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The Hip Fracture Surgery in Elderly Patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomised, controlled clinical trial

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**The HIPELD Study Investigators are listed in the Supplementary material.

Running title: Xenon anaesthesia for POD in hip fracture surgery

Abstract

Background. Postoperative delirium (POD) occurs frequently in elderly hip fracture surgery patients and is associated with poorer overall outcomes. Because xenon anaesthesia has neuroprotective properties, we evaluated its effect on the incidence of POD and other outcomes after hip fracture surgery.

Methods. This was a phase II, multicentre, randomised, double-blind, parallel-group, controlled clinical trial conducted in hospitals in six European countries (September 2010 to October 2014). Elderly (≥75 years-old) and mentally functional hip fracture patients were randomised 1:1 to receive either xenon- or sevoflurane-based general anaesthesia during surgery. The primary outcome was POD diagnosed through postoperative day 4. Secondary outcomes were POD diagnosed anytime after surgery, postoperative sequential organ failure assessment (SOFA) scores, and adverse events (AE).

Results. 256 randomised patients were treated with xenon (N=124) or sevoflurane (N=132). Through postoperative day 4, the incidence of POD with xenon (9.7%, 95% confidence interval [CI]: 4.5−14.9) or with sevoflurane (13.6%, 95% CI: 7.8−19.5) were not significantly different (P=0.33). Overall SOFA scores were significantly lower with xenon (least-squares mean difference: −0.33, 95% CI: −0.60 to −0.06; P=0.017). The incidences of serious AE (8.0% vs 15.9%; P=0.05) and fatal AE (0% vs 3.8%; P=0.06) were lower with xenon than with sevoflurane, respectively, but not significantly different.

Conclusions. Xenon anaesthesia did not significantly reduce the incidence of POD after hip fracture surgery. Nevertheless, exploratory observations concerning postoperative SOFA-scores, serious AE, and deaths warrant further study of the potential benefits of xenon anaesthesia in elderly hip fracture surgery patients.

Key words: anaesthesia, general; aged; delirium; hip fractures; xenon

Clinical trial registration: EudraCT 2009-017153-35; ClinicalTrials.gov NCT01199276

With an ever-aging population, hip fracture is a major medical problem that imposes huge medical, financial, and societal burdens, and impairs the quality of life for patients, care-providers, and care-givers.[1, 2] In the UK alone, there were over 67,000 hip fractures reported for the health care system in 2014.[3] Hip fracture is also associated with high 30-day mortality rates (8−10% in the UK) and high one-year mortality rates, which were reported to be 19−40% across several European countries.[3, 4]

Postoperative delirium (POD) is also strongly associated with hip fracture surgery in older patients, with reported incidence rates of 13−50%.[5-10] POD is an acute state of confusion associated with changes in the levels of consciousness, arousal, and cognition following surgery.[11] While usually short-lived, POD is associated with increased hospital stays and costs, higher morbidity and mortality, higher risks of institutionalisation, cognitive decline, dementia, and poorer overall outcomes.[5, 12-14]

The aetiology of POD is complex, poorly understood, and multifactorial.[15, 16] The risk of POD increases with age, pre-existing cognitive impairment, dementia, depression, comorbidity and vascular disease.[11, 16, 17] Recent data support the proposal that POD is a *cognitive disintegration* with a breakdown in neural network connectivity, possibly mediated through an increase in inhibitory γ-amino-butyric acid (GABA)-ergic tone, resulting in impaired integration of information in fronto-parietal networks.[15, 18] Indeed, many of the modifiable risk factors for POD interact with GABAergic signaling.[11, 15, 17, 19, 20]

The noble gas xenon is an anaesthetic that blocks *N*-methyl-D-aspartate receptors and activates two-pore-domain potassium channels but has no activity on GABA receptors.[21-23] Xenon has been demonstrated to exert organoprotective effects including neuro- and cardio-protection, and to maintain haemodynamic stability better than other anaesthetics.[21-30] In two small studies in cardiac surgery patients, xenon has exhibited potentially promising, though

inconsistent, effects in preventing POD.[29, 31] However, neither study was designed or powered to specifically address the prevention of POD by xenon.

Due to the potentially beneficial qualities of xenon, we hypothesised that the incidence of POD in hip fracture surgery patients would be lower with xenon-based anaesthesia than with sevoflurane-based anaesthesia. Thus, we conducted an international, multicentre, randomised, controlled clinical trial to specifically compare the incidence of POD and other outcomes in hip fracture surgery patients anaesthetised with either xenon or sevoflurane. The primary outcome was the incidence of POD within 4 days of surgery, while secondary exploratory outcomes included postoperative organ dysfunction, safety, and mortality.

Methods

Study Design

The design and protocol of the study have been published previously[32] and are summarised in the online Supplementary material. Briefly, this was a phase II, observer-blinded, parallel-arm, multicentre, randomised controlled trial conducted at 13 university or tertiary hospitals in six European countries (France, Belgium, Germany, Spain, UK, and Italy) between September 2010 and October 2014. The study protocol and subsequent substantial amendments were approved by local independent ethics committees and the competent regulatory authority in each country for each investigational site. The study was registered with EudraCT (2009-017153-35) and ClinicalTrials.gov (NCT01199276), and conducted according to Good Clinical Practice guidelines, any local guidelines, the Declaration of Helsinki (2008), and European Directive 2001/20/CE. Written informed consent was obtained from all subjects.

