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Original Article / Özgün Araştırma

Effects of Premedication on Heart Rate Variability at Induction of Anaesthesia: Comparison between Midazolam and Hydroxyzine

Premedikasyonun Anestezi İndüksiyonunda Kalp Atım Hızı Değişkenliği Üzerindeki Etkileri: Midazolam ve Hidroksizinin Karşılaştırılması

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Abstract / Öz

Objective: The present study was performed to compare the effects of midazolam premedication, which is useful for its anti-anxiety and amnesic effects, with antihistamine hydroxyzine on cardiac sympathetic and parasympathetic activities using heart rate variability (HRV) at induction of anaesthesia.

Methods: Eighty patients aged 40-60 years, with an American Society of Anaesthesiologists (ASA) physical status of I or II and undergoing general anaesthesia for neck and body surface surgery were randomised equally into midazolam and hydroxyzine groups. As a premedication, midazolam 0.06 mg kg^{-1} with atropine 0.5 mg (midazolam group) or hydroxyzine 1 mg kg^{-1} with atropine 0.5 mg (hydroxyzine group) were intramuscularly administered 15 min and 30 min before anaesthesia induction, respectively. Anaesthesia was induced with midazolam 0.1 mg kg^{-1} and thiopental 3 mg kg^{-1}. Oro-tracheal intubation was facilitated with vecuronium 0.15 mg kg^{-1}. Blood pressure, heart rate and HRV were measured at predetermined time points for 10 min after intubation.

Results: Systolic blood pressure and heart rate significantly increased after intubation in both groups and the increase was greater in the hydroxyzine group. The high frequency (HF) component decreased significantly in both groups, and no difference was found between the two groups. The low frequency component/HF ratio significantly increased in the hydroxyzine group but did not change in the midazolam group.

Conclusion: Midazolam but not hydroxyzine premedication inhibited sympathetic activation at induction of anaesthesia.

Keywords: Premedication, anaesthesia induction, heart rate variability, midazolam, hydroxyzine

Amaç: Bu çalışma, anksiyolitik ve amnezik etkilerinden dolayı faydalı olan midazolam premedikasyonunun ve antihistamin hidroksizinin anestezi indüksiyonu sırasındaki kardiyak sempatik ve parasempatik aktiviteler üzerindeki etkilerini, kalp atım hızı değişkenliği (HRV) kullanarak karşılaştırmak için yapılmıştır.

Yöntemler: Yaşları 40 ile 60 arasında değişen, Amerikan Anesteziyologlar Derneği (ASA: American Society of Anaesthesiologists) fiziksel durumu I veya II olarak sınıflandırılan ve boyun ve vücut yüzeyi ameliyatı için genel anestezi uygulanan 80 hasta, midazolam ve hidroksizin gruplarına eşit olarak randomize edildi. Premedikasyon olarak 0,5 mg atropin ile 0,06 mg kg^{-1} midazolam (midazolam grubu) veya 0,5 mg atropin ile 1 mg kg^{-1} hidroksizin (hidroksizin grubu) sırasıyla anestezi indüksiyonundan 15 dakika ve 30 dakika önce intramusküler olarak uyglandı Midazolam 0,1 mg kg^{-1} ve tiyopental 3 mg kg^{-1} ile anestezi başlatıldı. Vekuronyum 0,15 mg kg^{-1} oro-trakeal intübasyonu kolaylaştırdı. İntübasyon sonrası 10 dakika boyunca önceden belirlenen sürelerde kan basıncı, kalp atım hızı ve HRV ölçüldü.

Bulgular: Her iki grupta da intübasyon sonrasında sistolik kan basıncı ve kalp atım hızında anlamlı bir artış gözlendi ve hidroksizin grubundaki artış daha fazla bulundu. Iki grupta da yüksek frekans (HF) ögesi anlamlı şekilde düştü ve gruplar arasında istatiksel olarak anlamlı bir fark izlenmedi. Düşük frekans ögesi/HF oranı hidroksizin grubunda anlamlı derecede yükseldi, ancak midazolam grubunda değişmedi.

Sonuç: Midazolam premedikasyonu anestezi indüksiyonunda sempatik aktivasyonu inhibe ederken hidroksizin bu etkiyi göstermedi.

Anahtar Kelimeler: Premedikasyon, anestezi indüksiyonu, kalp atım hızı değişkenliği, midazolam, hidroksizin

Introduction

Premedication before anaesthesia has not been used in recent years. However, sometimes patients become agitated and have transient hypertension or arrhythmia before the induction of anaesthesia. An imbalance of cardiac sympathetic and parasympathetic activity might be one of the causes of these hemodynamic changes and can be harmful in some patients, i.e. those with cardiac disease, hypertension, or the elderly (1). In some cases, surgery should be postponed if excessive hypertension or arrhythmia is noted before the induction of anaesthesia.

