



Hemodynamic monitoring by USCOM during rapid sequence intubation (RSI) with Etomidate/Fentanyl or Ketamine/Midazolam

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Abstract

Background: Critically ill and septic patients often require emergency orotracheal intubation. Etomidate is associated with a reversible adrenal insufficiency which potentially increases the in-hospital mortality, particularly in patients with sepsis. Moreover; standard anesthetization might severely aggravate shock symptoms during rapid sequence induction (RSI). Ketamine with its known stabilizing effects on hemodynamics might be a reasonable alternative, particularly in septic patients.

Methods: This non-randomised, observational pilot study focuses on the influence of ketamine-based (K) vs an etomidate-based (E) anesthetization on hemodynamic parameters during RSI. Forty pts were assigned alternately to etomidate/fentanyl (n=20), or ketamine/midazolam (n=20) while monitoring with invasive blood pressure (IBP) and ultrasound cardiac output monitor (USCOM) measurements during RSI. The levels of vasopressors required prior to, during and after RSI were recorded.

Results: Fourty patients (median SAPS II score at ICU admission: 54 K, 50 E; median age: 59 yrs K, 56 yrs E) who needed sedation for emergency intubation were sedated either with etomidate/fentanyl or ketamine/midazolam. Noradrenalin demand and mean arterial pressure (MAP) prior to RSI were comparable (E: mean NA dose 0.2 mg/h, MAP 88 mmHg; K: mean NA dose 0.45 mg/h, MAP 75 mmHg) between the two groups. Moreover, mean MAP levels post RSI were 75 (E) and 76 (K) mmHg, respectively. The mean peak level of noradrenalin demand during RSI, though, was considerably higher within the etomidate group compared to the ketamine group (E 7.6 mg/h vs K 1.06 mg/h, p 0.01). Stroke volume index (SVI) and cardiac index (CI) increased during RSI (+3.8%/+3.0%) within the ketamine group, while SVI and CI decreased during RSI (-8.5%/-3.5%) within the etomidate group.

Conclusion: USCOM is an easily applicable and quick tool for the hemodynamic monitoring of critical ill patients. Moreover, this pilot study shows that RSI with ketamine/midazolam is a safe and valuable alternative to etomidate/fentanyl in patients who primarily require vasopressors.

Key words: Hemodynamic monitoring, USCOM, intubation, RSI, ketamine, etomidate

Background

Critically ill patients often require emergency orotracheal intubation. The concomitant use of a sedative and a paralytic agent is common for rapid sequence induction (RSI).

Etomidate is one of the most often used hypnotic agents with outstanding intubation conditions and hemodynamic tolerance even in patients with shock. However, it can cause a reversible adrenal insufficiency by the inhibition 11 β -hydroxylase [1,2]. An association between the use of etomidate and an increased morbidity of critically ill and septic patients due to adrenal insufficiency has been suggested in several studies [3-6].

Standard anesthetization might severely aggravate shock symptoms during RSI. Ketamine with its known stabilizing effects on hemodynamics might be a reasonable alternative, particularly in septic patients. A recently published randomized trial has shown that ketamine is a safe and valuable alternative to etomidate for endotracheal intubation in critically ill patients [7]. Jabre *et al.*, found that the percentage of patients with adrenal insufficiency was significantly higher in the etomidate group than in the ketamine group [7]. However, 28-day mortality did not differ significantly.

Thermodilution cardiac output measurements have been

routinely performed as part of intensive care practice since the introduction of the balloon-directed thermistor-tipped pulmonary artery catheter in the 1970s [8-10]. Introduced by Swan and Ganz the pulmonary artery catheter (PAC) became the gold standard for more than two decades [8,9]. However, arrhythmia, infection and possible pulmonary artery disruption have always been concerns related to the use of a PAC and led to a growing interest in the development of non-invasive hemodynamic monitoring devices [11-13]. One less invasive thermodilution-based technique consists of the pulse induced cardiac output device (PiCCO) but exclusively ultrasound-based devices as the USCOM monitor are entirely non-invasive methods for measuring CO [14-20]. Beside accuracy and the method related risks another crucial criterion consists of the time required for the determination of CO [21]. USCOM is a feasible, continuous-wave Doppler-based method which non-invasively measures CO in a fast and economical way [22].