During the course of the study, there were several protocol amendments. Due to enrolment that was slower than anticipated with five centres, the recruitment period was extended on four successive occasions, and eight study sites were added to achieve the target enrolment (one in Belgium, five in France, and two in Germany). The collection of survival information at 28-days post-surgery was also added because it was identified as a key outcome parameter in the UK's National Hip Fracture Database.[3]

Participants

Hip fracture patients ≥75 years old with planned surgery within 48 hours of fracture were eligible for study participation. Notable exclusion criteria included a history of severe dementia, Alzheimer's disease, schizophrenia, or moderate to severe depression; a recent

brain trauma or history of stroke; delirium, as determined by a shortened version of the Confusion Assessment Method (CAM),[33] which is a worksheet version adapted from the original CAM by SK Inouye;[34] or a score of < 24 in the Mini-Mental State Examination (MMSE). Complete exclusion criteria are listed in the online Supplementary material and in Coburn, et al 2012.[32]

Procedures

Patients were randomised to the xenon or sevoflurane treatment group using a blocked randomisation scheme stratified by centre, with a block size of six, and assigned to groups from a computer-generated list. Block size was not specified in the protocol nor communicated to the investigators to avoid predictability of the next treatment. Patient selection and follow-up visits and assessments were performed by a study physician who was blinded to the allocated anaesthetic (Physician 1). The identity of the randomisation-allocated anaesthetic was contained in an envelope bearing the sequential randomisation number of the patient and was revealed by the attending anaesthesiologist (Physician 2) who opened the envelope only immediately prior to surgery. Study Physicians 1 and 2 had no access to the case report forms of their physician counterparts. Study eligibility, vital signs, baseline scores for (i) delirium as determined by the CAM,[33] for (ii) Sequential Organ Failure Assessment (SOFA),[35] and for (iii) pain (by the visual assessment score [VAS]), as well as concomitant medications and diseases, were assessed at the selection visit.

Benzodiazepine premedication was avoided. General anaesthesia was induced with propofol (1−2 mg/kg), which was continued at 0.05−0.15 mg/kg per min for approximately 10 min until maintenance anaesthesia with the randomisation-allocated anaesthetic (either sevoflurane or xenon gas delivered using a Felix Dual™ Workstation [Air Liquide Medical Systems, France]) could be initiated. Patients in the xenon group received 60 ± 5% xenon (approximately 1 minimum alveolar concentration [MAC]) in oxygen (FiO_2 = 0.35 to 0.45);

patients in the sevoflurane group received 1.1−1.4% sevoflurane (1 MAC adjusted to age) in oxygen and medical air (FiO_2 = 0.35 to 0.45).[36] Depth of anaesthesia was monitored continuously using the Bispectral Index (BIS VISTA™, Aspect Medical Systems, Norwood, MA) and was kept between 40 and 60.

After weaning from anaesthesia, vital signs, recovery parameters, and the Aldrete score were monitored every 15 min until recovery was complete with a score of ≥ 9. Beginning at 3 hours after surgery and at twice-daily visits (10 am ± 30 min and 6 pm ± 30 min) through discharge (or for a maximum of 28 days), patients were assessed for POD, severity of pain (VAS), vital signs, concomitant medications, adverse events (AEs), and serious adverse events (SAEs). SOFA scores and laboratory analysis results were recorded at each visit through day 4 and were optional thereafter.

Outcomes

The primary endpoint was the occurrence of at least one episode of POD as assessed by the shortened worksheet version of the CAM within 4 days post-surgery. This worksheet includes the first four criteria of the full CAM, all of which are necessary and sufficient for detecting delirium.[33] The CAM assessment was performed by investigators (Physician 1 or a research nurse) who were blinded to the group allocation and who received extensive and specific training prior to the study according to the CAM training manual and coding guide.[34] Training was conducted by an external study-sponsored physician via a remote presentation during study site initiation. Secondary exploratory endpoints were POD from post-operative day 5 through discharge; SOFA on postoperative days 1−4; recovery parameters; and mortality. Safety was assessed from the AEs and SAEs recorded throughout the study and from laboratory parameters. Diagnostic criteria for specific AEs were those used in standard practice at each study site and were not standardised across the study sites.

Statistical analysis

The sample size was calculated based on an expected POD event rate of 30% within 4 days after surgery with sevoflurane anaesthesia.[32] It was estimated that this POD event rate would be 50% lower with xenon yielding an event rate of 15%. We estimated a large effect size (odds ratio of 0.50) for this older population, which is larger than what would be considered as a clinically significant improvement. Type I error was set to α=0.05 (two-sided conditions), and power was 80% to detect the 50% reduction. Power calculations were performed using nQuery Advisor® Version 6.01 (Statistical Solutions, Saugus, MA) and yielded 121 patients per group. With an expected dropout rate of 5%, the target enrolment was set to 256 randomised patients (128 per group).

In the primary analysis of the primary outcome, the POD incidence within 4 days post-surgery in each group in the intention-to-treat population was compared using a Pearson's X^2 test that included observed cases only. The Pearson's analysis was also repeated for the per-protocol population (patients with no major protocol deviations) in sensitivity analyses and to handle missing data. Sensitivity, secondary, exploratory, and post-hoc analyses are described in the Supplementary material. Statistical analyses were performed using SAS® software (SAS Institute, Cary, NC, USA) Version 9.2. Statistical significance for all tests was fixed at α=0.05 except for the selection of potentially important factors in the multivariate regression model in which α=0.10 was applied.