Midazolam premedication decreases preoperative anxiety and stress (2) and postoperative nausea and vomiting (3), potentiates thiopental induction (4) and enhances postoperative analgesia (5). Therefore, midazolam premedication is beneficial.

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Hydroxyzine is an H1 histamine inhibitor, which blocks allergic reaction and induces slight sedation and anti-anxiety; thus, it had previously been used as a premedication (6).

Heart rate variability (HRV) is a well-known non-invasive method to measure the balance of cardiac sympathetic and parasympathetic activities and has been used in many studies (7). A low frequency (LF) component (0.04-0.15 Hz) indicates cardiac sympathetic and parasympathetic activities, and a high frequency (HF) component (0.15-0.4 Hz) shows cardiac parasympathetic activity; therefore, LF/HF indicates cardiac sympathetic activity.

Induction of anaesthesia induces hemodynamic changes and a combination of midazolam and barbiturate is useful to decrease hemodynamic changes at induction, as shown in our previous study (8). We hypothesised that midazolam premedication further decreases hemodynamic change through midazolam-barbiturate-induced anaesthesia. The present study was performed to compare the effects of midazolam with hydroxyzine and midazolam with barbiturate premedications at induction of anaesthesia on cardiac sympathetic and parasympathetic activities using HRV.

Methods

After the approval of the research committee of the hospital and obtaining informed consent, 80 patients aged 40-60 years, with an American Society of Anaesthesiologists (ASA) physical status of I or II and undergoing general anaesthesia for neck and body surface surgery, were equally randomised into midazolam and hydroxyzine groups using an envelope method. Patients cardiac, respiratory, liver, renal, or brain disease; were obese (body mass index >30) or allergic to the agents of the study or any sedatives as habits before surgery were excluded.

As a premedication, midazolam 0.06 mg kg^{-1} with atropine 0.5 mg (midazolam group) for 15 min before anaesthesia induction or hydroxyzine 1 mg kg^{-1} with atropine 0.5 mg (hydroxyzine group) 30 min before anaesthesia induction were intramuscularly administered in the ward according to the routine procedure. After 100% oxygen inhalation for a few minutes, anaesthesia was induced with midazolam 0.1 mg kg^{-1} and thiopental 3 mg kg^{-1}. Oro-tracheal intubation was facilitated with vecuronium 0.15 mg kg^{-1}. Anaesthesia was maintained with sevoflurane 1%-2 % with nitrous oxide in 50% oxygen for 10 min after intubation; thereafter, fentanyl was added to sevoflurane and nitrous oxide.

Blood pressure was measured intermittently and heart rate and HRV were monitored continuously before induction, before intubation and at 1, 3, 5 and 10 min after intubation. HRV was measured using LRR-03™ (GMS, Tokyo, Japan) and analysed using the Mem Calc™ (Suwa Trust, Tokyo, Japan) software.

Power analysis was performed to detect the inter-group differences of LF and LF/HF with power of 0.95 and effect size of 0.25 using the G Power™ software (University Mannheim, Germany).

Statistical analysis

Data were shown as mean ± standard deviation or number of the patients. Statistical analysis was performed using factorial analysis of variance (ANOVA) and Chi-square test for demographic data and repeated measures ANOVA followed by a Student-Newman-Keuls test for measured parameters (StatView-J 5.0). A p value <0.05 was considered statistically significant.

Results

Power analysis indicated that 78 patients were necessary and hence 80 patients were enrolled. Demographic data were not different between the groups (Table 1).

Systolic blood pressure and heart rate significantly increased after intubation in both groups, and the increase was significantly greater in the hydroxyzine group (Figures 1 and 2). The HF decreased significantly in both groups, and no difference was found between the two groups (Figure 3). LF/HF significantly increased in the hydroxyzine group but did not change in the midazolam group (Figure 4).

Discussion

The results show that premedication with midazolam reduced the increase in blood pressure, heart rate and LF/HF caused by intubation after induction with midazolam and thiopental compared to hydroxyzine.

