The Effect of Nitrous Oxide on Ketamine Anesthesia

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The intra- and postoperative effects of nitrous oxide when used to supplement ketamine anesthesia were evaluated in 20 thermally injured patients. Each subject, acting as his own control, received ketamine anesthesia twice, once with and once without nitrous oxide. The dosage of ketamine was reduced 39 per cent and recovery time 63 per cent when nitrous oxide was added. Nitrous oxide significantly improved operating conditions, increased surgeons' and anesthesiologists' acceptance of ketamine, and decreased the incidence of unpleasant emergence phenomena. (Key words: Ketamine; Nitrous oxide.)

The use of ketamine as a sole anesthetic agent must occasionally be abandoned when random movements by the patient preclude safe and effective surgery. In addition, many patients find ketamine unpleasant because dreams or hallucinations may occur after anesthesia. Postanesthetic involuntary motor activity may complicate recovery-room care.

Adjuvants such as droperidol, diazepam, thiopental, and narcotics have been given before or at the end of anesthesia to decrease these problems; however, none has proven completely successful and results have often been contradictory.1-4 Potent inhalation agents such as halothane can be added when ketamine alone provides inadequate anesthesia, but these drugs obviate the advantages of ketamine anesthesia. Nitrous oxide-oxygen-ketamine has been used in pharmacologic studies,5,6 in clinical studies of induction agents,7-10 when ketamine alone was unsatisfactory,4,9-12 and when supplementation during prolonged anesthesia might reduce the ketamine dose and recovery time.11 However, no controlled study documenting the value of supplementing ketamine anesthesia with nitrous oxide has been reported. Therefore, we undertook to evaluate this technique.

Methods

Twenty thermally-injured patients at the United States Army Institute of Surgical Research were studied. Selection was limited to male and nonpregnant female patients, ages 15 to 55 years, of ASA physical status I through III. Each subject received ketamine anesthesia twice, once supplemented with nitrous oxide (4 l/min) and oxygen (2 l/min) and once with oxygen (6 l/min) alone, administered via a semiclosed system with CO2 absorption. The inhalation agent used first was chosen at random, and the alternate technique was used for the second anesthesia.

Atropine (0.01 mg/kg) was given intravenously 10 minutes prior to induction of anesthesia. Anesthesia was induced with ketamine, 2 mg/kg, iv. When loss of consciousness became apparent, the anesthetic mask was applied and the selected gas mixture delivered. Rubber head straps were used only to insure the absence of leaks; ventilation was spontaneous, and no effort was made to change the position of the patient's head unless some degree of respiratory obstruction occurred. No other drug was administered.

The physician administering the anesthetic, who was blinded to the inhalation agents used,

| Table 1. Effect of Nitrous Oxide on Ketamine Requirement |
|---------------------------------|---|---|---|
| Ketamine total dose (mg) | O2 | N2O-O2 | P |
| Operative time (min) | 753 ± 83* | 537 ± 84 | <0.05 |
| Ketamine requirement (μg/kg/min) | 54 ± 5 | 62 ± 8 | NS |
| 214 ± 12 | 130 ± 8 | <0.001 |

* Mean ± SE.
KETAMINE AND NITROUS OXIDE

Fig. 1. Scores for intraoperative observations. Each bar represents the mean for 20 patients. Significant differences are denoted by asterisks.

was responsible for determining the need for supplemental injections of ketamine, monitoring of the vital signs, preservation of the airway, and intraoperative evaluation of the anesthesia. A second anesthesiologist was responsible for randomly selecting the inhalation agents and insuring proper gas flow, since the flowmeters were hidden from the person actually giving the anesthetic.

Supplemental doses of ketamine (1.0 mg/kg) were administered when the patient manifested 1) purposeful movements such as withdrawal from painful stimuli, 2) response to verbal commands, 3) vocalization in response to pain, or 4) random movements which interfered with the operation.

During the operation, unconsciousness, analgesia, muscle relaxation (rigidity), random movements, operating conditions, salivation, physiologic homeostasis (blood pressure, heart rate, respiratory rate), and airway stability were evaluated subjectively and rated numerically as: ideal = 3; acceptable = 2; minimally acceptable = 1; unsatisfactory = 0. Immediately postoperatively, anesthesiologists’ and surgeons’ acceptance was assessed and graded in the same way.

Emergence was observed by the anesthesiologist who administered the anesthetic. Recovery time was measured both from the time of administration of the last dose of ketamine and from the end of operation to the time the patient responded appropriately when asked to state his full name. The incidence and severity of excitement and involuntary motor activity were graded at the end of operation and at 15-minute intervals during recovery.

