■ CLINICAL CONCEPTS AND COMMENTARY

Richard B. Weiskopf, M.D., Editor

Ketamine for Perioperative Pain Management

Sabine Himmelseher, M.D.,* Marcel E. Durieux, M.D., Ph.D.†

AS part of the effort to develop mechanisms-based approaches to pain therapy, renewed interest has focused on the use of ketamine for treatment of acute and chronic pain. In particular, the role of *N*-methyl-D-aspartate (NMDA) excitatory glutamate receptors in nociceptive transmission has been established in humans.[1–3] NMDA receptors participate in the development and maintenance of what can be called "pathologic pain" after tissue injury: increased pain perception as a result of pain sensitization, in part from synaptic plasticity.[1–3] Ketamine binds noncompetitively to the phencyclidine binding site of NMDA receptors[4] but also modifies them *via* allosteric mechanisms.[5] When studied at subanesthetic doses, its analgesic efficacy correlates well with its inhibiting action on NMDA receptor-mediated pain facilitation[4,6] and a decrease in activity of brain structures that respond to noxious stimuli.[7] Ketamine therefore represents a promising modality in several perioperative strategies to prevent pathologic pain.

Another reason for the renewed interest in ketamine is the availability of S(+) ketamine. Ketamine has a chiral center at the carbon-2 atom of the cyclohexanone ring, and therefore exists as the optical stereoisomers S(+) and R(-) ketamine.[4] Until recently, ketamine was marketed as a racemate, containing equimolar amounts of the enantiomers. S(+) ketamine has a fourfold greater affinity for NMDA receptors than does R(-) ketamine.[4] This difference results in a clinical analgesic potency of S(+) ketamine approximately two times greater than that of racemic and four times greater than that of R(-) ketamine, whereas S(+) ketamine has a shorter duration of action.[4,6,8]

We discuss the perioperative use of ketamine as an adjunct to general and regional anesthesia and to postoperative pain therapy. Focus will be on the administration of the drug at subanesthetic concentrations; we will refer to this as "subanesthetic ketamine."

Anti-nociceptive Therapy with Ketamine during Anesthesia

Intravenous Ketamine as an Analgesic Adjunct to General Anesthesia

Intravenous subanesthetic ketamine, when added as an adjunct to general anesthesia, reduced postoperative pain and opioid requirements in a variety of settings, from outpatient surgery to major abdominal procedures (level II evidence) (table 1).[9–16] However, some studies did not show this benefit (level II evidence) (table 1).[17,18] Two factors may explain these failures. First, beneficial effects of ketamine may be masked when the drug is used in small doses (<0.15 mg/kg) against the background of multimodal or epidural analgesia.[17] Second, the dosing schedule may be inadequate. Studies have compared the effects of ketamine administration before surgery with those of one ketamine administration at the end of surgery to test its "preemptive" analgesic properties. However, nociceptive and inflammatory signals are generated throughout surgery and after the procedure. A single injection of a short-acting drug such as ketamine either before or after incision will therefore not provide analgesia that lasts far into the postoperative period.[18] To prevent pathologic pain, ketamine needs to be applied at least throughout the operation and likely for a period of time into the postoperative phase, in an attempt to reduce sensitization of central and peripheral pain pathways. Thus, the adequacy of the ketamine administration schedule is a crucial component for pain prevention (fig. 1).

Dosing of ketamine when used for this purpose is affected by variety of factors, including the expected amount of pain, whether general or epidural anesthesia will be used, and whether ketamine will be applied intraoperatively or intraoperatively and postoperatively (level II evidence) (table 1). In a long-term outcome trial on adenocarcinoma surgery with general or epidural anesthesia, racemic ketamine injected as a 0.5 mg/kg preincisional bolus followed by an infusion of $0.25 \mathrm{~mg\cdot kg^{-1}\cdot h^{-1}}$ reduced postoperative morphine needs and the incidence of residual pain until the sixth postoperative month.[13] However, this was not the case when the drug was used at half the dose. After gastrectomy[12] or major renal surgery[14] with general or epidural anesthesia, ketamine improved postoperative pain relief after an intraoperative infusion of $500 \mathrm{~\mu g\cdot kg^{-1}\cdot h^{-1}}$ pre-

Table 1. Subanesthetic Ketamine as an Analgesic Adjunct to General Anesthesia or Combined General and Epidural Anesthesia

Reference	Quality Score	Size / Study Group	Study Setting / Anesthesia	Ketamine, Administration Schedule	Difference in Postoperative Outcome Measures after iv Ketamine	Difference in Side Effects after Ketamine	Comment
Menigaux et al.[9] 2001	5	25/25 C/pre	outpatient knee arthroscopy / GA, + pre-closure intraarticular LA and opiate	racemic, iv: 0.15 mg/kg	↓pain at rest / on mobilization, postop day 0,1,2 ↓analgesic need ↑walking ability, postop day 1	NS	↑early procedure-related functional outcome
Kwork et al.[10] 2004	5	45/45/45 C/preop/post	gynecologic laparoscopic surgery / GA	racemic, iv: 0.15 mg/kg preincisional or after wound closure	preincisional ketamine: ↓ pain over 6 h postop ↑ time to first analgesic request ↓ postop analgesic need	NS	one Ket dose, injected before opiate / trends for better recovery
Stubhaug et al.[11] 1997	5	10/10 C/pre	life kidney donation / GA + pre-closure intercostal LA	racemic, iv: 0.5 mg/kg preincisional + 120 µg/kg for 24 h + 60 µg/kg/h for 48 h	↓ mechanical hyperalgesia, postop day 1, 3, 7 ↓ wind-up pain, postop day 3 ↑ pain first h postop ↑ patient satisfaction	↓ PONV, postop day 1	↓pathologic pain
Aida et al.[12] 2000	4	31/30/29/31 C/EA/pre/EApre	gastrectomy / GA, or GA + intraop EA with opiate	racemic, iv: 1 mg/kg preincisional + 0.5 mg/kg/h intraop	best treatment: EA and ketamine, ↓ pain at rest / on movement, postop day 1, 2 ↓ analgesic need, postop day 1, 2	NS	↓effective analgesia after GA + Ket than after GA, EA + Ket
de Kock et al.[13] 2001	5	20/20/20 C/epi-prelow/high /20/20 /iv-prelow/high	adenocarcinoma surgery / GA + intraop EA with LA, opiate, and clonidine	racemic, epidural or iv (low or high): 0.25 or 0.5 mg/kg preincisional + 125 or 250 µg/kg/h intraop	best treatment: high dose iv ketamine, ↓ analgesic need, postop day 1-3 ↓ wound hyperalgesia, postop day 1-3 ↓ residual pain until 6th postop month	NS	↑long-term outcome ↓long-term pain after surgery
Kararmaz et al.[14] 2003	5	20/20 C/preop	renal surgery / GA + intraop EA with LA and opiate	racemic, iv: 0.5 mg/kg preincisional + 0.5 mg/kg/h intraop	↓ pain at rest for 6 h postop ↑ time to first analgesic request ↓ analgesic need, postop day 1, 2	↓postop nausea and pruritus	Ket injected during induction of GA
Snijdelaar et al.[15] 2004	5	14/14 C/preop	radical prostatectomy / GA	S+, iv: 100 µg/kg preoperative + 120 µg/kg/h intraop + postop PCA, bolus: 1 mg morphine, 0.5 mg S+	↓ analgesic need, postop day 1, 2 ↓ pain at rest, postop day 1, 2	NS	small-dose S+, started before first opiate, continued in PCA
Argiriadou et al.[16] 2004	5	15/15/15 C/pre/rep	major pelvic visceral surgery / GA + intra- and postop EA with LA	S+, iv: 0.5 mg/kg preincisional + placebo, or + 0.2 mg/kg repeated intraop	repeated S+: ↓ pain over 6 h postop ↓ analgesic need, postop day 1 ↑ postop patient mood	NS	↑postop analgesia despite postop EA
Ilkjaer et al.[17] 1998	5	30/30 C/pre	renal surgery / GA + intra- and postop EA with LA for 24 h, then opiate for 48 h	racemic, iv: 10 mg preincisional + 10 mg/h for 48 h	NS	↑feeling of sedation, postop day 1	effects overshadowed by postop EA
Dahl et al.[18] 2000	5	33/33/33 C/pre/post	abdominal hysterectomy / GA	racemic, iv: 0.4 mg/kg preincisional or after skin closure	NS	NS	one injection before incision, ineffective

