# Severe Toxic Damage to the Rabbit Spinal Cord after Intrathecal Administration of Preservative-free S(+)-Ketamine

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*Background:* Ketamine and S(+)-ketamine have been advocated for neuraxial use in the management of postoperative pain and severe intractable pain syndromes unresponsive to opioid escalation. Although clinical experience has accumulated with S(+)-ketamine, safety data on toxicity in the central nervous system after neuraxial administration of S(+)-ketamine are conflicting. In this study, neurologic and toxicologic effects on the spinal cord from repeated daily intrathecal administration of commercially available, preservative-free S(+)-ketamine were evaluated against placebo in a randomized, blinded design.

*Methods:* Eighteen white New Zealand rabbits were assigned to two groups receiving either 0.5 ml intrathecal S(+)-ketamine, 0.5% solution (12 rabbits), or 0.5 ml saline (6 rabbits) once a day for 7 consecutive days. During general anesthesia, an intrathecal catheter was placed between the fifth and sixth spinous processes (lumbar). Neurologic (according to Tarlov criteria) and histopathologic assessments were performed after 7 days of treatment.

*Results:* Postmortem investigation of the spinal cord and nerve roots revealed histopathologic lesions suggestive of toxic damage in 11 rabbits, from the group of 12 animals receiving S(+)-ketamine. These results were significantly different compared with 5 control animals (no histologic changes observed). There was no significant difference in neurologic status between the two groups after 7 days of intrathecal treatment.

*Conclusions:* The authors conclude that repeated intrathecal administration of preservative-free S(+)-ketamine in a clinically relevant concentration and dosage has, considering the extent and severity of the lesions, a toxic effect on the central nervous system of rabbits.

KETAMINE, a noncompetitive N-methyl-D-aspartate receptor antagonist, and its active enantiomer S(+)-ketamine have been administered epidurally and intrathecally for the treatment of acute perioperative pain and to provide adequate pain relief in neuropathic pain syndromes.[1,2] However, despite considerable clinical experience, there is still controversy in the literature (human and animal) as to the safety of ketamine and S(+)-ketamine for either intrathecal or epidural administration.[3]

Preclinical animal toxicity studies have yielded conflicting results regarding the occurrence of histopathologic lesions after intrathecal administration of ketamine.[3–5] Although several animal studies with different species found no evidence of neurotoxicity, in other trials, signs of neurotoxicity were observed after intrathecal administration of ketamine.[4–8] Subsequent studies investigating the potential neurotoxicity of ketamine suggested that preservatives such as benzethonium chloride and chlorobutanol used in the commercial solution of ketamine were responsible for the observed histopathologic findings.[4,5] In a recent case report, however, postmortem observation of the spinal cord and nerve roots revealed severe histologic abnormalities after long-term intrathecal administration of preservative-free S(+)-ketamine.[9] Because there is little information on toxicity in the central nervous system after neuraxial administration of relevant concentrations of S(+)-ketamine, studies on neurotoxicity are required before this technique can be recommended or discouraged for clinical practice. The purpose of the current randomized blinded study was to assess the neurologic and toxicologic effects on the spinal cord of New Zealand white female rabbits from repeated daily intrathecal administration of commercially available, preservative-free S(+)-ketamine.

## Materials and Methods

The study protocol was approved by the Animal Research Committee of the Academic Hospital at the University of Amsterdam (Amsterdam, The Netherlands). The rabbits were kept according to the National Guidelines for Care of Laboratory Animals in The Netherlands. Eighteen New Zealand white female rabbits weighing $3.6 \pm 0.2$ kg (mean $\pm$ SD) were used in this study. Before commencing the study, the rabbits were adapted (for 5 days) to wearing a protective vest.

### Study Protocol

Upon receipt, the animals were randomly assigned into two groups, consisting of 6 rabbits in the control group and 12 rabbits in the S(+)-ketamine group. The control group received 0.9% saline solution, 0.5 ml (pH 5.0), and the S(+)-ketamine group received commercially available, preservative-free S(+)-ketamine (Ketanest-S, 5 mg/ml; Pfizer, Capelle a/d Ijssel, The Netherlands), 0.5 ml (pH 4.5), equivalent to 0.7 mg/kg. The drugs were administered very slowly (lasting 3 min)

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intrathecally, once a day in the morning, for 7 consecutive days. After each administration, the dead space of the catheter was cleared with 0.2 ml isotonic saline.

