Travmatik Beyin Hasarı ve Ketamin Kullanımı

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SENİ
UYUTACAZ

Ketamin

- 1962 yılında Stevens tarafından bulunmuş olup insanlarda ilk kullanımı 1965 yılındadır.
- Diğer anestezik ilaçlardan önemli farkı, solunum ve kardiyovasküler sistemleri deprese etmemesidir.
- Fakat psikolojik yan etkileri mevcuttur.
- Hiperaljezik ve opiat etkisi sebebiyle kronik ağrı tedavisinde, nöroprotektif etkisi sebebiyle de anestezide kullanımı artmaktadır.

Nöroproteksiyon

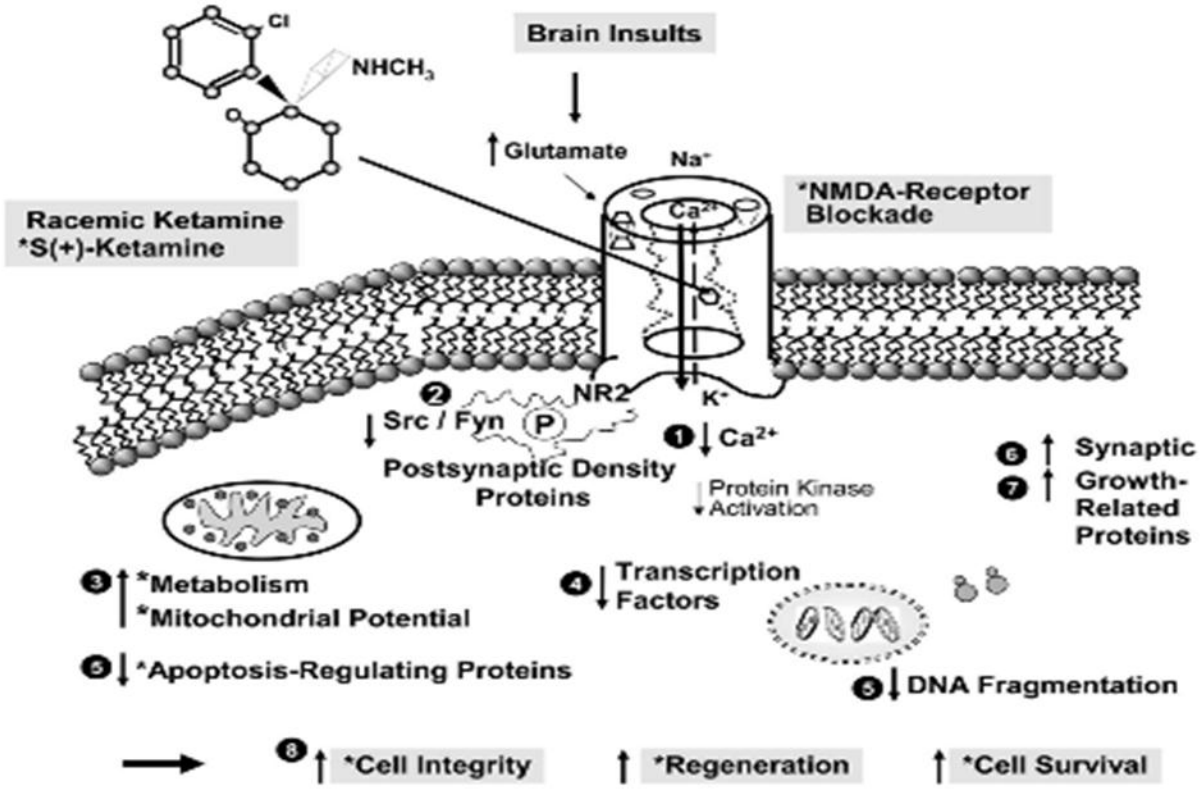

Figure 1. Pharmacological effects reported for racemic and *S*(+)-ketamine which are presumed to be relevant for neuroprotection. After onset of brain injury, blockade of excessive stimulation of *N*-methyl-D-aspartate (NMDA) receptors by ketamine reduces calcium influx through the receptor channel ①. This attenuates supraphysiological increases in the assembly and interaction of NMDA receptor subunits, postsynaptic density proteins, and other intracellular signaling systems such as protein kinases ②;. Thus, several kinase transduction cascades become less activated. This improves preservation of metabolism and maintenance of the mitochondrial transmembrane potential ③. This, in turn, reduces pathological activation of transcription factors ④. Proteins involved in apoptosis are less activated, which is associated with less DNA fragmentation ⑤. A better preservation of synaptic proteins occurs, and the expression of growth proteins indicating regeneration in adult neurons is enhanced. The prevention of pathological amplification of NMDA receptor signaling finally results in increased cellular survival, preserved cellular and synaptic integrity, and regenerative efforts. *Superiority of/effects induced by *S*(+)-ketamine, only.

Ketamin

- KC’de metabolize olur.
- Glukuronid türevleri ile birleşerek idrarla atılır.
- En önemli metaboliti norketamindir.
- Norketaminin analjezi etkisini uzattığı ön görülmüştür.

Ketamin

- İki izomeri mevcuttur. (S+, R-)
