Prospective randomised trial of propofol versus pethidine and mdiazolam

Sedation during transoesophageal echocardiography

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Summary

Background and aim: Transoesophageal echocardiography (TEE) is widely used. There is no consensus on the optimal sedation for TEE. We hypothesised that in patients undergoing TEE propofol more frequently causes a potentially dangerous drop in blood pressure than a combination of pethidine and midazolam. Therefore a single centre prospective randomised trial was performed.

Methods: A total of 201 patients who underwent TEE were randomised into two groups receiving either intravenous (IV) propofol (<50 years old: 50–60 mg bolus plus further boluses of 20–30 mg as required for sufficient sedation; >50 years old: 30–40 mg bolus plus further boluses of 10–20 mg as required) or a combination of IV pethidine and midazolam (IV bolus of 25 mg pethidin and 1–2 mg midazolam, further boluses of 1 mg midazolam as required). We recorded blood pressure, oxygen saturation, heart rate, duration of procedure, and complications. Patient comfort was assessed by use of a short questionnaire once consciousness was regained.

Results: The incidence of a reduction in systolic blood pressure of ≥30 mm Hg and to <100 mm Hg systolic was 9% in the propofol group and 6% in the pethidine/midazolam group (p = 0.43). The changes in systolic blood pressure (propofol group: –5.80% [standard deviation 20.48%], pethidine/midazolam group: –2.27% [SD 18.20%], p = 0.13) and diastolic blood pressure (propofol group: –1.28% [SD 14.12%], pethidine/midazolam group: –1.00% [SD –3.46–1.46%], p = 0.43) were not significantly different either, nor were changes in oxygen saturation and heart rate (p = 0.37 and 0.06, respectively).

There was no significant difference regarding patient satisfaction and comfort (dizziness, nausea, headache, feeling that the procedure was unpleasant, anxiety during procedure) between the groups except for the wish for deeper anaesthesia, which was more frequent in the propofol group (p = 0.03).

Conclusions: The risk of a drop in blood pressure was on average 50% higher for propofol than for pethidine/midazolam. However, this did not reach statistical significance. Both sedation regimens turned out to be safe and well tolerated (ClincalTrials.gov number NCT01567657).

Key words: transoesophageal echocardiography; sedation; propofol; midazolam; pethidine

Introduction

Transoesophageal echocardiography (TEE) is a widely used semi-invasive method for the examination of the heart. A broad spectrum of indications are well validated, such as assessment of structure and function of native and prosthetic valves, infective endocarditis, cardiac sources of emboli, aortic dissection, atheromas, congenital heart diseases, tumours, etc.

Propofol is often used as a sedative for gastroenterological endoscopy because of its effectiveness and good medical tolerability. There have been several studies comparing patient safety and comfort of the different sedatives during gastroenterological examinations.

Some studies have investigated the situation in outpatient settings where the sedative drugs were administered either by nurses or endoscopists themselves [1–3]. Therefore, only low risk patients (American Society of Anesthesiologists class I or II) were included. Patients undergoing TEE, however, are often at least intermediate risk patients with significant cardiovascular problems such as cerebrovascular disease, heart failure, or coronary or valvular heart disease.

In selected patients TEE is performed without sedation. Generally, cardiologists choose, rather than propofol, either midazolam or pethidine, midazolam in combination with pethidine, or rarely remifentanyl [4], ondansetron [5], or dexmedetomidine [6]. A well- known adverse reaction of propofol is a reduction in blood pressure. This raises the question as to whether the sedation with propofol for TEE is safe.

However, propofol may also have some potential pharmacokinetic advantages, such as fast onset of action and rapid recovery time with potentially less prolonged hypoventilation compared with midazolam [7]. Few reports have investigated patient safety and comfort during TEE under sedation, particularly with propofol [8–11]. To our knowledge, there is no randomised controlled study comparing blood pressure course in patients sedated with propofol versus patients sedated with a combination of pethidine and midazolam during TEE. Particularly in stroke patients a

drop in blood pressure can cause severe complications (decreased cerebral blood flow is a risk for poor stroke outcome) [12–14]. In gastroenterological evaluations, a relevant change in systolic blood pressure is definded by most authors as a drop of ≥25% and a drop to <90 mm Hg [15–17]. The present study thus compares two sedation protocols, i.e. propofol (PPF) or pethidine/midazolam (PTD/M), for their effects on blood pressure during TEE, as well as for patient safety and satisfaction.

In a small pilot study of 16 patients (8 per group), 3 patients in the PPF group (mean dose per patient: 100 mg) had relevant blood pressure drops compared with none in the PTD/M group. Based on these preliminary findings, we hypothesised that propofol may frequently cause potentially harmful hypotension.

