DIAZEPAM–KETAMINE ANAESTHESIA FOR OPEN HEART SURGERY
A "MICRO-MINI" DRIP ADMINISTRATION TECHNIQUE

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INTRODUCTION

ANAESTHESIA for cardiovascular surgery in patients with severe and deteriorating heart disease is one of the most challenging for anaesthesiologists. Recently, we reported[1] a new anaesthetic technique for this type of patient, using a combination of diazepam and pentazocine. In that series, we found that the use of a "Micro-Mini" drip infusion technique provided smoother anaesthesia and reduced the total dosage of the analgesic by 30 to 40 per cent compared to other techniques not using the "Micro-Mini" drip.

Our previous experimental and clinical studies of the analgesic property of ketamine revealed that, despite its rather short duration of action, it is more than twice as potent as an analgesic in low dosage compared with meperidine.[2] We proposed, therefore, to see if the smaller dosage involved, when administered with a continuous "Micro-Mini" drip technique, so that a more even blood plasma level resulted, (1) would provide sufficient analgesia throughout the operation, (2) would provide a more stable haemodynamic status without undesirable respiratory depression, (3) would minimize or eliminate the undesirable post-anaesthetic side effects which are frequently observed in adult patients who receive ketamine, using conventional methods.

During the past eight months, over 500 patients who underwent various types of open-heart operations were anaesthetized with a combination of diazepam and continuous "Micro-Mini" drip infusion of ketamine. In this paper, we present the data obtained from our clinical studies of the first 200 cases in which ketamine was used primarily as an analgesic rather than as an anaesthetic.

The results strongly suggest that this technique is one of the most promising methods of anaesthesia for critically ill patients with deteriorating heart disease.

MATERIALS AND METHODS

Two hundred patients, 145 males and 55 females, were anaesthetized with a combination of diazepam and ketamine. They ranged in age from 4 to 85 years and most of the patients were between 41 and 70. The average body weight was 74.4 kg in males and 69.9 kg in females. The type of operation and number of patients are listed in Table I. The majority of the patients fell within the A.S.A. classification III.

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TABLE I

TYPE OF OPEN HEART SURGERY (N = 200)

I.	Acquired Heart Disease:		
	Coronary Artery Bypass (CAB)	97	(48.5%)
	Valve Replacement	68	(34.0%)
	L. Ventricular aneurysmectomy 5		
	L. Ventricular aneurysmectomy (CAB) 13	18	(9.0%)
	Miscellaneous	2	(1.5%)
II.	Congenital heart disease:		
	ASD. VSD	8	(4.0%)
	Tetralogy of fallot	3	(1.5%)
	Miscellaneous	4	(2.0%)
		200	(100.0%)

TABLE II

HOLTER INFUSION PUMP (#911) DIAL SETTING AND FLOW RATE (ML/MIN)

	Tube size A (ml/min)	Tube size B (ml/min)	Tube size C (ml/min)	Tube size D (ml/min)
1.	1.13	2.52	4.5	10.4
2.	0.96	2.03	3.80	8.80
3.	0.78	1.44	3.10	7.30
4.	0.59	1.28	2.27	5.70
5.	0.42	0.88	1.52	3.90
6.	0.19	0.38	0.74	1.73

The adult patients received either atropine 0.4 mg only or diazepam 10 to 15 mg and atropine 0.4 mg intramuscularly approximately one hour prior to induction of anaesthesia.

Upon arrival in the operating room, pre-induction preparation consisted of establishment of two intravenous infusion routes, ECG electrodes, blood pressure cuff, rectal or tympanic membrane temperature probes and Foley urethral catheter. An ulnar artery was canulated for direct blood pressure monitoring and a CVP catheter was inserted under local infiltration anaesthesia. In several cases EEG was monitored and recorded.

