Aus der Klinik für Anästhesiologie

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Antagonisten am NMDA-Rezeptor in Anästhesiologie und Palliativmedizin - Innovative Arzneimittel und neue Indikationen

Habilitationsschrift

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Meinem Lieblingsmenschen und meinem großen Vorbild Dr. med. Sandra Hamada. Meiner am Tag der Fertigstellung dieser Habilitationsschrift geborenen, wundervollen Tochter Carla Elisabeth.

Inhaltsverzeichnis

Präambel und Übersicht der zugrundeliegenden Arbeiten

In dieser kumulativen Habilitationsschrift werden Untersuchungsergebnisse aus fünf Originalarbeiten diskutiert, die sich mit der Anwendung der N-Methyl-D-Aspartat (NMDA)-Rezeptor Antagonisten Xenon in der Anästhesiologie sowie Ketamin in der Palliativmedizin beschäftigen. Die den Kernaussagen der einzelnen Untersuchungen zugrunde liegenden Ergebnisse werden nachfolgend erörtert. Methodische Details und Ergebnisse sekundärer Zielvariablen sind den folgenden Originalarbeiten im Anhang zu entnehmen.

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5. Falk E, Schlieper D, van Caster P, Lutterbeck M, Schwartz J, Coredes J, Grau I, Kienbaum P, Neukirchen M: A rapid influence of S-ketamine on anxiety of palliative patients: a retrospective pilot study. BMC Palliat Care. 2020 Jan 3;19(1):1 doi 10.1186/s12904-019-0499-1.

Abkürzungsverzeichnis

AE	Adverse Event
AMG	Arzneimittelgesetz
AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazol-propionsäure
BIS	Bispectral Index
CAM	Confusion Assessment Method
CEA	Carotid Endarterectomy
cGMP	Zyklisches Guanosinmonophosphat
fMRT	Funktionelle Magnetresonanztomographie
FDA	Food and Drug Administration
GABA	γ-Amino-Buttersäure
ICD	Implantierbarer Cardioverter
kg	Kilogramm
L	Liter
MAC	Minimale Alveoläre Konzentration
Min	Minute
ml	Milliliter
MSA	Muskelsympathikusaktivität
NET	Noradrenalin Transporter
NMDA	N-Methyl-D-Aspartat
NO	Stickstoffmonoxid
POCD	Postoperative kognitive Dysfunktion
POD	Postoperatives Delir
QTc	Frequenz-korrigierte QT Zeit nach Bazett
(S)AE	(Serious) Adverse Event

SOFA	Sequential Organ Failure Assessment
STADI	State-Trait-Angst-Depressions-Inventar

1. Einleitung

Auf der Suche nach dem idealen Anästhetikum in der Anästhesie und einem sicher einsetzbaren Analgetikum mit zusätzlicher anxiolytischer und stimmungsaufhellender Wirkung in der Palliativmedizin geraten sehr schnell die Möglichkeiten der medikamentösen Blockade des NMDA-Rezeptors in den Fokus der Aufmerksamkeit.

Intravenös appliziertes Ketamin wird als NMDA-Rezeptor Antagonist bereits seit 1964 in der Notfallmedizin und Anästhesie als Analgetikum und Narkotikum eingesetzt [1]. Durch die spätere Entwicklung besser steuerbarer Anästhetika und aufgrund unterschiedlicher unerwünschter Wirkungen bei der Anwendung von Ketamin wurde die routinemäßige Anwendung in der Anästhesie jedoch verlassen. Lediglich in der Notfallmedizin kommt es aufgrund seiner analgetischen und zugleich sympathomimetischen, antikonvulsiven, bronchienerweiternden und erst in hohen Dosen atemdepressiven Wirkung noch zum Einsatz. In letzter Zeit erfährt Ketamin wieder zunehmende Aufmerksamkeit, nicht jedoch als Anästhetikum sondern als potentielles Antidepressivum [2]. Im März 2019 hat die Food and Drug Administration (FDA) für die USA das Enantiomer (S)-Ketamin (Esketamin) unter strengen Auflagen zur Behandlung der therapierefraktären Depression zugelassen.

Auch das inhalativ applizierte Edelgas Xenon wird als NMDA-Antagonist bereits seit 1951 am Patienten eingesetzt [3]. Xenon verfügt sowohl über hypnotische als auch analgetische Eigenschaften, wird nicht metabolisiert und flutet schnell an und ab. Im Gegensatz zu zahlreichen anderen Anästhetika kommt es – ähnlich wie bei Ketamin - unter einer Anästhesie mit Xenon weder zur Vasodilatation noch zur negativ inotropen Wirkung [4]. Nicht zuletzt wegen seiner günstigen

Pharmakokinetik und der stabilen Kreislaufverhältnisse unter Anästhesie wird Xenon oft als ideales Anästhetikum bezeichnet [5]. Aufgrund der geringen Verfügbarkeit in der Atmosphäre und der hohen Kosten seiner Isolation hat es sich aber bis heute nicht als Anästhetikum in der Routineversorgung durchgesetzt. Im Gegensatz zu den meisten anderen Anästhetika wirken die beiden NMDA-Rezeptorantagonisten Xenon und Ketamin nicht in erster Linie über inhibitorische γ-Amino-Buttersäure (GABA) Rezeptoren, sondern über eine Hemmung von NMDA-Rezeptoren [6]. Längst stehen jedoch nicht mehr nur die anästhetischen und analgetischen Eigenschaften eines Anästhetikums im Zentrum der Aufmerksamkeit. Vielmehr geht es darum, durch Anwendung moderner Substanzen, unerwünschte Interaktionen mit Outcome-relevanten Organsystemen wie dem Herz-Kreislaufsystem oder dem zentralen Nervensystem zu vermeiden [7]. Durch den gezielten Einsatz von Anästhetika mit neuroprotektiven Eigenschaften und kreislaufstabilisierender Wirkung könnte die Morbidität reduziert und damit eine gesteigerte Patientensicherheit erreicht werden. Im besten Fall wird hierbei auch der Patientenkomfort erhöht. Auch in diesem Zusammenhang rückt Xenon immer mehr in den Fokus der Aufmerksamkeit, da Xenon viele dieser von einem idealen Anästhetikum geforderten Eigenschaften in sich vereint.

Auch in der Palliativmedizin ist man auf der Suche nach Arzneimitteln, die für den Patienten sicher einsetzbar sind und neben analgetischen Eigenschaften auch einen positiven Einfluss auf weitere, den Patienten in dieser schwierigen Lebensphase beeinträchtigende Symptome, wie z.B. Angst und Depression, haben könnten. Hier rückt das ursprünglich aus der Anästhesie bekannte Ketamin aufgrund seiner potentiellen antidepressiven Wirkung zunehmend in den Blickpunkt.

1.1. Analgesie, Anxiolyse, Stimmungsaufhellung und Narkose durch NMDA-Rezeptorantagonisten

1.1.1. Der NMDA Rezeptor

Der NMDA-Rezeptorkomplex spielt eine wichtige Rolle im zentralen Nervensystem. Er ist ein elementarer Bestandteil der Neuroplastizität. Ohne ihn sind Lernen und Gedächtnisbildung nicht möglich.

Ebenso ist der NMDA-Rezeptor eine kritische Struktur der afferenten Signaltransduktion von Schmerzreizen vor allem auf Rückenmarksebene. Neben dem Rückenmark ist der NMDA-Rezeptor kortikal sowie im Soma von primär afferenten Neuronen in den dorsalen Wurzelganglien, peripheren Nerven und Endigungen primär afferenter Fasern in Haut und Muskeln vorhanden. Ebenso wie α-Amino-3-hydroxy-5-methyl-4-isoxazol-propionsäure (AMPA) und Kainat-Rezeptoren gehört der NMDA-Rezeptor zur Familie der ionotropischen Glutamatrezeptoren. Der NMDA-Rezeptor besteht aus NR1, NR2 und NR3 Untereinheiten und ist spannungsabhängig [8, 9]. Der NMDA-Rezeptor ist z.B. bei zentraler Sensitivierung [10], neuropathischen Schmerzen [11] und der opioidinduzierten Hyperalgesie [12] an einigen relevanten pathologischen Schmerzzuständen beteiligt.

Bei Ruhemembranpotential kann der Kanal durch Magnesium blockiert und damit deaktiviert werden. Bei Exzitation öffnet sich der Kanal und Calcium gelangt in die Zelle, was zu einer neuronalen Übererregbarkeit führt [13]. Durch intrazelluläre Bildung von Stickstoffmonoxid (NO) und zyklischem Guanosinmonophosphat (cGMP) ist das Ansprechen auf Opioidrezeptoragonisten reduziert und eine Hyperalgesie begünstigt.

Opioidrezeptoren und NMDA-Rezeptorkanäle beeinflussen sich gegenseitig. Eine Aktivierung von Opioidrezeptoren führt zu einer Phosphorylierung und damit zu einer Öffnung des NMDA-Rezeptorkanals. Dadurch kommt es im Rahmen einer kaskadenartigen Reaktion zur Down-Regulation der Opioidrezeptoren, was wiederum ebenfalls zu Hyperalgesie und zu einer Toleranz gegenüber Opioiden führt [12].

1.1.2. Anästhesie mit Xenon

1.1.2.1. Pharmakodynamik und Pharmakokinetik

Im Rahmen der pharmakokinetischen Eigenschaften inhalativer Anästhetika spielt vor allem die Löslichkeit im Blut eine große Rolle. Bei Substanzen mit niedrigem Blut/Gas Verteilungskoeffizienten (Xenon) und geringer Löslichkeit im Blut werden alveoläre Partialdruckdifferenzen rasch ausgeglichen, was zu einer schnellen Aufnahme der Substanz führt und zu einem schnellen Wirkungseintritt beiträgt. Nach Beendigung der Zufuhr des Anästhetikums kommt es zu einem schnellen Ausscheiden der Substanz und damit zu einem schnellen Wiedererlangen des Bewusstseins. Für die damit verbunden Aufwachzeiten ist die Kumulation des Anästhetikums im Fettgewebe klinisch bedeutsam, die vor allem von der Dauer der Anwendung und der Lipophilie der Substanz bestimmt wird [14, 15]. Diese mit der Kumulation verbundene verzögerte Freisetzung hat dann klinische Relevanz, wenn Patienten im Aufwachraum eingeschränkte Schutzreflexe aufweisen und damit postoperativ

einem deutlich höheren Risiko für postoperative pulmonale Komplikationen ausgesetzt sind [16]. Hier könnte sich der Einsatz gut steuerbarer Anästhetika wie Xenon positiv auf die postoperative Morbidität und damit auf eine Erhöhung der Patientensicherheit auswirken.

1.1.2.2. Interaktionen mit dem kardiovaskulären System

Alle bekannten (inhalativen) Anästhetika interagieren mit dem kardiovaskulären System [17]. Der postoperative Krankheitsverlauf der Patienten wird hier vor allem durch kreislaufdepressive Effekte aufgrund einer Vasodilatation und Reduktion des Herzzeitvolumens mit konsekutiver Hypotension einhergehend mit myokardialen Schädigungen negativ beeinflusst [7, 18-20]. Mechanistisch scheinen bei den kreislaufdepressiven Effekten vor allem die Auswirkungen verschiedener Anästhetika auf die Sympathikusaktivität von Bedeutung zu sein, die beim Menschen durch Ableitung der efferenten Sympathikusaktivität zur Muskulatur (MSA) gemessen und quantifiziert werden kann. Die gängigen inhalativen Anästhetika wie Isofluran, Sevofluran oder Desfluran dämpfen die MSA, wodurch weniger vasokonstriktorisch wirkendes Noradrenalin freigesetzt wird. In Kombination mit einer parallel zur MSA Reduktion häufig einsetzenden Dämpfung kardiovaskulärer Baroreflexe und einer intraoperativ aufgrund von Blutverlusten häufig vorkommenden Hypovolämie führt dies zu den unerwünschten intraoperativen Kreislaufdepressionen [21]. Derartige hypotensive Episoden wirken

sich vor allem bei älteren Patienten aggravierend auf die Entwicklung eines postoperativen Delirs und kognitiver Defizite aus [22]. Durch eine konsequente Vermeidung bzw. Behandlung dieser unter Allgemeinanästhesie auftretenden Kreislaufdepressionen können die Inzidenz postoperativer Komplikationen reduziert und damit auch Organfunktionsstörungen und Letalität gesenkt werden [23].
Aus diesem Grund scheint die weitere Erforschung und Erprobung des inhalativen Anästhetikums Xenon, welches im besten Fall keine negativen Auswirkungen auf das kardiovaskuläre System und eher neuroprotektive Eigenschaften aufweist, von besonderem Interesse.

1.1.2.3. Interaktionen mit dem rhythmogenen System

Pharmakologische Behandlungen gehen nicht selten mit einem Risiko der Induktion von Herzrhythmusstörungen, vor allem auch Veränderungen der kardialen Repolarisation, einher. So beeinflussen alle bisher untersuchten inhalativen Anästhetika kardiale Ionenkanäle, hier vor allem Kaliumkanäle, mit möglichen direkten negativen Auswirkungen auf das Reizleitungssystem und die Repolarisation kardialer Myozyten, was zu lebensbedrohlichen Herzrhythmusstörungen führen kann [24]. Sowohl unter Isofluran und Sevofluran als auch unter Desfluran ist eine Verzögerung der kardialen Repolarisation, gemessen als Verlängerung der QT-Zeit, beschrieben worden [25-29]. Um das Risiko kritischer Herzrhythmusstörungen, wie z.B. Torsades de pointes Tachykardien, so gering wie möglich zu halten, sind die Arzneimittelwirkungen auf

kardiale Ionenkanäle, gemessen als QT-Zeit genauestens zu untersuchen. Diesbezüglich lagen vor unserer Untersuchung bezüglich des inhalativen Anästhetikums Xenon keine Daten vor.

1.1.2.4. Interaktionen mit dem zentralen Nervensystem

Aufgrund zahlreicher - teilweise für die Induktion und Aufrechterhaltung einer Anästhesie essentieller - Interaktionen mit dem zentralen Nervensystem können durch die Anwendung von Anästhetika auch nach primärer Elimination der Substanz und damit nach Wiedererlangen des Bewusstseins anhaltende Beeinträchtigungen des zentralen Nervensystems auftreten. Diese äußern sich z.B. in Form eines postoperativen Delirs (POD). Das POD ist durch akute, häufig fluktuierende Veränderungen des Bewusstseins und der kognitiven Leistungsfähigkeit des Patienten gekennzeichnet [30, 31].

Unter postoperativer kognitiver Dysfunktion (POCD) versteht man eine Abnahme der kognitiven Funktion, insbesondere des Gedächtnisses und der exekutiven Funktionen, die auch länger nach einer Operation andauern kann. In einigen Fällen kann diese Störung auch irreversibel sein [32]. Die POCD unterscheidet sich vom POD. Mit dem POD geht häufig eine Reduktion des bewussten Erlebens sowie eine Beeinträchtigung der Aufmerksamkeit einher. Das POD kann in Form eines hypoaktiven, aber auch in Form eines hyperaktiven Delirs in Erscheinung treten. Auf Grund des fluktuierenden Verlaufs ist die Diagnose eines PODs anspruchsvoll

und erfolgt durch standardisierte Fragebögen, z.B. mit Hilfe der Confusion Assessment Method (CAM), die wiederholt eingesetzt werden sollen. Vor allem Patienten, die aufgrund einer proximalen Femurfraktur operiert werden, weisen eine hohe POD-Inzidenz (40-50%) auf [33-35]. Das Auftreten eines PODs ist mit einer 2-3-fach erhöhten Krankenhausverweildauer und Letalität assoziiert [36, 37]. Als pathophysiologisch ursächlicher Mechanismus für die Entwicklung wird in der Literatur eine gestörte kortikale Transmission GABA-erger Synapsen diskutiert. Die meisten (inhalativen) Anästhetika wirken ebenfalls, wie bereits eingangs erwähnt, durch Inhibition GABA-erger Synapsen, so dass diese Effekte durch Anwendung dieser Substanzen noch verstärkt werden könnten.

1.1.3. Analgesie, Stimmungsaufhellung und Anxiolyse mit Ketamin

Ketamin ist der potenteste kompetitive NMDA-Rezeptorantagonist, der durch Hemmung der nozizeptiven Signaltransduktion auf Rückenmarksebene seine Wirkung entfacht. Die analgetische bzw. anästhetische Wirkung ist dosisabhängig. Somit lässt sich abhängig von Applikationsdauer und Applikationsdosis eine Analgesie mit oder ohne Bewusstseinsverlust erreichen [38]. Die Schutzreflexe bleiben ebenso wie der Atemantrieb durch den dissoziativen Charakter in der Regel sehr lange erhalten. Aufgrund dieser Eigenschaften wird die Substanz vor allem in der Notfallmedizin oder bei kurzen

schmerzhaften Interventionen verwendet. Aufgrund seiner bronchodilatatorischen Eigenschaften findet es ebenfalls zur Durchbrechung eines Status asthmaticus und als Reservemedikament bei therapierefraktärem Schmerz Anwendung. Ketamin hat zusätzlich auch antiinflammatorische und opioidähnliche Wirkungen, die ebenfalls zur analgetischen Wirkung beitragen [39]. Erstmalig im Jahr 1962 von Calvins synthetisiert, wird Ketamin seit den 70er Jahren klinisch angewendet [8]. Seit dem Jahr 2015 steht die Substanz auf der Liste der essenziellen Medikamente der WHO.

1.1.3.1. Pharmakodynamik und Pharmakokinetik

Ketamin (2-(2-Chlorophenyl)-2-(methylamino)cyclohexanon) ist ein wasserlösliches Arylcyclohexylamin und damit ein Abkömmling des Phencyclidins. Es bindet, wenn die Kanäle offen sind, an die Phencyclidin-Bindungsstelle des NMDA-Rezeptors und verringert so die Häufigkeit der Kanalöffnungen. Es weist Wechselwirkungen mit anderen Ionenkanälen und Rezeptoren, wie z.B. Natrium- und Calziumkanälen, sowie Dopamin-, Opioid- sowie muskarinischen und nikotinischen Acetylcholin-Rezeptoren auf [8].

Ketamin ist optisch aktiv, so dass sowohl R- als auch S-Enantiomere mit unterschiedlichen pharmakodynamischen Eigenschaften vorliegen. Sowohl das Razemat als auch das S-Enantiomer sind als Arzneimittel zugelassen. Das S-Enantiomer weist eine höhere Affinität und Selektivität für den NMDA-Rezeptor auf und ist damit doppelt so wirksam wie das Razemat und circa viermal so wirksam wie das R-

Enantiomer [40]. Auch das Nebenwirkungsprofil des S-Enantiomers ist weniger stark ausgeprägt [1]. Ketamin induziert hepatische Enzyme und beschleunigt so seinen eigenen Stoffwechsel.

Ketamin kann über verschiedene Wege appliziert werden, es resultieren lediglich unterschiedliche Bioverfügbarkeiten (oral 17%, nasal 45%, sublingual 24-40% und rektal 30%) [41, 42]. Bei oraler Anwendung sind zum einen der sehr hohe first past Effekt und zum anderen die in der Leber über CYP3A4 erfolgte Umwandlung in Norketamin zu beachten [43]. Norketamin wirkt ebenfalls als NMDA-Rezeptorantagonist anästhetisch etwa ein Drittel schwächer – analgetisch jedoch äquipotent im Vergleich zu Ketamin. Norketamin wiederum wird weiter verstoffwechselt zu Dehydronorketamin. Ketamin ist im Gegensatz zu Xenon lipophil und weist eine Plasmaeiweißbindung von 30 Prozent auf [44]. Das Verteilungsvolumen entspricht bei Erwachsenen circa 2,3 l kg^{-1} Körpergewicht. Die durchschnittliche Clearance beträgt 12,6 ml min^{-1} kg^{-1} Körpergewicht. Die Plasmahalbwertszeit beträgt ca. 2,5 Stunden [41]. Die Elimination erfolgt in Form von konjugierten oder hydroxylierten Metaboliten überwiegend renal und biliär [45].

1.1.3.2.Interaktionen mit dem kardiovaskukläre-, dem gastrointestinalen-, und dem urogenitalen System

Eine Anästhesie mit razemischem Ketamin verringert baroreflektorisch die Aktivität des Sympathikus im Vergleich zum

Wachzustand, erhöht jedoch die Katecholamin-Plasmakonzentration, die Herzfrequenz sowie den arteriellen Druck und erhält die Sympathikus Antwort auf hypotensive Reize beim Menschen [46]. Das Enantiomer S(+)-Ketamin erhöht hingegen die MSA und den arteriellen Blutdruck. Trotz erhöhter MSA und erhöhtem arteriellen Druck bleibt der Anstieg des MSA als Reaktion auf eine arterielle Hypotonie erhalten [47]. Zu beachten ist ebenfalls das mögliche uro- und hepatobiliärtoxische Potential der Substanz. Zu den urotoxischen Symptomen gehören z.B. häufiges Wasserlassen, Harndrang, Dranginkontinenz, Dysurie, Unterbauchschmerzen und Hämaturie aufgrund von interstitieller Zystitis, Detrusorüberaktivität, Abnahme der Blasenkapazität, vesikourethraler Reflux, Hydronephrose, papilläre Nekrose sowie Niereninsuffizienz. Zu den hepatobiliären Symptomen gehören Bauchschmerzen u.a. aufgrund von Dilatationen oder Strikturen der Gallengänge [48]. Als Mechanismus kommen auch hier direkt toxische Schäden durch Ketamin oder einen seiner Metaboliten in Frage. Bei Einmalgabe ist nicht die maximale Plasmakonzentration verändert, sondern lediglich die Elimination verlängert. Dadurch kommt es bei kontinuierlicher Applikation oder wiederholter Gabe zur Kumulation [46]. Wechselwirkungen werden u.a. bei Kombination von Ketamin mit Benzodiazepinen oder durch gleichzeitige Applikation von CYP4A-Inhibitoren wie Clarithromycin oder Ketokonazol beschrieben. Bei kontinuierlicher oder wiederholter Ketamingabe wird bei diesen Arzneimittelkombinationen eine Kumulation beobachtet. Im Gegensatz führen CYP4A Induktoren wie Rifampicin oder Johanniskraut zur beschleunigten Elimination von

Ketamin [49].

1.1.3.3. Interaktionen mit dem zentralen Nervensystem

Nach Applikation von Ketamin kann es zu lebhaften Träumen und dissoziativen Wahrnehmungsstörungen mit Veränderungen des Körperbilds bis hin zu psychomimetischen Halluzinationen kommen, die sich durch eine ruhige Umgebung bei Applikation oder im Bedarfsfall durch Gabe von anxiolytisch wirkenden Benzodiazepinen gut kontrollieren lassen [1, 50]. Subanästhetische Ketamin-Dosen wurden aufgrund der psychomimetischen Wirkungen, der Störung von Konzentration, Erinnerung sowie Urteilsvermögen als pharmakologisches Modell für Schizophrenien verwendet [51]. Bei Patienten, die Ketamin über einen längeren Zeitraum missbräuchlich anwenden, werden Kurz- und Langzeitgedächtnis am ehesten durch einen Dopaminmangel im präfrontalen Kortex bedingt beeinträchtigt [52]. Neben direkten neurotoxischen Effekten waren in der funktionellen Magnetresonanztomographie (fMRT) im Bereich der weißen Substanz im frontalen und links-temporo-parietalen Kortex auftretende, dosisabhängige strukturelle Veränderungen, im anterioren zingulären Kortex, die mit einer reduzierten Aktivität einhergingen, sowie im linken Gyrus praecentralis, die mit einer gesteigerten Aktivität einhergingen, nachzuweisen [53].

1.2. Fragestellungen

Die Durchführung einer Allgemeinanästhesie mit inhalativen Anästhetika ist mit zahlreichen kardiovaskuklären, rhythmogenen sowie zentralnervösen Risiken vergesellschaftet. Auf der Suche nach dem idealen Anästhetikum stellen sich bezüglich der Durchführung einer inhalativen Allgemeinanästhesie mit dem Edelgas Xenon folgende Fragen bezüglich des Nebenwirkungsprofils:

1. Welchen Einfluss hat Xenon auf die Sympathikusaktivität und damit auf das kardiovaskuläre System?

2. Welchen Einfluss hat Xenon bzw. eine Xenon-basierte Allgemeinanästhesie auf die QT-Zeit und damit auf die Repolarisation des Herzens?

3. Welchen Einfluss hat eine Xenon-basierte Allgemeinanästhesie auf die Entwicklung von POD und damit auf das zentrale Nervensystem?

4. Welchen Einfluss hat eine Xenon-basierte Allgemeinanästhesie auf SSEPs und damit auf die Durchführbarkeit eines Neuromonitorings?

Eine Behandlung mit dem Analgetikum Ketamin könnte zusätzlich zum analgetischen Effekt positive Auswirkungen auf die bei Palliativpatienten häufigen Symptome Angst und Depression haben. Auf der Suche nach gut verträglichen Substanzen mit breitem symptomlindernden

Wirkspektrum auf verschiedenen Symptomebenen stellt sich bei primär analgetisch intendierter Behandlung mit S-Ketamin die folgende Frage:

5. Welchen Einfluss hat eine analgetische Behandlung mit S-Ketamin bei Palliativpatienten auf den Symptomscore State-Trait-Angst-Depressions-Inventars (STADI) und damit auf die Intensität der Symptome Angst und Depression?

2. Untersuchungen

2.1. Einfluss von Xenon auf Sympathikusaktivität und Kreislaufstabilität

Intraoperative Hypotension ist mit einem erhöhten Risiko für perioperative Komplikationen assoziiert. Dabei scheint es sich nicht nur um eine Assoziation, sondern auch um einen kausalen Zusammenhang zu handeln, da eine konsequente Behandlung geringfügiger Blutdruckabfälle die Wahrscheinlichkeit für das Auftreten postoperativer Organfunktionsstörungen verringert [23]. In der Anästhesiologie ist es daher sinnvoll, Anästhetika mit möglichst geringen kreislaufdeprimierenden Eigenschaften einzusetzen und die zu Grunde liegenden Mechanismen zu verstehen. Patienten, die eine Xenon Anästhesie erhalten, sind durch besonders stabile Kreislaufverhältnisse ausgezeichnet. Dabei ist bisher pathophysiologisch unklar, warum unter Xenonmonoanästhesie keine Blutdruckabfälle, sondern eher sogar ein diskreter Blutdruckanstieg beobachtet werden.

Da das sympathische Nervensystem sehr bedeutsam für die kurzfristige Regulation des arteriellen Blutdrucks ist, haben wir als Phase I Studie nach dem AMG die efferente MSA, die Plasmakonzentration des sympathischen Neurotransmitters Noradrenalin sowie Blutdruck und Herzfrequenz bei gesunden Probanden unter Xenon Anästhesie untersucht.

Bei acht gesunden Probanden ist die MSA durch Xenon Anästhesie nicht verändert. Allerdings wird eine Verdopplung der Noradrenalin-

Plasmakonzentration beobachtet, die mit einem Anstieg des arteriellen Blutdrucks einhergeht.

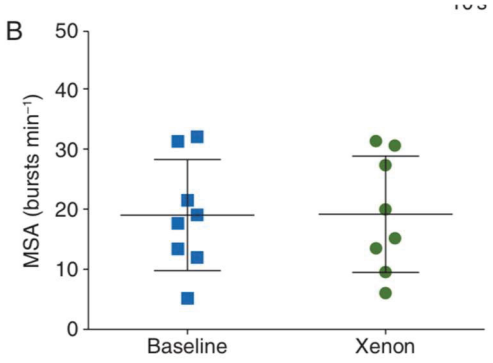

Abbildung 1 Einzeldatenpunkte, Mittelwerte und Standardabweichung der Muskel Sympathikus Aktivität (MSA) vor und nach Einleitung einer Xenon Monoanästhesie. Die MSA bleibt unter Xenon Monoanästhesie unverändert. (Elsevier, vorbehaltenes Recht des Autors)

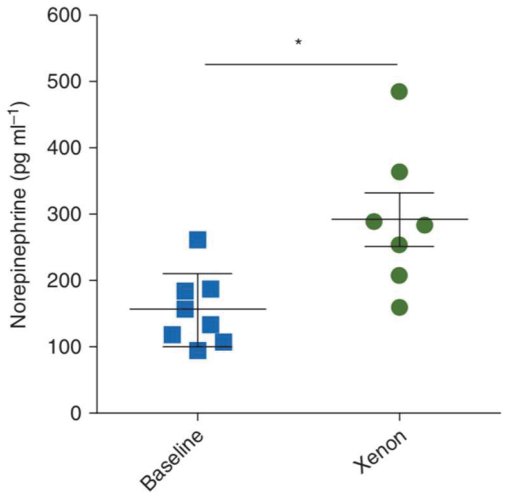

Abbildung 2 Einzeldatenpunkte, Mittelwerte und Standardabweichung der Norepinephrin Plasmakonzentration vor und nach Einleitung einer Xenon Monoanästhesie. Die Norepinephrin Plasmakonzentration bleibt unter Xenon Monoanästhesie unverändert. (Elsevier, vorbehaltenes Recht des Autors)

Es stellt sich jetzt die Frage, warum bei unveränderter MSA die Noradrenalin-Plasmakonzentration zunimmt.

In humanen Nebennierenepithel- und Neuroblastomzellen konnten wir eine durch Xenon vermittelte kompetitive NMDA-Rezeptorblockade und

dadurch eine Hemmung der Noradrenalinwiederaufnahme nachweisen. Dieser Effekt war vergleichbar mit einer Inkubation des in Zellkulturen häufig verwendeten NMDA-Rezeptorantagonisten MK-801 und konnte durch den natürlichen Agonisten Glycin aufgehoben werden.

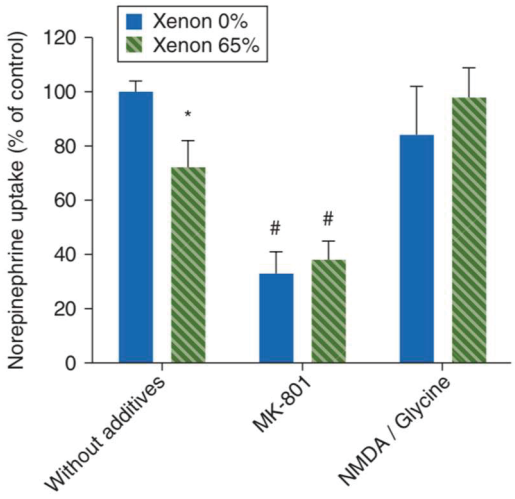

Abbildung 3 Effekt von Xenon auf die Norepinephrin Wiederaufnahme. Xenon (65%) hemmt die Wiederaufnahme von Norepinephrin. Spezifische NMDA-Inhibition mittels MK-801 (2 mikromol / Liter) imitiert diesen Effekt, während die agonistische Stimulation mit NMDA (25 mol / Liter) und Glycin (10 mmol / Liter) ihn umkehrte. Darstellung der Daten als Mittelwerte mit Standardabweichung (* $p<0.01$ vs. Xe 0%; # $p<0.01$ vs. ohne Zusätze (n=6, ANOVA und post hoc Bonferroni Test) (Elsevier, vorbehaltenes Recht des Autors)

Zusammenfassung: Xenon übt beim gesunden Probanden keinen Einfluss auf den efferenten Sympathikus zur Muskulatur aus. Die Kreislaufstabilität wird durch eine Hemmung von Noradrenalintransportern über einen NMDA-Rezeptor vermittelten kompetitiven Mechanismus ausgelöst. Dadurch ist vermehrt endogenes Noradrenalin zur Kreislaufstabilisierung synaptisch verfügbar, was gleichzeitig mit einer diskreten Erhöhung seiner Plasmakonzentrationen verbunden ist.