Results

From over 2000 hip fracture patients screened for the study, only 268 were enrolled and 260 were randomised to the treatment groups between September 2010 and October 2014 (Figure 1). Most pre-enrolment exclusions were due to low MMSE scores. Among these, 256 randomised patients were treated and eligible for analysis. Fourteen patients who had major protocol deviations were included in the intention-to-treat population but were excluded from per-protocol analyses. Most were excluded for multiple (≥5) missing CAM evaluations (9 patients) after surgery or for missing CAM evaluations at selection (3 patients). A total of 110 patients in the xenon group and 120 in sevoflurane group completed the study.

Patient Population

Baseline characteristics were similar for both groups (Table 1). Most patients in each group were women and the mean age was 84 years. Most patients had an ASA status of II or III and a moderate level of pain. Pre-operative SOFA scores were low; however, concomitant diseases such as hypertension, cardiac disorders, and musculoskeletal disorders were frequent (95%).

Hip Fracture Surgeries and Anaesthesia

Surgery-related data and duration of the procedures were similar for the two groups (Table 2). During recovery from anaesthesia, the times to open eyes, to react to verbal commands, and to extubation were all significantly shorter for xenon than for sevoflurane ($P<0.001$). The time to reach an Aldrete score of 9 was similar for both groups. Total length of hospital stay was similar for both groups, and ≥95% of the patients in each group were discharged from the hospital within 30 days after surgery. Depth of anaesthesia during surgery (BIS values;

Supplementary material, Figure S1) and haemodynamic variables during surgery (Supplementary material, Figure S2) were similar across groups.

POD Incidence

In the primary analysis, a total of 12 out of 124 (9.7%) patients in the xenon group vs. 18 out of 132 (13.6%) patients in the sevoflurane group had at least one POD episode during the first 4 days after surgery (Table 3). These incidence rates were not significantly different (P=0.33). Similar results were obtained for the per-protocol population (P=0.40) and in sensitivity analyses performed for only those patients who had undergone all planned CAM assessments up to the afternoon of day 4 and if all patients who were withdrawn due to an AE or who died were included in the analysis and considered to have had a POD episode (Supplementary material, Table S1).

Incidence rates for POD at 5 or more days after surgery or at any time after surgery were not significantly different (P=0.46 for each; Table 3). Six (4.8%) patients in the xenon group and 11 (8.3%) patients in the sevoflurane group had multiple POD episodes during the study. The mean time to a first POD episode during the first 4 days after surgery (also the Kaplan-Meier diagram in Supplementary material, Figure S3) and the mean duration of POD episodes were similar in both groups, with most episodes lasting 0.5 days.

In multivariate-factor logistic regression analyses of patient factors possibly associated with POD within the first 4 days after surgery, four were identified as important in preliminary screening: male gender, ASA status III, being a current smoker, and the presence of a previously diagnosed mild neurologic disorder at selection (Supplementary material, Table S2). Of these, only being a current smoker (adjusted odds-ratio [AOR] 5.35 [1.65−17.32]; P=0.005) and the presence of a previously diagnosed mild neurologic disorder (AOR 3.27 [1.12−9.57]; P=0.030) were statistically significant (P<0.05). The adjusted odds-

ratio (AOR) for POD with xenon treatment was not statistically significant (0.50 [95% CI 0.20−1.20]; P=0.12; Supplementary material, Table S2 and Figure S4).

Excessively deep anaesthesia and long delays before surgery have been reported to be risk factors for POD.[19, 37] However, in post-hoc analyses, we found no significant associations between POD and cumulative time at low BIS values (< 40; P=0.86) during surgery or between POD and time-to-surgery (P=0.34) (Supplementary material, Table S3).

SOFA Scores

Mean total SOFA scores (± SD) increased after surgery and were highest at day 1, with scores of 0.87 ± 0.94 in the xenon group and 1.19 ± 1.49 in the sevoflurane group (Supplementary material, Figure S5). Mean total score in the xenon group (0.57 ± 0.84) was significantly lower than in the sevoflurane group (1.01 ± 1.77) on day 3 only (P=0.04). Comparison of the overall difference in SOFA scores over time by repeated ANCOVA analysis yielded a statistically significant least-squares mean difference of −0.33 [95% CI −0.60− (−)0.06] (P=0.02) in favour of xenon.

Safety

AEs were reported for 114 of 125 patients (91.2%) in the xenon group (495 AEs) and for 125 of 132 patients (94.7%) in the sevoflurane group (573 AEs; Table 4). Most AEs were treatment-emergent and of mild-to-moderate severity, and about 50% in each group were considered by the investigators to be related to study treatment. SAEs were nearly twice as common in the sevoflurane group (45 for 21 patients) than in the xenon group (22 for 10 patients; P=0.05). The proportion of patients with SAEs that were graded severe was significantly greater in the sevoflurane group than in the xenon group (P=0.008).

