Low-Dose Mannitol Pretreatment Reduces Postoperative Nausea And Vomiting In Patients Undergoing Gynaecological Laparoscopic Surgery: A Randomized, Double-Blind, Placebo-Controlled Trial

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Research article

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Abstract

Background: Postoperative nausea and vomiting (PONV) is the most common and undesirable complications associated with anaesthesia, leading to discomfort in patients and extended hospital stays. The present study evaluates and compares the effects of preoperative low-dose mannitol infusion on PONV in patients undergoing gynaecological laparoscopic surgery.

Methods: Fifty-three patients were randomly allocated into 2 groups (mannitol group, Group M, and control group, Group C). In the group M, low dose of 20% mannitol (0.5g/kg) was applied 30 minutes before induction. In the group C, equal volume of 0.9% normal saline was infused. Both groups were maintained with Ringer's lactate in 8 ml/kg/h intraoperatively. The primary endpoint was the incidence and severity of PONV within the first postoperative 24h. The secondary endpoints were the average vascular resistance indexes (RI) and angle-corrected time-averaged flow velocity (TIMV) of bilateral vertebral artery (VA) and internal carotid artery (ICA) and cerebral blood flow volume (CBFV) using non-invasive Doppler ultrasound at time points just 5 min after laryngeal mask airway placement (T1—baseline); pneumoperitoneum started and position changed (T2); 15 minutes after pneumoperitoneum with the position change (T3); pneumoperitoneum stopped with a position change (T4); 15 minutes after pneumoperitoneum had stopped (T5).

Results: Within 24h after operation, the incidence of PONV in group M (28.0%) was significantly lower than group C (56.0%) ($P=0.045$). Compared with group C, the severity of PONV in group M was significantly lower ($P=0.040$). The RI of VA and ICA were statistically different between the two groups ($P<0.05$). No significant differences were observed in the VM of VA and ICA and CBFV between the two groups ($P>0.05$).

Conclusion: Pretreatment with a low dose of mannitol effectively reduced the incidence and severity of PONV in patients undergoing laparoscopic gynecological surgery by reducing the RI of the VA and ICA.

Trial registration: Chinese Clinical Trial Registry (ChiCTR-IPR-16007749, registered date: 12/01/2016.), http://www.chictr.org.cn

Background

The incidence of postoperative nausea and vomiting (PONV) is 30% in the general surgical population and as high as 80% in high risk cohorts[1]. The risk factors for PONV are female sex, history of PONV and/or motion sickness, non-smoking status, and use of postoperative opioids[2]. In addition, certain types of surgery may be associated with an increased risk of PONV including laparoscopic, bariatric, gynecological surgery, and cholecystectomy[3]. An estimated 80% of patients suffer from PONV after general anesthesia for gynecological laparoscopy surgeries during the first 24 hours in the absence of prophylactic antiemetic therapy[3, 4], which may reduce patient satisfaction and delay discharge from hospital. The Society for Ambulatory Anesthesia consensus guidelines recommend combination
antiemetic therapy in high-risk patients population and adoption of prophylactic strategies to reduce the baseline risk of PONV[3].

In order to improve the vision of the surgical field, CO₂ pneumoperitoneum and a concomitant head-down position (Trendelenburg position) are often applied to patients undergoing gynecological laparoscopy surgeries. While these positions offer significant surgical and technical advantages, they have the potential to significantly influence cerebral hemodynamic homeostasis. As evidenced in the literature, concomitant use of pneumoperitoneum and Trendelenburg position lead to an increase in intraabdominal pressure which may further provoke many systemic physiological alterations including a decrease in venous return and increase in cerebral blood flow and intracranial pressure (ICP)[5–7]. During laparoscopic gynaecological surgery, patients in the Trendelenburg position usually suffer from venous reflux in the brain, which may influence the incidence of PONV by increasing ICP and aggravating the cerebral oxygen metabolism imbalance. Mannitol is a long-established osmotic diuretic. It decreases ICP by decreasing the overall water content, cerebrospinal fluid volume, and blood volume[8, 9]. And mannitol improves cerebral perfusion, microcirculation, and hence, cerebral oxygenation by decreasing blood viscosity.

In the present study, we aimed to evaluate the effects of mannitol on the incidence and severity of PONV and assess its possible relevant mechanism. We hypothesis that low-dose mannitol could reduce PONV undergoing gynecological laparoscopic surgery patients.

**Methods**

**Declarations**

This study adheres to CONSORT guidelines.

