

Racemic ketamine in comparison to S-ketamine in combination with azaperone and butorphanol for castration of pigs

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Summary

In this prospective blinded randomised study, 28 male 9 week old pigs of bodyweight 25 kg, were anaesthetised for castration using 5 mg/kg azaperone, 0.2 mg/kg butorphanol and 0.4 mg/kg meloxicam, in conjunction with either 15 mg/kg racemic ketamine (Keta-Race) or 9 mg/kg S-ketamine (S-Keta), all drugs being injected intramuscularly. Anaesthesia induction, maintenance and recovery were timed and scored. Insufficient anaesthesia was supplemented with ¼ the initial dose of ketamine or S-ketamine, respectively, administered intravenously. A t-test was utilised for analysis of timings, and, for repeated recovery time data, ANOVA was used. In relation to quantification and timing of supplemental drug doses, a chi square test was used and the scoring was analysed by two sample Wilcoxon rank-sum test. Ketamine re-dosing was required in 23 animals on a total of 46 occasions distributed evenly throughout both groups. The only group differences occurred during recovery, with the S-Keta group showing earlier movements, sternal recumbency and ability to stand. Three pigs in each group showed muscle fasciculations during the recovery period, while an additional two animals of the Keta-Race group exhibited marked and unacceptable paddling in recovery. In conclusion, S-ketamine at a dose rate of 60% of that of racemic ketamine induced comparable anaesthesia for castration in pigs, but with superior recovery characteristics.

Keywords: pig, castration, S-ketamine, anaesthesia

Razemisches Ketamin im Vergleich zu S-Ketamin kombiniert mit Azaperon und Butorphanol zur Kastration von Schweinen

In dieser prospektiven, verblindeten, randomisierten Studie wurden 28 männliche 9 Wochen alte, 25 kg (geschätzt) schwere Schweine mit 15 mg/kg razemischem Ketamin oder 9 mg/kg S-Ketamin, in Kombination mit 5 mg/kg Azaperon, 0.2 mg/kg Butorphanol und 0.4 mg/kg Meloxicam intramuskulär kastriert. Die Einleitung, die eigentliche Anästhesie und die Aufwachphase wurden qualitativ bewertet und die Zeitdauern gemessen. Bei ungenügender Anästhesietiefe wurde ¼ der initialen Ketamindosis intravenös nachgespritzt. Mittels T-test und ANOVA wurde die Zeitdauer und mittels «two sample Wilcoxon rank-sum test» die Qualität bewertet. Bei 23 Tieren musste 46 mal Ketamin (gleichmässig in beiden Gruppen) nachdosiert werden. Die einzigen Unterschiede zwischen den Gruppen traten in der Aufwachphase auf. Mit S-Ketamin kam es früher zu Bewegungen, Sternal-lage und Aufstehen. Drei Tiere jeder Gruppe zeigten Muskelzuckungen und 2 zeigten mit razemischem Ketamin hektische Ruderbewegungen in der Aufwachphase. Zusammenfassend führte S-Ketamin in einer Dosierung von 60% des razemischen Ketamin zu vergleichbarer Anästhesie. Kein Schwein mit S-Ketamin zeigte eine nicht akzeptable Aufwachphase.

Schlüsselwörter: Schwein, Kastration, S-Ketamin, Anästhesie

Introduction

For more than a decade, ethical concerns surrounding castration of pigs without the use of anaesthetic agents have been prevalent. Although veterinary surgeons would be able to provide such a service, this is simply not financially viable for food animal production. Currently, Swit-

zerland is the only country in the world where farmers who – having participated in a state-run official course – are permitted to perform inhalation anaesthesia with isoflurane for this purpose. With isoflurane anaesthesia, the piglets quickly become unconscious and also recover within a few minutes following castration. Concerns relating to this method, however, are the lack of analgesia,

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and first and most important the waste gas depleting the ozone layer and the potential for chronic low-grade exposure of farmers and other people involved in the process. Furthermore, the contamination of the inhalation apparatus with microbials is a potential source for infection transmission, particularly since such equipment is commonly used across different farms to maximise cost effectiveness. An alternative to inhalation anaesthesia would be an injectable anaesthetic technique. The only injectable anaesthetic currently licensed for pigs is racemic ketamine (equal mixture of S(+) and R(–) isomers). This agent provides analgesia, can be injected intramuscularly and respiration and cardiovascular function are only minimally depressed. However, ketamine has to be used in combination with sedatives to offset muscle hypertonicity and also prevent unacceptably excitable recoveries. As azaperone is the only sedative registered for pigs, it is the drug of first choice in this regard. To optimize analgesia, butorphanol or local anaesthesia should also be included (Nussbaumer et al., 2011).

