Nitrous oxide inhalation for transoesophageal echocardiography: an alternative to benzodiazepine sedation?

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Aims Transoesophageal echocardiography (TEE) is usually performed using benzodiazepine sedation, which is a limiting factor for elderly patients or those with respiratory insufficiency. Kalinox®, an equimolar mixture of nitrous oxide and oxygen, with no depressive respiratory action and fast reversible effects, seems ideally suited for performing TEE but has never been evaluated. The aim of the present study was to evaluate the TEE feasibility and efficiency using Kalinox compared with the standard care using benzodiazepine.

Methods and results We prospectively enrolled 80 consecutive patients referred for TEE. In the 35 first patients, TEE was performed using intravenous benzodiazepine (Midazolam) and in the 45 last patients using Kalinox (nasal delivery). Pain and tolerance induced by the examination were evaluated on a 0–10 scale. Remembrance of the examination by the patient and quality of the TEE by the operator were also evaluated. All TEEs were performed by the same experienced operator. TEE duration was not different (6 ± 3 vs. 7 ± 4min, respectively, \( P = 0.57 \)). Patients in the Kalinox group felt TEE to be more difficult (\( P = 0.005 \)) and remembered the procedure more clearly (\( P < 0.0001 \)) but pain experience was not different (7 vs. 9% had a pain score \( \geq 5 \), respectively, \( P = 0.75 \)). Percentage of patients who agreed to have a second TEE if necessary was slightly lower (77 vs. 94%, respectively, \( P = 0.04 \)). The operator judged TEE quality satisfactory in similar proportions (76 vs. 68%, respectively, \( P = 0.44 \)).

Conclusion These preliminary results show that TEE using Kalinox is feasible, provides similar pain relief despite more discomfort for the patient, and acceptable conditions for the operator. Thus, Kalinox use could be considered as an alternative to benzodiazepine sedation for patients intolerant to benzodiazepines such as elderly or respiratory-insufficient patients.

KEYWORDS Nitrous oxide; Sedation; Transoesophageal echocardiography

Introduction

Transoesophageal echocardiography (TEE) is widely used all over the world for cardiovascular evaluation. It can be painful and uncomfortable and because of rare, but serious esophageal complications, TEE is considered as a semi-invasive investigation. It is usually performed using xylocaïn local anaesthesia and intravenous benzodiazepines (midazolam) sedation in order to optimize TEE tolerance and quality for the operator.\(^1\) However, potential respiratory depression and prolonged recovery time induced by benzodiazepines\(^2\) are major limitations of this technique, especially in elderly patients or those with respiratory insufficiency. Moreover, benzodiazepine sedation requires several hours of monitoring. Therefore, a simple and safe alternative to benzodiazepines sedation, which allows to perform TEE in both successful and comfortable conditions is desirable.

Kalinox®, an equimolar mix of oxygen (\( O_2 \)) and nitrous oxide (\( N_2O \)), has few contraindications and few adverse events.\(^3\) Its safety and analgesic effectiveness has been widely demonstrated in emergency units, in pediatric department,\(^4\) for invasive investigations such as digestive endoscopy\(^5\) or bronchoscopy, or biopsies of the prostate.\(^6\) It can be self-administrated through a mask, has a rapid onset of action and a short recovery time after discontinuation. Thus, Kalinox seems attractive for performing TEE but has never been evaluated in this indication. The aim of the present study was to evaluate the feasibility,
tolerance, and effectiveness of TEE using Kalinox compared with standard sedation using benzodiazepine.

Methods

Study design

All patients referred to our institution for TEE to the last author (D.M.Z.) were potential candidate for the present study. Exclusion criteria were age <18 years, contraindication to benzodiazepine or nitrous oxide including pregnancy. Eighty consecutive patients were prospectively enrolled. TEE was performed using intravenous benzodiazepine sedation (Midazolam) in the 35 first patients and using nasal delivery of Kalinox in the 45 last patients. In both groups, a local anaesthesia using lidocaine was first performed. Patients were monitored during and after TEE as usual.

Kalinox was administrated using a nasal mask connected to a one-way delivery circuit, allowing oral introduction of the transducer after a 4–6 min induction period. Midazolam dose was chosen by one-way delivery circuit, allowing oral introduction of the transducer.

Evaluation of TEE performances

After completing TEE and waiting for a normal recovery conscious state, patients were asked to answer the following questions:

(i) How painful was the TEE? (0–10 scale: 0, no pain; 10, very painful)
(ii) How did you tolerate the TEE? (0–10 scale: 0, extremely well; 10, extremely bad)
(iii) Would you agree to perform another TEE if necessary? (Yes or no)
(iv) Do you have any remembrance of the examination? (Yes or no)

A score ≥5 defined a painful or poorly tolerated TEE.

Quality of the TEE examination by the operator was scored on a 0–5 scale (0 for poor TEE quality and 5 for very good TEE quality allowing to obtain all desired information). TEE duration was also systematically recorded.

Statistics

Results were expressed as mean ± SD or percentage. Group comparisons were performed with y2 or t-test as appropriate using JMP® software. A P < 0.05 was considered significant.

Results

Transoesophageal echocardiography could be performed in all the 80 patients enrolled in the study. All TEEs were performed by the same experienced operator in order to minimize inter-observer variability. TEE indications were similar in both groups, mainly evaluation of valvular disease (87% in both group). There was no difference in age (57 ± 18 vs. 59 ± 14 years, P = 0.56) but patients in the Kalinox group were more frequently female (69% (n = 31) vs. 43% (n = 15), P = 0.02). No serious adverse event or complication was observed. Mean Midazolam dosage was 4.0 ± 1.0 mg.