Mortality

By the end of the study, only one patient in the xenon group and three patients in the sevoflurane group had ongoing SAEs (Table 4). No patients in the xenon group died but five patients in the sevoflurane group (3.8%) succumbed to fatal SAEs (P=0.06). Causes of death were septic shock and multi-organ failure; pneumonia and respiratory failure; pneumonia, septic shock and acute renal failure; right ventricular failure; and cardiac failure. Three of the patients who died had at least one POD episode within 4 days of surgery. Vital status at 28 days after surgery was available for 103 (83%) patients in the xenon group and 110 (83%) patients in the sevoflurane group; no additional deaths were reported.

Discussion

In this international randomised clinical trial, xenon-based anaesthesia did not significantly reduce the incidence of POD in elderly hip fracture surgery patients. Differences in secondary outcomes were either statistically significant and not clinically meaningful in this study (SOFA scores) or potentially clinically pertinent but not statistically significant (SAEs, mortality).

The incidence of POD following hip fracture surgery in the elderly is typically high.[5-9, 11] In the studies we used to calculate the sample size needed to evaluate the primary efficacy criterion of at least one POD episode within 4 days after surgery, the incidence varied between 28% and 50%;[6-10, 32, 38, 39] however, the actual incidence of POD in the sevoflurane control group (13.6%) was much lower than the expected rate (30%). The lower-than-expected incidence of POD in the sevoflurane group likely reflects our use of strict inclusion criteria; patients were excluded for any pre-operative signs of delirium, moderate to severe depression, or a poor functional mental state (MMSE score < 24). As a consequence, the patient population in the study may have differed from the general elderly population that routinely undergoes hip fracture surgery, in whom the incidence of POD is higher.[13, 16] Indeed, it proved difficult to recruit patients into the study because many patients who fulfilled the other inclusion criteria failed to satisfy the mental state criteria. We estimate that less than 15% of those screened were eligible for enrolment. Another contributing factor to the low incidence of POD may have been the use of BIS technology to monitor the depth of anaesthesia; in a recent meta-analysis, the incidence of POD was found to be lower with BIS-guided anaesthesia than with BIS-blinded anaesthesia or clinical judgment.[40]

The POD incidence in the xenon group was not 50% lower than in the sevoflurane group as required by the power analysis, but only 33% lower. Despite this, an overall

reduction of 33% in POD, if statistically significant, would still represent a clinically meaningful benefit, which future studies should consider. Nonetheless, the overestimations of both the POD-incidence rate and the effect size rendered the power of the study insufficient to detect significant differences between the two groups for the primary efficacy endpoint.

Despite the low incidence of POD in the study, we were able to identify two patient factors that were significantly associated with POD across groups: being a current smoker and having a previously diagnosed mild neurologic disorder.[13, 16, 41, 42]

The association of POD with the type of anaesthesia or anaesthetic agent used for surgery is unclear. There is some evidence that the incidence of POD may increase with the depth of anaesthesia, but regional anaesthesia was not found to be preventative, perhaps due to sedation in the regional anaesthesia group.[19, 43] In a small pilot study in 42 patients who received either xenon or sevoflurane-based anaesthesia during cardiac surgery, the incidence of POD was significantly lower in the group that received xenon;[29] although these latter results were not confirmed in our hip fracture surgery patients, the potential benefits of xenon in cardiac surgery patients await confirmation in a larger clinical trial.[44]

While xenon anaesthesia has previously demonstrated organoprotective properties and a superior haemodynamic profile compared to other anaesthetic agents,[22, 24-26, 29, 45, 46] we could not confirm these effects in hip fracture surgery patients. Though patients in the xenon-group had a slightly lower overall SOFA score (which could be interpreted as a sign for a certain degree of organoprotection), this difference was of marginal clinical relevance. Likewise, there were no significant differences between the groups in patients with SAEs (P=0.05) or in patients with fatal SAEs (P=0.06), though the proportion of patients with SAEs graded as severe was significantly smaller in the xenon group (P=0.008).

The study has several strengths and limitations. Specific inclusion and exclusion criteria resulted in a well-defined study population that was similar for the prospective risk of

developing POD across the treatment groups. The high temporal resolution consequent to the twice-daily CAM evaluations ensured that a high proportion of the POD episodes could be detected. The secondary efficacy endpoints and safety data facilitated assessment of the potential benefits of xenon anaesthesia on organoprotection and mortality. One limitation regarding mortality may be that 28-day follow-up results were available for only ~80% of the patients in each group. We used BIS technology to avoid variations in and excessively deep anaesthesia during surgery and to prevent depth of anaesthesia from becoming a confounding factor between treatment groups. BIS values were carefully monitored and mean values were consistently maintained and similar during surgery for both groups suggesting that similar levels of consciousness and exposure were obtained for these two different anaesthetics. A major limitation was the low overall incidence of POD, likely due to the restrictive exclusion criteria that eliminated many patients at high risk for developing POD, and may have been additionally reduced through our use of BIS to monitor the depth of anaesthesia.[40] It is also possible that some POD episodes were missed due to some inconsistencies in administration of the CAM across different staff and centres and by our use of the shortened, worksheet version of the CAM. Although the full 9-item CAM is recommended for maximum sensitivity, we considered the shorter CAM to be far more practical and reasonable for an international clinical trial employing twice-daily post-operative assessments. In addition, the four essential and validated criteria for determining delirium are included in the shortened CAM worksheet.[33, 47] Finally, while some training is recommended for optimal use,[47] and our study personnel received extensive and specific training according the CAM training manual prior to the study, we cannot be certain that the CAM was administered consistently across all study centres. Indeed, training can be a factor in delirium recognition by the CAM.[48] One aspect of delirium not considered in the current study was severity. The CAM-S tool provides a revised delirium scoring system that allows assessment of delirium severity.[49] Investigators

should bear these aspects in mind when designing clinical trials to investigate preventative measures for POD.

