Comparison of xenon with propofol for supplementary general anaesthesia for knee replacement: a randomized study

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Background. Xenon anaesthesia is associated with rapid recovery and may also offer protection against neuronal damage. The aim of this study was to compare xenon with propofol for supplementary general anaesthesia in patients undergoing knee replacement in spinal anaesthesia.

Methods. In total, 39 patients aged 60 or over were randomized to xenon 50–70% or propofol 3–5 mg kg⁻¹ h⁻¹. Vital signs and emergence time were recorded and cognitive function was assessed before operation, at discharge between the third and the fifth day and at 3 months using four neuropsychological tests.

Results. Propofol supplementation was necessary in six xenon patients (29%) because of detectable movement of the upper body. Emergence time was significantly shorter with xenon (260 s for xenon and 590 s for propofol, *P* = 0.001). There was no significant difference between the groups in blood pressure, heart rate, ventilatory frequency or end-tidal carbon dioxide concentration. No difference could be detected in cognitive function, which may be attributed to insufficient sample-size rather than the absence of a true difference.

Conclusions. Xenon was well tolerated for supplementary general anaesthesia in elderly spontaneously breathing patients but supplementation may be necessary. Compared with propofol, emergence was faster with xenon. A larger sample-size is needed if cognitive function is to be addressed.

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Xenon has been studied as a general anaesthetic since the mid-1950s.¹ It has a limited potency with a MAC at about 70% and it has been shown to have analgesic properties similar to those of nitrous oxide.² Xenon causes little haemodynamic depression³⁴ and it is associated with rapid recovery attributable to very low solubility.⁴ Xenon has been shown to possess neuro-protective effects in experimental studies. This protective effect has been detected both in connection with hypoxia and ischaemia, for instance in embryonic rat cortical neurons placed in an oxygen-free chamber and also in animals undergoing middle cerebral artery occlusion where xenon caused a reduction in infarct volume and improved functional outcome.⁵⁷

Especially in the elderly, there is a risk of postoperative cognitive dysfunction (POCD) after major surgery.⁵ POCD is a deterioration in memory and concentration as detected by neuropsychological testing days to months after surgery and anaesthesia. Age, type of surgery and duration of anaesthesia seem to be the most important risk factors. Given the neuro-protective properties of xenon, it is not unlikely that the drug would reduce the incidence of POCD. Xenon has mostly been used for general anaesthesia with controlled ventilation using tracheal intubation. For many lower body surgery procedures, however, regional anaesthesia is preferred with or without sedation. In this feasibility study we sought to compare the haemodynamic and...
respiratory stability and emergence times between xenon and propofol given as a supplementary general anaesthetic during regional anaesthesia with spontaneous ventilation through a laryngeal mask airway. In addition, we examined cognitive function before and after surgery to explore whether xenon was associated with less postoperative deterioration in cognitive function.

Methods
The study was carried out as a prospective, blinded and randomized trial. Randomization was carried out using numbered, sealed envelopes and the allocation sequence was concealed. Apart from the attending anaesthesia personnel, all personnel as well as the patient were blinded to the agent used during maintenance of anaesthesia. Blinding of the data collecting research nurse was accomplished by not allowing her access to the operating room, recovery room or the anaesthesia record.

The study was approved by the ethics committees in each centre and written informed consent was obtained from all patients. The included patients were undergoing knee replacement with spinal anaesthesia and were aged 60 yr or older. Patients were excluded if a laryngeal mask airway was contraindicated, for instance if BMI was >35 kg m⁻². Patients with an expected high operative risk were also excluded. This was defined as a plasma creatinine >200 μmol litre⁻¹ or an ASA physical status classification above III. Finally, patients were excluded if they had CNS disease including dementia, defined as a mini mental state examination score <24.

Pre-medication was not used but midazolam 1–5 mg (Dormicum®, Roche, Basel, Switzerland) was given i.v. immediately before the start of regional anaesthesia after initial monitoring with ECG, oscillometric blood pressure and pulse oximetry.

Spinal anaesthesia was performed with bupivacaine 15 mg (Marcain®, Astra-Zeneca, Södertälje, Sweden), Intrathecal morphine (Morfin, Duk®, Nycomed, Roskilde, Denmark) 0.1 mg was added or, as an alternative, an epidural catheter was inserted for postoperative analgesia.

Once an effective neural blockade had been established, 100% oxygen was given by a face mask for 3 min before induction of anaesthesia with propofol 1–2 mg kg⁻¹ (Propofol, B. Braun, Melsungen, Germany). A laryngeal mask airway (LMA Classic®, LMA North America, San Diego, CA, USA) was inserted and connected to a semi-closed anaesthetic circuit (Anmedic, Stockholm, Sweden).