We defined the primary endpoint as a reduction in systolic blood pressure of ≥30 mm Hg and to <100 mm Hg. Secondary endpoints were side effects and patient comfort.

Patients and methods

Patients

The study was approved by the local ethics committee. All patients gave their written informed consent. A total of 201 adult inpatients and outpatients undergoing TEE at a regional referral hospital for TEE were randomly allocated to either the PPF or the PTD/M sedation protocol in a controlled single-blind trial between January 2012 and January 2013.

Inclusion criteria were age over 18 years, and ability to give informed consent. Patients were excluded if the TEE was conducted in the emergency or intensive care unit. They were also excluded if they were pregnant, breast-feeding, or had a history of soybean, propofol, pethidine or midazolam allergy.

Sedation

All patients received two puffs of topical lidocaine 10% for pharyngeal anaesthesia at the beginning of the procedure and supplemental oxygen 2 l/min. Patients aged <50 years allocated to PPF (n = 12; 12%) received an intravenous (IV) bolus of 50–60 mg (irrespective of body surface area) [18], followed by IV boluses of 20–30 mg until sufficient sedation was accomplished.

Patients >50 years of age allocated to PPF (n = 85; 88%) received an IV bolus of 30–40 mg, followed by IV boluses of 10–20 mg, again until sufficient sedation was achieved. This classification according to age was made because it has been observed that elderly patients require lower doses of sedatives [19]. Patients allocated to PTD/M (n = 98) received a single IV bolus of 25 mg pethidine and an IV bolus of 1–2 mg midazolam (irrespective of height and weight). As required, they received further boluses of 1 mg midazolam up to a maximum dose of 7 mg. Patients who needed more than this maximum dose were excluded from analysis.

Monitoring

Baseline blood pressure was determined before administration of medication as the mean value of three consecutive blood pressure measurements at 2-minute intervals (automated blood pressure cuff). After onset of sedation, blood pressure measurements were repeated every 2 minutes. Oxygen saturation was monitored continuously via pulse oxymetry. Heart rhythm monitoring was provided by continuous electrocardiograpy.

At 60 minutes after the procedure, once full consciousness was regained, all patients were requested to fill in a questionnaire regarding comfort (degree of unpleasantness of procedure, degree of anxiety during procedure, wish for deeper sedation) and safety (dizziness, nausea, headache).

Statistical analysis

Data from patients who dropped out of the study were analysed up to that point in time. Owing to the rarity of events, Fisher's exact tests were used to examine the primary endpoint as well as the binary secondary endpoints.

Secondary endpoints based on continuous measures (systolic and diastolic blood pressure, oxygen saturation, heart rate) were examined as histograms and analysed with mixed effects models with patient ID as the random effect to account for within patient correlation. Significance of factors was assessed with two-sided Wald tests.

Continuous secondary endpoints (side effects and patient tolerance) assessed using five-point Likert scales (such as used on the questionnaire applied 60 minutes after randomisation) were compared between groups using nonparametric Mann-Whitney U-tests and, therefore, no distributional assumptions were required. Binary safety endpoints were analysed using Fisher's exact test.

Results

Study population demography

Table 1 shows that 87% of the included patients were over 50 years of age. In the PPF group 61% and in the PTD/M group 64% were males. Patients in the PPF group were slightly older and more likely to smoke. Patients sedated with the PTD/M combination had lower

Table 1: Baseline characteristics. Values are expressed in n (%) for categorical and mean ± standard deviation (SD) for continuous characteristics.

Baseline demographics	Propofol	Pethidine/Midazolam
	n = 95	n = 97
Age, years	n = 95, 66.9 ± 13.3	n = 97, 64.2 ± 13.6
Age, ≥50 years (yes)	n = 95, 83 (87%)	n = 97, 84 (87%)
Sex (male)	n = 95, 58 (61%)	n = 97, 62 (64%)
Smoker (yes)	n = 95, 26 (27%)	n = 97, 24 (25%)
BMI, kg/m^2	n = 95, 27.8 ± 5.8	n = 85, 27.2 ± 5.3
Body surface (KOF), m^2	n = 43, 1.8 ± 0.2	n = 48, 1.9 ± 0.3
Baseline systolic BP, mm Hg	n = 95, 142.4 ± 24.0	n = 97, 127.5 ± 21.3
Baseline diastolic BP, mm Hg	n = 95, 71.6 ± 13.3	n = 97, 65.0 ± 12.7
Baseline oxygen saturation, %	n = 95, 96.1 ± 2.3	n = 97, 96.6 ± 2.3
Baseline heart rate, beats/min	n = 94, 73.7 ± 14.5	n = 97, 75.6 ± 19.5
Sinus rhythm (yes)	n = 94, 84 (89%)	n = 97, 85 (88%)
Atrial fibrillation/atrial flutter (yes)	n = 94, 10 (11%)	n = 97, 12 (12%)
ASA score	n = 52,	n = 54,
Healthy	16 (31%)	23 (43%)
Mild systemic disease	27 (52%)	23 (43%)
Severe systemic disease	9 (17%)	8 (15%)