Conclusions

The incidence of POD in this study was not significantly lower with xenon anaesthesia than with sevoflurane anaesthesia. Our observations concerning postoperative SOFA-scores, SAEs, and mortality should be considered hypothesis-generating and warrant further study to assess the potential benefits of xenon anaesthesia in elderly hip-fracture surgery patients.

Declaration of interests

The institutions of MC, SR, BG, JAC, MLGP, AS, PK, MN, MSS, BB, HvO, AT, LA, LE, OL, XC, GMA, and RR received grant funds and/or patient inclusion fees from Air Liquide Santé International to conduct the study. MC, RDS, MM, AS, and RR received consulting fees and/or travel funds from Air Liquide Santé International. MC received grants, consulting fees, and travel funds from Baxter Healthcare and grants from German Research Foundation outside the submitted work. SR received unrestricted grants from Air Liquide Santé International and Air Liquide Belgium and speaking fees from Orion Pharma. MM is a co-founder of NeuroproteXeon that seeks to develop xenon for protection against acute ongoing neurological injury and could receive royalties from sales of xenon as a neuroprotective agent. MLNP was a full-time employee of Air Liquide Santé International during the study. MS is currently a full-time employee of Air Liquide Santé International.

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Contributors

A writing committee (MC, RDS, MM, SR, and RR) and a sponsor representative (MLNP) interpreted the results, prepared and reviewed the manuscript, and made the decision to submit it for publication. The writing committee had full access to all study data and final responsibility for the integrity and accuracy of the analyses. A steering committee of academic medical experts (MC, RDS, MM, and RR) and a sponsor representative (MLNP) oversaw the design and conduct of the study. The study sponsor participated in study design, data collection, data analysis according to a predefined statistical analysis plan, and data interpretation. All co-authors except RDS and MM acquired data. All authors reviewed the manuscript for important intellectual content and approved the final draft of the manuscript

and the decision to submit it for publication. Members of the steering committee (MC, RDS, MM, and RR) are the guarantors.

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References

21. Braithwaite RS, Col NF, Wong JB. Estimating hip fracture morbidity, mortality and costs. *Journal of the American Geriatrics Society* 2003; **51**: 364-70

42. Tajeu GS, Delzell E, Smith W, et al. Death, debility, and destitution following hip fracture. *The journals of gerontology Series A, Biological sciences and medical sciences* 2014; **69**: 346-53

73. Royal College of Physicians. The National Hip Fracture Database. 2015. Available from http://www.nhfd.co.uk (accessed March 1 2016)

94. Medin E, Goude F, Melberg HO, Tediosi F, Belicza E, Peltola M. European Regional Differences in All-Cause Mortality and Length of Stay for Patients with Hip Fracture. *Health economics* 2015; **24 Suppl 2**: 53-64

125. Furlaneto ME, Garcez-Leme LE. Delirium in elderly individuals with hip fracture: causes, incidence, prevalence, and risk factors. *Clinics (Sao Paulo)* 2006; **61**: 35-40

146. Galanakis P, Bickel H, Gradinger R, Von Gumppenberg S, Forstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. *International journal of geriatric psychiatry* 2001; **16**: 349-55

177. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *Journal of the American Geriatrics Society* 2000; **48**: 618-24

208. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society* 2001; **49**: 516-22

19. Sharma PT, Sieber FE, Zakriya KJ, et al. Recovery room delirium predicts postoperative delirium after hip-fracture repair. *Anesthesia and analgesia* 2005; **101**: 1215-20

410. Zakriya K, Sieber FE, Christmas C, Wenz JF, Sr., Franckowiak S. Brief postoperative delirium in hip fracture patients affects functional outcome at three months. *Anesthesia and analgesia* 2004; **98**: 1798-802

711. Sanders RD, Pandharipande PP, Davidson AJ, Ma D, Maze M. Anticipating and managing postoperative delirium and cognitive decline in adults. *BMJ* 2011; **343**: d4331

1012. Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology* 2009; **72**: 1570-5

1213. Inouye SK. Delirium in older persons. *The New England journal of medicine* 2006; **354**: 1157-65

1414. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Archives of internal medicine* 2008; **168**: 27-32

1715. Sanders RD. Hypothesis for the pathophysiology of delirium: role of baseline brain network connectivity and changes in inhibitory tone. *Medical hypotheses* 2011; **77**: 140-3

2016. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet* 2014; **383**: 911-22

2217. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. *Critical care medicine* 2015; **43**: 40-7

118. Cavallari M, Dai W, Guttmann CR, et al. Neural substrates of vulnerability to postsurgical delirium as revealed by presurgical diffusion MRI. *Brain : a journal of neurology* 2016

419. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clinic proceedings* 2010; **85**: 18-26

720. Wang J, Li Z, Yu Y, Li B, Shao G, Wang Q. Risk factors contributing to postoperative delirium in geriatric patients postorthopedic surgery. *Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists* 2015; **7**: 375-82

1021. Derwall M, Coburn M, Rex S, Hein M, Rossaint R, Fries M. Xenon: recent developments and future perspectives. *Minerva anestesiologica* 2009; **75**: 37-45

