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Effects of Combined Oral Contraceptive on Hemodynamic Response to Endotracheal Intubation

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Abstract

Background: The modern day anesthesiologist should demonstrate and understand a fluctuation in a women's perception of pain in relation to phase of menstrual cycle. Combined oral contraceptive is used to prevent pregnancy, it contains a small amount of 2 female sex hormones, drospirenone, has an effect similar to the natural corpus luteum and ethinylestradiol, a hormone with an estrogenic effect. Pain threshold during follicular phase is higher than later phases and this may affect various anesthetic techniques.

Objectives: The present study was designed to evaluate the effects of contraceptive pills on hemodynamic response to endotracheal intubation.

Methods: We enrolled, 600 female patients scheduled for elective surgery divided to (Group I; n=300) with a history of family planning by combined oral contraceptive pills contain drospirenone 3 mg and ethinylestradiol 30 µ for at least one month. (Group II; n=300) with regular menstrual cycle on 8-12 days after the 1st day of the last menstrual cycle. Mean arterial blood pressure and heart rate was recorded for all patients, just before endotracheal intubation, 1, 2, 3 and 5 min after intubation. Epinephrine and norepinephrine as stress hormones in the blood were measured before induction of anesthesia and immediately after intubation.

Results: The study as regard MABP showed that, there was significant difference between groups before intubation, in one and two min after intubation. Meanwhile, MABP measured at 3 and 5 min after intubation showed no significant difference between both groups. While HR showed significant difference between both groups only at one and two min after intubation There was insignificant increase in group I when compared with group II in level of epinephrine in the blood before induction and significant increase in group I when compared with group II in norepinephrine in the same period. While immediately after intubation there was significant increase in group I when compared with group II in level of both epinephrine and norepinephrine. Also, there was significant increase in group I and group II immediately after intubation when compared with pre- induction value.

Conclusion: Pretreatment with combined oral contraceptives increases the pressor response to laryngoscopy and the intubation of the trachea.

Keywords: Combined oral contraceptive; Hemodynamic response; Endotracheal intubation

Introduction

Induction of anesthesia and tracheal intubation may cause profound alteration of the hemodynamic state of the patient consequent to both the effects of anesthetic drug administered perioperatively and the adrenergic state of the patient. Hemodynamic responses of direct laryngoscopy and endotracheal intubation lead to increasing blood pressure, heart rate and catecholamines levels [1].

The association between the surgery induced neuroendocrine and inflammatory response, anesthetic management and both short-and long-term outcomes is increasingly recognized by the anesthesia community. Surgical injury to tissue causes a variety of profound physiologic reactions which are essential to the restoration of homeostasis. The response involves a surge of stress hormones (i.e. C-reactive protein (CRP), cortisol, and catecholamines), activation of the complement system, migration of leukocytes to the site of injury, and the release of cytokines (e.g. interleukins, tumor necrosis factor) [2,3].

Differences in pain perception between men and women have been demonstrated in the experimental and epidemiological literature [1,4]. Biological sex differences, such as gonadal hormones may provide partial explanation. Pain sensitivity changes across menstrual cycle [4,5]. A pattern of reduced sensitivity to pain has been claimed to be present during follicular phase relative to the luteal phase [6-8] combined oral contraceptive pills contain drospirenone 3 mg and ethinylestradiol 30 µ [9]. Women receive pills since 2nd day of menstruation for 21 days. This study tried to investigate the effect of contraceptive pills on hemodynamic response to endotracheal intubation.

Patients and Methods

After approval of ethical hospital committee and written informed consent, 600 female patients with American Society of

Anesthesiologists Class I or II scheduled for elective surgery were included in this study. They randomly divided by closed envelope method into Group I, three hundred patients with a history of family planning by combined oral contraceptive pills contain drospirenone 3 mg and ethinylestradiol 30 μ for at least one month. Group II, three hundred female patients with regular menstrual cycle on 8-12 days after the 1st day of the last menstrual cycle and received empty pills. All patients range between 18-38 years old.

Exclusion criteria included, irregular cycle, pregnancy, receiving analgesia within 24 h, receiving any drugs affecting blood pressure or heart rate, expected difficult intubation, history of hysterectomy or oophorectomy and amenorrhea.

Preoperative investigation included liver function tests, kidney function tests, complete blood picture, fasting and postprandial blood sugar, coagulation profile and ECG.

20 gauge intravenous cannulae were inserted for all patients. They were premedicated with tab. ranitidine 150 mg night before surgery and tab ranitidine 150 mg orally 1 h prior to surgery. All patients were premedicated with 2 mg intravenous midazolam 5 min before induction of anesthesia.

