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Original Article

Sex Differences in Conscious Sedation During Upper Gastrointestinal Panendoscopic Examination

*Yu-Hsuan Yen,[1] Tzu-Fu Lin,[1] Chen-Jung Lin,[1] Yi-Chia Lee,[2] Hon-Ping Lau,[1] Huei-Ming Yeh[1]**

Background/Purpose: Sex differences in response to noxious stimuli or analgesia have been demonstrated. We investigated sex differences in conscious sedation during upper gastrointestinal panendoscopic examination with regard to drug dose and entropy scores.

Methods: We investigated sex differences in 30 men and 30 women who were undergoing conscious sedation during upper gastrointestinal panendoscopic examination. The drug mixture was prepared as 5 mg midazolam plus 1 mg alfentanil diluted with normal saline to a volume of 10 mL. An initial injection of 4 mL was followed by an additional 1 mL every 1 minute, until the modified Observer Assessment of Alertness and Sedation (OAAS) rating scale was ≤ 3 when the panendoscope was inserted. Further injection was allowed thereafter. Entropy values, including state entropy (SE) and response entropy (RE), were monitored from baseline to full recovery.

Results: The volume of mixture needed to achieve an OAAS score of ≤ 3 was significantly lower in men than in women (4.4 ± 0.7 mL *vs.* 4.8 ± 0.8 mL, $p = 0.034$). The initial drug demand was not significantly influenced by age, body weight, or body height. The RE and SE values at the time of panendoscope insertion were not significantly different between men and women. The total volume for men was also significantly lower than that for women (5.7 ± 1.1 mL *vs.* 6.5 ± 1.4 mL, $p < 0.01$). The lowest RE and SE values during the procedure were not significantly different between men and women.

Conclusion: Women need more analgesic agents than men during panendoscopic examination. There was no significant difference between men and women with regard to anesthetic depth and response to noxious stimuli, as revealed by similar SE and RE values.

Key Words: entropy, panendoscopy, sedation, sex difference

Men and women are different in many aspects, including in the field of analgesia and anesthesia.[1] Men and women have different pain thresholds and responses to noxious stimulation. It has also been demonstrated that sex differences exist in pharmacokinetics and pharmacodynamics of anesthetic agents.[2–5] From a clinical perspective, these differences are of potential importance and might affect clinical practice. For patients who are undergoing upper gastrointestinal (UGI) panendoscopic

Departments of [1]Anaesthesiology and [2]Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan.

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***Correspondence to:** Dr Huei-Ming Yeh, Department of Anaesthesiology, National Taiwan University Hospital, 7 Chung Shan South Road, Taipei, Taiwan.
E-mail: e360038@yahoo.com.tw

examination, conscious sedation is increasingly used to reduce patient discomfort. Usually, short-acting medication is used because the panendoscopic examination can be accomplished within 30 minutes. However, sex difference has not been thoroughly investigated in this condition.

In the present study, we enrolled patients who were undergoing UGI panendoscopic examination who requested sedation and analgesia. We prospectively evaluated the sex differences in drug demand. We also used the entropy scores to monitor the patients' consciousness level. This is a newly developed electroencephalography-based monitoring method to evaluate consciousness. There are two components in the entropy measurement, namely state entropy (SE) and response entropy (RE). The SE value represents cortical state, whereas the RE value represents cortical state plus electromyographic signals.[6] Therefore, the RE score represents muscle contraction in response to pain stimulation.[7] We analyzed sex differences in SE/RE scores during the examination, as well as the factors that influenced drug demand.

Methods

The study protocol was approved by the Institutional Review Board of the National Taiwan University Hospital, and informed written consent was obtained from all patients. Sixty consecutive patients [30 male and 30 female; aged 16–65 years; American Society of Anesthesiologists (ASA) physical status class 1 or 2] scheduled for UGI panendoscopy who requested intravenous sedation were enrolled in this study. Those with known neurological disorders, chronic pain, history of psychological or analgesia drug use, chronic alcohol drinking, old age (> 65 years), and ASA class ≥ 3 were excluded.

