The effects of total intravenous anesthesia using propofol, ketamine, and vecuronium on cardiovascular response and wake up time

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Total intravenous anesthesia (TIVA) can be an effective alternative to inhalational anesthesia. Various techniques of TIVA have been associated with significant cardiovascular alterations and prolonged wake up times.

The purpose of this study was to determine if TIVA utilizing propofol, ketamine, and vecuronium would provide stable hemodynamics in normotensive ASA physical status I and II patients and allow rapid awakening upon completion of surgery.

Anesthesia was induced with propofol 1.0 mg/kg intravenously (IV), followed immediately by ketamine 1.0 mg/kg IV and vecuronium 0.1 mg/kg IV. Anesthesia was maintained by constant infusion of propofol 100-200 µg/kg/min and ketamine 17-34 µg/kg/min. This combination maintained hemodynamic stability and provided a rapid wake up time in 80% of the 40 subjects. The remaining 20% experienced significant tachycardia and hypertension or premature ventricular contractions. The mean wake up time was 9.7 minutes from time of neuromuscular blocking reversal to time of extubation.

TIVA can be accomplished with propofol, ketamine, and vecuronium; however, 20% of patients experienced side effects, which make this method less attractive compared to alternative anesthetic techniques.

Key words: General anesthesia, hemodynamics, ketamine, propofol, total intravenous anesthesia.

Introduction

Total intravenous anesthesia (TIVA) may be an appealing alternative to the standard inhalational agents more commonly used for several reasons. By not requiring a vaporizer, TIVA provides the anesthetist with greater mobility and eliminates "waste gas" pollution. TIVA has not been associated with the toxic effects (specifically renal and hepatic) of some of the inhalational agents. The ideal TIVA agent, which would provide hypnosis, analgesia, amnesia, anesthesia, and muscle relaxation, is not available. However, through a combination of various intravenous agents, it is possible to achieve a state of anesthesia readiness for the patient. The purpose of this study was to evaluate the combination of propofol, ketamine, and vecuronium in providing satisfactory TIVA.

Propofol can be used both for induction and maintenance of anesthesia and is known for its rapid onset and improved speed of recovery. It can, however, produce dose-dependent hemodynamic depression with little or no change in heart rate (HR).\(^1\) Ketamine is a sympathomimetic agent that produces increases in both HR and blood pressure (BP).\(^2\) By combining the hemodynamic depressant effects of propofol with the sympathomimetic effects of ketamine, the hypothesis was that...
there would be less alteration in HR and BP while still enabling rapid wake up times. Vecuronium is a neuromuscular blocking agent that has not been associated with HR or BP alterations. These three drugs were selected because of their unique properties to achieve TIVA while providing cardiovascular stability and allowing rapid wake up times.

Background

Various forms of TIVA have been available since the introduction of the barbiturates into anesthetic practice in the 1930s. Thiopental was used as the sole anesthetic agent at Pearl Harbor. Because of a lack of knowledge of the cardiovascular and respiratory depressant effects of the drug, an inordinate number of fatalities resulted, and intravenous anesthesia was deemed inappropriate. Since that time, intravenous agents with more desirable pharmacokinetic and pharmacodynamic profiles have been introduced into anesthetic practice, suggesting the use of TIVA for both induction and maintenance of anesthesia as an alternative to inhalational anesthesia.

However, many agents have been associated with untoward cardiovascular effects, making their clinical applicability questionable in patients that are at risk for cardiovascular complications. A technique using ketamine, midazolam, and vecuronium to provide TIVA for military surgery was studied and proved to be simple and versatile, but it was associated with significant elevations in HR and mean arterial pressure (MAP). Propofol and alfentanil also have been successfully used as a method of TIVA, but frequently there has been a significant decrease in MAP after induction and tracheal intubation. By combining propofol, ketamine, and vecuronium, the hypothesis was that this combination would provide for stable intraoperative hemodynamic status and rapid awakening times.