### Anesthesia and Monitoring

The rabbits were anesthetized with intramuscular ketamine (50 mg/kg) and xylazine (10 mg/kg). Subsequently, anesthesia was maintained with 1.5% isoflurane by mask in a mixture of 50% oxygen in air. Enrofloxacin (25 mg) was given before incision and continued until 2 days after surgery. During anesthesia, oxygen saturation and heart rate were measured using a tail oximeter.

### Operative Technique

Under sterile conditions, a straight midline incision was performed between the fifth and sixth spinous processes at lumbar level. After a laminectomy and removal of ligamentum flavum and epidural fat, the transparent dura mater with the spinal cord was exposed. After a small slit in the dura mater with leakage of cerebrospinal fluid, a 23-gauge polyamide catheter (Pajunk, Geisingen, Germany) was inserted 3 cm cephalic into the intrathecal space. The right position of the catheter was confirmed by cautious aspiration of cerebrospinal fluid. Subsequently, the free end of the catheter was tunneled subcutaneously and externalized at the nape of the neck. To protect the catheter, the animal wore a special protective vest. After anesthetic recovery, the neurologic status of the animals was assessed. Any evidence of neurologic (motor) dysfunction due to the implantation of the catheter itself resulted in exclusion from the study. Postoperative analgesia was accomplished by infiltration of the wound with 0.25% bupivacaine and intramuscular administration of buprenorphine (0.05 mg/kg), and 10 mg flunixin (Finadyne; Schering-Plough, Utrecht, The Netherlands). The intrathecal catheter remained in situ for 7 days.

### Measurements

The primary outcome parameter was the observed histopathologic changes in the spinal cord and spinal nerves after repeated intrathecal administration of $S(+)$-ketamine. Neurologic status of the animals (secondary outcome) was evaluated before start of treatment and 1 week after placement of the intrathecal catheter.

**Neurologic Evaluation.** During treatment, the animals were observed for any sign of neurologic impairment while moving around freely in the cages. The animals were scored neurologically on the five-point scale of Tarlov before the procedure and 8 days (end of treatment) after insertion of the catheter: 0 = paraplegia with no lower-extremity function; 1 = poor lower-extremity function, weak antigravity movement only; 2 = some lower-extremity function with good antigravity movement but inability to draw legs under body and/or hop; 3 = ability to draw legs under body and hop but not normally; 4 = normal motor function.[10] Because intra-

thecal administration of $S(+)$-ketamine could result in temporary gait deficits, neurologic status of the animals was assessed in the afternoon by an observer, blinded to the treatment allocation (and not responsible for the intrathecal administrations).

**Spinal Cord Pathology and Histopathologic Examination.** Eight days after insertion of the intrathecal catheter, the animals were anesthetized with intramuscular ketamine, 50 mg/kg, and xylazine, 10 mg/kg, followed by 1.5% isoflurane by mask in a mixture of 50% oxygen in air. After administration of heparin (2,500 U), animals were killed with pentobarbital (100 mg intravenously) and perfusion fixated (venous cannulas were placed transcardially and in the aorta) with 3.6% formalin after flushing with normal saline. The spinal cord was removed in toto (dorsal laminectomy was performed from S1 to T1) and immersed in 10% formalin for at least 10 days. The spinal cord in rabbit has a length of approximately 10–11 cm. The cord was therefore cut in three equal parts (cervical, thoracic, lumbar). From each proximal third part, sagittal sections of the cord were taken ±0.5 mm thick and embedded in paraffin. The remainder was longitudinally cut and also embedded. Per level, at least 24 slides, 6 for each transverse section and 6 for each longitudinal section, 6 μm thick, were cut and stained with hematoxylin and eosin, Klüver-Barrera, and Nissl. The slides were examined by a neuropathologist blinded to the drug (placebo or $S(+)$-ketamine) used. Sections were evaluated for the presence or absence of histologic alterations including myelin pallor, myelin loss, axonal swellings, central chromatolysis of neurons, subpial lymphocytic infiltration, infarction, gliosis, and leukodiapedesis. Neurohistopathologic damage was present if at least one out of six slices showed any of these changes.