1222. Preckel B, Weber NC, Sanders RD, Maze M, Schlack W. Molecular mechanisms transducing the anesthetic, analgesic, and organ-protective actions of xenon. *Anesthesiology* 2006; **105**: 187-97

1523. Sanders RD, Franks NP, Maze M. Xenon: no stranger to anaesthesia. *British journal of anaesthesia* 2003; **91**: 709-17

1724. Coburn M, Maze M, Franks NP. The neuroprotective effects of xenon and helium in an in vitro model of traumatic brain injury. *Critical care medicine* 2008; **36**: 588-95

1925. Fries M, Nolte KW, Coburn M, et al. Xenon reduces neurohistopathological damage and improves the early neurological deficit after cardiac arrest in pigs. *Critical care medicine* 2008; **36**: 2420-6

2226. Preckel B, Mullenheim J, Moloschavij A, Thamer V, Schlack W. Xenon administration during early reperfusion reduces infarct size after regional ischemia in the rabbit heart in vivo. *Anesthesia and analgesia* 2000; **91**: 1327-32

127. Rossaint R, Reyle-Hahn M, Schulte Am Esch J, et al. Multicenter randomized comparison of the efficacy and safety of xenon and isoflurane in patients undergoing elective surgery. *Anesthesiology* 2003; **98**: 6-13

428. Coburn M, Kunitz O, Baumert JH, et al. Randomized controlled trial of the haemodynamic and recovery effects of xenon or propofol anaesthesia. *British journal of anaesthesia* 2005; **94**: 198-202

729. Al Tmimi L, Van Hemelrijck J, Van de Velde M, et al. Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial. *British journal of anaesthesia* 2015; **115**: 550-9

1030. Neukirchen M, Hipp J, Schaefer MS, et al. Cardiovascular stability and unchanged muscle sympathetic activity during xenon anaesthesia: role of norepinephrine uptake inhibition. *British journal of anaesthesia* 2012; **109**: 887-96

1331. Stoppe C, Fahlenkamp AV, Rex S, et al. Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study. *British journal of anaesthesia* 2013; **111**: 406-16

1632. Coburn M, Sanders RD, Maze M, Rossaint R. The Hip Fracture Surgery in Elderly Patients (HIPELD) study: protocol for a randomized, multicenter controlled trial evaluating the effect of xenon on postoperative delirium in older patients undergoing hip fracture surgery. *Trials* 2012; **13**: 180

2033. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Annals of internal medicine* 1990; **113**: 941-8

2334. Inouye SK. *The Confusion Assessment Method (CAM): Training Manual and Coding Guide*. New Haven: Yale University School of Medicine, 2003

135. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Critical care medicine* 1998; **26**: 1793-800

536. Nickalls RW, Mapleson WW. Age-related iso-MAC charts for isoflurane, sevoflurane and desflurane in man. *British journal of anaesthesia* 2003; **91**: 170-4

737. Lee HB, Mears SC, Rosenberg PB, Leoutsakos JM, Gottschalk A, Sieber FE. Predisposing factors for postoperative delirium after hip fracture repair in individuals with and without dementia. *Journal of the American Geriatrics Society* 2011; **59**: 2306-13

1138. Marcantonio E, Ta T, Duthie E, Resnick NM. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. *Journal of the American Geriatrics Society* 2002; **50**: 850-7

1439. Zakriya KJ, Christmas C, Wenz JF, Sr., Franckowiak S, Anderson R, Sieber FE. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. *Anesthesia and analgesia* 2002; **94**: 1628-32

1740. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev* 2016; **3**: CD005563

1941. Oh ES, Li M, Fafowora TM, et al. Preoperative risk factors for postoperative delirium following hip fracture repair: a systematic review. *International journal of geriatric psychiatry* 2015; **30**: 900-10

2242. Hsieh SJ, Shum M, Lee AN, Hasselmark F, Gong MN. Cigarette smoking as a risk factor for delirium in hospitalized and intensive care unit patients. A systematic review. *Annals of the American Thoracic Society* 2013; **10**: 496-503

143. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. *Journal of Alzheimer's disease : JAD* 2010; **22 Suppl 3**: 67-79

544. Al Tmimi L, Van de Velde M, Herijgers P, et al. Xenon for the prevention of postoperative delirium in cardiac surgery: study protocol for a randomized controlled clinical trial. *Trials* 2015; **16**: 449

845. Ma D, Hossain M, Chow A, et al. Xenon and hypothermia combine to provide neuroprotection from neonatal asphyxia. *Annals of neurology* 2005; **58**: 182-93

1046. Ma D, Lim T, Xu J, et al. Xenon preconditioning protects against renal ischemic-reperfusion injury via HIF-1alpha activation. *Journal of the American Society of Nephrology : JASN* 2009; **20**: 713-20

1347. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. *Journal of the American Geriatrics Society* 2008; **56**: 823-30

1648. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM, Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Archives of internal medicine* 2001; **161**: 2467-73

1949. Inouye SK, Kosar CM, Tommet D, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Annals of internal medicine* 2014; **160**: 526-33

Figure Legend.

Figure 1. Patient disposition.