Methods

Population. The sample population for this study was selected from patients in the Pacific Northwest who receive their medical care from a military hospital. Subject selection was based on the following screening criteria:

1. ASA physical status I and II category patients.
2. Male/female (nonpregnant) patients.
3. Ages 18-50 years.
4. Elective surgeries expected to last a minimum of 45 minutes.

Patients with a history of hypertension, cardiovascular disease, cerebrovascular accident, or psychiatric illness were eliminated from this study. Patients with chronic pain, penile or breast implants, or who exhibited hysteria, depression, apathy, or other inappropriate behaviors during preoperative assessment were excluded from the study because of a higher incidence of dreaming associated with ketamine administration. Consent was obtained, and the study was approved by the Institutional Review Board. Patients were premedicated with diazepam 10-15 mg by mouth and ranitidine 150 mg by mouth 30-60 minutes preoperatively. Forty patients entered the study.

Methods for data collection. Systolic (SBP), diastolic (DBP), and MAP pressures along with HR and oxygen saturation (SaO2) were recorded every minute for 5 minutes prior to and following induction and at 5-minute intervals thereafter. The preoperative HR and BP were first obtained when the patient entered the operating room. Glycopyrrolate (0.015 mg/kg) was administered as an antisialagogue prior to induction of anesthesia. Anesthesia was induced with propofol 1.0 mg/kg IV followed immediately with ketamine 1.0 mg/kg and vecuronium 0.1 mg/kg. It was maintained by constant infusions of propofol 100-200 μg/kg/min and ketamine 17-34 μg/kg/min. The ketamine dose was derived from Restall’s 1988 study, in which he used ketamine 2.0 mg/kg/hr (33 mg/kg/min), midazolam, and vecuronium.

In the TIVA technique, ketamine and propofol both contributed to the anesthetic, so the ketamine dose was halved to 17 μg/kg/min to determine the lower range dose. A syringe pump and an IMED® infusion pump were used to administer the propofol and ketamine, respectively. The infusion rate of propofol was started at 150 μg/kg/min and adjusted on the basis of the patient’s hemodynamic response to surgery. The ketamine was started at 17 μg/kg/min and adjusted only when 200 μg/kg/min of propofol was being infused and additional anesthesia was needed. Vecuronium (0.04 mg/kg) was administered intermittently to maintain two twitches out of a train of four. The patients were ventilated with oxygen-enriched air with an FiO2 of 0.35 and a tidal volume of 10 mL/kg. The study was aborted when the HR or BP remained greater than 20% above the patient’s preoperative HR and BP for 10 minutes.

When the study first began, two patients who were hemodynamically stable were receiving the low range of doses for propofol (100 μg/kg/min) and ketamine (17 μg/kg/min). Because of a possible synergistic effect, the doses of propofol and ketamine were lowered to slightly below 100 μg/kg/min and 17 μg/kg/min, respectively. The two patients acknowledged that they were
aware during their surgery, resulting in alteration of the protocol and reinitiation of the study to reflect the new propofol and ketamine doses. No patients experienced recall when the maintenance doses were greater than 100 \( \mu g/kg/min \) for propofol and 17 \( \mu g/kg/min \) for ketamine. The patients in this pilot study were not included in the statistical analysis.

The propofol infusion was discontinued approximately 10-15 minutes before the estimated end of surgery. The ketamine infusion was discontinued approximately 30-40 minutes before the end of surgery. Residual neuromuscular blockade was reversed with neostigmine (0.07 mg/kg) and glycopyrrolate (0.015 mg/kg) at the end of surgery. Time in minutes was recorded from the administration of the neuromuscular blockade antagonist until tracheal extubation (wake up time).

Tracheal extubation was performed when the patient was able to follow commands and lift his or her head for 5 seconds. The patient’s behavior was recorded as satisfactory or unsatisfactory, based on his or her report of the presence or absence of visual or auditory illusions, hallucinations, or other inappropriate behavior not usually observed in the postanesthesia care unit (PACU) (Table I).