### Statistics

Normally distributed data were expressed as mean ± SD. Nonnormally distributed data were expressed as median and interquartile range (25th–75th percentile). Baseline weight and temperature data of the two groups were compared bidirectionally using a Student $t$ test. For neurologic status (modified Tarlov score) of the animals after intrathecal treatment, two-sided statistical comparisons were performed using the Mann–Whitney U test. In case of histopathologic lesions, a two-sided Fisher exact test was performed. To assess the strength of the association between neurologic status and the presence of histopathologic lesions in the spinal cord, the Spearman rank correlation coefficient was calculated and tested unidirectionally for significance. For all analyses, significance was set at a value of $P < 0.05$.

## Results

Eighteen rabbits were randomized and treated in this study. The two groups (6 rabbits in the placebo group,

**Table 1. Weight and Rectal Temperature before Placement of the Intrathecal Catheter; Neurologic Outcome and Neurohistopathologic Findings of the Spinal Cord, after 7 Days of Treatment**

| Rabbit No. | Weight, kg | Rectal Temperature, °C | Modified Tarlov Score | Microscopic Observations | | |
|---|---|---|---|---|---|---|
| | | | | Cervical | Thoracic | Lumbar |
| Control group (saline) | | | | | | |
| DZO 4 | 3.050 | 38.0 | 4 | Normal | Normal | Normal |
| EAU 9 | 3.740 | 37.8 | 4 | Normal | Normal | Normal |
| EAM 2 | 3.350 | 38.2 | 4 | Normal | Normal | Normal |
| EBF 5 | 3.550 | 38.2 | 4 | Normal | Normal | Normal |
| EBN 3 | 3.650 | 37.6 | 4 | Normal | Normal | Normal |
| Mean ± SD | 3.468 ± 0.275 | 38.0 ± 0.3 | | | | |
| S(+)-ketamine group | | | | | | |
| DZY 9 | 3.500 | 38.0 | 2 | Mild | Mild | Mild |
| EAO 8 | 3.860 | 38.0 | 3 | Normal | Mild | Mild |
| EAE 1 | 3.240 | 37.6 | 4 | Mild | Mild | Severe |
| EBL 9 | 3.550 | 38.6 | 3 | Severe | Severe | Severe |
| EBQ 3 | 3.810 | 38.2 | 4 | Severe | Mild | Mild |
| EAB 4 | 3.490 | 38.1 | 3 | Mild | Mild | Mild |
| EAH 2 | 3.490 | 37.9 | 1 | Mild | Severe | Severe |
| EBN 6 | 3.510 | 38.3 | 4 | Normal | Normal | Normal |
| EBO 2 | 3.880 | 38.4 | 2 | Mild | Mild | Mild |
| EBM 2 | 3.415 | 37.9 | 4 | Normal | Mild | Mild |
| EBR 7 | 3.780 | 37.9 | 4 | Mild | Normal | Severe |
| EBQ 8 | 3.835 | 38.1 | 4 | Normal | Mild | Severe |
| Mean ± SD | 3.613 ± 0.210 | 38.1 ± 0.3 | | | | |

Weight and rectal temperatures are expressed as mean ± SD. There were no significant differences in weight and rectal temperature between the two groups. Modified Tarlov score less than 4 indicates neurologic impairment. Histology was graded as normal, mild, or severe change by a neuropathologist blinded to the treatment. Normal: all specimens showed negative changes. Mild: changes including myelin pallor, myelin loss, axonal swellings, central chromatolysis of neurons, and subpial lymphocytic infiltration. Severe: the changes mentioned as mild plus infarction, gliosis, and leukodiapedesis.

12 rabbits in the S(+)-ketamine group) were similar with respect to sex (all rabbits were female), baseline body weight, and rectal temperature (table 1). One animal in the control group was killed during placement of the catheter because of intraoperative systemic complications (severe hypotension).

No rabbits were excluded because of neurologic deficits after catheter implantation. In one animal from the placebo group, neurologic evaluation was not possible 7 days after the start of treatment because of an accidental removal of the intrathecal catheter on day 5. In this animal, histopathologic examination was performed 6 days after intrathecal placement of the catheter. In the other rabbits, the intrathecal catheter remained *in situ* during the course of the study. These animals were available for neurologic assessment and postmortem examination of the spinal cord after 7 days of treatment.