No premedication was given before the examination. All patients were monitored with pulse oximetry, electrocardiography, and non-invasive blood pressure measurement. Nasal cannula with oxygen (5 L/min) was applied. After the skin of the forehead was carefully wiped with an alcohol swab and allowed to dry, the Entropy™ self-adhesive EEG electrode strips (ZipPrep; Aspect Medical Systems, Newton, MA, USA) were positioned on the forehead. The electrode was connected to an Entropy monitor (Datex-Ohmeda S5, Instrumentarium Corp., Helsinki, Finland). SE and RE were calculated by the spectral entropy plug-in module of the Datex-Ohmeda monitor.

The analgesic/sedative mixture was prepared as 5 mg midazolam and 1 mg alfentanil diluted with normal saline to a volume of 10 mL. The patient was injected intravenously with a 4-mL mixture as the loading dose. This regimen and dose were chosen according to past experiences in our hospital and previous survey in the literature.[8–10] An anesthesiologist measured the patient's response 2 minutes later using the modified Observer Assessment of Alertness and Sedation (OAAS) rating scale (Table 1).[10,11] If the patient was still alert 2 minutes after the injection, we injected the mixture in 1-mL amounts every minute until the OAAS score was ≤ 3, then the gastroenterologist

Table 1. Modified Observer Assessment of Alertness and Sedation scale and the distribution of scores after initial injection in men and women

Response and score	Women	Men
5: Responds readily to name spoken in normal tone	4	2
4: Lethargic response to name spoken in normal tone	15	8
3: Responds only after name is called loudly or repeatedly	7	10
2: Responds only after mild prodding or shaking	3	7
1: Does not respond to mild prodding or shaking	1	3
0: Does not respond to noxious stimuli	0	0
Total number	30	30

The average score was significantly higher in women than in men (3.6 ± 1.0 vs. 3.0 ± 1.1, p = 0.021).

began to insert the endoscope. An OAAS ≤ 3 was chosen according to ASA guidelines in sedation. Entropy scores (including SE and RE) were recorded from baseline to full recovery of the patient. Baseline scores, scores at endoscope insertion, scores after insertion, and the lowest scores (representing the deepest level of anesthesia) were compared between men and women. During the whole procedure, the hemodynamic status and noxious response (e.g. hand movement, grimace, and moaning) were recorded by an independent anesthesiologist who was blinded to the entropy score. Extra doses of the drug mixture were allowed if necessary, as judged by the above patient responses. Arterial oxygen saturation (SaO_2) was monitored throughout the procedure. Severe hypoxia was defined as $SaO_2 < 90\%$, which should be managed by positive pressure ventilation with a face mask, oxygen, and placement of an artificial airway.

All data were expressed as mean ± standard deviation or mean (range). Comparisons of drug demands and baseline characteristics between men and women were made using Student's *t* test. For comparison between drug demand and age, body weight, body height, procedure time, entropy scores and baseline heart rate, linear regression was used and R^2 and *p* values were reported. We also performed power analysis to calculate the number of patients needed to show a sex difference. With an α-value of 0.05, a β-value of 0.8 to detect a difference of 0.5 mL with an estimated standard deviation of 0.6 mL, the total case number needed was 54 (27 in each group). The statistical calculations were performed using SPSS version 11.0 (SPSS Inc., Chicago, IL, USA). A p value < 0.05 was considered significant.

Results

Table 2 shows the baseline characteristics of the patients. Body weight and body height were significantly greater in men than in women, but the age and ASA physical status were not significantly different. The hemodynamic parameters were not significantly different between men and women, except for heart rate (Table 3). The time from drug administration to endoscope withdrawal was not significantly different between men and women (11.2 ± 2.2 minutes *vs.* 11.5 ± 3.0 minutes). There were one man and one woman who were undergoing gastric biopsy during the procedure. During the UGI panendoscopic examination, no marked hypoxemia with $SaO_2 < 90\%$ or hypotension was noted. No patient suffered from delayed recovery.