All patients were visited 24 hours postoperatively and questioned regarding awareness during the operative procedure and the occurrence of dreams, hallucinations, and nausea and/or vomiting.

Statistical analysis

The analysis addressed preoperative, intraoperative, and postoperative SBP, DBP, MAP, HR, Sao2, and time to wake up of the 40 patients entered in the study. ANOVA was used to compare preoperative, intraoperative, and postoperative values. A post hoc Scheffe’ test was applied to the data. The result was considered to be statistically significant at 95\% \((P < 0.05)\) from HR and MAP at induction. A descriptive analysis was done of the wake up time.

Results

Forty patients entered the study. The types of surgical procedures performed are shown in Table II. The duration of anesthesia, time of wake up, and time spent in the PACU are shown in Table III. For all patients, induction was rapid, with no excitatory phenomena exhibited. The mean duration of anesthesia was 144.5 minutes. The average infusion rate of propofol was 120.9 \( \mu g/kg/min \), and of ketamine 17.2 \( \mu g/kg/min \) (Table IV).

| Table I |
| Percent of patients exhibiting unusual postanesthesia care unit (PACU) behavior, incidence of dreaming, incidence of a bad experience, and willingness to repeat anesthesia \((n = 40)\) |
| PACU behavior | Patient reports intraoperative dreaming | *Unusual experience in PACU | Repeat anesthesia |
| Satisfactory factory | Yes | No | Yes* | No | Yes | No |
| 95.1 | 4.9 | 10 | 90 | 14.6 | 85.4 | 90 | 10 |

* Difficulty focusing, blurred vision, prolonged wake up, dreaming, etc.

Cardiovascular effects. A statistically significant \((P < 0.05)\) increase in HR occurred 60 minutes after tracheal intubation (Figure 1). Of note, the HR began to decrease after intubation and was within 20\% greater than baseline at 30 minutes after intubation.

There was an initially significant increase in BP at intubation, which began to decrease after 1 minute and returned to near preoperative levels by 20 minutes. At no time was the BP lower than preinduction levels. Figure 2 presents the MAP findings. The study was aborted in four cases (10\%), three (7.3\%) of which demonstrated hypertension despite increasing levels of propofol, and one in which a new onset of unifocal ventricular dysrhythmias was observed. Both the hypertension and ventricular dysrhythmia resolved within minutes when inhalational agents and/or opioids were added. At no time during the study were patients treated with adjunctive agents such as beta blockers or vasodilators.

Recovery

The majority of subjects (90.2\%) were satisfied with the anesthetic and indicated they would
Table III
Mean (SEM) and range of duration of anesthesia, wake up time, and total time of recovery

<table>
<thead>
<tr>
<th>Number</th>
<th>Duration of anesthesia (minutes)</th>
<th>Minutes (range)</th>
<th>Reversal to extubation (minutes)</th>
<th>Range</th>
<th>Total time in PACU (minutes)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>144.5 (11.7)</td>
<td>17-360</td>
<td>9.7 (1.3)</td>
<td>2-40</td>
<td>78.8 (4.9)</td>
<td>60-180</td>
</tr>
</tbody>
</table>

Table IV
Mean (SEM) infusion rate of propofol and ketamine

<table>
<thead>
<tr>
<th>Number</th>
<th>Average dose of propofol (µg/kg/min)</th>
<th>Range</th>
<th>Average dose of ketamine (µg/kg/min)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>120.9 (4.6)</td>
<td>42-191</td>
<td>17.2 (0.56)</td>
<td>9-27</td>
</tr>
</tbody>
</table>

Discussion

A single intravenous (IV) agent that can manage all aspects of anesthesia needed for amnesia, hypnosis, analgesia, and muscle relaxation has not yet been developed. Currently, various IV drug combinations are required to provide “surgical readiness.” In this study, propofol, ketamine, and vecuronium were chosen to achieve these objectives.