The present non-randomised, observational pilot study aimed at the influence of ketamine-based (ketamine/midazolam) vs an etomidate-based (etomidate/fentanyl) anesthetization on hemodynamic parameters during RSI.

Patients and methods

Study setting and patients

Forty patients, who needed sedation for emergency intubation, were included in this non-randomized, prospective observational study. Patients were recruited from June 2010 until November 2010, on a ten-bed, non-cardiological medical ICU at the university hospital, Munich. The study protocol was approved by the institutional ethics committee. Informed consent was waived at inclusion because patients needed urgent intubation. Consent for data processing was given by patients, whenever possible, or by relatives and/or legally authorised representatives.

Patients who were 18 years or older who needed sedation for emergency intubation were prospectively enrolled in the study. Exclusion criteria were cardiac arrest and resuscitation, contraindications to one of the agents used for analgo-sedation, known pregnancy.

Patients were alternately assigned to anaesthetization either with etomidate /fentanyl or ketamine/midazolam for intubation. Patients within the etomidate group received first fentanyl (20-40 µg) followed by etomidate (0.2 mg/kg). Those who were assigned to ketamine received 2-4 mg midazolam, followed by ketamine (1.5 mg/kg) and immediately thereafter, rocuronium as intravenous bolus (1 mg/kg). After confirmation of intubation and tube placement (using capnometry), continuous sedation was initiated by the use of midazolam or propofol combined with sufentanil.

All patients were continuously measured for hemodynamics including heart rate, ECG, oxygen saturation, invasive blood pressure (IBP) and, intermittently, left-sided USCOM (aortal access) immediately prior to, during and after intubation (SVI,

stroke volume index; CI, cardiac index; SVRI, systemic vascular resistance index). To exclude inter-individual observer variability, measurements by USCOM were undertaken by the same investigator. The investigator who performed all the USCOM measurements was not blinded to the induction drugs given. All USCOM measurements were performed immediately prior to induction (first USCOM) and immediately post-intubation (second USCOM) but, throughout the cohort, prior to the start of the post-intubation sedation regime (with propofol or midazolam plus sufentanil). Moreover, all second USCOM measurements were undertaken during a similar ventilation setting (fiO₂ 1.0, PEEP 8 mbar).

The maximum use of norepinephrine during the procedure was recorded.

USCOM

The USCOM-device (USCOM Ltd, Sydney, Australia) is a non-invasive bedside method to evaluate cardiac output basing on continuous-wave Doppler ultrasound. After starting the USCOM device, the left-sided transaortic (CO_{US-A}) or right-sided transpulmonary access has to be chosen before the patients data like height, weight and gender are typed in. The flow profile is obtained by commonly using a 2.2 MHz transducer placed on the chest in either the left parasternal position to measure transpulmonary blood flow (right-sided access, 3rd to 5th parasternal intercostal space) or the suprasternal position to measure transaortic blood flow (left-sided access, suprasternal notch). The operator registries a Doppler flow curve with maximal blood flow which is characterized by a sharp, well-defined waveform with the clearest audible sound. The flow profile is displayed as a time velocity curve at the monitor (VTI=velocity time integral). Once the optimal flow profile is obtained, the trace is frozen. The USCOM device calculates CO by the product of stroke volume (SV) and heart rate (HR) where the SV is the product of the velocity time integral (VTI) and the cross-sectional area of the choosen valve (CSA). The valve cross-sectional area is given by the USCOM internal algorithm based on the formerly typed in patients data (height and gender).

Statistical analysis

Statistical analysis was performed with SPSS (SPSS for Windows, Version 15.0, SPSS Institute, Chicago, Ill., USA) using the t-test. A difference of p < 0.05 between the variables was considered as statistically significant.

Results

Baseline characteristics

All patients (23 male, 17 female) suffered from septic complications and required primarily catecholamines. The median age was 59 years (K) and 56 years (E) and the median SAPS Score was 54 (K) and 50 (E) points at ICU admission.

The majorities of the patients suffered from hemato-oncological or hepatological disease. Six patients had received

prior chemotherapy for solid tumors, and 10 patients suffered from other diseases. Intubation was indicated mainly for respiratory failure and/or sepsis (n = 33, 82.5%).

Detailed patients characteristics are given in **Table 1**.