*Neurologic Outcome*

Motor function was affected temporarily (±20 to 30 min, modified Tarlov scores ranging from 1 to 3) in all of the rabbits of the ketamine group after each daily intrathecal administration of S(+)-ketamine. The rabbits receiving saline displayed no signs of motor impairment or other neurologic deficits. Modified Tarlov scores, before and 7 days after the start of treatment, are shown in table 1. Neurologic deficit (modified Tarlov score lower than 4) was observed in six rabbits receiving S(+)-ketamine (table 1). There was, however, no significant difference

in modified Tarlov scores between the control group and the S(+)-ketamine group after 7 days of treatment (P = 0.063).

*Microscopic Pathologic Evaluation*

The histopathologic results are shown in table 1. Eleven rabbits from the group of animals receiving S(+)-ketamine presented histopathologic lesions suggestive for neurotoxicity. These results were significantly different compared with the control animals (no histologic changes observed; P = 0.001).

Histology of the spinal cords showed mild to severe gray and white matter damage. Most lesions were present around the spinal canal and consisted of small severely damaged areas resembling small infarctions. Identical subpial lesions were a frequent finding. In some cords, focal white matter damage was observed. The gray matter damage ranged from central chromatolysis of motor neurons to obvious necrosis of small areas. The damage around the central canal consisted of ependymal loss and subependymal necrotic lesions. The subpial lesions showed mainly myelin loss combined with axonal swellings, necrosis, and reactive leukodiapedesis. Vascular damage was not observed. Whether these lesions were in continuity with the subpial region or with the ependyma could not clearly be established (fig. 1).