Patient acceptance was evaluated 24 hours postoperatively by a modification of a method described by Garfield to determine dream patterns, sensory distortions, fear, memory of pain, and willingness to have the same anesthetic again.

Paired differences in ketamine dose, duration of anesthesia and operation, and recovery time were compared statistically by Student’s t test. Differences in scores were compared using the Wilcoxon matched-pairs signed-ranks test.

Results

Four patients were deleted from the study and replaced because of unsatisfactory anesthesia while receiving ketamine with oxygen. No anesthetic failure occurred with nitrous oxide supplementation.

The mean durations of operation and anesthesia were essentially the same for both trials
Table 2. Emergence Times after Ketamine with and without Nitrous Oxide Supplementation

<table>
<thead>
<tr>
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<th>$O_2$</th>
<th>N$_2$O-$O_2$</th>
<th>$P$</th>
</tr>
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<tbody>
<tr>
<td>From last ketamine (min)</td>
<td>47 ± 11*</td>
<td>26 ± 2</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td>From end of operation (min)</td>
<td>41 ± 11</td>
<td>15 ± 2</td>
<td>&lt;0.025</td>
</tr>
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</table>

* Mean ± SE.

The total dose of ketamine was significantly reduced ($P < 0.05$) when nitrous oxide was added. When expressed as micrograms per kilogram body weight per minute of anesthesia, ketamine dose was reduced 39 per cent by addition of N$_2$O (table 1).

Despite the smaller dose of ketamine, unconsciousness, analgesia, muscle relaxation, random movements, operating conditions, and surgeons' and anesthesiologists' acceptance were graded significantly higher in the group with nitrous oxide (fig. 1). Airway stability was the only criterion by which ketamine-oxygen proved superior. Fifty-five per cent of patients receiving nitrous oxide and 25 per cent of those receiving oxygen required some support of the mandible. Six patients in the nitrous oxide group and two patients in the oxygen group required nasopharyngeal airways, which were well tolerated. Endotracheal intubation was not necessary. No difference in salivation was seen, nor was it a problem in any patient.

Systolic blood pressures were increased 12 per cent and 17 per cent in the nitrous oxide and oxygen groups, respectively. Heart rates increased less than 10 per cent and respiratory rates increased slightly in both groups. Differences were not significant.

Emergence was significantly slower with ketamine-oxygen (table 2). Nitrous oxide supplementation resulted in a 63 per cent reduction in awakening time from the end of operation. In addition, excitement and involuntary motor activity in the postoperative period were more common and severe after ketamine-oxygen alone. Seven of 20 patients had some degree of agitation during recovery, and in four of these the degree of excitement interfered with postoperative care. Only one of the same 20 patients manifested mild agitation following ketamine with nitrous oxide supplementation.

When patients were interviewed 24 hours after operation, there was no difference between the two groups as to recall of postoperative pain, anxiety, or dreams (table 3). Amnesia for the surgical procedure was complete in both groups. Willingness to have the same anesthesia repeated was not found to be significantly different (table 4).

Discussion

Previous attempts to modify ketamine anesthesia have taken two forms; nitrous oxide has been added to ketamine to modify the intraoperative side-effects of the drug, and intravenous adjuvants have been administered, primarily to decrease the incidence of unpleasant emergence phenomena.

In the present study, we observed that nitrous oxide supplementation of ketamine anesthesia significantly improves operating conditions. "Muscle relaxation" as used here refers to the absence of the rigidity or hypertonicity frequently associated with ketamine. With nitrous oxide, this hypertonicity is replaced by a flaccidity resembling the state produced by the potent inhalation agents. In

Table 3. Patient Recall of Emergence Elicted 24 Hours After Operation*

<table>
<thead>
<tr>
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<th>$O_2$ (Per Cent)</th>
<th>N$_2$O-$O_2$ (Per Cent)</th>
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<tbody>
<tr>
<td>Pain</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Dreams</td>
<td>45</td>
<td>43</td>
</tr>
<tr>
<td>Unpleasant dreams</td>
<td>0</td>
<td>0</td>
</tr>
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</table>

* Differences were not statistically significant.