After the initial 4-mL injection, the percentages of OAAS score ≤ 3 were 67% (20/30) in men and 37% (11/30) in women. The percentage differed significantly between men and women ($p = 0.03$ by χ^2 test). The distribution of OAAS score after the first injection is shown in Table 1. The OAAS score was significantly higher in women than in men (3.6 ± 1.0 *vs.* 3.0 ± 1.1, $p = 0.021$). The volume of the mixture needed to achieve an OAAS

Table 2. Baseline characteristics of study patients

	Men ($n = 30$)	Women ($n = 30$)	*p*
Age (yr)	49.6 (34–64)	46.9 (30–65)	0.22
Weight (kg)	80.0 ± 12	57.4 ± 7.8	< 0.05
Height (cm)	171 ± 5.6	161 ± 6.4	< 0.05
ASA class (1/2)	19/11	20/10	0.79

ASA = American Society of Anesthesiologists.

Table 3. Baseline hemodynamic parameters and drug demands during the examination in men and women

	Men ($n = 30$)	Women ($n = 30$)	*p*
Blood pressure (mmHg)	127 ± 18/82 ± 14	125 ± 19/74 ± 13	0.72/0.23
Heart rate (beats/min)	88 ± 18	98 ± 21	< 0.05
O_2 saturation (%)	99.7 ± 0.7	99.0 ± 0.2	0.49
Drug demand at insertion (mL)	4.4 ± 0.7	4.8 ± 0.8	< 0.03
Total drug demand (mL)	5.7 ± 1.1	6.5 ± 1.4	< 0.01

score ≤ 3 in men was 4.4 ± 0.7 mL, which was significantly lower than 4.8 ± 0.8 mL in women ($p = 0.034$). The total volume in men was 5.7 ± 1.1 mL, which was also significantly lower than 6.2 ± 1.4 mL in women ($p = 0.01$). The percentages of further injection during endoscope insertion were 90% (27/30) in men and 87% (26/30) in women, and the amount of further injection was 1.3 mL and 1.7 mL, respectively. The body weight was significantly smaller in women than in men, therefore, the differences in drug dose were even larger if expressed as mL/kg body weight. We also analyzed the influence of other clinical parameters on drug demand. Table 4 shows that the volume of mixture needed to achieve an OAAS score ≤ 3 was not significantly influenced by age, body weight, body height, or procedure time. There was also no significant correlation between the volume and the RE and SE scores at the time of endoscope insertion or at the nadir point. Similar findings were observed for the total mixture volume, except that there was a significant negative correlation between age and total volume. Women and men had significantly different baseline heart rate; therefore, we also analyzed the relationship between baseline heart rate and drug demand in both groups. With linear regression, R^2 was 0.002, 0.064, and 0.019 and p was 0.759, 0.176, and 0.463 for all subjects, men and women respectively. This indicated that baseline heart rate had no significant influence on drug demand.

Table 5 shows the entropy scores during the examination in both sexes. Baseline entropy scores, RE and SE, were not significantly different between men and women, and neither were the entropy values when patients' conditions were deemed appropriate for endoscope insertion (OAAS score ≤ 3), and the values recorded throughout the examination. The lowest values of RE and SE during the examination did not differ significantly

Table 4. Univariate results of the influence of clinical parameters and entropy scores on drug demand

	Drug demand at insertion		Total drug demand	
	p	R^2	*p*	R^2
Sex	0.034*	–	0.010*	–
Body weight	0.362	0.014	0.212	0.027
Body height	0.118	0.042	0.099	0.046
Age	0.135	0.038	0.013*	0.102
Procedure time	0.457	0.010	0.625	0.004
SE at insertion	0.500	0.008	0.361	0.014
RE at insertion	0.578	0.005	0.447	0.010
Lowest SE	0.514	0.007	0.980	0.000
Lowest RE	0.771	0.001	0.937	0.000

**p < 0.05. R = correlation coefficient; SE = state entropy; RE = response entropy.*

Table 5. Entropy scores during the examination

	Men ($n = 30$)	Women ($n = 30$)	*p*
Entropy baseline			
RE	97.9 ± 1.8	97.6 ± 1.5	0.532
SE	88.9 ± 1.2	88.9 ± 1.6	0.854
Entropy (OAAS score ≤ 3)			
RE	92.2 ± 2.9	92.5 ± 3.2	0.675
SE	83.6 ± 2.0	84.3 ± 1.9	0.148
Entropy (after endoscope insertion)			
RE	93.1 ± 2.8	93.5 ± 3.1	0.608
SE	84.6 ± 2.3	85.2 ± 2.1	0.296
Entropy (lowest value during the examination)			
RE	84.5 ± 4.8	86.7 ± 4.0	0.064
SE	77.5 ± 4.5	78.7 ± 2.9	0.225

