Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial

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Editor's key points

- This study aimed at comparing the haemodynamic effects of a bispectral index (BIS)-guided etomidate and propofol infusion for anaesthesia induction in patients undergoing major abdominal surgery.
- Before intubation, no significant blood pressure, heart rate, nor cardiac index differences between the two groups were noticed.
- Propofol use resulted in less hypertension and tachycardia at and after intubation than etomidate, but in more hypotension.

Background. In a double-blind, randomized trial, we compared the haemodynamic effects of a bispectral index (BIS)-guided etomidate and propofol infusion for anaesthesia induction in patients undergoing major abdominal surgery.

Methods. Forty-six patients were randomly assigned to two groups based on the induction of anaesthesia, performed with a BIS value of 60 titrated infusion of etomidate (E group) or propofol (P group). Mean arterial pressure (MAP), cardiac index (CI), heart rate, and systemic vascular resistance index (SVRI) measurements were taken 1 min before induction and recorded at 1-min intervals for 20 min. P<0.05 was considered statistically significant.

Results. Before intubation, no significant differences between the two groups regarding the haemodynamics were noticed. At intubation and up to 7 min after intubation MAP (P=0.019) was significantly higher in the E group. CI was significantly higher in the E group with respect to the P group 2, 6, and 7 min after intubation. Twenty-three patients developed complications. The incidence of hypotension was higher in the P group than that in the E group (8 vs 3; P=0.08), and the incidence of hypertension was significantly higher in the E group than that in the P group (10 vs 2; P=0.007).

Conclusions. Our study showed that the use of propofol resulted in less hypertension and tachycardia at and after intubation than etomidate. But even with the reduced doses given with the BIS-guided protocol, it often caused significant hypotension.

Keywords: anaesthetics i.v., etomidate; anaesthetics i.v., propofol; consciousness monitors, bispectral index; heart, cardiac index

Accepted for publication: 29 September 2012

Propofol and etomidate are frequently used induction agents with similar onset and duration of action and to some extent different unwanted effects.1–6 Most studies, which compared the haemodynamic effects of both agents, were usually performed without monitoring the depth of anaesthesia, which raises the question to what extent the observed differences between both anaesthetics are related to the differences in the anaesthesia depth.5–7–13 In addition to this, the mechanisms of the haemodynamic changes are not completely understood since cardiac index (CI) was not measured in earlier studies.

The aim of our study was to compare the haemodynamic effects of the infusion of both agents during the induction, orotracheal intubation, and 10 min after intubation in a double-blind, randomized trial. Our hypothesis was that the titration of both anaesthetics to an appropriate depth of anaesthesia will reduce their required dose and alleviate negative haemodynamic effects after intubation. We were interested which agent causes more hypertension and tachycardia at intubation and which more hypotension and bradycardia after intubation. CI, mean arterial pressure (MAP), and heart rate (HR) were taken as the primary outcome variables.

Methods

We studied 46 ASA class III patients, undergoing major abdominal surgery because of cancer under combined general and epidural anaesthesia. The study was approved by the National Medical Ethics Committee (Ref.: 118/12/09) and registered at Current Clinical Trials (www.controlled-trials.com): ISRCTN68690518. Written informed consent was obtained from each patient.

The exclusion criteria were: left ventricular ejection fraction <30%, haemodynamic significant valve disease, inserted pacemaker, chronic abuse of alcohol, drugs or psychotropic agents, BMI >30, Mallampati 3 and 4, serum creatinine...
>120 mmol litre⁻¹, manifest liver disease, Alzheimer disease, and epilepsy.