Among the over 2000 patients who were screened for enrolment in the HIPELD study, 268 were enrolled. Records were not kept for patients not enrolled, but most of these patients failed to meet the MMSE score criterion. Of the enrolled patients, 260 patients were eventually randomised and 257 were treated and followed for safety. One non-randomised patient was treated with xenon anaesthesia and included in the safety population but was not included in any other analyses and did not complete the study (*). Of the 124 randomised patients treated with xenon, 118 participated in the study according to protocol and 110 completed the study. Of the 132 randomised patients treated with sevoflurane, 124 participated in the study according to protocol and 120 completed the study. Most patients excluded from the per-protocol analyses had multiple missing CAM evaluations (9 patients).

Tables

Table 1. Patient demographics and characteristics at selection.

Patient characteristics	Xenon (N=124)	Sevoflurane (N=132)
Men, n (%)[a]	34 (27.4)	29 (22.0)
Women, n (%)	90 (72.6)	103 (78.0)
Age, years		
Mean (SD)	83.8 (5.1)	84.4 (4.6)
Range	75.1−98.5	75.5−95.4
Body mass index, mean kg/m^2 (SD)	23.7 (3.8)	24.2 (4.3)
Type of hip fracture, n (%)		
Displaced femoral neck	50 (40.3)	52 (39.4)
Non-displaced or impacted femoral neck	31 (25.0)	26 (19.7)
Stable intertrochanteric fracture	15 (12.1)	20 (15.2)
Unstable intertrochanteric fracture	13 (10.5)	17 (12.9)
Other hip fracture	15 (12.1)	17 (12.9)
Smoking history, n (%)		
Never smoked	92 (75.4)	109 (83.2)
Ex-smoker	19 (15.6)	14 (10.7)
Current smoker	11 (9.0)	8 (6.1)
Alcohol consumption, n (%)		
Never	86 (70.5%)	92 (70.8%)
Occasionally	29 (23.8%)	36 (27.7%)
Regularly	7 (5.7%)	2 (1.5%)
ASA status, n (%)		
ASA I	5 (4.2)	7 (5.5)
ASA II	74 (61.7)	75 (58.6)
ASA III	41 (34.2)	46 (35.9)
ASA IV	0 (0.0)	0 (0.0)
Pain/VAS, mean mm (SD)	38 (25)	36 (23)
Total MMSE score, mean (SD)	27.1 (1.8)	27.1 (1.7)
Delirium diagnosis by CAM, n (%)		
Yes	0 (0)	0 (0)
No	122 (100)	131 (100)
Missing	2	1
Total SOFA score, mean (SD)[b]	0.61 (0.95)	0.69 (1.03)
Concomitant diseases, n (%)		
At least one concomitant disease	120 (96.8)	125 (94.7)
Hypertension	89 (71.8)	92 (69.7)
Dyslipidaemia	19 (15.3)	14 (10.6)
Diabetes mellitus	10 (8.1)	18 (13.6)
Hypercholesterolemia	12 (9.7)	14 (10.6)

Type 2 diabetes mellitus	11 (8.9)	15 (11.4)
Cardiac disorders	42 (33.9)	46 (34.8)
Musculoskeletal/connective tissue disorders	32 (25.8)	26 (19.7)
Renal/urinary disorders	23 (18.5)	29 (22.0)
Gastrointestinal disorders	26 (21.0)	25 (18.9)
Nervous system disorders	19 (15.3)	20 (15.2)
Psychiatric disorders	20 (16.1)	15 (11.4)
Respiratory/thoracic/mediastinal disorders	19 (15.3)	16 (12.1)
Eye disorders	14 (11.3)	13 (9.8)

1ASA, American Society of Anesthesiologists; CAM, Confusion Assessment Method; MMSE,

2mini mental state examination; n, number of patients with the characteristic or for which

3results are available; N, number of patients in the group; SD, standard deviation; SOFA,

4sequential organ failure assessment; VAS, visual analogue scale.

5[a]Percentages are calculated for patients without missing data, which included >95% of the

6patients in each group, except where noted otherwise.

7[b]Mean total scores calculated for 85 patients in the xenon group and 72 patients in the

8sevoflurane group without missing values.

Table 2. Intra-operative and post-operative characteristics of hip fracture surgeries.

Characteristic	Xenon (N=124)	Sevoflurane (N=132)	*P* value
Type of hip fracture surgery performed, n (%)			
Hemi-arthroplasty of the hip	31 (25.0)	23 (17.4)	
Total hip replacement: cemented	21 (16.9)	19 (14.4)	
Dynamic hip screw	12 (9.7)	12 (9.1)	
Total hip replacement: non-cemented	4 (3.2)	3 (2.3)	
Other	56 (45.2)	75 (56.8)	
Mean time interval between hip fracture and surgery, hours (SD)	47.9 (40.1)	37.4 (27.4)	
Duration of anaesthesia, minutes (SD)			
Mean duration of induction	21.6 (14.1)	20.5 (12.8)	
Mean duration of maintenance	105.2 (47.9)	89.9 (37.7)	
Mean total duration	125.8 (50.9)	109.3 (38.7)	
Mean duration of surgery, minutes (SD)	72.4 (39.1)	62.0 (31.1)	
Anaesthesia recovery parameters			
Mean time to Aldrete score of ≥ 9, hours (SD)	0.70 (1.20)	0.72 (0.72)	0.22[a]
Median time to open eyes, minutes (range)	4.0 (0−363)[b]	8.0 (0−33)	<0.001[c]
Median time to react on verbal command, minutes (range)	5.0 (0−363)[b]	8.5 (1−33)	<0.001[c]
Median time to extubation, minutes (range)	5.4 (0−373)[b]	9.1 (1−35)	<0.001[c]
Hospitalization			
Mean time to discharge, days (SD)	10.8 (5.2)	11.4 (6.2)	0.53[b]
Patients discharged within 30 days, n	120	125	
Patients not discharged within 30 days, n	4	2	
Patients who died, n	0	5	

n, number of patients with the characteristic; N, number of patients in the group; SD, standard deviation.