The three-item, 1-5 quality scale of Jadad was used for assessment of trials. A study quality score of 4 reflects a randomized, double-blind controlled trial with description of an adequate method of randomization; a score of 5 reflects the additional description of numbers and reasons for study withdrawals. iv = intravenous, intraop = intraoperative, postop = postoperative, C = control, pre = ketamine before skin incision, but after first opiate, preop = ketamine before first opiate and before skin incision, preoperatively, post = ketamine after wound or skin closure, EA = epidural anesthesia, Ket = ketamine, epi-prelow/high = epidural preincisional ketamine, lower / higher study dose, iv-prelow/high = intravenous preincisional ketamine, lower / higher study dose, rep = repeated ketamine, GA = general anesthetic, S+ = S(+) ketamine, PCA = postoperative patient-controlled analgesia, PONV = postoperative nausea and vomiting, NS = no significant difference between indicated ketamine and other groups.

Fig. 1. For prevention of pathologic pain after severe tissue injury, ketamine administration should cover the entire duration of high-intensity noxious and inflammatory stimulation, not simply the initial trauma. *N*-methyl-D-aspartate receptors should be blocked during ongoing intraoperative as well as postoperative transmission of nociceptive impulses. Postoperative mobilization may elicit delayed waves of afferent painful stimuli. Regarding acute opiate tolerance-related phenomena, it is as yet unclear whether ketamine is best administered before first use of opioids.
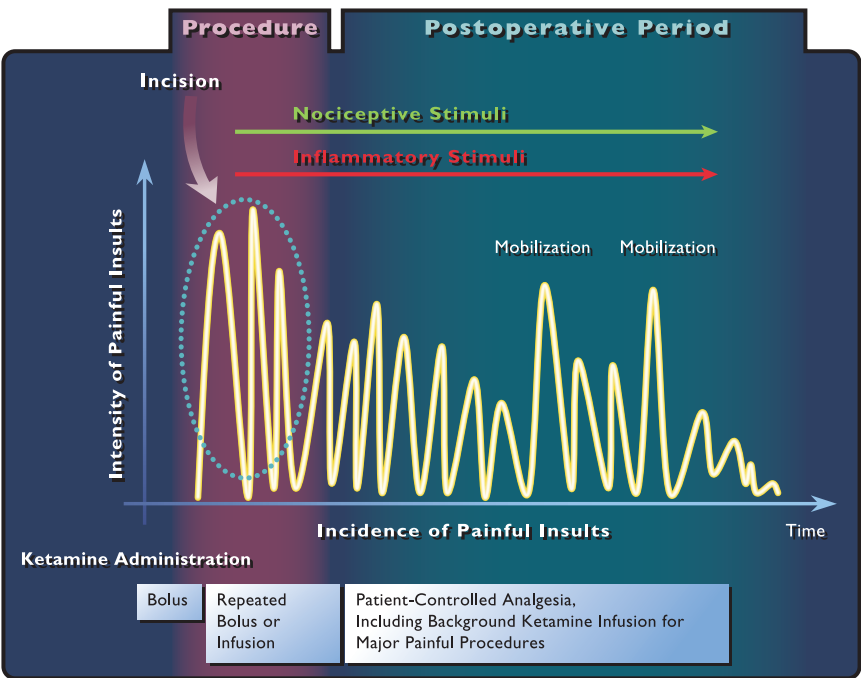
ceded by a preincisional bolus of 1 mg/kg[14] or 0.5 mg/kg.[12] In patients undergoing major pelvic visceral procedures with general or epidural anesthesia, we found less postoperative pain when 0.5 mg/kg preincisional S(+) ketamine was followed by repeated 0.2 mg/kg boluses, as compared with preincisional S(+) ketamine alone.[16] After radical prostatectomy with general anesthesia, opiate needs and pain at rest were reduced after a 0.1 mg/kg preoperative S(+) ketamine bolus and an intraoperative infusion of 120 μg·kg^{-1}·h^{-1}, followed by patient-controlled analgesia (PCA) with boluses of 1 mg morphine and 0.5 mg S(+) ketamine.[15] In less painful surgery such as nephrectomy, a preincisional bolus of 0.5 mg racemic ketamine followed by a 24 h-infusion of 120 μg·kg^{-1}·h^{-1} and then of 60 μg·kg^{-1}·h^{-1} for 48 h reduced hyperalgesia surrounding the incision.[11]

Table 2. Proposal for Use of Intravenous Ketamine as an Analgesic Adjunct to General Anesthesia and PCA

Ketamine	Procedure	Intravenous Dosage		
		Before Incision	**During Surgery**	**After Surgery**
Racemic	painful, e.g., major visceral surgery	0.50 mg/kg	infusion: 500 μg/kg/h or bolus: 0.25 mg/kg, repeated at 30-min intervals. If procedure $\geq$ 2 h, stop use 60 min before end of surgery.	background infusion: 120 μg/kg/h for 24 h, then 60 μg/kg/h for 48 h (or longer as necessary) and opioid-based PCA.
Racemic	less painful, e.g., hip surgery	0.25 mg/kg	infusion: 250 μg/kg/h or bolus: 0.125 mg/kg, repeated at 30-min intervals.	PCA, bolus: 1 mg ketamine and 1 mg morphine.
S(+)	painful, e.g., major visceral surgery	0.35 mg/kg	infusion: 400 μg/kg/h or bolus: 0.2 mg/kg, repeated at 30-min intervals. If procedure $\geq$ 2 h, stop use 30 min before end of surgery.	background infusion: 85 μg/kg/h for 24 h, then 60 μg/kg/h for 48 h (or longer as necessary) and opioid-based PCA, or PCA only, bolus: 0.5 mg S(+) ketamine and 1 mg morphine.
S(+)	less painful e.g., lumbar spine surgery	0.20 mg/kg	infusion: 200 μg/kg/h or bolus: 0.1 mg/kg, repeated at 30-min intervals.	PCA, bolus: 0.25 mg S(+) ketamine and 1.5 mg morphine.