**Participants selection**

This was a prospective, randomized, doubleblind study approved by the Medical Ethical Committee of The First Affiliated Hospital of Wannan Medical College, AnHui, Wuhu, China(no: [2015] 17) and registered at www.chictr.org (identifier: ChiCTR-IPR-16007749). Written and informed consent has been taken from all patients before enrollment.

Participant screening was performed the day before surgery. The inclusion criteria were: (1) scheduled for elective laparoscopic gynecological laparoscopy surgery;(2) age between 18 and 65 years old;(3) American Society of Anesthesiologists (ASA) physical status I or II;(4) with a body mass index (BMI) between 18–24 kg/m², (5) non-smoker. Patients who met any of the following criteria were excluded:(1) history of motion sickness or PONV,(2)vestibular dysfunction,(3)diabetes mellitus,(4)chronic obstructive pulmonary disease,(5)severe cardiovascular and cerebrovascular diseases,(6)gastrointestinal disease, (7)actively menstruating, and use of antiemetics or steroids within 24 h prior to surgery,(8)pregnant or breast-feeding patients,(9)liver and kidney dysfunction,(10)electrolyte disturbance,(11)preoperative
hemoglobin level less than 90 g/L,(12)internal cervical artery, vein and vertebral artery stenosis, malformation, or atherosclerotic plaque formation,(13)unforeseen adverse events, such as massive bleeding, drug allergy, or anesthesia accidents,(14)transferred to ICU after surgery,(15)ultrasound measurement data, or postoperative nausea and vomiting data collection failed.

Randomization and drug administration

Random numbers were generated by computer software in a 1:1 ratio. Fifty-three patients undergoing laparoscopic gynecologic surgery were randomly assigned to 2 groups, namely the mannitol group (Group M) and the control group (Group C). Study drugs were prepared according to the randomization results by a study coordinator who was blinded to the study period. Each of the Group M patients was initiated on a 0.5 g/kg of 20% mannitol infusion, 30 minutes before anesthesia induction. While for patients in the Group C, an equal volume of 0.9% normal saline was given at the same time. Patients and the anesthesia practitioners were blinded with the group allocation, and the investigator who analyzed the data was blinded to group assignment and was not involved in the postoperative assessments.

Anesthesia and perioperative care

Prior to the induction of anesthesia, routine monitoring included heart rate (HR), non-invasive arterial pressure (NIBP), electrocardiography, pulse oxygen saturation, and end-tidal carbon dioxide partial pressure (P_{ET}CO_{2}) were applied intraoperatively. Non-invasive mean arterial blood pressure (MAP) was recorded at 5 min intervals throughout the procedure.

General anesthesia was induced intravenously with 0.02 mg/kg midazolam, 2 mg/kg propofol, 0.5 µg/kg sufentanil, 0.6 mg/kg rocuronium was administered to facilitate laryngeal mask airway insertion. Total intravenous anesthesia was provided with propofol (6–8 mg/kg·h) and remifentanil (0.15–0.20 µg/kg·min) and intermittent rocuronium as needed. The NIBP and HR were adjusted within ± 20% from baseline values. P_{ET}CO_{2} was adjusted between 35 and 45 mmHg intraoperatively by changing tidal volume and respiratory rate. Carbon dioxide pneumoperitoneum of the two groups was established using an intra-abdominal pressure between 10-12 mmHg. The patients were in the Trendelenburg position (-30°) during the surgery. Ringer's lactate solution was infused during operation at a rate of 8 ml/kg/h. At the end of the surgery, all patients received continuous intravenous analgesia (2 µg/kg sufentanil and 100 mg flurbiprofen, total volume 100 mL, 3 mL/h) and were transported to the PACU.

Data collection

Data were collected by research personnel who were blinded to the randomization and not involved in the clinical care. Baseline characteristics of patients such as age, height, body weight, ASA class and preoperative hemoglobin level were recorded. Intra-operative parameters including cerebral hemodynamic and hemodynamic parameters, duration of surgery, total fluid administered, intraoperative blood loss, intraoperative urine output and type of surgery were collected. Postoperative data including presence and severity of nausea and vomiting.
Outcome measurements

The primary outcome was the incidence and severity of PONV over the first 24 h postoperative hours with the time of removal of the laryngeal mask airway defined as time 0. Patients who experienced at least one episode of nausea, vomiting or retching or any combination of these during the first 24 h after surgery were considered to have PONV. The score of nausea and vomiting is based on WHO’s grading standards for nausea and vomiting, nausea and vomiting are divided into I to IV grade. Grade I, no nausea or vomiting; Grade II, only nausea, no vomiting; Grade III, nausea and vomiting are obvious, but no gastric contents are vomited, and medical treatment is required; Grade IV, difficult to control sexual vomiting, vomiting of contents such as gastric juice and need for drug control. Patients of grade III or IV were given 8 mg of ondansetron intravenously.