All patients were fasting overnight, had the same bowel cleansing procedure, and took their regular medication on the morning of the surgery except angiotensin-converting enzyme inhibitors. Premedication consisted of oral midазo-лам 0.1 ± 0.02 mg kg⁻¹ 1 h before surgery. Upon arrival to the operating theatre, an i.v. line was placed and Ringer’s solution 10 ml kg⁻¹ was administered until the measurements were started, non-invasive blood pressure was measured, and ECG and pulse oximeter monitors were attached. An epidural catheter was inserted in the lower thoracic region and 3 ml of 2% lidocaine (Xylocaine 2%, AstraZeneca, UK) were administered epidurally 20 min before the start of the measurements. An arterial line was placed into the radial artery and the LiDCOrapid monitor (LiDCCardiac Sensor Systems, Cambridge, UK) for measuring CI was attached. BIS electrodes were placed and A-2000 BIS monitor XP platform (Aspect Medical Systems, Cambridge, MA, USA) with a smoothing rate of 15 s was attached. The perfusor (Alaris CC for 50 ml syringe, Cardinal Health, Dublin, Ireland) with the anaesthetic agent for induction was prepared by an independent contributor. The anaesthetic agent was determined by a coin flip.

The patients were randomly assigned to one of the two treatment groups with respect to the anaesthetic agent used for induction of anaesthesia. The propofol group (P group) received propofol (Propoven Fresenius 1%, Fresenius Kabi, Bad Homburg, Germany) at the infusion speed during induction of 0.5 mg kg⁻¹ min⁻¹ and the etomidate group (E group) received etomidate (Etomidat-Lipuro 2%, B. Braun, Melsungen, Germany) at the infusion speed of 0.05 mg kg⁻¹ min⁻¹. One minute after the baseline haemodynamic measurements were taken, fentanyl (Fentanyl, Janssen-Cilag Pharma, Belgium) 3 μg kg⁻¹ was administered intravenously. Two minutes after fentanyl administration, an infusion of the anaesthetic agent was initiated. As soon as the BIS value reached 60, the anaesthetic infusion was stopped and the consumed dose of the anaesthetic was recorded by the independent contributor. We measured the time from the start of the anaesthetic infusion until the following: the loss of palpebral reflex, the decrease in the BIS value to 60, and the orotracheal intubation. After palpebral reflex loss, rocuronium 0.6 mg kg⁻¹ (Esmeron, N.V. Organon, Oss, Netherlands) was given and 1 min later the patient was orotracheally intubated by the main examiner who was unaware of the induction agent type. Each intubation was successful at the first attempt and took <20 s. After intubation, the patient was mechanically ventilated (Dräger-Primus, Germany) with a mixture of oxygen and air (1:1) with the addition of sevoflurane 1 vol% which was included into the gas mixture immediately after intubation and reached 1 vol% in the gas mixture ~10 min after intubation. The tidal volume was 7 ml kg⁻¹, the breathing frequency was 12 min⁻¹, and fresh gas flow was 2 litre min⁻¹. Haemodynamic and BIS measurements were activated 1 min before i.v. fentanyl administration. They were recorded every minute for 20 min. End-tidal CO₂ (etCO₂) and end-tidal sevoflurane (etSevo) were recorded at intubation and every 5 min after intubation. Data were stored in an IBM-compatible computer. Systemic vascular resistance index (SVRI) was calculated as follows: SVRI = MAP/CI × 80.

All complications were treated after 1 min of their duration. Hypotension (MAP ≤ 55 mm Hg) was treated with phenylephrine 50 μg until the desired clinical effect was achieved. Hypertension (MAP ≥ 100 mm Hg) was treated with fentanyl 1 μg kg⁻¹ up to three times and afterwards with a nitroglycerine infusion (10–100 μg min⁻¹). Bradycardia (HR ≤ 40 min⁻¹) was treated with atropine 0.3 mg up to three times and afterwards with ephedrine 5 mg. Tachycardia (HR ≥ 90 min⁻¹) was treated with fentanyl 1 μg kg⁻¹ up to three times.