Blood pressure, heart rate and catecholamine use during RSI

Prior to RSI, patients within both groups (K ketamine, E etomidate) were comparable regarding heart rate (HR, K 104 vs E 107 bpm; p 0.67) and mean arterial pressure (MAP, K 75 vs E 88 mmHg; p 0.07). Moreover, the 'baseline' level of catecholamine use (norepinephrine, NA) was roughly similar (NA, K 0.45 vs E 0.2 mg/h; p 0.11).

Post RSI, HR and MAP were similarly comparable between the two groups (HR, K 115 vs E 113 mmHg; p 0.80) and mean arterial pressure (MAP, K 76 vs E 75 mmHg; p 0.9). The peak level of norepinephrine to maintain the MAP during sedation, though, was considerably higher in patients who received the etomidate regimen (NA, K 1.06 vs E 7.6 mg/h; p 0.01).

Detailed information is given in **Table 2, Figure 1 and 2**.

USCOM measurements during RSI (CI, SVI, SVRI)

USCOM measurements were performed immediately prior to RSI, during RSI and post RSI (mean Δ between first and second

USCOM (minutes): 5.7 (K) vs 6.33 (E) (p 0.46). We recorded the following parameters: SVI, stroke volume index; CI, cardiac index; and SVRI, systemic vascular resistance index.

Prior to RSI, median CI and SVI was comparable within both groups (mean SVI E 29.3 mL/m² vs SVI K 31.3 mL/m², p 0.55; mean CI E 2.9 L/min/m² vs CI K 3.3 L/min/m², p 0.23). The mean SVRI (dyn x s x cm⁻⁵/m²) was higher in the etomidate group (2925(E) vs 2098 (K), p 0.04).

While mean SVI/CI (mL/m²/L/min/m²) minimally increased during RSI (prior RSI 31.3/3.3, post RSI; 32.5/3.4, Δ+3.8%/+3.0%) within the ketamine group, mean SVI/CI (mL/m²/L/min/m²) slightly decreased in the etomidate group (prior RSI 29.3/2.9, post RSI 26.8/2.8, Δ -8.5%/-3.5%). Mean SVRI (dyn x s x cm⁻⁵/m²) increased in the ketamine group and decreased in the etomidate group (Δ K +10.2%, Δ E -3.8%). Detailed information is given in **Table 2**.

Table 2. Hemodynamic parameters (by USCOM) prior to and after RSI

	ketamine n = 20	etomidate n = 20	P value *
Mean MAP (mmHg)			
prior to RSI	75 ±21.1	88 ±22.3	0.07
post RSI	76 ±28.5	75 ±31.7	0.9
Δ MAP mmHg (%)	+1 (+1.3)	-3 (-14.8)	
Mean HR (bpm)			
prior to RSI	104 ±25.4	107 ±28.3	0.67
post RSI	115 ±24.4	113 ±29.8	0.80
Δ HR bpm (%)	+11 (+10.6)	+6 (+5.6)	
Mean CI (L/min/m ²)			
prior to RSI	3.3 ±1.3	2.9 ±0.9	0.23
post RSI	3.4 ±1.5	2.8 ±1.1	0.19
Δ CI L/min/m ² (%)	+0.1 (+3.0)	-0.1 (-3.5)	
Mean SVI (ml/m ²)			
prior to RSI	31.3 ±10.2	29.3 ±10.5	0.55
post RSI	32.5 ±13.3	26.8 ±10.4	0.15
Δ SVI ml/m ² (%)	+1.2 (+3.8)	-2.5 (-8.5)	
Mean SVRI (dyn x s x cm ⁻⁵ /m ²)			
prior to RSI	2098 ±805	2925 ±1092	0.04
post RSI	2312 ±1118	2813 ±1414	0.32
Δ SVRI dyn x s x cm ⁻⁵ /m ² (%)	+214 (+10.2)	-112 (-3.8)	
Mean NA (maximum)*			
prior to RSI (mg/h iv)	0.45 ±0.6	0.2 ±0.3	0.11
post RSI (mg/h iv)	1.06 ±0.7	7.6 ±10.2	0.01
Δ NA (%)	+0.61 (+136)	+7.4 (+3.400)	