General anesthesia was induced with 5 mg/kg thiopental sodium, then 0.5 mg/kg atricurim. After 2 min endotracheal intubation with 7 mm cuffed endotracheal tube was done by using a Macintosh 3 laryngoscope blade with an experienced intubator. Anesthesia was maintained by 2% isoflurane in 100% O_2 with controlled ventilation to maintain end tidal CO_2 between 35-40 mmHg. By using optimal level of inhalational anesthetic and by titration of opioids, the desired clinical effect can be obtained.

Mean arterial blood pressure and heart rate was recorded for all patients just before endotracheal intubation, 1, 2, 3 and 5 min after intubation. Monitoring included, non-invasive blood pressure, ECG, heart rate, pulse oximetry, capnography. If endotracheal intubation failed in the first trial of intubation within 60 s, this patient was excluded. The investigator who administered the drug, the anaesthesiologist who performed the injections and the patients were unaware of the group allocated and the drug that was received by the patient. After this, all measurements were made by another observer who was blinded to the patient group.

Measurements

We recorded for each patient his vital parameters including heart rate, mean systemic arterial blood pressure before induction of anesthesia, 1, 2, 3 and 5 min after intubation. Blood samples were taken from each patient for measurement of epinephrine and norepinephrine as stress hormones in the blood before induction of anesthesia and immediately after intubation.

First postoperative analgesic dose was 1 μg/kg intravenous fentanyl when VAS is 4 or more (visual analogue pain score (VAS) between 0 and 10{0=no pain, 10=most severe pain}), after that patient was assessed for pain relief every 10 min and increments of 0.5 μg /kg IV fentanyl was given until pain is relieved.

After that, the pain score was every 4 h in 24 h and fentanyl was given in a dose of 1 μg/kg when VAS is 4 or more. Any out breaking pain was treated with increments of fentanyl in a dose of 0.5 μg/kg. The total requirement of fentanyl was calculated in the both groups. Incidence of complications such as postoperative nausea and vomiting, or shivering was recorded.

Statistics

The full detailed form is: SPSS 20, IBM, Armonk, NY, United States of America. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (X^2) test of significance was used to compare proportions between two qualitative parameters.

Results

As regard demographic data, there was no significant difference between both groups; those data were recorded (Table 1). The study as regard MABP showed that, there was significant difference between groups before intubation, in one and two min after intubation.

Meanwhile, MABP measured at 3 and 5 min after intubation showed no significant difference between both groups. Also there was significant difference inside both groups at one and two min when compared with pre-induction values (Table 2).

While HR showed significant difference between both groups only at one and two min after intubation and significant difference inside both groups at 1 and 2 min when compared with pre-induction values (Table 3).

As regard (Table 4) there was significant increase in group I when compared with group II in the total postoperative analgesic dose (in 24 h). There is no significant difference between both groups in the incidence of postoperative complications in 24 h (Table 5).

There is an insignificant increase in group I when compared with group II in level of epinephrine in the blood before induction and significant increase in group I when compared with group II in norepinephrine in the same period (Tables 6 and 7).

While immediately after intubation there was significant increase in group I when compared with group II in level of both epinephrine and norepinephrine. Also, there was significant increase in group I and group II immediately after intubation when compared with pre-induction value.

	Group I (n=300)	Group II (n=300)	P value
Age (years)	33 ± 9	32 ± 9	0.174
Weight (Kg)	85 ± 7	86 ± 10	0.156
Time of tracheal intubation (Sec)	45 ± 8	46 ± 9	0.151

Table 1: Demographic data of the patients.

	Group I (n=300)	Group II (n=300)	P value
Before intubation	98 ± 12	95 ± 13	0.003*
1 min after intubation	124 ± 13 (0.001*)	92 ± 12 (0.003*)	0.001*
2 min after intubation	127 ± 14 (0.001*)	98 ± 12 (0.003*)	0.001*
3 min after intubation	96.5 ± 11 (0.111)	96 ± 13 (0.347)	0.111
5 min after intubation	96.2 ± 12 (0.067)	94.3 ± 12 (0.493)	0.053

Table 2: Changes in MABP (mmHg) of the patients.

	Group I (n=300)	Group II (n=300)	P value
Before intubation	80 ± 12	78.4 ± 11	0.089
1 min after intubation	120 ±17 (0.001*)	105 ± 16 (0.001*)	0.001*
2 min after intubation	117 ± 15 (0.001*)	104 ± 13 (0.001*)	0.001*
3 min after intubation	81.2 ± 17 (0.360)	79.6 ± 8 (0.127)	0.167
5 min after intubation	81.7 ± 11 (0.071)	80 ± 12 (0.089)	0.071

Table 3: Changes in HR (b/m) of the patients.

	Group I (n=300)	Group II (n=300)	P value
The total requirement of fentanyl in µg (in 24 h)	896.3 ± 124.1	857.4 ± 120.5	0.001*

Table 4: The total postoperative analgesic dose (in 24 h).