All doses are given per kg body weight. PCA = patient-controlled analgesia

The following dosing schedule can therefore be proposed: In painful procedures, a 0.5 mg/kg slow bolus injection of ketamine before or after induction of general anesthesia, but before incision, may be used; this may be followed by repeated injections of 0.25 mg/kg ketamine at 30-min time intervals or a continuous infusion of 500 $\mu g \cdot kg^{-1} \cdot h^{-1}$. For procedures lasting longer than 2 h, drug administration ends at least 60 min before surgery to prevent prolonged recovery. In procedures expected to be less painful, a 0.25 mg/kg ketamine bolus before incision may be injected; this may be followed by 30-min injections of 0.125 mg/kg ketamine or an infusion of 250 $\mu g \cdot kg^{-1} \cdot h^{-1}$. With S(+) ketamine, doses can be reduced to approximately 70% of the dose of racemic ketamine when continuously administered; its use ends 30 min before wound closure (table 2). It is advisable to administer the first bolus doses or the first 20 min of an infusion under careful monitoring of patient hemodynamic response. With reduced nociception, many patients show declines in blood pressure and heart rate. Further doses are then titrated according to the individual response. Under general anesthesia, less anesthetic will be required when ketamine is used in this manner. After administration of subanesthetic ketamine as suggested, ketamine-treated *versus* control patients did not show an increase in postoperative adverse psychic effects, sedation, or nausea and vomiting.[9–16,18] Nevertheless, for premedication, a benzodiazepine such as 3.75–7.5 mg oral midazolam or 5–10 mg oral diazepam has been recommended.[19] To continue pain relief in the postoperative period, PCA with an analgesic plus ketamine combination may be beneficial (table 2).

Ketamine as an Analgesic Adjunct to Regional Anesthesia and Analgesia

The addition of ketamine to a local anesthetic or other analgesics in peripheral or neuraxial anesthesia and analgesia improves or prolongs pain relief (level II evidence) (table 3).[20–24] A decrease in drug-related side effects (sedation, pruritus, or adverse psychological reactions) has also been found, mainly because the required drug doses could be reduced.[25,26] These effects may relate to blockade of central and peripheral NMDA receptors and/or an antinociceptive action complementary to that of the other drugs used. Central and peripheral sensitization may thus be prevented.

Although peripheral human NMDA receptors have been identified[1,2] and ketamine shows local anesthetic-like properties, its peripheral effects at small doses (<0.15 mg/kg) do not provide profound local analgesia when used alone.[27] At neuraxial sites, ketamine exerts analgesia when used as a sole agent at higher doses, but its utility is limited by psychotomimetic reactions, at least in awake patients.[28] The resorption and uptake of peripheral or neuraxial ketamine has not yet been systematically analyzed. Based on data from epidural and caudal use, ketamine gains rapid access to the systemic circulation with high bioavailability (level III evidence).[29–31] After preoperative use in children, caudal S(+) ketamine reduced postoperative pain better than intramuscular[29] or intravenous S(+) ketamine.[30] As plasma concentrations are mostly similar after caudal and intramuscular ketamine,[29] this benefit likely resulted from neuroaxial rather than systemic action. When 0.5 mg/kg epidural *versus* 0.5 mg/kg intravenous racemic ketamine were compared in adults undergoing gastrectomy, less postoperative pain was also found after epidural use.[31] Higher plasma concentrations and a longer elimination half-life but decreased maximum plasma concentrations were reported for 48 h after epidural as compared with intravenous ketamine.

Trials investigating intraoperative ketamine as an analgesic additive to epidural regimens have reported improved analgesia and a local anesthetic or opioid-sparing effect that lasts into the postoperative period (level II evidence) (table 3).[21,22] Psychotomimetic effects and postoperative nausea and vomiting were similar in ketamine-treated and control patients. When epidural subanesthetic S(+) ketamine combined with a local anesthetic was injected preincisionally in orthopaedic surgery, beneficial effects over 48 h were reported,[22] suggesting that a single injection of epidural or local S(+) ketamine may reduce pain beyond the intraoperative period. However, administration of epidural subanesthetic racemic ketamine and morphine before surgical incision did not result in a relevant postoperative effect as compared to use of morphine (although patients treated with ketamine received less intraoperative opioids).[32] When racemic ketamine was added to a local anesthetic in an interscalene brachial plexus block, no increase in postoperative analgesia was reported.[33] Thus, the concept that pain prevention requires repeated or continuous intraoperative drug use to counteract ongoing peripheral and spinal noxious stimulation appears to be as valid for regional anesthesia as for general anesthesia.

Caudal analgesia added to general anesthesia is an effective regimen for pediatric surgery, but it may be associated with prolonged motor blockade and complications such as systemic toxicity after accidental intravascular injection of local anesthetics or with respiratory depression after opiate use. Studies assessing caudal ketamine have shown efficient analgesia for both intraoperative and postoperative periods (level II evidence) (table 3). Racemic ketamine provided improved pain relief of prolonged duration when added to local anesthetics,[24] and 0.5–1 mg/kg S(+) ketamine produced analgesia when administered alone or in combination with other anesthetics.[23,29,30] Postoperatively, no increase in psychotomimetic effects were reported after racemic ketamine ≤0.5 mg/kg or S(+) ketamine ≤1 mg/kg. This may be related to the fact that the children received

Table 3. Subanesthetic Ketamine as an Analgesic Adjunct to Regional Anesthesia and Analgesia