- S+ izomeri R- izomerine göre daha fazla elimine olup daha fazla etki göstererek EEG'yi daha fazla baskılamaktadır.
- Ketaminin iv kullanımına ek olarak im, transkutaneal, oral (%20-30 etki) ve intranazal (%40-50 etki) kullanımları da mevcuttur.

- Ketaminin,

  - düşük molekül ağırlıklı,
  - fizyolojik pH’a yakın,
  - yağda çözünürlüğünün yüksek,
  - kan beyin bariyerini hızlı geçmesi,
  - etkisini kısa sürede göstermesi önemli özellikleridir.

Ketamin

- Santral Sinir Sistemi
  - Ketamin disosiyatif anestezi yapan bir intravenöz anestezik ajandır. Hastaların derin analjezi etkisinde olduğu fakat gözlerini açık tuttuğu ve birçok refleksini (kornea, öksürme, yutkunma, öğürme) sürdürdüğü görülmüştür.

  - Talamokortikal sistemin depresyonu, limbik sistemin aktivasyonu sonucu beynin bu iki bölgesi disosiye olmakta (ayrılmakta), katalepsi, hafif sedasyon, amnezi ve analjezi ile karakterize bu tabloya da disosiyatif anestezi denmektedir.


Genel anesteziye gerek yoktu, lokal yaptık. Sadece dilini uyuşturduk.
Çığlık atıp bağırma diye.

Ketamin

- Santral Sinir Sistemi
  - Pupilleri dilate eder ve nistagmus oluşturabilir.
  - Göz yaşı ve tükrük salgılanmasını artırır.
  - İskelet kas tonusu artırır.
  - Nosiseptif (ağrı ve acı verici uyartıya duyarlı; bu nitelikte uyartıyı alma ve iletme yeteneğine sahip) santral sensitizasyonu baskılar.
  - Ketamin dozu ile SSS etki süresi doğru orantılıdır.
  - Benzodiazepinler, ketaminlerin etki süresini artırır.
  - Opiat kullanımından sonra akut toleransı azalır.

Ketamin

- Santral Sinir Sistemi
  - Etkilerini opiat benzeri ve NMDA reseptörleri üzerinden gösterir.
  - Yan etkilerinde Naloxan kullanılabilir.

Ketamin

- Ketamin kullanımı sonucu istenmeyen psikolojik reaksiyonlar ortaya çıkabilir.
- Bunlar çeşitlilik göstermekle birlikte en sık görülenleri;
  - Canlı rüyalar
  - İlizyonlar
- Bu yan etkiler yaşa (yaşlılar ↓), doza (yüksek doz ↑), cinsiyete (erkeklerde ↓) göre değişebilir.
- Yan etkileri için benzodiazepinler (midazolam, lorazepam, diazepam) kullanılabilir.