Combining the data from both groups, there was a significant correlation between the presence of neuro-
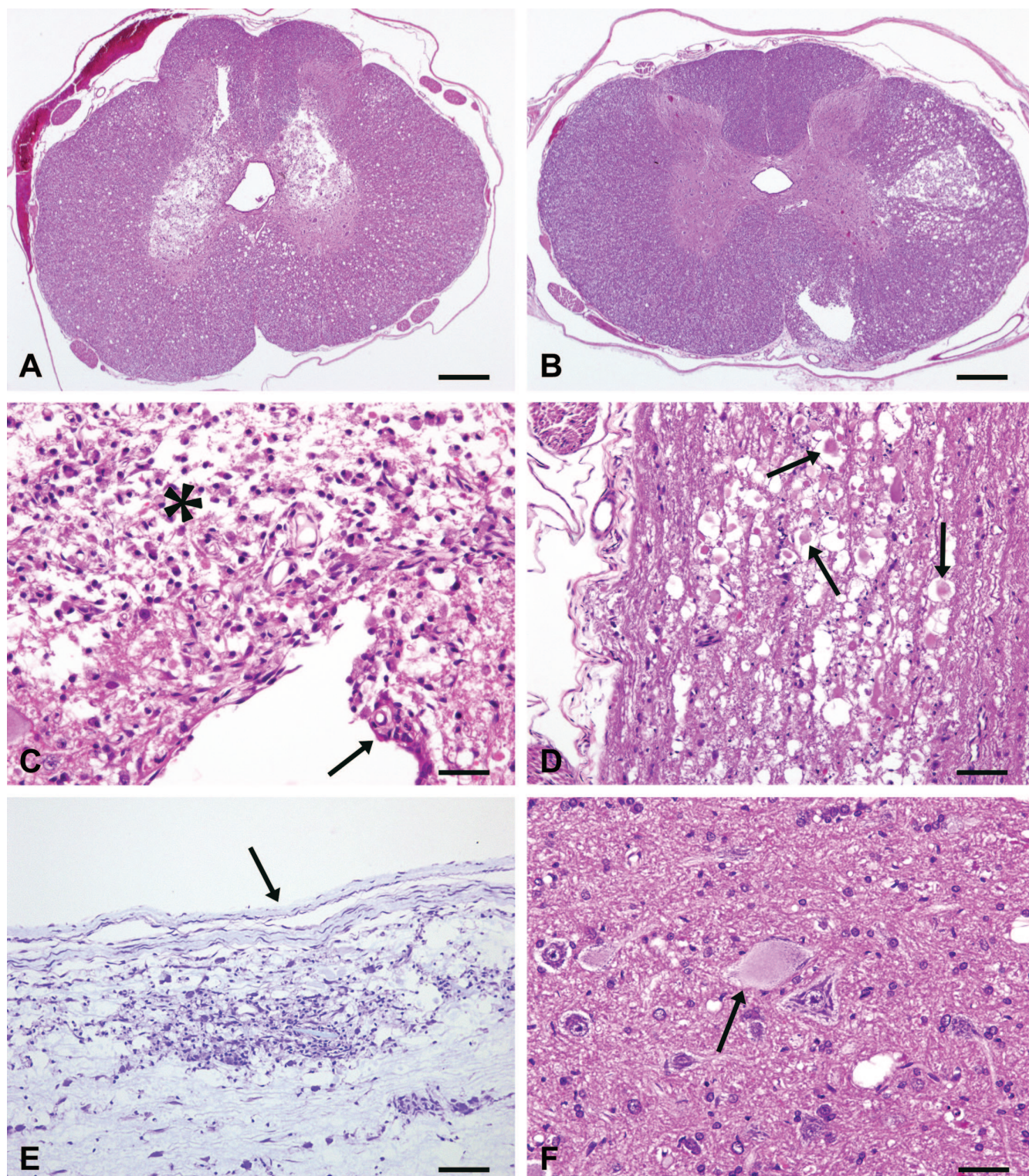
**Fig. 1. Histopathologic findings in the spinal cord of the rabbit after intrathecal administration of *S*(+)-ketamine. (*A*) Rabbit EAH 2. Thoracic spinal cord with severe necrotic lesions around the central canal and posterior column (hematoxylin and eosin [H&E] staining; *bar* = 550 μm). (*B*) Rabbit EAE 1. Cervical spinal cord with necrotizing lesions in the lateral and anterior spinal tracts (H&E staining; *bar* = 550 μm). (*C*) Rabbit EAH 2. Large magnification of lesion around the central canal. Some ependymal cells remain (*arrow*). * Necrotizing lesion (H&E staining; *bar* = 100 μm). (*D*) Rabbit EAE 1. Axonal swellings (*arrows*) in subpial lesion in the long tracts of the spinal cord (H&E staining; *bar* = 100 μm). (*E*) Rabbit EAE 1. Necrotizing subpial lesion with a cellular infiltrate. The pia mater is indicated by *arrow* (Nissl staining; *bar* = 200 μm). (*F*) Rabbit EAB 4. Central chromatolysis (*arrow*) in the anterior horn of the cervical spinal cord (H&E staining; *bar* = 60 μm).**

logic injury (assessed by the modified Tarlov score) and the presence of histopathologic lesions in the spinal cord ($r = 0.533$; $P = 0.014$). In addition, there was no significant correlation between neurologic impairments and histopathologic changes of the spinal cord in the ketamine group.

## Discussion

The results of the current blinded, placebo-controlled study in rabbits showed morphologic evidence of neurotoxicity after 7 days of repeated (once a day) subarachnoid administration of commercially available, preservative-free 0.5% S(+)-ketamine. Postmortem examination demonstrated severely damaged spinal cords in eight animals. Apparently, there were predilection sites for spinal cord damage caused by S(+)-ketamine. The lesion sites, subpial and around the central canal, suggested both that there was an immediate toxic effect on the tissue exposed to S(+)-ketamine and that the subpial and subependymal regions were the first to be affected. Both axonal swellings and the chromatolysis suggested also a more profound noxious neuronal effect. In some instances, the extent of the lesions looked vascular, because of the extent and sharp borders of some of the lesions, but vascular changes were not observed. Obviously, the damage resulted finally in necrosis.

Questions have been raised about the potential neurotoxicity of the neuraxial use of ketamine,[4] although the safety of this approach is supported by a number of clinical studies and case reports with no neurologic or behavioral changes suggesting neurotoxicity.[2,11,12] In addition, in one study with rabbits, single intrathecal administration of 0.3 ml preservative-free S(+)-ketamine, 1% (not commercially available), produced spinal analgesia with no histopathologic lesions in the spinal cord.[4] However, the use of single-injection techniques does not reveal any information about long-term use of a drug.[13] Because single-shot administration of S(+)-ketamine has a short-term effect only, safety studies on prolonged administration of this analgesic are necessary before widespread use in the treatment of pain in humans, which may last several days (postoperative pain) to several months (neuropathic cancer pain).