ASA = American Society of Anesthesiologists physical status classification measure (1: healthy person; 2: mild systemic disease; 3: severe systemic disease);
BMI = body mass index; BP = blood pressure.

systolic and diastolic blood pressure. Other baseline characteristics were similar between the groups. Information about medications was available for only 54% of patients in the PPF and 47% of patients in the PTD/M groups. Medication use was similar between the two groups.

Patient flow

The flow of patients through the study is shown in figure 1. Of the 201 patients enrolled into the study, 192 received the assigned sedation protocol (fig. 1). Two patients crossed over to the other group, three patients received a dosage different from that specified in the proposal, and in four patients it was unclear whether the dose was per protocol. Additionally, four patients were enrolled erroneously (i.e. enrolled twice).

Primary endpoint

We found that the incidence of blood pressure drops (a reduction in systolic blood pressure of ≥30 mm Hg and to <100 mm Hg systolic) was 9% in those sedated with PPF and 6% in those sedated with PTD/M (table 2). Although we found that the risk of a drop in blood pressure was on average 1.5 times higher for PPF than PTD/M, this difference was not statistically significant (table 2). Similarly, although the changes in systolic blood pressure and diastolic blood pressure under PPF sedation tended to be larger than those under PTD/M sedation, the differences were not significantly diverging (table 2). Heart rate, however, was found to increase slightly less under PPF sedation in comparison with PTD/M (table 2).

We found congruent patterns in the stratified analysis (table 3). Interactions between the sedation protocol applied and both sex and age were insignificant for all five endpoints tested (a drop in blood pressure within 30 minutes, both systolic and diastolic blood pressure, blood oxygen saturation, and heart rate during the 30 minutes; table 3). Thus, there was no evidence that sexes and age groups responded differently to the two sedatives.

Side effects and patient tolerance

Patients receiving PPF did not report discomfort during or directly after TEE, such as dizziness (p = 0.28), nausea (p = 0.23), headaches (p = 0.68), a feeling that the procedure was unpleasant (p = 0.14) or anxiety (p = 0.57) more or less frequently than patients receiving PTD/M. More patients sedated with PPF, however, reported a wish for deeper sedation than those sedated with PTD/M (p = 0.03).

Discussion

The primary objective of this controlled single-blind trial was to determine whether relevant decreases in blood pressure are more likely to occur in patients under sedation with PPF or the combination of PTD/M.

Table 2: Safety endpoints.

	Propofol	Pethidine/Midazolam		
Events within 30 minutes	**n (%)**	**n (%)**	**Risk ratio (95% CI)**	**p- value**
Drop in blood pressure	9 (9.18)	6 (6.06)	1.53 (0.57–4.14)	0.43
Change during the first 30 minutes	**Mean (SD)**	**Mean (SD)**	**Difference (95% CI)**	**p-value**
Systolic blood pressure, mm Hg	–5.80 (20.48)	–2.27 (18.20)	–3.09 (–7.08–0.90)	0.13
Diastolic blood pressure, mm Hg	–1.28 (14.12)	–0.09 (10.80)	–1.00 (–3.46–1.46)	0.43
Oxygen saturation, %	1.05 (2.88)	0.85 (3.17)	0.33 (–0.39–1.05)	0.37
Heart rate, beats/min	0.56 (9.71)	3.03 (9.09)	–2.03 (–4.16–0.10)	0.06

CI = confidence interval; SD = standard deviation
Data are number of patients (%) for binary endpoints and mean ± SD for continuous endpoints. Differences are from linear mixed-effects regression models with patient as the random effect.The p-values are two-sided from superiority testing with a Fisher's exact test for the primary endpoint and Wald tests for the continuous endpoints.