Abbreviations: MAP, mean arterial pressure; RSI, rapid sequence induction; * t-test; NA, norepinephrine; HR, heart rate; CI, cardiac index; SVI, stroke volume index; SVRI, systemic vascular resistance index; SVI, stroke volume index; SVV, stroke volume variance; ±SD, standard deviation
 * Norepinephrine 0.1 mg/h = 1.67 µg/min. (averaged 70 kg = 0.023 µg/kg/min)

Table 1. Patient baseline characteristics (at ICU admission, prior to RSI)

baseline characteristics n=40			
	ketamine group n = 20	etomidate group n = 20	n (%)
median age (years)	59	56	range 31 - 91
gender (m / f)	11 / 9	12 / 8	
median SAPS II score	54	50	range 24 - 81
Underlying disease			
liver cirrhosis & GI bleeding	6	5	11 (27.5)
acute leukaemia	5	1	6 (15.0)
lymphoma	2	5	7 (17.5)
solid tumor	3	3	6 (15.0)
other	4	6	10 (25.0)
Need for intubation, due to ...			
Respiratory failure			
and/or Sepsis	16	17	33 (82.5)
Sopor or coma *	1	-	1 (2.5)
GI bleeding	3	3	6 (15.0)
Outcome			
Day 30 mortality rate	60% (12/20)	50% (10/20)	22/40 (55%)
Mean time between USCOM			
Δ (min. ±SD)	5.7 (±2.34)	6.3 (±2.85)	

Abbreviations: *sopor or coma not related to sepsis (hepatic encephalopathy; GI, gastrointestinal; SD, standard deviation.

Figure 1. MAP prior to - and post RSI (mean \pm standard deviation)

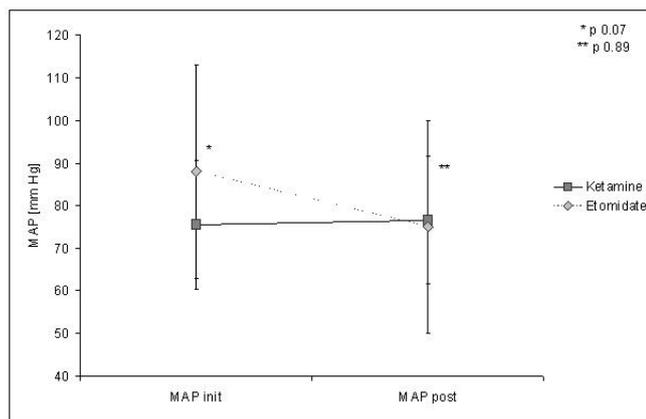
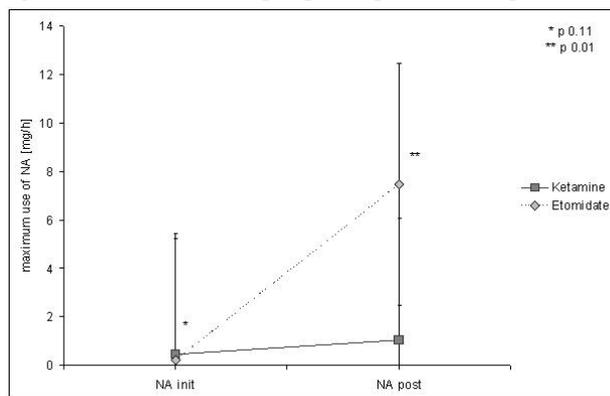


Figure 2. Peak level of norepinephrine prior to - and post RSI



Outcomes

Twelve of 20 patients within the ketamine group have died within 30 days (day 30 mortality rate 60%), and 10 of 20 patients have died in the etomidate group (day 30 mortality rate 50%). Overall day 30 mortality was 55%.

Discussion

Although adrenal axis dysfunction arises to some extent after etomidate use for RSI, the effect of such adrenal suppression on patients' outcome remains debated. Several studies have reported increased mortality in patients who had received one bolus of etomidate [4,5,23]. However, these findings have not been confirmed by other investigators [24,25]. Results from a recent randomized trial indicated, that ketamine compared to the use of etomidate was comparable with regard to 28-day mortality [7]. The percentage of patients with adrenal insufficiency was significantly higher in regards to the etomidate group than in the ketamine group, but mortality did not differ significantly. Adrenal insufficiency is probably associated with increased mortality in critically ill patients, including those with sepsis; however, whether the adrenal axis suppression

and mortality are the result of some underlying process, or whether it causes death, has never been established [7].