Reference	Quality Score	Size / Study Group	Study Setting / Anesthesia, Analgesia	Ketamine, Administration Schedule	Difference in Postoperative Outcome Measures after Ketamine	Difference in Side Effects after Ketamine	Comment
Epidural Ketamine							
Abdel-Ghaffar et al.[21] 1998	5	21/21/21 C/pre/ post	abdominal hysterectomy / GA + EA	racemic, epidural: 30 mg before induction of GA or 20 min after induction of GA	best treatment: ketamine use before GA ↑ time to first analgesic request ↓ analgesic need over 48 h postop	NS	large dose range of intraoperative alfentanil
Himmelseher et al.[22] 2001	5	21/21 C/pre	total knee arthroplasty / EA with 1% ropivacaine	S+, epidural: 0.25 mg/kg before incision	↓ pain at rest / on movement, postop day 1,2 ↓ analgesic need over 48 h postop ↑ rating of pain therapy	NS	S+, small dose effective as one injection
Subramaniam et al.[32] 2001	5	25/25 C/add	major upper abdominal surgery / GA + EA with single dose morphine, injected before GA	racemic, epidural: 1 mg/kg added to EA opiate	↑ time to first analgesic request	NS	↓ intraop analgesic requirements after Ket
Caudal Ketamine							
De Negri et al.[23] 2001	4	21/21/21 C/Clon/ add	minor surgery / GA + CA with 0.2% ropivacaine	S+, caudal: in addition, 0.5 mg/kg, or clonidine, caudal 2 µg/kg	best treatment: caudal S+, ↑ postop duration of analgesia	NS	caudal S+ is a better analgesic than caudal clonidine
Martindale et al.[30] 2004	5	20/20/20 C/Bupi/ add	hernia repair, orchidopexy / GA + CA with 0.25% bupivacaine	S+, caudal: in addition, 0.5 mg/kg, or iv, 0.5 mg/kg	best treatment: caudal S+, ↑ time to first analgesic request ↓ analgesic need over 24 h postop	NS	principal effect from neuraxial rather than systemic action
Regional Analgesia							
Azevedo et al.[20] 2000	5	26/26 C/add	gynecological abdominal surgery / EA with 1% lidocaine	racemic, transdermal: postop patch with 25 mg / 24 h delivery	↑ time to rescue analgesic request ↓ rescue analgesic need over 24 h postop	NS	transdermal ketamine, novel drug preparation
Rosseland et al.[27] 2003	5	15/15/15 C/add/im	arthroscopic knee surgery / GA	racemic, intraarticular: 10 mg bolus, or im, 10 mg	after im, but not after intraarticular ketamine: ↓ early pain at 15 min after study drug injection ↑ time to first analgesic request ↑ global evaluation scores	NS	80 pts. assessed / pts. with moderate to severe pain were included, only
Lee et al.[33] 2002	4	20/20/20 C/add/iv	forearm or hand surgery / interscalene brachial plexus block with 0.5% ropivacaine	racemic, added to LA in plexus block: 30 mg bolus, or iv, 30 mg	NS	NS	one injection before incision / effects likely overshadowed by LA

The three-item, 1-5 quality scale of Jadad was used for assessment of trials. A study quality score of 4 reflects a randomized, double-blind controlled trial with description of an adequate method of randomization; a score of 5 reflects the additional description of numbers and reasons for study withdrawals. GA = general anesthesia, C = control, pre = ketamine before induction of GA or skin incision, post = ketamine after induction of GA, postop = postoperative, S+ = S(+) ketamine, CA = caudal anesthesia, Clon = clonidine, Bupi = bupivacaine, add = ketamine administered in addition to control regime, iv = intravenous, im = intramuscular, LA = local anesthetic, pts = patients, NS = no significant difference between indicated ketamine and other groups.

general anesthesia during the time when systemic drug concentrations were high enough to cause undesired effects. Nevertheless, although there may be advantages over traditionally used caudal anesthetics, further data are needed to assure the safety of caudal ketamine in children at these young ages.

Toxicity Issues in Neuraxial Ketamine Use

Toxic reactions after prolonged neuraxial exposure to racemic ketamine formulations with preservatives (benzethonium chloride or chlorobutanol) have been reported in animal species. A case of spinal neurotoxicity after continuous intrathecal racemic ketamine infused over 3 weeks has been reported.[34] Despite controversy about the risk-benefit ratio of neuraxial use of ketamine in humans, several facts may help to reach a practical standpoint in this issue. First, chemical cytotoxicity from preservatives unrelated to ketamine has long been known. Only preservative-free preparations must therefore be employed for neuraxial use. Second, the risk of spinal toxicity is generally increased after extended drug exposure. However, dose-response studies in pigs did not reveal neurotoxicity after prolonged epidural preservative-free ketamine,[35] and patients with terminal cancer pain did not show signs of toxicity after repeated spinal preservative-free subanesthetic ketamine.[36] Third, physiologic NMDA receptor activity is necessary for cell survival and cerebral function, and rodent data suggest harmful consequences of profound NMDA receptor blockade.[37] Programmed death occurred in central neurons of the immature rat brain and vacuolization selectively developed in the cingulate and retrosplenial cortex of adult rats after high ketamine doses.[37] Importantly, coadministration of a gamma-aminobutyric acid receptor agonist prevented these effects. At this time, we think that lack of detailed toxicity data in noncancer patients only allows for preservative-free epidural ketamine use in smaller, subanesthetic doses and within the setting of clinical trials.

Pain Therapy with Ketamine in Postanesthesia Care

Ketamine and Opiate-Tolerance Phenomena

In addition to inhibition of sensitization in nociceptive pathways, prevention of opiate-related activation of pronociceptive systems and opiate tolerance may be another mechanism of pain prevention by ketamine. The development of rapid tolerance and delayed hyperalgesia after intraoperative and postoperative use of different opioids has been reported in surgical patients.[38–40] Although the mechanisms that allow ketamine to be an analgesic and opiate-sparing agent after opiate exposure remain poorly understood, two emerging concepts may be important (fig. 2). First, at neuronal synapses, scaffolding proteins such as postsynaptic density protein-95 (PSD-95) and postsynaptic density protein-93 (PSD-93) connect NMDA receptors to the cytoskeleton and to key signaling systems, such as neuronal nitric oxide synthase.[1] Recent rodent data show obligatory involvement of PSD-95 and PSD-93 in NMDA receptor-mediated neuropathic and chronic pain[41] and critical roles for PSD-95 and neuronal nitric oxide synthase in opioid tolerance.[42] Second, in sensitization or developing tolerance, activated protein kinase C and tyrosine kinase cascades facilitate association of key signaling molecules with PSD proteins and NMDA receptors.[1,43] This activates protein kinases, resulting in NMDA receptor phosphorylation and up-regulation. Enhanced downstream signaling potentiates NMDA function and thus pain sensation. Rat studies in brain ischemia indicate that ketamine decreases injury-triggered increases in interactions between NMDA receptor, PSD-95, and protein kinases. This reduces nitric oxide-related neurotoxicity and finally brain damage.[44] Thus, a ketamine-induced decrease in unfavourable PSD interaction with protein kinases and pain signaling systems may represent a common mechanism underlying reduced pain sensitization and opiate tolerance phenomena.

In the clinical situation, supplementing remifentanil-based anesthesia with preoperative subanesthetic ketamine reduced the need for both intraoperative remifentanil and postoperative opioid analgesia in abdominal surgery.[45] However, in another study,[46] a preincisional bolus of 0.5 mg/kg S(+) ketamine followed by an infusion of 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ until 2 h after emergence from higher-dose remifentanil anesthesia did not decrease pain after cruciate ligament repair (level II evidence) (table 4). S(+) ketamine, however, was started after general anesthesia was induced with remifentanil. Therefore, it has to be clarified whether ketamine should be administered before or after first opioid use and whether ketamine doses must be adapted to opioid concentrations or the duration of opioid infusion.