In this study, repeated intrathecal administration of S(+)-ketamine resulted in histopathologic changes in the spinal cord of the rabbit. These results were significantly different compared with the control animals. The presence of histopathologic lesions in the spinal cord did not correlate significantly with neurologic impairments assessed with the modified Tarlov score in the ketamine group. There was no significant difference in neurologic status between the two groups after 7 days of intrathecal treatment.

In addition, not all animals receiving intrathecal S(+)-ketamine developed deterioration in neurologic function despite evidence of severe histologic toxicity. A possible explanation may be the lack of precision of the modified Tarlov score to assess neurologic function. However, these data may also imply that clinical observations alone may not provide sufficient evidence for assessing the safety index of intrathecal administration of S(+)-ketamine. Therefore, this observed lack of convergence emphasizes the importance of assessing spinal histopathology to evaluate the neurotoxicity of spinal drugs.[14]

The histopathologic lesions detected in our study may be due to an excessive N-methyl-D-aspartate receptor antagonism by S(+)-ketamine. This antagonism may produce neurotoxicity attributed to an inactivation of an inhibitory mechanism (involving a blockade of glutamate N-methyl-D-aspartate receptors on γ-aminobutyric acid–mediated interneurons, which are responsible for a tonic inhibition of excitatory pathways) resulting in an excitotoxic injury with cell necrosis and apoptosis.[15] In addition, there is evidence to suggest that prolonged N-methyl-D-aspartate receptor antagonism hinders endogenous mechanisms for neuronal survival and neuroregeneration.[16] Factors other than S(+)-ketamine including low pH and the injection volume of the intrathecal solution and mechanical damage caused by the intrathecal catheter may be responsible for the observed histopathologic changes. However, previous reports with intrathecal catheters administering solutions with similar pH and injection volume did not demonstrate histologic findings suggestive of neurotoxicity.[5,17,18] Moreover, we did not observe histopathologic changes in our control group receiving saline.

Intrathecal administration of S(+)-ketamine produced signs of neurotoxicity in this preclinical model. However, the spinal cord of the rabbit may be more sensitive than the human spinal cord in demonstrating neurotoxicity after intrathecal administration of S(+)-ketamine.[19] Because the observed histopathologic lesions may be model dependent, translation of our findings into the equivalent clinical (human) situation may be difficult. In previous studies, however, the rabbit model did demonstrate the ability to show spinal cord pathology after intrathecal drug treatments (ketamine and midazolam) compared with saline.[7,18] In addition, in this study, we used the commercially available, preservative-free S(+)-ketamine formulation in a relevant concentration (0.5%) and dosage (0.7 mg/kg once a day), also clinically used for intrathecal pain treatment in humans (daily doses ranging from 50 to 75 mg S(+)-ketamine).[13,20,21]

A drawback of our study was the intrathecal bolus administration of S(+)-ketamine that could have been responsible for an increased cerebrospinal fluid level of S(+)-ketamine in combination with a decreased spinal cord flow, responsible for the observed neurotoxicity. However, intrathecal administration of a comparable daily dose of S(+)-ketamine by continuous infusion resulted also in histopathologic changes of the spinal cord.[9]

Treatment of acute perioperative pain (improved and prolonged analgesia, especially after caudal administration in pediatric anesthesia) and pain relief in neuropathic pain syndromes could be improved after neuraxial administration of S(+)-ketamine. This study was primarily designed to evaluate neurotoxicity after prolonged intrathecal administration of S(+)-ketamine. However, in cases of an unintentional dura puncture during caudal or epidural administration of S(+)-ketamine (bolus administration of 1 mg/kg), the concentration of this drug could reach toxic levels in the cerebrospinal fluid. In this view, more safety studies must be performed to evaluate acute neurotoxicity after high doses of intrathecal S(+)-ketamine.

