Intranasal Application of Xenon Reduces Opioid Requirement and Postoperative Pain in Patients Undergoing Major Abdominal Surgery

A Randomized Controlled Trial

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ABSTRACT

Background: Both central sensitization after peripheral tissue injury and the development of opioid tolerance involve activation of *N*-methyl-D-aspartate (NMDA) receptors. At subanesthetic doses the NMDA receptor antagonist xenon suppresses pain-evoked sensitization of pain-processing areas in the central nervous system. Although numerous studies describe the effect of NMDA receptor antagonists on postoperative pain, clinical studies elucidating their intraoperative analgesic potency when applied in a low dosage are still largely missing.

Methods: To analyze the analgesic effect of low-dose xenon using new application methods, the authors tested nasally applied xenon as an add-on treatment for analgesia in 40 patients undergoing abdominal hysterectomy. Within a randomized double-blind placebo-controlled study design, intraoperative and postoperative requirement of opioids as well as postoperative subjective experiences of pain were measured as primary outcome variables.

Results: Intranasal application of xenon significantly reduced intraoperative opioid requirement (mean difference [MD] −2.0 μg/min; 95% CI [CI_{95}] −0.53 to −3.51, Bonferroni correction adjusted *P* value [p_{corr}] = 0.028) without relevant side effects and significantly reduced postoperative pain (MD −1.34 points on an 11-point rating scale; CI_{95} −0.60 to −2.09, p_{corr} = 0.002). However, postoperative morphine consumption (MD −8.8 μg/min; CI_{95} 1.2 to −18.8, p_{corr} = 0.24) was not significantly reduced in this study.

Conclusions: Low-dose xenon significantly reduces intraoperative analgesic use and postoperative pain perception. Because NMDA receptor antagonists suppress central sensitization, prevent the development of opioid tolerance, and reduce postoperative pain, the intraoperative usage of NMDA receptor antagonists such as xenon is suggested to improve effectiveness of pain management within a concept of multimodal analgesia.

What We Already Know about This Topic

- Xenon acts in part as an *N*-methyl-D-aspartate receptor antagonist
- Whether low concentrations of xenon affect intraoperative analgesia is unknown

What This Article Tells Us That Is New

- Intranasal application of a low concentration of xenon during abdominal hysterectomy reduced intraoperative opioid requirement as well as acute postoperative pain

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Role of N-Methyl-D-Aspartate Receptors in Pain Management

THE *N*-methyl-D-aspartate (NMDA) receptor is an excitatory glutamate receptor that is involved in the modulation of prolonged pain states induced by central sensitiza-

tion.[1–3] NMDA receptor antagonists such as ketamine and dextromethorphan have been shown to be useful in the reduction of acute postoperative pain and analgesic consumption. Small doses of NMDA receptor antagonists led to a reduced postoperative requirement of opioids and suppressed the development of tolerance to opioids and opioid-induced hyperalgesia.[4–6] Therefore, a concomitant application of small doses of NMDA receptor antagonists within a concept of multimodal analgesia is suggested.[4,7]

Xenon—An Ideal Anesthetic Agent

The noble gas xenon derives its name from the Greek "stranger" because of its rarity, representing no more than 8.75×10^{-6} % of the atmosphere.[8] For more than 50 yr[9] xenon has been used in clinical anesthetic practice[10] and has proven to be a potent inhalation anesthetic with analgesic and organ-protective properties.[11,12] The preponderance of evidence is that xenon acts *via* noncompetitive inhibition of NMDA receptors.[12–14] However, it cannot be ruled out that other targets of xenon also mediate inhibitory effects of the noble gas. [15–18] Xenon's safety and efficacy profile currently appear to be unequalled, and only its relatively high costs and limited resources have precluded its widespread clinical use.[11]

Intranasal Drug Application

Intranasal drug administration is a noninvasive method that allows therapeutic agents that do not cross the blood-brain barrier to be delivered to the central nervous system (CNS). This method eliminates the need for systemic delivery, thereby reducing unwanted systemic side effects.[19–22] Lipid-soluble agents are absorbed rapidly and efficiently across the nasal membrane into the bloodstream *via* the transcellular pathway with a plasma profile resembling that of an intravenous injection. Once these agents reach the bloodstream, they can diffuse freely through the blood-brain barrier and reach the CNS. This diffusion is qualified by the degree of lipid solubility and molecular size, with small lipophilic atoms such as xenon passing through the membrane more easily than larger and polar molecules.[20] Therefore, intranasal delivery may offer a new economic strategy for targeting xenon to the brain and avoid excessive loss by exhalation.[22]

Rationale for the Study

Approximately 30–80% of patients complain about moderate to severe postoperative pain and inadequate postoperative pain relief may delay recovery, lead to a prolonged hospital stay, and increase medical costs.[23–26] In a recently published study using functional neuroimaging, we found xenon to inhibit the CNS response in regions associated with pain processing such as the insular and primary somatosensory cortices.[1] Moreover, increased pain tolerance induced by intranasally applied xenon has already been observed in a placebo-controlled experimental human study.[22] To analyze the analgesic effect of low-dose xenon using a new application method within the clinical setting, we tested nasally applied xenon as an add-on treatment for analgesia in patients undergoing abdominal hysterectomy. We predicted that xenon relieves postoperative pain serving as the main effect variable. Furthermore, we predicted that intraoperative and postoperative requirements of opioids representing indirect indicators of treatment effects would decrease under xenon compared with placebo.