Ketamin

- Solunum Sistemi
  - Minimal etki gösterir.
  - İndüksiyon dozunun (2mg/kg) bolus şekilde verilmesi sonucu solunum sayısını azaltır. Çocuklarda görülme sıklığı daha fazladır.
  - Yüksek dozlarda kullanımı nadiren apneye sebep olabilir.

Ketamin

- Solunum Sistemi
  - Bronşial kasları gevşetir.
  - Bu etkisini sempatomimetik üzerinden gösterir.
  - Bronkospazımda pulmoner kompliyansı artırır.
  - Bronkodilatasyon etkisi sebebiyle astım tedavisinde kullanılabilir (Bu konuda tartışmalı diğer bir durum).

Ketamin

- Solunum Sistemi
  - Tükrük salgısını artırdığı için özellikle çocuklarda hava yolu obstrüksiyonlarına bunun sonucunda da laryngospazma yol açabilir.

Ketamin

- Kardiyovasküler Sistem
  - Ketamin kan basıncını, nabızı, kardiyak outputu artırır.
  - Hemodinamik değişiklikler ketamin dozuyla ilişkili değildir.
  - Pulmoner arter basınç artışına sebep olabilir.
  - Negatif inotropik etki gösterebilir.

Ketamin

- Kardiyovasküler Sistem
  - Ketamin kullanımı sonuncu taşikardi ve hipertansiyon gelişebilir.
  - Benzodiazepinler, inhale anestezikler ve propofol ketaminin bu etkilerini azaltır.

Ketamin

- Ketamin anestezik amaçlı premedikasyonda, sedasyonda, indüksiyonda ve ağrı tedavisinde kullanılabilir.

- Ketaminin,
  - solunum ve kardiyovasküler sistem hastalığı olanlarda,
  - hipovolemi veya kardiomyopati sonucu hemodinamisi kötü olanlarda yan etkisi çok azdır.

Ketamin

- Kan kaybının eşlik ettiği travmalarda,
- Septik şokta,
- Kardiyak tamponatda,
- Perikarditte,
- Konjenital kalp hastalıklarında (sağdan sola şantı olanlarda)
- Malign hipertermide kullanılabilir

Ketamin

- Ketaminin; propofol veya midazolam ile birlikte kullanılması valvular veya iskemik kalp hastalarında kardiyak etki süresini artırır.

- Ketaminin, benzodiazepam veya sufentanil ile kullanımıyla da yan etkileri olan taşikardi, hipertansiyon ve psikolojik dengesizlikleri önlenebilir.

Ketamin

- Ketamin çocuklarda sedasyon amaçlı kullanılabilir.
- Özellikle; kardiyak katerizasyonda, radyoterapide, radyolojik çalışmalarda, kıyafet değiştirme ve diş ile ilgili işlemlerde.

Ketamin

- Genel anestezi indüksiyonu
  - İv: 0.5-2 mg/kg
  - İm: 4-6 mg/kg
- Genel anestezi idamesi
  - İv: 0.5-1 mg/kg, 15-45 µg/kg/dk
- Sedasyon ve analjezi
  - İv: 0.2-0.8 mg/kg
  - İm: 2-4 mg/kg
- Engelleyici analjezi
  - İv: 0.15-0.25 mg/kg

Ketamin

- Yan etkileri
  - Kafa içi basıncı artırır (Prospektif bilgisi ve FDA halen uyarıyor).
  - Solunum apnesi yapabilir.
  - Glokoma sebep olabilir.
  - HT
  - Taşikardi
  - Psikiyatrik hastalıkları (şizofren, deliryum) indükleyebilir.
  - Nörotoksik etkisinden dolayı (klorobutanol) subaraknoid ve epidural kanamalarda kontrendikedir.

