Ketanest In Septic Shock

Published: 31-12-2008
Last updated: 11-05-2024

Primary Objective: To compare ketanest induction and maintenance to etomidate induction and maintenance with midazolam and fentanyl on hemodynamic, ventilatory and endocrine parameters during the first 2h after the diagnosis of sepsis and in need of...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON32350

Source
ToetsingOnline

Brief title
KISS

Condition

- Other condition
- Bacterial infectious disorders

Synonym
sepsis

Health condition

ernstig zieke intensive care patienten

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ketamine-S, ketanest, sepsis

Outcome measures

Primary outcome

These variables are measured every hour during the first 8 hours. However,

these variables will be measured every 10 minutes during:

1. the first 2 hours following the induction of anesthesia (0-1h)

2. the first 2 hours after the switch to midazolam/fentanyl anesthesia (2-3).

CVP (10 min average)

HR/BP (10 min average)

MAP (10 min average)

Urine output (60 min average)

ScvO2

Resuscitation volume (specific sum)

Inotropic support (value of rate and cumulative dose)

Vasopressor support (value of rate and cumulative dose)

Secondary outcome

1. ventilatory and oxygen delivery variables

Airway pressures / FiO2 / tidal volume / Arterial blood analysis / Lactate/Hb,

are measured every hour during the first 4 hours, and after 8 hours.

2. Adverse psychological reactions

During the observation period, checking the medical record upto 24 hours after

induction, and, if possible, asking the patient for adverse psychological

effects as soon as possible after awaking and after extubation.

3. Adrenal gland responsiveness

Before induction: basal serum total cortisol, free cortisol, and

11beta-deoxycortisol

At 6 and 24 hrs after induction of anesthesia: basal serum total cortisol, free

cortisol, and 11beta-deoxycortisol followed by a standard high dose (250 ug of

synthetic ACTH) Synacthentest, with measurements of total, free cortisol and

11-beta deoxycortisol at 0, 30 and 60 minutes.

4. Inflammatory markers

Baseline, 6 and 24 hours: IL6, TNFa

Study description

Background summary

Ketamine is a NMDA receptor antagonist causing dissociative anesthesia, introduced in the 1970s. Advantages like spontaneous breathing, hemodynamic stability, and the combination of anesthesia and analgesia were offset by adverse psychological reactions, like hallucinations. Besides, it is also a cheap anesthetic, and therefore frequently used in developing countries nowadays.
However, since the introduction of its S(+) enantiomer, ketanest, in 1990, there has been a renewed interest in the clinical applicability of this drug. Ketanest is associated with fewer side effects (1). One particular interesting area may be its use during early sepsis if it is decided that the patient should be intubated and ventilated. Patients presenting with sepsis or septic shock receive early goal-directed therapy, according to the surviving sepsis campaign guidelines (2,3), in an attempt to restore normal physiology. The use of ketanest during sepsis may have some striking advantages contributing to the restoration of normal physiology.
The first advantage may be cardiovascular stability. All induction agents,

including ketanest, are cardiodepressive. However, ketamine may be the least cardiodepressive induction agent (4). Ketanest causes an, central nervous system mediated, increased sympathetic nervous system activity overruling the direct cardiodepressive effects. Consequently, and in contrast to other induction agents, cardiac output and blood pressure usually rise during the induction phase. Some concern may be justified about the use of ketanest in critically ill, catecholamine depleted, patients (5), since they cannot increase their sympathetic nervous system activity. However, a randomised clinical trial on this matter is lacking.

During sedation with ketamine, van der Linden and co-workers ((7) found ketamine to preserve cardiovascular stability better than other anesthetic agents in dogs with induced septic shock. Notably, in the same study, the authors noted that ketamine appeared to have the least deleterious effects on the hypoxic tissues, as lactate levels fell only in the ketamine group.

Finally, it is conceivable that stimulating the sympathetic nervous system, instead of infusing exogeneous catecholamines, contributes to the restoration of normal physiology.

The second advantage may be the preservation of spontaneous ventilation and bronchodilation. The former will preserve diaphragm tone, thus contributing to the prevention of atelectasis. The latter is probably caused by both, direct effects on the smooth muscles of the airway, and indirect effects through the increased sympathetic nervous system activity. The bronchodilation caused will reduce airway resistance. The preservation of spontaneous ventilation and brochodilation together will maintain, or possibly improve, compliance. It remains to be seen whether this effect is of enough importance to be detected in septic patients.