Data were analysed with the IBM SPSS Statistics 18 statistical software. Patients’ characteristics and baseline values were compared using a t-test for independent samples, the Kruskal–Wallis test, and χ² where appropriate. The analysis of variance for repeated measurements with Bonferroni correction was performed to compare the haemodynamic effects between the two groups and compare the haemodynamic data before, during, and after intubation with baseline values. P ≤ 0.05 was considered statistically significant.

Sample size calculation to detect a difference in CO of 1 litre min⁻¹ (± 1.3 litre min⁻¹) among treatment groups with a probability level of 0.05 and power of 0.80 yielded a sample size of 22 patients for each treatment group.

Results

The flow diagram of the conduct of the study is shown in Figure 1. We randomized 48 patients. Two patients were excluded from data analysis as a result of technical problems. Therefore, 46 patients were included in the analysis. No significant differences between the two groups with respect to patient characteristics, diagnoses, baseline haemodynamic, and BIS measurements (Table 1) were noticed.

The mean consumed anaesthetic dose was 1.14 ± 0.33 mg kg⁻¹ for propofol and 0.15 ± 0.05 mg kg⁻¹ for etomidate. The time from the start of the anaesthetic infusion until the loss of palpebral reflex (P=0.002), the time from the start of the infusion until BIS value 60 (P=0.003), and the time from the start of the infusion until orotracheal intubation (P=0.003) were significantly longer in the E group compared with the P group (Table 2).

Haemodynamic data measured during the study and the BIS values for both study groups are shown in Table 3. Before intubation, there were no significant differences between the groups with respect to haemodynamics, BIS, and saturation. In the period immediately before intubation MAP, CI, and HR decreased significantly compared with baseline in both groups of patients, while the SVRI remained almost unchanged.
During intubation, there were no significant differences between the two groups with respect to CI, SVRI, HR, and BIS (Table 3). In the P group, MAP was significantly lower than in the E group \((P=0.019)\). In the P group, MAP did not change during intubation and remained significantly decreased with respect to baseline. However, in the E group, MAP increased during intubation and reached approximately the baseline value. In both groups, CI was still significantly decreased at intubation compared with baseline. In the P group, SVRI was significantly increased, whereas in the E group, no significant change in SVRI at intubation was noticed compared with baseline. Both groups showed no significant differences in HR at intubation compared with baseline.

After intubation, MAP was significantly higher until 7 min after intubation \((P<0.05)\) in the E group with respect to the P group (Table 3). In the E group, CI was significantly higher 2 \((P=0.039)\), 6 \((P=0.038)\), and 7 \((P=0.024)\) min after intubation. There were no significant differences between the two groups with respect to HR and SVRI during the measurements after intubation. In both groups, MAP, CI, and HR were significantly decreased after intubation until the end of measurements compared with baseline, except 1 min after intubation, when there were no significant differences compared with baseline in all these parameters in the E group and HR in the P group. In the P group, SVRI was significantly increased after intubation compared with baseline. In the E group, SVRI was significantly increased 8–11 and 13 min after intubation compared with baseline.

The time course of per cent change in MAP, CI, HR, SVRI, and BIS with respect to baseline is shown in Figure 2. In the E group, the per cent change in MAP significantly increased compared with the P group from the time of

**Fig 1** CONSORT flow diagram of the study.
intubation until 7 min after intubation. At the time of intubation and the whole time after intubation, the per cent change in CI was significantly higher in the E group compared with the P group.

There were no significant differences among the groups with respect to per cent change in SVRI and HR at and after the intubation.