Xenon or propofol was then administered to a level where subjects tolerated the laryngeal mask airway but remained spontaneously breathing with no detectable movement of the upper body.

The general anaesthetic agent was determined by randomization, either xenon inhalation in inspired concentration of 65% (Xenon, AGA Gas AB, Lidingö, Sweden) in oxygen or propofol 3–5 mg kg⁻¹ h⁻¹. The xenon group inhaled xenon in oxygen. The target concentration of xenon was 65% (vol%) but concentrations between 60 and 70% were within the accepted range. Xenon was administered using a prototype of a dosing device supplied by Linde Gas (Pullach, Germany). In case of hypoxaemia, the dose was lowered in steps of 10% at a time.

The propofol group received propofol i.v. (3–5 mg kg⁻¹ h⁻¹). In addition, this group inhaled 35% oxygen as a mixture of air/oxygen.

If movement of the upper body was detected then propofol or alfentanil (Rapifen®, Janssen-Cilag, Birkerød, Denmark) could be given i.v. All patients underwent unilateral knee replacement and a thigh tourniquet was inflated to pressures between 300 and 320 mm Hg before skin incision. At the end of surgery, the xenon/oxygen or air/oxygen gas mixture was turned off, and 80% oxygen in air was applied via a face mask or a nasal catheter. Postoperative pain relief was achieved using acetaminophen orally (Panodil®, GlaxoSmithKline Consumer, Ballerup, Denmark) and morphine i.v. or orally. This was combined with epidural bupivacaine or ropivacaine (Naropin®, Astra-Zeneca, Södertälje, Sweden), and sufentanil (Sufenta®, Janssen-Cilag, Birkerød, Denmark) for 2 or 3 days after surgery if an epidural catheter had been inserted.

Blood pressure, heart rate, ventilatory frequency and end-tidal carbon dioxide concentration were recorded every 5 min during surgery. Emergence time was defined as the time from termination of propofol or xenon until the patient could state name and date of birth.

Cognitive testing was done by a research nurse with the ISPOCD neuropsychological test battery. The assessment of cognitive function was based on the following seven variables from four neuropsychological tests: cumulative number of words recalled in three trials and the number of words at delayed recall from the visual verbal learning test; the time and number of errors in part C of the concept shifting test; the time and error scores from the third part of the Stroop colour word interference test and the number of correct answers from the letter digit coding test.

Testing was done on three occasions: 1–5 days before surgery, at discharge 3–5 days after surgery, and 10–14 weeks after surgery. A specially trained research nurse, otherwise not involved in the study, carried out all testing.

Statistics
For continuous variables, mean is reported with SD, but for duration of anaesthesia and amount of drug used, median is reported with range because these variables were not normally distributed.

Mann–Whitney rank sum test was used for comparison of emergence time, systolic blood pressure, heart rate, ventilatory frequency and end-tidal carbon dioxide concentration between the two groups. No correction for multiple comparisons was used. For proportions, 95% confidence interval is reported and χ²-test is used for comparison of cognitive
dysfunction and nausea and vomiting. P-values less than 5% were considered statistically significant.

This study was a feasibility study. However, we also intended to explore if xenon was associated with a reduction in the incidence of POCD. The primary outcome was the mean probability of xenon being associated with less cognitive deterioration in the seven test variables. In this so-called ‘selection design’ the results of the seven neuropsychological test variables were considered in the following way: for each patient and variable, the difference between the preoperative and postoperative test result was calculated. The two groups were compared for each variable and we calculated the probability of xenon being associated with better performance than propofol. If no difference exists, then this probability is close to 0.5. If xenon is associated with better performance, then this probability is larger than 0.5. In this way, seven probabilities for each postoperative test session were calculated and a mean probability of all seven could be calculated for xenon ($P_x$) and propofol ($P_p$), respectively. The sample-size calculation in the selection design was based on the assumption that the incidence of POCD could be reduced from 30% (with propofol) to 15% with xenon, based on published data from our group. A sample size of 38 assumes a 50% reduction using this approach (Statisticon AB, Uppsala, Sweden, additional details presented in Appendix).

In addition to this, the incidence of POCD was calculated based on Z-scores and a previously collected normative material. First, the changes in performance of the seven test variables were calculated for each patient and the average learning effect was subtracted from these changes and the result was divided by a control group SD to obtain a Z-score for the seven test variables. A composite Z-score was obtained by first adding the Z-scores for each of the chosen tests. This Z-score sum was also calculated for age-matched control individuals and the SD of these were again used to normalize the patient’s Z-score sum into a composite Z-score for each of the two postoperative sessions. Patients had POCD when two out of seven Z-scores in individual tests or the combined Z-score were 1.96 or more, a criterion based on a previous study where additional details are reported for the control subjects.

