Hypercapnic hyperventilation shortens emergence time from Propofol and Isoflurane anesthesia

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ABSTRACT

Objective: The aim of this study is to compare the effects of hypercapnic hyperventilation and normocapnic normoventilation on emergence time from propofol and isoflurane anesthesia.

Methods: In this clinical trial, the differences in emergence time were evaluated in 80 patients undergoing elective abdominal surgery in Alzahra University hospital, Isfahan, Iran, in 2011-2012. Patients were randomly divided into four groups (groups 1-4) receiving isoflurane hypercapnic hyperventilation, isoflurane normocapnic normoventilation, propofol hypercapnic hyperventilation, and propofol normocapnic normoventilation, respectively. Hypercapnia was maintained by adding CO₂ to the patient’s inspired gas during hyperventilation. The emergence time and the duration of stay in recovery room in the four groups were measured and compared by one-way analysis of variance (ANOVA) and least significant difference tests.

Findings: The average emergence time in groups 1, 2, 3, and 4 were (11.3 ± 3.2), (15.2 ± 3.8), (9 ± 4.2) and (11.8 ± 5.3) min, respectively. These differences were significant (P = 0.001). In patients receiving propofol hypercapnic hyperventilation, the emergence time was faster than in other groups. There was also a significant difference in duration of stay in recovery room between the groups (P = 0.004). Patients who received isoflurane hypercapnic hyperventilation had a shortest length of stay in the recovery room.

Conclusion: The emergence time after intravenous anesthesia with propofol can be shortened significantly by using hyperventilation and hypercapnia, without any side effects.

Keywords: Emergence; hypercapnia; hyperventilation; isoflurane; propofol

INTRODUCTION

Rapid removal of anesthetic drugs to the end of the surgical procedures allows for a shorter recovery time from anesthesia. Rapid consciousness is desirable because it allows patients to leave the operation suite quickly. In inhalational anesthesia, the recovery time depends on alveolar ventilation, solubility of the drug in blood and tissue, and cerebral blood flow.[1,2] Applying hyperventilation at the end of the surgery speeds the reduction of alveolar and arterial concentration of the anesthetic, but it also increases the elimination rate of CO₂ from lungs, which can lead to hypocapnia.[3] A decrease in arterial pressure of CO₂ (PaCO₂) by hyperventilation depresses respiratory drive; and subsequently may slow the return of spontaneous breathing.[4,5] Moreover, hypocapnia decreases the rate of clearance of anesthetic from the brain by reduction of cerebral blood flow.[6,7] For this reason, some anesthetic machines are equipped with CO₂ tanks to prevent the reduction of PaCO₂ and therefore to maintain normal to slightly increased PaCO₂.[8]

Sakata and Nishant showed that hyperventilation reduces the volatile anesthetic from the lungs and rebreathing to induce hypercapnia can significantly shorten the recovery time.[3,9,10] and Brosnan et al., in a study on horses, concluded that hypercapnic hypopnea decreases time to standing without influencing anesthetic recovery quality.[4,11]
Propofol is becoming the most common intravenous agent used for induction as well as maintenance of anesthesia. It is an alkylphenol with a rapid recovery.\cite{12}

Kuipers et al., demonstrated that although the principal site for elimination of propofol is the liver, it undergoes extensive uptake and first-pass elimination in the lungs.\cite{13}

By dilating cerebral arteries, hypercapnia increases cerebral blood flow by 6% for each mmHg increase in PaCO\textsubscript{2} and results in rapid clearance of volatile anesthetic from the brain tissue.\cite{14,15} It also enhances respiratory drive, and therefore shortens the emergence time from inhaled anesthesia. Of course, this situation will be formed if anesthetic concentration does not change till the end of the surgery. Otherwise, the risk of intra-operative awareness of patient exist.\cite{16}

Akca et al., showed that mild intra-operative hypercapnia increases subcutaneous, tissue, and cerebral oxygenation.\cite{17} Therefore, it may enhance respiratory drive and provide better cognitive functions postoperatively in addition to accelerating the emergence time from anesthesia and reducing the hospital costs.\cite{18}

In this study, by considering the extensive uptake and first-pass elimination of propofol in the lungs and the effect of hyperventilation and hypercapnia on emergence time, we aimed to compare the emergence times with hypercapnic hyperventilation and normocapnic normoventilation in two methods of propofol and isoflurane anesthesia.