Induction of anaesthesia in adult patients undergoing open-heart operations with cardiopulmonary bypass was accomplished by intravenous administration of diazepam and ketamine. The induction dose of diazepam was 0.3 to 0.5 mg/kg and the initial dose of ketamine was approximately 1 mg/kg. Initially, diazepam was administered intravenously in 5 mg increments at intervals of a few minutes until the patient became calm and well sedated. After the first dose of diazepam, ketamine diluted to 0.1 per cent solution (1 mg/1 ml in 5 per cent dextrose in water) was infused by either a Holter infusion pump (Model No. 911) or a "Micro-Mini" drip chamber (50 drops per 1 ml – Buretrol #2C 0133 – Baxter Laboratories). The infusion rates using the different sizes of tubing for the Holter infusion pump were calculated in the laboratory and are shown in Table II. The No. C infusion tubing, with rates ranging from 4.5 ml to 0.74 ml per minute, was found to be suitable for the administration of ketamine. The highest rate (dial 1 = 4.5 mg/min) was used for induction. When the "Micro-Mini" drip chamber was used during induction, ketamine solution was administered with the roller or Harvard regulator fully open,

which provided approximately 5 to 8 ml/min (5 to 8 mg/min) infusion depending upon the height of the fluid level in the container above the infusion point. During induction the patient was hyperoxygenated and denitrogenated with a high flow of oxygen by mask and the respiratory pattern was observed. In selected cases, a voltex (Ohio) respirometer was used for pulmonary function study during induction. The patient received approximately 1 mg/kg of ketamine intravenously (usually 60 to 80 ml, depending upon the patient's body weight), then the remainder of the calculated dose of diazepam modified according to the response to the initial dose was administered slowly into the intravenous infusion tubing highly diluted by a rapid flow rate to avoid vein irritation.

When the patient lost consciousness, a tracheal tube was inserted using succinylcholine chloride (0.8 mg/kg) intravenously as the relaxant. Paediatric patients were induced with a high concentration of cyclopropane (50 per cent) in oxygen, or by 5 per cent or 10 per cent ketamine (5 mg/kg) given by the intramuscular route. A 2-per-cent solution of succinylcholine chloride was given intramuscularly (2 mg/kg) and naso-tracheal intubation was done using a Jackson-Rees tracheal tube. Anaesthesia was maintained by 50 per cent nitrous oxide and oxygen and incremental intravenous administration of diazepam (5 mg each). When the Holter infusion pump was used, ketamine solution was administered with the lowest infusion rate (dial setting 6 = 0.74 ml = 0.74 mg per minute). When the "Micro-Mini" drip chamber was used, ketamine solution was administered approximately 1 drop per 2 to 4 seconds (0.5 to 0.3 ml = 0.5 mg to 0.3 mg per minute). The rates of ketamine administration were controlled by changing the dial setting of the Holter infusion pump or by the regulator of the intravenous tubing according to the patient's response to the surgical stimulation. Non-depolarizing muscle relaxant, either d-tubocurarine chloride (0.2 mg/kg) or 0.1 per cent of pancuronium bromide (0.04 mg/kg) was administered initially after induction to facilitate controlled respiration and an additional dose (d-tubocurarine chloride 3 to 6 mg or pancuronium bromide 1 to 2 mg) was given when indicated during maintenance.

During cardiopulmonary bypass, ketamine solution was administered continuously directly to the oxygenator and other drugs were also administered into the oxygenator during cardiopulmonary bypass as indicated. In the later cases of this study, diazepam 5 to 15 mg and ketamine 150 mg were diluted in 150 ml of 5 per cent dextrose in water and used for maintenance of anaesthesia by the same infusion technique. Blood gas analysis was done prior to and every 30 minutes during cardiopulmonary bypass in the open-heart cases.

The ketamine infusion was discontinued when sternal suturing was started, and nitrous oxide was discontinued when the subcutaneous suture was begun. Upon completion of the operation, the tracheal tube was left *in situ* to facilitate post-operative respiratory support, and the patients were ventilated by a volume-limited ventilator (Mörch's piston ventilator) using moderate hyperventilation, in the intensive care unit.

Blood gases were analyzed periodically for 6 to 24 hours post-operatively. Post-anaesthetic complications which directly related to the ketamine administration were recorded during the post-operative course.