2.2. Einfluss von Xenon auf die QT-Zeit

Viele in der Anästhesie und Schmerztherapie gebräuchliche Pharmaka wie z.B. inhalative Anästhetika [54], Succinylcholin [55] oder Methadon [56] können die QT-Zeit u.a. durch Blockade von schnell reagierenden Ionenkanälen, so genannten human ether-ago-go-related gene (HERG) Kaliumkanälen, verlängern und so zu lebensbedrohlichen Herzrhythmusstörungen führen. Um bei Patienten mit angeborenen oder erworbenen Störungen der kardialen Repolarisation (z.B. Long QT-Syndrom) auf Pharmaka mit QT Zeit verlängerndem Potential verzichten zu können bzw. um auch bei Patienten ohne Long QT-Syndrom nicht zeitgleich mehrere Substanzen mit potentiell QT-Zeit verlängernder Wirkung einzusetzen, ist es essentiell, die Wirkungen von Xenon auf die QT-Zeit zu kennen. So können schwerwiegende perioperative Herzrhythmusstörungen, z.B. in Form von Torsades de Pointes Tachykardien, verhindert werden.

Aus diesem Grund untersuchten wir an acht gesunden Probanden und an 35 Patienten während abdominalchirurgischen oder traumatologischen Eingriffen den Effekt einer Xenon-Anästhesie auf die QT Zeit. Bei den gesunden Probanden wurde die QT-Zeit vor Einleitung der Narkose, nach Denitrogenisierung und unter Xenon Monoanästhesie untersucht. Bei den Patienten wurde die QT-Zeit vor Einleitung der Narkose, nach Anästhesie Einleitung mit Propofol und Remifentanil und während der Narkose mit Xenon und Remifentanil in jeweils drei aufeinander folgenden Intervallen ausgewertet und daraufhin mit der Formel nach Bazett in die herzfrequenzkorrigierte QT-Zeit (QTc)

umgerechnet.

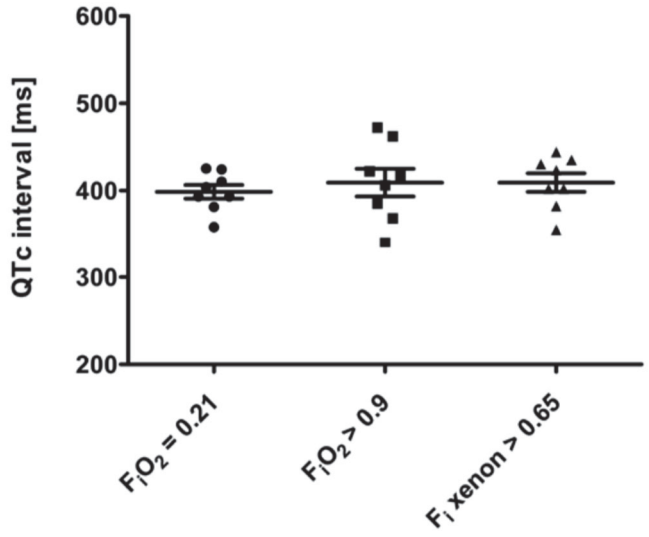

Abbildung 4 Einzeldatenpunkte, Mittelwerte und Standardabweichung der QTc Zeit der acht Probanden vor Narkoseeinleitung, nach Denitrogenisierung und unter Xenon Monoanästhesie (Wolters Kluwer Health Inc., reproduziert mit Genehmigung)

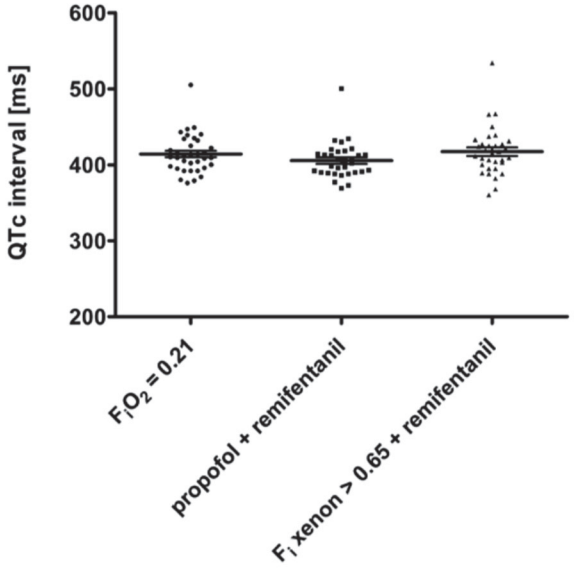

Abbildung 5 Einzeldatenpunkte, Mittelwerte und Standardabweichung der QTc-Zeit der 35 Patienten vor Narkoseeinleitung, unter Propofol-Remifentanil Anästhesie und unter Xenon-Remifentanil Anästhesie (Wolters Kluwe Health Inc. reproduziert mit Genehmigung)

Sowohl bei den gesunden Probanden als auch bei den Patienten veränderte eine Monoanästhesie mit Xenon bzw. eine

Kombinationsanästhesie aus Xenon und Remifentanil die QTc-Zeit nicht. Somit ist davon auszugehen, dass Xenon sowohl bei Patienten mit Long QT-Syndrom als auch bei Patienten, die bereits andere auf die QT-Zeit Einfluss nehmende Substanzen einnehmen oder erhalten, ohne das Risiko einer QT-Zeit Verlängerung einsetzbar ist.

Zusammenfassung:

Das Anästhetikum Xenon zeigt bei gesunden Probanden in der Monoanwendung und bei Patienten, die für abdominalchirurgische / traumatologische Eingriffe eine Xenon- / Remifentanil-Anästhesie erhalten, keinen Einfluss auf die QTc-Zeit und erscheint somit im Hinblick auf die nicht gegebene Begünstigung gefährlicher Herzrhythmusstörungen sicher einsetzbar.

2.3. Einfluss von Xenon auf die Entwicklung eines postoperativen Delirs

Die Entwicklung eines POD nach operativen Eingriffen und Anästhesie ist gerade bei älteren Patienten häufig und mit einem schlechten Outcome assoziiert. Xenon zeigt im Tierversuch neuroprotektive Eigenschaften, so dass eine Anästhesie mit Xenon beim Menschen die Inzidenz eines postoperativen Delirs reduzieren könnte. Hierzu führten wir unter Federführung der Klinik für Anästhesiologie des Universitätsklinikums Aachen (Leiter der klinischen Prüfung: Prof. Dr. med. Mark Coburn) gemeinsam mit 13 Partnern in sechs europäischen Ländern eine randomisierte, verblindete, kontrollierte, multizentrische Phase II Studie nach dem AMG durch. Im Rahmen dieser Studie erhielten kognitiv uneingeschränkte Patienten mit einem Alter über 75 Jahren mit proximaler Femurfraktur in der Kontrollgruppe eine Standard Sevofluran-Anästhesie und in der Interventionsgruppe eine Xenon-basierte Anästhesie. Die primäre Zielvariable war die Inzidenz eines PODs am vierten postoperativen Tag. Sekundäre Zielvariablen waren u.a. die Entwicklung eines postoperativen Delirs während des Krankenhausaufenthaltes, das postoperative Sequential Organ Failure Assessment (SOFA) und das Auftreten von Serious Adverse Events (SAE). Das Auftreten eines postoperativen Defizits wurde mittels des Ergebnisses des Testinstruments CAM erhoben.

Insgesamt wurden 256 Patienten, davon 40 Patienten aus unserer Klinik, in die Untersuchung eingeschlossen, von denen 124 mit Xenon und 132 mit Sevofluran anästhesiert wurden. Die Inzidenz des Delirs betrug unter Xenon 9,7 % (95% KI:4,5-14,9) und unter Sevofluran 13,6 % (95 %

KI:7,8-19,5). Der gemessene Unterschied erreichte jedoch keine Signifikanz.

Metric	Xenon (N=124)	Sevoflurane (N=132)	P-value*
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† [%]	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, h (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)	

Tabelle 1 Inzidenz und Charakteristika von Episoden eines postoperativen Delirs (POD) bei Patienten mit proximaler Femurfraktur. Alle POD Episoden wurden mittels Confusion Assessment Method (CAM) diagnostiziert. (Elsevier, vorbehaltenes Recht des Autors)

Bezogen auf die sekundären Zielvariablen war der SOFA Score signifikant niedriger unter Xenon-Anästhesie im Vergleich zur Sevofluran-Anästhesie. Für Xenon und Sevofluran lag die Inzidenz von SAE und tödlichem SAE bei 8,0% vs 15,9% (p=0.05) bzw. 0% vs 3,8% (p=0.06).

	Xenon (N=125)		Sevoflurane (N=132)		P-value
	Patients with at least one, n (%)	Total AEs, n	Patients with at least one, n (%)	Total AEs, n	
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]

Tabelle 2. Zusammenfassung der „Safety"-Daten. Inzidenz von Adverse Events (AE) und Serious Adverse Events (SAE) sowie der jeweiligen „Outcomes" der Ereignisse (Elsevier, vorbehaltenes Recht des Autors)

Xenon Anästhesie reduzierte somit in dieser Untersuchung nicht die Inzidenz des POD. Dies mag damit zusammenhängen, dass auf Grund einer durch die gewählten Einschlusskriterien bedingten positiven Patientenselektion (kognitiv nicht eingeschränkt) die Inzidenz der primären Zielvariablen POD nicht 30 Prozent, sondern lediglich 14 Prozent in der Kontrollgruppe beträgt. Damit ist eine Reduktion der Delirinzidenz um 30 Prozent nicht mit hinreichender Power mit der geplanten Fallzahl nachweisbar. Zur statistischen Absicherung eines solchen Effekts wäre eine Erhöhung der Fallzahl auf über 1.000 Patienten erforderlich gewesen. Der signifikant reduzierte SOFA Score sowie die zwar nicht signifikant aber dennoch reduzierte Rate von SAE könnte somit als möglicher Hinweis auf Vorteile einer Xenon-basierten Anästhesie gegenüber der herkömmlichen Standardanästhesie mit Sevofluran gedeutet werden.

Zusammenfassung: Die Inzidenz eines postoperativen Delirs war in dieser Studie bei einer Xenon-basierten Anästhesie nicht signifikant niedriger als bei einer Sevofluran-basierten Standardanästhesie. Unsere Beobachtungen bezüglich eines signifikant reduzierten SOFA Scores, der reduzierten SAE Rate sowie der reduzierten Sterblichkeit können zukünftige Hypothesen generieren, die in weiteren Studien untersucht werden sollten, um die protektiven Effekte einer Xenon Anästhesie bei älteren Patienten zu untersuchen.

2.4. Einfluss von Xenon auf somatosensorisch-evozierte Potentiale

Zahlreiche, vor allem inhalative Anästhetika führen zu einer Veränderung von Variablen, die im Rahmen von Neuromonitoring wichtige diagnostische Informationen über intraoperativ entstehende Schädigungen des Nervensystems liefern können. Dazu gehören auch somatosensorisch evozierte Potentiale (SSEP). Um Veränderungen in der Amplitudenhöhe und der Latenz bei kritischen Eingriffen an den hirnversorgenden Gefäßen oder bei neurochirurgischen Operationen nicht unbegründet als Auswirkung der operativen Intervention zu werten, ist es sinnvoll und wichtig, die Auswirkungen einzelner Anästhetika auf SSEPs zu kennen. Zum perioperativen Neuromonitoring und zur Detektion zerebraler Ischämien werden dabei u.a. kortikal die Antworten auf Stimulationen des Nervus medianus mittels Messung der Amplitude und Latenz der N20 Welle aufgezeichnet. Da Xenon für die Anästhesie bei derartigen Eingriffen viele günstige Eigenschaften wie z.B. Kreislaufstabilität und ggf. sogar neuroprotektive Eigenschaften aufweist, untersuchten wir im Rahmen einer observativen Kohortenstudie die Effekte einer Xenon Anästhesie auf SSEPs bei 20 gefäßchirurgischen Patienten, die sich einer Desobliteration der Arteria carotis unterzogen. Als primäre Zielvariablen wurden dazu Amplitude und Latenz der N20 Welle, als sekundäre Zielvariablen der mittlere arterielle Blutdruck, der Bedarf an Norepinephrin zur Aufrechterhaltung eines ausreichenden arteriellen Blutdrucks sowie die Narkosetiefe (Narcotrend Index) unter Propofol-basierter und unter Xenon-basierter Anästhesie untersucht.

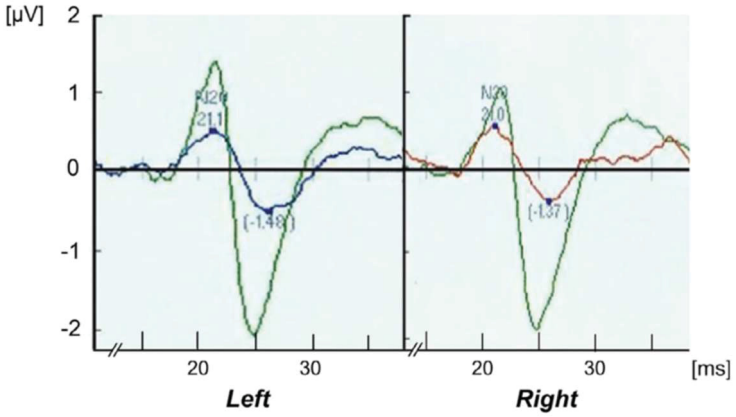

Abbildung 6. Repräsentative Aufzeichnung evozierter Potentiale eines Patienten unter Propofol-basierter Anästhesie (grün) im Vergleich zu Xenon-basierter Anästhesie (blau bzw. rot) für die linke und rechte Hemisphäre. (Elsevier, vorbehaltenes Recht des Autors)

Unter Xenon in einer durchschnittlichen inspiratorischen Konzentration von 62% waren die SSEPs zuverlässig allzeit ableitbar. Bei gleicher Narkosetiefe (Narcotrend Index Propofol 38 vs. Xenon 39) war unter Xenon-basierter Anästhesie im Vergleich zu Propofol-basierter Anästhesie die SSEP-Amplitude signifikant reduziert (OP-Seite: Propofol 3.7 vs. Xenon 1.4 mikrovolt, $p<0.001$; Kontralaterale Seite: Propofol 3.6 vs 1.4 mikrovolt, $p<0.001$). Die Latenz unterschied sich zwischen beiden Anästhesieregimen nicht (OP-Seite: Propofol 23 versus 23 ms, $p=0.34$; Kontralaterale Seite: Propofol 23 versus .23 ms, $p=0.97$).

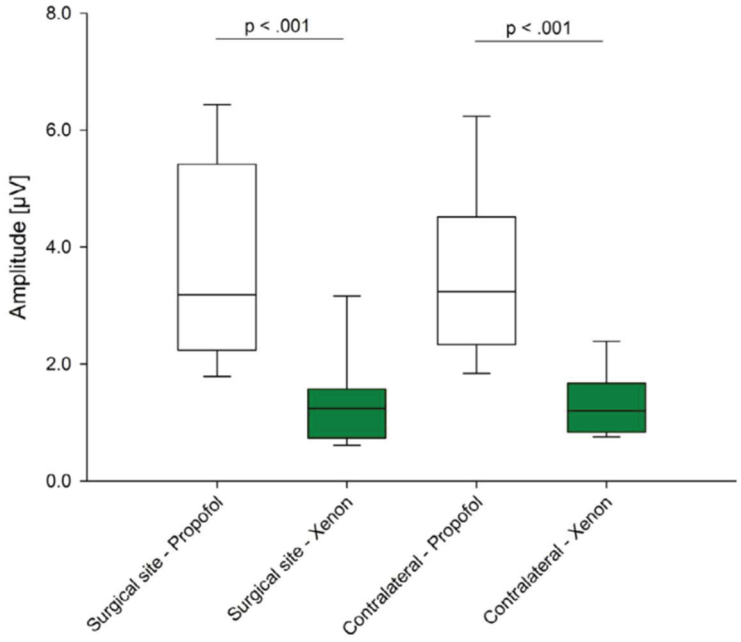

Abbildung 7. Mittelwerte und Standardabweichung der Amplitude der N20 Welle von SSEPs während Propofol-basierter Anästhesie (grau) und während Xenon-basierter Anästhesie (grün) getrennt für die operierte und die nicht operierte Seite (Elsevier, vorbehaltenes Recht des Autors)

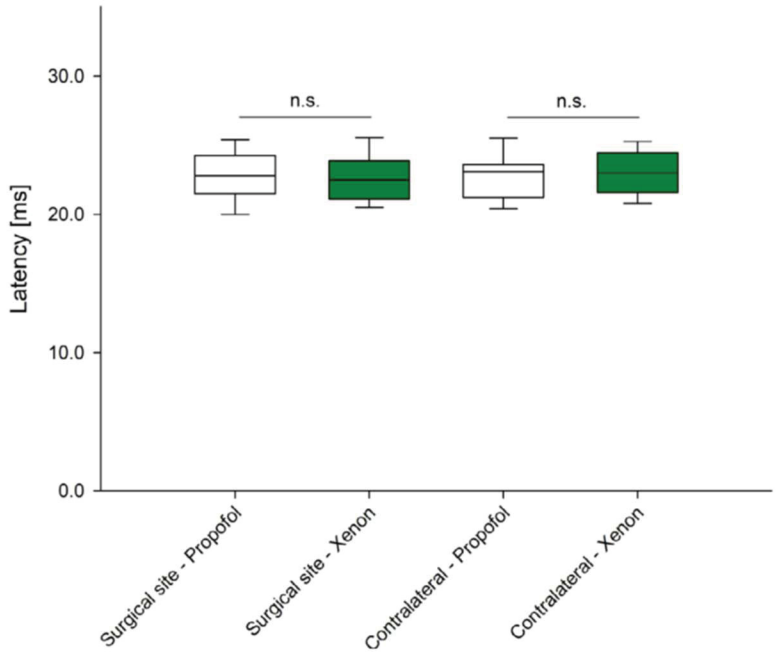

Abbildung 8. Mittelwerte und Standardabweichung der Latenz der N20 Welle von SSEPs während Propofol-basierter Anästhesie (grau) und während Xenon-basierter Anästhesie (grün) getrennt für die operierte und die nicht operierte Seite (Elsevier, vorbehaltenes Recht des Autors)

Der mittlere arterielle Blutdruck (Propofol 90.6 versus Xenon 93.1, p=0.4) blieb unverändert, während der Norepinephrinbedarf (Propofol 0.067 vs. Xenon 0.028 mikrogram/kg/Min) unter Xenon halbiert war.

Somit beeinflusst Xenon in einer Konzentration von 1 MAC die Messung somatosensorisch evozierter Potentiale dahingehend, dass es die Amplitude der N20 Welle um 50 Prozent reduziert, nicht jedoch deren Latenz. Wählt man also Xenon als Anästhetikum bei gefäß- oder neurochirurgischen Operationen, bei denen ein Neuromonitoring notwendig ist, so ist als präoperativer Ausgangswert der Wert nach Beendigung des Xenon Einwaschvorgangs und nach Stabilisierung dieser Baseline zu wählen.

Zusammenfassung:

Ein Monitoring von SSEPs ist auch unter hohen Dosen von Xenon verlässlich durchführbar. Die Amplitude der N20 Welle wird zwar deutlich reduziert, nicht aber die Latenz. Somit ist die Höhe der Amplitude nach Erreichen von steady state Bedingungen unter Xenon-basierter Anästhesie als Baseline zu wählen, mit der dann eventuelle intraoperative Veränderungen, die auf eine Schädigung schließen lassen, verglichen werden müssen.

2.5. Einfluss von S-Ketamin auf Angst und Depression

S-Ketamin wird in der Anästhesie in niedrigen Dosierungen vor allem als Analgetikum und in höheren Dosierungen als Hypnotikum appliziert. Auch in der Palliativmedizin findet S-Ketamin als Analgetikum bei therapierefraktären Schmerzen trotz leitliniengerechter Schmerztherapie nach WHO Stufenschema Anwendung [57-59]. Palliativpatienten leiden oft unter Ängsten und Depressionen [60]. Die beiden Symptome Angst und Depression führen im Sinne des „Total Pain"-Konzeptes auch häufig zu höher empfundener Symptomlast im Bereich der Schmerzen [61, 62]. Zusätzlich gehen sie mit einer deutlich verminderten Lebensqualität sowie einer verminderten Überlebenszeit einher [63]. Bei den Therapieoptionen von Ängsten kommen neben nicht medikamentösen Therapieverfahren medikamentöse Behandlungen mit Benzodiazepinen in Betracht, die jedoch mit erheblichen Nebenwirkungen wie Sedierung, Verwirrtheit und Steigerung der Sturzneigung verbunden sein können. Bei der medikamentösen Therapie von Depressionen spielen Antidepressiva und hier in erster Linie Serotonin-Wiederaufnahmehemmer eine zentrale Rolle. Diese zeigen jedoch bei alleiniger Anwendung nur in ca. 30 Prozent der Fälle eine ausreichende Wirkung. Auch wenn die medikamentöse antidepressive Therapie mit psycho- oder verhaltenstherapeutischen Verfahren kombiniert wird, bleiben über 30 Prozent der Patienten therapierefraktär [64]. Zeitkritisch ist ebenfalls die notwendige Geduld bis zum gewünschten Wirkungseintritt der antidepressiven Therapie von mindestens vier Wochen. Aus diesem Grund und der häufig zeitlich begrenzten

Lebenserwartung werden vor allem bei Palliativpatienten dringend schnell einsetzende Therapiemöglichkeiten benötigt. Für die überwiegend als Analgetikum und Hypnotikum eingesetzte Substanz S-Ketamin gibt es Anhaltspunkte, die einen derartigen schnellen antidepressiven Wirkungseintritt vermuten lassen [65]. Somit scheint die Substanz vor allem bei Palliativpatienten eine Therapiealternative darzustellen, die zu Beginn unserer Untersuchung jedoch weder in den USA noch in Europa mit dieser Indikation zugelassen war. Um die Vermutung der schnell einsetzenden antidepressiven Wirkung von S-Ketamin bei Palliativpatienten zu quantifizieren, führten wir auf unserer Palliativstation eine retrospektive Untersuchung bei Patienten durch, die zur Behandlung therapierefraktärer Schmerzen einmalig S-Ketamin in einer Dosierung von 0,25 mg kg^{-1} erhielten. Der Fokus lag auf der in diesem Patientenkollektiv auftretenden Inzidenz von Angst und Depression. Ausgewertet wurden nach einer orientierenden Fallzahlberechnung die in der klinischen Routine regelmäßig erhobenen Screening Daten des STADI von acht Patienten mit einer nach Alter und Geschlecht vergleichbaren Kontrollgruppe. Die Prädiktorvariablen waren der Messzeitpunkt vor und nach den in analgetischer Absicht applizierten (S)-Ketamingaben, die Gruppenzugehörigkeit und der Unterschied zwischen den im STADI erhobenen Angst- und Depressionsskalen. Außerdem wurden die möglichen Auswirkungen von Störvariablen in die Untersuchung mit einbezogen. Vergleicht man die (S)-Ketamingruppe mit der Kontrollgruppe, so ergibt sich bei multivariater Analyse ein signifikanter Unterschied in Bezug auf die Belastung der Palliativpatienten durch Angst und Depression. Bei univariatem Vergleich

ergibt sich ein signifikanter Unterscheid in Bezug auf Angst, nicht jedoch in Bezug auf Depression. Auch wenn man die möglichen Störvariablen in einer multivariaten Analyse berücksichtigt, blieb der Effekt erhalten.

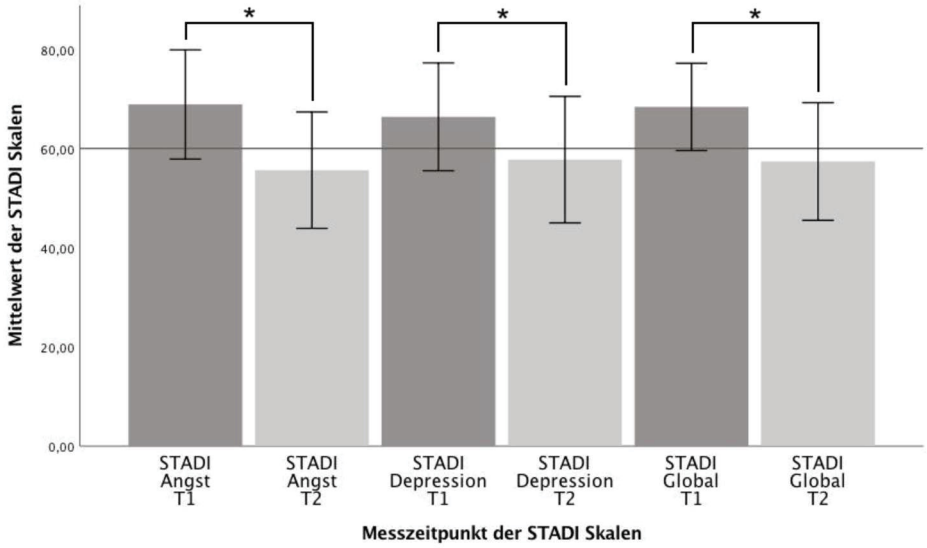

Abbildung 9: Mittelwerte und Standardabweichung der STADI-Skalen Angst, Depression und Global von T1 zu T2 bei der S-Ketamingruppe (*n* = 8) mittels t-Test für abhängige Stichproben bei einseitiger Signifikanzprüfung. Fehlerbalken ± 1 *SD;* * Irrtumswahrscheinlichkeit α < 0,05.(Springer Nature, vorbehaltenes Recht des Autors)

Bei pathologisch erhöhten Messwerten zum Messzeitpunkt T1 (>60) befinden sich die Messwerte zum Zeitpunkt T2, also nach (S)-Ketamingabe wieder im Normbereich (40-60). Da der STADI mehrmals wöchentlich (aber nicht täglich) beurteilt wurde, betrug die Zeitspanne zwischen den STADI-Messungen maximal 4 Tage. Bei den Patienten, die mit S-Ketamin behandelt werden mussten, war der erste Messpunkt (T1) das letzte Mal, dass der STADI vor der Verabreichung von S-Ketamin bewertet wurde. Der zweite Messpunkt (T2) war die erste STADI-Auswertung nach S-Ketamin-Verabreichung. In der Kontrollgruppe war T1 die erste STADI-Auswertung ab dem zweiten Tag

des Aufenthalts, und T2 war der Zeitpunkt der nächsten STADI-Auswertung. Die Effektstärken der beschriebenen Mittelwertveränderungen bei der Depressionsskala des STADI liegen hierbei im mittleren und bei der Angstskala des STADI im hohen Bereich, so dass dies als Hinweis auf einen positiven Effekt gedeutet werden kann.

STADI-Skala	**Teststatistik** $t(7)$	**Sig. 1-seitig** p	**Effektstärke** d
Angst	4,91	**0,001***	1,20
Depression	2,18	**0,033***	0,79
Global	3,52	**0,005***	1,25

* Irrtumswahrscheinlichkeit $\alpha < 0,05$
Interpretation von Cohens d: $0,10 \leq d < 0,50$ kleiner Effekt; $0,50 \leq d < 0,80$ mittlerer Effekt und $0,80 \leq d$ großer Effekt.

Tabelle 3 Effektstärken der beschriebenen Mittelwertsveränderungen der T-Werte der STADI Skalen Angst, Depression und Global von T1 (vor S-Ketamingabe) zu T2 (nach S-Ketamingabe) mittels t-test für abhängige Stichproben bei einseitiger Signifikanzprüfung (Springer Nature, vorbehaltenes Recht des Autors)

Unsere Untersuchung bestätigt die Hypothese, dass durch niedrigdosiertes S-Ketamin eine schnelle, vor allem anxiolytische, aber auch antidepressive Wirkung erreicht werden kann. Insgesamt zeigte sich, dass die Wirkung von S-Ketamin am stärksten unmittelbar nach der S-Ketamingabe war und dann mit der Zeit abnahm. Da die Aussagekraft einer retrospektiven Untersuchung limitiert ist, sind hier weitere standardisierte und randomisierte Untersuchungen in Form von Studien,

die dem Arzneimittelgesetz (AMG) unterliegen, notwendig.

Zusammenfassung:

S-Ketamin kann in der Anwendung bei Palliativpatienten nach den Ergebnissen dieser retrospektiven Untersuchung neben der analgetischen auch eine schnell einsetzende anxiolytische und antidepressive Wirkung haben.

2.6. Zusammenfassung der Ergebnisse

Einfluss von Xenon auf Sympathikusaktivität und Kreislaufstabilität

- Xenon übt beim gesunden Probanden keinen Einfluss auf den efferenten Sympathikus zur Muskulatur aus. Die Kreislaufstabilität wird durch eine Hemmung der Noradrenalin-wiederaufnahme vermittelt, die wiederum durch NMDA-Rezeptor vermittelte Hemmung von Noradrenalintransportern hervorgerufen wird.

Einfluss von Xenon auf die QT-Zeit

- Das Anästhetikum Xenon zeigt bei gesunden Probanden in der Monoanwendung und bei Patienten, die für abdominalchirurgische / traumatologische Eingriffe eine Xenon- / Remifentanil-Anästhesie erhalten, keinen Einfluss auf die QTc-Zeit und erscheint somit im Hinblick auf eine nicht vorhandene Begünstigung gefährlicher Herzrhythmusstörungen sicher einsetzbar.

Einfluss von Xenon auf die Entwicklung eines postoperativen

kognitiven Defizits

- Die Inzidenz eines postoperativen Delirs ist bei Xenon-basierter Anästhesie nicht signifikant niedriger als bei Sevofluran. Unsere Beobachtungen bezüglich eines signifikant reduzierten SOFA Scores, der reduzierten SAE Rate sowie der reduzierten Sterblichkeit können eine Beitrag dazu leisten, zukünftige Hypothesen zu generieren, die in weiteren Studien untersucht werden sollten, um die protektiven Effekte einer Xenon-basierten Anästhesie bei älteren Patienten zu untersuchen.

Einfluss von Xenon auf somatosensorisch evozierte Potentiale

- Ein Monitoring von SSEPs ist unter Xenon-basierter Anästhesie verlässlich durchführbar. Die Amplitude der N20 Welle wird zwar deutlich reduziert, nicht aber die Latenz. Somit ist die Höhe der Amplitude nach Erreichen von steady state Bedingungen unter Xenon als Baseline zu wählen, mit der dann eventuelle intraoperative Veränderungen, die auf eine Minderperfusion des Gehirns schließen lassen, verglichen werden müssen.

Einfluss von S-Ketamin auf Angst und Depression

- S-Ketamin kann in der Anwendung bei Palliativpatienten nach den Ergebnissen dieser retrospektiven Untersuchung neben der analgetischen auch eine schnell einsetzende anxiolytische und ggf. sogar antidepressive Wirkung entfalten.

3. Diskussion

3.1. Einfluss von Xenon auf Sympathikusaktivität und Kreislaufstabilität

In vivo verdoppelt sich unter Xenon Mono-Anästhesie bei gesunden Probanden trotz unveränderter Muskel-Sympathikusaktivität die Plasma Noradrenalinkonzentration. In vitro konnte zudem von uns gezeigt werden, dass klinisch relevante Dosen Xenon die Wiederaufnahme von Noradrenalin in humanen Neuroblastomzellen durch einen NMDA-Rezeptor-abhängigen Mechanismus reduzieren. Unsere Untersuchungen erklären damit die erhöhten Noradrenalinkonzentrationen im synaptischen Spalt und im Plasma, die zu der unter Xenon-Anästhesie beobachteten kardio-vaskulären Stabilität beitragen.