Materials and Methods

Subjects

The entire study was conducted from October 2008 to April 2009 at the Department of Gynecology and Obstetrics of the University Hospital of Ulm, Germany. We recruited 40 American Society of Anesthesiologists physical status I and II patients scheduled for elective abdominal hysterectomy (fig. 1). Recruitment by the involved gynecologist was always performed at least 1 day before surgery. The unpaid patients gave written informed consent before the study conforming with the Declaration of Helsinki and in accordance with the local ethics board (University of Ulm). None had a history of neurologic or psychiatric disorders or any sign of a nasopharyngeal disease. A history of adverse reactions to anesthetics, diabetes mellitus, any relevant renal, liver, or heart (including arterial hypertension) disease, regular alcohol consumption of more than 20 g per day,[27] drug abuse, or taking sedatives or long-acting analgesic drugs were the exclusion criteria.[28]

Monitoring Drugs and Drug Delivery

Patients were monitored with a five-lead electrocardiogram, noninvasive blood pressure sampling, and pulse oximetry (patient monitoring system; Datex-Ohmeda, Helsinki, Finland) at a sample rate of 5 min. A Primus anesthesia workstation (Dräger, Lübeck, Germany) fitted with a desflurane (Baxter, Deerfield, IL) vaporizer unit was used to measure end-expiratory carbon dioxide and desflurane concentrations. A Bispectral Index (BIS) module (BIS® brain monitor, Aspect Medical Systems, Norwood, MA) integrated into the patient monitoring system was used to continually analyze the level of consciousness during anesthesia. Although the BIS has been shown to be suitable to survey the depth of hypnosis[29] during xenon-induced anesthesia, the effect of low-dose xenon on BIS values is unknown. Therefore, data were recorded but not displayed during surgery to ensure blinding. Syringe pumps (Perfusor compact, B/Braun, Melsungen, Germany) were used for intraoperative administration of remifentanil (GlaxoSmithKline, London, United Kingdom) and postoperative patient-controlled opioid application (Graseby PCA Pump 3300, SIMS Graseby, Watford, United Kingdom). Morphine (Merck Pharma GmbH, Darmstadt, Germany) demand doses were 2 mg with a 4-min application period followed by a 6-min lockout pe-