Perioperative management of opioid-resistant or severe chronic pain is a major clinical problem. Although there has been limited formal research on this topic, a recent study in postoperative surgical patients with morphine-resistant pain found that intravenous subanesthetic ketamine combined with morphine improved pain relief at smaller morphine doses than did morphine alone (table 4).[40] Moreover, ketamine-treated patients showed better oxygen saturation and greater wakefulness. Ketamine may also be used for pain therapy in the chronic opioid-tolerant patient, especially when other options have failed (level IV evidence).[43] Although controlled trials are lacking, a "challenge" with subanesthetic ketamine may even be attempted in opioid-addicted patients.[47] If pain is reduced, ketamine can be titrated to provide analgesia and prevent escalating opioid/analgesic needs. However, two recent reviews on
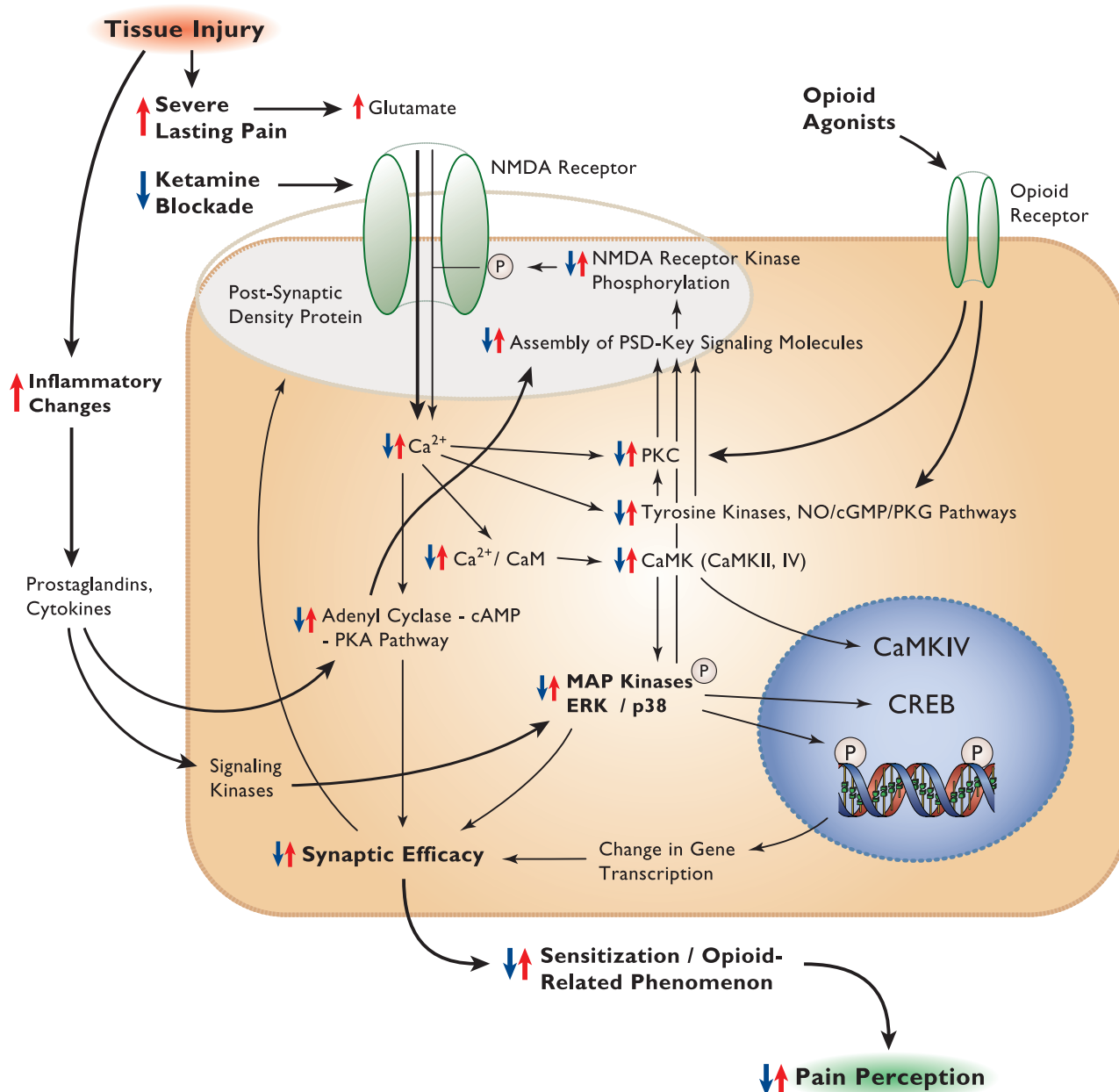
Fig. 2. In sensitization and opioid tolerance-related phenomena, pathologic pain is an expression of neuronal plasticity. After activation of intracellular kinase cascades, transcription-independent phosphorylation of key membrane receptors and channels, such as the *N*-methyl-D-aspartate (NMDA) receptor, is initiated. This increases neuronal excitability for tens of minutes after cessation of the initiating stimulus. Long-term hypersensitivity is also regulated by mitogen-activated protein kinases (MAP kinases) *via* transcription of gene products. Protein kinase (PK) C, a series of other protein kinase families, and nitric oxide (NO)/cGMP/PKG are activated after NMDA-mediated increases in intracellular calcium (Ca^{2+}) or μ-opioid receptor binding to opioid receptors. Increased Ca^{2+} stimulates Ca^{2+}/calmodulin, and Ca^{2+}/calmodulin kinase (CaMK) pathways. These and inflammatory transmitters stimulate adenyl cyclase – cAMP – PKA signaling. Several cascades then converge on MAP kinases, such as the extracellular signal-regulated kinases (ERK). These processes facilitate association of key signaling molecules with postsynaptic density (PSD) proteins in the NMDA receptor. This leads to kinase phosphorylation of NMDA receptor subunits and up-regulation of NMDA receptor currents. Enhanced downstream signaling ensues and, in this vicious circle, potentiates NMDA receptor function and synaptic efficacy and, thus, pain sensitization. In long-term hypersensitivity, CaMK and inflammation-related signaling kinases converge on MAP kinases, such as p38MAP kinases, which is followed by phosphorylation of promoters with the initiation of gene transcription. The cAMP response element binding protein (CREB), MAP kinases, and CaMKIV may also cause transcription *via* direct phosphorylation of gene promoters. Intervention with ketamine blocks NMDA receptor currents and connected downstream signaling. Regarding pain sensitization and opioid phenomenon, a common mechanism underlying ketamine's preventive action appears to be the perturbation of increased assembly of PSD proteins – tyrosine kinase – NMDA receptor protein subunits. This reduces phosphorylation and functional NMDA receptor up-regulation. In the future, the cascades presented may evolve as important targets for new pain reducing drugs with similar but more specific responses than those caused by ketamine. ↑ = pathophysiological increase or activation, ↓ = pathophysiological decrease or reduction, ↑ = increase or activation related to severe pain or opioid use, ↓ = decrease or reduction related to ketamine blockade.