Results

Following the initial doses of diazepam and ketamine, all but two patients were well sedated, with adequate respiration, stable blood pressure and heart rate. No increased salivation was observed. One male patient (53 years of age and body weight 70 kg) who underwent coronary artery bypass required diazepam 65 mg to sedate him. A female patient became restless and started to move her extremities during induction. Both patients required nearly twice as much diazepam for induction as was estimated from body weight. Verbal communication was possible during the induction period. Administration of the remainder of the calculated dose of diazepam produced a rather deeper level of anaesthesia. Respiratory changes and blood gas studies during the induction period are shown in Figure 1. The blood pressure and heart-rate changes from the induction of anaesthesia to the beginning of cardiopulmonary bypass are shown in Figure 2. There was very little change in respiration, blood pressure or heart rate during this period. In the cardiopulmonary bypass cases, although the administration of intravenous fluid was minimized during the induction period, 73 patients who had single or double valve replacement maintained stable haemodynamic states. One female patient, 70 years of age, who was to have mitral valve replacement, required neosynephrine 0.1 mg on two occasions and atropine 0.8 mg intravenously for treatment of bradycardia associated with hypotension during induction. After tracheal intubation and following the succinylcholine chloride, blood pressure generally tended to increase in varying degrees for a short time; however, the pulse rate remained essentially unchanged in most cases. Blood pressure returned to the pre-induction level within a few minutes after the patient received a dose of either d-tubocurarine chloride (9 to 12 mg), or pancuronium (2 to 3 mg) intravenously to facilitate controlled respiration. No tachycardia or rise in blood pressure was observed after pancuronium bromide. Anaesthesia was easily maintained by incremental administration of diazepam (5 mg each) and continuous "Micro-Mini" drip administration of 0.1 per cent ketamine solution or diazepam and ketamine mixture solution, supplemented with 50 per cent nitrous oxide. The latter was discontinued and oxygen alone was administered during cardiopulmonary bypass and whenever a high concentration of oxygen was required. The rate of ketamine infusion was varied according to clinical assessment, increase in blood pressure or appearance of lacrimation as well as response to the operative procedures. In the majority of the cases, administration of 0.6 ± 0.15 ml/minute of 0.1 per cent ketamine solution or approximately 0.7 mg/kg/hour provided a satisfactory analgesia throughout the operation. The appearance of the pharyngeal reflex, pupillary reaction and movement of the eyeballs are not frequently observed during maintenance. Five patients (2.5 per cent) received chlorpromazine 2.5 mg to 7.5 mg because mean perfusion pressure tended to exceed 100 mm Hg during cardiopulmonary bypass. Continuous administration of "Micro-Mini" drip infusion of ketamine was necessary from the termination of the cardiopulmonary bypass to the closure of the sternum. After discontinuation of 50 per cent nitrous oxide, the majority of the patients (90 per cent) responded to verbal stimulation within a few minutes. Nineteen patients (9.5 per cent) were drowsy or responded equivocally to verbal command in the intensive care unit.

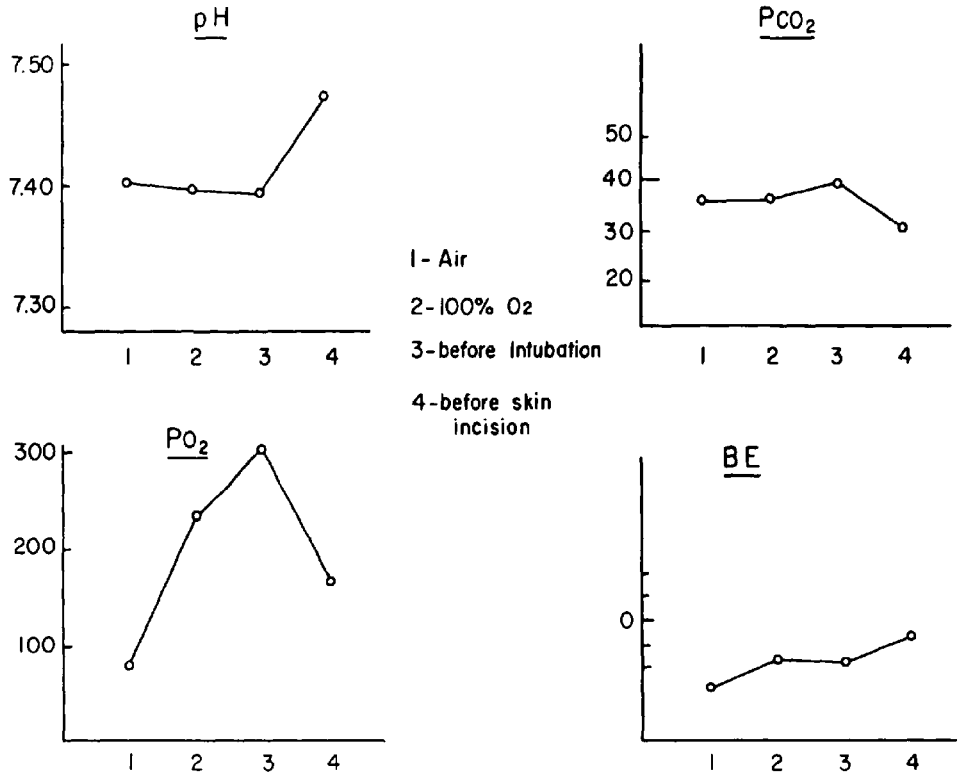

FIGURE 1. Blood gas changes.