**METHODS**

This was a single-center, balanced randomization, parallel group clinical trial conducted in St Alzahra University Hospital, Isfahan (Iran), from September 2011 to March 2012. After obtaining approval from Institutional Ethical Committee, and informed consent from all patients, 80 adult patients undergoing elective abdominal surgery (less than 120 min), were included in this study by simple sampling method. Sample size was determined by using results of similar studies conducted previously.\cite{3,9,10}

Patients with history of cardiopulmonary disease, high intracranial pressure (ICP), pulmonary hypertension, and need for controlled hypertension during the surgery were excluded. Other criteria for exclusion included bleeding that needs transfusion and complications such as pneumothorax, cardiac arrest, and other unpredictable events during the surgery.

Patients were randomly assigned to four groups according to a computer-generated random list. They were premedicated with 1-2 mg of midazolam, and general anesthesia was induced with fentanyl (1 µg/kg), of thiopenthal sodium (5-7 mg/kg), and atracurium (1.0 mg/kg). After tracheal intubation, the respiratory rate was set at 10 breaths/min and the tidal volume was adjusted to keep the end-tidal CO\textsubscript{2} (EtCO\textsubscript{2}) concentration at 35-40 mmHg. A gas analyzer measured the inspired and EtCO\textsubscript{2} and anesthetic concentrations continuously. Then, the patients randomly received either isoflurane (1.2% expired concentration) or propofol (50-150 mg/kg) for maintenance of anesthesia, plus nitrous oxide (N\textsubscript{2}O) (50%) in oxygen (O\textsubscript{2}) and morphine (0.1 mg/kg).

Intra-operative monitoring included electrocardiogram, heart rate (HR), invisible arterial pressure, pulse oximetry, thermometer, and a gas analyzer measuring the inspired and EtCO\textsubscript{2} and anesthetic concentrations continuously.

When the surgeon applied the first adhesive wound closure strip, the vaporizer was turned off in the isoflurane group and propofol infusion was stopped in the propofol group; then, the O\textsubscript{2} flow was increased to 10 L/min.

At this time, the patients alternatively received either hypercapnic hyperventilation or kept at normocapnic normoventilation during emergence.

For the hyperventilated patients, we increased the respiratory rate to 16 breaths/min and the tidal volume as needed to double the minute ventilation. Additionally, to produce hypercapnia, EtCO\textsubscript{2} was increased by manual addition of gas from a 100% carbon dioxide tank to the gas mixing chamber that was adjusted to keep the EtCO\textsubscript{2} concentration at 45-50 mmHg.

For the patients who were not hyperventilated, the respiratory rate and tidal volume were left unchanged. In all groups, tracheal extubation was done after getting a positive response to command to open their eyes and mouth. Then, the time from when the vaporizer was turned off or propofol was discontinued until the patients first opened their eyes, after calling them by name every 30 s and making the request to open their eyes, was recorded. The duration of stay in recovery room was also recorded for all patients.

Therefore, patients were divided randomly into four groups (20 patients each) as follows:

- **Group 1:** Isoflurane hypercapnic hyperventilation
- **Group 2:** Isoflurane normocapnic normoventilation
- **Group 3:** Propofol hypercapnic hyperventilation
- **Group 4:** Propofol normocapnic normoventilation

For all groups, systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, saturation of arterial
blood \((\text{SaO}_{2})\), and body temperature were measured at 2 min before induction of anesthesia and then every 5 minutes after induction, till the end of anesthesia.

Analysis was performed using SigmaStat version 2.03 (Aspire Software International). The groups were compared using Chi-Square square test, Fisher’s exact test, and analysis of variance (ANOVA). The results were expressed as mean ± SD. \(P\) values \(\leq 0.05\) were considered to be significant.