Table 4. Subanesthetic Ketamine in the Setting of Opiate-Related Phenomenon and Postoperative Analgesia

Reference	Quality Score	Size / Study Group	Study Setting / Anesthesia, Analgesia	Ketamine, Administration Schedule	Difference in Outcome Measures after Ketamine	Difference in Side Effects after Ketamine	Comment
Remifentanil-Related Opioid Phenomenon							
Guignard et al.[45] 2002	5	25/25 C/preop	colorectal surgery / remifentanil-based GA, desflurane at 0.5 MAC and remifentanil started at 15 μg/kg/h	racemic, iv: 0.15 mg/kg + 120 μg/kg/h until skin closure	↓ intraop remifentanil need ↑ time to first analgesic request ↓ analgesic need over 24 h postop	NS	small dose, started before remifentanil infusion began
Jaksch et al.[46] 2002	5	15/15 C/pre	arthroscopic knee ligament repair / GA, TCI with propofol (target 2 - 4 μg/ml) and remifentanil (7.5 - 60 μg/kg/h)	S+, iv: 0.5 mg/kg + 120 μg/kg/h until 2 h after emergence	NS	NS	S+, started after remifentanil infusion began
Postoperative Opioid-Resistant Pain							
Weinbroum[46] 2003	4	114/131 C/add	major surgery / GA / when postop pain after at least 100 μg/kg mophine in 30 min still 6 ≥ (10-point VAS), start of study	racemic, iv: 250 μg/kg + 15 μg/kg morphine, versus 30 μg/kg mophine, alone, up to 3 times in 10 min, until pain ≤ 4	after first study drug injection: ↓ pain at 10 and 120 min ↓ number of injections necessary for pain ≤ 4 at 10 and 120 min ↑ feeling of well-being at 120 min	↑ wakefulness and oxygen saturation at 10 min in PACU: ↓ nausea / vomiting ↑ sensation of light-headedness	rapid, sustained more than additive effect after combined Ket / morphine
Postoperative Patient-Controlled Analgesia							
Guillou et al.[50] 2003	5	47/54 C/add	major abdominal surgery / GA / PCA with morphine, 1 mg bolus	racemic, iv PCA: in addition 0.5 mg/kg bolus + 120 μg/kg/h for 24 h, then + 60 μg/kg/h for 24 h	↓ analgesic need over 48 h postop ↓ pain at rest at 16 and 44 h postop ↓ pain on mobilization at: 16, 20, and 40 h postop	NS	in SICU: ↑ analgesia with low-dose background Ket infusion
Chia et al.[52] 1998	5	46/45 C/add	major surgery / GA / epi-PCA with morphine, 0.05 mg bolus, 2 mg Bupi, and 10 μg epinephrine	racemic, epi-PCA: in addition 1 mg bolus	↓ pain during cough / on movement postop day 1, 2, 3 ↓ pain at rest postop day 1, 2 ↓ analgesic need, postop day 1, 2	NS	↑ analgesia in multimodal epidural PCA regime
Burstal et al.[53] 2001	4	33/37 C/add	abdominal hysterectomy / GA / PCA with morphine, 1 mg bolus	racemic, iv PCA: in addition 2 mg bolus	↓ time period to require PCA	↑ side effects: 4 pts with dysphoria, 4 pts with pruritus	more Ket-treated pts. withdrawn because of side effects
Unlugenc et al.[54] 2003	4	30/30/30 C/Mg/add	major abdominal surgery / GA / PCA with morphine, 0.875 mg bolus	racemic, iv PCA: in addition 0.0125 mg bolus, or Mg, 30 mg bolus	minor effect after Ket and Mg, ↓ pain and discomfort at 15, 30, 60 min postop: ↓ analgesic need over 12 and 24 h postop	NS	too small Ket dose, below effectiveness for analgesic effect

The three-item, 1-5 quality scale of Jadad was used for assessment of trials. A study quality score of 4 reflects a randomized, double-blind controlled trial with description of an adequate method of randomization; a score of 5 reflects the additional description of numbers and reasons for study withdrawals. C = control, preop = ketamine administration started before start of remifentanil infusion, pre = ketamine administration started before skin incision, but after start of remifentanil infusion, add = ketamine administered in addition to control regime, GA = general anesthesia, MAC = minimal alveolar concentration, postop = postoperative, TCI = target-controlled infusion, Bupi = bupivacaine, iv = intravenous, S+ = S(+) ketamine, VAS = visual analog scale, PACU = post-anesthesia care unit, SICU = surgical intensive care unit, (epi-) PCA = (epidural) postoperative patient-controlled analgesia, Mg = Magnesium, pts = patients, Ket = ketamine, NS = no significant difference between indicated ketamine and other groups.

ketamine as an analgesic adjunct in chronic pain patients conclude that further data are needed before routine use can be recommended (level I evidence).[48,49]

Ketamine-Opioid Combinations in Patient-controlled Analgesia

After surgery, the combined use of ketamine and an opiate analgesic for intravenous PCA has been tested on general wards and in the intensive care unit. Although several studies reported less pain and decreases in analgesic need and adverse effects such as postoperative nausea and vomiting, sedation, or respiratory insufficiency,[15,49–52] some did not find remarkable benefits after ketamine (level II evidence) (table 4).[53,54] Although this has been explained by the nature of the insult (with less painful surgery requiring less postoperative pain therapy), two issues complicate the interpretation of the data. First, most of the drugs applied were chosen on purely empirical grounds with little knowledge of analgesic efficacy of ketamine-opiate combinations. Sometimes dosages were based on body surface area, ketamine bolus applications and background infusions were compared, or doses less than those known to be analgesic were used.[54] However, the dose of ketamine combined with morphine for PCA depends on the morphine dosing scheme, and interindividual variability in opiate drug requirement is well known. Second, patients were studied with rather global assessment tools such as pain ratings or immediate analgesic need after surgery. To identify long-term effects, parameters such as long-lasting hyperalgesia, patient convalescence, and outcome variables such as length of hospital stay need to be studied. The first issue has been approached with optimization models restricted by side effects for morphine combined with ketamine.[51] For lumbar spine and hip surgery, the model converged to a morphine:ketamine ratio of 1:1 and a lockout interval of 8 min for postoperative intravenous PCA. Very low pain scores and a negligible incidence of sedation, bradypnea, postoperative nausea and vomiting, pruritus, and psychotomimetic effects suggest that such combinations should be studied further. Nevertheless, after "painful" procedures, an infusion of low-dose ($<150 \ \mu g \cdot kg^{-1} \cdot h^{-1}$) intravenous ketamine combined with PCA appears to be the most promising analgesic technique[11,50] (level II evidence) (table 4).