Side effect	Group I (n=300)	Group II (n=300)	P value
Shivering (%)	19 (6.3%)	17 (5.7%)	0.731
Nausea, vomiting (%)	37 (12.3%)	30 (10%)	0.364

Table 5: Incidence of postoperative complications (in 24 h) (%)

	Group I (n=300)	Group II (n=300)	P value
Before induction (%)	0.175 ± 0.118	0.165 ±.102	0.267
Immediately after intubation (%)	0.199 ± 0.112	0.182 ±.077	0.031*
P value	0.011*	0.022*	

Table 6: Level of epinephrine (nmol/L) in the blood before induction of anesthesia and immediately after intubation.

	Group I (n=300)	Group II (n=300)	P value
Before induction	1.109 ± 0.061	1.081 ± 0.041	0.001*
Immediately after intubation	1.209 ± 0.083	1.100 ± 0.042	0.001*
P value	0.001*	0.001*	

Table 7: Level of norepinephrine (nmol/L) in the blood before induction of anesthesia and immediately after intubation.

Discussion

Previous studies had demonstrated a fluctuation in a women's perception of pain in relation to phase of menstrual cycle [7]. Pain threshold during follicular phase is higher than later phases [7,8]. Sex hormones such as progesterone affect beta-endorphine and meta-enkephaline which are known to mediate response thresholds to aversive stimulation. For estrogen there are 2 peaks occurring on days 9-14 and 21-25 days of menstrual cycle [9]. For progesterone, only trace elements are present up to 15 days with peak values occurring during days 21-25 after 1st day of menstruation. Factors other than circulating levels of reproductive hormones could impact on women. For example, plasma noradrenaline levels show significant increase in luteal phase as compared to follicular phase [10]. It is conceivable that the higher luteal phase noradrenaline is causally related to the greater oestradiol levels, leading to partial inactivation by reducing tissue uptake or competitive suppression of catechol-O-methyl transferase [11]. Because of combined oral contraceptive contains a small amount of 2 female sex hormones, drospirenone, has an effect similar to the natural corpus luteum and ethinylestradiol, a hormone with an estrogenic effect, so higher catecholamine levels mainly noradrenaline occur among oral-contraceptive users and this explained our results where there was significant increase in group I when compared with group II in level of both epinephrine and norepinephrine immediately after intubation and significant increase in group I when compared with group II in level of norepinephrine only in pre-induction period.

There have been a few studies which have measured catecholamine levels after intubation. Our results are consistent with those of Russell et al. [12] and Shribman et al. [13] who reported significant elevations in serum levels of norepinephrine and epinephrine after laryngoscopy and tracheal intubation. Hassan and colleagues [14] concluded that during laryngoscopy and endotracheal intubation, putting the tube between the cords and inflating the cuff in the infraglottic area contributes significantly to sympathoadrenal response produced by supraglottic stimulation.

In this study, we have demonstrated significant increase in MABP at before intubation, 1st and 2nd min while HR at 1st and 2nd min just after tracheal intubation in group I as compared to group II. These effects are postulated to high level of female sex hormones. This study is the first study to investigate the effect of combined oral contraceptives on hemodynamic response to tracheal intubation. Large prospective epidemiologic studies have shown that long-term use of oral contraceptives holding estrogen cause an increase in blood pressure and intensely increase the risk of hypertension [15]. During treatment with estrogen progestogen oral contraceptive preparations, blood levels of angiotensin II measured by radioimmunoassay were raised to three times the normal value [16].

So, in our study, the high baseline of MABP in group one is explained by elevated serum angiotensin II. In the Collaborative Study of Stroke in Young Women, [17] hemorrhagic stroke may happen among oral-contraceptive users. The Royal College of General Practitioners' study also reported the relationship between hypertension and current oral-contraceptive use with esteem to hemorrhagic stroke [18].

The previous studies proved that pain threshold with the follicular phase are higher than luteal phase. Herren in 1933 study appears to be the 1st to examine the effect of menstrual cycle on perception of experimentally induced pain. Robinson and Short [19] concluded that women's breast sensitivity to pressure pain and touch was superior just after mid-cycle and later at menstruation.

Pfleeger et al. [20] investigated the relationships among menstrual cycle, blood pressure and ischemic pain sensitivity in women and revealed significant increase in pain tolerance and threshold in follicular phase.

In our study, blood pressure, HR, catecholamine levels and the total postoperative analgesic dose showed positive correlation with pain threshold in all phases. Kovac AL [21] and his colleagues concluded that menstrual cycle phases can affect rate pressure product (RPP) response to tracheal intubation. There was significant increase in RPP response to tracheal intubation in luteal phase as compared to follicular phase.

Conclusion

Pretreatment with combined oral contraceptives increases the pressor response to laryngoscopy and the intubation of the trachea.

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