**RESULTS**

Eighty patients in four groups who were receiving either propofol or isoflurane anesthesia were enrolled in this study. The four groups were similar with regard to patient characteristics data, hemodynamics, body temperature, \text{SaO}_{2}, and the duration of surgery and anesthesia [Table 1].

In the propofol groups, the times to open eyes after turning off the vaporizer was significantly \((P = 0.003)\) shorter with hypercapnia and hyperventilation \((9 \pm 4.2 \text{ min})\) than with normocapnia and normoventilation [Table 2].

In the isoflurane groups also, the emergence time was shorter in patients receiving hypercapnic hyperventilation \((11.3 \pm 3.2 \text{ min})\) than in those receiving normocapnic normoventilation \((15.2 \pm 3.8 \text{ min})\), and this difference was statistically significant [Table 2].

The duration of stay in recovery room was \(25.8 \pm 2.2, 28.1 \pm 6.8, 28 \pm 7.3,\) and \(27 \pm 10.5 \text{ min}\) in groups 1, 2, 3, and 4, respectively, and interestingly, patients in group 4 (isoflurane hypercapnic hyperventilation) had a statistically significant shorter duration of stay in recovery room [Table 2].

None of the patients developed any intra- or post-operative complications that would have resulted in additional interventions beyond routine management.

**DISCUSSION**

Considering previous studies about the duration of inhalational anesthesia, we evaluated the effect of hyperventilation and hypercapnia on emergence time in propofol anesthesia and compared it with isoflurane anesthesia. We found that hypercapnia with hyperventilation shortened the emergence time by \(9 \pm 4.2 \text{ min}\) after propofol anesthesia and by \(11.3 \pm 3.2 \text{ min}\) after isoflurane anesthesia. In earlier studies, Sakata et al., found that emergence time after

### Table 1: Demographic characteristics data of the studied patients

| Variable    | Isoflurane | Propofol |
|-------------|------------|----------|
| Gender (M/F)| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic|
|             | Normoventilation | Normoventilation | Normoventilation | Normoventilation |
| Gender (M/F)| 12/8 (n=20)   | 13/7 (n=20)   | 10/10 (n=20)    | 13/7 (n=20)     |
| Age (years) | 38±2.5       | 39±1.35     | 36±3.12         | 38±2.5          |
| Weight (Kg) | 71.18±6.5    | 70.5±4.2    | 68±5.5          | 67±5.3          |
| Height (cm) | 168.3±8.4    | 170.3±8.4   | 170.3±7.2       | 172.3±7.2       |

Data are presented as mean ± SD

### Table 2: Vital signs, duration of surgery, duration of anesthesia, emergence time, and length of stay in recovery room in four study groups

| Variable                  | Isoflurane | Propofol |
|---------------------------|------------|----------|
|                           | Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic| Hypercapnic|
|                           | Normoventilation | Normoventilation | Normoventilation | Normoventilation | Normoventilation | Normoventilation | Normoventilation | Normoventilation |
| Body temperature (°C)     | 36.4±0.31  | 36.2±0.31  | 36.7±0.22     | 36.1±0.3      | 0.18          |
| Heart rate (beat/min)     | 86±12.2    | 82±12.8    | 80±9          | 78±12.2       | 0.13          |
| Respiratory rate (beat/min)| 16±2.4    | 14.4±3.4   | 15.8±2.2      | 14.1±3.5      | 0.1           |
| \text{O}_2 \text{Saturation} (%) | 98.4±4.5  | 97.8±5.6   | 98.5±12.5     | 98.2±5.6      | 0.88          |
| \text{PaO}_2 (mmHg)       | 90.4±5.33  | 89.7±2.1   | 96±7.6        | 97±11.2       | 0.33          |
| Duration of surgery (min) | 61±20.4    | 62±24.5    | 59.4±25       | 59.5±22.5     | 0.58          |
| Duration of anesthesia (min) | 78.5±22.3 | 76±26.7    | 75.6±27.4     | 78.4±25       | 0.63          |
| Emergence time (min)      | 11.3±3.2   | 15.2±3.8   | 9±4.2         | 11.8±5.3      | 0.001*        |
| Length of care in recovery room (min) | 25.8±2.2 | 28.1±6.8   | 28±7.3        | 27±10.5       | 0.049*        |