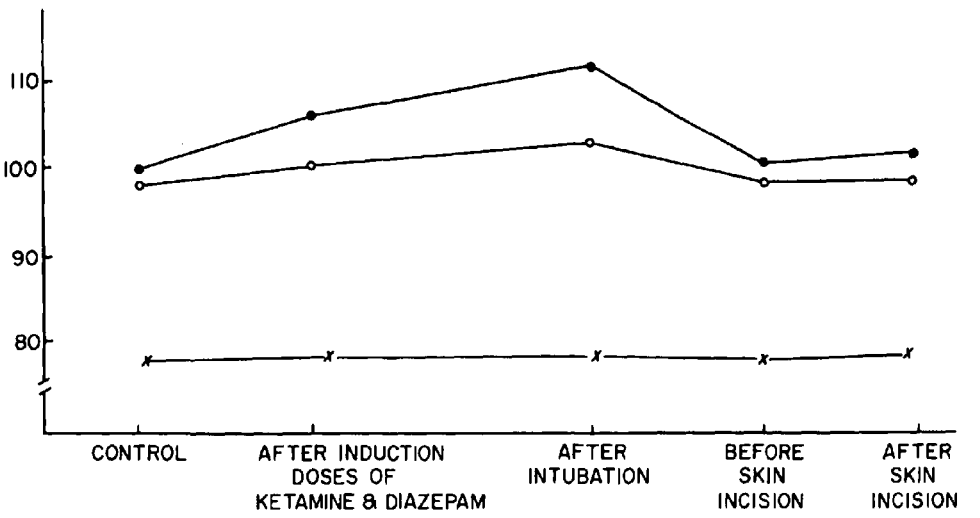

FIGURE 2. Per cent change in B.P. ● – Systolic, ○ – Diastolic, × – Pulse rate.

TABLE III

ANAESTHETIC TIME AND AVERAGE DRUG DOSAGES (N = 183)

Type of operation	No.	Sex	B.W. (kg)	Anaes. time (hrs)	Diazepam (mg)	Ketamine (mg)	DTC (mg)
CAB	97	M	74.3	5:19	50.2± 6.2	270±19.4	31.5
		F	64.4	3:36	35.0± 8.1	236±14.0	21.0
Valve replacement	68	M	76.6	4:02	32.0±11.2	263±21.0	29.5
		F	63.3	3:13	30.7±14.0	261±10.3	22.0
Ventricular aneurysmectomy and CAB	18	M	76.9	4:50	36.1±10.6	283±14.3	31.0
		F	70.1	5:03	35.3± 8.8	266±11.6	23.0
Total Average		M	75.9	4:43	39.4± 9.3	272±18.2	30.5
		F	65.8	4:04	33.6±10.3	254±11.9	22.3

Table III shows the anaesthetic time for the various types of operation and the average dosage of drugs used to maintain adequate anaesthesia.

It is our routine to leave the tracheal tube in place for post-operative respiratory support. In the immediate post-operative period, the majority of the patients remained calm and responded to verbal instructions. Approximately 80 per cent of the patients received morphine 3 to 5 mg and droperidol 2.5 to 7.5 mg intravenously within two hours, because these patients became very alert and tended to react to post-operative pain and the tracheal tube. The effect of analgesic and tranquillizer medication lasts 4 to 6 hours (average 5 hours 20 minutes) and intravenous analgesic medication was repeated according to the individual patient's need. All patients received intravenous analgesic medication 1 to 5 times by the second post-operative day. No patient experienced hallucinations; however, four patients (2.0 per cent) said they had a dream in the first post-operative day. Two patients (1 per cent) definitely remembered defibrillation. The rest of the patients had total (24 = 12 per cent), or anterograde (161 = 80.5 per cent) amnesia post-operatively.