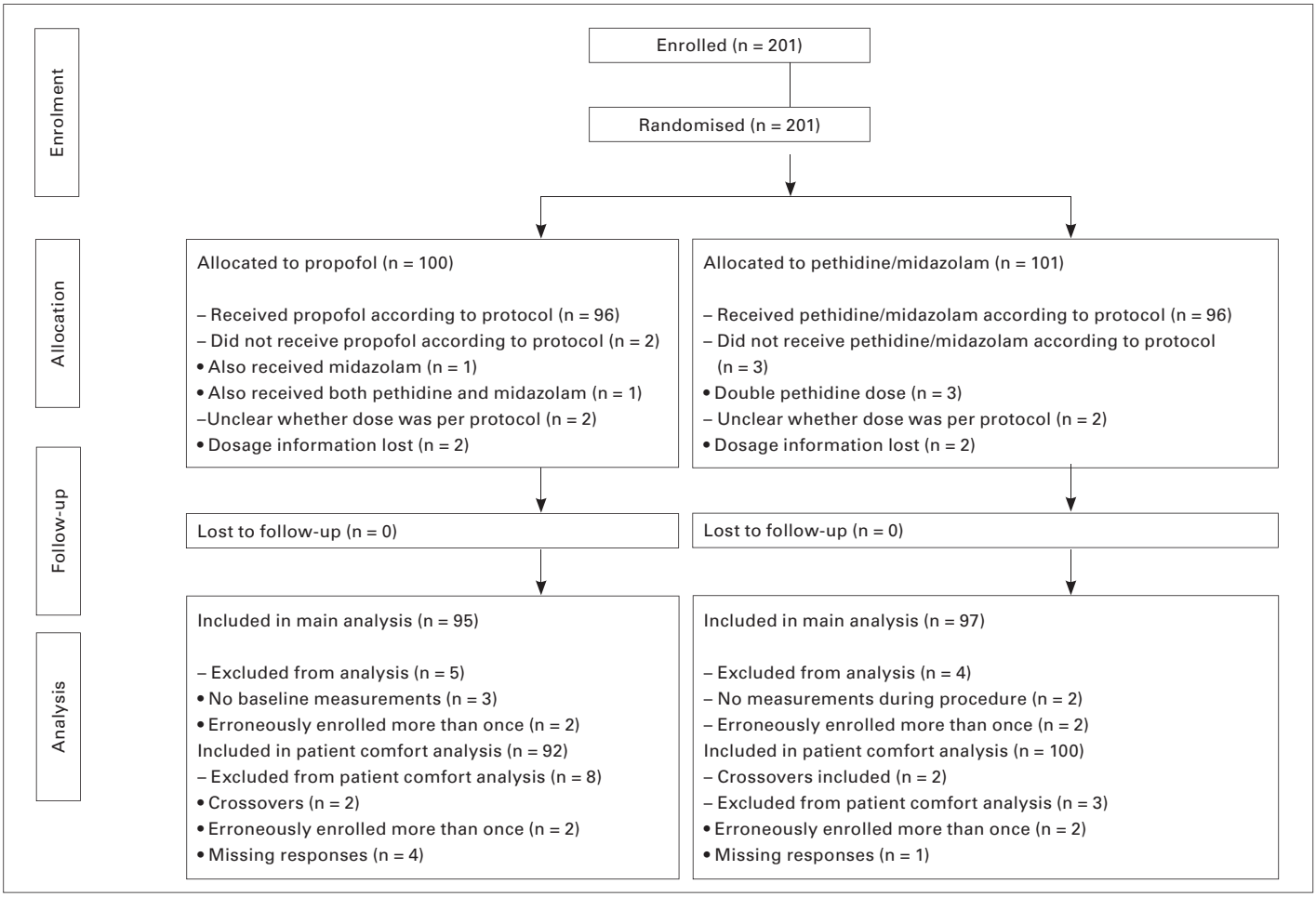

Figure 1: Patient flow diagram.

Secondary objectives were to assess the effect of the sedatives on patient comfort and safety.

Changes in systolic blood pressure tended to be more marked in patients sedated with PPF than with PTD/M. However, these differences were neither statistically significant nor clinically relevant.

With the observed event rates, the trial was underpowered to detect a risk reduction in systolic blood pressure drop and a much larger study would be required to obtain conclusive results. Probably by play of chance, event rates differed markedly between the pilot study and this trial. Notwithstanding, because of the blood pressure drops experienced by some patients in the pilot study, we might have tended to use smaller doses of PPF than in the pilot study. This hypothesis could be confirmed by the finding that more patients sedated with PPF reported a wish for deeper sedation than those sedated with PTD/M. The mean PPF dosage (87.5 ± 47.4 mg) was indeed smaller than in the pilot study and considerably lower than generally found in gastroenterological trials (>200 mg) [20, 21]. The mean midazolam dosage was 3.05 ± 1.39 mg (in combination with a pethidine dose of 25 mg).