Während die Muskel-Sympathikusaktivität sehr gut mit kardialer und renaler Sympathikusaktivität korreliert, ist es eher unwahrscheinlich, dass die Sympathikusaktivität anderer Organsysteme in relevanter Weise zum beobachteten Anstieg der Noradrenalin Plasmakonzentration beiträgt [17, 66-69].

Wie kann ein Anstieg der Noradrenalin Plasmakonzentration bei unveränderter Muskel-Sympathikusaktivität erklärt werden? Durch Noradrenalin Transporter (NET) werden physiologisch circa 90 % des Noradrenalins, welches überwiegend aus dem sympathischen Nervensystem stammt, wiederaufgenommen, während nur 10 % des freigesetzten Noradrenalins den Blutkreislauf erreicht [70]. Wir haben beobachtet, dass Xenon in anästhetischer Dosierung die

Noradrenalinwiederaufnahme um ca. ein Drittel reduziert. Berücksichtigt man, dass eine reduzierte Aktivität des NET zu einem vierfachen Anstieg der Menge an Noradrenalin führt, die dann den synaptischen Spalt verlassen kann, so könnte dies zu der Verdoppelung der Noradrenalinplasmakonzentration und den beobachteten sympathomimetischen Effekten führen [71]. Darüber hinaus können auch andere Mechanismen wie eine reduzierte hepatische Katecholamin-Clearance [72] oder eine größere Freisetzung von Noradrenalin unter Xenon Anästhesie [73] nicht ausgeschlossen werden.

Yoshida und Kollegen berichteten nach Analyse von Daten, die durch Mikrodialyse gewonnen wurden, dass Xenon die Freisetzung von Noradrenalin im zerebralen Kortex von Ratten erhöht [73]. Obwohl hier klar gezeigt wurde, dass die Applikation von Xenon in klinisch relevanten Dosierungen einen relevanten Anstieg von dialysiertem Noradrenalin und daher auch der extrazellulären Noradrenalin Konzentration verursacht, erlauben die Ergebnisse nicht zwischen erhöhter Noradrenalin Freisetzung und reduzierter Wiederaufnahme als auslösendem Mechanismus zu unterscheiden. Unsere Daten sind in Einklang mit den Ergebnissen von Yoshida et al. und deuten darauf hin, dass eine gehemmte Wiederaufnahme eine wichtige Rolle für das vermehrte Noradrenalin im Plasma unter Xenon-Anwendung spielen könnte. Eine erhöhte zentrale noradrenerge Aktivität führt zu einer erhöhten sympathischen Innervation, die wiederum durch die Baroreflexhemmung vermindert wird. Somit wurde die MSA trotz des erhöhten arteriellen Drucks nicht verändert, was auf einen veränderten Sollwert des Baroreflexes hindeutet [74].

Überraschenderweise kam es trotz eines Anstiegs des arteriellen Drucks und unbeeinträchtigter Baroreflexe nicht zu einem Anstieg der Herzfrequenz. Die Regulation der Herzfrequenz ist noch komplexer als die sympathischen Baroreflexe des Gefäßsystems, da diese zusätzlich noch unmittelbar durch die parasympathische Innervation moduliert werden. Allerdings haben wir die Parasympathikusaktivität zum Herzen bei unseren Probanden nicht untersucht. Dennoch könnte ein ähnlicher Regulationsmechanismus auch für die Herzfrequenzkontrolle während Xenon-Anästhesie verglichen mit der MSA im Gefäßsystem verantwortlich sein. Der Baroreflexgain ist bei unseren Probanden unter Xenon-Anästhesie trotz des erhöhten arteriellen Blutdrucks nicht verändert. Wir sind der Ansicht, dass diese Beobachtung durch die Hemmung der Noradrenalin-Aufnahme im Gehirn und die damit zunehmende MSA verursacht werden könnte. Daher kann der Sollwert des sympathischen Baroreflexes zu höheren arteriellen Drücken hin verändert sein. Die zentrale sympathische Innervation des Herzens kann auf ähnliche Weise moduliert werden.

Es ist bekannt, dass Xenon seine anästhetischen und analgetischen Wirkungen ähnlich wie Ketamin zumindest teilweise durch die Hemmung von NMDA-Rezeptoren ausübt [3, 75-77].

Razemisches Ketamin erhöhte den arteriellen Druck und die Noradrenalin-Plasmakonzentrationen, während die MSA aufgrund der Baroreflexhemmung gesenkt wurde [46]. Anstelle direkter Effekte auf die sympathische Aktivität verursacht Ketamin eine Hemmung der NET-Funktion, was zu einer beeinträchtigten Wiederaufnahme führt, die zum Teil von der NMDA-Rezeptor-Expression abhängt, was bereits früher

berichtet und durch unsere Daten bestätigt wurde [78, 79]. Dementsprechend erreicht ein größerer Anteil des von den Neuronen freigesetzten Noradrenalin die systemische Zirkulation, was zu einem Anstieg der Noradrenalin-Plasmakonzentration führt. Während Xenon die Noradrenalin-Aufnahme über einen NMDA-Rezeptor-abhängigen Mechanismus hemmt, hemmt Ketamin die NET-Funktion auch in Abwesenheit von NMDA-Rezeptoren. Dieses Phänomen bedarf weiterer Untersuchungen.

Die Hemmung der NET-Funktion trotz unveränderter MSA stellt einen Mechanismus für eine höhere Herzleistung und einen höheren systemischen Gefäßwiderstand bei Patienten unter Xenon Anästhesie dar [80]. Selbst bei Patienten mit deutlich eingeschränkter linksventrikulärer Funktion, die sich einer ICD-Implantation unterziehen mussten, waren der arterielle Druck und die Herzfunktion nicht beeinträchtigt. Darüber hinaus erklären unsere Ergebnisse die Aufrechterhaltung der linksventrikulären Kontraktilität unter Xenon-basierter Anästhesie, sowohl bei Patienten ohne kardiovaskuläre Erkrankung als auch bei Patienten vor aorto-coronaren Bypass-Operationen [81]. Im Gegensatz zu den meisten anderen Anästhetika sind selbst bei leicht erhöhtem arteriellen Blutdruck nicht nur die MSA, sondern auch die sympathischen Baroreflexe unverändert [17]. Somit bleibt das kardiovaskuläre System trotz einer tiefen Allgemeinanästhesie in der Lage, auf Herausforderungen wie z.B. perioperative Hypovolämie oder Blutungen zu reagieren.

In vielen Studien am Tier und am Menschen wurde Xenon in Kombination mit Opioiden appliziert, so dass die beschriebenen kardiovaskulären

Effekte nicht allein auf Xenon zurückgeführt werden konnten. Da die Noradrenalinplasmakonzentrationen bei Patienten unter Xenon-Remifentanil Anästhesie abnahmen und bei Hunden zunahmen, konnte man den zugrunde liegenden Mechanismus für die beobachtete hämodynamische Stabilität nicht auf das sympathische Nervensystem zurückführen [82, 83]. Da Opioide die MSA in Ruhe verringern und der sympathische Baroreflexgain zunimmt, ist die Kombination von Xenon und Opioiden klinisch sehr gut verträglich, erlaubt aber keine Bewertung der intrinsischen Wirkung von Xenon [84]. Zusätzlich zu den möglichen Auswirkungen des beschriebenen Mechanismus auf die Hämodynamik können verstärkt agonistische Effekte von Noradrenalin auf α_2-Adrenozeptoren weitreichende Auswirkungen auf die klinische Anästhesie haben [85]. Darüber hinaus sind NMDA-Rezeptor-Antagonismus und Noradrenalin als Schlüsselmediatoren bei der Schmerzmodulation bekannt [86]. Daher können die Ergebnisse dieser Studie eine Grundlage für weitere Untersuchungen der spinalen inhibitorischen Mechanismen der Xenon-vermittelten Antinozizeption bilden.

Unsere Ergebnisse legen nahe, dass die Wirkung von Xenon auf die Noradrenalin-Wiederaufnahme von der Anwesenheit von NMDA-Rezeptoren abhängt. Darüber hinaus ahmt die spezifische Hemmung von NMDA-Rezeptoren durch den kompetitiven NMDA-Rezeptorantagonisten MK-801 die Wirkung von Xenon auf die NET-Aktivität nach. Dieser Befund wird durch eine andere Studie gestützt, in der nachgewiesen wurde, dass MK-801 die Noradrenalin-Freisetzung aus dem präfrontalen Kortex der Ratte signifikant erhöht [87]. Der

genaue Mechanismus, durch den die durch Xenon induzierte NMDA-Rezeptor Hemmung eine Verringerung der NET-Aktivität induziert, muss jedoch noch geklärt werden.

3.2. Einfluss von Xenon auf die QT-Zeit

Eine Xenon-Monoanästhesie verändert das QTc-Intervall bei gesunden Probanden nicht. Auch bei Patienten mit präoperativ normaler QTc-Zeit verlängert eine Xenon-basierte Anästhesie das QTc-Intervall im Vergleich zu den Ausgangswerten nicht. Zusammenfassend lässt sich somit feststellen, dass Xenon ein normales QTc-Intervall nicht verlängert. Darüber hinaus wurden unter Xenon Anästhesie keine ventrikulären Arrhythmien beobachtet.

Die Applikation von Allgemein- und Regionalanästhetika ist in der Regel ein unvermeidbarer und unabhängiger Risikofaktor im Rahmen der Durchführung eines chirurgischen Eingriffs. Daher ist es von großer Bedeutung, potenzielle Probleme und Nebenwirkungen von Anästhetika zu analysieren. Das Wissen um mögliche Nebenwirkungen ermöglicht es, die Risiken, die sie für Patienten darstellen, zu minimieren. Unter Berücksichtigung eines vergleichsweise hohen und variablen Operationsrisikos ist es häufig schwierig, die möglicherweise vorteilhaften Wirkungen moderner Anästhetika (z.B. Desfluran) oder Anästhesietechniken (z.B. thorakale Epiduralanästhesie) nachzuweisen, obwohl die klinischen Vorteile offensichtlich erscheinen [88]. Mehr als drei Jahrzehnte nach der Einführung von Droperidol in die anästhesiologische Praxis wurde über medikamenteninduzierte lange

QT-Syndrome in Verbindung mit der Verabreichung von Droperidol berichtet. In diesen Fällen konnte eine abnorme kardiale Repolarisation durch ein verlängertes QTc-Intervall von mehr als 440 ms im Oberflächen-EKG identifiziert werden [89]. Patienten, die an einem hereditär verlängerten QTc-Syndrom leiden, sind durch ein QTc-Intervall von mehr als 500 ms charakterisiert [90, 91]. Das damit verbundene Risiko kritischer ventrikulärer Arrhythmien und Berichte über mehrere Todesfälle nach Verabreichung von mehr als 5 mg Droperidol führten zu einer Black-Box-Warnung durch die FDA und zur Rücknahme von Droperidol vom europäischen Markt. Große retrospektive Studien weisen darauf hin, dass niedrig dosiertes Droperidol, welches zur Behandlung von postoperativer Übelkeit und Erbrechen eingesetzt wurde, nicht mit einer erhöhten Inzidenz von polymorphen ventrikulären Tachykardien oder einer erhöhten Mortalität assoziiert war [92, 93]. Dies scheint auf die in diesen Studien vorliegende niedrig dosierte Anwendung von Droperidol zurückzuführen zu sein. Diese zeigt die Notwendigkeit, die Auswirkungen von Medikamenten auf die Repolarisation von Kardiomyozyten zu erkennen, insbesondere bei Patienten ohne kardiovaskuläre Erkrankung und bei Patienten mit bereits bestehenden Repolarisationsstörungen. Obwohl große präklinische und klinische Studien zur Wirkung von Anästhetika auf den menschlichen Körper unabdingbar sind, können auch kleinere Studien mit klar definierten Zielvariablen dazu beitragen, unbekannte anästhesiologische Risikofaktoren zu identifizieren.

Frühere Studien haben gezeigt, dass Propofol das QTc-Intervall nicht verändert. Inhalationsanästhetika, Thiopental und verschiedene Opioide

könnten jedoch mit einer Erhöhung der Dauer des kardialen QT-Intervalls assoziiert sein [24]. So konnte z.B. gezeigt werden, dass Sevofluran das QTc-Intervall sowohl bei Kindern (414 ± 21 ms vs. 433 ± 28 ms, P < 0,01) als auch bei Erwachsenen (413 ± 19 ms vs. 444 ± 24 ms; P < 0,05) verlängert [27, 94, 95]. Der zugrundeliegende Mechanismus ist vermutlich eine Blockade der schnell wirkenden Komponente des kardialen Kaliumkanals, von dem angenommen wird, dass er für die kardiale Repolarisation verantwortlich ist [96, 97]. Im Gegensatz zu hohen Dosen von Fentanyl und Sufentanil verringerte Remifentanil, das in Dosen verabreicht wurde, die mit denjenigen vergleichbar waren, die unsere Patienten erhielten, das kardiale QT-Intervall signifikant und verhinderte seinen Anstieg als Reaktion auf eine Intubation [98]. Somit kann Remifentanil die QT-Intervallverlängerung durch andere Anästhetika maskieren. Da Xenon das QTc-Intervall bei unseren Freiwilligen jedoch nicht veränderte, wenn es allein verabreicht wurde, ist es sehr unwahrscheinlich, dass solche Effekte bei Patienten auftreten. Unsere Ergebnisse stimmen mit früher veröffentlichten Daten überein, die zeigen, dass Xenon weder in menschlichen Vorhofmyozyten noch in isolierten Meerschweinchenherzen auf diese Kanäle wirkt [99, 100]. In unserer Patientenkohorte entdeckten wir zufällig einen Patienten mit einem bereits bestehenden Long QT-Syndrom und einem Basis-QTc-Intervall von 505 ms. Sein QT-Intervall nahm unter Xenon-/ Remifentanil-Anästhesie weiter zu. Er hatte keine kardiovaskulären oder Anästhesie-relevanten Vorerkrankungen, nahm nicht regelmäßig Medikamente ein und entwickelte auch keine Bradykardien unter Xenon- / Remifentanil Anästhesie. Leider verweigerte der Patient eine genetische Testung, so

dass wir nicht klären konnten, ob die Ursache seines Long QT-Syndroms eine der bekannten Genmutationen war. Auch wenn Xenon ein präoperativ normales QT-Interval nicht verändert, deutet diese Beobachtung darauf hin, dass zusätzliche Studien notwendig sind, um die Auswirkungen von Xenon auf Patienten mit vorbestehendem Long QT-Syndrom zu untersuchen. Auch wenn eine sympathische Aktivierung im Allgemeinen das QTc-Interval zu verlängern scheint und Xenon dafür bekannt ist, die Noradrenalin Plasmakonzentration zu erhöhen, konnten wir keine verlängerten QTc-Syndrome bei den Probanden unter Xenon Monoanästhesie oder bei Patienten ohne vorbestehendes Long QT-Syndrom während Xenon- / Remifentanil Anästhesie beobachten [101, 102]. Diese Ergebnisse deuten zudem darauf hin, dass eine indirekte sympathische Aktivierung das QTc-Interval wahrscheinlich nicht über einen Noradrenalin abhängigen Mechanismus verlängert. Zusammenfassend bestätigen sowohl unsere Daten von gesunden Probanden als auch von Patienten ohne vorbestehendes long QT-Syndrom klinisch die Ergebnisse von vorher veröffentlichten elektrophysiologischen in vitro Studien, dass Xenon die kardiale Repolarisation nicht beeinflusst.

3.3. Einfluss von Xenon auf die Entwicklung eines postoperativen Delirs

In dieser internationalen, multizentrischen, randomisierten, klinischen Studie reduzierte die Xenon-basierte Anästhesie die Inzidenz von POD bei älteren Patienten mit Hüftfrakturen nicht signifikant. Die Unterschiede in den sekundären Endpunkten waren entweder statistisch signifikant

und klinisch nicht aussagekräftig (SOFA-Scores) oder potenziell klinisch relevant, aber nicht statistisch signifikant (SAEs, Mortalität). Die Inzidenz eines POD nach Hüftfraktur-Operationen bei älteren Menschen ist typischerweise hoch [33, 34, 37, 103, 104]. In den Studien, die wir zur Berechnung der Stichprobengröße verwendeten, schwankte die Inzidenz zwischen 28% und 50% [33, 34, 104-108]. Die tatsächliche Inzidenz von POD in der Sevofluran-Kontrollgruppe (13,6%) war jedoch viel geringer als die erwartete Rate (30%). Die geringer als erwartete Inzidenz von POD in der Sevofluran-Gruppe spiegelt wahrscheinlich unsere Anwendung strenger Einschlusskriterien wider; so wurden Patienten mit präoperativen Symptome, die mit einem Delir vereinbar wären, Depressionen oder eingeschränkter kognitiver Fähigkeiten (MMSE-Score<24) ausgeschlossen. Daraus folgt, dass sich die Patientenpopulation in der Studie möglicherweise von der allgemeinen älteren Bevölkerung unterschied, die sich routinemäßig einer Hüftfrakturoperation unterzieht und bei der die Inzidenz des POD höher ist [109, 110]. Tatsächlich erwies es sich als schwierig, Patienten für die Studie zu rekrutieren, da viele Patienten, die die anderen Einschlusskriterien erfüllten, die Kriterien für den für die Teilnahme obligaten guten kognitiven Zustand nicht erfüllten. Tatsächlich mussten 2000 Patienten gescreent werden, von denen dann lediglich 268 Patienten die Einschlusskriterien erfüllten und bei denen keine Ausschlusskriterien für die Teilnahme an der Studie vorlagen. Der Anteil an Patienten, die hätten eingeschlossen werden können, jedoch eine Teilnahme abgelehnt haben, war dabei vernachlässigbar. Ein weiterer Faktor für die geringe Inzidenz eines POD könnte der Einsatz der BIS-

Technologie zur Überwachung der Narkosetiefe gewesen sein; in einer kürzlich durchgeführten Cochraneanalyse wurde festgestellt, dass die Inzidenz eines POD bei Bispectral Index (BIS)-gesteuerter Anästhesie geringer ist als bei BIS-verblindeter Anästhesie nach rein klinischem Urteilsvermögen [111]. Bei der Fallzahlberechnung nahmen wir eine Effektstärke von 50 Prozent durch Xenon-basierte Anästhesie an. Demgegenüber war die POD Inzidenz in der Xenon-Gruppe lediglich um 33 Prozent niedriger als in der Sevofluran-Gruppe. Zur Absicherung eines solchen Unterschiedes hätte die Fallzahl auf mehr als 1000 Patienten erhöht werden müssen. Trotz der geringen Inzidenz des PODs in der Studie konnten wir zwei Patientenfaktoren identifizieren, die signifikant mit dem Risiko für das Auftreten eines PODs assoziiert waren: Raucher zu sein und eine präoperativ diagnostizierte leichte neurologische Störung zu haben. [109, 110, 112, 113]. Der Zusammenhang zwischen dem POD und der Art der Anästhesie oder des Anästhetikums, das bei der Operation verwendet wird, ist unklar. Es gibt Hinweise darauf, dass die Inzidenz von POD mit der Tiefe der Anästhesie zunehmen kann. [114]. Andere Untersuchungen konnten hingegen keine Vorteile eines Regionalanästhesieverfahrens im Vergleich zur Allgemeinanästhesie zeigen, was möglicherweise auf einer zu tiefen zusätzlichen Sedierung bei Patienten mit regionalen Anästhesieverfahren beruhen könnte [32]. In einer kleinen Pilotstudie an 42 Patienten, die während einer Herzoperation entweder eine Xenon- oder eine Sevofluran-basierte Anästhesie erhielten, war die Inzidenz des PODs in der Gruppe, die eine Xenon-basierte Allgemeinanästhesie erhielt, signifikant niedriger [115].

Während die Xenon-basierte Anästhesie zuvor organprotektive Eigenschaften und ein überlegenes hämodynamisches Profil im Vergleich zu anderen Anästhetika gezeigt hat, konnten wir diese Effekte bei Patienten mit Hüftfrakturen nicht bestätigen. Obwohl die Patienten in der Xenon-Gruppe einen etwas niedrigeren SOFA-Gesamtwert aufwiesen (was als Zeichen für einen gewissen Grad an Organprotektion interpretiert werden könnte), war dieser Unterschied nur von marginaler klinischer Relevanz. Ebenso gab es in der Xenon-Gruppe keine signifikanten Unterschiede zwischen den Gruppen bei Patienten mit SAEs (p=0.05) oder bei Patienten mit tödlichen SAEs (p=0.06), wobei der Anteil der Patienten mit als schwer eingestuften SAEs in der Xenon-Gruppe signifikant geringer war (p=0.008) [5, 115-120]. Die Studie hat mehrere Stärken und Schwächen. Spezifische Ein- und Ausschlusskriterien führten zu einer gut definierten Studienpopulation, die hinsichtlich des prospektiven Risikos der Entwicklung eines PODs in allen Behandlungsgruppen ähnlich war. Die hohe zeitliche Auflösung, die sich aus den zweimal täglich durchgeführten CAM-Auswertungen ergab, stellte sicher, dass ein hoher Anteil der Delir-Episoden detektiert werden konnte. Eine Einschränkung hinsichtlich der Bewertung der Mortalität könnte sich daraus ergeben haben, dass 28-Tage-Follow-up-Ergebnisse nur für ~80% der Patienten in jeder Gruppe verfügbar waren.

Wir setzten die BIS-Technologie zur Anästhesietiefenmessung ein, um Schwankungen und Phasen zu tiefer Anästhesie während der Operation möglichst zu vermeiden. Gleichzeitig konnte dadurch weitestgehend ausgeschlossen werden, dass die Narkosetiefe zu einem Störfaktor zwischen den Behandlungsgruppen wird. Die BIS-Werte wurden

sorgfältig überwacht, und die Mittelwerte wurden während der Operation in beiden Gruppen stabil und ähnlich gehalten.

Es ist auch möglich, dass einige Delir-Episoden durch Verwendung der verkürzten Version des CAMs unerkannt blieben. Obwohl der vollständige Neun-Punkte-CAM für maximale Sensitivität empfohlen wird, hielten wir den kürzere CAM für eine internationale klinische Studie mit zweimal täglicher postoperativer Beurteilung für praktikabler. Darüber hinaus sind die vier wesentlichen und validierten Kriterien für das Erkennen eines Delirs in dem verkürzten CAM enthalten [121, 122]. Obwohl für eine optimale Anwendung eine sorgfältige Schulung empfohlen wird und unser Studienpersonal vor der Studie eine solche umfassende und spezifische Schulung gemäß dem CAM-Schulungshandbuch erhalten hat, können wir nicht mit letzter Sicherheit feststellen, ob der CAM in allen Studienzentren einheitlich durchgeführt wurde. Tatsächlich kann die Schulung ein Faktor bei der Erkennung des Delirs durch den CAM sein [123]. Ein Aspekt des Delirs, der in der vorliegenden Studie nicht berücksichtigt wurde, war der Schweregrad. Das CAM-S-Tool bietet ein überarbeitetes Delir-Scoring-System, das eine Bewertung des Delir-Schweregrades ermöglicht [124]. Zukünftig sollten diese Aspekte bei der Planung klinischer Studien zur Untersuchung präventiver Maßnahmen für ein POD berücksichtigt werden. Die Inzidenz eines POD war in dieser Studie mit Xenon-basierter Anästhesie nicht signifikant niedriger als mit Sevofluran-basierter Anästhesie. Die tendenziell günstigen Effekte einer Xenon-basierten Anästhesie auf postoperative SOFA-Scores, SAEs und Mortalität rechtfertigen jedoch weitere Studien zur Beurteilung des potenziellen

Nutzens der Xenon-Anästhesie bei älteren, kritisch kranken Patienten.

3.4. Einfluss von Xenon auf somatosensorisch-evozierte Potentiale

Unter Allgemeinanästhesie ist die Messung der SSEP eine zuverlässige Technik, mit der selbst diskrete Einschränkungen der zerebralen Durchblutung, z.B. während chirurgischer Eingriffe an den Carotiden, nachgewiesen werden können [125]. Eine zerebrale Hypoperfusion wirkt sich sowohl auf die Amplitude als auch auf die Latenz der N20-Wellen aus. Normalerweise wird ein kombiniertes Kriterium von entweder einer 50-prozentigen Abnahme der N20-Wellenamplitude oder einer 10-prozentigen Zunahme der N20-Wellenlatenz gewählt, um signifikante Veränderungen der SSEP zu definieren [126-128]. Xenon reduzierte die Amplitude der N20-Welle auf die Hälfte, ohne die Latenz zu beeinträchtigen. Die Messung der SSEP unter Xenon Anästhesie war in jedem Fall möglich und musste in keinem Fall abgebrochen werden. Allerdings schränken alle klinisch gebräuchlichen Inhalationsanästhetika die Bewertung der SSEP ein, indem sie dosisabhängig die Amplitude der N20-Welle reduzieren und die Latenz verlängern: Bei einer MAC von 1,0 nimmt die Amplitude der N20-Welle unter Isofluran um 66 Prozent, unter Desfluran um 55 Prozent und unter Sevofluran um 33 Prozent ab, während die Latenz unter Isofluran um 18 Prozent, unter Sevofluran um 16 Prozent, und unter Desfluran um 12 Prozent zunimmt [129-131]. Die von uns beobachtete Abnahme der N20-Wellenamplitude unter 1,0 MAC Xenon von 50 Prozent ist somit vergleichbar mit der Wirkung, die während 1,0 MAC Desfluran beobachtet wurde [6, 130, 132]. Dies kann

die Beurteilung von Veränderungen der SSEPs, die durch eine Minderperfusion bedingt sind, erschweren. Schon eine Xenon-Konzentration von 35 Volumenprozent reduzierte die Amplitude motorisch evozierter Potentiale. Obwohl die Hemmung sensorisch und motorisch evozierter Potentiale verschiedene neuronale Pfade und Rezeptoren involviert, scheint es wahrscheinlich, dass die Hemmung der SSEP-Amplitude durch Xenon einer Dosis-Wirkungs-Beziehung folgen könnte, wie sie für andere Inhalationsanästhetika beschrieben wurde [129, 131]. Eine eventuelle, dosisabhängige Beziehung der Abnahme der N20-Wellenamplitude durch Xenon wurde von uns jedoch nicht quantifiziert.

Propofol reduziert im Gegensatz zu inhalativen Anästhetika die Amplitude der N20-Welle in einem viel geringeren Ausmaß [131, 133]. Daher ist eine auf Propofol basierende total intravenöse Anästhesie trotz eines erhöhten Risikos einer durch Propofol induzierten Vasodilatation häufig die Methode der Wahl während einer Carotis Endariektomie (CEA) [17]. Bei Patienten, die sich einer CEA unterziehen, zeigt Xenon insbesondere auch im Vergleich zum Propofol einige vielversprechende Eigenschaften, die auf mindestens drei verschiedenen Mechanismen beruhen können: (1) Es gibt Hinweise auf neuroprotektive Wirkungen der Xenon-Applikation bei Schädigungen im Zusammenhang mit einer zerebralen Ischämie / Reperfusion [134-138] und (2) Xenon hält den systemischen arteriellen Druck aufrecht und verbessert das Verhältnis von zerebralem Blutfluss und zerebraler Stoffwechselrate, wodurch die Netto-Sauerstoffversorgung des Gehirns erhöht wird [4, 81, 102, 139-141]. Schließlich ermöglicht die rasche Entwöhnung von der Xenon-

Anästhesie die sofortige postoperative neurologische Beurteilung sowie das Erkennen neu aufgetretener neurologischer Defizite [142, 143].

Bemerkenswert ist, dass andere Inhalationsanästhetika und Propofol die Anästhesie hauptsächlich über Agonismus an GABA-Rezeptoren induzieren, während Xenon in erster Linie NMDA-Rezeptoren hemmt [6, 75, 144, 145]. Somit scheint der Einfluss der Anästhetika auf die N20-Wellenamplitude offenbar unabhängig vom Zielrezeptor zu sein.

Die vorgestellten Daten ergänzen die Ergebnisse aus früheren tierexperimentellen Studien: Utsumi et al. applizierten 70 Volumenprozent Xenon bei Katzen, die mit 2 Volumenprozent Sevofluran anästhetisiert waren, und fanden eine ähnliche Reduktion der somatosensorisch evozierten N1-Wellenamplitude (-42 bis -62 Prozent) [146]. Darüber hinaus maßen Yamamoto et al. myogene motorisch evozierte Potentiale bei Kaninchen, die eine Allgemeinanästhesie mit Ketamin und Fentanyl erhielten, und fanden eine 50% niedrigere Erfolgsrate und eine fast vollständige Abschwächung der Amplitude, wenn zusätzlich 70 Prozent Xenon appliziert wurde [147].

Aufgrund der Schmerzhaftigkeit der Platzierung der für die SSEP Messung notwendigen Elektroden konnte keine Messung der SSEPs im Wachzustand erhoben werden. Es konnten aber im Rahmen der Untersuchung die SSEPs während Propofol- und Xenon-basierter Anästhesie miteinander verglichen werden. Da gut dokumentiert ist, dass Propofol, wenn überhaupt, nur eine minimale Wirkung auf die SSEP hat, gibt es Grund zur Annahme, dass der Wechsel zwischen Propofol- und Xenon-Anästhesie die alleinige Wirkung von Xenon auf die SSEPs darstellt [131, 148]. Alle Bewertungen wurden vor Beginn der operativen

Maßnahmen vorgenommen. Das Studiendesign wurde so gewählt, um den direkten Effekt von Xenon auf die SSEP nachzuweisen. In einem nächsten Schritt sollte untersucht werden, inwieweit die durch Xenon induzierte N20-Wellenamplitudenreduktion die Sensitivität der SSEPs für den Nachweis einer zerebralen Minderperfusion beeinträchtigt. In unserer Untersuchung haben wir lediglich das kortikale Potential zu einem peripheren Sensorstimulus gemessen und keine zusätzliche spinale Ableitung erfasst. Daher konnten wir nicht zwischen zerebralen und spinalen Wirkungen von Xenon unterscheiden. Diese Unterscheidung dürfte jedoch im klinischen Alltag von untergeordneter Bedeutung sein.

Allein auf der Grundlage dieser Studie kann noch nicht abschließend beurteilt werden, ob Xenon das Anästhetikum der Wahl für Patienten darstellt, die eine CEA erhalten. Es sollte nun mit einem randomisierten Studiendesign untersucht werden, ob während einer Xenon- im Vergleich zu einer Propofol-Anästhesie gleichermaßen stabile zerebrale Perfusionsverhältnisse herrschen. Weitere Studien sollten sich auf neurologische Ergebnisse nach CEA unter Xenon im Vergleich zu anderen Anästhetika konzentrieren.

Des Weiteren sollte zukünftig untersucht werden, ob die präklinischen Daten, die Hinweise auf mögliche neuroprotektive Eigenschaften von Xenon geben, tatsächlich zu einer klinischen Verbesserung des Outcomes führen [116, 136-138, 149, 150].