The titration of IV agents can be challenging. The anesthesia provider must administer such

100 µg/kg/min for propofol and 17 µg/kg/min for ketamine. Several patients (14.6%) had unusual experiences, including blurred vision, difficulty focusing, prolonged awakening, and dreaming in the PACU.

Figure 1
Mean heart rate (beats per minute) over time (minutes)

*Statistical difference \( P < 0.05 \) from heart rate induction
Time 0 denotes intubation.
agents with an understanding of the drug's volume of distribution, clearance, and therapeutic blood levels so that, at the end of the surgical procedure, the patient will wake up in a clinically reasonable period of time. An effective method of achieving this is to administer a loading dose to "fill" the volume of distribution, followed by a variable rate infusion to replace the drug lost by clearance and elimination.

Similarly, the effects of TIVA are related to its plasma concentration, which produces a clinically measurable effect (i.e., prevention of movement in 50% of patients). The plasma level is affected by such factors as the agent's volume of distribution, clearance, and therapeutic blood level. With this knowledge, the anesthesia provider can then titrate the dose for each individual drug based on clinical judgment. For example, the volume of distribution may be increased in a geriatric or cirrhotic patient and decreased in a trauma or hypovolemic patient.

The inability to continuously monitor the plasma level of intravenous agents as readily as volatile agents (through end-tidal measurements), along with the irretrievability of fixed IV agents once they have been administered, add to the challenge of using a TIVA approach. Two of the main impediments when using TIVA is the problem of determining the depth of anesthesia and avoiding the possibility of patient awareness during surgery. Theoretically, there is no difference in the quality of anesthesia and the difficulty of determining anesthetic depth between anesthesia produced by IV agents and that produced by inhalational agents.

In the pilot study, two patients experienced awareness when the doses of propofol and ketamine were lowered. The fact that there is no reliable and objective index that indicates awareness during TIVA may be a restricting factor in its use.

Diazepam, which has been shown to minimize the emergence phenomena associated with ketamine, was provided as a premedication to all patients. How much diazepam contributed to the low incidence of adverse emergence reactions in this study population cannot be determined. As a result, a benzodiazepine premedicant may be an important adjunct to the TIVA technique. Additional studies will be required to evaluate the need for a benzodiazepine and whether propofol might

**Figure 2**

Mean arterial blood pressure over time (minutes)

*Statistical difference (P < 0.05) from mean arterial blood pressure induction

Time 0 denotes intubation.
be an acceptable alternative for reducing emergence phenomena in the absence of diazepam.

Blunting the hemodynamic responses to intubation can be a challenge for the anesthesia provider. In this study, both HR and MAP levels were significantly (*P* < 0.05) elevated to more than 20% above preoperative baseline within minutes after intubation.

The mean awakening time was 9.7 minutes, and the total time in the PACU was 78.8 minutes. It is important to note, however, that one patient had an awakening time of 40 minutes and another spent 3 hours in the PACU experiencing delusions and dreaming. Fourteen percent of the patients experienced difficulty focusing, blurred vision, dreaming, and awakening times greater than 60 minutes. Propofol, ketamine, and vecuronium TIVA does not reliably provide rapid awakening and recovery, which also limits its use.

Conclusion

Although the majority of patients had no complications associated with propofol, ketamine, and vecuronium TIVA, many experienced a variety of problems; 7% had significant tachycardia and hypertension, and 2% (one patient) had premature ventricular contractions. Although awareness did not occur with the study doses of propofol and ketamine, it is difficult to determine the dose required to prevent awareness. Several patients reported unusual experiences, including dreaming, difficulty focusing, and blurred vision.

The study found that propofol, ketamine, and vecuronium TIVA works well in approximately 80% of ASA physical status I and II patients. Approximately 20% of the patients experienced significant tachycardia, hypertension, and premature ventricular contractions, which make this an unattractive anesthetic technique when absolute cardiovascular control and/or a rapid wake up time must be achieved.

REFERENCES


AUTHORS

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