Original Article

Effects of intra-operative end-tidal carbon dioxide levels on the rates of post-operative complications in adults undergoing general anesthesia for percutaneous nephrolithotomy: A clinical trial

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Abstract

Background: A retrospective study has shown lesser days of hospital stay in patients with increased levels of intra-operative end-tidal carbon dioxide ($ETCO_2$). It is probable that hypercapnia may exert its beneficial effects on patients' outcome through optimization of global hemodynamic and tissue oxygenation, leading to a lower rate of post-operative complications. This study was designed to test the hypothesis that higher values of intra-operative $ETCO_2$ decrease the rate of post-operative complications.

Materials and Methods: In this randomized, double-blind clinical trial, 78 adult patients scheduled for percutaneous nephrolithotomy (PCNL) were prospectively enrolled and randomly divided into three groups. $ETCO_2$ was set and maintained throughout the procedure at 31-33, 37-39 and 43-45 mmHg in the hypocapnia, normocapnia and hypercapnia groups, respectively. The rates of post-operative complications were compared among the three groups.

Results: Seventy-five patients completed the study (52 male and 23 female). Ten (38.5%), four (16%) and two (8.3%) patients developed post-operative vomiting in the hypocapnia, normocapnia and hypercapnia groups, respectively ($P = 0.025$). The nausea score was significantly lower in the hypercapnic group compared with the other groups (3.9 ± 1.8, 3.2 ± 2.1 and 1.3 ± 1.8 in the hypocapnia, normocapnia and hypercapnia groups, respectively; $P = 0.000$). Time to return of spontaneous respiration and awakening were significantly decreased in the hypercapnia group compared with the other groups ($P < 0.01$).

Conclusion: Mild intra-operative hypercapnia has a protecting effect against the development of post-operative nausea and vomiting and decreases the duration of emergence and recovery from general anesthesia.

Key Words: Carbon dioxide, hypercapnia, hypocapnia, nausea and vomiting, post-operative complications

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INTRODUCTION

Mild hypocapnia, loosely defined as an end-tidal carbon dioxide ($ETCO_2$) of 30-35 mmHg,[1] was traditionally used as adjunct to general anesthetics and was used extensively in anesthetized patients under mechanical ventilation to reduce the anesthetic requirement.

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Recent studies questioned the value of induced hypocapnia and showed the oxygenation benefits of mild hypercapnia during general anesthesia in laboratory and clinical settings, most of them related to intensive care patients. Other than the proven value of permissive hypercapnia in lung-injured patients,[2] studies on patients under general anesthesia found higher values of $ETCO_2$ associated with improved cardiac index, tissue perfusion, global hemodynamics and oxygenation.[3-8] However, the effects of intra-operative arterial or alveolar carbon dioxide tension on the course of the post-operative period have rarely been evaluated through control studies. An initial prospective study showed the protective effects of hypercapnia on the post-operative cognitive dysfunction,[9] although a subsequent study failed to show any difference regarding psychomotor activity between the hypercapnic and hypocapnic patients.[10] A retrospective study on the electronic records of more than 3000 patients undergoing colectomy or hysterectomy showed reduced length of hospital stay with higher values of $ETCO_2$.[11] The exact cause of lower hospital stay in the hypercapnic group has not been differentiated in the study. Mild hypercapnia through improved tissue oxygenation has some beneficial effect on the cardiorespiratory, gastrointestinal and neurologic variables, which directly or indirectly causes improved post-operative condition and lower hospital stay. Post-operative nausea and vomiting (PONV) is also an important and common factor that may lead to increased morbidity and hospital stay. Hypocapnia has been shown to be associated with an increased risk of nausea and vomiting in patients with vestibular system disorders,[12] but its effect on PONV has not been studied in a controlled study. Hypercapnia may enhance the respiratory drive, which affects the post-operative care of the patients. Hypercapnia, by improving the hemodynamic state, tissue perfusion and oxygenation,[3,4] may contribute to a superior quality of post-operative course and lower hospital stay. The present study was designed in a sample of adult patients undergoing percutaneous nephrolithotomy (PCNL) under general anesthesia with mechanical ventilation to test the hypothesis that a mild increase in the value of intra-operative $ETCO_2$ reduces the rate of post-operative anesthesia complications compared with normal or lower values.