Psychotomimetic Side Effects

The most common concerns about ketamine as an analgesic agent are related to its mind-altering effects. This is of special relevance when the compound is to be used in conscious patients. Quiet, relaxed surroundings contribute to a reduced incidence of these side effects, and when ketamine is administered alone, the prophylactic use of a sedative agent such as 3.75–7.5 mg oral midazolam has generally decreased their incidence and severity.[19] In the setting of postoperative PCA, most

trials did not find a difference in adverse psychotomimetic effects (level II evidence).[11,50–52,54] Effects were dose-dependent and less likely with small doses (<0.15 mg/kg). When ketamine was used as an infusion at less than 10 mg/h, cognitive impairment was negligible.[11,50] Side effects appear to be similar after S(+) *versus* racemic ketamine, but volunteers who received equianalgesic doses of both reported less tiredness and impaired cognitive capacity after S(+) ketamine.[55] In the recovery period, improved mood was found in patients who received intraoperative S(+) ketamine[16] or propofol and racemic ketamine.[56]

Conclusion

Pain therapy can be improved using intraoperative and postoperative ketamine in a variety of surgical procedures and anesthetic techniques. In particular, the intraoperative use of intravenous subanesthetic ketamine in general anesthesia provides pain prevention in the postoperative period. The most important limitation to the available studies is the lack of evaluation of long-term outcome measures. We do not know whether ketamine use will translate into better recovery profiles or improved functional outcome. There is also insufficient evidence to show a clear benefit of S(+) ketamine as compared with racemic ketamine. For future study, the evaluation of intravenous ketamine as an adjunct to general anesthesia appears to be a priority given the promising results and the ease with which such a regimen could be implemented.

References

1. Petrenko AB, Yamakura T, Baba H, Shimoji K: The role of *N*-methyl-D-aspartate receptors in pain: A review. Anesth Analg 2003; 97:1108–16

2. Cairns BE, Svenson P, Wang K, Hupfeld S, Graven-Nielsen T, Sessler D, Berde CB, Arendt-Nielsen L: Activation of peripheral NMDA receptors contributes to human pain and rat afferent discharges evoked by injection of glutamate into the masseter muscle. J Neurophysiol 2003; 90:2098–105

3. Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz G: The development and maintenance of human visceral pain hypersensitivity is dependent on the *N*-methyl-D-aspartate receptor. Gastroenterology 2004; 126:683–92

4. Oye I, Paulsen O, Maurset A: Effects of ketamine on sensory perception: Evidence for a role of *N*-methyl-D-aspartate receptors. J Pharmacol Exp Ther 1992; 260:1209–13

5. Orser BA, Pennefather PS, MacDonald JF: Multiple mechanisms of ketamine blockade of *N*-methyl-D-aspartate receptors. ANESTHESIOLOGY 1997; 86:903–17

6. Arendt-Nielsen L, Nielsen J, Petersen-Felix S, Schnider TW, Zbinden AM: Effect of racemic mixture and the (S+)-isomer of ketamine on temporal and spatial summation of pain. Br J Anaesth 1996; 77:625–31

7. Langso JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Sipila H, Kurki T, Silvanto M, Scheinin H: Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. ANESTHESIOLOGY 2003; 99:614–23

8. Mathisen LC, Skjelbred P, Skoglund LA, Oye I: Effect of ketamine, an NMDA receptor inhibitor, in acute and chronic orofacial pain. Pain 1995; 61:215–20

9. Menigaux C, Guignard B, Fletcher D, Sessler DI, Levron JC, Chauvin M: Intraoperative small-dose ketamine enhances analgesia after outpatient knee arthroscopy. Anesth Analg 2001; 93:606–12

10. Kwok RF, Lim J, Chan MT, Gin T, Chiu WK: Preoperative ketamine improves postoperative analgesia after gynaecologic laparoscopic surgery. Anesth Analg 2004; 98:1044–9

11. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful

suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32

12. Aida S, Yamakura T, Baba H, Taga H, Fukuda S, Shimoji K: Preemptive analgesia by intravenous low-dose ketamine and epidural morphine in gastrectomy: A randomized double-blind study. ANESTHESIOLOGY 2000; 92:1624–30

13. de Kock M, Lavand'homme P, Waterloos H: Balanced analgesia in the perioperative period: Is there a place for ketamine? Pain 2001; 92:373–80

14. Kararmaz A, Kaya S, Karaman H, Turhanoglu S, Ozyilmaz AM: Intraoperative intravenous ketamine in combination with epidural analgesia: postoperative analgesia after renal surgery. Anesth Analg 2003; 97:1092–6

15. Snijdelaar DG, Cornelisse HB, Schmid LR, Katz J: A randomized, controlled study of peri-operative low dose S(+)-ketamine in combination with postoperative patient-controlled S(+)-ketamine and morphine after radical prostatectomy. Anaesthesia 2004; 59:222–8

16. Argiriadou H, Himmelseher S, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M, Kochs E: Improvement of pain treatment after major abdominal surgery by intravenous S(+)-ketamine. Anesth Analg 2004; 98:1413–8

17. Ilkjaer S, Nikolajsen L, Hansen TM, Wernberg M, Brennum J, Dahl JB: Effect of IV ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth 1998; 81:707–12

18. Dahl V, Ernoe PE, Steen T, Raeder JC, White PF: Does ketamine have preemptive effects in women undergoing abdominal hysterectomy procedures. Anesth Analg 2000; 90:1419–22

19. Suzuki M, Tsueda K, Lansing PS, Tolan MM, Fuhrmann TM, Sheppard RA, Hurst HE, Lippmann SB: Midazolam attenuates ketamine-induced abnormal perception and thought process but not mood changes. Can J Anaesth 2000; 47:866–74

20. Azevedo VM, Lauretti GR, Pereira NL, Reis MP: Transdermal ketamine as an adjuvant for postoperative analgesia after gynecological abdominal surgery using lidocaine epidural blockade. Anesth Analg 2000; 91:1479–82

21. Abdel-Ghaffar ME, Abdulatif M, Al-Ghandi A, Mowafi H, Anwar A: Epidural ketamine reduces postoperative epidural PCA consumption of fentanyl/bupivacaine. Can J Anaesth 1998; 45:103–9

22. Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, Martin J, Jelen-Esselborn S, Kochs E: Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. Anesth Analg 2001; 92:1290–5

23. De Negri P, Ivani G, Visconti C, De Vivo P: How to prolong postoperative analgesia after caudal anaesthesia with ropivacaine in children: S-ketamine versus clondine. Pediatr Anaesth 2001; 11:679–83

24. Panjabi N, Prakash S, Gupta P, Gogia AR: Efficacy of three doses of ketamine with bupivacaine for caudal analgesia in pediatric inguinal herniotomy. Reg Anesth Pain Med 2004; 29:28–31

