Managing specific problems within anesthesia

Alexander Sartorius

Head of ECT Research and Supervison
Head, Research Group Translational Imaging
Department of Psychiatry and Psychotherapy
Central Institute of Mental Health (CIMH)
Medical Faculty Mannheim
University of Heidelberg
ECT – anesthesia:

1. Ketofol – two stones to catch one bird?
2. Oxygen – the good gas!
3. What’s that on the printout / monitor?
Part 1: Ketofol
<table>
<thead>
<tr>
<th>substance</th>
<th>typical dose range (mg/kg)</th>
<th>anticonvulsive effect (relative)</th>
<th>remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>methohexital</td>
<td>0.75-1.0</td>
<td>1-2</td>
<td>former gold standard, cardiovascular depression</td>
</tr>
<tr>
<td>thiopental</td>
<td>2-5</td>
<td>2</td>
<td>cardiovascular depression</td>
</tr>
<tr>
<td>propofol</td>
<td>1-2</td>
<td>3</td>
<td>shorter seizures, higher seizure threshold</td>
</tr>
<tr>
<td>etomidate</td>
<td>0.2-0.3</td>
<td>0</td>
<td>myocloni</td>
</tr>
<tr>
<td>S-ketamine</td>
<td>0.5-1.5</td>
<td>0</td>
<td>low doses pro-psychotic, higher blood pressure</td>
</tr>
<tr>
<td>alfentanil</td>
<td>0.01-0.015</td>
<td>0</td>
<td>longer time of apnoe, cardiovascular depression</td>
</tr>
<tr>
<td>remifentanil</td>
<td>0.001-0.008</td>
<td>1</td>
<td>similar to alfentanil ?</td>
</tr>
</tbody>
</table>

Adapted from:
Folkerts HW.  
Electroconvulsive therapy. Indications, procedure and treatment results  
Nervenarzt. 2011 Jan;82(1):93-102

Swartz CM  
Electroconvulsive and neuromodulation therapies.  
2009 Cambridge Univ, Cambridge New York Melbourne
Etomidate – a review of robust evidence for its use in various clinical scenarios

G. Erdoes, R. M. Basciani and B. Eberle
Department of Anaesthesiology and PainTherapy, University Hospital Bern, Bern, Switzerland

Etomidate is an intravenous hypnotic with a favourable clinical profile in haemodynamic high-risk scenarios. Currently, there is an active debate about the clinical significance of the drug’s side effects and its overall risk–benefit ratio.

Etomidate-induced transient adrenocortical suppression is well documented and has been associated with increased mortality in sepsis. In surgical patients at risk of hypotensive complications, however, a review of current literature provides no robust evidence to contraindicate a single-bolus etomidate induction. Large randomised controlled trials as well as additional observational data are required to compare safety of etomidate and its alternatives.
ECT – anesthesia:

- thiopental 3-5 mg/kg
- methohexital 50-120 mg
- propofol 1-2 mg/kg
German guidelines for tx of status epilepticus

1. lorazepam up to 10mg i.v.
2. phenytoin up to 30 mg/kg KG i.v.
3. phenobarbital 20 mg/kg KG i.v.
4. thiopental 4-7 mg/kg KG i.v.

vs. propofol 1-2 mg/kg KG i.v.

vs. midazolam or valproate
Dosing of ECT anesthetics

- experience of the anesthesiologist
- experience from previous ECT sessions
  - time needed for full recovery
  - patient remembers muscle relaxation
  - systematic / non-systematic movements of the “cuffed” limb
- objective criteria for “dosing” and “timing”

do not exist …

Anaesthetic technique in the practice of ECT.
Collins IP, Scott IF.
Bispectral Index Monitoring (BIS)

- has been developed to prevent intraoperative awareness

- uses combined EEG/EMG to derive a measure for “cortical integrity” inter alia by analyzing coherences between different frequency bands

- More precisely: bispectrum is a 3rd order Fourier transformation that includes amplitude, phase AND coherence information. BIS is a normalized index function of the bispectrum.

\[
\begin{array}{ll}
0 & \text{electrically silent brain} \\
100 & \text{fully vigilant patient}
\end{array}
\]
Bispectral Index Monitoring (BIS)

- BIS more valid regarding “hypnosis” compared with other algorithms like spectral edge frequency (SEF), median frequency (MF), or delta, theta, alpha, beta power

How does a typical BIS time course looks like?