**Results**

In total, 41 patients were included and randomized, but only 39 patients received a study drug (21 received xenon and 18 propofol, Table 1) and this population is described in the following (Fig. 1). Only 36 patients underwent neuropsychological testing at discharge and at 3 months, 35 patients could be assessed.

In the xenon group, depth of sedation was found to be adequate with an inspired xenon concentration of 60–70% in eight patients and with a xenon concentration of 50–60% in 10. A median dose of 34 (19–125) litres of xenon was used in this group. In six patients, additional doses of propofol (total supplementary dose 50–330 mg) were necessary to ensure adequate depth of anaesthesia during maintenance. In three patients, this was primarily related to a significant leak around the laryngeal mask.

In the propofol group, a total median dose of 559 mg (370–2380 mg) propofol was given. No opioids were necessary in any patient during surgery.

Emergence was significantly faster among the xenon-treated patients [median 260 (range 110–660) s, propofol group median 590 (range 195–976) s, $P=0.001$], the 95% confidence interval for the difference was 160–390 s (Fig. 2).

Heart rate, systolic blood pressure, ventilatory frequency and end-tidal carbon dioxide concentrations were not significantly different between the groups, but heart rate tended to be lower and systolic blood pressure tended to be higher in the xenon group (Table 2).

The most common postoperative event registered was nausea and vomiting. Nausea was reported in 2/21 (9.5%,

| Table 1 Patient characteristic data and duration of anaesthesia. Data are mean (sd) or, for duration of anaesthesia, median is reported with range |
|-----------------|-----------------|-----------------|
| Age (yr)        | 71 (8)          | 70 (6)          |
| Weight (kg)     | 78 (16)         | 78 (11)         |
| BMI             | 27 (5)          | 27 (3)          |
| Sex (male/female)| 6/15            | 7/11            |
| Duration of anaesthesia (min) | 70 (58–279) | 74 (60–238) |

Fig 1 Inclusion of patients for knee replacement with spinal anaesthesia and xenon vs propofol.
1–30%) and 3/18 (16.7%, 4–41%) patients in the xenon and propofol group, respectively, \( P = 0.85 \). In the xenon group, 8/21 (38%, 18–62%) patients vomited once or more during the first 24 h compared with 2/18 (11%, 1–35%) in the propofol group, \( P = 0.12 \). The second most common postoperative event was hypotension requiring intervention in three patients in each group.

Two deaths occurred during the 3-month follow-up period after surgery. From the propofol group a male patient with known history of ischaemic heart disease died because of myocardial infarction on the fourth postoperative day. From the xenon group a female patient died 48 days after surgery as a result of diffuse peritonitis related to a gastric ulcer.

Neuropsychological test results are shown in Table 3. The selection design analysis did not indicate that xenon was associated with less cognitive dysfunction (Table 4). The incidence of POCD at discharge was 7/20 (35.0%, 15–59%) \( \text{vs} \) 6/16 (37.5%, 15–65%) for the xenon and propofol groups, respectively \( (P=0.88) \). At 3 months, the corresponding values were 3/18 (16.7%, 4–41%) \( \text{vs} \) 2/16 (12.5%, 2–38%) for the xenon and propofol groups, respectively \( (P=0.77) \).

**Discussion**

There are three major findings in this study. Firstly, xenon was well tolerated for supplementary general anaesthesia in spontaneously breathing elderly patients. However, in about 30% of the patients, xenon was not sufficient for adequate anaesthesia as a sole agent, but this was related to significant leak around the laryngeal mask in half of them. Secondly, emergence was faster in the xenon group as compared with the propofol group, and the emergence time in the xenon group was more or less independent of duration of anaesthesia. Lastly, a high incidence of POCD was found in both groups at discharge and this feasibility study therefore did not support our assumption that xenon was associated with less POCD.