The secondary outcomes included average resistance index (RI) and angle-corrected time-averaged flow velocity (TIMV) of the internal carotid arteries (ICA) and the vertebral arteries (VA) by using the Doppler (SonoScape S8, SonoScape Medical Corp, Shenzhen, Guangdong, China) and CBFV at each time point (Fig. 1). The average RI or TIMV of the VA and ICA were the average of the RI or TIMV of the left and right VA and ICA measured at the same time point. Measurements were thus performed at five timepoints: 5 min after laryngeal mask airway placement before pneumoperitoneum (T1: baseline); pneumoperitoneum started and the patient’s position changed (T2); 15 minutes after pneumoperitoneum with the position change (T3); pneumoperitoneum stopped with a position change (T4); 15 minutes after pneumoperitoneum had stopped (T5).

CBFV was calculated according to Albayrak[10]:

1) Cross-sectional area (A) = (D/2)²×π;
2) CBFV per unit area (FV) = TAMV × A × 60;
3) Total CBFV of the vertebral arteries = FV of the left vertebral artery + FV of the right vertebral artery;
4) Total CBFV of the internal carotid arteries = FV of the left internal carotid artery + FV of the right internal carotid artery;
5) CBFV = Total CBFV of the internal carotid arteries + total CBFV of the vertebral arteries.

Sample size calculation

The sample size was estimated based on the adverse reactions with a type I error of 0.05 and a power of 80% using PASS15.0.5. An estimated 80% of patients suffer from PONV after general anesthesia for gynecological laparoscopy surgeries during the first 24 hours in the absence of prophylactic antiemetic therapy[3]. Based on our pilot study, the incidence of PONV in gynecological laparoscopic surgery patients who received 0.5 g/kg mannitol 30 minutes before the induction of anesthesia was 35%, to allow for a possible dropout rate of 20%, a sample size of 20 patients in each group was necessary. we aimed to enroll 25 patients in each group.

Statistical Analysis

The normality of measurement data distribution was tested by the Shapiro-Wilk test. Measurement data of normal distribution (age, height, etc.) were presented as the mean ± standard deviation and were
analyzed by Student's t test. Measurement data of non-normal distribution were presented as the median (Q1, Q3) and analyzed by the Mann–Whitney U test. Categorical data were presented as percentage, and assessed by the Chi-square test (ASA class and incidence of PONV) or Mann–Whitney U test (type of surgery and the severity of PONV). Differences in the cerebral hemodynamic parameters and hemodynamic changes were compared by repeated-measures ANOVA. A $P$ value less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS software (version 16; SPSS, Chicago, IL, USA).

**Results**

**Demographic characteristics**

Among 53 patients eligible for this study and three patients were excluded from the analysis. Following this, one patient was excluded because ultrasound measurement data failed, and two patients were excluded because they were transitioned to open surgery. As a result, 50 patients completed the study: 25 in each group, a flowchart is shown in Fig. 2. There were no significant differences with regard to patient's baseline characteristics, intraoperative characteristics and the type of surgery between the two groups (Table 1).

**Incidence and severity of PONV**

The primary outcome was the incidence of PONV over the first 24 h postoperative hours, and we found that the incidence of PONV in group G (28.0%) was significantly lower than group C (56.0%) ($P = 0.045$), and the severity of PONV between the two groups was statistically different ($P = 0.040$) (Table 2).

**Hemodynamic and breath parameters**

There was no statistical difference in the data of HR, MAP and $P_{ET\text{CO}_2}$ between two groups at five corresponding time points ($p > 0.05$) (Table 3).