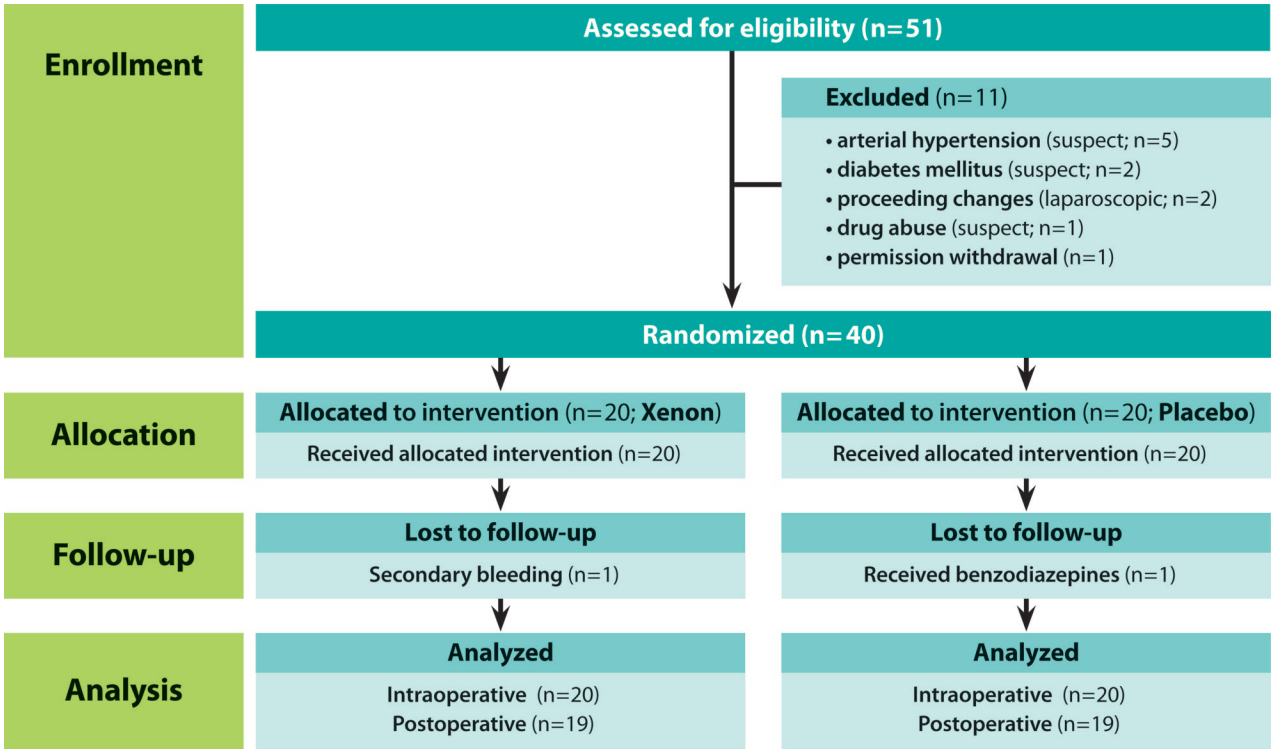

Fig. 1. Flow diagram: 51 patients were assessed for eligibility and 11 patients were excluded during preoperative reevaluation because latent arterial hypertension, untreated diabetes mellitus, and drug abuse (hypnotics) were suspected. Two patients initially scheduled for abdominal hysterectomy finally received laparoscopic surgery. Forty patients were allocated into one of two equally sized groups (xenon [*verum*], air [*placebo*]). One patient of the xenon group was lost to postoperative follow-up because of secondary bleeding, and one patient of the placebo group was postoperatively excluded because she accidentally received lorazepam.[60]

riod, with no maximum limit and no background infusion. Assessment of intensity of acute pain was performed using the 11-point numeric rating scale (0–10; 0 = no pain and 10 = unbearable pain).[24,30]

The xenon application system contained a low-pressure metalized gas reservoir, xenon-proof tubes connected by multidirectional stopcocks and tube clamps (B/Braun), a pressure control unit (data recording; Greisinger GMH 3150, Regenstauf, Germany), two peristaltic pumps for flow adjustment (Bäder, Ulm, Germany), and a drain tube placed in the mouth of the patient leading to exhaust (fig. 2). Therefore, concentrations of xenon within the nasopharyngeal space could be kept constant over time and never decreased below 80% ($[Xe]_{exhaust}$ = 89.7 ± 4.6%; 2 volunteers, unblinded; assessed 10′, 20′, and 30′ after start of application). Air and xenon were delivered at a rate of 1.0 l/h. Xenon 4.0 was obtained from *Air Liquide Santé* International (Paris, France).

Study Design

This was a prospective, randomized, double-blind, parallel-group trial to evaluate the effects of nasally applied xenon on intraoperative and postoperative opioid requirement and postoperative evaluated pain scores. Because there were only two treatment arms (air, xenon) with an *a priori* fixed number of patients (20 per each arm), a simple randomization scheme was used with a vector of random numbers to generate an *a priori* list for randomized treatment assignments. According to this randomization list, patients received either xenon or air. The study supervisor, who did not participate in the assessment, prepared an unlabeled gas reservoir filled with either the colorless and odorless xenon or air as placebo. The anesthetists who provided the anesthesia and the intensive care unit (ICU) staff participating in the pain assessments were blinded for individual treatments. Patients were also blinded for group assignment and both blindings were maintained until the end of the study. The patients were asked to abstain from alcohol and excessive coffee consumption (defined as 5 cups or 400 mg caffeine[31]) for 24 h and from drinking and eating for 8 h before undergoing surgery. They were informed that the intranasal application device would deliver either xenon or placebo (air). The patients received a standardized oral and written instruction on the study design and postoperative usage of numeric rating scales and patient-controlled analgesia (PCA) devices on the evening before surgery. The same physician performed anesthesia and acquisition of intraoperative data. Postoperative assessment of pain was obtained by ICU staff using numeric rating scales. As a second and more indirect index for postoperative pain, the requirement of morphine was recorded by PCA pumps. Individual histories of require-