At intubation, $e_{CO_2}$ was $4.3\pm0.1$ kPa in the P group and $4.4\pm0.1$ kPa in the E group ($P=0.073$). Five minutes after intubation, $e_{CO_2}$ was $4.2\pm0.2$ kPa in the P group and $4.3\pm0.2$ kPa in the E group ($P=0.089$), etSevo was $0.47\pm0.07$ vol% in the P group and $0.54\pm0.07$ vol% in the E group ($P=0.383$). Ten minutes after intubation, $e_{CO_2}$ was $4.3\pm0.1$ kPa in the P group and $4.2\pm0.2$ kPa in the E group ($P=0.221$), etSevo was $0.96\pm0.06$ vol% in the P group and $0.95\pm0.06$ vol% in the E group ($P=0.816$). There were no significant differences between both groups after intubation regarding $e_{CO_2}$ and etSevo.
During the study, we did not observe any signs of ischaemia, ECG, or ST-segment changes in any patient and no patient reported of awareness. The number of patients with complications and the need for rescue medication is shown in Table 3. Twenty-three patients developed complications; 10 in the P group and 13 in the E group (P=0.376) (Table 4). All complications appeared at or after intubation. There were no significant differences among the groups with respect to bradycardia (P=0.63) and tachycardia (P=0.31) (Table 4). The incidence of hypotension was higher in the P group (P=0.08) and the incidence of hypertension was significantly higher in the E group (P=0.007). A similar difference between the groups was noted with respect to rescue medication (Table 4).

**Discussion**

We studied the influence of the infusion of etomidate and propofol titrated to a BIS value of 60 on changes in haemodynamics before, at, and 10 min after orotracheal intubation in patients undergoing major abdominal surgery. Our study showed that the use of propofol resulted in less hypertension and tachycardia at and after intubation than etomidate. Our study showed that the use of propofol resulted in less hypertension and tachycardia at and after intubation than etomidate. Before intubation, no significant differences between the two groups regarding the haemodynamics were noticed. But even with the reduced doses given with the BIS-guided protocol, propofol often caused significant hypotension.

The CI was measured with the LiDCORapid monitor providing beat-to-beat measurement of CI by analysing the arterial blood pressure tracing. The displayed values are nominal and are derived from a population-based normograph, which may not be absolutely accurate.14 The calculation of CI by arterial pressure waveform analysis could be influenced by several confounders, such as changes in vascular tone (e.g. during intubation) or vasoactive drugs.15 16 In the literature, there is only one study of LiDCORapid validation.17 The authors report that uncalibrated pulse power analysis fails to reliably measure the absolute value of cardiac output in patients undergoing coronary artery bypass surgery. We decided to use LiDCORapid because it only requires a standard radial arterial line and were interested in trends of CI rather than the absolute values. There are no studies in the literature evaluating the validity of the LiDCORapid to follow the changes in CI, but any possible bias, if present, is probably equally distributed between both treatment groups and probably did not influence our results.

The BIS monitor is a well-established monitor for measuring the depth of anaesthesia.18 19 We used it to titrate the induction agents to a BIS value of 60. Our goal was to intubate at a BIS value of ~50, which is in the lower third of the recommended range for general anaesthesia (BIS of 45–60).20 21 and the reported theoretical time delay of the BIS monitor is 10–15 s or even more compared with real time.

In the literature, the recommended bolus induction dose is 1.5–2.5 mg kg⁻¹ for propofol and 0.15–0.4 mg kg⁻¹ for etomidate.2 3 6 In our study, the mean consumption of propofol was 1.14 mg kg⁻¹ (range: 0.4–1.86 mg kg⁻¹) and the mean consumption of etomidate was 0.15 mg kg⁻¹ (range: 0.05–0.25 mg kg⁻¹) to reach the same anaesthesia depth, which was at or below the minimal recommended dose for bolus induction. There was a wide range of dosages needed for induction.