MATERIALS AND METHODS

This clinical trial was registered at the UMIN Clinical Trials Registry (UMIN-CTR: UMIN000009161) and was conducted during April-September 2012. The Ethics Sub-committee of Research Department, Faculty of Medicine, Isfahan University of Medical Sciences, approved this study (Ref: 390543, Feb 1, 2012).

After obtaining written, informed patient consent, 78 adult (aged 18 years old or over) otherwise healthy patients scheduled for PCNL were enrolled prospectively in this double-blinded, parallel-group study. The reason for selecting only one type of surgical procedure was to abolish the effects of surgical procedure on the outcome variables of the study and, because the main investigator was working in the urological operating room and nephrolithotomy was one of the most common surgical procedures, we decided to select this type of operation for the study. Patients with a history of PONV, recent general anesthesia (last 6 months) with volatile anesthetics, cardio-respiratory diseases, elevated blood urea nitrogen or creatinine (more than 30 and 1.8 mg/dL, respectively), addiction, smoking and those with a body mass index more than 30 kg/m^2 were excluded from the study. The study was performed at the Al-Zahra Medical Center, a university teaching hospital located in Isfahan, central area of Iran. No premedication was used. Anesthesia was induced using thiopental 5 mg/kg and fentanyl 2 µg/kg. Tracheal intubation was facilitated with atracurium 0.5 mg/kg. Anesthesia was maintained with isoflurane 0.8-1.2% and N_2O 50% in oxygen plus supplemental doses of atracurium 0.1 mg/kg every 30 min. Patients were placed in a prone position during the procedure. Ventilation was controlled during the operation using an anesthesia machine ventilator, with a tidal volume of 8 mL/kg. The patients were allocated to three different groups of $ETCO_2$. Through alteration of respiratory rate in range of 6-18 breaths/min, $ETCO_2$ (measured using an ALBORZ Patient Care Monitor, SAADAT Medical Equipment Producer, Tehran, Iran) was set and maintained at 31-33, 37-39 and 43-45 mmHg in the hypocapnic, normocapnic and hypercapnic groups, respectively(). After tracheal intubation, morphine was administered at 0.1 mg/kg as a narcotic supplement. At the end of the procedure, isoflurane was discontinued and ventilation was switched to manual assist. After return of spontaneous respiration, reversal of neuromuscular blockade was performed using neostigmine 0.04 mg/kg co-administered with atropine 0.02 mg/kg. The trachea was extubated after return of airway reflexes when the patient had a sufficient depth and rate of breathing. Thereafter, patients were transferred to a post-anesthesia care unit. Pulse oximetry, capnography, electrocardiography and non-invasive blood pressure were monitored throughout the procedure. The same monitoring procedures, except capnography, were performed in the post-anesthesia care unit. Patient allocations to the $ETCO_2$ groups were performed with the method of minimization[13] using age (<41, 41-65 and >65 years old), gender and body mass index (<22, 22-26 and >26 kg/m^2) as minimization factors. The $ETCO_2$ groups were assigned using equal allocation ratios. Marginal balance was used for calculation of the imbalance score among the $ETCO_2$ groups. To enforce randomization, patients were enrolled to the preferred group with a 0.7 base probability. A computer program was used to carry out the task of minimization.[14] Immediately after induction of anesthesia, the levels of the minimization factors corresponding to each patient were entered into the software by the third author of the study who was not involved in data acquisition. He was responsible for manipulating the respiratory rate and keeping $ETCO_2$ in the target range as proposed by the software. Intra-operative data were gathered by the second author of the study. Although he was not involved in setting $ETCO_2$, it was not practical to blind him about the level of $ETCO_2$. After discontinuation of the volatile anesthetic and start of manual assist ventilation, $ETCO_2$ monitoring was disconnected and the patient was handed to an anesthesia nurse who was not aware of the patient allocation. She was responsible for tracheal extubation, delivery of patient to the recovery room and recording of post-operative data.