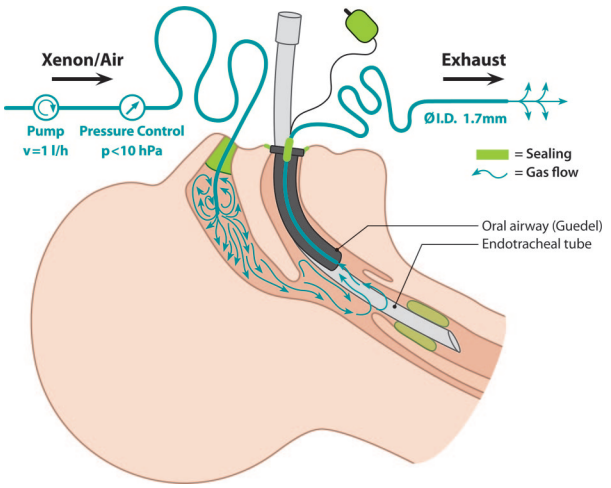

Fig. 2. Schematic representation of the application system. Using two xenon-proof tubes (*blue*) and xenon-proof sealing devices (*green*), xenon or air was delivered into the nasopharyngeal space of the intubated patients at a rate of 1.0 l/h by adjustable peristaltic pumps. A drain tube (ID 1.7 mm) in the mouth of the patient (*via* a Guedel airway) led to exhaustion. Using endotracheal tubes with inflatable cuffs the tracheobronchial tree was sealed against leakage of respiratory gases or desflurane. In the opposite direction a pulmonary contamination with xenon was avoided.

ment were read out after discharge from the ICU and collected in a spreadsheet.

Premedication with 0.03 mg/kg midazolam and infusion of 6.25 ml/kg hydroxyethyl starch (6% 130/0.42, B/Braun) to ensure hemodynamic stability was performed 20 min before surgery (table 1). All patients intravenously received 1 g metamizole (Ratiopharm, Ulm, Germany), 4 mg ondansetrone (GlaxoSmithKline), and 0.2 mg glycopyrrolate (Riemser Arzneimittel AG, Greifswald, Germany) to avoid nasopharyngeal secretion and to ensure short diffusion distances. Anesthesia was induced by 1.5 mg/kg propofol (B/Braun), 1.5 μg/kg fentanyl (Janssen-Cilag, Neuss, Germany), and 0.35 mg/kg atracurium (GlaxoSmithKline) to facilitate tracheal intubation. After induction, desflurane was administered at 0.5 minimum alveolar concentration; using automatic minimum alveolar concentration level monitoring of the Primus anesthesia workstation with an oxygen flow of 300 ml/min. Application of xenon and infusion of remifentanil at a rate of 0.5 mg/h was started 10 min before onset of skin incision. Although the hypnotic state was kept constant at 0.5 minimum alveolar concentration and documented by real-time processing of electroencephalography signals (BIS), the infusion rate of remifentanil was adjusted to responses due to inadequate analgesia – either autonomic (*e.g.*, indicated by an increase/decrease in systolic blood pressure or heart rate by more than 20% from baseline[32]; tearing, sweating) or somatic (*e.g.*, movement).

At the time of removal of surgical dressing, the patients were connected to a PCA pump and a first bolus of 2 mg morphine was applied. After extubation was performed, all patients were taken to an ICU to ensure a safe and immediate opioid-based pain treatment. Metamizole (1 g) was applied intravenously every 6 h, and the patients had the option to obtain up to 12 mg/h morphine by the PCA pump. In addition, patients could receive morphine from ICU staff to intervals of 3 mg/10 min until they gain a numeric rating scale score of 4 in terms of an escape medication. Upon the patients' arrival to ICU, sedation level was assessed with the Observer's Assessment of Alertness/Sedation scale: 5 = responds readily to name spoken in normal tone; 4 = lethargic response to name spoken in normal tone; 3 = responds only after name is called loudly or repeatedly; 2 = responds only after mild prodding or shaking; and 1 = does not respond to mild prodding or shaking.[33]

Blood Gas Analysis

The local ethics committee (University of Ulm) gave permission to this invasive investigation within two healthy volun-

Table 1. Study Design

	Preparation 20 min	Surgery 125 min (Mean)	ICU 24 h
Supporting drugs	HES 6% 6.25 ml/kg	—	—
	Ondansetrone 4 mg	—	—
	Glycopyrrolate 0.2 mg	—	—
	Midazolam 0.03 mg/kg	—	—
	Atracurium 0.35 mg/kg	—	—
Analgesic drugs	Metamizole 1 g	—	Metamizole 1 g
	Fentanyl 1.5 μg/kg	—	—
Hypnotic Drugs	Propofol 1.5 mg/kg	Desflurane *0.5 MAC, constant*	—
Verum/Placebo	—	Xenon or Placebo	—
Opioid consumption	—	Remifentanil *Adjusted to response*	Morphine *Patient controlled*
Pain assessment	—	—	NRS Scores (0–10)

Assessment of treatment effects was performed measuring intraoperative requirement of remifentanil (while the hypnotic state was kept constant) and postoperative patient-controlled morphine consumption within a randomized double-blind placebo-controlled study design. In addition, postoperative treatment effects were assessed using an 11-point numeric rating scale (NRS).

HES = Hydroxyethyl starch; ICU = intensive care unit; MAC = minimum alveolar concentration.