We used intramuscular midazolam 0.06 mg kg^{-1} for 15 min before anaesthesia or hydroxyzine 1 mg kg^{-1} for 30 min before anaesthesia, both with atropine. In the previous studies, for patients aged 40 to 60 years, midazolam 0.06 mg kg^{-1} was the choice for intramuscular premedication with atropine (9), and intramuscular premedication with midazolam should be administered 15 min before entering the operation room (10). Therefore, we used this protocol of midazolam. As for hydroxyzine, there are no studies showing the optimal dose and time of hydroxyzine premedication; hence, we followed the routine clinical practice in our country. Atropine was also added as our routine practice to decrease adverse reaction, such as increased secretion or vagal reflex by intubation.

Table 1. Demographic data

	Midazolam	Hydroxyzine
Age (years)	56±4	53±6
Gender (male/female)	18/22	15/25
Height (cm)	158 ± 10	161 ± 9
Body weight (kg)	55 ± 11	57 ± 10
Surgery		
Mastectomy	14	18
Thyroidectomy	12	14
Resection of parotid gland	14	8
Duration of surgery (min)	128±36	137±41

Mean ± standard deviation

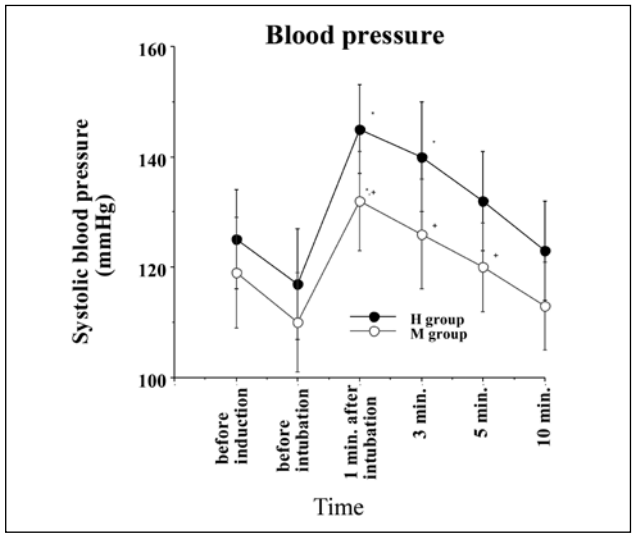

Figure 1. Blood pressure changes at predetermined time points
*p<0.05 vs. the value before induction, +p<0.05 vs. H group. H: hydroxyzine; M: midazolam; bars show standard deviation

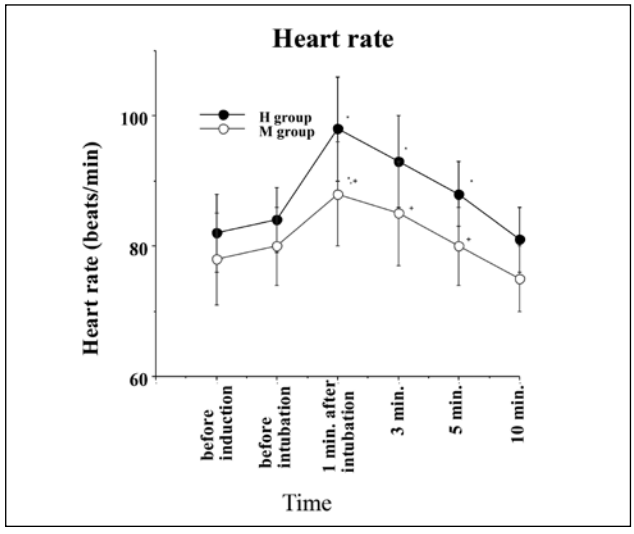

Figure 2. Heart rate changes at predetermined time points
*p<0.05 vs. the value before induction, +p<0.05 vs. H group. H: hydroxyzine; M: midazolam; bars show standard deviation

We induced anaesthesia with midazolam 0.1 mg kg^{-1} and thiopental 3 mg kg^{-1} without any opioids because opioids had stronger effects on sympathetic and parasympathetic activities compared to midazolam and hydroxyzine, which may obscure the difference of the effects of midazolam and hydroxyzine. In addition, we have shown that midazolam 0.1 mg kg^{-1} and thiamylal 2.8 mg kg^{-1} were the best combination doses at induction of anaesthesia (11). Therefore, we used the present combination. Induction of anaesthesia with barbiturate decreased HF and the total power and increased LF/HF (12, 13). The addition of midazolam to barbiturate induction decreased these changes (14). The hydroxyzine group in the present study showed changes in HRV similar to those in our previous study (14) but the midazolam group inhibited LF/HF increase.