A. Sartorius et al., Pharmacopsychiatry. 2006.
Our 1. study on depth of anesthesia: thiopental

Depth of anesthesia:

If BIS - or “light” anesthesia - or better: less anticonvulsive action resulting from anesthetics is important

Why we don’t use an anesthetic without anticonvulsive properties?
ECT and ketamine

pros:

1. Ketamine probably possesses a unique intrinsic antidepressive potential

2. Ketamine has no anticonvulsive action

3. Ketamine may posses neuroprotective properties as an NMDA-antagonist

4. Ketamine is comparable with amantadine and memantine, which are used as 2nd / 3rd line therapy in catatonia.

cons:

1. Ketamine acts non-depressively on the cardio-vascular systemie (like e.g. barbiturates)

2. Ketamine dose-dependently induces psychiatric side-effects (basically derealisation and depersonalisation, which can lead to anxiety)
dose-effect relation

- Ketamine racemate in mg/kg bw i.m. as bolus

Problem:
- Too much ketamine: longer recovery-room time
- Too less ketamine: post ictal agitation, psychomimetic side effects

Other problems:
The use of ketamine in ECT anaesthesia:
A systematic review and critical commentary on efficacy, cognitive, safety and seizure outcomes.
Gálvez V, McGuirk L, Loo CK.
in a multiple logistic regression model, higher adequacy was significantly related with anesthesia ($p<0.001$) - favoring etomidate and ketamine over thiopental and propofol.

Impact of ketamine, etomidate, thiopental and propofol as anesthetic on seizure parameters and seizure quality in electroconvulsive therapy: A retrospective study
Carolin Hoyer, Laura Kranaster, Christoph Janke, Alexander Sartorius
Eur Arch Psychiatry Clin Neurosci 2013
Propofol:

Anesthetic of choice for short anesthesia!
But it is an extremely potent anticonvulsant:


The aim of this study was to assess the efficacy and tolerability/acceptability of 6 anesthetic agents in ECT for depressive disorders. We systematically reviewed 14 double-blind randomized controlled trials (610 participants). Efficacy was measured by the mean scores on validated depression scales at 6 ECT (or the nearest score if not available), number of responders at the end of treatment and seizure duration. The acceptability was measured by the proportion of patients who dropped out of the allocated treatment, and the tolerability by the number of serious adverse events and post-treatment cognition assessment.

After excluding the trials responsible for heterogeneity, depression scores of patients who were administered methohexital were found to be significantly more improved than those who received propofol ($p = 0.001$).
On the contrary, those who were administered propofol had lower depression scores than those with thiopental at the end of treatment ($p = 0.002$). Compared to propofol, methohexital was found to be significantly associated with higher seizure duration ($p = 0.018$). No difference was found for the acceptability profile (all $p > 0.05$). In summary, ketamine and methohexital may be preferred to propofol or thiopental in regard of effectiveness in depression scores and increased seizure duration. Further studies are warranted to compare ketamine and methohexital.

But: low number of included studies, problems with heterogeneity, overall no impressive differences
combined anesthesia:

- S- ketamine plus remifentanil
- S- ketamine plus dexmedetomidine

opioid, syringe pump
syringe pump
### Dexmedetomidine studies:

<table>
<thead>
<tr>
<th>comparator</th>
<th>results</th>
<th>study type</th>
<th>published</th>
</tr>
</thead>
<tbody>
<tr>
<td>propofol versus propofol + dexmedetomidine</td>
<td>seizure length and recovery time better for</td>
<td>retrospective</td>
<td>J ECT 2013</td>
</tr>
<tr>
<td>propofol + dexmedetomidine versus midazolam</td>
<td>less PIA and less propofol</td>
<td>RCT</td>
<td>J Anesth 2009</td>
</tr>
<tr>
<td>propofol + dexmedetomidine versus saline</td>
<td>less acute hyperdynamic response</td>
<td>RCT</td>
<td>Acta An Scand 2008</td>
</tr>
<tr>
<td></td>
<td>prevents PIA</td>
<td>3 case reports</td>
<td>J ECT 2x 2013, 2010</td>
</tr>
</tbody>
</table>
Dexmedetomidine + S-Ketamine, own data…: 

n=178 ECTs

Table 3: Multivariate repeated measurement logistic regression analysis for prediction of PIA-occurrence

|                          | OR   | Standard error | z    | p>|z| | [95% CI]       |
|---------------------------|------|----------------|------|------|----------------|
| Dexmedetomidine use       | 0.059| 0.049          | -3.38| 0.001| 0.011-0.303    |
| Unilateral                | 0.587| 0.648          | -0.48| 0.630| 0.067-5.114    |
| S-ketamine dose           | 0.070| 0.093          | -2.01| 0.045| 0.005-0.937    |
| Stimulation dose          | 1.010| 0.008          | 1.21 | 0.226| 0.993-1.027    |