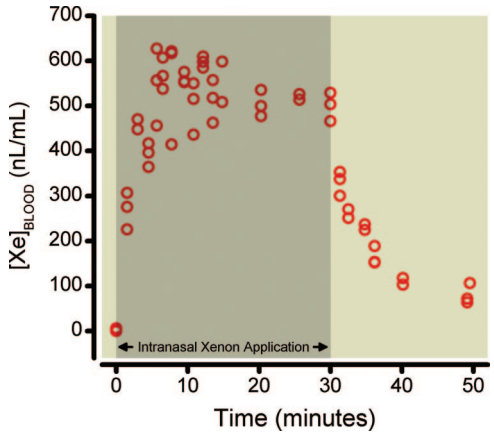

Fig. 3. Blood gas analysis. Concentrations of xenon measured in the blood ($[Xe]_{BLOOD}$) of the internal jugular vein of two volunteers. Intranasal application of xenon for 30 min at a rate of 1.0 l/h followed by 20 min of washout using oxygen at a rate of 8 l/min. A steady state was reached within approximately 10 min providing evidence for a direct pathway from nose to brain.

teers. The right internal jugular vein of the female subjects undergoing intranasal application of xenon was punctured under ultrasound guidance, and 2–3 samples of 2 ml blood were taken at the time points denoted in figure 3. For position control of the intravenous catheter (BD Insyte, 20 GA, 1.1 × 48 mm; Becton Dickinson, Franklin Lakes, NJ), a gas analysis (ABL 800 Flex analysis system; Radiometer, Copenhagen, Denmark) of the aspirable blood was performed. Xenon concentrations of the blood samples were measured by static headspace gas chromatography mass spectrometry.[34]

Statistical Analysis

Due to novelty of the experimental setup as an add-on treatment to a clinically standardized anesthetic protocol and the lack of specific *a priori* information on expectable condition or group differences, computation of power analyses could not be realized. Therefore, we estimated the required number of subjects for a randomized double-blind placebo-controlled parallel-group study design analyzing comparable pain studies using different concentrations of xenon in humans.[10,22,35–37]

Subjective pain ratings (numeric rating scale) as group averages over the postoperative time course of 24 h served as the main outcome variable. Further primary outcome variables were group averages of intraoperative remifentanil requirement (μg/min) and group averages of postoperative morphine consumption (mg/min) representing indirect indicators of treatment effects. Treatment effects were investigated using three separate Student t tests for independent samples. The overall nominal level of α was set to $P < 0.05$. To adjust for multiple comparisons a Bonferroni correction was applied [*e.g.*,[38]] of the two-sided P values obtained by the three separate tests on the primary outcome variables. All statistical tests were computed using the software STATISTICA 6.1 (StatSoft, Inc., Tulsa, OK).

Results

Blood Gas Analysis

Concentrations of xenon measured in the blood of the internal jugular vein of two volunteers reached a steady state of approximately 500 nl/ml after 10 min of intranasal application. Upon washout the concentration decayed exponentially toward zero within approximately 30 min after offset (fig. 3). Blood samples taken from peripheral veins (right basilic vein; n = 12 samples) at the same time never contained more than 20 nl/ml xenon. Monitoring of hemodynamic and respiratory parameters and postsession debriefing of subjects receiving intranasal xenon did not reveal any relevant side effects (nausea, vomiting, changes of end-tidal carbon dioxide concentrations, *etc.*).

Subjects

We studied 40 female patients undergoing abdominal hysterectomy, 20 in the xenon group and 20 in the placebo group (fig. 1). In addition, eight women (four in each group) underwent adnexectomy. The groups were comparable with respect to age, body mass index, American Society of Anesthesiologists physical status category, baseline values of heart rate, and mean arterial pressure. Table 2 shows the patient

Table 2. Patient Characteristics

	Placebo		Xenon			
	Mean	SD	Mean	SD	t (38)	*P* Value
Size, cm	166.65	6.46	164.70	6.94	−0.920	0.363
Weight, kg	69.60	8.52	65.65	11.33	−1.246	0.220
BMI, kg/m^2	25.18	3.88	24.29	4.43	−0.672	0.506
Age, yr	48.30	6.59	45.45	7.26	−1.300	0.201
ASA Category	1.75	0.44	1.55	0.51	−1.322	0.194
HR, beats/min	71.50	10.95	73.80	13.85	−0.628	0.534
MAP, mmHg	93.95	12.31	93.90	13.45	−0.012	0.990

There are no statistically significant differences between groups on either variable listed.

ASA = American Society of Anesthesiologists physical status category; BMI = body mass index; HR = heart rate; MAP = mean arterial pressure.