3.5. Einfluss von Ketamin auf Angst und Depression

Diese retrospektive Pilotstudie liefert die ersten Daten für eine positive Wirkung von S-Ketamin auf die psychische Belastung von Patienten in der Palliativmedizin. Wir finden einen Effekt auf Depressionen und Angstzustände mit einem primären Effekt auf Angstzustände. Unser Ergebnis entspricht früheren Studien, die zeigten, dass Ketaminrazemat ähnliche Effekte bei Patienten in der Palliativmedizin zeigt [151, 152]. Aufgrund des günstigeren Nebenwirkungsprofils vor allem in Bezug auf psychotrope Nebenwirkungen verwenden wir bevorzugt S-Ketamin als Analgetikum bei Palliativpatienten. Nach unserem Wissen wurde die Wirkung des Enantiomers S-Ketamin bei Patienten in der Palliativmedizin bisher nicht systematisch untersucht. Es wird berichtet, dass S-Ketamin einen positiven Effekt auf Angstzustände bei chirurgischen Patienten mit kurativem Therapiekonzept hat und es wurde kürzlich von der FDA als Nasenspray zugelassen. Diese Zulassung ist allerdings nur auf die Kombination mit einem oralen Antidepressivum und nur für die Therapie therapieresistenter Depressionen beschränkt [1]. S-Ketamin könnte jedoch auch für Patienten mit einer lebensbegrenzenden Erkrankung außerhalb der FDA-Zulassung nützlich sein. Diese Studie könnte somit ein erster Schritt auf dem Weg zu einer Zulassung von S-Ketamin zur Behandlung von Angstzuständen bei Patienten in der Palliativmedizin sein.

Die positive Wirkung von S-Ketamin bestand hauptsächlich bei Angst ohne signifikante Auswirkungen auf Depressionen. Der Einfluss von S-Ketamin auf die Angst hatte durchweg große Effektstärken. Unsere

Daten deuten darauf hin, dass die Behandlung mit S-Ketamin auch in der klinischen Routine wirksam sein könnte. In unserer Studie reduzierte S-Ketamin die globalen STADI-Werte bei 5 von 8 Patienten um einen klinisch relevanten Wert. Weitere prospektive, randomisierte Studien sind erforderlich, um die Wirksamkeit zu belegen.

Der Einfluss von S-Ketamin auf Depressionen zeigte hauptsächlich mittlere Effektstärken. Der signifikante Effekt mit einer großen Effektgröße von S-Ketamin auf psychische Belastung wurde hauptsächlich durch die Verringerung der Angst verursacht. Die Analysen zeigten jedoch auch, dass S-Ketamin sowohl Angst als auch Depression reduzierte. Selbst nach Berücksichtigung der Störvariablen blieb der signifikante Effekt auf die Angst bestehen. Es gab auch keine Hinweise auf anhaltende psychomimetische Nebenwirkungen in der S-Ketamin-Gruppe bis zum nächsten Morgen. Im Gruppenvergleich gab es keine Hinweise auf eine anhaltende Schmerzreduktion durch S-Ketamin bis zum nächsten Morgen.

Die ausgeprägte Wirkung von S-Ketamin auf die Angstzustände von Patienten in der Palliativmedizin könnte mit den Besonderheiten dieser Patientengruppe zusammenhängen. In einem Fallbericht über zwei Hospiz-Patienten, die eine Einzeldosis Ketaminrazemat (0,5 mg kg^{-1} Bolus per os) zur Behandlung von Angst und Depression erhielten, zeigte sich ein positiver Effekt, wobei die Angst in den ersten vier Tagen stärker abnahm [152]. Darüber hinaus kam es bei beiden Patienten zu einer Verbesserung der Schmerzwahrnehmung mit einem Maximum am vierten und achten Tag nach der Ketamingabe. In einer Machbarkeitsstudie wurde bei Bewohnern eines stationären Hospizes

die Wirkung täglicher oraler Verabreichung von Ketaminrazemat (0,5 mg kg^{-1} Bolus per os) über 28 Tage auf Angst und Depression untersucht. Es zeigte sich eine signifikante Reduktion (Reduktion der Fragebogenwerte > 30 Prozent) der Angst unter Ketaminrazemat nach drei Tagen mit einer mittleren Effektgröße (d = 0,67). Bei Depressionen gab es nach 14 Tagen eine signifikante Reaktion mit einer großen Effektstärke (d = 1,14). Nach 28 Tagen zeigte sich ein signifikanter Effekt mit großer Effektstärke bei Angst (d = 1,34) und Depression (d = 1,34). Die Schmerzen waren jedoch unverändert [152].

Die Ergebnisse unserer Arbeit und der beiden Hospizstudien deuten darauf hin, dass S-Ketamin und Ketaminrazemat bei Patienten mit einer lebenslimitierenden Erkrankung primär abschwächend auf die Angst wirken können. Ob es sich hierbei um ein besonderes Wirkmuster bei dieser Patientengruppe handelt, bedarf weiterer Klärung.

In unserer Studie konnte in den Gruppenvergleichen kein positiver Effekt von S-Ketamin auf Depressionen festgestellt werden. Der erste univariate Gruppenvergleich ergab jedoch eine mittlere Effektgröße (r = 0,32) für Depressionen. Eine Post-hoc-Stichprobengrößenberechnung mit G*Power 3.1 zeigte, dass insgesamt n = 20 Patienten notwendig wären, um einen signifikanten Effekt auf Depression für eine gruppenweise Interaktion in einer zweiseitig gemischten ANOVA zu bestimmen [153]. Eine prospektive Studie würde also nach unseren Daten 20 Patienten oder mehr benötigen.

In dieser Studie deutet die deskriptive Interpretation der Daten darauf hin, dass mehr Patienten in der S-Ketamin-Gruppe als in der Kontrollgruppe auf der Station starben. Ein kausaler Zusammenhang mit S-Ketamin ist

aus den folgenden Gründen jedoch nicht plausibel. Im Allgemeinen sterben etwa 60 Prozent der Patienten auf der Palliativstation [154]. Somit kann die Mortalität der S-Ketamin-Gruppe als unauffällig betrachtet werden. Zudem zeigte eine Studie von Irwin et al., dass die tägliche orale Gabe von Ketaminrazemat über 28 Tage zu keinen schwerwiegenden unerwünschten Ereignissen führte. Es gab keine Veränderungen der Vitalparameter (Blutdruck, Herzfrequenz und Atemfrequenz) während des Verlaufs ihrer Studie. Eine leichte Zunahme der Symptome bei 12,5 Prozent der Patienten war auf Durchfall, Schlafstörungen und Unruhe zurückzuführen. Darüber hinaus zeigten die Patienten eine Abnahme der Symptombelastung im Zusammenhang mit gastrointestinalen, neurologischen und psychiatrischen Symptomen. Weitere Studien zur Wirkung von Ketaminrazemat auf die psychische Gesundheit von Hospiz-Patienten und von psychiatrischen Patienten berichten ebenfalls über eine niedrige Rate von unerwünschten Ereignissen [151, 152]. Die häufigsten unerwünschten Ereignisse bei Patienten, die Ketaminrazemat (0,50 mg/kg über 40 min i. v.) als Therapie einer behandlungsresistenten Depression erhielten, waren Schläfrigkeit, Schwindel, schlechte Koordination und ein seltsames oder unwirkliches Gefühl [2]. Diese Symptome traten meist in den ersten zwei Stunden nach Beginn der Infusion auf, nahmen nach vier Stunden ab und sistierten nach 24 Stunden.

Eine deskriptive Synopse der in dieser Studie erhobenen Daten legt nahe, dass die S-Ketamin-Gruppe eine Gruppe von Patienten mit einer höheren Symptombelastung war als die Kontrollgruppe. Die S-Ketamin-Gruppe zeigte bei den Ausgangs STADI vor Ketamingabe T-Werte über

der kritischen Grenze von 60. Darüber hinaus berichtete die S-Ketamingruppe zu beiden Zeitpunkten über mäßige Schmerzen. Ferner zeigte die S-Ketamingruppe zu beiden Messzeitpunkten einen höheren Pflegebedarf als die Kontrollgruppe (wie durch den AEDL-Score angezeigt). Im Durchschnitt wurde die S-Ketamin-Gruppe auch weniger psychoonkologisch behandelt. Es wäre plausibel, dass der reduzierte körperliche Zustand der S-Ketamingruppe, der sich in einem erhöhten Pflegebedarf und einer erhöhten Mortalität auf der Station manifestierte, die Möglichkeit zur Teilnahme an psychoonkologischen Interventionen verringerte.

Die Einschränkungen dieser Studie resultieren aus der geringen Fallzahl und ihrem retrospektiven Design. Aufgrund des retrospektiven Designs sind die Daten nur begrenzt geeignet, um die Wirkung von S-Ketamin zu messen. Das beste Intervall zur Messung der maximalen Effekte von Ketamin oder S-Ketamin ist ein Tag nach der Verabreichung von Ketamin oder S-Ketamin. In unserer Studie lagen in der S-Ketamingruppe mehrere Tage zwischen T1 und T2, was die gemessene Wirkung von S-Ketamin auf Angstzustände und Depressionen verringert haben könnte. Die Daten zeigten jedoch eine stärkere Reduktion der durch Angst und Depression verursachten psychischen Belastung einen Tag nach der Verabreichung von S-Ketamin als vier Tage nach der Verabreichung von S-Ketamin. Somit stimmen diese Daten mit dem zeitlichen Verlauf der Wirkung von Ketamin überein [155]. Darüber hinaus erlaubt der retrospektive Ansatz keine Bewertung, wie die Patienten die Wirkungen von S-Ketamin wahrgenommen haben und wie sie den Nutzen und die Risiken einer S-Ketamin-Behandlung

einschätzen. Eine nicht gegebene randomisierte Zuordnung zur Therapiegruppe kann zu einer systematischen Verzerrung führen. In dieser Studie wurde die Gruppenzugehörigkeit in erster Linie durch therapierefrektäre Schmerzen bestimmt. In diesem Zusammenhang deuten zusätzliche Patientendaten darauf hin, dass die S-Ketamin-Gruppe eine Patientenpopulation mit einer höheren Symptombelastung war. So hatten die Patienten in der S-Ketamin-Gruppe, die an refraktären Schmerzen litten, noch andere physische und psychische Symptome, die sie von den Patienten der Kontrollgruppe unterschieden. Die STADI-Scores für Angst und Depression waren in der S-Ketamin-Gruppe signifikant höher als in der Kontrollgruppe bei T1. Um statistische Fehler, die sich aus der Auswahl der Kontrollgruppe ergaben, zu minimieren, generierten wir eine weitere Kontrollgruppe. Diese alternative Matching-Strategie berücksichtigt die psychische Belastung. Dennoch sind unsere Ergebnisse zur Wirkung von S-Ketamin bei Anwendung der alternativen Matching-Strategie im Wesentlichen die gleichen. Um andere statistische Fehler zu vermeiden, berechneten wir die Alpha- und Test-Retest-Zuverlässigkeit von Cronbach, um die Zuverlässigkeit unserer Instrumente nachzuwesein. Bei den Varianzanalysen stellten wir sicher, dass alle Annahmen bezüglich Normalverteilung, Homogenität der Varianz und Homogenität der Kovarianzmatrizen erfüllt waren.

Der retrospektive Ansatz und die kleine Stichprobengröße lassen kaum eine Verallgemeinerung unserer Ergebnisse zu. Trotz dieser Einschränkungen können unsere Daten eine Grundlage für zukünftige prospektive Studien bilden, die erforderlich sein werden, falls S-Ketamin als Nasenspray von der Europäischen Arzneimittelagentur und anderen

Aufsichtsbehörden weltweit (primär für andere Indikationen) zugelassen ist. Nachfolgende Studien werden eine empirische Grundlage für die Behandlung von Angstzuständen und Depressionen mit S-Ketamin bei Patienten in der Palliativmedizin liefern. Der erste Schritt wären prospektive Machbarkeitsstudien, einschließlich qualitativer Daten, wenn die Stichprobengröße voraussichtlich gering sein wird. Weitere Studien könnten doppelblinde, randomisierte und plazebokontrollierte Studien umfassen. Im Verlauf dieser Studien sollten die Fragen nach dem Wirkungsmuster, den optimalen Applikationsformen und der Wahl der Medikation (S-Enantiomer vs. Razemat) geprüft werden.

Die Ergebnisse dieser retrospektiven Studie wären mit einem raschen positiven Einfluss von S-Ketamin vereinbar, vor allem bei Angstzuständen. Sollte sich dies in größeren, prospektiven Studien an Patienten, die unter schwerer psychischer Belastung leiden, bestätigen, könnten diese von den positiven Effekten von S-Ketamin profitieren. Die Ergebnisse stehen im Einklang mit vorhandenen Daten zu Ketamin und seiner Wirkung auf psychische Belastung. Das rasche Einsetzen der Wirkung von S-Ketamin sowie seine anxiolytischen und möglicherweise antidepressiven Wirkungen könnten die Palliativversorgung von Patienten erheblich verbessern.

3.6. Synthese und Ausblick

NMDA-Rezeptorantagonisten sind in der Anästhesiologie, Intensiv- und Palliativmedizin bedeutsame Arzneimittel. Während Xenon als inhalatives Anästhetikum eine sehr günstige Pharmakokinetik aufweist

und dadurch ein rasches Erwachen aus der Anästhesie sicherstellt, wäre das intravenös und nun auch nasal anwendbare Ketamin mit längerer Wirkdauer bereits in geringen Dosen zur Analgesie und bei palliativen Patienten zur Stimmungsaufhellung einsetzbar. Beiden Arzneimitteln ist eine Hemmung von Noradrenalintransportern zu eigen. Da die efferente Sympathikusaktivität nicht direkt gehemmt wird und Kreislaufreflexe erhalten bleiben, wird eine besondere hämodynamische Stabilität sowohl unter Xenon als auch unter Ketamin erreicht. Da zunehmend ältere und kritisch Kranke einer operativen Therapie zugeführt werden, sind Kreislaufstabilität und Neuroprotektion durch Xenon wahrscheinlich vorteilhaft und möglicherweise sogar relevant für ein günstiges Behandlungsergebnis. Zur Analgesie und beim Palliativpatienten scheint die längere, in der Anästhesie eher nachteilige, Wirkdauer des Ketamins von Vorteil zu sein. Bemerkenswert sind hier die über die pharmakologisch erwartbare Elimination des Ketamins hinausgehende anxiolytische und antidepressive Wirkung. Zusammenfassend zeigen wir in Abhängigkeit vom Applikationsweg und der Pharmakokinetik einen differenzierten Einsatz der beiden verfügbaren NMDA-Rezeptorantagonisten Xenon und Ketamin in Anästhesiologie und Palliativmedizin. Es ist zu hoffen, dass zukünftige klinische Studien die Indikationen weiter schärfen und Effekte nachweisen werden, die sich positiv auf den Krankheitsverlauf auswirken.

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6. Publikationen der zugrundeliegenden Originalarbeiten

6.1 Cardiovascular stability and unchanged muscle sympathetic activity during xenon anaesthesia: role of norepinephrine uptake inhibition.

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BJA

CLINICAL PRACTICE

Cardiovascular stability and unchanged muscle sympathetic activity during xenon anaesthesia: role of norepinephrine uptake inhibition

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Editor's key points

- The mechanism of the effect of xenon (Xe) on cardiovascular stability was studied.
- Human volunteers anaesthetized with Xe alone had increased arterial pressure.
- In cells, Xe decreased the uptake of norepinephrine (NE) by inhibiting the NE transporter, thereby increasing local NE availability.
- This may explain cardiovascular stability during Xe anaesthesia.

Background. Intraoperative hypotension is associated with increased risk of perioperative complications. The *N*-methyl-D-aspartate (NMDA) receptor (NMDA-R) antagonist xenon (Xe) induces general anaesthesia without impairment of cardiac output and vascular resistance. Mechanisms involved in cardiovascular stability have not been identified.

Methods. Muscle sympathetic activity (MSA) (microneurography), sympathetic baroreflex gain, norepinephrine (NE) plasma concentration (high-performance liquid chromatography), anaesthetic depth (Narcotrend® EEG monitoring), and vital parameters were analysed *in vivo* during Xe mono-anaesthesia in human volunteers (n=8). *In vitro*, NE transporter (NET) expressing HEK293 cells and SH-SY5Y neuroblastoma cells were pre-treated with ketamine, MK-801, NMDA/glycine, or vehicle. Subsequently, cells were incubated with or without Xe (65%). NE uptake was measured by using a fluorescent NET substrate (n=4) or [^{3}H]NE (n=6).

Results. *In vivo*, Xe anaesthesia increased mean (standard deviation) arterial pressure from 93 (4) to 107 (6) mm Hg and NE plasma concentration from 156 (55) to 292 (106) pg ml^{-1}, P<0.01. MSA and baroreflex gain were unaltered. *In vitro*, ketamine decreased NET activity (P<0.01) in NET-expressing HEK293 cells, while Xe, MK-801, and NMDA/glycine did not. Xe reduced uptake in SH-SY5Y cells expressing NET and NMDA-Rs (P<0.01). MK-801 (P<0.01) and ketamine (P<0.01) also reduced NET activity, but NMDA/glycine blocked the effect of Xe on [^{3}H]NE uptake.

Conclusions. *In vivo*, Xe anaesthesia does not alter sympathetic activity and baroreflex gain, despite increased mean arterial pressure. *In vitro*, Xe decreases the uptake of NE in neuronal cells by the inhibition of NET. This inhibition might be related to NMDA-R antagonism and explain increased NE concentrations at the synaptic cleft and in plasma, contributing to cardiovascular stability during Xe anaesthesia.

Keywords: adrenergic regulation; autonomic nervous system; norepinephrine; sympathetic activity; xenon anaesthesia

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Intraoperative hypotension is associated with increased risk of perioperative complications.[1 2] Until now, it is unclear whether decreased arterial pressure causes increased postoperative mortality or it is an indicator of severity of the disease and therefore independently associated with adverse outcome.[3] Nevertheless, intraoperative hypotension is often unfavourable and usually requires immediate reversal with i.v. applied vasopressors, such as norepinephrine (NE). Most common anaesthetics interfere with sympathetic cardiovascular control and impair cardiac output and also vascular resistance, resulting in a decrease in mean arterial pressure.[4] In contrast, during xenon (Xe)-based anaesthesia, arterial pressure is maintained or even increased.[5 6] However, mechanisms of this important observation have not been identified. To assess the effects of Xe on the cardiovascular system, perioperatively administered drugs should be avoided, such that the effect of Xe alone can be identified.

The sympathetic nervous system is responsible for short-term arterial pressure regulation at rest and during cardiovascular challenges (e.g. hypovolaemia). Muscle sympathetic

activity (MSA) correlates well with muscle vascular resistance. When a 50% increase in MSA was induced by lower body negative pressure, blood flow measured in the forearm and calf decreased significantly.[7 8] Therefore, increased MSA may counteract arterial hypotension by increasing systemic vascular resistance.[4] Despite the idea of individual regulation of sympathetic outflow to various organs, MSA correlates well with cardiac and renal sympathetic outflow.[9 10]

Microneurography is the only technique available to directly assess MSA in humans. Its advantage is the ability to detect rapid changes in sympathetic nerve traffic. Accordingly, it can be used to study both static and dynamic situations, for example, determination of the offset and the gain in situations of sympathetic activation induced by certain challenges. Thus, direct evaluation of MSA by microneurography may elucidate mechanisms underlying the cardiovascular stability during Xe anaesthesia in humans.[4]

We therefore tested the hypothesis that in healthy volunteers, administration of Xe increases NE plasma concentration by increased MSA and maintains sympathetic baroreflexes.

When NE plasma concentration was increased during Xe without sympathetic activation, we further speculated that Xe increases NE plasma concentration by the inhibition of NE transporters, irrespective of sympathetic outflow.

Methods

In vivo study

After IRB approval of the study protocol (IRB Medical Faculty, University of Düsseldorf, study ID MO-LKP-394, October 26, 2009), this open-label, single-group assignment phase I clinical trial was approved by the German Authorities (BfArm, EudraCT-No. 2009-012449-48) and registered at www.ClinicalTrials.gov (NCT01043419). The clinical trial was performed in accordance with the Helsinki Declarations and GCP Regulations. Healthy volunteers, who had been recruited with the help of adverts in the medical school, were enrolled and gave written informed consent. Trial monitoring and data management were done by the clinical trials coordinating centre at the University Hospital Düsseldorf, Germany.

Eight non-premedicated, healthy, normotensive volunteers [ASA classification I, mean age 25 (2) yr, male/female: 6/2, mean BMI: 23.5 (1.8) kg m^{-2}] were included in this study. None of the subjects was taking any medication. After an overnight fast, all subjects were studied in the supine resting position in the morning.

Muscle sympathetic activity

Multiunit postganglionic MSA was recorded by microneurography (Supplementary methods) in the peroneal nerve at the fibular head as previously described.[11–14] The nerve signal was amplified, filtered (bandpass, 0.5–2 kHz), and fed through a discriminator for further noise reduction and audio monitoring (662C-3 Nerve Traffic Analysis System, University of Iowa, Bioengineering, USA). An integrated mean voltage signal was obtained by passing the original signal through a resistance–capacitance circuit. MSA recording sites were accepted when burst amplitude was at least twice as great as baseline noise, bursts occurred 1.2–1.4 s after an R-wave of the ECG, and reproducible increases in MSA were obtained in response to a standardized challenge (apnoea of >40 s). Subsequently, MSA bursts were counted and expressed as burst frequency (bursts min^{-1}) during 3–5 min recording periods.

Cardiovascular variables

Heart rate was determined from the surface ECG. After determination of resting arterial pressure by oscillometry at the right upper arm, a catheter (20 G) was inserted into the left radial artery under local anaesthesia and radial arterial pressure was continuously recorded by electromanometry.

NE plasma concentrations

Arterial blood drawn from the radial arterial catheter was sampled at specific intervals into chilled tubes with EDTA, cooled to +4°C, and immediately centrifuged. Plasma was stored at −80°C until analysis using high-performance liquid chromatography with electrochemical detection in an authorized laboratory (Dr Limbach, Heidelberg, Germany). The lower detection limit was 10 pg ml^{-1} with a normal reference range of 165–460 pg ml^{-1}.

Blood gas analyses

Arterial oxygen and carbon dioxide partial pressures and also pH and base excess were assessed by standard blood gas measurements (ABL 700 series, Radiometer, Willich, Germany).

Data recording and processing

Analogue variables (MSA, ECG, radial arterial pressure) were fed into a personal computer and digitized (sampling frequency: 200 Hz, DT 3000, Data Translation Bietigheim-Bissingen, Germany). All analyses were performed with computer support (offline) using customized software (Professor Dr M. Elam and T. Karlsson, Göteborg, Sweden).

Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations

Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations were determined as previously described (Supplementary methods).[14] During a 3–5 min observation period, all diastolic pressures and corresponding MSA bursts were determined compensating for a baroreflex delay of 1.2–1.4 s.

For the calculation of baroreflex gain during spontaneous pressure fluctuations, all diastolic pressures of individual heartbeats were grouped into intervals of 2 mm Hg. For each of these pressure categories, the percentage of cardiac cycles associated with a sympathetic burst (burst incidence) was plotted against the mean of the individual's diastolic pressures followed by a linear regression analysis.

The slope of this regression line represents the individual's sympathetic baroreflex gain during spontaneous arterial pressure fluctuations. For graphical data presentation, the lowest diastolic arterial pressure during each observation period was inserted into the linear equation of the regression analysis. Accordingly, corresponding nerve activities could be calculated for the lowest diastolic arterial pressure observed in each individual.[14]

Treatment protocol

The final 5 min of a 30 min resting period was used to calculate baseline MSA and spontaneous baroreflex gain. Subsequently, oxygen ($F_{I_{O_2}}>0.9$) was administered via a closed facemask by a commercially available Xe anaesthesia machine (Tangens 2C mobile 12, EKU Elektronik, Leiningen, Germany), indicating breathing frequency, minute ventilation, gas measurement, and EEG monitoring of anaesthesia depth (Narcotrend®, Drs B. and A. Schulz, Hannover, Germany). After subjects' adaptation to the facemask and closed circuit breathing, the final 5 min of a 20 min resting period was used to calculate MSA and spontaneous baroreflex gain. Then, arterial blood samples were obtained for determination of blood gases and catecholamine plasma concentrations. Xe anaesthesia was induced with 70% Xe in oxygen (LENOXe, Air Liquide Santé, Paris, France). After achieving steady-state conditions with end-tidal Xe concentrations of at least 60%, MSA and spontaneous baroreflex gain were determined from 3 to 5 min recording periods. Again, arterial blood samples were obtained for determination of blood gases and catecholamine plasma concentrations. At the end of the study, Xe administration was discontinued and volunteers awoke from anaesthesia.

In vitro study

Cell cultures

Human epithelial kidney cells (HEK239) stably expressing human NE transporters (hNET),[15] their parental wild-type cells (HEK293 wild-type), and human neuroblastoma cells (SH-SY5Y; ATCC® number CRL-2266) have been characterized before.[16] All cell lines were cultured under equal conditions including a humidified atmosphere containing 5% carbon dioxide at 37°C and were grown in Dulbecco's Modified Eagle Medium (DMEM; Gibco, Life Technologies, Carlsbad, CA, USA) supplemented with 10% heat-inactivated fetal calf serum and 50 U ml^{-1} penicillin and 50 μg ml^{-1} streptomycin. Reverse transcriptase–polymerase chain reaction (RT–PCR) and western blot analysis to confirm expression of NET and *N*-methyl-D-aspartate-receptor (NMDA-R) were performed using standard protocols as described previously (Supplementary methods).[17] For western blot analysis, mouse monoclonal anti-NET antibody (cat no. MAB5620; Millipore, Billerica, MA, USA) and rabbit monoclonal anti-NMDA-R1 (D65B7) antibody (cat. no. 5704; Cell Signaling, Danvers, MA, USA) were used as primary antibodies. For RT–PCR, total RNA from HEK293 cells (wild-type and hNET) and SHSY5Y cells was extracted using Trizol Reagent (Ambion, Life Technologies) according to the manufacturer's protocol. RNA was reverse transcribed and amplified. The primer sequences were as follows: for hNET 5′-GGATTGATGCCGCA ACTCAGA-3′, hNET-rev 5′-GGCCTCTGGATACAGGATGA-3′ (306 bp, 35 cycles), for NMDA-R subunit 1 5′-AACCTGCAGAA CCGCAAG-3′, NMDA-R subunit 1_rev 5′-GCTTGATGAGCAGGT CTATGC-3′ (333 bp, 35 cycles), and for glyceraldehyde 3-phosphate dehydrogenase (GAPDH) 5′-ACCACAGTCCATGCCA TCAC-3′ and GAPDH_rev 5′-TCCACCACCCTGTTGCTGT3′ (451 bp, 25 cycles). PCR products were electrophoresed on 1.5% agarose gels and photographed under UV light with a digital camera (Photometrics, Tucson, AZ, USA).

The i.v. anaesthetic and NMDA-R antagonist ketamine was used as a positive control as the inhibitory effect on NE uptake has been described before.[18 19] Additionally, the specific NMDA-R antagonist MK-801 was used to evaluate the role of specific NMDA-R antagonism on NE uptake and the highly potent NET inhibitor desipramine was used to determine the degree of unspecific NE uptake in the used cell culture model. Unless stated otherwise, reagents were purchased from Sigma Aldrich (St Louis, MO, USA).

Xe gas application

A pre-made gas mixture containing Xe (Xe 65%, O_2 30%, CO_2 5%) and a gas mixture without Xe (N_2 65%, O_2 30%, CO_2 5%; negative control) were provided by Air Liquide Santé. To investigate the concentration–response relationship, additional gas mixtures containing 32.5% or 50% Xe were used. All experiments were performed in a specialized gas chamber under temperature control as described before (Supplementary methods).[20] Briefly, dishes containing cells were placed on a tray in the centre of the chamber. The respective gas mixtures were administered from below the culture dishes and distributed by a fan inside the chamber. Gas concentrations were monitored at the outlet of the chamber by a gas analyzer (Capnomatic Ultima; Datex, Helsinki, Finland). The temperature within the chamber was kept at 37°C by means of a heating plate installed at the bottom of the chamber. A temperature-controlling device (Model T48; Red Lion Controls, York, PA, USA) connected to a thermometer probe exactly regulated the heating plate and thus the temperature within the chamber.

Fluorescence-based uptake assay

For measurements of neurotransmitter uptake, cells were detached from tissue culture flasks, counted, and plated on poly-D-lysine (0.1 mg ml^{-1})-coated, black 96-well plates at a density of 1×10^5 cells per well. Subsequently, cells were allowed to adhere for at least 12 h. For pre-treatment with ketamine (1 mmol litre^{-1}), desipramine (5 μmol litre^{-1}), a combination of *N*-methyl-D-aspartic acid (25 μmol litre^{-1}; NMDA) and glycine (10 μmol litre^{-1}), MK-801 (2 μmol litre^{-1}), or no additive (vehicle; negative control), the culture medium was replaced with substances diluted in Hank's buffered salt solution (HBSS; Gibco Invitrogen) supplemented with 0.1% bovine serum albumin. Treated cell culture

plates were placed in the gas application chamber as described above and the Xe or control gas mixture was applied for 20 min. A fluorescent substrate for neurotransmitter transporters[21] was then added following the manufacturer's recommendations (Neurotransmitter Uptake Kit; Molecular Devices, Sunnyvale, CA, USA) followed by incubation for 20 min during continued gas application. The fluorescent substrate is combined with a masking dye that prevents fluorescence unless the substrate has been transported into the cell. Therefore, the fluorescence intensity of samples at a wavelength of 520 nm was detected after excitation at 440 nm using a fluorescence plate reader (Synergy 2; BioTek Instruments, Winooski, VT, USA) as a measure for substrate uptake immediately after the end of incubation time.

[^{3}H]NE uptake assay

To determine intracellular [^{3}H]NE content, cells were detached from tissue culture flasks, counted, and plated on poly-D-lysine (0.1 mg ml^{-1})-coated, clear 6-well plates at a density of 1×10^5 cells per well. After at least 12 h incubation for cell adherence, pre-treatment with ketamine (1 mmol litre^{-1}), desipramine (5 μmol litre^{-1}), NMDA (25 μmol litre^{-1}), glycine (10 μmol litre^{-1}), MK-801 (2 μmol litre^{-1}), or vehicle (HBSS buffer; negative control) during gas application as described above was performed. After 20 min of gas application, [^{3}H]NE (200 nmol litre^{-1}) was added. After a further 5 min, [^{3}H]NE uptake was stopped by washing all samples with ice-cold phosphate-buffered saline (PBS; Gibco Invitrogen). Cells were then lysed by 5 min exposure to a solution containing 300 mmol litre^{-1} NaCl, 25 mmol litre^{-1} Tris–HCl, and 0.1% Triton-100. The cell lysates were then resuspended with 1 ml PBS and transferred to analysis tubes containing 4 ml of scintillation fluid (Ultima Gold; PerkinElmer, Waltham, MA, USA). The amount of intracellular [^{3}H]NE was measured by means of decay counts per minute using a liquid scintillation counter (Tricarb 2100 TR; Packard, Berkshire, UK).

Data analysis and statistics

Values from fluorescence-based uptake measurements and decay counts per minute from scintillation counting were normalized to samples that were pre-treated with vehicle (negative controls), while subtracting the mean background fluorescence that was detected despite maximal transporter inhibition with desipramine (5 μmol litre^{-1}).

All data are expressed as mean [standard deviation (SD)]. Differences between means were tested by Student's *t*-test or one- or two-way analysis of variance (ANOVA) followed by Bonferroni's *post hoc* test as appropriate. Graph Pad Prism Software version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). A *P*-value of <0.05 was considered significant.

Results

In vivo

Xe anaesthesia was successfully performed in all subjects reaching an end-tidal Xe concentration of 63 (6)%. All volunteers lost consciousness when the end-tidal Xe concentration reached 40–50%, and did not respond to verbal or touch stimuli. The EEG-index (Narcotrend®) decreased from 98 (1) to 46 (10) indicating anaesthesia. Subjects' spontaneous movements resulted in a loss of MSA recording sites in five out of eight subjects during emergence from anaesthesia. Two subjects with a history of postoperative nausea and vomiting during previous anaesthesia experienced short-lasting nausea and vomiting immediately after awakening. Further adverse events were not observed.