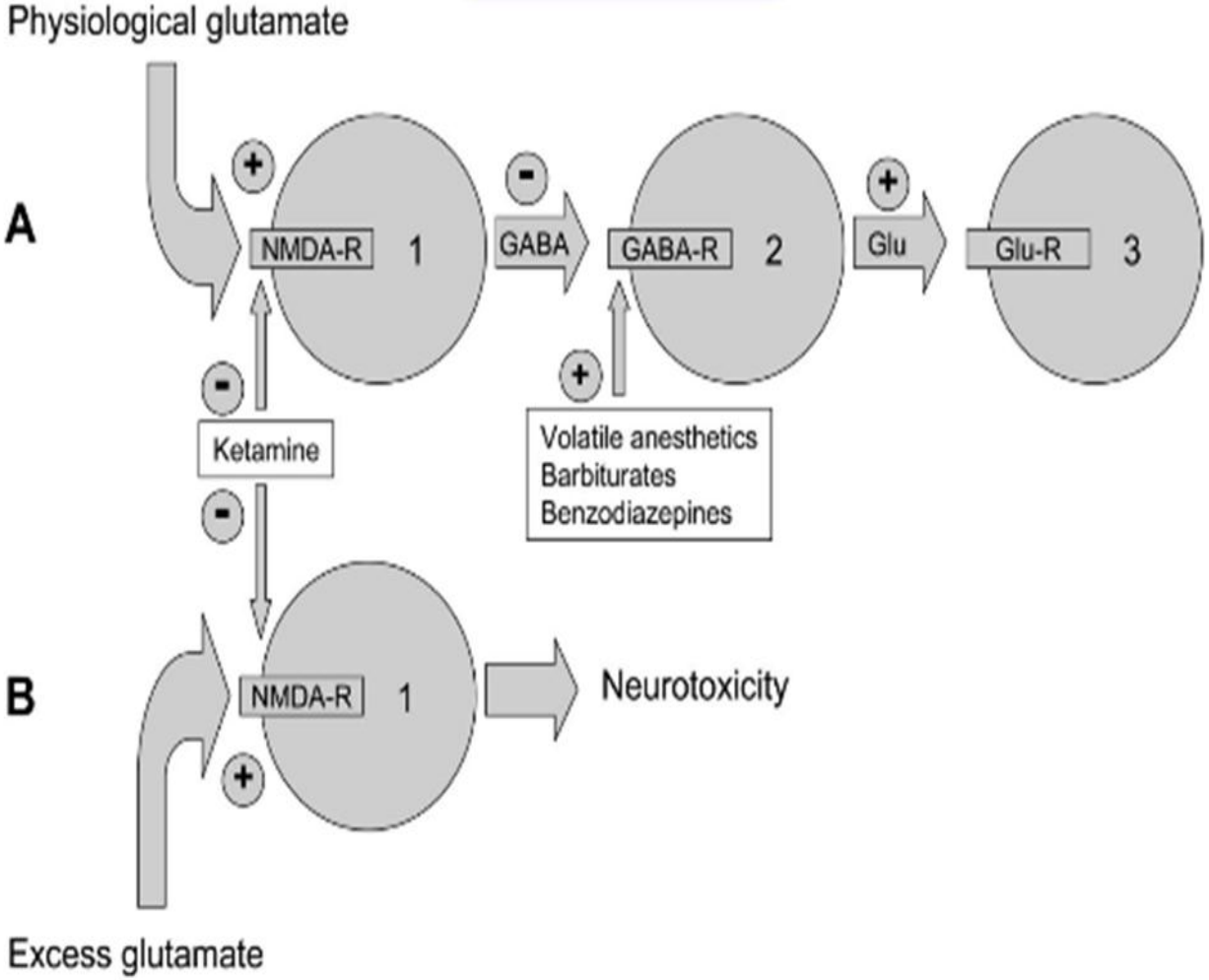

Figure 2. Because of the requirement for physiological glutamate signaling, and the toxic effects of excessive glutamate signaling, *N*-methyl-D-aspartate (NMDA) receptor block by ketamine can have both beneficial and detrimental effects. The toxic effects can be prevented by a γ-aminobutyric acid (GABA) receptor agonist, as explained: A, the physiological glutamate signaling pathway is shown. Stimulation of cell 1 with glutamate results in release of GABA. This inhibits cell 2, and as a result, cell 3 is exposed to a limited amount of glutamate, only. In the presence of ketamine, the inhibition of cell 2 by GABA is diminished. The result is an overexcitation of cell 3, and resulting damage, as observed in retrosplenial cortex and cingulate gyrus in adult rats exposed to ketamine. The detrimental effect can be blocked by administration of exogenous GABA agonists (volatile anesthetics, barbiturates, or benzodiazepines), which will prevent glutamate secretion from cell 2. B, Toxic glutamate signaling is shown. An excess glutamate, acting through NMDA receptor, induces cellular toxicity. This effect is blocked by ketamine. NMDA-R – NMDA receptor, GABA-R – GABA receptor, Glu – glutamate, Glu-R – glutamate receptor, + – stimulating effect, − – inhibiting effect.