Changes in blood pressure or heart rate more than 25% compared with the baseline values at any time from 15 min after tracheal intubation to the time of anesthetic discontinuation and from 10 min after extubation to the end of the recovery period were recorded. Need for transfusion to compensate for surgical bleeding was also recorded. Dysrhythmias including more than 25% change in heart rate were also recorded. Different emergence and recovery time intervals were recorded with respect to such events as return of respiration, extubation and awakening. Patency of upper airway at 1 min after extubation was rated as fully patent, mild-to-moderate obstruction and severe-to-complete obstruction. Occurrence of stridor, laryngospasm, breath holding, desaturation, shivering, restlessness and vomiting during the recovery period were recorded. Post-operative nausea was rated from a minimum of 0 to a maximum of 10 using the verbal analogue scale. The primary outcome measure in this study was the rate of post-operative complications. In addition, the rates of major intra-operative complications (>25% change in blood pressure, dysrhythmia and need for transfusion) were compared among the three groups.

Statistical analysis

Data were reported as mean ± SD or *n* (%). χ^2 test and analysis of variance were used to compare the frequency and numerical data, respectively, among the three $ETCO_2$ groups. Numerical data with significantly non-normal distribution were compared among the three groups using the Kruskal-Wallis test. Bonferroni's correction to *P*-values was applied for *post hoc* pair-wise comparisons. Regarding frequency data, when there were expected counts of less than 5 in some categories, two of the three groups were merged to convert the cross-tabulation into a 2 × 2 table suitable for Fisher's exact test. Merging was performed in a meaningful way to yield two groups, either hypocapnia versus non-hypocapnia or hypercapnia versus non-hypercapnia. A *P*-value <0.05 was considered as statistically significant. A pilot study on the three groups of patients, five in each group, was carried out using nausea score as the outcome variable to calculate the necessary sample size. After analysis of pilot data based on the formula suggested by Cohen[15] for sample size determination in analysis of variance, an effect size index of approximately 0.38 was obtained for the effect of $ETCO_2$ on the value of nausea score. This yielded a sample size of approximately 23 patients/group, considering a study power of at least 80% for a 0.05 two-sided significance level. The final sample size was fixed at 26 patients in each group (total 78 subjects).

RESULTS

A total of 78/114 patients assessed for eligibility were enrolled in the study from April to September 2012 [Figure 1]. The surgical plan of one patient in the normocapnia group and another patient in the hypercapnia group changed during the operation from PCNL to open surgery due to the development of surgical complications. In one patient from the hypercapnia group, the target $ETCO_2$ range was not reached despite a minimum ventilatory rate of 6/min. Therefore, the final analysis was performed on the remaining 75 patients. The baseline characteristics were similar among the three groups [Table 1].

Five patients in the hypocapnic group had a significant increase in the intra-operative blood pressure ($P = 0.004$ compared with the merged non-hypocapnic groups). No other significant difference was noted among the groups regarding the intra-operative incidences of decreased blood pressure, dysrhythmias or need for transfusion [Table 2].

Time to the return of spontaneous respiration and to awakening were significantly decreased in the hypercapnia group compared with the other groups [Figure 2].

The hypercapnic group had a significantly lower value for nausea score and had significantly fewer episodes of vomiting ($P < 0.05$, Table 3).