MSA was similar during oxygen breathing and during breathing of room air without a mask 19 (9) and 20 (10) bursts min^{-1}, respectively. Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations significantly decreased during oxygen breathing from 4.6 (1.7) to 3.7 (1.5) bursts 100 heartbeats^{-1} mm Hg^{-1} (P=0.02), while arterial pressure and heart rate remained unchanged.

After induction of Xe anaesthesia (70%), MSA was not altered. Representative recordings of MSA during oxygen breathing and also during Xe anaesthesia of all subjects are shown in Figure 1A. Generally, Xe anaesthesia did not alter MSA (Fig. 1B) and sympathetic baroreflex gain during spontaneous arterial pressure fluctuations (Fig. 2). However, despite unchanged sympathetic outflow, NE plasma concentrations increased significantly from 156 (55) to 295 (106) pg ml^{-1} ($P<0.01$; Fig. 3). This increase in NE plasma concentration was associated with a significant increase in mean arterial pressure from 93 (4) to 107 (6) mm Hg ($P<0.05$), while heart rate remained unchanged [awake 63 (10) beats min^{-1}; Xe 70 (10) beats min^{-1}; P=0.12].

Xe anaesthesia was also associated with an increase in spontaneous breathing frequency and minute ventilation (Table 1). Arterial carbon dioxide partial pressure and pH were not altered; oxygen partial pressure was decreased as after Xe anaesthesia ($F_{I_{O_2}} \approx 0.35$; Table 1).

In vitro

RT–PCR of hNET HEK293 and SH-SY5Y cells confirmed stable expression of hNET, while hNET expression was not detected in parental HEK293 wild-type cells (Supplementary Fig. S1). Additionally, stable gene expression of NMDA-R subunit 1 was detected only in SH-SY5Y cells, and was absent from HEK293 hNET and HEK293 wild-type cells (Supplementary Fig. S1). Western blot analysis of protein expression confirmed these findings (Supplementary Fig. S1).

Fluorescence-based uptake experiments (n=4) revealed that fluorescence intensity was decreased in HEK293 hNET cells (not expressing NMDA-R) by ketamine (1 mmol litre^{-1}; $P<0.01$; Fig. 4A). On the contrary, Xe (65%), MK-801 (2 μmol litre^{-1}), and also NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) in combination did not exhibit any effects (Fig. 4A). As expected, there was no specific increase in fluorescence intensity and therefore NET activity in HEK 293 wild-type cells (data not shown).

In contrast, Xe reduced fluorescence intensity in SH-SY5Y neuroblastoma cells expressing NMDA-R in addition to hNET

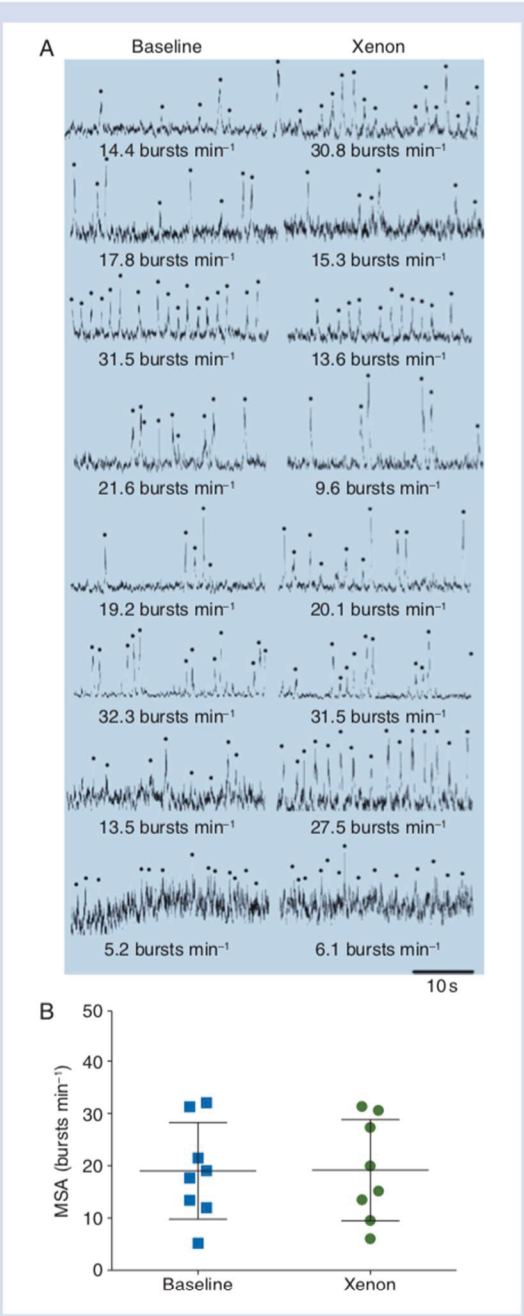

Fig 1 MSA during Xe mono-anaesthesia. (A) Original recordings of MSA of each subject (n=8) in the awake state (baseline) and during Xe anaesthesia. Bursts considered for analysis are indicated by a dot. In four individuals, there was no change in MSA, while two exhibited an increase and two a decrease. (B) Xe anaesthesia does not alter MSA compared with baseline values as determined from 3 to 5 min recording periods. Data presented as individual data points and mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia.

(P<0.01, Fig. 4B). While MK-801 and ketamine also reduced NET activity, both P<0.01, the combination of these substances with Xe had no additive effect (Fig. 4B).

Radiometric results (n=6) confirmed the inhibition of NE uptake in SH-SY5Y cells by Xe (P<0.01; Fig. 5) and MK-801, P<0.01). The combination of Xe and MK-801 did not exhibit additive effects compared with the application of MK-801 alone. The agonistic combination of NMDA and glycine reversed the inhibition of NE uptake by Xe almost completely (Fig. 5).

To investigate a possible concentration–response relationship, additional experiments were conducted comparing the effect of 0, 32.5, 50, and 65% Xe (Fig. 6). While 32.5% Xe did not lead to a significant effect, 50% Xe resulted in a reduction in NE uptake function (n=6; P<0.05). Increasing Xe concentration to above 65% had no further effect.

Discussion

Despite unchanged sympathetic outflow to muscle, NE plasma concentrations almost doubled during Xe anaesthesia in healthy volunteers. As shown *in vitro*, clinically relevant concentrations of Xe decreased the uptake of NE in human neuroblastoma cells by an NMDA-R-dependent mechanism. Thus, our findings explain increased NE concentrations at the synaptic cleft and in plasma, contributing to the observed cardiovascular stability in patients during Xe.

We have demonstrated that NE plasma concentrations are increased during Xe mono-anaesthesia in healthy volunteers, despite unchanged sympathetic outflow to muscle. Since sympathetic outflow to muscle correlates well with cardiac and renal sympathetic activity, it is rather unlikely that sympathetic activation to other organ systems accounts for the observed increase in NE plasma concentrations.[4 9 10 22] Nevertheless, how can an increase in NE plasma concentration be explained in the face of unchanged sympathetic activity? NE reuptake transport restores about 90% of NE originating predominantly from sympathetic nerves, while only about 10% of released NE reaches the blood stream.[23] We found that Xe inhibited NE uptake by approximately one-third at a concentration that is commonly used for maintaining anaesthesia. Considering that a reduction in NET reuptake function could possibly lead to an increase in NE escaping from the synaptic cleft (extra-neuronal turnover) by up to four times, this effect may lead to increased systemic spillover and therefore contribute to the doubled NE plasma concentration and the observed sympathetic effects.[24] Nevertheless, other mechanisms such as reduced hepatic catecholamine clearance[25] or increased release of NE[26] during Xe anaesthesia cannot be excluded.

Yoshida and colleagues[26] recently reported that Xe increases the release of NE in the cerebral cortex of rats as measured using a microdialysis technique. Although they clearly demonstrated that Xe at a clinically relevant concentration induced a considerable increase in dialysed NE and therefore extracellular NE concentration, their results do not allow discrimination between increased NE release and

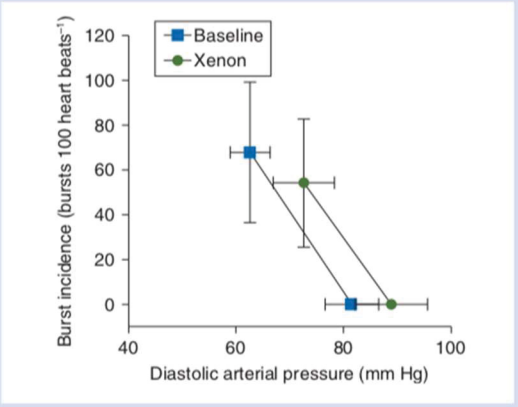

Fig 2 Sympathetic baroreflex gain during Xe mono-anaesthesia. Sympathetic baroreflex gain during spontaneous arterial pressure fluctuations in the awake state ($F_{I_{O_2}}$>0.9) and during Xe anaesthesia. Although the overall range of observed diastolic arterial pressures is slightly shifted to higher pressures by Xe, the slope of the regression line indicating the sympathetic response to spontaneous arterial pressure variations is not altered (n=8). Data presented as mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia.

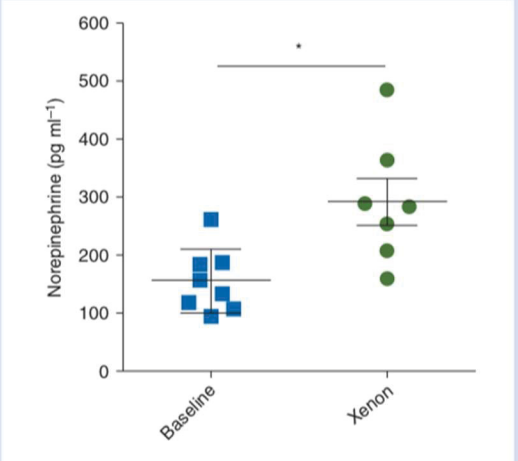

Fig 3 Effect of Xe mono-anaesthesia on NE plasma concentrations. NE plasma concentration was significantly increased during Xe anaesthesia compared with awake state (n−7). Data are presented as individual data points and mean (SD). Blue squares are baseline values and green circles are during Xe anaesthesia. *P<0.01 (n=7; baseline *vs* Xe treatment, paired Student's t-test).

inhibited reuptake as the responsible mechanism. Our data clearly support their findings and suggest that inhibited reuptake might play an important role for increased NE

Table 1 Results of blood gas analysis and respiratory parameters. Data are presented as means (SD). *P<0.01

	Awake ($F_{I_{O_2}}$>0.9)	Xenon anaesthesia (end-tidal concentration 63%)
P_{O_2} (mm Hg)	471 (29)	173 (19)*
pH	7.41 (0.02)	7.43 (0.04)
P_{CO_2} (mm Hg)	40 (3)	45 (6)
Base excess (mmol litre^{-1})	1.0 (1.1)	1.3 (1.6)
Respiratory rate (bpm)	12.1 (2.4)	23.1 (7.6)*
Minute ventilation (litre min^{-1})	6.9 (2.0)	10.9 (2.1)*

during Xe application. Increased central noradrenergic activity yields increased sympathetic outflow that in turn is immediately decreased by baroreflex inhibition. Thus, MSA was not altered, despite increased arterial pressure, indicating an altered setpoint of the baroreflex.[27]

Despite an increase in arterial pressure and unimpaired baroreflexes, heart rate surprisingly did not decrease. Regulation of heart rate is even more complex than sympathetic baroreflexes to the vasculature because it is immediately modulated by parasympathetic innervation as well. However, we did not study parasympathetic outflow to the heart in our volunteers. Nevertheless, a similar line of arguments may apply also to heart rate control during Xe compared with muscle sympathetic outflow to the vasculature. First, sympathetic baroreflex gain is not altered in our volunteers during Xe, despite increased arterial pressure. We believe that this observation is caused by the inhibition of NE uptake in the brain and therefore increasing sympathetic outflow. Thus, the setpoint of sympathetic baroreflexes may be altered to higher arterial pressures. Central sympathetic innervation of the heart may be modulated in a similar manner.

Xe is known to exert its anaesthetic and analgesic properties at least in part by the inhibition of NMDA-Rs[28–30] similar to ketamine.[31] Racemic ketamine increased arterial pressure and NE plasma concentrations, while MSA was actually decreased due to baroreflex inhibition.[13] Instead of direct effects on sympathetic outflow, ketamine causes an inhibition of NET function leading to impaired reuptake in part depending on NMDA-R expression as reported earlier and confirmed by our data.[18 32] Accordingly, a greater fraction of NE released from neurones reaches the systemic circulation, leading to an increase in NE plasma concentration. While Xe inhibits NE uptake via an NMDA-R-dependent mechanism, ketamine inhibits NET function even in the absence of NMDA-R. This phenomenon warrants further investigation.

We would like to point out that the inhibition of NET function despite unchanged MSA is a reasonable mechanism for even increased cardiac output and systemic vascular

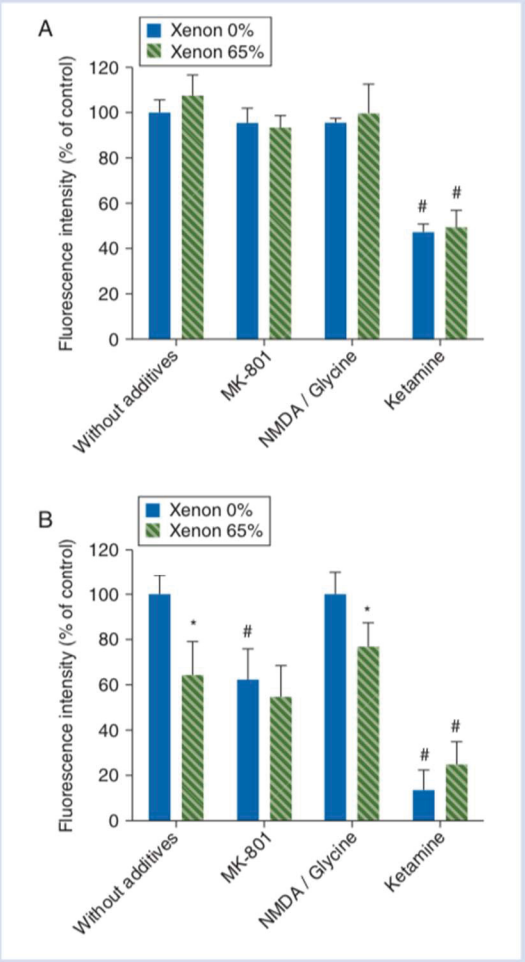

Fig 4 Effect of Xe on neurotransmitter transporter function. (A) In HEK293 cells overexpressing only hNETs in the absence of NMDA receptors, fluorescence intensity as a measure for neurotransmitter uptake was not changed by incubation with 65% Xe compared with control conditions. Ketamine (1 mmol litre^{-1}) inhibited neurotransmitter uptake. Coapplication of Xe had no additive effect. (B) In human neuroblastoma cells (SH-SY5Y) endogenously expressing NETs and NMDA receptors, Xe inhibited neurotransmitter uptake significantly. Specific NMDA inhibition by MK-801 (2 μmol litre^{-1}) mimicked this effect, while additional agonistic stimulation with NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) restored neurotransmitter uptake in the presence of Xe to the level of controls. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with 65% Xe. *$P<0.01$ *vs* Xe 0%; #$P<0.01$ *vs* without additives ($n=4$; two-way ANOVA and *post hoc* Bonferroni test).

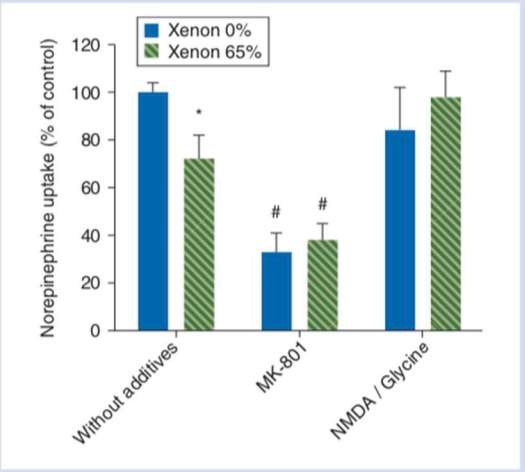

Fig 5 Effect of Xe on uptake of [^{3}H]NE. Confirming the results of fluorescence-based measurements, Xe (65%) inhibited the uptake of [^{3}H]NE. Specific NMDA inhibition by MK-801 (2 μmol litre^{-1}) mimicked this effect, while the agonistic stimulation with NMDA (25 μmol litre^{-1}) and glycine (10 μmol litre^{-1}) reversed it. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with 65% Xe. *$P<0.01$ *vs* Xe 0%; #$P<0.01$ *vs* without additives ($n=6$; two-way ANOVA and *post hoc* Bonferroni test).

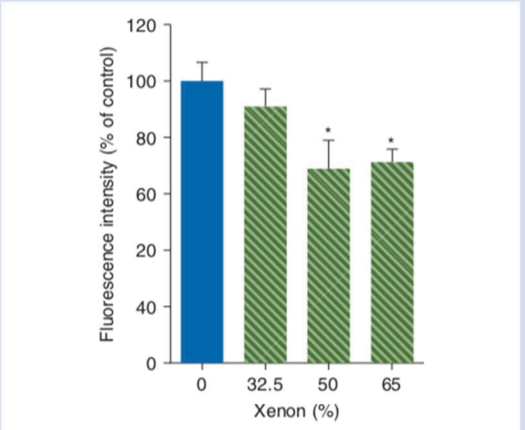

Fig 6 Concentration-dependent inhibition of neurotransmitter transporter function. The effect of 32.5% was not significantly different from control conditions, but 50% Xe inhibited neurotransmitter uptake. Increasing the concentration to 65% Xe did not enhance inhibition. Data are presented as mean (SD). Blue bars are values after 0% Xe treatment, and green striped bars are values after treatment with Xe. *$P<0.05$ ($n=6$; all values *vs* controls without Xe, one-way ANOVA and *post hoc* Bonferroni test).

resistance in patients undergoing Xe-based anaesthesia.[33] Even in patients with markedly impaired left ventricular function undergoing cardioverter defibrillator implantation,

arterial pressure and cardiac function were not depressed. Furthermore, our results explain maintained left ventricular contractility during Xe anaesthesia, either in patients without cardiovascular disease or in those awaiting coronary artery bypass surgery.[5] In contrast to most other anaesthetics, not only resting sympathetic outflow but also sympathetic baroreflexes are not impaired even at slightly increased arterial pressure.[4] Thus, the cardiovascular system is still able to respond to challenges, for example, perioperative hypovolaemia or haemorrhage, despite general anaesthesia.

In many animal and human studies, Xe has been administered in combination with opioids so that the described cardiovascular effects could not be attributed to Xe alone. Since NE plasma concentrations were reported to be decreased in patients anaesthetized with a combination of Xe and remifentanil[34] and increased in dogs,[35] the underlying mechanism for the observed haemodynamic stability had not been pinpointed to the sympathetic nervous system. Since opioids decrease MSA at rest and sympathetic baroreflex gain,[12] the combination of Xe and opioids is clinically very favourable but does not allow an evaluation of the intrinsic effect of Xe.

Whether maintained arterial pressure during Xe-based anaesthesia translates into a decrease in perioperative morbidity and mortality is currently being evaluated in larger randomized controlled multicentre trials (www.clinicaltrials.gov NCT01120405 and NCT00919126).

In addition to the potential effects of the described mechanism on haemodynamics, enhanced agonistic effects of NE on α-2-adrenoceptors may have widespread implications for clinical anaesthesia.[36] Furthermore, NMDA-R antagonism and NE are known to be key mediators in pain modulation.[37] Therefore, the findings of this study encourage further investigation of spinal inhibitory mechanisms of Xe-mediated antinociception.

Our findings suggest that the effect of Xe on NE uptake depends on the presence of NMDA-R. Furthermore, specific inhibition of NMDA-R by MK-801 mimics the effect of XE on NET activity. This finding is supported by another study demonstrating that MK-801 significantly increases NE release from rat prefrontal cortex.[38] Nevertheless, the exact mechanism by which NMDA-R inhibition by Xe induces a reduction in NET activity remains to be elucidated.

Limitations

It was the goal of our study to assess the effects of Xe anaesthesia on muscle sympathetic outflow. Accordingly, we did not administer other additional anaesthetics despite the comparatively low anaesthetic potency of Xe (MAC_{50} 50–70 vol%). Cardiovascular variables were recorded in unconscious participants while Narcotrend® EEG monitoring (values of 40–60) confirmed general anaesthesia. Participants were spontaneously breathing via a facemask so that tracheal intubation and mechanical ventilation were avoided. Nevertheless, ~1 MAC_{50} of Xe was achieved without significant respiratory depression. In contrast, even a doubling of minute ventilation was observed while end-tidal P_{CO_2} remained unchanged. Since oxygenation was not impaired, we may exclude pulmonary atelectasis but rather assume increased impact of dead space ventilation cardiac output to be the major cause of increased minute ventilation during Xe anaesthesia. Furthermore, metabolism and CO_2 production are ultimately linked to cardiac output. The inhibition of NE uptake during unchanged sympathetic outflow may increase cardiac output and metabolism. As observed in a canine model, i.v. infusion of NE increases cardiac output and CO_2 production in a linear fashion.[39] Accordingly, we speculate that increased NE concentration at the level of adrenergic receptors may have caused the observed increase in P_{CO_2} and ventilation. As heart rate did not change significantly during Xe anaesthesia, increased cardiac inotropy may be speculated to be the cause. However, a slight decrease in heart rate without changes in arterial pressure under Xe anaesthesia after induction with propofol has been reported in volunteers previously.[40] These, at first glance, contradictory results to our observation can be explained: subjects in our study were not receiving any other medication while in the study by Rex and colleagues, propofol was administered for induction of anaesthesia. Accordingly, residual propofol at calculated plasma concentrations even below 1 $\mu g\ ml^{-1}$ may have caused a reduction in efferent sympathetic activity[41 42] counteracting the sympathetic effects of Xe.

MSA may be influenced by respiration and at least in males, breathing rate correlates positively with sympathetic activity and total peripheral resistance.[43] However, while all volatile anaesthetics increase spontaneous breathing rate up to several hundred per cent, isoflurane, sevoflurane, and desflurane markedly decrease MSA.[4] Thus, it seems rather unlikely that MSA during Xe anaesthesia is maintained solely by increased breathing rate.

We would have preferred to evaluate the effect of Xe on the baroreflex setpoint more extensively reported previously.[13] Unfortunately, because of spontaneous movements during Xe anaesthesia, it was not possible to normalize arterial pressure by titrating nitroprusside before losing the MSA recording site.

One limitation of the *in vitro* observations is that the fluorescence-based assay does not only measure the uptake function of NET but also the function of dopamine and serotonin transporters.[21] Therefore, after achieving positive results by the fluorescent screening method, a specific uptake assay using radiolabelled NE was used to confirm that Xe reduces NE uptake.

In conclusion, NE plasma concentrations and arterial pressure increase during Xe anaesthesia, despite MSA and sympathetic baroreflex gain remaining unaltered. Xe inhibits NE uptake *in vitro* in an NMDA-R-dependent manner. This mechanism may be responsible for increased concentrations of NE at the synaptic cleft and in plasma and therefore contribute to the haemodynamic stability of patients during Xe anaesthesia.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

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Declaration of interest

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6.2 Xenon Does Not Increase Heart Rate-corrected Cardiac QT Interval in Volunteers and in Patients Free of Cardiovascular Disease.

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Xenon Does Not Increase Heart Rate–corrected Cardiac QT Interval in Volunteers and in Patients Free of Cardiovascular Disease

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ABSTRACT

Background: Impaired cardiac repolarization, indicated by prolonged QT interval, may cause critical ventricular arrhythmias. Many anesthetics increase the QT interval by blockade of rapidly acting potassium rectifier channels. Although xenon does not affect these channels in isolated cardiomyocytes, the authors hypothesized that xenon increases the QT interval by direct and/or indirect sympathomimetic effects. Thus, the authors tested the hypothesis that xenon alters the heart rate–corrected cardiac QT (QTc) interval in anesthetic concentrations.

Methods: The effect of xenon on the QTc interval was evaluated in eight healthy volunteers and in 35 patients undergoing abdominal or trauma surgery. The QTc interval was recorded on subjects in awake state, after their denitrogenation, and during xenon monoanesthesia ($F_{et}Xe > 0.65$). In patients, the QTc interval was recorded while awake, after anesthesia induction with propofol and remifentanil, and during steady state of xenon/remifentanil anesthesia ($F_{et}Xe > 0.65$). The QTc interval was determined from three consecutive cardiac intervals on electrocardiogram printouts in a blinded manner and corrected with Bazett formula.

Results: In healthy volunteers, xenon did not alter the QTc interval (mean difference: +0.11 ms [95% CI, −22.4 to 22.7]). In patients, after anesthesia induction with propofol/remifentanil, no alteration of QTc interval was noted. After propofol was replaced with xenon, the QTc interval remained unaffected (417 ± 32 ms *vs.* awake: 414 ± 25 ms) with a mean difference of 4.4 ms (95% CI, −4.6 to 13.5).

Conclusion: Xenon monoanesthesia in healthy volunteers and xenon/remifentanil anesthesia in patients without clinically relevant cardiovascular disease do not increase QTc interval. **(Anesthesiology 2015; 123:542-7)**

ANESTHETIC properties of xenon have been known for more than 50 yr.[1] Because of its very low solubility in blood and brain as well as a lack of metabolism, xenon has been considered to be an almost ideal anesthetic.[2] Because of its low solubility, xenon is characterized by a high minimum alveolar concentration of 50 to 70%, which allows for monoanesthesia before surgery but requires additional analgesia during surgical stimulation.

In contrast to halogenated inhalative anesthetics, xenon maintains sympathetic activity while norepinephrine reuptake is even slightly decreased, so that cardiac output and arterial pressure are stable during xenon-based anesthesia.[3] Because perioperative arterial hypotension is associated with increased morbidity and mortality,[4–6] patients at risk for perioperative cardiovascular events may benefit from xenon-based anesthesia by avoiding arterial hypotension. At the same time, many of these high-risk patients are at risk for critical ventricular arrhythmias. Many anesthetics and/or analgesics may provoke polymorphic ventricular tachycardia such as torsade-de-pointes tachycardia by altering cardiac repolarization. Prolongation of the heart rate–corrected cardiac QT (QTc) interval is a commonly accepted indicator for

What We Already Know about This Topic

- Many anesthetics may provoke polymorphic ventricular tachycardia by altering cardiac repolarization
- Prolongation of the heart rate–corrected cardiac QT (QTc) interval is a commonly accepted indicator of the risk of polymorphic ventricular tachycardia
- Because xenon maintains sympathetic activity and slightly decreases norepinephrine uptake and sympathetic activation in general is thought to increase the QTc interval, the effects of xenon on cardiac repolarization and QTc interval was determined in 8 volunteers and 35 patients

What This Article Tells Us That Is New

- No prolongation of cardiac QT intervals was observed in volunteers during xenon monoanesthesia or in patients without preexisting long QT syndrome during xenon-based anesthesia

This article has been presented at the Annual Meeting of the American Society of Anesthesiologists in Chicago, Illinois, on October 17, 2011 (Xenon-based anesthesia does not alter QT interval), and at the Annual Meeting of the European Society of Anaesthesiology "euroanaesthesia" in Paris, France, on June 12, 2012 (The influence of xenon anesthesia on QTc interval).

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the risk of polymorphic ventricular tachycardia.[7] Although there is lack of evidence of a critical threshold value, prolongation of the QTc interval by more than 20 ms from baseline or absolute values of more than 500 ms are considered clinically relevant.[7–9] Because the effects of xenon on cardiac repolarization and the QTc interval are unknown, we tested the hypothesis that xenon in anesthetic concentrations alters the QTc interval.

Materials and Methods

After obtaining local institutional review board approval (Ethikkommission der Medizinischen Fakultät der Heinrich-Heine Universität, Düsseldorf, Germany, Ref. No.: MO-LKP-394+3386 and Ethikkommission der Ärztekammer Berlin, Germany, Ref. No.: ETH-019/08) and a written informed consent from all participants in the study, xenon-based anesthesia was evaluated in eight healthy volunteers (Eudra CT No.: 2009-012449-48, ClinicalTrials.gov Identifier: NCT01043419), and in a clinical observational study including 35 patients (German Federal Institute for Drugs and Medical Devices [BfArM] study number AL-PMS-01/07GER) subject to xenon-based anesthesia.

Volunteers

The data presented in the study are secondary outcome variables of a previously published clinical trial.[3] Eight nonpremedicated healthy and normotensive volunteers were included in this study in January and February of 2010. Inclusion criteria were age 18 to 65 yr and exclusion of any preexisting disease (American Society of Anesthesiologists class I). None of the subjects was taking prescription or nonprescription drugs. After an overnight fast, all subjects were studied in the supine resting position in the morning. After a resting accommodation period, oxygen was administered for denitrogenation ($F_{IO_2} > 0.95$, $F_{EO_2} > 0.92$) *via* a closed facemask (Classic Star®; Dräger Medical, Germany) without positive end-expiratory pressure. After the subjects' adaptation to facemask and spontaneous breathing in this closed-circuit setting, xenon monoanesthesia was induced with a targeted inspiratory xenon concentration of 70% (LENOXe®; Air Liquide Santé, France) and 30% oxygen. Surface electrocardiogram (ECG) and radial arterial pressure were recorded continuously. For the determination of QTc intervals, ECG printouts were analyzed at three standardized time points: (1) in the awake state, 5 min before denitrogenation, (2) after denitrogenation, after having reached an inspiratory oxygen fraction greater than 95%, and (3) 15 min after xenon introduction and during steady state of xenon monoanesthesia ($F_iXe > 65\%$). After completion of the study protocol, xenon administration was discontinued and subjects awoke from anesthesia.

Patients

Patients included in this postmarketing observational study assessing the safety of xenon-based anesthesia were presumed to be free of cardiovascular disease. The study comprised patients scheduled for abdominal or trauma surgery between April 2009 and February 2011. Inclusion criteria were age 18 to 65 yr, written informed consent about the study enrollment, absence of regional anesthesia, and lack of preexisting pathologic medical conditions relevant to anesthesia in the patients' history (American Society of Anesthesiologists class I to II). After an overnight fast, all subjects were studied in the supine resting position.

After oral premedication with midazolam (75 to 150 μg/kg), general anesthesia was induced and initially maintained by intravenous propofol (initial bolus of 2.5 mg/kg + continuous infusion of 6 mg kg^{-1} min^{-1}), remifentanil (0.2 μg kg^{-1} min^{-1}), and rocuronium (0.6 mg/kg). After denitrogenation ($F_{IO_2} > 0.95$), xenon administration was initiated with 70% xenon (LENOXe®; Air Liquide Santé) in oxygen. After achieving inspiratory fraction of xenon of $F_iXe > 0.6$ and sufficient depth of anesthesia (EEG-based measurement of anesthesia depth [Narcotrend®; Narcotrend Gruppe, Germany] value of ≤30), propofol was discontinued. Noninvasive blood pressure was taken every 3 min, and surface ECG was recorded continuously. For the determination of QTc interval, ECG printouts were analyzed at three standardized time points: (1) in the awake state, 5 min before the beginning of denitrogenation, (2) 10 min after anesthesia induction with propofol and remifentanil, that is, during total intravenous anesthesia, and (3) 15 min after discontinuation of propofol, during steady state of xenon/remifentanil anesthesia ($F_iXe > 60$) and before surgical incision.

Measurement of the QTc Interval

The QTc interval was determined from three consecutive cardiac intervals of ECG printouts (lead II, feed 50 mm/s) and corrected using the Bazett formula.[10] All analyses were performed by the same board-certified cardiologist (P.R.), who was blinded with respect to the subject and to the time point of ECG recording.