Table 4. Willingness to Receive Same Anesthetic again Elicted 24 Hours after Operation*

<table>
<thead>
<tr>
<th></th>
<th>$O_2$ (Per Cent)</th>
<th>N$_2$O-$O_2$ (Per Cent)</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>35</td>
<td>55</td>
</tr>
<tr>
<td>Indifferent</td>
<td>60</td>
<td>45</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
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* Differences were not statistically significant.
addition, random or involuntary movements are significantly diminished by the use of nitrous oxide. Ginsberg\(^a\) was unable to control involuntary motor activity with nitrous oxide in six patients after numerous administrations of ketamine failed to reduce their intensity. Knox\(^a\) in a large series, failed to comment on the usefulness of nitrous oxide in relieving hypertonicity and random movements. However, he did observe that the incidence of this side-effect was proportional to the dose of ketamine used. The improvement seen with nitrous oxide in our series may in part be related to the decreased dose of ketamine permitted by the use of the gas, as alluded to by Knox. However, we believe that the increased anesthetic depth provided by nitrous oxide was the primary factor in improving relaxation.

Corssen\(^b\) found that analgesia could be enhanced by the administration of nitrous oxide when inadequate doses of ketamine were administered. The improvement in operating conditions in our study resulted not only from decreased motor activity and greater analgesia provided by nitrous oxide, but from the ability of the gas to blunt the rapid changes in anesthetic depth characteristic of un-supplemented ketamine anesthesia. It was these beneficial effects of nitrous oxide which significantly increased surgeons' and anesthesiologists' acceptance of ketamine anesthesia.

Intravenous adjuvants have not been reported to decrease the incidence of unpleasant intraoperative side effects of ketamine anesthesia, nor do they significantly modify the cardiovascular changes seen. Beeley\(^c\) reported that droperidol (75 \(\mu g/kg\)) administered intravenously prior to induction of ketamine anesthesia decreased the incidence of restlessness, crying, and screaming during emergence. Hallucinations and their recall were also significantly diminished. Diazepam and thiopental, administered postoperatively, produced no beneficial effects. With intravenous droperidol premedication, Sadove\(^d\) found subjective improvement in ketamine emergence as judged by anesthesiologists, surgeons, recovery room personnel, and patients. However, with doses similar to those used by Beeley, he observed no decrease in the incidence of hallucinations. With high doses (240 \(\mu g/kg\)) of droperidol, Sadove's patients experienced decreased dreaming and delirium during emergence, but complaints of dizziness were more common. Erbuth\(^e\) could find no improvement in emergence with various combinations of chlorpromazine, diazepam, and droperidol compared with placebo therapy. Bovill\(^f\) noted that diazepam or droperidol, administered postanesthetically, decreased the incidence and severity of emergence delirium, but felt that the somnolence produced by these adjuvants obviated their usefulness when administered after operations of short duration. Beeley also described increased somnolence after postanesthetic return of orientation when droperidol was used for premedication.

In the present study, nitrous oxide significantly reduced agitation during emergence. Dundee\(^g\) observed that emergence delirium is directly proportional to the dose of ketamine administered, and this may to some extent explain our results. However, with strict adherence to our criteria for administering additional ketamine, not only did prompt recovery with less agitated emergence and absence of

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**Fig. 2.** Scattergram showing the relationship between weight in kilograms and dosage of ketamine in mg/min. Regression equations for \(O_2\) and \(N_2O\) are given in order to allow calculation of dose from body weight. The regressions are both significant, \(P \leq 0.01\), by analysis of variance.
somnolence occur, but superior operating conditions were achieved.

The relationship between the dose of ketamine necessary to maintain anesthesia in milligrams per minute and body weight in kilograms was examined (fig. 2). The correlation coefficients (0.74 for oxygen and 0.75 for nitrous oxide supplementation) indicate that total body weight was a reasonably good guide for determining dosage when our criteria for ketamine supplementation were strictly observed.

The four patients who were deleted from the study deserve specific comment. Two patients who had previously undergone satisfactory nitrous oxide-oxygen-ketamine anesthesia could not be adequately anesthetized with ketamine-oxygen alone, even when several supplemental doses of the intravenous agent were given rapidly early in the course of anesthesia. Random movements and movement in response to pain precluded safe operative conditions in both cases. Another patient, during his first anesthesia with ketamine-oxygen, manifested moderately severe tonic-clonic movements following induction. Supplementation with nitrous oxide was followed by prompt cessation of undesirable motor activity in all three patients. The fourth patient, following his first anesthesia (ketamine-oxygen), experienced unpleasant dreams and was unwilling to receive ketamine again. Since the first three patients did not complete the study, their data could not be included in the statistical analysis of results. However, the fact that all three patients had salutary responses to the addition of nitrous oxide serves to emphasize the usefulness of nitrous oxide supplementation to ketamine anesthesia.

References
1. Bessey L, Malamed S, Radnay P, et al: Reduction of the psychotomimetic and circula-