The hypercapnia group had lower incidences of post-operative airway-related problems such as stridor, laryngospasm, desaturation, breath holding and

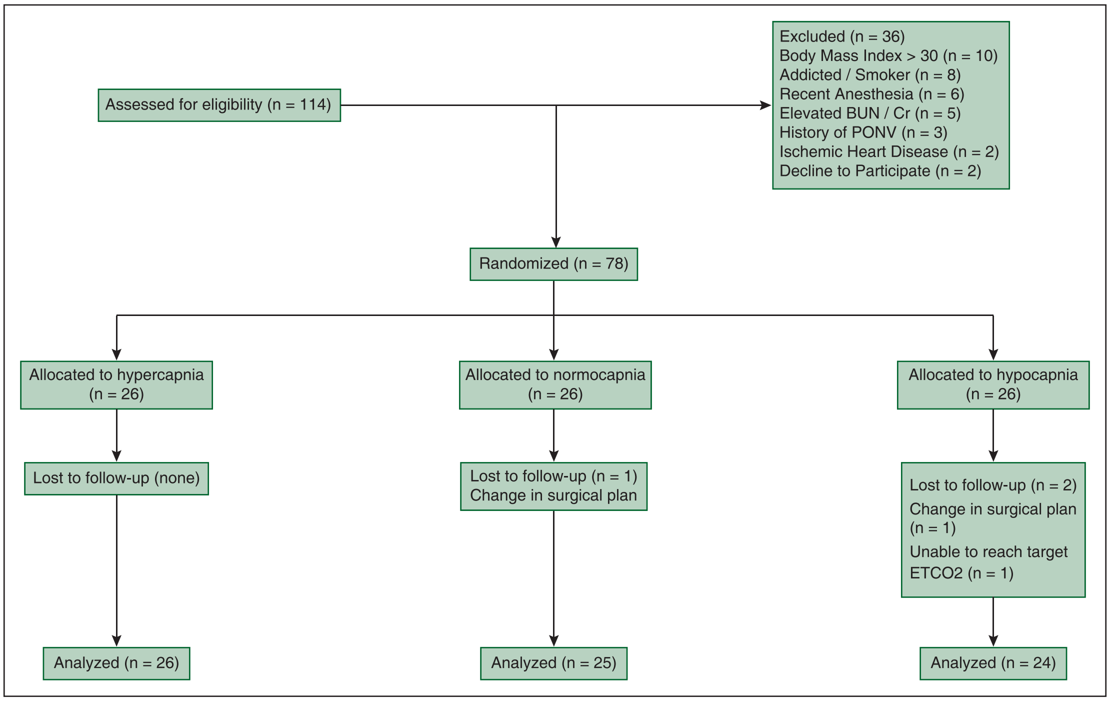

Figure 1: Study enrolment, randomization, follow-up and final analysis

Table 1: Baseline characteristics of the patients in the three groups. Data are mean ± SD or *n* (%)

	Hypocapnia (*n* = 26)	Normocapnia (*n* = 25)	Hypercapnia (*n* = 24)
Age (years)	43.7±13.4	42.2±14.5	45.4±14.2
Height (cm)	170±9.9	168±6.7	168±8.8
Weight (kg)	73.5±12.1	71.9±10.8	71.8±9.9
Body mass index (kg/m^2)	25.4±2.9	25.4±3.6	25.4±3.3
Heart rate (beats/min)	82±11.3	78±14.9	86±15.4
Systolic blood pressure (mmHg)	126±18.1	131±16.8	132±13.4
Diastolic blood pressure (mmHg)	81±13.1	81±13.6	82±8.9
Blood urea nitrogen (mg/dL)	16.1±5.3	15.9±4.9	15.5±4.7
Creatinine (mg/dL)	1.08±0.24	0.97±0.18	1.1±0.27
Pulse oximetric saturation (%)	95.7±1.3	95.9±2.1	95.5±1.8
Hematocrit	43.9±4.9	43.9±4.6	42.7±4.2
Duration of surgery (min)	121±21.5	119±36.9	127.5±40.5
Gender			
Male	18 (69)	18 (72)	16 (67)
Female	8 (31)	7 (28)	8 (33)

No significant difference among the groups

post-extubation airway obstruction compared with the other groups. But, none of these figures reached statistical significance.