Travmatik Beyin Yaralanmaları

- TBY, önemli bir mortalite ve morbidite nedeni olmaya devam etmaktedir.
- USA'da, her yıl 1.4 milyon insanın travmatik beyin yaralanmasına maruz kaldığı düşünülmektedir.
- Genellikle künt (motorlu taşıt kazaları, düşmeler) ya da penetran (delici-kesici alet, ateşli silah gibi) yaralanmalarla etkilenmektedir.

- ATLS’ye göre;

- 13-15 Hafif TBY
- 9-12 Orta TBY
- 3-8 Ciddi/Ağır TBY

- Hafif TBY'lerde ana tedavi gözlemdir.
- Ancak orta ve ağır TBY'larında primer ve sekonder hasarın önlenmesine yönelik tedaviler tanı süreci ile bir arada olmak zorundadır (Hipoksemi, hipotansiyon, artmış ICP ve azalmış serebral perfüzyon).
- Ağır TBY ve hipotansiyonun bir arada olduğu olgularda mortalitede önemli artışlar bildirilmiştir.
- Ayrıca artmış ICP ve nöbetler de sekonder beyin hasarında artışa neden olabilmektedir.

Hangi sedoanaljezik ilaç daha etkili? Tekli mi tercih edelim kombine mi kullanalım?

	İCP	Antikonvülzan
Thiopental	↓↓	↓↓
Methohexital	↓↓	↓↓
Propofol	↓↓	↓↓
Ketamin	=/↑	(↓)
Midazolam	↓	↓↓
Opioide	=/↓	=
Succinylcholin	↑	=
Nichtdepolarisierende Relaxanzien	=	=

- Ketamin için en çok üzerinde durulan konu ICP artışıdır.
- Doğal olarak TBY hastalarında kullanılması noktasında çeşitli tereddütler mevcuttur.
- Literatür incelendiğinde günümüze kadar olan çalışmalarda farklı sonuçlar elde edilmiştir.