Data are presented as number of patients and mean ± SD; \text{PaO}_2: Arterial partial pressure of oxygen; *Significant difference
CONSORT diagram of the study

inhalational anesthesia (isoflurane, desflurane and sevoflurane) was shortened when hyperventilation and hypercapnia were used.[3,9,10]

Our findings about vapor anesthetics confirm the previous results, showing that hypercapnia with hyperventilation accelerates recovery in isoflurane anesthesia. In fact, in vapor anesthesia, hyperventilation alone, rapidly removes anesthetic from the lungs, keeps the alveolar concentration low, and maintains a high anesthetic concentration gradient between pulmonary capillary blood and alveolar gas.[3] Hypercapnia also, dilates cerebral arterial smooth muscles and increases cerebral blood flow as much as 6% per mmHg change in arterial PaCO₂ and if the concentration of anesthetic in the arterial blood is less than the brain concentration, the higher cerebral blood flow will cause more rapid clearance of volatile anesthetic from the cerebral tissue.[3,16]

It is well known that propofol has a rapid clearance and its principal site for elimination is the liver.[12] Hyperventilation by raising intrathoracic pressure will decrease venous return, which in turn will decrease cardiac output and hepatic blood flow.[17] Therefore, the reduction in hepatic clearance of propofol is predicted when hyperventilation is applied.[18]

However, the principal site for elimination of propofol is the liver,[13] but the total clearance of propofol often exceeds hepatic blood flow;[19] therefore, extra hepatic clearance is thought to contribute to its elimination.[13] Kuipers et al., reported that the contribution of pulmonary elimination to the total clearance of propofol can be significant, and as their results show that propofol undergoes extensive uptake and first-pass elimination in the lungs.[13]

Moreover, due to the dilatory effect of hypercapnia on cerebral arteries, cerebral blood flow increases and the higher cerebral blood flow will cause more rapid clearance of anesthetic from the cerebral tissue.[10,19] Therefore, hypercapnia along with hyperventilation at the emergence time in propofol anesthesia may overcome the effects of hyperventilation on hepatic clearance of propofol.

Thus, the possible reason for shorter emergence time from propofol anesthesia with hypercapnia and hyperventilation may be the combination of extensive uptake and the first-pass elimination of this anesthetic in the lungs as well as the rapid clearance of it from the cerebral tissue induced by hypercapnia.

Furthermore in both kind of anesthesia (propofol or isoflorane based) hypercapnia and hyperventilation are important in rapid removing of anesthetic's drugs from the brain. The recovery time will be less if the anesthesiologist decreases the anesthetic's concentration before the procedure ends (tapering). Although tapering can accelerate recovery, hypercapnia with hyperventilation may be preferred when sustained anesthetizing concentrations might be useful to reduce the risk of intra-operative awareness, inadequate analgesia, or patient movement.

We found that emergence time after propofol and isoflurane was shorter when hyperventilation was
used to rapidly flush the anesthetic from the lungs and hypercapnia was induced by manual addition of gas from a 100% carbon dioxide tank. When a rapid emergence after surgical procedures is needed, hypercapnic hyperventilation should be considered in these cases where it is important to maintain an anesthetic concentration of the propofol or isoflurane right up to the end of the procedure. Therefore, in clinical practice, when surgery ends abruptly and without warning, hypercapnic hyperventilation may be useful to shorten the emergence time. Applying more degrees of hypercapnia in future studies may accentuate our findings.

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AUTHORS’ CONTRIBUTION

A. Yaraghi made substantial contributions to data base search, proposal preparation, and data collection. M. Golparvar contributed in conception of the study, database search, proposal preparation, writing and revising the manuscript. R. Talakoub carried out randomization and manuscript preparation. H. Sateie contributed in proposal and manuscript preparation, and data collection. A. Mehrabi carried out sample size calculation and statistical analysis.

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