Number of observations: 176, number of groups: 7.

combined anesthesia:

- S- ketamine plus remifentanil  
  opioid, syringe pump
- S- ketamine plus dexmedetomidine  
  syringe pump
- S- ketamine plus propofol
combined anesthesia:

- ketamine plus propofol = ketofol:

But keep in mind:

- Ketofol is **not** i.v. ketamine and then add i.v. propofol !!!

You can apply either a mixture OR propofol and then ketamine
Search results
Items: 6

1. **The safety and efficacy of adjunctive ketamine in electroconvulsive therapy: Response to Drs. Fong and Boyer.**
   - McGirr A.
   - PMID: 25163193
   - Similar articles

2. **A systematic review and meta-analysis of randomized controlled trials of adjunctive ketamine in electroconvulsive therapy: efficacy and tolerability.**
   - McGirr A, Berlim MT, Bond DJ, Neufeld NH, Chan PY, Yatham LN, Lam RW.
   - PMID: 25584151
   - Similar articles

3. **Ketofol-Dexmedetomidine combination in ECT: A punch for depression and agitation.**
   - Shams T, El-Masry R.
   - PMID: 25024469 Free PMC Article
   - Similar articles

4. **Is ketamine-propofol mixture (Ketofol) an appropriate alternative induction agent for electroconvulsive therapy?**
   - Firouzian A, Tabassomi F.
   - PMID: 24383006 Free PMC Article
   - Similar articles

5. **Ketofol in electroconvulsive therapy anesthesia: two stones for one bird.**
   - PMID: 22023080
   - Similar articles

6. **Ketofol (mixture of ketamine and propofol) administration in electroconvulsive therapy.**
   - PMID: 22417028 Free Article
   - Similar articles
Anesthesia beyond the usual suspects:

- Ketofol

Ketofol in electroconvulsive therapy anesthesia: two stones for one bird.

Table 1  Seizure duration and recovery times of patients

<table>
<thead>
<tr>
<th>Incident</th>
<th>Propofol group (n = 30)</th>
<th>Ketamine group (n = 30)</th>
<th>Ketofol group (n = 30)</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor seizure (s)</td>
<td>29.3 ± 5.1</td>
<td>37.2 ± 3.2*</td>
<td>34 ± 5.8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Spontaneous breathing (s)</td>
<td>252 ± 13.1</td>
<td>266.6 ± 11.5*</td>
<td>260.7 ± 8.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Open eyes (s)</td>
<td>413.1 ± 19.8</td>
<td>538.8 ± 43.2*+</td>
<td>436.2 ± 32.1</td>
<td>&lt;0.001, &lt;0.001</td>
</tr>
<tr>
<td>Obey commands (s)</td>
<td>514.3 ± 38.7</td>
<td>576.5 ± 37.6*+</td>
<td>519.9 ± 31.1</td>
<td>&lt;0.001, &lt;0.001</td>
</tr>
</tbody>
</table>

* p < 0.001 (post hoc Bonferroni) compared with group propofol
+ p < 0.001 (post hoc Bonferroni) compared with group ketofol
OBJECTIVE:
The objective of this review is to investigate existing literature in order to delineate whether the use of anaesthesia and timing of seizure induction in a new and optimised way may improve the efficacy of electroconvulsive therapy (ECT).

METHODS:
PubMed/MEDLINE was searched for existing literature, last search on 24 June 2015. Relevant clinical studies on human subjects involving choice of anaesthetic, ventilation and bispectral index (BIS) monitoring in the ECT setting were considered. The references of relevant studies were likewise considered.

RESULTS:
Propofol yields the shortest seizures, etomidate and ketamine the longest. Etomidate and ketamine+propofol 1 : 1 seems to yield the seizures with best quality. Seizure quality is improved when induction of ECT is delayed until the effect of the anaesthetic has waned - possibly monitored with BIS values. Manual hyperventilation with 100% O2 may increase the pO2/pCO2-ratio, which may be correlated with better seizure quality.