Apart from the above-mentioned underpowering based on the pilot study with high event rates, there are other limitations of this trial. The imbalance of baseline systolic blood pressure between the two groups could have biased the results, as could the cardiologists being aware of what sedation protocol patients were receiving.

Nevertheless, the fact that merely a relatively low PPF dose is required for an appropriate TEE sedation plus the finding that there were no statistically significant differences between the PPF and PTD/M groups has some importance. During the study, we did not witness a single serious complication with any intervention. Of course, there are further risks associated with PPF sedation apart from a possible drop in blood pressure. High PPF doses may result in loss of swallowing reflexes [22]. We speculate that patients unable to swallow (to facilitate probe insertion) are at risk of potential injury by probe malposition. This might be an additional reason to use either low PPF doses or rather PTD/M to sedate high-risk patients undergoing TEE.

Table 3: Primary endpoints stratified by sex and age.

Events within 30 minutes	n (%)	n (%)	Risk ratio (95% CI)	p-value
Drop in blood pressure				
Sex				0.86
Female	2 (5.41)	1 (2.86)	1.89 (0.18–19.95)	
Male	7 (11.86)	5 (7.94)	1.50 (0.50–4.45)	
Age				0.74
<50 years	0 (0.00)	1 (7.69)	0.36 (–9.22–9.94)	
≥50 years	9 (10.59)	5 (5.88)	1.82 (0.64–5.21)	
Change during the first 30 minutes	**Mean (SD)**	**Mean (SD)**	**Difference (95%CI)**	**P value**
Systolic blood pressure, mm Hg				
Sex				0.43
Female	–2.37 (20.40)	–0.06 (20.15)	–1.15 (–8.10–5.79)	
Male	–7.88 (20.27)	–3.46 (16.96)	–4.44 (–9.18–0.31)	
Age				0.91
<50 years	–2.66 (15.33)	1.22 (15.80)	–3.64 (–11.60–4.31)	
≥50 years	–6.20 (21.01)	–2.89 (18.53)	–2.98 (–7.40–1.44)	
Diastolic blood pressure, mm Hg				
Sex				0.43
Female	–0.47 (14.60)	2.60 (11.15)	–2.28 (–6.53–1.97)	
Male	–1.77 (13.81)	–1.54 (10.33)	–0.35 (–3.28–2.59)	
Age				0.53
<50 years	–2.66 (14.19)	0.09 (10.80)	–3.04 (–9.23–3.15)	
≥50 years	–1.11 (14.11)	–0.12 (10.80)	–0.71 (–3.37–1.96)	
Oxygen saturation, %				
Sex				0.43
Female	1.51 (3.31)	1.54 (2.36)	0.02 (–0.93–0.98)	
Male	0.77 (2.55)	0.48 (3.48)	0.48 (–0.50–1.45)	
Age				0.53
<50 years	–0.04 (3.19)	0.87 (2.01)	–0.25 (–2.13–1.63)	
≥50 years	1.18 (2.81)	0.85 (3.34)	0.41 (–0.36–1.19)	
Heart rate, beats/min				
Sex				0.43
Female	0.55 (9.08)	1.76 (8.82)	–1.32 (–4.60–1.96)	
Male	0.57 (10.08)	3.71 (9.17)	–2.41 (–5.18–0.36)	
Age				0.90
<50 years	1.58 (12.11)	4.85 (8.88)	–2.40 (–8.71–3.91)	
≥50 years	0.43 (9.36)	2.71 (9.10)	–1.97 (–4.22–0.29)	

CI = confidence interval; SD = standard deviation
Values are n (%) or mean (SD). Differences are from linear mixed-effects models. Interaction-values for the drop in blood pressure are from a Mantel-Haenszel test of homogeneity to test the interaction between sex and sedative or age and sedative. The p-values for the differences in the first 30 minutes are from Wald tests of the interaction between sex and sedative or age and sedative.

Conclusions

The comparison of PPF sedation versus PTD/M sedation shows no statistically significant difference regarding clinically relevant drop in blood pressure and patient comfort and safety. We found that the risk of a drop in blood pressure was on average 1.5 times higher with PPF than with PTD/M, but the difference was not statistically significant. Both sedation protocols turned out to be safe and well tolerated. However, it has to be considered that the administered PPF doses were relatively low and accordingly more patients sedated with PPF reported a wish for deeper sedation than those sedated with PTD/M.

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The full list of references is included in the online version of the article at www.cardiovascmed.ch.

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