Table 3. Anesthesia—Comparison of Groups

	Placebo		Xenon			
	Mean	SD	Mean	SD	t (38)	*P* Value
Duration of surgery/min	130.50	69.15	118.00	56.06	0.582	0.564
$Desflurane_{et}$/vol %	3.37	0.17	3.43	0.14	1.121	0.269
MAC	0.50	0.004	0.50	0.01	0.904	0.372
BIS	47.71	8.17	49.17	6.36	0.631	0.532
HR/bpm	61.22	9.42	56.83	8.40	−1.556	0.128
MAP/mmHg	84.37	11.59	79.83	10.06	−1.324	0.193
$_{et}CO_2$	36.51	1.12	35.80	1.51	−1.650	0.107
FIO_2	0.58	0.07	0.59	0.07	0.256	0.799
S_pO_2/%	98.70	0.47	98.97	0.43	1.660	0.105
Gas flow (O_2)/l/min	0.30	0	0.30	0	—	—

Data obtained throughout anesthesia at a sample rate of 5 min (n [placebo] = 506; n [xenon] = 486). There are no statistically significant differences between groups on intraoperative conditions and treatment effects.

BIS = Bispectral index; $_{et}CO_2$ = end-tidal carbon dioxide concentration; HR = heart rate; MAC = minimum alveolar concentration; MAP = mean arterial pressure; SpO_2 = peripheral oxygen saturation.

characteristics for both groups. All patients were hemodynamically stable throughout the anesthetic period, and none of the patients had an intraoperative blood loss greater than 100 ml. One patient in each group was excluded from postoperative analysis – one accidentally received benzodiazepines and the other had to be revised due to secondary bleeding 6 h after extubation.

Anesthesia

During anesthesia all relevant parameters were comparable for both groups: duration of surgery, desflurane dosage (end-tidal desflurane concentration, minimum alveolar concentration), oxygenation, ventilation (end-tidal carbon dioxide concentration), and flow settings (fractional inspired oxygen tension, gas flow). There were no significant group differences of the measured BIS values, blood pressures (mean arterial pressure) or heart rates (table 3). Upon patients' arrival to the ICU there were no statistical significant differences of the sedation level (Observer's Assessment of Alertness/Sedation scale). Vomiting occurred in two patients in each group (table 4).

Treatment Effects on Primary Outcome Variables

All treatment effects on the primary outcome variables are summarized in table 5. With the hypnotic state kept constant at 0.5 minimum alveolar concentration, the infusion rate of remifentanil was adjusted to patient responses and could therefore be used as an indicator for intraoperative analgesic requirement. A two-tailed Student *t* test contrast revealed that remifentanil requirement was significantly reduced in the xenon-treated group compared with placebo with an average reduction of 2.02 μg/min (fig. 4). Furthermore, sub-

Table 4. Summary of Postoperative Events

	Placebo (n = 19)		Xenon (n = 19)			
	Mean	SD	Mean	SD	t (36)	*P* Value
OASS (ICU)	4.37	0.68	4.32	0.82	−0.215	0.831
TFA (min)	30.79	18.36	29.95	15.78	−0.152	0.880
URA	7.42	6.13	4.57	3.934	−1.701	0.098
Vomiting	2		2		—	
Excluded (postoperative)	1		1			
Σ Morphine use (mg/24 h)	1,146		904			
PCA + ICU staff per group						
Σ Morphine use (mg/24 h)	57		12			
ICU staff per group						
NRS 7–10 (*severe*)	9		1		—	
NRS 4–6 (*moderate*)	46		25			
NRS 1–3 (*mild*)	30		50			
NRS 0 (*none*)	10		19			

ICU = intensive care unit; NRS = Numeric rating scale: number of ratings within 24 h postoperative, classification (*none* - *severe*) according to [30]; OASS = Observer's Assessment of Alertness/Sedation scale, data obtained upon arrival to the ICU; PCA = patient-controlled analgesia; TFA =Time to first request for analgesia; URA = Number of unsuccessful requests for analgesia due to PCA pump lockout time.

Table 5. Summary Statistics of Primary Outcome Variables

		Placebo	Xenon	MD	CES	test statistic	*P* Value	p_{corr}
Remifentanil	n	20	20	—	—	—	—	—
Requirement	mean	10.42	8.39	2.02	0.87	t (38) = 2.74	0.0092	0.028
(μg/min)	SD	2.83	1.69	—	—	—	—	—
—	Conf. (−95.0%)	9.09	7.61	0.53	—	—	—	—
—	Conf. (+95.0%)	11.74	9.18	3.51	—	—	—	—
Morphine	n	19	19	—	—	—	—	—
Consumption	mean	0.042	0.033	0.009	0.58	t (36) = 1.79	0.0813	0.244
(mg/min)	SD	0.016	0.014	—	—	—	—	—
—	Conf. (−95.0%)	0.034	0.026	−0.001	—	—	—	—
—	Conf. (+95.0%)	0.050	0.040	0.019	—	—	—	—
Pain scores	n	19	19	—	—	—	—	—
(NRS; 0–10)	mean	3.69	2.35	1.34	1.19	t (36) = 3.66	0.0008	0.002
—	SD	1.00	1.24	—	—	—	—	—
—	Conf. (−95.0%)	3.21	1.75	0.60	—	—	—	—
—	Conf. (+95.0%)	4.18	2.95	2.09	—	—	—	—

Effect sizes are Cohen effect sizes (CES); Mean difference (MD) between both groups (placebo *vs.* xenon); NRS = numeric rating scale; p_{corr} = Bonferroni correction adjusted *P* values according to the three Student *t* tests. Observed *P* values are two-tailed.

jective pain intensity averaged over five time points (time of arrival in the ICU and 3, 6, 12, and 24 h after extubation) was significantly decreased in the xenon than in the placebo group. Reduction of average pain intensity was 1.34 points (fig. 4) with respect to an 11-point numeric rating scale ranging from no pain (= 0) to worst pain imaginable (= 10). Although overall morphine requirement was numerically reduced by approximately 0.01 mg/min on average in patients who had received xenon during surgery, this difference against the placebo group was not statistically significant.