Statistics

Data were collected on logistical concerns in both clinical studies. Accordingly, no *a priori* power calculation was performed.

Statistical analysis was performed using statistical software IBM SPSS Statistics 22 (IBM Deutschland GmbH, Germany) and Stata/IC 10.0 (StataCorp LP, USA). Data are expressed as means ± SD. Differences in means of time point variables were tested by one-way repeated-measures ANOVA followed by the Newman–Keuls *post hoc* test. CIs (95%) were calculated for mean differences of QTc intervals.

The following null hypothesis was tested: means of variables are altered by xenon compared with the awake state or after propofol induction (two tailed). The null hypothesis was rejected in case of an α error of less than 0.05.

Table 1. Volunteers' and Patients' Characteristics

	Volunteers (n = 8)	Patients (n = 35)
Sex (male/female)	6/2	18/17
Age (yr)	25 ± 2	44 ± 11
BMI (kg/m²)	23.5 ± 1.8	26.7 ± 1.8
ASA status	I	I + II

ASA = American Society of Anesthesiologists; BMI = body mass index.

Results

General cohort data of volunteers and patients are summarized in table 1.

Volunteers

All enrolled participants completed the study protocol. Denitrogenation (F_{IO_2} > 0.95) did not alter their arterial pressure or heart rate. As previously reported, xenon monoanesthesia with 63 ± 6% end-tidal concentration increased mean arterial pressure (93 ± 5 mmHg at rest *vs.* 107 ± 6 mmHg under xenon anesthesia) without any effect on the heart rate (64 ± 10 min^{-1} *vs.* 70 ± 10 min^{-1}, respectively).[3] Xenon did not change the QTc interval at any measurement time point (awake subjects: 398 ± 42 ms *vs.* after denitrogenation: 409 ± 45 ms [P = 0.55] and *vs.* xenon anesthesia: 409 ± 30 ms [P = 0.43] when compared with awake patients; fig. 1). Mean difference in QTc interval length between denitrogenation and xenon anesthesia period was +0.11 ms (95% CI, −22.4 to 22.7). All volunteers were breathing spontaneously achieving arterial normocarbia (45 ± 6 mmHg) and an arterial oxygen partial pressure of 173 ± 19 mmHg. Two of the eight volunteers experienced short-lasting nausea and vomiting immediately after awakening. Both volunteers reported a history of nausea after general anesthesia. No other adverse events were observed.

Patients

All patients enrolled in the study completed the protocol. Induction of anesthesia with propofol, remifentanil, and rocuronium decreased arterial pressure (systolic/diastolic: from 129 ± 13 mmHg/70 ± 8 mmHg to 97 ± 8 mmHg/51 ± 6 mmHg, P < 0.001) as well as heart rate (from 69 ± 11 min^{-1} to 61 ± 12 min^{-1}, P < 0.001). Administration of xenon (end-tidal concentration: 65 ± 5%) and discontinuation of propofol significantly increased arterial pressure (to: systolic/diastolic: 113 ± 13 mmHg/62 ± 8 mmHg, P < 0.001 *vs.* propofol/remifentanil) and further decreased heart rate (to: 58 ± 10 min^{-1}, P = 0.04 *vs.* propofol/remifentanil).

The average QTc interval was unchanged during propofol/remifentanil anesthesia (P = 0.06) with a mean difference of −8.5 ms (95% CI, −15.2 to −1.8). Xenon did not change the QTc interval compared with the preanesthetic baseline level (417 ± 32 ms *vs.* awake: 414 ± 25 ms, P = 0.3; fig 2), and the mean difference in individual patients being +4.4 ms (95% CI, −4.6 to 13.5).

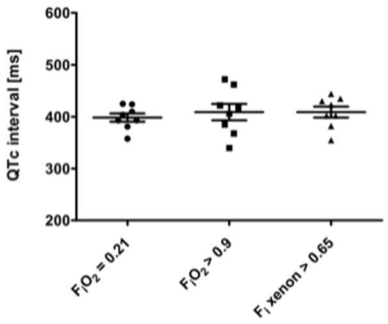

Fig. 1. Depicted are *data points* from each individual volunteer (n = 8), means and SD of heart rate–corrected cardiac QT interval awake, after denitrogenation before xenon and during xenon monoanesthesia. F_{IO_2} = inspiratory oxygen fraction; FI xenon = inspiratory xenon fraction; QTc interval = heart rate–corrected cardiac QT interval.

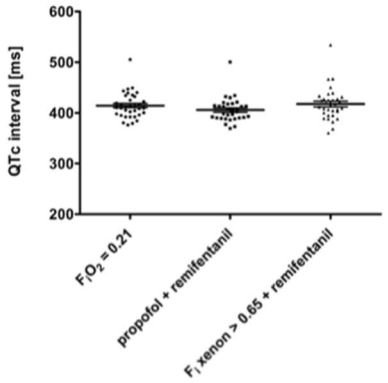

Fig. 2. Depicted are *data points* from each individual patient (n = 35), means and SD of heart rate–corrected cardiac QT interval awake, during general anesthesia with propofol/remifentanil before xenon and during xenon/remifentanil anesthesia. F_{IO_2} = inspiratory oxygen fraction; FI xenon = inspiratory xenon fraction; QTc interval = heart rate–corrected cardiac QT interval.

Noteworthy was a further increase of an initially pathological QTc interval before anesthesia from 505 to 534 ms (+29 ms) in one patient during xenon/remifentanil anesthesia. The patient showed no signs of cardiac arrhythmia (fig. 2).

Postoperative nausea and vomiting occurred in 6 of the 35 patients (17%). No other adverse events were observed.

Discussion

The current study is the first to demonstrate that xenon monoanesthesia does not alter QTc interval in healthy volunteers. Moreover, our data indicate that in patients with normal QTc interval, xenon-based anesthesia does not

increase the QTc interval as compared with the awake baseline values. In summary, xenon does not prolong a normal QTc interval. Of interest is also that we did not observe any ventricular arrhythmias associated with xenon administration throughout the study.

The anesthetic effect of xenon has been discovered more than 50 yr ago, and it might be considered as an almost ideal anesthetic.[11,12] In contrast to other inhalational anesthetics, sympathetic activity is maintained during xenon anesthesia while norepinephrine reuptake even decreases slightly, which results in increased plasma norepinephrine concentrations.[3,13] This contributes to stable cardiac output and arterial pressure during xenon-based anesthesia. Although no definitive proof of arterial hypotension as a cause of increased perioperative morbidity/mortality has been scientifically demonstrated so far, hypotension is commonly considered to be an undesired side effect during an anesthetic.[4–6] Xenon-based anesthesia may facilitate achieving this goal. Whether this favorable pharmacodynamic profile of xenon is able to improve patient outcome is a matter of current investigation.[14] Both general and regional anesthetics are still an unavoidable independent risk factor of any surgical and in particular major surgical procedures. Therefore, it is of great importance to analyze potential problems and side effects of anesthetic drugs. The knowledge of potential side effects allows us to minimize the risks they pose on our patients. However, taking into consideration a comparably high and variable surgical risk, it is not trivial to demonstrate the beneficial effects of modern anesthetics (*e.g.*, desflurane) or anesthetic techniques (*e.g.*, thoracic epidurals) although clinical advantages appear obvious.[15,16] More than 3 decades after the introduction of droperidol into anesthesia practice, drug-induced long QT syndromes have been reported in association with administration of droperidol. In those cases, abnormal cardiac repolarization could be identified by a prolonged QTc interval more than 440 ms in the surface ECG.[17] Patients suffering from inherited long QT syndrome are characterized by a QTc interval longer than 500 ms.[18,19] The associated risk of critical ventricular arrhythmias and reports of several deaths after administration of more than 5 mg droperidol led to a black box warning by the U.S. Food and Drug Administration and withdrawal of droperidol from the European market.[20] Interestingly, large retrospective trials indicate that low-dose droperidol used for the treatment of postoperative nausea and vomiting in the surgical population was not associated with an increased incidence of polymorphic ventricular tachycardia or increased mortality,[21,22] most likely because of the low-dose use of droperidol. This case demonstrates the necessity to detect and recognize the effects of drugs on repolarization of cardiomyocytes, particularly in patients without cardiovascular disease and in those with preexisting repolarization abnormalities. Although large preclinical and clinical studies of the anesthetic drugs' impact on human body have clear advantages, smaller studies with well-defined outcome variables may help to identify unknown anesthetic risk factors.

Previous studies have shown that propofol does not alter QTc interval. Inhalational anesthetics, thiopental and several opioids, however, might be associated with an increase in the cardiac QT interval duration.[7] For instance, sevoflurane was shown to prolong the QTc interval in both children (414 ± 21 ms *vs.* 433 ± 28 ms, $P < 0.01$)[23,24] and adults (413 ± 19 ms *vs.* 444 ± 24 ms; $P < 0.05$).[25] The underlying mechanism is presumably a blockade of the fast-acting component of the cardiac delayed rectifier potassium channel, which is believed to be responsible for cardiac repolarization.[26,27] In contrast to high doses of fentanyl and sufentanil, remifentanil administered in doses comparable with the ones that our patients received significantly decreased the cardiac QT interval and prevented its increase in response to tracheal intubation.[28] Thus, remifentanil may mask QT interval–prolonging effects of other anesthetics. However, because xenon did not alter the QTc interval in our volunteers when given alone, it is very unlikely that such effects occur in patients. Our results are in accordance with previously published data showing no effects of xenon on those channels either in human atrial myocytes or in isolated guinea pig hearts.[29,30]

In our patient cohort, we accidentally detected a patient with a preexisting long QT syndrome and a baseline QTc interval of 505 ms. His QT interval increased further under xenon/remifentanil anesthesia. He did not have history of a cardiovascular or any other anesthesia-relevant preexisting pathological condition, did not take any regular medication, and did not develop bradycardia during xenon/remifentanil anesthesia. Unfortunately, the patient refused genetic testing, so that we were unable to find out whether his long QT interval was the result of mutation of any of the genes typically associated with the syndrome. Although xenon does not alter a normal QTc interval, this finding suggests that further studies are warranted to evaluate the potential influence of xenon on the QTc interval in patients experiencing inherited or acquired long QT syndromes.

Although sympathetic activation in general is thought to increase the QTc interval[31] and xenon is known to increase norepinephrine plasma concentrations,[3] we did not observe prolonged QTc intervals in volunteers during xenon monoanesthesia or in patients without preexisting long QT syndrome during xenon-based anesthesia. These results also suggest that indirect sympathetic activation does not increase QTc interval through a norepinephrine-dependent mechanism.

In summary, our data from both healthy volunteers and patients free of cardiovascular disease and without preexisting long QT syndrome provide clinically based support to previous *in vitro* electrophysiological findings that xenon does not alter cardiac repolarization.

Limitations of the Study

In the current study, we analyzed the effects of xenon on the QT interval in healthy volunteers and patients presumably free of cardiovascular disease. Our data cannot be directly extrapolated to predict the effects of xenon on patients with preexisting cardiac repolarization pathology.

Second, the effects of xenon on the QT interval were studied at 65% end-tidal xenon concentration only. However, it is conceivable that the effect of xenon on the QTc interval could be dose dependent and this was not analyzed in our study. Accordingly, one cannot exclude the possibility of an effect of xenon on cardiac repolarization at lower end-tidal xenon concentrations.

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Competing Interests

Dr. Reyle-Hahn has received fees for lectures from Air Liquide Medical, Düsseldorf, Germany. Dr. Kienbaum has been consulting for Air Liquide Medical, and Baxter Deutschland GmbH, Unterschleissheim, Germany. The other authors declare no competing interests.

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Address correspondence to Dr. Neukirchen: Department of Anesthesiology, Medical Faculty, Heinrich-Heine-University, Moorenstr. 5, D-40225 Düsseldorf, Germany. martin.neukirchen@med.uni-duesseldorf.de. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

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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, randomized clinical trial

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Abstract

Background: Postoperative delirium 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 delirium and other outcomes after hip fracture surgery.

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

Results: Of 256 enrolled patients, 124 were treated with xenon and 132 with sevoflurane. The incidence of delirium with xenon (9.7% [95% 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). For xenon and sevoflurane, the incidence of serious AEs and fatal AEs was 8.0% *vs* 15.9% (P=0.05) and 0% *vs* 3.8% (P=0.06), respectively.

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

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

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

Editor's key points

- Postoperative delirium is common in the elderly and is associated with poor outcome.
- Xenon has been shown to have neuroprotective properties in animal studies.
- This study found no evidence that xenon-based anaesthesia reduced the incidence of delirium after hip fracture surgery in the elderly.
- This study is likely to be underpowered, so beneficial effects of xenon may have gone undetected.

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 in 2014.[3] Hip fracture is also associated with high 30-day mortality rates (8 – 10% in the UK) and high one-yr 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 after 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, preexisting 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.

As a result of the potentially beneficial qualities of xenon, we hypothesized that the incidence of POD in hip fracture surgery patients would be lower with xenon-based anaesthesia than with sevoflurane-based anaesthesia. We therefore conducted a clinical trial to specifically compare the incidence of POD and other outcomes in hip fracture surgery patients anaesthetized with either xenon or sevoflurane.

Methods

Study design

The design and protocol of the study have been published previously[32] and are summarized in the Supplementary material. Briefly, this was a phase II, observer-blinded, parallel-arm, multicentre, randomized 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. As a result of 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 yr old with planned surgery within 48 h 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 Supplementary material and in Coburn, et al. 2012.[32]

Procedures

Patients were randomly assigned to the xenon or sevoflurane treatment groups using a blocked randomization 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 randomization-allocated anaesthetic was contained in an envelope bearing the sequential randomisation number of the patient and was revealed to the attending anaesthetist (Physician 2) who opened the envelope only immediately before 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]) and 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 10min until maintenance anaesthesia with the randomization-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 h after surgery and at twice-daily visits [10 am (30min) 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 four 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 four 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 assignment and who received extensive and specific training before 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 postoperative day five through discharge; SOFA on postoperative days one to four; 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 harmonised across the study sites.

Statistical analysis

The sample size was calculated based on an expected POD event rate of 30% within four 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 $\alpha = 0.05$ (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 randomized patients (128 per group).

In the primary analysis of the primary outcome, the POD incidence within four days post-surgery in each group in the intention-to-treat population was compared using a χ^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 $\alpha = 0.05$. However, a value of $\alpha = 0.10$ was applied during the initial two-factor regression analysis to identify potentially confounding factors to be used in the subsequent multivariate regression analysis, and during the stepwise backward selection of these factors in the multivariate regression model.

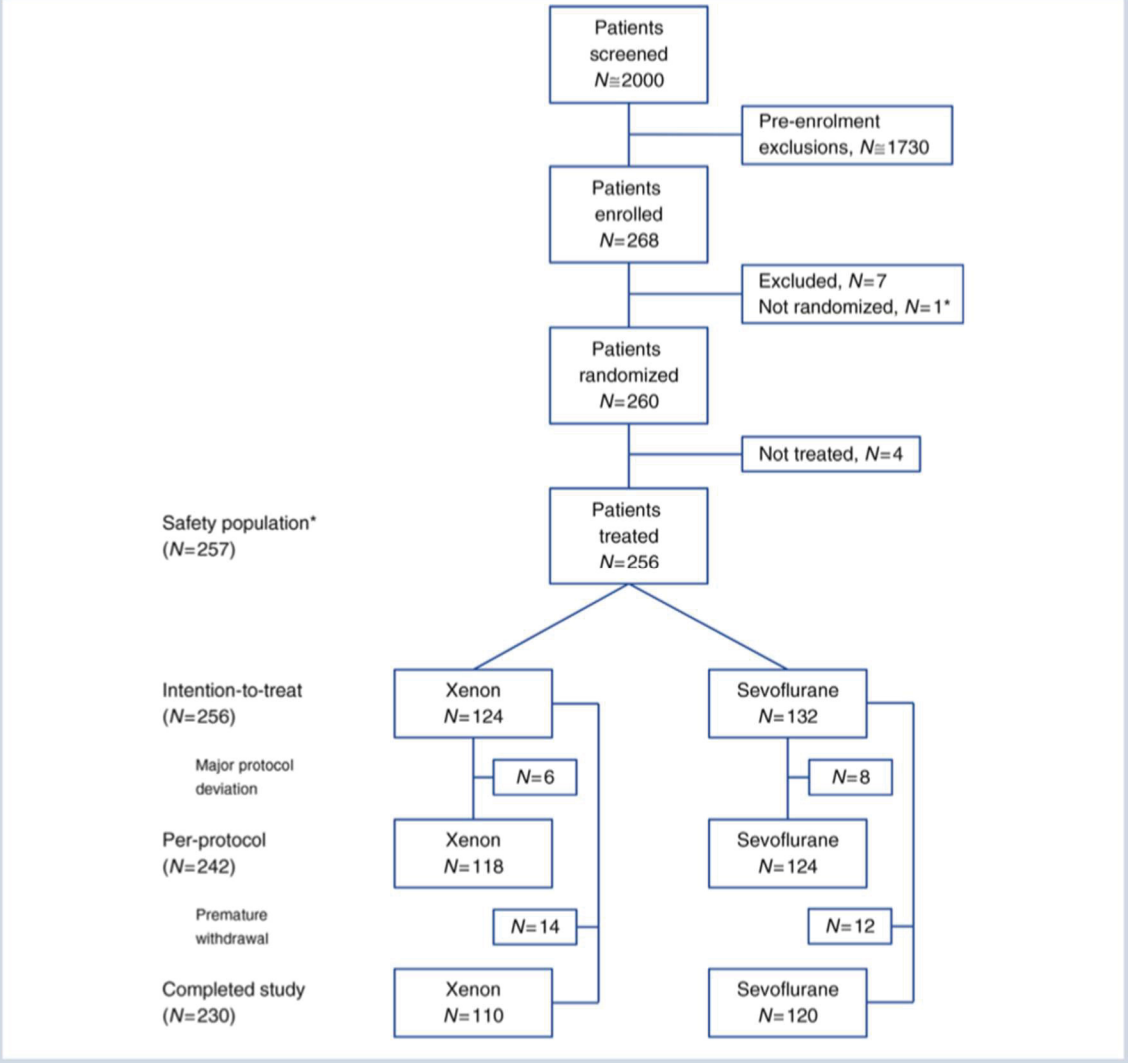

Fig 1. **Patient disposition.** Among the over 2000 patients who were screened for enrolment in the HIPELD study, 268 were enrolled. Records were not kept for patients not enrolled, but most of these patients failed to meet the MMSE score criterion. Of the enrolled patients, 260 patients were eventually randomly assigned and 257 were treated and followed for safety. One non-randomized 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 (*). Most patients excluded from the per-protocol analyses had multiple missing CAM evaluations (nine patients).

Results

From over 2000 hip fracture patients screened for the study, only 268 were enrolled and 260 were randomly assigned to the treatment groups between September 2010 and October 2014 (Fig. 1). Most pre-enrolment exclusions were because of low MMSE scores. Among these, 256 randomized 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 (≥five) missing CAM evaluations (nine patients) after surgery or for missing CAM evaluations at selection (three 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 yr. Most patients had an ASA physical status of II or III and a moderate level of pain. Pre-operative SOFA scores were

Table 1 Baseline patient characteristics. CAM, Confusion Assessment Method; MMSE, mini mental state examination; n, number of patients with the characteristic or for which results are available; N, number of patients in the group; SD, standard deviation; SOFA, sequential organ failure assessment; VAS, visual analogue scale. *Percentages are calculated for patients without missing data, which included >95% of the patients in each group, except where noted otherwise. †Mean total scores calculated for 85 patients in the xenon group and 72 patients in the sevoflurane group without missing values

Patient characteristics	Xenon (N=124)	Sevoflurane (N=132)
Men, n (%)*	34 (27.4)	29 (22.0)
Women, n (%)	90 (72.6)	103 (78.0)
Age, yr		
Mean (SD)	83.8 (5.1)	84.4 (4.6)
Range	75.1 – 98.5	75.5 – 95.4
BMI, 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 physical 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)†	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)

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 nine 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 Fig. S1) and haemodynamic variables during surgery (Supplementary Fig. S2) were similar across groups.

Postoperative delirium incidence

In the primary analysis, a total of 12 out of 124 (9.7% [95% CI: 4.5 14.9%]) patients in the xenon group *vs* 18 out of 132 (13.6% [95% CI: 7.8 –19.5%]) patients in the sevoflurane group had at least one POD episode during the first four days after surgery (Table 3). These incidence rates were not significantly different

Table 2 Intraoperative and postoperative characteristics of hip fracture surgeries. *Treatment groups compared using the log-rank test. †One patient in the xenon group had an extraordinarily long recovery time of 363 min. No other patient in either group had a recovery time longer than 33 min. ‡Treatment groups compared using the Wilcoxon rank sum test for quantitative variables

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, h (SD)	47.9 (40.1)	37.4 (27.4)	
Duration of anaesthesia, min (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, min (SD)	72.4 (39.1)	62.0 (31.1)	
Anaesthesia recovery parameters			
Mean time to Aldrete score of ≥ 9, h (SD)	0.70 (1.20)	0.72 (0.72)	0.22*
Median time to open eyes, min (range)	4.0 (0–363)†	8.0 (0–33)	<0.001‡
Median time to react on verbal command, min (range)	5.0 (0–363)†	8.5 (1–33)	<0.001‡
Median time to extubation, min (range)	5.4 (0–373)†	9.1 (1–35)	<0.001‡
Hospitalization			
Mean time to discharge, days (SD)	10.8 (5.2)	11.4 (6.2)	0.53†
Patients discharged within 30 days, n	120	125	
Patients not discharged within 30 days, n	4	2	
Patients who died, n	0	5	

(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 because of an AE or who died were included in the analysis and considered to have had a POD episode (Supplementary Table S1).

Incidence rates for POD at five 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 four days after surgery (also the Kaplan-Meier diagram in Supplementary Fig. 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 four

Table 3 Incidence and characteristics of postoperative delirium (POD) episodes in hip-fracture surgery patients. Results shown for all randomized, 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; POD, postoperative delirium. *Treatment groups compared by χ^2test. †Per-protocol population: xenon (N=118); sevoflurane (N=124)

Metric	Xenon (N=124)	Sevoflurane (N=132)	P-value*
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† [%]	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, h (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)	

days after surgery, four were identified as potentially important after backward selection: male gender, ASA physical status III, being a current smoker, and the presence of a previously diagnosed mild neurologic disorder at selection (Supplementary Table S2). Of these potential confounders, 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 significantly associated with POD (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 Table S2 and Fig. 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 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 Fig. 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 three 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 to −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

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. 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 four days of surgery.

Discussion

In this international randomized clinical trial, xenon-based anaesthesia did not significantly reduce the incidence of POD

Table 4 Safety summary. 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; ND, not determined; SAE, serious adverse event. *χ^2 test for patients with at least one specified AE. [†]Fisher's exact test for patients with at least one specified AE

	Xenon (N=125)		Sevoflurane (N=132)		P-value
	Patients with at least one, n (%)	Total AEs, n	Patients with at least one, n (%)	Total AEs, n	
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]

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 after 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 four 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 preoperative 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: 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 as a result of 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 orga- noprotective properties and a superior haemodynamic profile compared with 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 did not interrogate death registries to accommodate for missing data. 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 because of 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 as a result of 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 nine-item CAM is recommended for maximum sensitivity, we considered the shorter CAM to be far more practical and reasonable for an international clinical trial using twice-daily postoperative 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 before 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.

Authors' contributions

Study design/planning: M.C., R.D.S., M.M., R.R., M.L.N.P.
Study conduct: all authors except R.D.S., M.M.

Data analysis: M.S.
Writing paper: M.C., R.D.S., M.M., S.R., R.R., M.L.N.P.
Revising paper: all authors

Declaration of interest

The institutions of M.C., S.R., B.G., J.A.C., M.L.G.P., A.S., P.K., M.N., M.S.S., B.B., H.v.O., A.T., L.A., L.E., O.L., X.C., G.M.A., and R.R. received grant funds and/or patient inclusion fees from Air Liquide Santé International to conduct the study. M.C., R.D.S., M.M., A.S., and R.R. received consulting fees and/or travel funds from Air Liquide Santé International. M.C. received grants, consulting fees, and travel funds from Baxter Healthcare and grants from German Research Foundation outside the submitted work. S.R. received unrestricted grants from Air Liquide Santé International and Air Liquide Belgium and speaking fees from Orion Pharma. M.M. 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. M.L.N.P. was a full-time employee of Air Liquide Santé International during the study. M.S. is currently a full-time employee of Air Liquide Santé International.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.11.015

Appendix

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6.4 The effect of xenon-based anesthesia on somatosensory-evoked potentials in patients undergoing carotid endarterectomy

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Original Article

The Effect of Xenon-Based Anesthesia on Somatosensory-Evoked Potentials in Patients Undergoing Carotid Endarterectomy

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Objectives: The aim of this study was to investigate the influence of xenon-based anesthesia on somatosensory-evoked potentials.
Design: Observational cohort study.
Setting: University hospital.
Participants: Twenty subsequent adult patients undergoing elective carotid endarterectomy.
Interventions: Xenon-based anesthesia.
Measurements and Main Results: Cortical-evoked responses to median nerve stimulation were quantified by measurement of the amplitude and latency of the N20 wave, which are typically assessed during carotid surgery to detect intraoperative cerebral hypoperfusion and ischemia. Primary (N20 amplitude and latency) and secondary (mean arterial pressure, norepinephrine requirements and depth of anesthesia) were assessed during (1) propofol/remifentanil and (2) subsequent xenon/remifentanil anesthesia. Xenon at an inspiratory fraction of 62.5 ± 7% decreased norepinephrine requirement (0.067 ± 0.04 *v* 0.028 ± 0.02 μg/kg/min, $p < 0.001$), and mean arterial pressure was unchanged (90.6 ± 15.0 *v* 93.1 ± 9.6 mmHg, $p = 0.40$). Somatosensory-evoked potentials were available in all patients during xenon/remifentanil. Despite similar depth of anesthesia (Narcotrend index 38.4 ± 6.2 *v* 38.5 ± 5.8) during propofol and xenon, N20 amplitude was reduced after xenon wash-in from 3.7 ± 1.7 to 1.4 ± 2.8 μV, $p < 0.001$ on the surgical and 3.6 ± 1.6 to 1.4 ± 0.6 μV, $p < 0.001$ on the contralateral side. N20 latency remained unchanged during xenon (22.9 ± 2.1 *v* 22.5 ± 2.8 ms, $p = 0.34$ and 22.9 ± 2.0 *v* 22.9 ± 3.0, $p = 0.97$).
Conclusions: Xenon influences somatosensory-evoked potentials measurement by reducing N20 wave amplitude but not latency. When xenon is considered as an anesthetic for carotid endarterectomy, wash-in needs to be completed before carotid surgery is commenced to provide stable baseline somatosensory-evoked potential measurement.

Key Words: xenon; anesthesia; evoked potentials, somatosensory; endarterectomy, carotid; intraoperative monitoring; neurophysiological monitoring

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Dr. Neukirchen, Dr. Schaefer, Dr. Legler, and Mr. Hinterberg have no conflicts of interest to declare. Prof. Kienbaum has been consulting for Baxter GmbH Germany, Air Liquide Medical GmbH Germany and TEVA Ratiopharm Germany and received lecture fees and traveling expenses from these companies. He is an associated editor of *BMC Anaesthesiology*.

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ANESTHESIA WITH the noble gas xenon is characterized by stable hemodynamics with comparably small vasopressor requirements.[1–5] Owing to a very low blood-gas partition coefficient of 0.12,[6,7] xenon provides rapid weaning from anesthesia[8–12] and facilitates immediate neurologic assessability after surgery.[10] Additionally, xenon prevents neuronal cell death both after mechanical[13,14] and ischemic[15–18] damage. Taken together, these characteristics qualify xenon as an attractive choice for patients undergoing surgery of brain-supplying arteries such as carotid endarterectomy (CEA), when general anesthesia cannot be avoided. However, when the patient is unconscious, intraoperative neuromonitoring is crucial to detect and treat surgery-related cerebral ischemia. Somatosensory-evoked potentials (SSEP) induced by peripheral nerve stimulation, are an effective and highly sensitive indicator of acute cerebral ischemia.[19] Unfortunately, all inhalation anesthetics depress the amplitude of SSEP and prolong stimulation-to-detection latency in a dose-dependent manner.[20,21] Whereas propofol seems to exert only minor effects on SSEP,[22,23] cardiovascular depression[24,25] and variability in recovery from anesthesia[26] are considered to be clinical disadvantages for patients undergoing CEA. No data exist regarding the influence of xenon on intraoperative monitoring of SSEP. Therefore, the authors investigated the influence of xenon-based anesthesia on SSEP in patients undergoing routine CEA.

Methods

After approval by the local ethics committee (#3867, Ethikkommission der medizinischen Fakultät der Heinrich-Heine Universität, Düsseldorf), 20 consecutive patients undergoing routine xenon-based anesthesia for CEA were included in this retrospective cohort study. Data were derived from anesthesia charts and routinely stored digital SSEP readings. The necessity of informed consent regarding the use of routinely assessed data was waived by the ethics committee.

Anesthesia

Xenon-based general anesthesia was conducted as to institutional standard: any sedative premedication was avoided. Upon arrival at the operating room, a catheter was placed in the radial artery and anesthesia was induced with propofol (1.5-2.5 mg/kg) and remifentanil (0.5 μg/kg/min). Endotracheal intubation was facilitated with rocuronium (0.6 mg/kg). After intubation, anesthesia was maintained with propofol (6 mg/kg/h) and remifentanil (0.2 μg/kg/min), until nitrogen washout (expiratory O_2 fraction ≥95%) was completed. Subsequently, xenon wash-in was started with a targeted inspiratory concentration of 60% (equal to 1.0 MAC) xenon in oxygen (Tangens 2C mobile 12 ventilator, EKU Elektronik, Leiningen, Germany). The application of 1.0 MAC xenon with remifentanil is standard in the authors' institution and has been applied in the majority of previously published studies,[2,3,27–30] therefore likely reflecting standard of care in most institutions. Of note, as opposed to volatile anesthetics, insufficient data exist on the modification of the required xenon MAC through additional infusion of remifentanil.

To control for equivalent depth of anesthesia during propofol and xenon-based anesthesia, patients were monitored using the Narcotrend index (Narcotrend Group, Hannover, Germany). When targeted xenon concentrations were reached, propofol was discontinued and anesthesia was maintained with xenon and remifentanil. Continuous infusion of norepinephrine was initiated to maintain a systolic blood pressure of both no less than 70% of preinduction values or at least 120 mmHg and a mean arterial pressure of at least 75 mmHg. During carotid cross-clamping, systolic blood pressure was elevated to 160 mmHg by increasing norepinephrine infusion rate, as to institutional standards. Throughout the surgery, the possibility to discontinue xenon and re-establish propofol-based anesthesia was given at the discretion of the vascular surgeon, the attending anesthesiologist, and the neuromonitoring technician.

Measurement of SSEP

After induction of anesthesia, the anode and cathode needle electrode for median nerve stimulation were placed 2 centimeters proximal the wrist of the left and right forearm by a specialized technician. Then, bilateral cranial electrodes were placed after the internationally standardized 10-20 electrode system.[31] SSEP were monitored separately for the left and right side (Nicolet Endeavor CR Monitor, Natus Medical Inc, Pleasanton, CA) and monitoring was continued throughout anesthesia. When stable conditions were reached (ie, absence of artefacts owing to manipulation of the patient), initial SSEP measurements under propofol-remifentanil-based anesthesia were made. After completion of xenon wash-in, propofol was discontinued and measurements during xenon-remifentanil-based anesthesia were made before any surgical manipulation of the carotid artery was conducted.