DISCUSSION

Results of this study show that mild intra-operative hypercapnia reduces PONV. Mild hypercapnia causes a nearly five-fold decrease in the incidence of

Table 2: Incidence of major intra-operative changes (>25%) in blood pressure, dysrhythmia and need for transfusion. Data are *n* (%)

	Hypocapnia (*n* = 26)	Normocapnia (*n* = 25)	Hypercapnia (*n* = 24)
>25% change in blood pressure			
Increase[a]	5	0	0
Decrease	7	12	7
Dysrhythmia[b]	6	8	5
Need for transfusion	2	1	2

[a]P = 0.004, comparing hypocapnic with the merged non-hypocapnic (normocapnic + hypercapnic) patients using Fisher's exact test. [b]Including >25% changes in heart rate and other types of dysrhythmias

post-operative vomiting compared with hypocapnia and a two-fold decrease in vomiting compared with normocapnia. In other words, the probability of post-operative vomiting will decreased by a factor of two for every 6 mmHg increase in intra-operative $ETCO_2$. Hypocapnia, on the other hand, causes a considerable delay in the return of spontaneous respiration at the end of the procedure together with higher incidences of increased intra-operative blood pressure.

The beneficial effect of hypercapnia on PONV may be related to enhanced global perfusion and oxygenation and its particular effects on cerebral and gastrointestinal tissues, with the accompanying improvement in gastrointestinal or neurologic functions that are the main effector sites for PONV.[3,16,17] Enhanced tissue oxygenation has been

Table 3: Comparing post-operative data among the three groups. Data are mean ± SD or *n* (%)

	Hypocapnia (*n* = 26)	Normocapnia (*n* = 25)	Hypercapnia (*n* = 24)	*P**
Nausea score (0–10)	3.9±1.8	3.2±2.1	1.3±1.8	0.000
Respiratory rate 1 min after extubation (/min)	17.6±3.5	17.8±4.7	18.5±5.0	
Morphine consumption in recovery room (mg)	7.7±1.3	8.6±1.5	7.8±1.5	
>25% change in blood pressure				
Increase	6 (23)	3 (12)	1 (4)	
Decrease	2 (7.7)	2 (8)	0 (0)	
Dysrhythmia	7 (27)	7 (28)	5 (21)	
Shivering	6 (23)	3 (12)	1 (4.2)	
Stridor	3 (11.5)	4 (16)	2 (8.3)	
Laryngospasm	1 (3.8)	1 (4)	0 (0)	
Restlessness	3 (11.5)	2 (8)	2 (8.3)	
Vomiting	10 (38.5)	4 (16)	2 (8.3)	0.025
Desaturation	1 (3.8)	3 (12)	0 (0)	
Breath holding	2 (7.7)	0 (0)	0 (0)	
Airway patency at 1 min post-extubation Fully patent	19 (73.1)	16 (64)	20 (83.3)	
Mild-to-moderate obstruction	6 (23.1)	8 (32)	4 (16.7)	
Severe-to-complete obstruction	1 (3.8)	1 (4)	0 (0)	

*Only for significantly different values

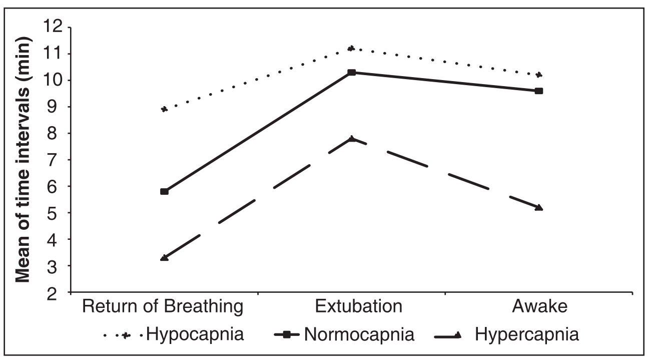

Figure 2: Comparing the means of different emergence and recovery time intervals among the three groups. Time intervals are sequential, i.e., each time point is from a previous point. The first time interval is from discontinuation of anesthetic. Plotted data are means ± SD. *$P < 0.01$