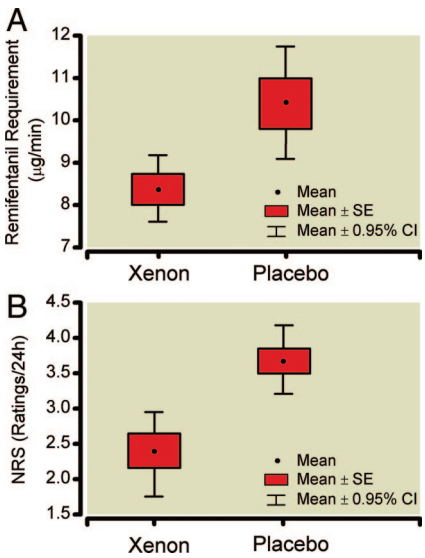

Fig. 4. Treatment effects on primary outcome variables. Intranasally applied xenon significantly reduces intraoperative requirement of opioids and postoperative pain. Box plots showing (*A*) group averages of intraoperative remifentanil requirement (μg/min) and (*B*) subjective pain ratings (0–10 numeric rating scale; 0 = no pain and 10 = unbearable pain) as group averages over the postoperative time course (24 h). NRS = numeric rating scale; SE = standard error of the mean.

Discussion

In this study we measured opioid requirement for major abdominal surgery within a randomized double-blind placebo-controlled study design. We showed that intranasally applied xenon significantly reduces intraoperative requirement of opioids without relevant side effects (*e.g.*, vomiting, increased sedation[36,39]) and reduces postoperative pain. Postoperative opioid consumption was only numerically decreased.

Intranasal Application of Xenon

Xenon in many respects is an ideal anesthetic agent with anesthetic, analgesic, and neuroprotective properties. The main limiting factor for the widespread use of xenon has been its very high cost. However, costs can be reduced using alternative application methods such as intranasal application avoiding excessive loss by exhalation. Nasally administered drugs are able to reach the CNS by neural pathways (olfactory and trigeminal) or the bloodstream.[20,21] However, the apolar and highly lipophilic nature of the chemically inert and structureless xenon is well known[10,40] and lipid-soluble agents are absorbed predominantly across the nasal membrane into the bloodstream with a bioavailability of up to 100%. Once in the bloodstream, they can diffuse freely through the blood-brain barrier and reach the CNS.[20] In this study, we demonstrated a fast wash-in kinetic of xenon completed within approximately 10 min suggesting an extraneural route. Note that the pharmacokinetic analysis primarily represents a confirmation in humans for the *a priori*-obtained analysis in the cerebral compartment of pigs[22] under comparable conditions. There are no statistically significant differences between xenon concentrations in the venous blood comparing both species. Therefore, we assume that after approximately 15 min an intracranial equilibrium state was reached, and based on these results we developed the timeline of our study design.

Assessment of Xenon's Effect

Numerous studies describe the effect of NMDA receptor antagonists on postoperative pain,[4] and there is an ongoing discussion in the literature about application of treatment before or at the end of surgery.[41] However, clinical studies elucidating their intraoperative analgesic potency in contrast to placebo or applied in a low dosage are still largely missing.

Postoperative opioid consumption is commonly used as an index for postoperative pain[4] and was insignificantly decreased by about 20% within the xenon group of our study. This lack of significance is probably due to the hedonic component inherent in morphine because its pleasant and inebriating characteristics are well known.

Because postoperative usage of morphine is not only due to pain, subjective ratings of postoperative pain intensity evaluated by the ICU staff must be taken into consideration as the main outcome variable. Results clearly indicate that patients' subjective feeling of pain was significantly reduced in the group that received xenon during surgery. Furthermore, based on previous studies this reduction also appears to be clinically relevant.[42,43] Patients were able to obtain up to 30 mg/h of morphine *via* PCA (12 mg/h) and ICU staff (18 mg/h). Note that despite this excessive dosage the patients of the placebo group were not able to reduce their pain to the level of patients who had received xenon. Therefore, our data suggest that opioids are inappropriate to mimic or completely replace the analgesic effect of xenon.