**The cerebral hemodynamic parameters changes**

There was no statistical difference in the average VM of VA and ICA between the two groups ($P > 0.05$). Compared with T1, the average VM of VA and ICA were increased in both groups at T2; The average VM of VA and ICA in the group G patients was significantly higher than T1 at T3 ($P < 0.05$). The average RI of VA and ICA were statistically different between the two groups ($P < 0.05$). Compared with T1, the average RI of VA and ICA were increased in both groups at T2 ~ T4; The average RI of VA and ICA in the group M were significantly lower than group C at T3 ~ T5 ($P < 0.05$). There was no statistical difference in CBFV between the two groups ($P > 0.05$). Compared with T1, the CBFV of the two groups was significantly increased at T2 and T3 ($P < 0.05$); The CBFV of group M patients was significantly higher than group C at T3 ($P < 0.05$) (Table 4).
Discussion

In this study, we evaluated the effect of low-dose mannitol on PONV in gynecological patients who underwent laparoscopic surgery in the first 24 h after surgery. The incidence and severity of PONV in laparoscopic gynecological surgery patients were lower when using intravenous mannitol, 30 minutes before the induction of anesthesia. There was no statistical difference in the average VM of VA and ICA and CBFV between the two groups. However, the average RI of VA and ICA were significantly different between the two groups.

PONV is an unpleasant experience and distressing adverse events after general anesthesia, especially in the first 24 h postoperatively[3]. Females undergoing laparoscopic gynecological surgery are particularly susceptible to PONV, with the reported incidence being as high as 70 ~ 85%[11]. Females have a more than two and half times greater risk of experiencing PONV than males[12, 13]. Based on these factors, we chose female patients who planned to undergo gynecological laparoscopic surgery under general anesthesia as our study subjects.

Recently, numerous studies have investigated the incidence of PONV in different patients undergoing different types of surgeries or anesthesia[14, 15]. Li et al [16] investigated the incidence of PONV in patients undergoing gynecological laparoscopic surgery, with a similar anesthesia management to our study. In their study, the incidence of PONV was 52.5% in the control group patients, followed by morphine alone for postoperative intravenous patient-controlled analgesia. In our study, the incidences of PONV were 56.0% (control group) (Table 2).

Carbon dioxide pneumoperitoneum and Trendelenburg position are the major contributors to elevated ICP during gynecological laparoscopic surgery[17, 18]. Among the many strategies available to reduce the ICP during surgery is mannitol administration[19]. The recommended mannitol dosage for ICP reduction is 0.25 ~ 1.0 g/kg [20]. The patients in the present study were administered 0.5 g/kg mannitol in 30 minutes before the induction of anesthesia. Mannitol induces diuresis and reduces the ICP within 15 ~ 30 min of its intravenous administration[21]. So, the volume of urine in group M during the surgery was significantly higher than groups C (Table 1). And the hemodynamic changes did not differ between the two groups (Table 3).

So far, no direct monitoring of cerebral blood flow is in routine clinical use. In the present study, we used ultrasound technology to observe the relevant parameters of VA and ICA and to calculate CBFV, trying to explore the mechanism of mannitol. The RI reflects the cerebral blood flow resistance, and RI value is proportional to cerebral blood flow resistance[22]. In addition, RI is closely related to ICP, RI increases with increasing of ICP. In this study, the average RI of VA and ICA in the group M were significantly lower than group C at T3 ~ T4 (Table 4). It shows that mannitol reduces cerebral circulation resistance through dehydration and diuresis, reduces ICP and then reduces PONV.

Mousa and colleagues[23] reported that administration of 0.5 g/kg mannitol during the pre-induction period was found to improve regional cerebral oxygen saturation in patients undergoing laparoscopic
surgery. CBFV is an important non-invasive index used to reflect the cerebral oxygen metabolic condition[24]. The results of this study shown that the CBFV of the two groups increased to different degrees at each time point. This result is consistent with that reported in a study by Schramm and colleagues[25], who reported that the effect of gravity under the Trendelenburg position could result in an increased reflux of the venous blood in the lower limbs, leading to increased cardiac output and CBFV. However, there was no statistical difference in CBFV and the average VM of VA and ICA between the two groups in the present study. The reason may be that when the MAP fluctuates in the range of 60 ~ 150 mmHg, the cerebrovascular keep the cerebral blood flow relatively stable through autoregulation.

The following limitations of our study must be considered. Firstly, the study subjects were limited only to healthy female with no additional risk of PONV. Our aim was to conduct research on relatively high PONV risk patients who were undergoing laparoscopic surgeries. Therefore, it is hard to generalize our findings to other type of surgeries and other different population. Secondly, we did not administer PONV prophylaxis. This was because we tried to investigate the baseline risk, which could have been masked by prophylactic antiemetics. Thirdly, we only measured the blood flow parameters of the extracranial VA and ICA, but did not observe the degree of venous drainage. This was because the veins are easy to collapse and ultrasound cannot obtain accurate data. The lastly, a more accurate estimation of the effects mannitol on cerebral hemodynamics would require the invasive measurement of ICP. However, owing to the lack of evidence supporting the use of invasive monitoring in patients undergoing elective laparoscopic procedures, the techniques was not performed.