OAAS = Observer Assessment of Alertness and Sedation scale; RE = response entropy; SE = state entropy.

between men (RE 84.5 ± 4.8, SE 77.5 ± 4.5) and women (RE 86.7 ± 4.0, SE 78.7 ± 2.9).

Discussion

In animal or human studies, sex difference in response to noxious stimuli or analgesia agents has been demonstrated, although some controversies still exist. Chia et al have found that men are more susceptible to postoperative pain upon movement and require more morphine by patient-controlled analgesia than women during the first three postoperative days.[5] However, to the contrary, we found that women needed more analgesic agent than men (4.8 ± 0.8 mL *vs.* 4.4 ± 0.7 mL) to achieve an optimal sedative status during UGI panendoscopic examination. We also demonstrated that > 60% of women needed an additional injection after the initial injection before endoscope insertion. A higher initial dose can be considered for woman. The contradictory findings can be attributed to several possible reasons. First, the duration of painful stimuli was different (minutes *vs.* hours or days), and this could have influenced the drug demand. Second, the operative methods and sites of stimulation were not identical. Finally, the pharmacokinetic properties might have been different for morphine and midazolam/alfentanil, whose volume of distribution is higher in women than in men.[12] All the above reasons might have contributed to a lower dose requirement in men.

In our study, we used a mixture of midazolam (5 mg) and alfentanil (1 mg) as the anesthetic agents. Analgesic effect was dominant in this regimen because there was a synergistic effect and the dosage of midazolam was low. This formula was suitable for titrating the dose without causing respiratory depression or unfavorable hemodynamic status. We defined an OAAS score ≤ 3 as the ideal point for inserting the endoscope. Usually, the gastroenterologist could insert the endoscope without difficulty. The lowest RE/SE values during the examination were 84.5 ± 4.8/77.5 ± 4.5 in men and 86.7 ± 4.0/78.7 ± 2.9 in women. We found that the optimal SE value ranged from 70 to 80 during UGI panendoscopic examination when midazolam and alfentanil were used.

Bispectral index has been used to evaluate sedative level during surgery or procedural sedation, with good correlation with clinical observation.[13,14] Its usefulness has been confirmed in UGI panendoscopic examination.[15] However, it has poor correlation with analgesic effect.[11] Entropy has been newly developed to monitor patients' consciousness and has been demonstrated to be as effective as bispectral index in clinical practice.[16,17] Furthermore, there are two components in entropy measurement. SE and RE were both recorded to represent cortical state and cortical state plus electromyographic signal, respectively.[6] The RE score therefore represents muscle contraction in response to noxious stimulation. During noxious stimuli, there is an increase in RE value alone, or an increase in the difference between SE and RE.[7,18] We found that SE and RE scores were not significantly different between men and women. This suggests that there was no significant difference between men and women with regard to anesthetic depth and response to noxious stimuli.

The patients were divided according to sex; therefore, it was not feasible to blind the study during patient evaluation. Also, it was not feasible to randomize the patients. There could have been bias because this was not a randomized double-blind study. Serum drug concentrations were not measured in this study, and we could not tell whether the difference was due to pharmacodynamics or pharmacokinetics. Patient satisfaction score was not measured. An initial 4-mL of mixture was given as the loading dose. It is possible that some patients might need < 4 mL to achieve an OAAS score of ≤ 3. Therefore, the exact volume might have been overestimated. However, the overestimation occurred in both groups and we still demonstrated that women needed more additional doses than men.

In conclusion, we found that women needed a higher dose of analgesic agents than men during UGI panendoscopic examination, whereas

there was no significant difference between men and women with regard to anesthetic depth and response to noxious stimuli, as revealed by similar RE and SE values.

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