Jabre *et al.*, concluded that ketamine is a safe and valuable alternative to etomidate for RSI in critically ill patients, particularly in septic patients, even though the study might not have had sufficient power to show a significant increase in morbidity related to the use of etomidate in patients with sepsis.

This pilot study aimed to evaluate the influence of a ketamine-based vs an etomidate-based anesthetization on hemodynamic parameters measured by USCOM immediately prior to, during and post RSI. Intubation was indicated mainly for respiratory failure and/or sepsis.

Clearly, the still accepted clinical standard for CO measurement is the intermittent thermodilution technique which itself has its own inherent variability [26-28]. USCOM is a noninvasive cardiac output monitor based on the transthoracic measurement of Doppler flow velocity over the aortic and pulmonary outflow tract. It is easy to operate, and CO is displayed 'beat by beat'. Following a short booting time the device can be used immediately. The technique is reported to be easily learned after a short period by non-physicians [29,30]. Previously reported trials investigated the accuracy of USCOM in various settings and most of them found an acceptable agreement between the USCOM CO measurements and those determined by a thermodilution-based method [15,29,22,31-34,16,35,20]. Although, it is critical to report, that an inferior accuracy for USCOM was reported by other authors who found that CO measurements by USCOM do not reliably represent absolute values as compared to pulmonary artery catheter thermodilution technique [36,35].

Prior to RSI, patients were roughly comparable regarding baseline hemodynamic parameters (HR, MAP, CI, and SVI) and norepinephrine use. But the peak level of norepinephrine to maintain MAP during induction, though, was considerably higher in patients who received etomidate/fentanyl for sedation (NA, K 1.06 vs E 7.6 mg/h; p 0.01). Post RSI USCOM measurements showed slightly increased means of SVI/CI (mL/m^2 , $\text{L}/\text{min}/\text{m}^2$; Δ +3.8%, +3.0%) within the ketamine group, whereas those in the etomidate group decreased (prior RSI 29.3/2.9, post RSI 26.8/2.8; Δ -8.5%/-3.5%). The mean SVRI ($\text{dyn} \times \text{s} \times \text{cm}^{-5}/\text{m}^2$) increased in the ketamine group and decreased in the etomidate group (Δ K +10.2%, Δ E -3.8%).

The present data confirm the conclusion of Jabre *et al.* regarding safety and valuability of ketamine use for RSI. Moreover, USCOM measurements during RSI support the excellent hemodynamic tolerance of ketamine in the present patients setting. Considering the contraindications, ketamine advanced to our 1st choice sedative in septic patients requiring intubation.

However, drawing final conclusions from the present study is almost impossible. The patients' number is considerably low. Moreover, patients were alternately, but not randomly assigned to receive either etomidate or ketamine. Moreo-

ver, there is a limitation since the patients have received a combination (etomidate/fentanyl vs ketamine/midazolam) for RSI. We cannot exclude that differences in hemodynamic changes during RSI can be attributed to the drug combination given. Furthermore, USCOM itself is associated with some restrictions. Patients in our study for instance, were ventilated mechanically post-RSI which contributes to difficulties in CO measurements by an ultrasound-based device. Moreover, some studies indicated that USCOM tends to underestimate the real CO value when it is relatively high [16-18]. On the contrary, such a difference does not appear in Su *et al's* research [17,18]. They investigated patients with liver cirrhosis because of their unique hyperdynamic status with high CO values ranged up to 13.6 L/min, and found that even at high CO values, USCOM still reliably measures CO [17,18].

Conclusion

We agree with Jabre *et al.*, that ketamine is a safe and valuable alternative to etomidate for RSI. Particularly, in septic patients, with primary necessity for vasopressants, USCOM measurements during RSI support the excellent hemodynamic tolerance of ketamine in such a patients setting. For hemodynamic monitoring, USCOM is easy to use, and the physician will obtain a result in an unbeatable period of time. It seems to be appropriate in situations where CO measurement is most pertinent to patient management.

Competing interests

The Author's declare that they have no competing interests.

Authors contributions

Geiger S, Stemmler HJ, Strecker N, Horster S – study design, patient recruitment, USCOM examinations, preparation of manuscript
Tischer J, Pastore A, Hausmann A – data management, preparation of manuscript.

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