Mean TEE duration was not different between groups (6 ± 3 min in the Kalinox group vs. 7 ± 4 min in the benzodiazepine group, P = 0.57). Patients in Kalinox group felt TEE to be more difficult than those in the Midazolam group (47% (n = 21) vs. 17% (n = 6) had a tolerance score ≥5, respectively, P = 0.005) but pain experience was similar (7% (n = 3) vs. 9% (n = 3) had a pain score ≥5, respectively, P = 0.75). TEE remembrance was significantly different. Seventy-six percent of the patients in the Kalinox group (n = 34) had a good remembrance of the examination compared with only 18% (n = 6) in the Midazolam group (P < 0.0001). Percentage of patients agreeing to perform another TEE if necessary was slightly lower in the Kalinox group (77% (n = 32) vs. 94% (n = 32), respectively, P = 0.04). TEE quality, as assessed by the operator, was similar, with a contributive examination in 76% (n = 34) of patients in the Kalinox group and 68% (n = 23) in the Midazolam group (P = 0.44).

Discussion

The present study demonstrates the feasibility of performing TEE using inhaled nitrous oxide, with acceptable patients’ tolerance and good conditions for the operator.

Since TEE introduction in the early 1980s, its effectiveness as a major diagnostic tool in cardiovascular disease has been widely demonstrated. TEE is usually performed under local anaesthesia and intravenous administration of benzodiazepine to improve patients’ tolerance and consequently TEE quality for the operator. However, benzodiazepines sedation can induce serious adverse effects such as respiratory depression and paradoxical reaction and requires several hours of monitoring because of its prolonged recovery period. Consequently, sedation using benzodiazepines should be used cautiously in elderly patients or those with severe respiratory insufficiency. Ideal analgesia-sedation for TEE should be effective on pain and anxiety, have few contraindications, few adverse events, a short lifetime, and a fast disappearance of its analgesic-sedative effects after cessation of its administration. Such an ideal analgesia-sedation is to date not available.

Kalinox has an established safety record in many clinical situations4-7 and has few contraindications. It should not be used in patients with abnormal conscious status, or intra cranial hypertension, in patients with body-trapped air (pneumothorax, air embolism, recent underwater dive, emphysema) in whom gas expansion might be dangerous or during pregnancy (first 3 months). Pharmacodynamics of Kalinox is well known. Kalinox is effective after few minutes of inhalation and its effect reverses 4-5 min after discontinuation.8 Oxymetry monitoring is not necessary because patients are breathing a 50% mixture of oxygen resulting in an only relative hyperoxemia. Because of its fast reversible effects and its lack of sedative properties, it is usually allowed to drive after Kalinox administration.8,9 Thus Kalinox properties make it very attractive for performing TEE but to our knowledge it never been evaluated in this indication.

Our preliminary study clearly shows that using Kalinox, TEE is feasible and indeed TEE could be performed in all patients. Compared with intravenous benzodiazepines injection, patients in the Kalinox group feel TEE to be more uncomfortable. Nitrous oxide has analgesic but no sedative action, and thus a large part of our patients had a good remembrance of the examination resulting in a worst tolerance and a lower proportion of patients agreeing to perform another TEE if necessary. However, Kalinox was as efficient on pain relief than benzodiazepines and the quality of the examination for the operator was not different. It is worth noting that we did not observe any serious adverse event.
in the present study. With Kalinox, one patient had a burst of laughing requiring stopping inhalation and several patients felt to be in a dreamlike state. Thus, because of the higher discomfort observed under Kalinox, we believe that benzodiazepine should remain the first line sedation regimen. However, for patients intolerant to benzodiazepines, for elderly or respiratory-insufficient patients as well as for ambulatory patients avoiding the need of several hours of monitoring, Kalinox could be considered as a useful alternative.

Several limitations of the present study need to be underlined. Firstly, this is an open non-randomized study and even if all TEEs were performed by the same operator in order to minimize inter-observer variability, we can not exclude some bias. Secondly, there was no control group, but superiority of benzodiazepines sedation vs. placebo is well accepted and we used high dosage of Midazolam (mean dose 4.0 ± 1.0 mg, median 3.75 mg). Thirdly, total number of patients enrolled in the present study may appear limited but this is a preliminary study evaluating for the first time the feasibility and effectiveness of Kalinox for TEE examination. Fourthly, a score ≥5 was used as threshold for painful or poorly tolerated TEE. Similar results were observed using other thresholds such as three or four. Finally, Kalinox is more expensive than Midazolam (10€ vs. <1€) but this is marginal compared with TEE cost and it avoids hours of monitoring, which must be also taken in account. Overall, this first experience, despite several limitations, gives us encouraging data and supports a future randomized study.

**Conclusion**

This preliminary study shows that TEE using Kalinox is feasible, provides similar pain relief despite more discomfort for the patient, and acceptable conditions for the operator compared with the standard care using benzodiazepines sedation. Thus, Kalinox could be considered as an alternative to benzodiazepine sedation for TEE for patients intolerant to benzodiazepines, elderly or respiratory-insufficient patients, or for ambulatory patients avoiding the need of several hours of monitoring.
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Conflicts of Interest: none declared.

References