Statistical Analysis and Sample Size Estimation

The authors tested the primary hypothesis that xenon influences the N20 amplitude, defined as the difference between the N20 and P25 peak, as well as the latency of the N20 wave after median nerve stimulation. Because the prevalent carotid stenosis might impair measurement of N20 amplitude and latency, the analysis was conducted separately for the surgical and contralateral side. Secondary outcomes included norepinephrine consumption and mean arterial pressure. After inspection for normal distribution using histograms, a paired student's t-test was applied and two-sided alpha was set to 0.05. Finally, the change in N20 amplitude and latency (Δ_{amp} and Δl_{at}) from propofol to xenon-based anesthesia was compared between the surgical and contralateral side. All calculations were made with STATA IC 10.1 (StataCorp, College Station, TX). Values are reported as mean (standard deviation).

A 1.0 minimum alveolar concentration (MAC) of desflurane reduces SSEP amplitude by 53% from 5.8 ± 2.1 μV to 2.7 ± 1.3 μV (effect size 1.7), as compared with awake baseline after 7.5 mg of oral midazolam.[21] The authors estimated a

Table 1
Patient and Surgical Characteristics

Age (y)	70 ± 10
Female	6 (30)
ASA status (I/II/III)	0/7/13 (0/35/65)
Height (cm)	172 ±9
Weight (kg)	83 ±17
Surgical site	
Left	9 (45)
Right	11 (55)
Clinical presentation of carotid stenosis	
Symptomatic	9 (45)
Asymptomatic	9 (45)
Reoperation	2 (10)
Comorbidities	
Coronary artery disease	9 (45)
Arterial hypertension	19 (95)
Diabetes mellitus	7 (35)
Chronic obstructive pulmonary disease	3 (15)
Renal insufficiency	5 (25)

NOTE. Values are mean ± standard deviation or absolute numbers (%).
Abbreviation: ASA, American Society of Anesthesiologists.

reduction of 30% to be clinically relevant (effect size 0.95). Thus, sample size estimations yielded a required sample of at least 17 patients to achieve a power of 95%.

Results

Viable data were available from all patients and the authors included all 20 patients in the analysis. Table 1 depicts patient and surgical characteristics.

Anesthesia

Inspiratory xenon concentrations were 62.5 ± 7% after wash-in. There was no difference in depth of anesthesia, indicated by Narcotrend index during propofol and xenon-based anesthesia (38.4 ± 6.2 *v* 38.5 ± 5.8). There was a slight increase in end-tidal carbon dioxide concentrations from propofol to xenon (33 ± 2 *v* 35 ± 3 mmHg, p = 0.01). Xenon decreased norepinephrine requirements from 0.067 ± 0.04 to 0.028 ± 0.02 μg/kg/min, p < 0.001, and mean arterial pressure was unchanged (90.6 ± 15.0 *v* 93.1 ± 9.6 mmHg, p = 0.40).

Measurement of SSEP

Figure 1 depicts a representative recording during propofol and after xenon wash-in. Xenon decreased the amplitude of N20 wave by 59.6 ± 23% on the surgical and 54.2 ± 28% on the contralateral side, as compared with propofol-based anesthesia (p < 0.001, Fig 2). N20 wave latency remained unchanged (Fig 3). When comparing the surgical with the contralateral side, the authors found no difference in the change of amplitude or latency (Δ_{amp} 2.3 ± 1.6 μV *v* 2.2 ± 1.6 μV, p = 0.53 and Δ_{lat} −0.4 ± 1.8 *v* −0.02 ± 2.0 ms, p = 0.08, respectively). There was no case where discontinuation of xenon was necessary because of impairment of SSEP.

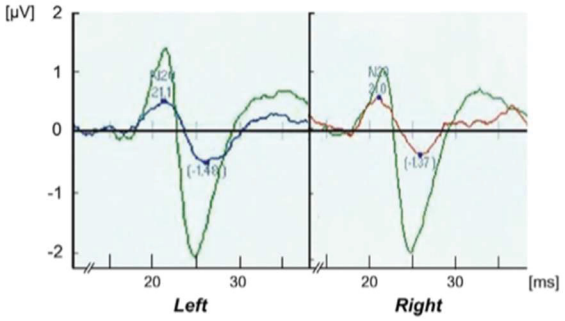

Fig 1. Representative recording of evoked somatosensory potentials from one patient during propofol/remifentanil (*green*) and xenon/remifentanil (*blue and red*) for the left and right hemisphere.

Thus, xenon-based anesthesia was continued throughout surgery in all patients.

Discussion

Xenon reduced N20 wave amplitude to half, without affecting latency. Measurement of SSEP was still feasible during xenon inhalation, which did not have to be discontinued in any case.

Under general anesthesia, assessment of SSEP is a reliable technique that detects even small amounts of cerebral hypoperfusion.[19] However, all inhalational anesthetics interfere with SSEP assessment by reducing amplitude and prolonging latency of the N20 wave in a dose-dependent manner[20,22]: at a minimal alveolar concentration of 1.0, N20 wave amplitude decreases by 55% during desflurane, 33% during sevoflurane, and 66% during isoflurane, whereas latency increases by 12% during desflurane, 16% during sevoflurane, and 18% during

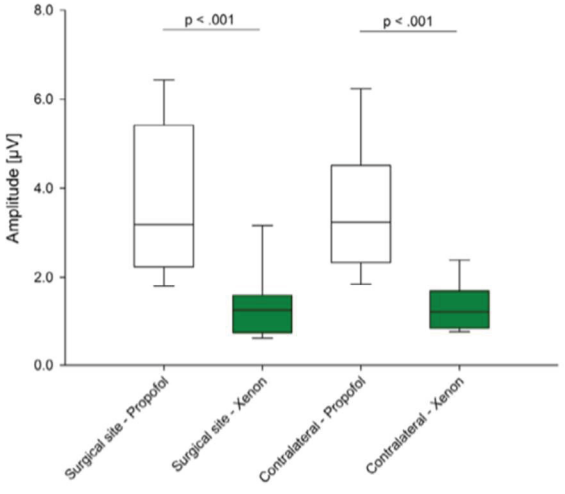

Fig 2. Amplitude of the N20 wave of evoked somatosensory potentials during propofol/remifentanil (*grey*) and xenon/remifentanil (*green*), separate for the surgical and contralateral side. Boxes indicate median with interquartile range, whiskers indicate 10th and 90th percentile.

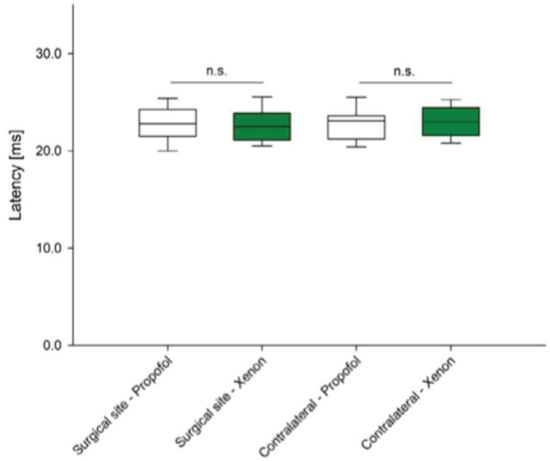

Fig 3. Latency of the N20 wave of evoked somatosensory potentials during propofol/remifentanil (*grey*) and xenon/remifentanil (*green*), separate for the surgical and contralateral side. Boxes indicate median with interquartile range, whiskers indicate 10th and 90th percentile. N.s., not significant.

isoflurane.[21] In the clinical setting, this may impede the assessment of changes in SSEP owing to hypoperfusion and ischemia. Although the application of additional opioids such as remifentanil allows for reduction in age-adjusted minimum alveolar concentration to typically 0.7,[32] it has been shown that the induced changes are large between 0 and 0.7 and small above 0.7 minimum alveolar concentration.[21] In contrast, propofol depresses N20 amplitude to a much smaller extent,[22,33] a propofol-based, total intravenous anesthesia is the technique of choice in several anesthesia departments during CEA, despite an increased risk of propofol induced vasodilatation.[34]

Cerebral hypoperfusion both affects N20 wave amplitude and latency[35] and usually a combined criterion of either a 50% decrease in N20 wave amplitude or 10% increase in N20 wave latency is chosen to determine significant changes in SSEP.[35–37] The observed reduction in N20 wave amplitude by 54 to 59% during approximately 1.0 MAC of xenon is comparable to the effect observed during 1.0 MAC of desflurane and isoflurane.[21,38] Of note, whereas other inhalational anesthetics and propofol provide anesthesia mainly via agonism at γ-aminobutyric acid receptors,[39] xenon primarily inhibits N-methyl-d-aspartate receptors,[40,41] although it has been questioned whether this is responsible for its hypnotic properties.[42] Nonetheless, anesthetics influence on N20 wave amplitude is apparently independent from the targeted receptor. Additionally, virtually all other inhalational anesthetics,[21,22] including nitrous oxide,[33,38] reduce N20 wave latency. Together, this results in a reduction of SSEP sensitivity by 20%, when inhalational anesthetics are applied.[36] Because xenon did not influence N20 wave latency, it may allow for more reliable SSEP monitoring than inhalational anesthetics, although this needs to be confirmed by direct comparison.

The data presented extend the results from previous animal studies: Utsumi et al.[43] applied 70% xenon to cats anesthetized with 2% sevoflurane and found a similar reduction in somatosensory evoked N1 wave amplitude (−42 to 62%). Furthermore, Yamamoto et al.[44] measured myogenic motor-evoked potentials in rabbits anesthetized with ketamine and fentanyl and found a 50% lower success rate and almost abolished amplitude when 70% xenon was applied during single pulse stimulation. At a xenon concentration of only 35%, the influence of xenon on motor-evoked potentials was reduced. Furthermore, this effect was partially reversed when train pulse stimulation was used, suggesting that xenon acts on a dose-response relationship in competition to the applied stimulus. Although inhibition of sensory and motor evoked potentials involves different neuronal pathways and receptors, it seems likely that inhibition of SSEP amplitude by xenon might as well follow a dose-response relationship, as has been described for other inhalational anesthetics.[20,22]

For patients undergoing CEA, xenon shows some promising properties which may be based on at least 3 different mechanisms: (1) there is evidence suggesting neuroprotective effects of the application of xenon application during cerebral ischemia-reperfusion injury[15–17,45,46]; and (2) xenon maintains systemic arterial pressure and[1,4,47,48] enhances the ratio of cerebral blood flow to cerebral metabolic rate,[49] increasing net oxygen supply of the brain.[3] Finally, rapid weaning from xenon anesthesia[8,12] allows immediate assessment of postoperative neurologic status and detection of neurologic deficit. Nonetheless, routine use of xenon-based anesthesia in those patients requires feasibility of neuromonitoring to detect intraoperative cerebral hypoperfusion.

The authors did not have to discontinue xenon in any case owing to impairment of SSEP measurements. Next to the fact that xenon did not influence N20 wave latency, this was because further reductions of N20 wave amplitude owing to carotid clamping and insufficient intracerebral anastomosis could still be detected once a stable baseline had been established after wash-in of the noble gas. Therefore, the authors conclude that SSEP monitoring is feasible during xenon-based anesthesia. However, based solely on this study, the authors cannot yet conclude if xenon-based anesthesia should be the anesthetic of choice for patients undergoing CEA. A head-to head randomized trial is now warranted to elucidate if relevant cerebral hypoperfusion can be equally detected during xenon and propofol anesthesia, and further trials should focus on neurologic outcomes after CEA under xenon as compared with other anesthetics.

Limitations

The aim of this study was to assess the influence of xenon-based anesthesia on SSEP, measured by amplitude and latency of the evoked N20 wave. There were no measurements of SSEP in the awake state, but the authors compared SSEP during propofol and xenon-based anesthesia. This was simply because placement of bilateral wrist and cranial needle electrodes can be painful, which is why electrodes are usually placed only after induction of anesthesia. Because it has been well documented that propofol has, if at all, only minimal effect on

SSEP,[22,23] the authors are confident that changes between propofol and xenon anesthesia depict the effect of xenon on SSEP. All assessments were made before surgery was commenced and the authors did not compare SSEP sensitivity during carotid cross-clamping between xenon and a control. The authors chose this study design because they wanted to demonstrate the direct effect of xenon on SSEP. When comparing xenon to control during periods of cerebral hypoperfusion, it is impossible to differentiate between neuroprotective effects of xenon[14,17,45,46,50] and direct effects of SSEP. As the next step, it needs to be determined to what extent xenon-induced N20 wave amplitude reduction impairs sensitivity of SSEP for detection of cerebral hypoperfusion. Furthermore, the authors did not quantify any dose-dependent relationship of the decrease in N20 wave amplitude by xenon. Nevertheless, the authors assessed the effects of xenon in the typical dose administered to achieve anesthesia of sufficient depth. Finally, the authors measured the cortical potential to a peripheral sensor stimulus, as it is routinely done in their clinic. Therefore, no additional spinal recording was conducted and therefore the authors cannot distinguish between cerebral and spinal effects of xenon. However, this differentiation should be of minor importance in the clinical setting.

It remains to be proven if the promising preclinical data regarding the neuroprotective properties of xenon[14,17,45,46,50] actually translate into improvement of patient outcome, which so far has not been easy to confirm.[27] In this context, the influence of xenon on SSEP monitoring will have to be accounted for when designing an appropriate trial.

Declaration of Competing Interest

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6.5 A rapid influence of S-ketamine on anxiety of palliative patients: a retrospective pilot study.

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RESEARCH ARTICLE Open Access

A rapid positive influence of *S*-ketamine on the anxiety of patients in palliative care: a retrospective pilot study

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Abstract

Background: Patients in palliative care need rapid-acting pharmacological options for psychological distress. N-methyl-D-aspartate antagonist ketamine is known to have a fast onset of anti-depressant and anxiolytic action. Its *S*-enantiomer *S*-ketamine (or esketamine) is an analgesic used as a routine treatment for refractory pain as an intravenous infusion (0.25 mg/kg over 45 min). This study investigates whether *S*-ketamine pain therapy has a positive impact on psychological distress caused by anxiety and depression in palliative care.

Methods: Patient routine data from a palliative care unit of a tertiary care hospital were used in a retrospective analysis after positive ethics approval. Eight patients, who received analgesic *S*-ketamine treatment, were compared to a control group matched by gender and age. The main analysis was conducted using three-way mixed MANOVA followed by two-way mixed ANOVA. Target variables were the values for anxiety and depression in the state-trait anxiety-depression inventory STADI. The predictor variables were the time of measurement before (T1) and after (T2) *S*-ketamine application and group membership.

Results: Comparison of the *S*-ketamine group ($n = 8$; 4 male, 4 female; average age 52 years) with the control group ($n = 8$; 3 male, 5 female; average age 55 years) revealed a significant multivariate effect on anxiety and depression $F(1, 14) = 4.78$; $p = 0.046$; $r = 0.50$. The univariate comparisons showed a significant reduction of the anxiety scores from T1 to T2 in the *S*-ketamine group compared to the control group $F(1, 14) = 10.14$; $p = 0.007$; $r = 0.65$. With regard to depression, there was no significant reduction from T1 to T2 in the group comparison $F(1, 14) = 1.60$; $p = 0.23$; $r = 0.32$. No long-lasting effects on pain were found.

Conclusions: Our findings show that psychological distress of patients in palliative care may improve after a single administration of *S*-ketamine, which mainly alleviates anxiety in those patients. Limitations of this study arise from non-randomization, retrospective analysis and low sample size. Therefore, further prospective and ideally randomized studies are necessary.

Keywords: *S*-ketamine, Esketamine, Ketamine, Anxiety, Depression, Psychological distress, Palliative care, Total pain

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Background

The total pain concept is most useful in palliative care as pain may occur on a physical, psychological, social and spiritual level [1, 2]. It is well established that physical pain and psychological distress are connected [3]. About two thirds of patients with advanced cancer suffer from pain, and more than half of those experience moderate to severe pain [4]. The WHO cancer pain relief guidelines are the standard therapy for pain [5, 6], which may achieve acceptable pain relief in over 50% of the treated patients [7]. Thus, there is still a sizeable group of patients with pain refractory to pharmacological treatment [8]. The N-methyl-D-aspartate (NMDA) receptor is an important structure in the conduction of pain signals [9] and is relevant to pathological pain states [10, 11].

Ketamine is a non-competitive NMDA-receptor antagonist that is effective in the treatment of refractory cancer pain [12–16]. Reviewing the existing data for ketamine as an adjuvant to opioids for cancer pain, Bell et al. concluded that the data is not yet sufficient to evaluate the usefulness of ketamine [17–19]. Other authors came to the same conclusion but also considered ketamine as a reasonable option for refractory, severe neuropathic and chronic pain [20–22].

Ketamine has dose dependent analgesic and anesthetic properties with sympathomimetic side effects while preserving protective reflexes [23]. It belongs to the WHO essential medicines [24]. Ketamine binds at the phencyclidine binding site of the NMDA receptor and interacts with other receptor types like opioid and cholinergic receptors [25, 26]. It is used in clinical practice as a racemic mixture in a 1:1 ratio of the *R*- and *S*-enantiomer of ketamine and as pure *S*-ketamine [27]. *S*-ketamine has the potency to block the NMDA-receptor about two times stronger than *R*-ketamine [28]. The anesthetic potency of *S*-ketamine is about twice as high as racemic ketamine and three to four times higher than *R*-ketamine [29]. Ketamine has psychotomimetic side effects including perceptual distortion and cognitive disorganization [30]. Ketamine also induces hallucinations and changes in mood and body image [23, 29]. It is abused as a recreational drug and can cause addiction [31]. The abuse of ketamine is associated with urological, neuropsychiatric, hepatobiliary and gastrointestinal complications [32]. In the treatment of depressive or anxious patients, racemic ketamine (0.50 mg/kg), as an i. v. infusion lasting 40 min, has an anti-depressive and anxiolytic effect [33, 34]. This effect begins a few hours after application, peaks at 24 h and lasts about one week [35]. The effect can be maintained through repeated application of racemic ketamine [36, 37]. There is also evidence of an anti-depressant [38, 39] and anxiolytic effect of enantiomer *S*-ketamine [29]. Recent clinical studies indicate that nasal application of *S*-ketamine in combination with an oral antidepressant reduces treatment-resistant depression [40–44]. The United States Food and Drug Administration (FDA) recently approved *S*-ketamine as a nasal spray to be used in conjunction with an oral antidepressant for the therapy of treatment-resistant depression [45]. The positive psychological effect of ketamine is attributed to an induction of neuroplasticity, which reverses the negative effect of stress and depression on neural cells and synapses [46]. Key enzymes in this process are BDNF (brain derived neurotrophic factor) [47] and mTor (mechanistic target of rapamycin) [48].

The rapid effect of ketamine on stress, anxiety and depression may be of huge importance for the treatment of psychiatric conditions of patients in palliative care. A total of 29% of patients in palliative care suffer from adjustment disorder, anxiety disorders or depression [49]. Anxiety and depression are related to a lower quality of life [50]. Depression and hopelessness are associated with a desire for hastened death [51] and higher rates of suicide [52]. Additionally, research data suggests that physical and psychological symptoms are interlinked. For example, there is a positive association of depression and anxiety with pain [53] and with physical symptom burden in patients in palliative care [54]. Moreover, anxiety and depression are associated with higher mortality in cancer patients [55]. Current pharmacological therapy options include benzodiazepines for anxiety and antidepressants for depression [56]. Benzodiazepines have a fast onset of action, but also limiting side effects like sedation, confusion, loss of coordination, addiction and paradox effects [56, 57]. Antidepressants often need about six weeks to achieve remission and do not have an effect in one third of depressive patients [58]. Six weeks is a long time for palliative care patients; too long for many. Thus, there is a need for fast-acting and reliable therapy options for these patients. Existing evidence points to a positive influence of racemic ketamine on depression and anxiety of patients in palliative care [59, 60].

In our specialized palliative care unit (SPCU) we regularly use *S*-ketamine (0.25 mg/kg i. v. infusion over 45 min) as an analgesic treatment for therapy refractory pain. *S*-ketamine is favored over racemic ketamine because it has higher analgesic and anesthetic potency and it shows less psychotomimetic side effects [29]. In a retrospective pilot study, we analyzed clinical routine data. We investigated whether an analgesic therapy with *S*-ketamine has a positive impact on psychological distress caused by anxiety and depression of patients in palliative care compared to a control group. This research question is of high interest because, to our knowledge, there is a lack of data regarding the influence of *S*-ketamine on psychological distress of patients in palliative

care. Additional statistical calculations are performed to address variables with potential confounding influence, i.e. pain, need for physical care, received psychological support, received specialized palliative patient treatment, duration of anti-depressant therapy and medication with benzodiazepines, opioids and antidepressants. Furthermore, hints for longer lasting analgesic and psychotomimetic effects of *S*-ketamine are examined. The main hypothesis is that compared to a control group, an analgesic *S*-ketamine infusion reduces psychological distress caused by anxiety and depression. Additionally, it is hypothesized that even after taking the confounding variables into account, the positive effect of *S*-ketamine on psychological distress remains.

Methods

Study design

This pilot study is a retrospective analysis of routine patient data over a one-year period (April 2016 to March 2017). Inclusion criteria for the *S*-ketamine group were a minimum age of 18 years old, analgesic treatment with a *S*-ketamine infusion and sufficient data for comparison before and after *S*-ketamine administration. Inclusion criteria for the control group were a minimum age of 18 years old and sufficient data for comparisons at two measurement points. Patients with the first measurement point on the day of admission were excluded from the control group to avoid confounding influences of admission procedures. Patients from both the *S*-ketamine group and control group were offered the same kind of specialized palliative care treatment. The only difference was that the control group did not need *S*-ketamine for pain control and therefore was not treated with *S*-ketamine. This study uses the STROBE guidelines for reporting observational studies [61].

Setting

The analyzed data were collected in a clinical routine during a standard inpatient treatment in the SPCU of a university hospital in Germany. The SPCU offers specialized palliative care with beds for eight patients. The patients usually suffer from many different and complex symptoms. The team consists of physicians, nurses, psychologists, physiotherapists, art therapists, social services professionals, spiritual welfare professionals, volunteers and others.

Measurements

Primary study outcome variables

The State Trait Anxiety Depression Inventory (STADI) [62] is a validated questionnaire for evaluating depression and anxiety as states and as traits [63]. STADI has been available since 2013 and used in clinical settings [64] including this study's SPCU for routine assessment. The internal consistency is at least $\alpha = 0.81$. Standard values are available based on a representative test group ($N = 3150$) [63]. The STADI allows the calculation of scores for anxiety and depression. The global score is the sum of the anxiety and the depression scores and can be interpreted as psychological distress in the sense of negative affectivity. The state and trait section of the questionnaire consists of 20 items. For depression, anxiety and the global score, standardized comparison values are available according to age and gender. Using these standard tables, the individual raw values are normalized into T-scores. A T-score is a standardized score with a mean of 50 and a standard deviation of 10. A T-value > 60 is classified as pathological [62]. The state part of this questionnaire was evaluated upon admission and at regular intervals of 1 to 5 days during the stay in the SPCU.

Potential confounding variables of primary outcomes

Pain is part of the Palliative Symptom Burden Score (PSBS) [65, 66], which is routinely used in the SPCU. Pain was assessed using the numerical rating scale for pain (NRS) with a range from no pain (0) to the worst imaginable pain (10). Pain with NRS values below 3 is considered to be mild, values between 3 and 6 are moderate and values over 6 are high. During standard care on the ward, the PSBS is assessed three times a day at intervals of 8 h; the first, second and third evaluations take place during the periods from 12 am to 8 am, from 8 am to 4 pm and from 4 pm to 12 am, respectively. There is a positive association between depression and pain [53], so the NRS of the PSBS is considered to be a potential confounder.

Activities and existential experiences of life (AEDL) score The AEDL is a measurement tool based on the concept of nursing process management [67]. The following 9 aspects are rated on five-level Likert-items (range: 0–4): *resting/sleeping, moving, washing/dressing, eating/drinking, excretion, communicating, finding occupation/finding sense and meaning, safe environment* and *social surroundings*. A total scale value has a range from 0 to 36. Higher values represent a greater limitation and thus a higher need for care and support. On the ward, the AEDL is evaluated once a day. The AEDL is considered to be a confounder because stronger limitations in physical functioning, role functioning and social functioning are significantly correlated with higher anxiety and depression [50].

Psycho-oncological treatment The patients received psychological and psycho-oncological support in the form of psychotherapy, art therapy and animal-assisted therapy. Psychological support can reduce anxiety and

depression [56]. Thus, we used the time spent on psycho-oncological treatment as a confounding variable. Time was used to measure the dose of the interventions because psychotherapy has been shown to have a dose-effect-relationship [68, 69]. The total amount of therapy time in minutes, up to the considered points of measurement, was used to indicate the amount of psychological and psycho-oncological treatment.

Palliative care treatment Patients received a specialized palliative treatment every day of the stay through the synergistic work of all employed professionals. The number of days on the SPCU was used as a measure of the extent of this specialized, inpatient palliative care. Because the synergistic work of all employed professionals including physicians and psychologists may reduce anxiety and depression, the amount of palliative care treatment is considered to be a confounding variable.

Days with antidepressants Because the positive effect of antidepressants on mood depends on the length of intake, the number of days with antidepressants on the SPCU is considered to be a confounder.

Medication Any intake of antidepressants, benzodiazepines or opioids on the points of measurement was considered, regardless of the time of day or whether it was the standard medication or was given on demand. Because the intake of antidepressants, benzodiazepines and opioids may exert an acute effect on mood, these medications are considered to be confounders.

Secondary study outcome variables

To assess whether there is a prolonged positive influence of *S*-ketamine on pain, the NRS of the PSBS was considered as a secondary variable. Restlessness and anxiety were considered as possible psychotomimetic side effects of *S*-ketamine. The combined item restlessness/anxiety is also part of the PSBS which is routinely used in the SPCU. The ordinal scaled item has a range from 0 to 4 with 0 for *no impairment*; 1 for *occasionally impaired - patient can express the cause for restlessness/anxiety*; 2 for *restlessness/anxiety are occurring frequently - care needed*; 3 for *restlessness/anxiety are occurring despite medication,* and 4 for *pronounced restlessness, panic and/or suicidal tendencies*.

Time of assessments

Because STADI was assessed several times a week (but not daily), the time span between STADI measurements was up to 4 days. For the patients requiring *S*-ketamine treatment, the first measurement point (T1) was the last time the STADI was evaluated before *S*-ketamine administration. The second measurement point (T2) was the first STADI evaluation after *S*-ketamine administration. In the control group, T1 was the first STADI evaluation from the second day of the stay, and T2 was the time of the next STADI evaluation. Furthermore, for some analyses, the morning before *S*-ketamine administration (Z1) and the morning after *S*-ketamine administration (Z2) were taken into account. For the control group, Z1 was the morning of T1 and Z2 was the morning of the day after T1. The scores of the first of the three daily evaluations were used for the main analyses using the variables pain and restlessness/anxiety of the PSBS.

Statistical analyses

Data were analyzed using IBM SPSS 25.0 for Macintosh [70]. After recoding negative items of STADI, reliability was calculated for STADI and for AEDL to T1 and T2 using Cronbach's α. Test-retest-reliability was calculated between the scores of the first and second daily evaluation at T2 with Pearson's *r* for pain and Spearman's ρ for restlessness/anxiety. A propensity score was calculated using logistic regression with group membership (*S*-ketamine, control) as the target variable and age and gender as predictor variables. Patients of the control group were matched 1:1 without replacement to the *S*-ketamine group using the nearest neighbor method without a specified caliper width. To measure the balance between the groups, *z*-differences were calculated [71]. Absolute z-differences lower than 1.41 are considered as appropriate [72]. The main analyses were conducted using multivariate and univariate analyses of variance. Target variables were STADI T-values for anxiety and depression as well as psychological distress, i.e. the combination of anxiety and depression. The predictors used for the analyses were: 1) The group membership (group; *S*-ketamine vs. control; between subject factor), 2) The measurement points (time; T1 vs. T2; within subject factor) and 3) The difference between STADI anxiety and depression values (here abbreviated as *anxdep*; anxiety vs. depression; within subject factor). Subsequently, interval scaled confounders were included separately as covariates in an analysis of covariance. Nominal scaled confounders (medication) were included separately as predictors in a multivariate analysis of variance. To determine if there is a difference of medication intake between T1 and T2, thus requiring a separate analysis of both points of measurement in the multivariate analyses of variance, the association of medication intake at T1 and T2 was calculated with the phi (φ) coefficient. In order to analyze the prolonged effect of *S*-ketamine on pain, a univariate analysis of variance was calculated, with pain as a dependent variable, and group membership (group; *S*-ketamine vs. control; between subject factor) and measurement points (time; Z1 vs. Z2;

within subject factor) as predictors. A Wilcoxon signed-rank test was used for comparisons of repeated measures of restlessness/anxiety at Z1 and Z2 as a measure for prolonged psychotomimetic side effects of *S*-ketamine. Assumptions of normal distribution, homogeneity of variance and homogeneity of covariance matrices were tested before analyzing the data via analyses of variance.

Because of the exploratory approach of this study, different hypotheses were tested, while no adjustments for multiple comparisons were made to correct for the familywise error. Considered as significant results for all statistical analyses were $p < 0.05$. Results with $0.05 < p < 0.10$ were regarded as a trend to significance. Effect size r for statistical comparisons were calculated with the following equations [73]:

$$r = \sqrt{\frac{F(1, df_{Residual})}{F(1, df_{Residual}) + df_{Residual}}}$$

and

$$r = \frac{z}{\sqrt{N}}$$

According to Cohen, values of r of 0.1, 0.3 and 0.5 were classified as small, medium and large effect sizes, respectively [74].

Results

Sample description

There were $n = 8$ patients who were treated with *S*-ketamine for refractory pain with sufficient data available. In the control group, seventeen patients with sufficient data at two points in time were included. Two patients with the first STADI evaluation on the day of admission were excluded to prevent the admission procedure from confounding the data. Accordingly, eight patients from the *S*-ketamine group and fifteen patients from the potential control group contribute to the final analyses. The control group was adjusted to the *S*-ketamine group by age and gender, using propensity score matching. The absolute z-difference for age (0.38) and gender (female: 0.51) were below 1.41 and thus appropriate. The sample characteristics are shown in Table 1. Figure 1 shows the changes of the STADI global values from T1 to T2 for the *S*-ketamine group. As can be seen from the trajectories, 5 out of 8 patients improved from a clinical point of view, i.e. their STADI global levels decreased by more than 10 points (Fig. 1).

Descriptively, the *S*-ketamine group differs from the control group in terms of parts of the sample characteristics. More patients from the *S*-ketamine group than patients from the control group died on the ward, indicating that the control group was fitter than the *S*-ketamine group. Furthermore, at T1 the *S*-ketamine group had higher STADI values (STADI > 60) compared to the control group (STADI < 60). The *S*-ketamine group had moderate pain (NRS ≥ 3), compared to the control group, which had mild pain (NRS < 3) at Z1 and Z2. In Fig. 1, the changes of the values of the STADI global scores are more pronounced if T2 is one day after *S*-ketamine treatment rather than 4 days.

The confounding variables: pain, AEDL, psycho-oncological treatment, days with antidepressants, palliative care treatment and medication are shown in Table 2. Moreover, with regard to the confounding variables at T1 and T2, the *S*-ketamine group differs descriptively from the control group. The *S*-ketamine group had moderate pain and the control group had mild pain at both points of measurement. In relation to the AEDL, which represents need for care, the *S*-ketamine group had higher scores at both measurement points than the control group. The *S*-ketamine group made less use of the psycho-oncological treatment than the control group at both points of measurement. With regard to medication, more patients from the *S*-ketamine group took antidepressants at T1 compared to the control group. Furthermore, all patients of the *S*-ketamine group took opioids at both measurement points.