The third advantage may be the antiinflammatory effect of ketanest. Mazar and collegeas (8) found that in mice with sepsis ketamin reduced mortality, leucocyte recruitment, as well as tumor necrosis factor a (TNFa) and interleukin (IL) 6 levels. Roytblat and co-workers (9) found that a single dose of ketamine (0.25 mg/kg) before cardiopulmonary bypass (CPB) suppressed the increase in serum IL6 during and after coronary bypass grafting (CABG) in man. Likewise, Bartoc and co-workers (10) found ketamine (0.5 mg/kg) to attenuate increases in C-reactive protein (CRP), IL6 and IL10 while decreasing vasodilation after CPB in man.

These advantages suggest ketanest to be a potentially beneficial induction and sedation agent in patients with sepsis in need of ventilatory support. However, to the best of our knowledge, randomised clinical trials into this matter are non-existent, as has been noted before (11).

Most physicians may be inclined to induce anesthesia with etomidate in patients with septic shock, regarding its favourable effect on cardiovascular stability. However, in recent years increasing evidence points out that even a single shot of etomidate may cause adrenal insufficiency (12,13). This growing awareness on the adverse effects of etomidate and the growing evidence on the potential advantages of ketanest induction in critically ill septic patients urges a study on the comparison of both agents.

Study objective

Primary Objective: To compare ketanest induction and maintenance to etomidate induction and maintenance with midazolam and fentanyl on hemodynamic, ventilatory and endocrine parameters during the first 2h after the diagnosis of sepsis and in need of mechanical ventilation.
We hypothesise that (restoration of) a adequate circulation are reached sooner and with less inotropic support, fluids and RBC transfusions using ketanest.

Secondary Objective(s): Furthermore, we hypothesise that adrenal gland is not suppressed following induction of anesthesia with ketanest, in contrast to induction with etomidate.

Study design

prospective single center randomized not-blinded clinical trial

Intervention

Patients accepted for this study are randomised to either the ketanest (K) or etomidate (E) group. The primary objective in patients with septic shock is restoration of adequate tissue perfusion. The only a priori difference in treatment will be the induction and maintenance agent.
The K protocol demands induction with ketanest (1.0 mg/kg) and rocuronium 1.2 mg/kg, followed by maintenance with ketanest (1-3mg/kg/h). The E group is induced with etomidate 0.2 mg/kg and rocuronium 1.2 mg/kg, followed by maintenance with midazolam (4-10 mg/h) and fentanyl (100ug/h). Maintenance doses must be titrated to effect.
Two hours after induction of anesthesia (i.e. start of the intervention) maintenance with ketanest will be switched to midazolam and fentanyl. Sedation with midazolam and fentanyl must be continued for at least 22 hours in order to prevent adverse psychological effects.

Study burden and risks

Ketamine is well known for its psychological side effects. Ketanest is associated with less side-effects (1). It has been hypothesised that adverse psychological reactions are only associated with recovery from ketanest anesthesia. These adverse psychological reactions (incidence ranges from 3-100%) consist of hallucinations, illusions, confusion and vivid dreaming, are normally short lived, and (partially) prevented by midazolam. There is no data on the appropriate rate or duration of midazolam infusion.
In this study ketanest infusion will be stopped 2 hours after induction of anesthesia, and replaced by fentanyl infusion. Midazolam and fentanyl will be infused continuously for at least another 23 hours, in order to prevent possible adverse psychological reactions associated with recovery from ketanest

anesthesia.

Contacts

Public
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
1081 HV Amsterdam
NL
Scientific
Vrije Universiteit Medisch Centrum

de Boelelaan 1117
1081 HV Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. fullfilling SIRS criteria with a supposed infectious cause,
2. in need for ventilatory support.
3. to be intubated on the ICU.

Exclusion criteria

1. <18 years and >80 years old.

2. symptomatic coronary artery disease.
3. due to have surgery within 4 hours.
4. already on corticosteroid therapy
5. pregnancy.
6. pulmonary hypertension.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2008
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ketanest
Generic name:	Ketamin-S
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	31-12-2008
Application type:	First submission

Review commission: METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-002598-11-NL
CCMO	NL22992.029.08