In summary, there is no doubt, considering the extent and severity of the lesions, that prolonged intrathecal use of S(+)-ketamine has a serious toxic effect on the central nervous system in rabbits. In this study, however, neurologic assessment of the animals during treatment provide insufficient evidence for proving these neurotoxic effects. Our results underline the necessity of assessing spinal histopathology before neuraxial administration of drugs may be used for clinical practice. Based on our findings we conclude that the use of neuraxial S(+)-ketamine in humans should be avoided because the histologic lesions caused by this agent suggest a neurotoxic effect. The possible benefits do not justify clinical application, and we should look for a replacement of S(+)-ketamine, administered neuraxially, to improve pain management.

# References

1. Walker SM, Goudas LC, Cousins MJ, Carr DB: Combination spinal analgesic chemotherapy: A systemic review. Anesth Analg 2002; 95:674–715

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

3. Eisenach JC, Yaksh TL: Epidural ketamine in healthy children: What's the point? (letter). Anesth Analg 2003; 96:626

4. Malinovsky JM, Lepage JY, Cozian A, Mussini JM, Pinaudt M, Souron R: Is ketamine or its preservative responsible for neurotoxicity in the rabbit? ANESTHESIOLOGY 1993; 78:109–15

5. Hodgson PS, Neal JM, Pollock JE, Liu SS: The neurotoxicity of drugs given intrathecally (spinal). Anesth Analg 1999; 88:797–809

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

7. Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, Souron R: Ketamine and midazolam neurotoxicity in the rabbit. ANESTHESIOLOGY 1991; 75:91–7

8. Ahuja BR: Analgesic effect of intrathecal ketamine in rats. Br J Anaesth 1983; 55:991–5

9. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH: Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain. Pain 2005; 117:231–5

10. Nylander WA Jr, Plunkett RJ, Hammon JW Jr, Oldfield EH, Meacham WF: Thiopental modification of ischemic spinal cord injury in the dog. Ann Thorac Surg 1982; 33:64–8

11. Subramaniam K, Subramaniam B, Steinbrook RA: Ketamine as adjuvant analgesic to opioids: A quantitative and qualitative systematic review. Anesth Analg 2004; 99:482–95

12. Almenrader N, Passariello M, D'Amico G, Haiberger R, Pietropaoli P: Caudal additives for postoperative pain management in children: S(+)-ketamine and neostigmine. Paediatr Anesth 2005; 15:143–7

13. Yaksh TL, Rathbun ML, Provencher JC: Preclinical safety evaluation for spinal drugs, Spinal Drug Delivery. Edited by Yaksh TL. Amsterdam, Elsevier Science, 1999, pp 417–37

14. Yaksh TL, Allen JW: The use of intrathecal midazolam in humans: A case study of process. Anesth Analg 2004; 98:1536–45

15. Farber NB, Kim SH, Dikranian K, Jiang XP, Heinkel C: Receptor mechanisms and circuitry underlying NMDA antagonist neurotoxicity. Mol Psychiatry 2002; 7:32–43

16. Hoyte L, Barber PA, Buchan AM, Hill MD: The rise and fall of NMDA antagonists for ischemic stroke. Curr Mol Med 2004; 4:131–6

17. Borgbjerg FM, Svensson BA, Frigast C, Gordh T Jr: Histopathology after repeated intrathecal injections of preservative-free ketamine in the rabbit: A light and electron microscopic examination. Anesth Analg 1994; 79:105–11

18. Erdine S, Yücel A, Özyalcin S, Özyuvaci E, Talu GK, Ahiskali B, Apak H, Savci N: Neurotoxicity of midazolam in the rabbit. Pain 1999; 80:419–23

19. Tucker AP, Lai C, Nadeson R, Goodchild CS: Intrathecal midazolam: I. A cohort study investigating safety. Anesth Analg 2004; 98:1512–20

20. Vranken JH, van der Vegt MH, Kal JE, Kruis MR: Treatment of neuropathic cancer pain with continuous intrathecal administration of S(+)-ketamine. Acta Anaesthesiol Scand 2004; 48:249–52

21. Benrath J, Scharbert G, Gustorff B, Adams HA, Kress HG: Long-term intrathecal S(+)-ketamine in a patient with cancer-related neuropathic pain. Br J Anaesth 2005; 95:247–9