Table 1. Cerebral Hemodynamic Effects of Ketamine in Human

Reference	Quality score	Size/study group	Dose, ketamine	Hemodynamics ↑ increase, ↓ decrease, ↔ no change	Study setting/ intracranial compliance	Concomitant medication	Ventilation
Mayberg et al. (11) 1995	NA	20 Ket	1 mg/kg bolus, racemic	↔ MAP, CPP, $AVDO_2$ ↓ VMCA, ICP	Neurosurgical patients, mildly raised ICP	Isoflurane anesthesia with N_2O	Controlled, normoventilation
Strebel et al. (12) 1995	3	6/6/6/6 Ket/ C/Mid/ Esm	2 mg/kg bolus, racemic	↑ VMCA and ↑ MAP ↓ VMCA and ↔ MAP ↑ VMCA and ↓ MAP	Neurosurgical patients, no cerebral compromise	Isoflurane anesthesia + 0.1 kg/mg midazolam, or 5 mg esmolol boli	Controlled, normoventilation
Kolenda et al. (16) 1996	5	16/17 Ket/ Fen	65 mg/kg/d racemic, cont. infusion	↑ MAP and CPP, compared to fentanyl	Head-injured patients, ICU/ increased ICP	6.5 mg/kg/d midazolam, cont. infusion	Controlled, normoventilation
Albanese et al. (17) 1997	NA	8 Ket	1, 3, 5 mg/kg racemic, bolus	↔ MAP, CPP, $SvjO_2$, ↔ VCMA/ ↓ ICP	Head-injured patients, ICU/ increased ICP	3 mg/kg/h propofol, cont. infusion	Controlled, normoventilation
Bourgoin et al. (18) 2003	5	12/13 Ket/ Suf	4.92 ± 1.5 mg/ kg/h racemic, cont. infusion	↔ ICP and CPP, ↑ HR, compared to sufentanil	Head-injured patients, ICU/ increased ICP	98.4 ± 30 mg/kg/h midazolam, cont. infusion	Controlled, normoventilation
Sakai et al. (26) 2000	3	7/7/8 Awa/ Pro/ProKet	2 mg/kg/h racemic, cont. infusion	↔ MAP, HR, VMCA no cerebral compromise ↔ VMCA, $paCO_2$, compared to propofol alone	Surgical patients, propofol, cont. infusion	6 mg/kg/h normoventilation	Controlled or hypo- or hyper- ventilation
Nagase et al. (27) 2001	3	15/15 Ket/C	1 mg/kg racemic, bolus	↔ VMCA, compared to isoflurane alone	Surgical patients, no cerebral compromise	Isoflurane anesthesia without N_2O	Controlled, hypoventilation
Engelhard et al. (28) 2001	3	12/12 ProKet/ Sevo	2.5 mg/kg/h S+, cont. infusion	↔ autoregulatory index, compared to sevoflurane anesthesia	Surgical patients, no cerebral compromise	1.5–2.5 μg/kg/ml propofol, targeted plasma concentration	Controlled, normoventilation
Vollenweider et al. (29) 1997	NA	10/10/10 S+/R−/C	Each isomer: 15 mg bolus + 0.84–1.2 mg/kg/h, cont. infusion	S+: ↑ rCMRGlu anterior cingulate, frontal, parietal, left sensorimotor cortices, thalamus R−: ↓ rCMRGlu temporomedial cortex, left insula	Volunteers, no cerebral compromise	None	Spontaneous
Holcomb et al. (30) 2001	NA	13/10 Ket/C	0.3 mg/kg bolus, racemic	↑ rCBF in anterior cingulate, medial, inferior, frontal cortices ↓ rCBF (relative) in cerebellum	Volunteers, no cerebral compromise	None	Spontaneous
Langsjö et al. (8) 2003	NA	9 Ket	30, 100, 300 ng/ ml racemic, targeted plasma concentration	Global ↑ rCBF, highest in anterior cingulate, thalamus, putamen, frontal cortices, ↔ $rCMRO_2$, ↑ rCBV frontal cortex	Volunteers, no cerebral compromise	None	Spontaneous

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REVIEW ARTICLE

Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent?

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Summary

In rapid sequence induction of anaesthesia in the emergency setting in shocked or hypotensive patients (e.g. ruptured abdominal aortic aneurysm, polytrauma or septic shock), prior resuscitation is often suboptimal and comorbidities (particularly cardiovascular) may be extensive. The induction agents with the most favourable pharmacological properties conferring haemodynamic stability appear to be ketamine and etomidate. However, etomidate has been withdrawn from use in some countries and impairs steroidogenesis. Ketamine has been traditionally contra-indicated in the presence of brain injury, but we argue in this review that any adverse effects of the drug on intracranial pressure or cerebral blood flow are in fact attenuated or reversed by controlled ventilation, subsequent anaesthesia and the greater general haemodynamic stability conferred by the drug. Ketamine represents a very rational choice for rapid sequence induction in haemodynamically compromised patients.

See the corresponding editorial in this issue, pp 37–39.

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Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension

Clinical article

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Object. Deepening sedation is often needed in patients with intracranial hypertension. All widely used sedative and anesthetic agents (opioids, benzodiazepines, propofol, and barbiturates) decrease blood pressure and may therefore decrease cerebral perfusion pressure (CPP). Ketamine is a potent, safe, rapid-onset anesthetic agent that does not decrease blood pressure. However, ketamine's use in patients with traumatic brain injury and intracranial hypertension is precluded because it is widely stated that it increases intracranial pressure (ICP). Based on anecdotal clinical experience, the authors hypothesized that ketamine does not increase—but may rather decrease—ICP.