shown to decrease the probability of post-operative wound infection.[18] Increase in tissue oxygenation in response to hypercapnia has been equated to a 50% increase in inspiratory oxygen concentration.[4] Hypocapnia, on the other hand, reduces the cerebral and splanchnic blood flow by global reduction of cardiac output and local vasoconstriction.[19] In addition, hypocapnia causes a shift of the oxyhemoglobin dissociation curve to the left, which further lowers the tissue oxygenation.[20] Johnson[21] showed that systemic hypocapnia results in reduced mesenteric oxygen associated with a decrease in the mesenteric oxygen extraction ratio.

In analogy with the rationale of increased benefit from hypercapnia in certain vascular surgeries like carotid endarterectomy,[22] or in the treatment of central retinal artery occlusion,[23,24] it may be concluded that mild hypercapnia is of clinical value for the prevention of PONV in certain high-risk patients.[25]

Although carbon dioxide has contradictory effects on blood pressure in different settings of general anesthesia, this study supports the findings of Schwartz and colleagues, indicating the tendency of hypocapnia to increase blood pressure under isoflurane anesthesia.[26] Hypocapnia has been used to prevent surges of blood pressure due to CO_2 insufflation during laparoscopic cholecystectomy.[27] The present study has failed to confirm this beneficial effect of hypocapnia and, indeed, hypocapnia has been associated with higher incidences of increased intra-operative blood pressure compared with the non-hypocapnia groups, which may be due to the differences in the settings and the protocols of the two studies.

Hypocapnia may worsen the severity of laryngospasm, while hypercapnia may have a protecting effect against unwanted airway reflexes such as laryngospasm in the perioperative period.[28-30] Although the hypercapnia group patients had fewer post-operative airway-related complications, due to the limited sample size, this study fails to demonstrate the significant beneficial effects of hypercapnia on the patency of the airway.

There has been a concern for increased surgical blood loss and need for transfusion in the presence of hypercapnia-induced peripheral vasodilatation. The present study shows that hypercapnia does not increase the intra-operative blood loss and does not affect the need for transfusion, which is in accordance with a previous study on surgical blood loss during endoscopic sinus surgery.[31]

Although hypocapnia can increase the breath-holding time, which theoretically may lead to hypoxia,[32] this study fails to show a significant increase in the incidence of post-operative breath holding.

Another beneficial effect of hypercapnia is on shortening emergence from general anesthesia, which has been proved in previous clinical studies and experimental models.[33-36] This study shows that hypercapnia dramatically decreases the time to return of spontaneous respiration and awakening. In addition to accelerating the return of spontaneous respiration, hypercapnia lowers the time to awakening, which has been attributed to increased cerebral perfusion and enhanced clearance of anesthetics from the brain.[33]

In conclusion, the results of this study show a dramatic decrease in PONV associated with mild hypercapnia. Regarding other post-operative complications, although there was a trend toward increasing rates of post-operative complications, however, the resultant figures for other complications such as shivering, laryngospasm and desaturation was not statistically significant. This may be due to the relatively rare occurrence of these complications, particularly in the setting of a prospective clinical trial with enhanced anesthesia care, which further reduced the incidence of these complications. Therefore, future researches with larger sample sizes may be necessary to answer the prevalence of rare post-operative complications and its relation to the level of intra-operative $ETCO_2$. In addition, the observed benefits of hypercapnia can only be attributed to the mild degrees of hypercapnia (i.e., less than 50 mmHg). Further studies for higher values of $ETCO_2$ may be necessary to determine its effect on the post-anesthesia complications.

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