Xenon as a sole agent was not sufficient to maintain adequate depth of anaesthesia in all patients. This finding may be explained by the fact that xenon was administered in inspired concentrations up to 70% only, resulting in mixed expired concentrations in the magnitude of 55–60 vol%, which is less than 1 MAC. In some patients, a leak around the laryngeal mask limited the ability to obtain the desired xenon concentration. In addition, we are aware of the important limitation that depth of anaesthesia was evaluated simply based on clinical observation where we aimed at a spontaneously breathing patient accepting the laryngeal

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**Table 3** Intraoperative vital signs for elderly patients undergoing knee replacement with spinal anaesthesia and supplementary general anaesthesia using xenon \( (n=21) \) or propofol \( (n=18) \). Mean values with SD

<table>
<thead>
<tr>
<th></th>
<th>Xenon</th>
<th>Propofol</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of drug</td>
<td>82 (18)</td>
<td>75 (11)</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>71 (15)</td>
<td>73 (15)</td>
<td>0.61</td>
</tr>
<tr>
<td>60 min</td>
<td>67 (15)</td>
<td>71 (15)</td>
<td>0.34</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of drug</td>
<td>124 (24)</td>
<td>122 (22)</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>114 (16)</td>
<td>109 (19)</td>
<td>0.17</td>
</tr>
<tr>
<td>60 min</td>
<td>126 (23)</td>
<td>112 (19)</td>
<td>0.06</td>
</tr>
<tr>
<td>Ventilatory frequency (min(^{-1}))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of drug</td>
<td>15 (5)</td>
<td>13 (4)</td>
<td>0.91</td>
</tr>
<tr>
<td>30 min</td>
<td>16 (4)</td>
<td>16 (3)</td>
<td>0.81</td>
</tr>
<tr>
<td>60 min</td>
<td>16 (4)</td>
<td>15 (3)</td>
<td></td>
</tr>
<tr>
<td>End-tidal carbon dioxide (kPa)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Start of drug</td>
<td>5.1 (0.4)</td>
<td>5.1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>5.5 (0.6)</td>
<td>5.8 (0.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>60 min</td>
<td>5.4 (0.6)</td>
<td>5.8 (0.9)</td>
<td>0.11</td>
</tr>
</tbody>
</table>
The objective was to be sufficiently confident that the changes in neuropsychological test results for xenon and propofol were similar. The neuro-protective properties of xenon have been demonstrated primarily in connection with hypoxic and ischaemic neuronal damage in animal models. It is not known whether POCD is caused by such events in connection with surgery and anaesthesia. A larger sample-size is needed if cognitive function is to be addressed in a more rigorous design. It is possible that a true advantage associated with xenon may be detected in other settings such as cardiac surgery and also the composition and analysis of neuropsychological tests are of huge importance.9,13 The incidence of POCD found at discharge was rather high but at 3 months, the results seem well in line with earlier data.10

In conclusion, xenon seems to be well tolerated for supplementary general anaesthesia in elderly spontaneously breathing patients but supplementation may be necessary because of limited potency. Compared with propofol, emergence was faster with xenon. A larger sample-size is needed if cognitive function is to be addressed.

Acknowledgement
Financial support was received from Linde Gas Therapeutics, Hamburg, Germany.

Appendix

Sample-size calculation using ‘selection design’

The incidence of POCD in this population was expected to be 20–30%. By using xenon it was hypothesized that the incidence of POCD could be reduced by 50%. Even though that classification was not of primary interest it was used to simplify the sample-size calculation.

The objective was to be sufficiently confident that the point estimate for the xenon group was lower than or equal to the propofol group, provided that there is a true difference.

\[
\pi_x = \text{true incidence of POCD xenon.} \\
\pi_p = \text{true incidence of POCD propofol.} \\
\hat{\pi}_x = \text{estimated incidence of POCD xenon.} \\
\hat{\pi}_p = \text{estimated incidence of POCD propofol.}
\]
The sample size was derived by finding a sufficiently large \( n \) to satisfy:

\[
Pr(\hat{\pi}_d = \hat{\pi}_p - \hat{\pi}_x > 0 \mid \pi_p, \pi_x) > 0.80.
\]

\[
\hat{\pi}_x \sim N \left( \pi_x, \frac{\pi_x(1-\pi_x)}{n} \right).
\]

\[
\hat{\pi}_p \sim N \left( \pi_p, \frac{\pi_p(1-\pi_p)}{n} \right).
\]

\[
\hat{\pi}_d = \hat{\pi}_p - \hat{\pi}_x \sim N \left( (\pi_p-\pi_x), \sqrt{\frac{\pi_p(1-\pi_p)}{n} + \frac{n\pi_x(1-\pi_x)}{n}} \right).
\]

If \( \pi_x = 0.15, \pi_p = 0.30 \) then 19 patients give \( P(\hat{\pi}_d > 0) > 0.87 \) and if \( \pi_x = 0.10, \pi_p = 0.20 \) 19 patients give \( P(\hat{\pi}_d > 0) > 0.81 \). Hence, a sample size of 19 patients per group was judged to be appropriate for the study.

References

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