[a]Treatment groups compared using the log-rank test.

[b]One patient in the xenon group had an extraordinarily long recovery time of 363 minutes. No other patient in either group had a recovery time longer than 33 minutes.

[c]Treatment groups compared using the Wilcoxon rank sum test for quantitative variables.

Table 3. Incidence and characteristics of POD episodes in hip-fracture surgery patients.

Metric	Xenon (N=124)	Sevoflurane (N=132)	*P* value[a]
At least one POD episode by post-surgery day 4, n (%) [95% CI] – intention-to-treat	12 (9.7) [4.5−14.9%]	18 (13.6) [7.8−19.5%]	0.33
At least one POD episode by post-surgery day 4, n (%) [95% CI] – per-protocol[b]	12 (10.2) [4.7−15.6%]	17 (13.7) [7.7−19.8%]	0.40
At least one POD episode on post-surgery day 5 or later, n (%) [95% CI]	5 (4.0) [0.6−7.5%]	8 (6.1) [2.0−10.1%]	0.46
At least one POD episode during the study, n (%) [95% CI]	14 (11.3) [5.7−16.9%]	19 (14.4) [8.4-20.4%]	0.46
Number of POD episodes, n (%)			
0	110 (88.7)	113 (85.6)	
1	8 (6.5)	8 (6.1)	
2	3 (2.4)	5 (3.8)	
≥3	3 (2.4)	6 (4.5)	
Mean time to first POD episode within post-surgery day 4, hours (SD)	28.9 (34.3)	24.4 (25.8)	
Duration of *first* POD episode within post-surgery day 4			
Episodes, n	12	18	
Mean duration, days (SD)	0.87 (0.96)	0.91 (0.80)	
0.5 day, n (%)	9 (75.0)	10 (55.6)	
1−2 days, n (%)	2 (16.7)	7 (38.9)	
3−4 days, n (%)	1 (8.3)	1 (5.6)	

Results shown for all randomised, treated patients (intention-to-treat population). All POD episodes diagnosed by CAM. CAM, Confusion Assessment Method; CI, confidence interval for percentage of patients with a POD episode of the type described; n, number of patients with the characteristic or number of episodes; N, number of patients in treatment group; POD, post-operative delirium.

[a]Treatment groups compared by Pearsons's X^2 test.

[b]Per-protocol population: xenon (N=118); sevoflurane (N=124).

Table 4. Safety summary.

	Xenon (N=125)		Sevoflurane (N=132)		
	Patients with at least one, n (%)	Total AEs, n	Patients with at least one, n (%)	Total AEs, n	*P* value
AEs	114 (91.2)	495	125 (94.7)	573	0.27[a]
Severe	13 (10.4)	19	22 (16.7)	50	0.14[a]
Treatment-emergent	114 (91.2)	457	123 (93.2)	540	0.55[a]
Severe	12 (9.6)	18	21 (15.9)	49	0.13[a]
Considered to be related to study treatment	65 (52.0)	150	62 (47.0)	157	0.42[a]
Most common AEs (>20% of patients)					
Anaemia	45 (36.0)	--	60 (45.5)	--	ND
Hypotension	44 (35.2)	--	53 (40.2)	--	ND
Elevated CRP	29 (23.2)	--	25 (18.9)	--	ND
Gastrointestinal disorders	36 (28.8)	--	34 (25.8)	--	ND
SAEs	10 (8.0)	22	21 (15.9)	45	0.05[a]
Treatment-emergent	10 (8.0)	22	21 (15.9)	45	0.05[a]
Severe	4 (3.2)	6	16 (12.1)	30	0.008[a]
Considered to be related to study treatment	1 (0.8)	1	5 (3.8)	8	0.21[c]
Most common SAEs (> 2% of patients)					
Pneumonia	0 (0)	--	4 (3.0)	--	ND
Acute myocardial infarction	1 (0.8)	--	3 (2.3)	--	ND
Respiratory failure	0 (0)	--	3 (2.3)	--	ND
SAE outcomes					
Ongoing	1 (0.8)	1	3 (2.3)	3	0.62[b]
Recovered	9 (7.2)	19	13 (9.8)	26	0.45[a]
Recovering	1 (0.8)	2	3 (2.3)	4	0.62[b]
Recovered with sequelae	0 (0.0)	0	2 (1.5)	2	0.50[b]
Death	0 (0.0)	0	5 (3.8)	9	0.06[b]
Unknown	0 (0.0)	0	1 (0.8)	1	1.00[b]

Results shown for all treated patients (Safety set). AE, adverse event; CRP, C-reactive protein; n, number of patients with the specified category or type of AE; N, number of patients in the group; ND, not determined; SAE, serious adverse event.

[a]X^2 test for patients with at least one specified AE.

[b]Fisher's exact test for patients with at least one specified AE.