circumstances.

Another potential limitation of this study was lack of interrater reliability. Respiratory therapists were trained by the principal investigator (CRC) to recognize possible emergence reactions, and members of the study group corroborated the presence of all adverse effects. However, no further attempt was made to verify findings between study personnel. Lack of interrater reliability would be expected to have the most effect on emergence reaction severity ratings, particularly the more subjective categories such as patient distress and the need for treatment (Table 3). Despite this, we believe that because all respiratory therapists received identical training sessions and used a standardized data collection instrument, at least the presence of adverse effects, including emergence reactions, was accurately recorded.

Finally, to evaluate whether patients were satisfied with the combination of midazolam and ketamine, they were asked whether they would choose the same sedation regimen if they required another painful procedure in the future. Since an alternative regimen was not provided, it is conceivable that some patients were not satisfied, but stated they would choose the same sedation regimen because something, even if it were not entirely satisfactory, would be better than nothing at all. However, we believe this is not the case. First, if patients did inquire about other sedation regimens for hypothetical future use, they were told that physicians did have alternatives to midazolam and ketamine. In addition, the respiratory therapists completing the data collection instrument corroborated that all but one patient expressed high satisfaction with the combination, including those who experienced adverse effects. Thus we are confident that the patients who indicated they would choose the same sedation regimen again did so because they were satisfied with this combination of drugs.

To increase the safety of this combination, future studies should be aimed at identifying the lowest dose of midazolam that will reduce or eliminate emergence reactions. In addition, the optimal regimen for procedural sedation and analgesia in adult ED patients, or for subsets of patients undergoing different types of painful procedures, remains to be determined.

CONCLUSIONS

The combination of midazolam and ketamine provides effective procedural sedation and analgesia in adult ED patients, and appears to be safe. To reduce the risk of respiratory depression, we recommend using ideal body weight when calculating the dose of midazolam. In addition, the use of ketamine must be avoided in patients with active respiratory infections.

The authors thank the ED staff at Hurley Medical Center for their assistance in carrying out this study. In addition, they are indebted to the Hurley Medical Center respiratory therapists for their tireless work and attention to detail. Finally, a special thanks to Dr. John Younger for his assistance with statistical analysis.

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REFLECTIONS

What do you remember most about the early years of ABEM?

"What I remember the most about the early years of the American Board of Emergency Medicine is the singular, concerted, and unified efforts of all emergency physicians without regard to personal agenda in pursuing the single goal in establishing emergency medicine as a rightful specialty."

GEORGE PODGORNY, MD
First President of ABEM, 1976–1981
ABEM Director, 1976–1988