### Table 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Propofol</th>
<th>Etomidate</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>103 (28)</td>
<td>142 (45)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time until palpebral reflex loss (s)</td>
<td>133 (36)</td>
<td>179 (55)</td>
<td>0.003</td>
</tr>
<tr>
<td>Time until BIS = 60 (s)</td>
<td>189 (28)</td>
<td>229 (48)</td>
<td>0.003</td>
</tr>
<tr>
<td>Time until orotracheal intubation (s)</td>
<td>235 (37)</td>
<td>269 (48)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>MAP (mm Hg)</th>
<th>CI (ml min⁻¹ m⁻²)</th>
<th>SVRI (dyne s cm⁻⁵ m⁻²)</th>
<th>HR (s⁻¹)</th>
<th>BIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>96 (13)</td>
<td>3.44 (0.94)</td>
<td>2387 (702)</td>
<td>72 (12)</td>
<td>96 (4)</td>
</tr>
<tr>
<td>4</td>
<td>99 (12)</td>
<td>3.44 (0.98)</td>
<td>2342 (661)</td>
<td>71 (13)</td>
<td>93 (6)</td>
</tr>
<tr>
<td>7</td>
<td>85 (14)</td>
<td>2.60 (1.12)</td>
<td>2557 (715)</td>
<td>67 (15)</td>
<td>59 (13)</td>
</tr>
<tr>
<td>10</td>
<td>98 (15)</td>
<td>2.59 (0.88)</td>
<td>2568 (664)</td>
<td>69 (12)</td>
<td>57 (12)</td>
</tr>
<tr>
<td>13</td>
<td>103 (28)</td>
<td>2.59 (0.91)</td>
<td>2557 (715)</td>
<td>72 (12)</td>
<td>96 (4)</td>
</tr>
</tbody>
</table>

P.<0.05 between the groups. †P.<0.05 with respect to baseline.

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Fig 2 Time course of per cent change in mean arterial pressure, cardiac index, systemic vascular resistance, heart rate and absolute bispectral index values. MAP, mean arterial pressure; CI, cardiac index; SVRI, systemic vascular resistance index; HR, heart rate; BIS, bispectral index.

*P < 0.05 between the groups. †P < 0.05 with respect to baseline.
We decided to use the mentioned speed of infusion of both anaesthetics on the basis of the already described pharmaco-kinetics and pharmacodynamics\(^1\) 22–24 and reports found in the literature (0.50 and 0.75 mg kg\(^{-1}\) min\(^{-1}\) for propofol and 0.1 mg kg\(^{-1}\) min\(^{-1}\) for etomidate).\(^2\) 25 26 Our goal was to titrate both agents to the same BIS value; we were also interested whether the chosen infusion speeds are comparable in terms of similar induction time. The results show that all measured times were on average significantly longer in the E group because of the wider range of dosages required for induction compared with the P group. The mean calculated infusion speed of etomidate was 0.087 mg kg\(^{-1}\) min\(^{-1}\) (57% faster) to achieve the same mean induction time compared with propofol.

In our study, no significant differences were found between the groups in haemodynamics before intubation. During this period, MAP, CI, and HR decreased significantly in both groups. The differences between the groups appeared at and during the first 7 min after intubation when MAP and CI were higher in the E group. The E group was the less effective in minimizing hypertension and tachycardia. As shown in Figure 1, the increase in MAP at and after intubation in the E group was caused by an increase in CI, while the time course of SVRI change was similar in both groups.

No study comparing the effects of BIS-guided induction of anaesthesia with propofol and etomidate on cardiac output before and after intubation was found in the available literature. There are few studies comparing both agents after bolus administration with respect to their effects on CI before, at, and after intubation. Except the mentioned, the depth of anaesthesia was not measured.\(^8\) 27–29 Larsen and colleagues\(^8\) compared the haemodynamic effects of propofol (1.5 mg kg\(^{-1}\)) and etomidate (18 mg) in geriatric patients undergoing major upper abdominal surgery. Similar to our study, they found that both agents decreased MAP, CI, and HR to the same extent after induction and etomidate did not prevent the haemodynamic stress at intubation. Singh and colleagues\(^27\) compared etomidate (0.2 mg kg\(^{-1}\)) and propofol (1.5 mg kg\(^{-1}\)) in patients with coronary artery disease and left ventricular dysfunction. They found that MAP, CI, and HR were significantly decreased after induction and increased after intubation in comparison with the baseline with no significant differences between the groups. Haessler and colleagues\(^28\) studied the influence on haemodynamics of propofol (1.5 mg kg\(^{-1}\)) and etomidate (0.25 mg kg\(^{-1}\)) in patients with aortic insufficiency and coronary artery disease. They found that propofol induced severe hypotension predominantly in patients with severe three-vessel disease. For this reason, they aborted the study in this group whereas in the group of patients with aortic insufficiency both agents seemed to be appropriate for the induction. Only Bendel and colleagues\(^29\) measured the anaesthesia depth with the BIS monitor in their study comparing the haemodynamic effects of propofol and etomidate after slow bolus administration (titrating to BIS 60 or less) until intubation in patients with aortic stenosis. They found that propofol is twice as likely to cause hypotension during induction as etomidate. They also observed a decrease in CI and no change in HR during the induction in both groups with no differences between the groups. It is difficult to compare the results of our study with the studies mentioned above since the study design and the patient groups are very different.