Conclusions

In conclusion, 30 minutes before the induction of anesthesia, pretreatment with a low dose of mannitol effectively reduced the incidence and severity of PONV in patients undergoing laparoscopic gynecological surgery. Further, we shown that mannitol reduced the occurrence of PONV, mainly by decreasing the resistance index of the VA and ICA, without changing the cerebral artery blood flow. These results may be used as an alternative treatment to inhibit PONV.

Abbreviations

PONV: postoperative nausea and vomiting; ASA: American Society of Anesthesiologists; BMI: Body mass index; HR: Heart rate; MAP: Mean arterial pressure; SPSS: Statistical Product for Social Sciences; VA: vertebral artery; ICA: internal carotid artery; RI: resistance index; VAVM: angle-corrected time-averaged flow velocity of vertebral artery, ICAVM: angle-corrected time-averaged flow velocity of internal carotid artery; VARI: the average resistance index of vertebral arteries; ICARI: the average resistance index of internal carotid artery. CBFV: cerebral blood flow volume

Declarations
Acknowledgements
Not applicable.

Authors’ contributions
Study design and supervision: HXC, WJG. Data collection: GJL. Data analysis: HXC, JD. Drafting/writing paper: HXC. Revising manuscript: WJG. Final approval of manuscript: all authors.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The Ethics Committee of The First Affiliated Hospital of Wannan Medical College approved the study protocol (Number 2015–17). Written informed consent was obtained from each recruited parturient after providing them with adequate explanations regarding the aims of this study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Tables

Table 1 Clinical characteristics and intraoperative variables
|                           | Group C (n=25) | Group M (n=25) | $p$-value |
|---------------------------|---------------|----------------|-----------|
| Age (years)               | 41.56±8.54    | 40.16±11.59    | 0.629     |
| Height (cm)               | 161.00±4.34   | 161.12±3.99    | 0.919     |
| Body weight (kg)          | 56.72±5.04    | 57.14±4.89     | 0.766     |
| BMI (kg/m$^2$)            | 21.89±1.52    | 21.99±1.43     | 0.765     |
| Preoperative hemoglobin level (g/L) | 114.80±11.72 | 118.24±14.13  | 0.353     |
| Operation time (min)      | 89.40±36.27   | 87.80±38.71    | 0.881     |
| Administered fluid volume (ml) | 936.00±457.69 | 1000.00±453.69 | 0.622     |
| Intraoperative blood loss (ml) | 130.00±70.36 | 158.00±92.06  | 0.233     |
| Intraoperative urine output (ml) | 304.40±127.90 | 424.40±175.31 | 0.008*    |
| ASA class [n (%)]         |               |                | 0.564     |
| I                         | 11(44.0%)     | 9(36.0%)       |           |
| II                        | 14(56.0%)     | 16(64.0%)      |           |
| Type of surgery (n)       |               |                | 0.646     |
| oophorectomy              | 11            | 8              |           |
| Hysterectomy              | 12            | 17             |           |
| oophorectomy and Hysterectomy | 2            | 0              |           |

Values are expressed as the mean ± standard deviation or n (%).

*Significance difference in compared with group C ($P<0.05$).

Abbreviations: Group C, control group; Group M, mannitol group; BMI body mass index; ASA American Society of Anesthesiologists.

**Table 2** Comparison of overall postoperative nausea and vomiting outcomes
|                          | Group C (n=25) | Group M (n=25) | p-value |
|--------------------------|----------------|----------------|---------|
| Total 24 h PONV (n/%)    | 14(56.0)       | 7(28.0)        | 0.045*  |
| PONV classification      |                |                | 0.040*  |
| Grade I                  | 11(44.0)       | 18(72.0)       |         |
| Grade II                 | 5(20.0)        | 3(12.0)        |         |
| Grade III                | 5(20.0)        | 3(12.0)        |         |
| Grade IV                 | 4(16.0)        | 1(4.0)         |         |

Data are presented as n (%).

* Significance difference in compared with group C (P<0.05).

Abbreviations: Group C, control group; Group M, mannitol group; PONV postoperative nausea and vomiting.

Due to technical limitations, table 3 & 4 is only available as a download in the Supplemental Files section.