CONCLUSION:
Etomidate or a 1 : 1 ketamine and propofol combination may be the best method to achieve general anaesthesia in the ECT setting. There is a need for large randomised prospective studies comparing the effect of methohexital, thiopental, propofol, ketamine, propofol+ketamine 1 : 1 and etomidate in the ECT treatment of major depressed patients. These studies should investigate safety and side effects, and most importantly have antidepressant efficacy and cognitive side effects as outcome measures instead of seizure quality.
Own experiences with ketofol:

- anesthesiologists are excited
- less time in recovery room
- less side effects regarding post ictal agitation and psychomimetic problems
- propofol is still critical regarding seizure threshold/induction
Own experiences with ketofol:

- Data* on mixture (propofol/S-ketamine):

<table>
<thead>
<tr>
<th></th>
<th>mean</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>propofol</td>
<td>53 mg</td>
<td>20 mg</td>
<td>130 mg</td>
</tr>
<tr>
<td>S-ketamine</td>
<td>62 mg</td>
<td>20 mg</td>
<td>100 mg</td>
</tr>
<tr>
<td>Ratio of propofol/S-ketamine</td>
<td>0.87</td>
<td>0.4</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Thus a ratio of ~1:1 propofol/S-ketamine was clinically sufficient,

Which corresponds to 1:2 propofol/ketamine

* Retrospective data from the first 30 patients and ca. 500 ECT sessions
1. Lighter anesthesia is more effective (not so with ketamine and etomidate)

2. PIA risk increases with lighter anesthesia!
   (up to 50% with unmodified ECT (Andrade et al., Indian J Psychiatry. 2012))

=> Not less anesthetic, but more time!

3. PIA risk decreases with post ECT dexmedetomidine treatment

4. Ketofol decreases PIA risk and it might be anyway a good choice
Part 2: Oxygen
Capnometria:

**Figure 2:** Mean time course of transcutaneously measured pCO₂ and pO₂ level. The mean onset of (pre-)oxygenation, muscle relaxation, start of ECT and 2 minutes post ECT are labeled.

New Evidence for Seizure Quality Improvement by Hyperoxia and Mild Hypocapnia.
Aksay SS, Bumb JM, Janke C, Hoyer C, Kranaster L, Sartorius A.
J ECT. 2014 Mar 12.

<table>
<thead>
<tr>
<th></th>
<th>Lowest Quartile of tcpO₂ (&lt;199 mm Hg)</th>
<th>Utmost Quartile of tcpO₂ (&gt;357 mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Energy</td>
<td>Seizure Quality</td>
</tr>
<tr>
<td>Lowest quartile of tcpCO₂ (&lt;36 mm Hg)</td>
<td>63 ± 5</td>
<td>3.41 ± 0.17</td>
</tr>
<tr>
<td>Utmost quartile of tcpCO₂ (&gt;45 mm Hg)</td>
<td>72 ± 4</td>
<td>3.16 ± 0.28</td>
</tr>
</tbody>
</table>

Errors indicated are standard error of the mean.
New Evidence for Seizure Quality Improvement by Hyperoxia and Mild Hypocapnia.
Aksay SS, Bumb JM, Janke C, Hoyer C, Kranaster L, Sartorius A.
J ECT. 2014 Mar 12.
Part 3: What’s going on?
Shivering
Another shivering
Postanesthetic shivering (PAS) is shivering after anesthesia is not fasciculating, is not myocloni, is not restless legs!

The intensity of PAS may be graded using the scale described by Crossley and Mahajan:

0 = no shivering;
1 = no visible muscle activity but piloerection, peripheral vasoconstriction, or both;
2 = muscular activity in only one muscle group;
3 = moderate muscular activity in more than one muscle group but no generalized shaking;
4 = violent muscular activity that involves the whole body.
Rare side effect of propofol:

video
Very different from myocloni frequently seen with etomidate and sometimes even with S-ketamine:

video
Typical fasciculations due to succinylcholine: video
Shivering:

video
Treatment of PAS

1. clonidine
2. dexmedetomidine
3. mivacurium instead of succinylcholine
4. probably more often with barbiturates / propofol and less with ketamine

What is the place of clonidine in anesthesia? Systematic review and meta-analyses of randomized controlled trials.
Sanchez Munoz MC, De Kock M, Forget P.

Systematic Quality Assessment of Published Antishivering Protocols.
Choi KE, Park B, Moheet AM, Rosen A, Lahiri S, Rosengart A.

Efficiency and safety of ondansetron in preventing postanaesthesia shivering.
He K, Zhao H, Zhou HC.