Methods. The authors conducted a prospective, controlled, clinical trial of data obtained in a pediatric intensive care unit of a regional trauma center. All patients were sedated and mechanically ventilated prior to inclusion in the study. Children with sustained, elevated ICP (> 18 mm Hg) resistant to first-tier therapies received a single ketamine dose (1–1.5 mg/kg) either to prevent further ICP increase during a potentially distressing intervention (Group 1) or as an additional measure to lower ICP (Group 2). Hemodynamic, ICP, and CPP values were recorded before ketamine administration, and repeated-measures analysis of variance was used to compare these values with those recorded every minute for 10 minutes following ketamine administration.

Results. The results of 82 ketamine administrations in 30 patients were analyzed. Overall, following ketamine administration, ICP decreased by 30% (from 25.8 ± 8.4 to 18.0 ± 8.5 mm Hg) ($p < 0.001$) and CPP increased from 54.4 ± 11.7 to 58.3 ± 13.4 mm Hg ($p < 0.005$). In Group 1, ICP decreased significantly following ketamine administration and increased by > 2 mm Hg during the distressing intervention in only 1 of 17 events. In Group 2, when ketamine was administered to lower persistent intracranial hypertension, ICP decreased by 33% (from 26.0 ± 9.1 to 17.5 ± 9.1 mm Hg) ($p < 0.0001$) following ketamine administration.

Conclusions. In ventilation-treated patients with intracranial hypertension, ketamine effectively decreased ICP and prevented untoward ICP elevations during potentially distressing interventions, without lowering blood pressure and CPP. These results refute the notion that ketamine increases ICP. Ketamine is a safe and effective drug for patients with traumatic brain injury and intracranial hypertension, and it can possibly be used safely in trauma emergency situations. *(DOI: 10.3171/2009.1.PEDS08319)*

Revising a Dogma: Ketamine for Patients with Neurological Injury?

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We evaluated reports of randomized clinical trials in the perioperative and intensive care setting concerning ketamine's effects on the brain in patients with, or at risk for, neurological injury. We also reviewed other studies in humans on the drug's effects on the brain, and reports that examined ketamine in experimental brain injury. In the clinical setting, level II evidence indicates that ketamine does not increase intracranial pressure when used under conditions of controlled ventilation, coadministration of a γ-aminobutyric acid (GABA) receptor agonist, and without nitrous oxide. Ketamine may thus safely be used in neurologically impaired patients. Compared with other anesthetics or sedatives, level II and III evidence indicates that hemodynamic stimulation induced by ketamine may improve cerebral perfusion; this could make the drug a preferred choice in sedative regimes after brain injury. In the laboratory, ketamine has neuroprotective, and *S*(+)-ketamine additional neuroregenerative effects, even when administered after onset of a cerebral insult. However, improved outcomes were only reported in studies with brief recovery observation intervals. In developing animals, and in certain brain areas of adult rats without cerebral injury, neurotoxic effects were noted after large-dose ketamine. These were prevented by coadministration of GABA receptor agonists.

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The Emerging Use of Ketamine for Anesthesia and Sedation in Traumatic Brain Injuries

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SUMMARY

Background—Traditionally, the use of ketamine for patients with traumatic brain injuries is contraindicated due to the concern of increasing intracranial pressure (ICP). These concerns, however, originated from early studies and case reports that were inadequately controlled and designed. Recently, the concern of using ketamine in these patients has been challenged by a number of published studies demonstrating that the use of ketamine was safe in these patients.

Aims—The purpose of this article was to review the current literature in regards to using ketamine in patients with traumatic brain injuries in different clinical settings associated with anesthesia, as well as review the potential mechanisms underlying the neuroprotective effects of ketamine.