In the past, anaesthesia with ketamine combinations in piglets produced higher mortality than castration without anaesthesia, (McGlone and Hellman, 1988; Lahrmann et al., 2005), and prolonged and uncontrollable recoveries were also observed (McGlone and Hellman, 1988). S-ketamine, the more active enantiomer of racemic ketamine, has only recently become available, and has been shown, in several species, to produce equipotent anaesthesia at 50–60% of the racemic ketamine dose. Its use also resulted in considerably shorter and better quality recoveries in humans, horses, dogs, cats and syrian hamsters (Erhardt et al., 2001; Larenza et al., 2008a; Larenza et al., 2009a).

The purpose of the present study was to evaluate and compare S-ketamine with racemic ketamine as part of an injectable anaesthetic technique for castration in pigs, with the hypothesis being that intramuscular anaesthesia with S-ketamine at 60% of the dose of racemic ketamine, in combination with azaperone and butorphanol, would produce equivalent anaesthesia and analgesia, and faster recovery of improved quality.

Animals, Material and Methods

Animals

The study was a blinded randomised prospective case-controlled field study, performed according to the guidelines for good clinical practice under the bylaws of the Swiss experimental animal research. Twenty-eight, nine week old male pigs, were included in the study. Their estimated weight was 25 kg BW (body weight), and drug doses were calculated based on this estimate. During the subsequent anaesthesia, their precise weight was measured to retrospectively calculate the exact dose rates given. The pigs were starved overnight, but always had free access to water.

Anaesthesia

On the morning of the experiment, the animals were separated into groups each containing 3–5 pigs. One group after the other was brought into a box where anaesthesia was induced, with each animal in the individual groups being injected at three-minute intervals. When castration of the last pig of one group was completed, the new group was then introduced into the anaesthesia induction box and, at that point, the anaesthetic agents were injected as described for the previous group. All pigs received 5 mg/kg BW azaperone (Stresnil® ad us. vet., solution for injection, Biokema, Lausanne, Switzerland) and 0.2 mg/kg BW butorphanol (Morphasol® – 10 ad us. vet., Dr. E. Graeub AG, Berne, Switzerland), together with either 9 mg/kg BW S-ketamine (Keta-S® ad us. vet., 60 mg/ml, solution for injection, Dr. E. Graeub AG, Berne, Switzerland) (group S-Keta), or 15 mg/kg BW racemic ketamine (Ketasol® – 100 ad us. vet., 100 mg/ml, solution for injection, Dr. E. Graeub AG, Berne, Switzerland) (group Keta-Race), all mixed in one syringe and administered intramuscularly (IM) into the neck area. Additionally, meloxicam (Metacam® – 20 mg/ml ad us. vet., Boehringer Ingelheim GmbH, Basel, Switzerland) was administered IM at a dose of 0.4 mg/kg BW. Castration was performed by residents of the Section of Pig Medicine, Department of Farm Animals or clinical students of the Vetsuisse Faculty, University of Zurich, Switzerland.

Scoring

Three anaesthesia phases were defined, during which scoring and timing took place: anaesthesia induction (while the pigs were losing consciousness), anaesthesia maintenance (while being unconscious) and anaesthesia recovery (when the pigs were awakening). The anaesthesia induction and recovery phases were videotaped and scored retrospectively. The pigs were not restrained at any point. Fifteen minutes after initial drug injection, depth of anaesthesia was first judged by an experienced anaesthetist (Regula Bettschart-Wolfensberger). If an animal did not become immobile within 15 minutes after its first intramuscular injection, it was re-dosed with ½ the initial dose of both azaperone and the respective ketamine (2.5 mg/kg BW azaperone and 7.5 mg/kg BW racemic ketamine or 4.5 mg/kg BW S-ketamine) IM. Once in lateral recumbency and immobile, the pigs were lifted onto the surgery table and stimulated by nasal septum pinching (tA). If a pig demonstrated a purposeful reaction (flinching or gross movement) in response to either being moved to the table or to pinching of the nasal septum, or to other stimuli during the castration phase (weighing, skin preparation or surgical manipulation), it was re-dosed with ¼ the initial dose of the respective ketamine intravenously (IV) into an auricular vein. After re-dosing, the pig was left to relax for 45 seconds before re-assessing anaesthesia by again pinching the nasal septum. If further

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Table 1: Scores used to judge anaesthesia induction, recovery and maintenance phase in 28 pigs undergoing castration.

Anaesthesia induction			
Score	Ataxia	Paddling	Lying down, and getting up
0	No ataxia	No paddling	None and 1 x getting up
1	Single ataxia	Single occurrence of paddling	> 1 x getting up
2	Repeated ataxia	Repeated paddling	> 3 x getting up
3	Continuous ataxia	Continuous paddling	> 6 x getting up
Anaesthesia maintenance			
Score	Quantity of movements	Intensity of movements	Vocalisation
0	No movement	No movement	No vocalisation
1	Single movement	Movement of one extremity	Single vocalisation
2	Repeated movement	Movement of more than one extremity	Repeated vocalisation
3	Continuous movement	Spinal cord inclusive	Continuous vocalisation
4		Like 3, but stronger	
Recovery from anaesthesia			
Score	Paddling	Convulsions	Attempts to stand
0	No paddling	No convulsion	One attempt
1	Single occurrence of paddling	Single convulsion	> 1 attempt
2	Repeated paddling	Repeated convulsions	> 3 attempts
3	Continuous paddling	Continuous convulsions	> 6 attempts

reaction occurred an additional ¼ dose of the respective ketamine was again administered IV, until no response was observed to the nasal septal pinching. Subsequently, preparation of the surgical site and, thereafter, the surgery were initiated. If a response (flinching or movement) was observed to either clamping of the spermatic cord or to traction on the testicle, 2.5 ml of lidocaine (Lidocain HCl 2%, Kantonsapotheke Zurich, Switzerland) was injected directly into the testicle.