Primary study outcome variables

Cronbach's α for all STADI scales at T1 and T2 was above 0.91 and therefore the reliability was classified as good. Three-way mixed multivariate analyses of variance (MANOVA) were conducted with anxiety and depression as target variables. Predictors were group, time and anxdep. The results are shown in Table 3. Figure 2 shows STADI values of anxiety and depression according to group membership and measurement points. There was a significant interaction between group and time with a medium effect size, caused by the reduction of anxiety and depression, i.e. psychological distress, from T1 to T2 in the *S*-ketamine group. There was no significant interaction between group, time and anxdep, suggesting that there was a similar effect of *S*-ketamine on anxiety and depression in the *S*-ketamine group.

Subsequently conducted two-way mixed analyses of variance (ANOVA) were calculated separately for anxiety and depression using group and time as predictors (Table 4). Regarding anxiety, group-by-time interaction was significant with a large effect size. Pairwise comparison of the changes of the STADI anxiety values showed a significant reduction in the *S*-ketamine group $F(1, 14) = 19.89$; $p = 0.001$; $r = 0.77$ from T1 to T2 but not in the control group $F(1, 14) = 0.002$; $p = 0.97$; $r = 0.01$ (Fig. 2A). There was no significant interaction between group and time regarding depression but there was still a medium effect size (Table 4; Fig. 2B).

Table 1 Sample characteristics of the *S*-ketamine and the control group

Variables	Categories	*S*-ketamine group	Control group
Group size [a]		8	8
Gender [a]	Female	4	5
	Male	4	3
Age [b]		52.13 ± 13.25	54.63 ± 13.23
Diagnosis at admission [a]	Breast cancer	0	3
	Cancer of unknown primary	1	1
	Cervical cancer	1	1
	Glioblastoma	1	0
	Colorectal cancer	1	0
	HIV	1	0
	Liver cancer	0	1
	Lung cancer	2	0
	Ovarian cancer	0	1
	Pancreatic cancer	0	1
	Prostate cancer	1	0
Length of stay in SPCU (days) [b]		14.63 ± 7.69	13.00 ± 3.42
Mode of discharge [a]	Home	0	4
	Hospice	3	1
	Other clinic	0	2
	Died on the ward	5	1
Points of measurement (days) [b]	T1	5.63 ± 2.88	3.38 ± 1.06
	T2	8.00 ± 3.70	7.50 ± 2.45
	Z1	5.88 ± 2.90	3.38 ± 1.06
	Z2	6.88 ± 2.90	4.38 ± 1.06
STADI anxiety [b]	T1	68.88 ± 11.01	57.38 ± 13.38
	T2	55.63 ± 11.73	57.50 ± 12.46
STADI depression [b]	T1	66.38 ± 10.88	59.25 ± 12.51
	T2	57.75 ± 12.75	59.00 ± 13.40
STADI global [b]	T1	68.38 ± 8.80	59.38 ± 13.66
	T2	57.38 ± 11.87	59.00 ± 13.27
Pain [b]	Z1	3.88 ± 1.64	2.88 ± 2.10
	Z2	3.50 ± 1.77	2.75 ± 1.67
Restlessness/anxiety [c]	Z1	1.00 (1.00–1.75)	1.00 (0–1.75)
	Z2	1.00 (1.00–1.00)	1.00 (0–1.75)

[a] = *n*
[b] = *M* ± *SD*
[c] = *Mdn* (*IQR*)

Potential confounding variables of primary outcomes

Test-retest-reliability for pain at T2 showed high correlation ($r = 0.95$; $p < 0.001$; $n = 15$) and Cronbach's α of AEDL at T1 and T2 was above 0.87 and therefore the reliability was classified as good. The confounders pain, AEDL, psycho-oncological treatment, days with antidepressants and palliative care treatment are displayed in Table 2. To consider the influence of these interval-scaled confounders, two-way mixed multivariate analyses of covariance (MANCOVA) were calculated, using anxiety and depression as target variables. The predictors were group and time. Each confounder with its value to T1 and T2 was included separately as a covariate in each analysis. The results of the two-way mixed MANCOVAs are shown in Table 5. There was a significant interaction of group and time, even after taking into account the confounding variables as covariates. In the following two-way mixed analyses of covariance (ANCOVA), there

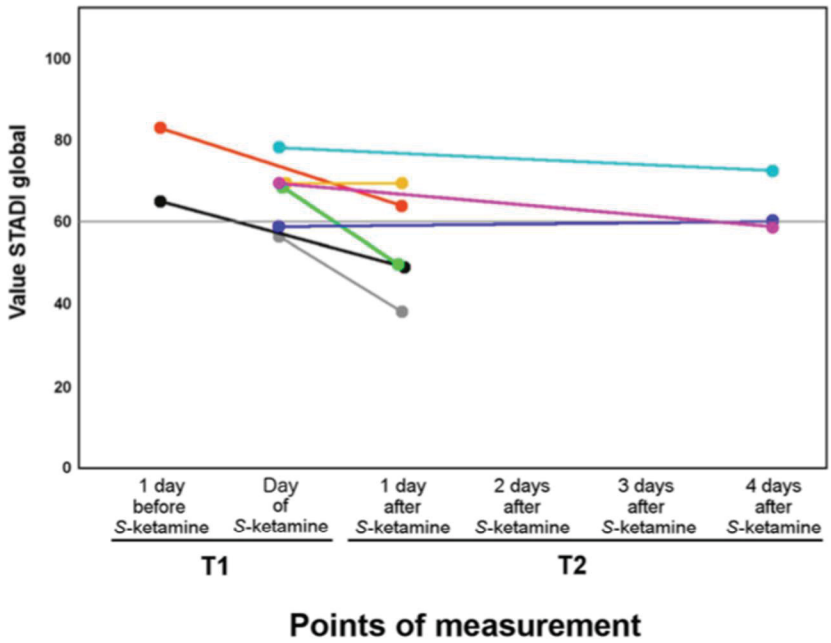

Fig. 1 Changes in the STADI global values of the S-ketamine group from T1 to T2. STADI values were assessed on several days a week and therefore not available 2 to 3 days after S-ketamine application. The circles at the beginning and end of each line are measured data points, while the connecting lines are shown to identify each individual

were significant group-by-time interactions for anxiety with large effect sizes. However, the same kind of ANCOVA for depression was not significant, but had small to medium effect sizes.

The intake of benzodiazepines, antidepressants and opioids is shown in Table 2 according to group and points of measurement. The intake of these medications was considered separately for confounding influences by including these nominal-scaled variables as predictors in the analyses. The analyses were conducted with a three-way mixed MANOVA with anxiety and depression as target variables. The predictors were group, time and medication. The intake of opioids could not be included in these analyses because there were no patients in the *S*-ketamine group who did not take opioids.

To assess whether there is a difference of medication intake between the points of measurement, phi (ϕ) was calculated as a measurement of association of medication intake between T1 and T2. There was a strong and significant relationship between the intake of antidepressants with $\phi(16) = 0.76$; $p = 0.002$ and benzodiazepines with $\phi(16) = 0.59$; $p = 0.018$ on T1 and T2. Because the intake of medication is relatively equivalent at T1 and T2, it did not matter which point of measurement was chosen in the further analyses. Therefore, the intake of benzodiazepines and antidepressants on T1 was used as a between-subject variable in a three-way mixed MANOVA. Target variables were anxiety and depression, and predictor variables were group, time and medication. The results are shown in Table 6. Even after considering the intake of benzodiazepines at T1 as a confounding variable in the three-way mixed MANOVA, there was a significant group-by-time interaction. Furthermore, when controlling for antidepressants there was a tendency for a significant group-by-time interaction. There was no significant interaction between group, time and medication in these analyses, suggesting no discernible association between the intake of benzodiazepines or antidepressants and the improvement of the *S*-ketamine group.

Three-way mixed ANOVAs were calculated for benzodiazepines and for antidepressants. The effect of antidepressants was analyzed with the three-way mixed ANOVA despite the related non-significant group-by-time interaction in the three-way mixed MANOVA. The results are shown in Table 6. These analyses showed significant group-by-time interactions for anxiety with a large effect size. There was also a significant effect of antidepressants intake on T1. This effect is caused because the overall anxiety scores of patients who took antidepressants on T1 ($M = 65.89$; $SD = 10.39$) were higher than those patients who did not take antidepressants on T1 ($M = 52.07$; $SD = 7.16$). For the target variable depression there were no significant group-by-time

Table 2 Confounding variables

Confounder	Points of measurement	S-ketamine group		Control group	
Pain [a]	T1	4.00 ± 1.85		2.88 ± 2.10	
	T2	3.50 ± 1.77		2.88 ± 1.73	
AEDL [a]	T1	14.50 ± 7.69		8.00 ± 4.63	
	T2	15.88 ± 7.70		9.38 ± 5.24	
Psycho-oncological treatment (minutes) [a]	T1	53.75 ± 55.92		72.00 ± 60.47	
	T2	68.75 ± 68.86		124.50 ± 90.17	
Days with antidepressants [a]	T1	2.38 ± 2.97		1.25 ± 1.83	
	T2	3.88 ± 4.12		2.88 ± 3.31	
Palliative care treatment (days) [a]	T1	5.63 ± 2.88		3.38 ± 1.06	
	T2	8.00 ± 3.70		7.50 ± 2.45	
Benzodiazepines [b]	T1	yes	6	yes	5
		no	2	no	3
	T2	yes	6	yes	4
		no	2	no	4
Antidepressants [b]	T1	yes	6	yes	3
		no	2	no	5
	T2	yes	6	yes	5
		no	2	no	3
Opioids [b]	T1	yes	8	yes	7
		no	0	no	1
	T2	yes	8	yes	7
		no	0	no	1

[a] = $M \pm SD$
[b] = n

interactions. These analyses showed small effect sizes. There was no significant interaction between group, time and medication for either of the target variables.

Secondary study outcome variables

Test-retest-reliability for restlessness/anxiety at T2 showed high correlation ($\rho = 0.92$; $p < 0.001$; $n = 15$) and was therefore classified as good. The item restlessness/anxiety was considered to be a measure of persistent psychotomimetic side effects of *S*-ketamine. Possible changes in restlessness/anxiety, from the morning before *S*-ketamine administration to the morning after, were analyzed with the Wilcoxon Signed Rank Test. The predictor variables were the measurement points Z1 and Z2. There were no significant changes in restlessness/anxiety $T = 0$; $z = -1.00$; $p = 0.32$; $r = -0.35$ from Z1 to Z2. Thus, we found no evidence for a persistent psychotomimetic effect of *S*-ketamine.

The change in pain from Z1 to Z2 was analyzed between the groups using a two-way mixed ANOVA. The predictor variables were time and group. There was no significant interaction between group and time $F(1, 14) = 0.11$; $p = 0.75$; $r = 0.09$. This means that regarding

Table 3 Three-way mixed MANOVA; target variables: anxiety, depression; predictor variables: group, time and anxdep

		Test statistics	Significance 2-tailed	Effect size
STADI scales	Effect	$F(1, 14)$	p	r
Anxiety and depression	Group	0.60	0.45	0.20
	Anxdep	0.11	0.75	0.09
	Group x anxdep	0.17	0.69	0.11
	Time	4.89	**0.044***	0.51
	Group x time	4.78	**0.046***	0.50
	Anxdep x time	0.76	0.40	0.23
	Group x anxdep x time	1.05	0.32	0.26

*p: statistical significance $p < 0.05$

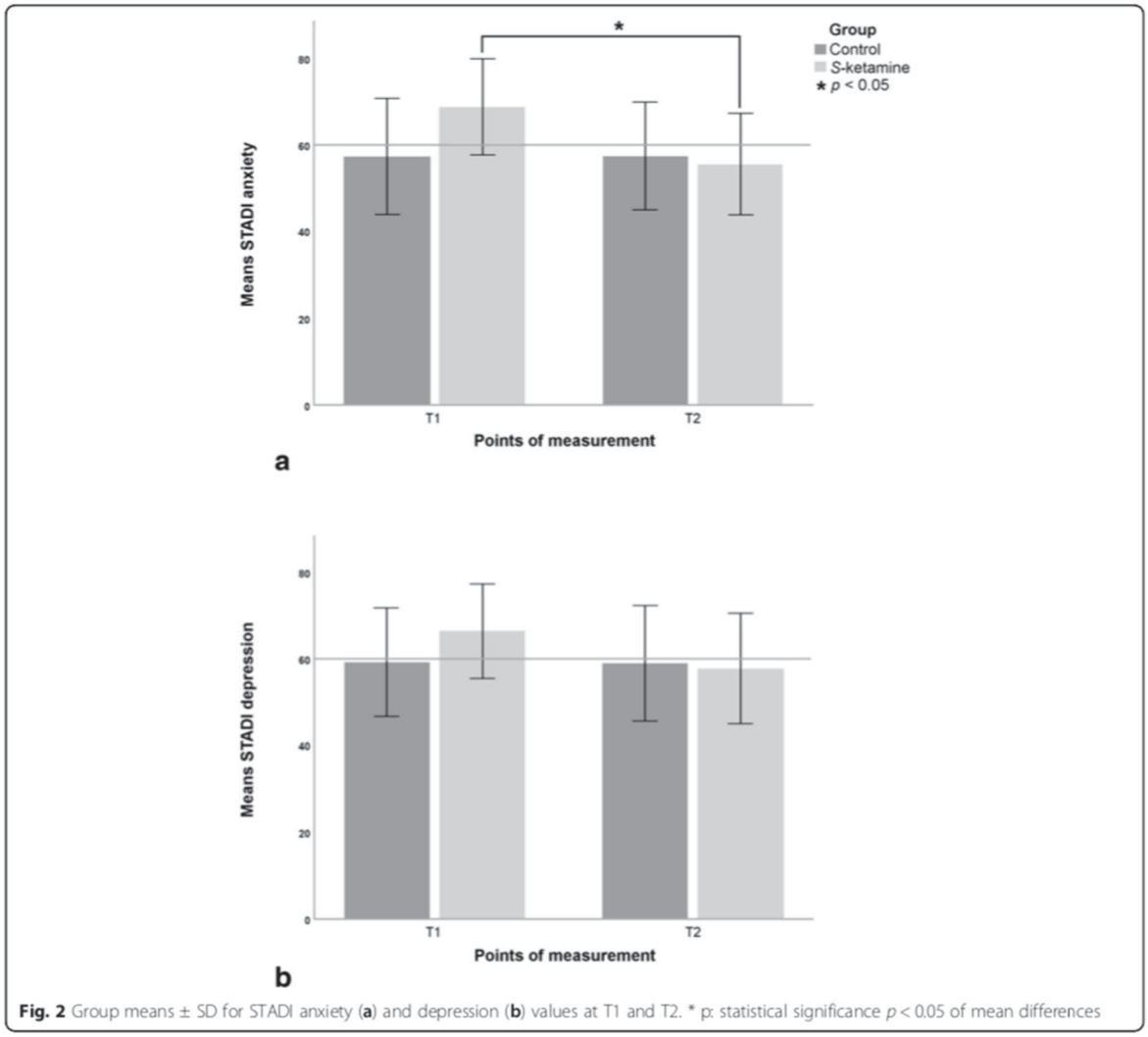

Fig. 2 Group means ± SD for STADI anxiety (**a**) and depression (**b**) values at T1 and T2. * p: statistical significance $p < 0.05$ of mean differences

Table 4 Two-way mixed ANOVA; target variables: anxiety and depression; predictor variables: group and time

		Test statistics	Significance 2-tailed	Effect size
STADI scale	Effect	*F*(1, 14)	*p*	*r*
Anxiety	Group	0.71	0.41	0.22
	Time	9.76	**0.007***	0.64
	Group x time	10.14	**0.007***	0.65
Depression	Group	0.31	0.59	0.15
	Time	1.80	0.20	0.34
	Group x time	1.60	0.23	0.32

*p: statistical significance $p < 0.05$

pain, the changes in the *S*-ketamine group from Z1 to Z2 were not significantly different from those of the control group of Z1 to Z2. Thus, we found no evidence of a prolonged analgesic effect of *S*-ketamine.

What influence does the psychological distress at T1 have on the results? Descriptively, the *S*-ketamine and the control group differed according to the STADI values of anxiety and depression at T1. To adjust these STADI scale values, and thus make the groups more comparable, an alternative propensity score matching strategy was used, i.e. with STADI global score at T1, together with age and gender (see Additional files). Using this alternative matching strategy, we had STADI values of over 60 at T1 as well as for the control group (Additional file 1: Table S1; Additional file 7: Figure S1). Even with this matching, a significant effect of *S*-ketamine on

Table 5 Two-way mixed MANCOVA (multivariate) and two-way mixed ANCOVA (univariate) with confounders as covariates

		Multivariate		Univariate					
		Anxiety & depression		Anxiety			Depression		
Covariates at T1 and T2		Test statistics	Sig. 2-tailed	Test statistics	Sig. 2-tailed	Effect size	Test statistics	Sig. 2-tailed	Effect size
	Effect	*F*(2, 12)	*p*	*F*(1, 13)	*p*	*r*	*F*(1, 13)	*p*	*r*
Pain	Group	0.23	0.79	0.49	0.50	0.19	0.32	0.58	0.15
	Time	4.90	**0.028***	8.79	**0.011***	0.64	1.73	0.21	0.34
	Group x time	5.31	**0.022***	9.15	**0.010***	0.64	1.54	0.24	0.33
AEDL	Group	0.21	0.81	0.09	0.77	0.08	0.08	0.78	0.08
	Time	3.44	**0.066**$^{+}$	7.20	**0.019***	0.60	2.61	0.13	0.41
	Group x time	5.32	**0.022***	9.48	**0.009***	0.65	1.60	0.23	0.33
Psychooncological treatment (minutes)	Group	0.67	0.53	1.45	0.25	0.32	0.48	0.50	0.19
	Time	7.77	**0.007***	16.76	**0.001***	0.75	4.60	**0.051**$^{+}$	0.51
	Group x time	4.27	**0.040***	8.22	**0.013***	0.62	0.68	0.43	0.22
Days with antidepressants	Group	0.10	0.91	0.22	0.65	0.13	0.10	0.76	0.09
	Time	2.43	0.13	4.48	**0.054**$^{+}$	0.51	0.61	0.45	0.21
	Group x time	4.95	**0.027***	9.39	**0.009***	0.65	1.51	0.24	0.32
Palliative care treatment (days)	Group	0.15	0.86	0.32	0.58	0.15	0.18	0.68	0.12
	Time	2.66	0.11	4.71	**0.049***	0.52	4.95	**0.044***	0.53
	Group x time	4.41	**0.037***	6.89	**0.021***	0.59	0.33	0.58	0.16

*p: statistical significance $p < 0.05$
^{+}p: trend to statistical significance: $0.05 < p < 0.10$

anxiety remained in the ANOVA and ANCOVA (Additional file 2: Table S2, Additional file 3: Table S3, Additional file 4: Table S4, Additional file 5: Table S5, Additional file 6: Table S6 and Additional file 7: Figure S1a).

Discussion

This retrospective pilot study provides the first evidence of a positive effect of *S*-ketamine on the psychological distress of patients in palliative care. We find a multivariate effect on depression and anxiety with a primary effect on anxiety. Our result corresponds to earlier studies showing that ketamine racemate shows similar effects in patients in palliative care [59, 60, 75]. To our knowledge, the effect of the purified enantiomer *S*-ketamine on patients in palliative care has not been analysed previously. *S*-ketamine is reported to have a positive effect on anxiety in surgical patients without palliative diagnosis [29], and has recently been approved as nasal spray by the FDA – but only when used in conjunction with an oral antidepressant and only for the therapy of treatment-resistant depression [45]. We hope that for patients with a life-limiting disease, *S*-ketamine can be useful outside the FDA approval. This study may be a first step towards the approval to treat anxiety of patients in palliative care with *S*-ketamine.

The positive effect of *S*-ketamine was mainly on anxiety with no significant effect on depression. The influence of *S*-ketamine on anxiety had consistently large effect sizes. Our data indicate that S-ketamine treatment may be effective in routine clinical practice. In our study, *S*-ketamine reduced the global STADI values by a clinically relevant level in 5 out of 8 patients (Fig. 1). Thus, we estimate the number needed to treat is approximately 2. Further studies are needed to establish the effectiveness.

The influence of *S*-ketamine on depression showed mainly medium effect sizes. The significant effect with a large effect size of *S*-ketamine on psychological distress was mainly caused by the reduction in anxiety. However, the analyses also showed that the changes in anxiety and depression due to *S*-ketamine were similar. Thus, *S*-ketamine had an analogical effect on anxiety and depression. Even after taking the confounding variables into account, the significant effect on anxiety remained. There was also no evidence of persistent psychotomimetic side effects in the *S*-ketamine group until the next morning. Furthermore, there were no indications of a sustained pain

Table 6 Three-way mixed MANOVA (multivariate) and three-way mixed ANOVA (univariate) analysis of the effect of medication

		Multivariate		Univariate					
		Anxiety & depression		Anxiety			Depression		
		Test statistics	Sig. 2-tailed	Test statistics	Sig. 2-tailed	Effect size	Test statistics	Sig. 2-tailed	Effect size
Med.	Effect	$F(2, 11)$	p	$F(1, 12)$	p	r	$F(1, 12)$	p	r
B T1	Group	0.59	0.57	0.92	0.36	0.27	0.05	0.83	0.06
	Time	3.23	**0.079**$^{+}$	5.96	**0.031***	0.58	0.95	0.35	0.27
	B T1	0.94	0.42	0.19	0.68	0.12	1.65	0.22	0.35
	Group x B T1	0.87	0.45	0.54	0.48	0.21	0.11	0.74	0.10
	Time x B T1	0.18	0.84	0.33	0.58	0.16	0.04	0.84	0.06
	Group x time	4.28	**0.042***	6.71	**0.024***	0.60	0.44	0.52	0.19
	Group x time x B T1	0.99	0.40	0.03	0.86	0.05	1.35	0.27	0.32
A T1	Group	0.01	0.99	0.01	0.91	0.03	0.02	0.90	0.04
	Time	2.95	**0.094**$^{+}$	6.24	**0.028***	0.58	2.14	0.17	0.39
	A T1	3.17	**0.082**$^{+}$	6.80	**0.023***	0.60	1.53	0.24	0.34
	Group x A T1	0.70	0.52	1.52	0.24	0.34	0.41	0.54	0.18
	Time x A T1	0.57	0.58	1.21	0.29	0.30	0.46	0.51	0.19
	Group x time	3.03	**0.090**$^{+}$	5.62	**0.035***	0.56	0.99	0.34	0.28
	Group x time x A T1	1.41	0.29	0.15	0.71	0.11	0.86	0.37	0.26

Med.: Medication
B T1: Benzodiazepines at T1
A T1: Antidepressants at T1
*p: statistical significance $p < 0.05$
^{+}p: trend to statistical significance: $0.05 < p < 0.10$

reduction by *S*-ketamine until the next morning in the group comparison.

The pronounced effect of *S*-ketamine on the anxiety of patients in palliative care may be related to the peculiarities of this group of patients. In a case report on two hospice patients receiving a single dose of ketamine racemate (0.50 mg/kg bolus per os) to treat psychological distress, there was a positive effect on anxiety and depression, with a more pronounced reduction in anxiety over the first four days [60]. In addition, both patients experienced an improvement in pain perception with a maximum of four and eight days after ketamine administration. In a feasibility study, the effect of daily oral administrations over 28 days of ketamine racemate (0.50 mg/kg bolus per os) on anxiety and depression was investigated [75]. There was a significant response (reduction of questionnaire scores > 30%) of anxiety to ketamine racemate after three days with a medium effect size (d = 0.67). For depression, there was a significant response after 14 days with a large effect size (d = 1.14). After 28 days a significant effect was sustained with large effect sizes for anxiety (d = 1.34) and depression (d = 1.34). However, pain was unchanged [75].

The results of our work and the two hospice studies suggest that *S*-ketamine and ketamine racemate act primarily on anxiety in patients with a life-limiting disease. Whether this is a special pattern of action in these group of patients requires further clarification.

In our study, a positive effect of *S*-ketamine on depression could not be identified in the group comparisons. However, the initial univariate group comparison (Table 4) found a medium effect size (r = 0.32) for depression. A post-hoc sample size calculation with G*Power 3.1 [76, 77] showed that a total of n = 20 patients would be necessary to determine a significant effect on depression for a group-by-time interaction in a two-way mixed ANOVA. Thus, according to our data, a prospective study would need 20 patients or more.

In this study, the descriptive interpretation of the data suggests that more patients in the *S*-ketamine group than in the control group died on the ward (Table 1). A causal relationship to *S*-ketamine is not plausible for the following reasons: In general, about 60% of the inpatients in the SPCU die on the ward [78]. Thus, the mortality of the *S*-ketamine group can be considered average. Furthermore, a study by Irwin et al. [75] showed that daily oral administrations of ketamine racemate for 28 days led to no serious adverse events. There were no changes in vital signs (blood pressure, heart rate and respiratory rate) during the course of their study. A mild increase of symptoms in 12.5% of patients were related to diarrhea, sleeping problems and restlessness. In addition, the patients showed a decrease in symptom burden related to gastrointestinal, neurological and psychiatric symptoms. Further studies on the effect of ketamine racemate on the mental health of hospice patients [59, 60] and of psychiatric patients [79] also report a low

rate of adverse events. The most frequent adverse events in patients receiving ketamine racemate (0.50 mg/kg over 40 min i. v.) as a therapy of treatment resistant depression were drowsiness, dizziness, poor coordination and a strange or unreal feeling [79]. These symptoms were mostly experienced in the first two hours after the beginning of the infusion, diminishing after four hours and practically ceasing after 24 h.

A descriptive synopsis of the data collected in this study suggests that the *S*-ketamine group was a group of patients with a higher symptom burden than the control group. The *S*-ketamine group showed, at T1, STADI T-values over the critical limit of 60. In addition, the *S*-ketamine group reported moderate pain at both time points. Furthermore, the *S*-ketamine group showed, at both points of measurement, a need for more care than the control group (as indicated by the AEDL score). On average, the *S*-ketamine group also had less psycho-oncological treatment. It is plausible that the reduced physical status of the *S*-ketamine group, which was manifested in increased need for care and increased mortality on the ward, reduced the possibility of participating in psycho-oncological interventions.

Limitations

The limitations of this study results from its retrospective design, which prevented randomization. Because of the retrospective design, the data is not optimal to measure the effect of *S*-ketamine. The best interval to measure the maximum effects of ketamine or *S*-ketamine is one day after administration of ketamine or *S*-ketamine. In our study, there were several days between T1 and T2 in the *S*-ketamine group (Fig. 1), which may have reduced the measured effect of *S*-ketamine on anxiety and depression. However, the obtained data (Fig. 1) showed a stronger reduction of psychological distress caused by anxiety and depression one day after *S*-ketamine administration than four days after *S*-ketamine administration. Thus, these data are consistent with the time course of the effect of ketamine [80]. Furthermore, the retrospective approach does not allow an evaluation of how the patients have perceived the effects of *S*-ketamine and how they assess the benefits and risks related to *S*-ketamine treatment. Non-randomization can lead to systematic bias. In this study, the group membership was systematic, because only the patients suffering from refractory pain received *S*-ketamine. In this context, additional patient data indicates that the *S*-ketamine group was a patient population with a higher symptom burden. Thus, the patients in the *S*-ketamine group, who suffered from refractory pain, still had other physical and psychological symptoms, which distinguished them from patients in the control group. The STADI scores for anxiety and depression were significantly higher in the *S*-ketamine group than in the control group at T1. To minimize statistical errors arising from the selection of the control group, we generated another control group. This alternative matching strategy takes psychological distress into account. Still, when using the alternative matching strategy, our results on the effect of *S*-ketamine are essentially the same (see Additional files). To avoid other statistical errors, we calculated Cronbach's alpha and test-retest-reliability to ensure good reliability of our instruments. For the analyses of variance, we ensured that all assumptions of normal distribution, homogeneity of variance and homogeneity of covariance matrices were met.

A further limitation of our study is the non-randomization and the small sample size, which makes it difficult to generalize the data. Despite this limitation, our results provide the basis for prospective studies, which will be needed as soon as *S*-ketamine is approved as nasal spray by the European Medicines Agency and other regulators around the world. Subsequent studies will provide an empirical basis for the treatment of anxiety and depression with *S*-ketamine of patients in palliative care. The first step would be prospective feasibility studies, including qualitative data if sample size is expected to be low. Further studies could include double-blinded, randomized and placebo-controlled trials. During the course of these studies, the questions on the pattern of effects, the optimal forms of application and the choice of medication *S*-enantiomer vs. racemate should be considered.

Conclusions

The results of this retrospective study indicate a rapid positive influence of *S*-ketamine, primarily on anxiety. Patients who suffer from severe psychological distress may benefit from the positive effects of *S*-ketamine. The results are consistent with existing data related to ketamine and its effect on psychological distress. The rapid onset of *S*-ketamine action, as well as its anxiolytic and possible anti-depressant effects, can significantly improve the palliative care of patients. This study is limited due to non-randomization, retrospective design, and low sample size. Thus, there is a need for further studies.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12904-019-0499-1.

Additional file 1: Table S1. Sample characteristics of the S-ketamine group and the control group.

Additional file 2: Table S2. Confounding variables.

Additional file 3: Table S3. Three-way mixed MANOVA; target variables: anxiety, depression; predictor variables: group, time and anxiety/depression (anxdep).

Additional file 4: Table S4. Two-way mixed ANOVA; target variables: anxiety and depression; predictor variables: group and time.

Additional file 5: Table S5. Two-way mixed MANCOVA (multivariate) and two-way mixed ANCOVA (univariate) with confounders as covariates.

Additional file 6: Table S6. Three-way mixed MANOVA (multivariate); three-way mixed ANOVA (univariate).

Additional file 7: Figure S1. Group means ± SD for STADI anxiety (A) and depression (B) values at T1 and T2.

Abbreviations

A T1: Antidepressants at T1; AEDL: Activities and existential experiences of life; ANCOVA: Univariate analysis of covariance; ANOVA: Univariate analysis of variance; Anxdep: Anxiety vs. depression; B T1: Benzodiazepines at T1; FDA: The United States Food and drug administration; MANCOVA: Multivariate analysis of covariance; MANOVA: Multivariate analysis of variance; NRS: Numerical rating scale (for pain); PSBS: Palliative symptom burden score; SPCU: Specialized palliative care unit; STADI: State trait anxiety depression inventory; T: T-values as standard score; T1: day of the last STADI evaluation before *S*-ketamine (control group: day of the first STADI evaluation from the second day of the stay); T2: day of the first STADI evaluation after *S*-ketamine (control group: day of the next STADI evaluation after T1); Z1: PSBS evaluation on the morning before *S*-ketamine (control group: PSBS evaluation on the morning of T1); Z2: PSBS evaluation on the morning after *S*-ketamine (control group: PSBS evaluation on the morning of the day after T1)

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Authors' contributions

E. F., M. N., J. S., J. C. and P. K. designed the project. E. F., P. v. C., M. L. and M. N. extracted the data. E. F., I. G., D. S. and M. N. analyzed the data. All authors wrote the article. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study received a positive ethics approval from the Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf, Germany (Study-ID: 6021R; 25 July 2017). An amendment for the inclusion of a control group and confounding variables received a positive ethics approval on 20 February 2018. The data for the retrospective analysis were clinical routine data, which were anonymized at the point of data acquisition. The need for individual consent to participate was waived by the Ethics Committee. This study was obtained according to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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