Results—Studies examining the use of ketamine for induction, maintenance, and sedation in patients with TBI have had promising results. The use of ketamine in a controlled ventilation setting and in combination with other sedative agents has demonstrated no increase in ICP.

Conclusions—The role of ketamine as a neuroprotective agent in humans remains inconclusive and adequately powered; randomized controlled trials performed in patients undergoing surgery for traumatic brain injury are necessary.

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ORIGINAL ARTICLE

Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials

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Abstract

Background Ketamine is traditionally avoided in sedation management of patients with risk of intracranial hypertension. However, results from many clinical trials contradict this concern. We critically analyzed the published data of the effects of ketamine on intracranial pressure (ICP) and other cerebral hemodynamics to determine whether ketamine was safe for patients with hemodynamic instability and brain injuries.

Methods We systematically searched the online databases of PubMed, Medline, Embase, Current Controlled Trials, and Cochrane Central (last search performed on January 15, 2014). Trial characteristics and outcomes were independently extracted by two assessors (Xin Wang, Xibing Ding). For continuous data, mean differences (MD) were formulated. If the P value of the chi-square test was >0.10 or I^2 <50 %, a fixed-effects model was used; otherwise, the random effects model was adopted.

Results Five trials ($n = 198$) met the inclusion criteria. Using ICP levels within the first 24 h of ketamine administration as the main outcome, the use of ketamine leads to the same ICP levels as opioids [MD = 1.94; 95 % confidence interval (95 % CI), −2.35, 6.23; $P = 0.38$]. There were no significant differences in mean arterial pressure values between the two groups (MD = 0.99; 95 % CI, −2.24, 4.22; $P = 0.55$). Ketamine administration was also comparable with opioids in the maintenance of cerebral perfusion pressure (MD = −1.07; 95 % CI, −7.95, 5.8; $P = 0.76$).

Conclusions The results of this study suggest that ketamine does not increase ICP compared with opioids. Ketamine provides good maintenance of hemodynamic status. Clinical application of ketamine should not be discouraged on the basis of ICP-related concerns.

Keywords Ketamine · Opioids · Intracranial pressure · Hemodynamic instability · Brain injuries

Introduction

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REVIEW ARTICLE

The Ketamine Effect on ICP in Traumatic Brain Injury

F. A. Zeiler · J. Teitelbaum · M. West · L. M. Gillman

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Abstract Our goal was to perform a systematic review of the literature on the use of ketamine in traumatic brain injury (TBI) and its effects on intracranial pressure (ICP). All articles from MEDLINE, BIOSIS, EMBASE, Global Health, HealthStar, Scopus, Cochrane Library, the International Clinical Trials Registry Platform (inception to November 2013), reference lists of relevant articles, and gray literature were searched. Two reviewers independently identified all manuscripts pertaining to the administration of ketamine in human TBI patients that recorded effects on ICP. Secondary outcomes of effect on cerebral perfusion pressure, mean arterial pressure, patient outcome, and adverse effects were recorded. Two reviewers independently extracted data including population characteristics and treatment characteristics. The strength of evidence was adjudicated using both the Oxford and GRADE methodology. Our search strategy produced a total 371 citations. Seven articles, six manuscripts and one meeting proceeding, were considered for the review with all utilizing ketamine, while documenting ICP in severe TBI patients. All studies were prospective studies. Five and two studies pertained to adults and pediatrics, respectively. Across all studies, of the 101 adult and 55 pediatric patients described, ICP did not increase in any of the studies during ketamine administration. Three studies reported a significant decrease in ICP with ketamine bolus. Cerebral perfusion pressure and mean blood pressure increased in two studies, leading to a decrease in vasopressors in one. No significant adverse events related to ketamine were recorded in any of the studies. Outcome data were poorly documented. There currently exists Oxford level 2b, GRADE C evidence to support that ketamine does not increase ICP in severe TBI patients that are sedated and ventilated, and in fact may lower it in selected cases.

Electronic supplementary material The online version of this article (doi:10.1007/s12028-013-9950-y) contains supplementary material, which is available to authorized users.

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TEŞEKKÜRLER...