In this series, one male patient who had triple coronary bypass grafts could not come off cardiopulmonary bypass because of advanced degeneration of the myocardium. One female patient who had mitral valve replacement developed shock immediately after she was transferred to the intensive care unit and expired a few hours later despite every possible effort to resuscitate her. One male patient who had mitral valve replacement developed pulmonary oedema soon after sternal closure, which responded well to rapid digitalization, diuretics and the insertion of the intra-thoracic aortic balloon. Transient mild pulmonary oedema occurred in the first post-operative day in one female patient who had a repeat mitral valve replacement. An intrathoracic aortic balloon was inserted in five patients (2.5 per cent) at the end of the operation to support coronary circulation. Other post-operative complications encountered during the first seven post-operative days are shown in Table IV.

DISCUSSION

Ketamine is a useful anaesthetic for critically ill patients. It does not depress respiration or the cardiovascular system. Its use has been advocated for cardio-

TABLE IV

IMMEDIATE POST-OPERATIVE COMPLICATION (N = 200)

Cardiac arrest	2	Immediate P.O. 1 POD 1
Ventricular Fibrillation	3	POD 1 resuscitated
Pulmonary edema	2	Immediate P.O. resuscitated
Pneumonia	5	POD 3, 4, 5, 5, 5
Oliguria	2	POD 1
Twitching	2	Immediate P.O.
Shivering	11	Immediate P.O.
Drowsiness	19	Immediate P.O.
Semiconsciousness	2	Awake POD 2, 3
Dreams	4	POD 1

Many patients had multiple minor complications.
POD – Post-operative Day.

vascular surgery by some,[3-7] because it maintains blood pressure and is anti-arrhythmic. Radney, *et al*[8] recommends it for paediatric cardiac surgery. On the other hand, Kreuscher, *et al.*[9] and Traber, *et al.*[10] felt that ketamine might overstress the damaged myocardium. Takahashi[11] concluded that ketamine was contraindicated in patients with pulmonary hypertension. Gassner, *et al.*[12] concluded that the changes in pulmonary haemodynamics are caused by increased cardiac output rather than vasoconstriction or vasodilatation. Tweed, *et al.*[13,14] felt that ketamine is contraindicated where an increase in arterial pressure is unwanted.

Kopriva[15] found that although blood pressure and cardiac output increased after ketamine, systemic resistance and left ventricular stroke work remained unchanged. However, ventricular stroke work did increase after intubation.

The mode of administration of intravenous anaesthesia is of some importance. Three methods are used: (1) as a bolus or boli, (2) as a continuous drip of dilute solution through commercial intravenous sets, or (3) a combination of both these methods. Heretofore, ketamine was usually given intramuscularly or intravenously as a bolus injection. We found several papers[16-18] in the literature where it was administered by continuous drip. Chodoff and Stella[16] noted that blood pressure rise was noticeably less using this method.

When continuous drip methods are used with ordinary giving sets, there is a tendency to overdose. Increasing the rate of drop per minute automatically increases the size of each drop.[19] Dose is considerably greater than would be expected from the number of drops/min. Use of a "Micro-Mini" drip leads to more accurate dosing.

In this series, anaesthesia was smooth and simple. Nearly all patients had complete anterograde amnesia and 25 per cent had retrograde amnesia. Hallucinations, dreams or excitement were almost totally absent. Post-operative disorientation was seen in a very small number of cases. The duration of post-operative analgesia was rather short. About two-thirds of the patients received analgesics within two hours.

We felt the "Micro-Mini" drip technique ensured a more even and adequate plasma level which in turn ensured adequate even levels of analgesia. We had already used this technique in our diazepam-pentazocine study with excellent results. This technique seems suitable for any intravenous agent which is metabolized rapidly when the dilution is chosen carefully. We suggest the term MPAD,

Minimal Plasma Analgesic Dose, to denote analgesic potency as "MAC" is used for inhalation anaesthesia.

We have discussed the advantages of diazepam in anaesthesia for cardiovascular surgery elsewhere.[1]

SUMMARY

Two hundred open-heart cases were anaesthetized with a diazepam-ketamine combination. The results were excellent. A "Micro-Mini" drip technique insured low, even, but adequate dose levels of ketamine and less drug was used. Induction and maintenance are simple and smooth. Effects on the cardiovascular system and respiratory system are minimal. The margin of safety is wide and 100 per cent oxygen can be used whenever needed.

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