Effectiveness of dexmedetomidine use in general anesthesia to prevent postoperative shivering: a systematic review.
Hoffman J, Hamner C.
Snooring
Geriatric ECT at 160% RUL. Concordance 0.72. PSI 47% (artifact). Coherence 71%, max. heart rate 90 bpm. Midictal amplitude 63uV.
Post stimulus asystole

Geriatric ECT at 160% RUL. Concordance 0.72. PSI 47% (artifact).
Coherence 71%, max. heart rate 90 bpm. Midictal amplitude 63uV.
Asystolia (physiologic) of > 12s.
Asystolia appears shorter in our printout (printout starts at the end of charge delivery!)
Risk factors for post-stimulus asystole

1. age
2. BIL
3. subconvulsive stimuli (especially together with beta-antagonists)
Incidence of post-stimulus asystole

- > 50% !!!

- conclusion:  
  1. frequent! (probably very physiologic, low risk)
  2. BIL > RUL > BF
  3. age
quetiapine 0-0-0-300 mg
venlafaxin 75-0-0-0 mg
donepezil 0-0-0-5 mg
torasemid 5-0-0-0 mg
L-thyroxin 25-0-0-0 µg
aspirin 0-0-100 mg
pantoprazol 0-0-40-0 mg
Conclusion:

Caution!

Noradrenergic drugs can massively increase blood pressure and are proarrhythmogenic!

Abstract

CONTEXT: Medication resistance is the leading indication for use of electroconvulsive therapy (ECT) in major depression. The practice of stopping antidepressant medications prior to ECT derived from studies in the 1960s and 1970s in nonresistant samples. There is also continuing controversy regarding the relative efficacy and adverse effects of right unilateral and bilateral ECT.

OBJECTIVE: To test the hypotheses that, compared with placebo, concomitant treatment with nortriptyline or venlafaxine during the ECT course enhances short-term efficacy without a meaningful effect on adverse effects and reduces the rate of post-ECT relapse, and to test the hypotheses that high-dose, right-sided, unilateral ECT is equivalent in efficacy to moderate-dosage bilateral ECT and retains advantages with respect to cognitive adverse effects.

DESIGN: Prospective, randomized, triple-masked, placebo-controlled study conducted from 2001 through 2005.

SETTING: Three university-based hospitals.

PATIENTS: Of approximately 750 consecutive patients referred for ECT, 319 with a major depressive episode consented, were randomized to pharmacological or ECT treatment conditions, and received at least 1 ECT treatment.

MAIN OUTCOME MEASURES: Scores on the Hamilton Rating Scale for Depression, remission rate following completion of ECT, and selective measures of cognitive adverse effects.

RESULTS: Treatment with nortriptyline enhanced the efficacy and reduced the cognitive adverse effects of ECT relative to placebo. Venlafaxine resulted in a weaker degree of improvement and tended to worsen cognitive adverse effects. High-dosage right unilateral ECT did not differ or was superior to bilateral ECT in efficacy and resulted in less severe amnesia.

CONCLUSIONS: The efficacy of ECT is substantially increased by the addition of an antidepressant medication, but such medications may differ in whether they reduce or increase cognitive adverse effects. High-dose, right-sided, unilateral ECT is at least equivalent to moderate-dosage bilateral ECT in efficacy, but retains advantages with respect to cognitive adverse effects.
Pacemaker?
Pacemaker

- ECT is per se proarrythmogenic (thus pacemaker is good)

- ICDs might be problematic due to theoretical dysfunction (i.e. stimulation) during the seizure
Pacemaker / ICD

video
Pacemaker and stimulation

video
to conclude:

- shivering / myocloni / fasciculations / restless legs can happen

- ECT proarrhythmogenic

- post stimulus asystolia is frequent and physiologic

- post ictal asystolia is rare and potentially problematic

- pacemaker / ICDs are non-problematic
Thank You
Acknowledgement:

Director (Central Institute of Mental Health):
A. Meyer-Lindenberg

Department of Psychiatry and Psychotherapy
Laura Kranaster
Suna Su Aksay
Jan Malte Bumb
Anna Becker
Juliane Beuschlein

Department of Anaesthesiology and Critical Care Medicine
Christoph Janke
Dmitry Remennik

Alumni:
Franz-Josef Andres
Andreas Krier
Walter Hewer
Eva-Maria Munoz-Canales
Bogata D. Bundy
Jutta Kammerer
Carolin Hoyer