25. Taura P, Fuster J, Blasi A, Martinez-Ocon J, Anglada T, Beltran J, Balust J, Tercero J, Garcia-Valdecasas JC: Postoperative pain relief after hepatic resection in cirrhotic patients: The efficacy of a single small dose of ketamine plus morphine epidurally. Anesth Analg 2003; 96:475–80

26. Togal T, Demirbilek S, Koroglu A, Yapici E, Ersoy O: Effects of S(+) ketamine added to bupivacaine for spinal anaesthesia for prostate surgery in elderly patients. Eur J Anaesthesiol 2004; 21:193–7

27. Rosseland LA, Stubhaug A, Sandberg L, Breivik H: Intra-articular (IA) catheter administration of postoperative analgesics: A new trial design allows evaluation of baseline pain, demonstrates large variation in need of analgesics, and finds no analgesic effect of IA ketamine compared with IA saline. Pain 2003; 104:25–34

28. Hawksworth C, Serpell M: Intrathecal anesthesia with ketamine. Reg Anesth Pain Med 1998; 23:283–8

29. Koinig H, Marhofer P, Krenn CG, Klimscha W, Wildling E, Erlacher T, Nikolic A, Turnheim K, Semsroth M: Analgesic effects of caudal and intramuscular S(+)-ketamine in children. ANESTHESIOLOGY 2000; 93:976–80

30. Martindale SJ, Dix P, Stoddart PA: Double-blind randomized controlled trial of caudal versus intravenous S(+)-ketamine for supplementation of caudal analgesia in children. Br J Anaesth 2004; 92:344–7

31. Xie H, Wang X, Liu G, Wang G: Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously. Clin J Pain 2003; 19:317–22

32. Subramaniam K, Subramaniam B, Pawar DK, Sennaraj B: Preoperative epidural ketamine in combination with morphine does not have a clinically relevant intra- and postoperative opioid-sparing effect. Anesth Analg 2001; 93:1321–6

33. Lee IO, Kim WK, Kong MH, Lee MK, Kim NS, Choi YS, Lim SH: No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiol Scand 2002; 46:821–6

34. Karpinski N, Dunn J, Hansen L, Masliah E: Subpial vacuolar myelopathy after intrathecal ketamine: report of a case. Pain 1997; 73:103–5

35. Errando CL, Sifre C, Moliner S, Valia JC, Gimeno O, Minguez A, Boils P: Subarachnoidal ketamine in swine—pathological findings after repeated doses: Acute toxicity study. Reg Anesth Pain Med 1999; 24:146–52

36. Yang CY, Wong CS, Chang JY, Ho ST: Intrathecal ketamine reduces morphine requirements in patients with terminal cancer pain. Can J Anaesth 1996; 43:379–83

37. Hardingham GE, Bading H: The yin and yang of NMDA receptor signalling. Trend Neurosci 2003; 26:81–9

38. Chia YT, Liu K, Wang JJ, Kuo MC, Ho ST: Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46:872–7

39. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher P, Chauvin M: Acute opioid tolerance: Intraoperative remifentanil increases postoperative pain and morphine requirement. ANESTHESIOLOGY 2000; 93:409–17

40. Weinbroum AA: A single small dose of postoperative ketamine provides rapid and sustained improvement in morphine analgesia in the presence of morphine-resistant pain. Anesth Analg 2003; 96:789–95

41. Tao YX, Rumbaugh G, Wang GD, Petralia RS, Zhao C, Kauer FW, Zhuo M, Wenthold RJ, Raja SN, Huganir RL, Bredt DS, Johns RA: Impaired NMDA receptor-mediated postsynaptic function and blunted NMDA receptor-dependent persistent pain in mice lacking postsynaptic density-93. J Neurosci 2003; 23:6703–12

42. Liaw WJ, Zhang B, Tao F, Yaster M, Johns RA, Tao YX: Knockdown of spinal cord postsynaptic density protein-95 prevents the development of morphine tolerance in rats. Neuroscience 2004; 123:11–5

43. De Leon-Casasola OA: Cellular mechanisms of opioid tolerance and the clinical approach to the opioid tolerant patient in the postoperative period. Best Pract Res Clin Anaesthesiol 2002; 16:521–5

44. Hou XY, Zhang GY, Yan JZ, Chen M, Liu Y: Activation of NMDA receptors and L-type voltage-gated calcium channels mediates enhanced formation of Fyn-PSD95-NR2A complex after transient cerebral ischemia. Brain Res 2002; 955:123–32

45. Guignard B, Coste C, Costes H, Sessler DI, Lebrault C, Morris W, Simonnet G, Chauvin M: Supplementing desflurane-remifentanil anesthesia with small-dose ketamine reduced perioperative opioid analgesic requirements. Anesth Analg 2002; 95:103–8

46. Jaksch W, Lang S, Reichhalter R, Raab G, Dann K, Fitzal S: Perioperative small-dose S(+)-ketamine has no incremental beneficial effects on postoperative pain when standard-practice opioid infusions are used. Anesth Analg 2002; 94:981–6

47. Guy H, Waeber JL, Infante NK, Clerque F: Ketamine combined with morphine for the management of pain in an opioid addict. ANESTHESIOLOGY 2002; 96:1265–66

48. Bell R, Eccleston C, Kalso E: Ketamine as an adjuvant to opioids for cancer pain (Cochrane review). Cochrane Database Syst Rev 2003; 1:CD003351

49. Hocking G, Cousins MJ: Ketamine in chronic pain management: An evidence-based review. Anesth Analg 2003; 97:1730–9

50. Guillou N, Tanguy M, Seguin P, Banger B, Champion JP, Malledant V: The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. Anesth Analg 2003; 97:843–7

51. Sveticic G, Gentilini A, Eichenberger U, Luginbuhl M, Curatolo M: Combinations of morphine with ketamine for patient-controlled analgesia: A new optimization method. ANESTHESIOLOGY 2003; 98:1195–205

52. Chia YY, Liu K, Liu YC, Chang HC, Wong CS: Adding ketamine in a multimodal patient-controlled epidural regimen reduces postoperative pain and analgesic consumption. Anesth Analg 1998; 86:1245–9

53. Burstal R, Danjoux G, Hayes C, Lantry G: PCA ketamine and morphine after abdominal hysterectomy. Anaesth Intensive Care 2001; 29:246–51

54. Unlugenc H, Ozalevli M, Guler T, Isik G: Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. Eur J Anaesthsiol 2003; 20:416–21

55. Pfenninger EG, Durieux ME, Himmelseher S: Cognitive impairment after small-dose ketamine isomers in comparison to equianalgesic racemic ketamine in human volunteers. ANESTHESIOLOGY 2002; 96:357–66

56. Kudoh A, Takahira Y, Katagai H, Takazawa T: Small-dose ketamine improves the postoperative state of depressed patients. Anesth Analg 2002; 95:114–8