The number of patients developing complications was not significantly different between the groups. However, the incidence of hypotension was significantly higher in the E group, where hypertension always appeared at and/or immediately after intubation. One cause could be an inadequate dose of etomidate despite the adequate BIS value because BIS was not originally validated with etomidate. However, studies showed that BIS is a reliable monitor for measuring anaesthesia depth in the case of etomidate.\(^24\) Lallemand and colleagues\(^10\) also report no difference in hypertension and tachycardia at and after intubation at doses of 0.2, 0.3, and 0.4 mg kg\(^{-1}\). In the P group, one patient had hypertension at intubation and one patient hypertension 10 min after intubation as a result of unexplained reasons. The incidence of hypotension was higher in the P group with the differences between the groups approaching statistical significance limit (P=0.08). As expected, more patients in the P group experienced only hypotension, which occurred in the first 5 min after intubation and after that. In both groups, there was no correlation between the induction dose and the incidence of side-effects.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Number of patients developing complications and rescue medication in each group. *Data are median (range). †P&lt;0.05 between the groups. OTI, orotracheal intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Propofol</td>
</tr>
<tr>
<td>Hypotension</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Dose (µg)</td>
<td>100 (50–200)*</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>5</td>
</tr>
<tr>
<td>Atropine</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>0.45 (0.3–0.6)*</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Dose (mg)</td>
<td>0.075 (0.05–0.1)*</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Dose (µg)</td>
<td>0</td>
</tr>
</tbody>
</table>
BIS-guided anaesthesia induction: propofol or etomidate

We are aware that the relative large dose of fentanyl (for ASA III patients) and the test dose of local anaesthetic via epidural catheter could have had synergistic depressant haemodynamic effects in both groups through the whole time of our study. But in the E group fentanyl did not prevent the intubation stress. After intubation, sevoflurane which was introduced with a slow wash-in technique to delay its haemodynamic (baroreflex depression, depression of the contractility of the heart) and anaesthetic effects (which are concentration dependent) could also have had synergistic depressant haemodynamic effects in both groups, predominantly after the first 5 min after intubation once the concentration in the expired gas reached >0.5 vol% in both groups.

In conclusion, our study showed that the use of propofol resulted in less hypertension and tachycardia at and after intubation than etomidate. But even with the reduced doses given with the BIS-guided protocol, it often caused significant hypotension. However, the use of etomidate was not related to a more stable haemodynamics compared with propofol, especially because of its inability to prevent an increase in HR and blood pressure at and after intubation and its potential to cause hypotension in some patients despite titration to an appropriate anaesthesia depth. Perhaps certain more specific groups of patients, who are sometimes unable to express a stress response after intubation (e.g. elderly and debilitated patients, might profit from the induction with etomidate). To evaluate the haemodynamic effects of both drugs, titrated to the appropriate anaesthesia depth in these groups of patients, further studies are needed.

Acknowledgement
The authors thank Sebastian Möller for help with data preparation and statistical analysis.

Declaration of interest
None declared.

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Handling editor: M. M. R. F. Struys