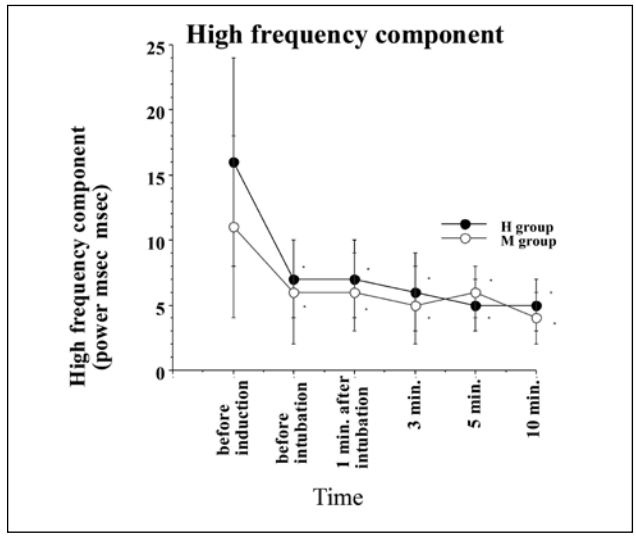

Figure 3. High frequency component changes at predetermined time points
*p<0.05 vs. the value before induction. H: hydroxyzine; M: midazolam; bars show standard deviation

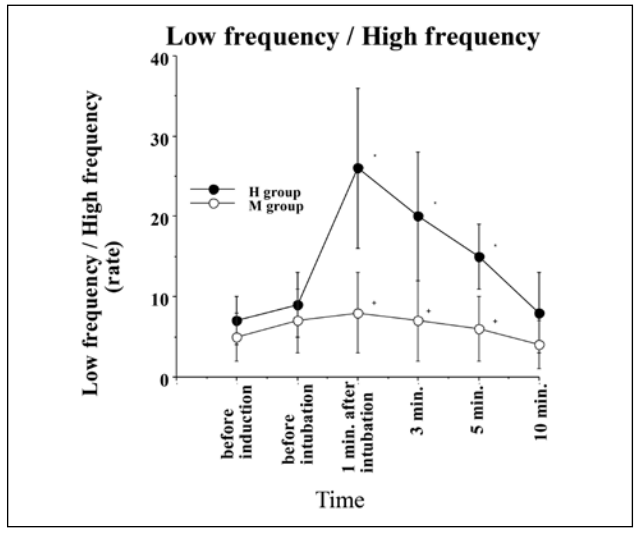

Figure 4. HF/LF component changes at predetermined time points
*p<0.05 vs. the value before induction, +p<0.05 vs. H group. H: hydroxyzine; M: midazolam; HF: high frequency; LF: low frequency; bars show standard deviation

There are some other studies reporting the effects of midazolam premedication on hypnotic drug dose requirements. The anaesthetic dose of thiopental decreased to one-half after premedication with midazolam 0.1 mg kg^{-1} (15). Kissin et al. (16) showed reduction of hypnotic dose of thiopental to two-thirds after premedication with midazolam 0.02 mg kg^{-1}. Barbiturates and benzodiazepines interact through their effects on the γ-amino butyric acid (GABA) receptor; barbiturates allosterically enhance benzodiazepine binding to the $GABA_A$ receptor (17). However, there are no studies of the effects of midazolam premedication on the induction with midazolam and barbiturate. Midazolam decreases peripheral vascular resistance, thereby reducing the raised blood pressure (18). Therefore, in the present study, blood pressure decreased by midazolam premedication.

Some controversies exist about the effects of midazolam on HRV. Midazolam 0.1 mg kg^{-1} decreased HF by vagolytic effect (19), while Komatsu et al. (20) reported that midazolam 0.3 mg kg^{-1} decreased LF and increased HF showing sympathetic depression. Midazolam induces parasympathetic dominance at very high doses (20) but sympathetic dominance at low doses (19). According to Michaloudis et al. (21), intramuscular midazolam 0.08 mg kg^{-1} decreased LF and HF for 30 min and subsequently restored, and LF/HF did not change. Ikeda et al. (22) showed midazolam premedication increased LF and LF/HF and decreased HF. There are no studies on the changes in HRV by hydroxyzine. In the present study, HF decreased similarly between the midazolam and hydroxyzine groups but LF/HF increased in the hydroxyzine group, while it did not change in the midazolam group. LF/HF increased when patients arrived at the operating room, which was reduced by midazolam premedication as shown by Ikeda et al. (22). These suggest that sympathetic activation at induction of anaesthesia was inhibited by midazolam premedication but not by hydroxyzine.

Conclusion

Midazolam, but not hydroxyzine premedication, inhibited sympathetic activation at induction of anaesthesia with midazolam and thiopental.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Kamakura Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

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Hasta Onamı: Yazılı hasta onamı bu çalışmaya katılan hastalardan alınmıştır.

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