During general anesthesia hypnotic and analgesic drug effects are interacting.[44] The hypnotic effects of anesthetic agents can be estimated by its end-tidal partial pressure and can be controlled by real-time processing of electroencephalography signals (*e.g.*, BIS[29,45,46]). Because opioid consumption was the primary intraoperative outcome parameter in this study, all patients received a general balanced anesthesia with desflurane at 0.5 minimum alveolar concentration to minimize the influence of hypnotic drugs on pain processing. We used remifentanil to prevent responses due to inadequate analgesia – indicated either autonomically (*e.g.*, blood pressure, heart rate, tearing) or somatically (*e.g.*, movement).

The pharmacokinetic profile of remifentanil is relatively unaltered by extremes of age and the presence of coexisting conditions such as obesity. Its blood concentration has been found to be proportional to the dose administered throughout the recommended dose range.[44] Therefore, remifentanil is an ideal agent to achieve comparable results relatively independent of patient characteristics. Because both groups (placebo and xenon) were similar in terms of end-tidal desflurane concentrations and BIS values, a constant and comparable hypnotic state of the patients can be assumed. Therefore, the additional intraoperative requirement of remifentanil in the placebo group of approximately 25% can clearly be attributed to a relatively increased pain perception – or in other words to an analgesic effect of nasally applied xenon. These results are in accordance with clinical studies using high-dose xenon (F_{iXe} = 70%) leading to a significantly reduced requirement of opioids[10,37,43] or hypnotic anesthetics[46] to suppress noxious stimulation.

The Effect of NMDA Receptors on Pain Perception

Although several other molecular targets have been discussed on which xenon may exert its effects under certain *in vitro* conditions,[12,16–18] the NMDA receptor type is thought to be the prime molecular effect site for xenon's analgesic properties *in vivo*.[2,12,14] Central sensitization results mainly from the activation of glutamate receptors in the CNS triggered by nociceptive afferent input from the periphery.[3] In a recently published study, we showed an enhanced responsiveness of pain processing areas to repeated painful stimulation using functional magnetic resonance imaging experiments. This enhancement was suppressed by the NMDA receptor antagonist xenon at subanesthetic doses providing evidence for an involvement of NMDA receptors in pain-evoked *long-term potentiation* related synaptic plasticity in the human brain.[1] Moreover, we described an increased pain tolerance induced by intranasally applied xenon within a multimodal and multistructured placebo-controlled experimental human study.[22]

In the current study we showed that xenon significantly reduces postoperative pain in patients by more than 30% within the first 24 h after major abdominal surgery. This is in accordance with clinical studies using the NMDA receptor antagonists ketamine or dextromethorphan.[4,40] Because fast removal of xenon by exhalation[47,48] after terminating the delivery at the end of surgery is suggested by the kinetic study (see fig. 3), the postoperative effect of xenon is far beyond the duration of its presence in the biophase in concentrations that can provide direct pharmacologic effects. Decreased pain intensity beyond this point is regarded as the indirect effect resulting from prevention of pain sensitization processes.[49]

Therefore, the postoperatively reduced pain intensity is well explained by suppressed pain-evoked *long-term potentiation* related processes of synaptic plasticity. Because sensitization processes occur within 30 min,[1] they may also contribute to the decreased intraoperative analgesic requirement within in this study.

Furthermore, there are also relevant interactions between NMDA receptors and opioids. Although morphine, fentanyl, and other opioids produce antinociception through μ-receptor agonist activity and the activation of monoaminergic descending pathways at the spinal level,[6,50] they also activate NMDA receptors, resulting in hyperalgesia and the development of tolerance to opioids.[51] Remifentanil, the opioid we used in this study to determine intraoperative analgesic requirement, presents distinguishing characteristics compared with other opioids. It is a potent, short-acting opioid metabolized by plasma and tissue esterases. These interesting properties allow infusion of high doses during a short time period without compromising a predictable and rapid recovery.[44,47] However, recent human studies have demonstrated difficult postoperative pain management [52–55] and remifentanil was described to potentiate NMDA recep-

tor activity *via* μ-opioid receptors[56] leading to hyperalgesia.[57–59] Thus, if this was the type of tolerance or resistance involved in the intraoperative response to surgical stimulation in our patients, then the improved analgesia of the xenon group can be explained by an interaction of xenon with NMDA receptors that could have been activated by either or both of the perioperative nociceptive inputs and by the administration of opioids.

Conclusion

The concept of multimodal analgesia is the current trend in postoperative pain management. This implies that a single antagonist may not be sufficient to prevent postoperative pain if other pathways are not blocked.[5] Low-dose xenon sufficiently reduces pain perception and analgesic use as demonstrated by functional magnetic resonance imaging measurements,[1] experimental pain studies,[22] and the results of this clinical study. Intranasally delivery offers a new economic strategy for targeting xenon to the brain and the promising results presented here call for future studies to determine the relevance of this application method as an add-on treatment for analgesia and neuroprotection under several clinical conditions.

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