At pre-determined scoring time points, the exact time was recorded and scoring took place. The scoring system used is detailed in Table 1. During anaesthesia induction, the following activities were recorded: the first time the pig assumed sternal recumbency following drug administration (tF), when the pig remained in lateral recumbency without attempting to rise again (tG), and when the pig demonstrated no further movement (tH). During anaesthesia, the timepoints documented were: when the pig was first touched and pinched on the nasal septum (tA), when the animal was brought onto the surgery table and placed in dorsal recumbency (tB), time of first cut (tC1), the first pinching of the spermatic cord (tD1), time of the second cut (tC2), and the second pinching of spermatic cord (tD2). The time the castration was completed (tE) was noted, as well as when the pig was removed from the surgery table and brought into the recovery box. The duration of the castration was calculated from the first cut (tC1) to the end of the surgery (tE). During recovery, the timepoints recorded were: time of the first movement (tK), time of attainment of sternal recumbency (tL), and time of standing (defined as the pig being able to walk

at least 4 steps without falling over) (tM). All times were recorded in seconds following the first drug administration.

As soon as one test animal was able to stand, it was removed to another box, so the remaining unconscious pigs were less disturbed.

Statistics

Statistical analysis was performed with the program STATA® (StataCorp., 2009; Stata Statistical Software: Release 12.0; College Station, TX, USA: StataCorp LP). To compare the timings between the groups S-Keta and Keta-Race, a t-test was used. Repeated recovery time data was analysed by ANOVA. To compare the two treatment groups regarding additional doses of anaesthetics, a chi square test was used. Differences in scores between the two treatments were analysed using a two sample Wilcoxon rank-sum test. To rule out differences between timing and scoring within the castration phase a GLM (general linear model) or, in special cases, logistic regression with the co-variable time was used. The level for significance was set at $p \leq 0.05$ and a p-value between > 0.05 and 0.2 was recorded as a tendency.

Results

All 28 pigs survived the anaesthesia and were successfully castrated. There was no difference between the two groups concerning body weight (mean weights: S-Keta

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26 kg, Keta-Race 25 kg), mean total dose rates in ml of the test drugs (S-Keta 5.42 ml/pig and Keta-Race 5.16 ml/pig) or mean duration of surgery (S-Keta 571 secs, Keta-Race 642 secs). Two animals in the S-Keta group had to be re-dosed with $\frac{1}{2}$ the initial doses of azaperone and the test drug intramuscularly. Before the start of surgery, 23 out of the 28 pigs needed additional IV ketamine/S-ketamine, but there was no difference between the groups. Overall, 13 pigs in the S-Keta group on 25 occasions, and 10 pigs in the group Keta-Race on 21 occasions, required re-dosing. Most of the top-ups were administered between first touch and moving onto the surgery table. Only three pigs (S-Keta: 2; Keta-Race: 1) needed supplemental anaesthetic while being castrated. Details are given in Table 2. Heavier pigs needed significantly more supplemental racemic or S-ketamine. In both groups, three animals required lidocaine injected into one of the testicles, and in group S-Keta, two animals had both testicles injected. During anaesthesia induction, there was a tendency for the Keta-Race group to attain sternal and lateral recumbency (tF) in a shorter period of time, specifically, after a mean of 253 secs (with a 95 % confidential interval of 177–330 secs) compared to 602 secs (with a 95 % confidential interval of 152–1051 secs) for S-Keta. No differences between the two groups were determined concerning scores for “ataxia”, “paddling” and “lying down & getting up”. In 10 animals of the S-Keta group, no paddling during anaesthesia induction was observed, one animal paddled once, two animals paddled repetitively, and one animal showed continuous paddling. In the Keta-Race group, six animals showed no paddling, six animals paddled once, one pig paddled repetitively, and one pig showed continuous paddling. There was no difference in time from first stimulation to end of castration between the two groups, and duration of castration was also not different between the groups. On average, in the S-Keta and Keta-Race groups, respectively, the pigs were immobile after 629 and 458 secs, and the surgery took 571 and 642 secs. During castration, the number of times the pigs moved, the intensity of movements, and vocalisation were not significantly different between the two groups. Overall, most animals reacted with movement when first touched and pinched in the nasal septum or when moved onto the surgery table. When the second spermatic cord was clamped, three animals of the S-Keta group vocalised either once or repetitively.

During recovery, the first movements were observed significantly earlier in the S-Keta group (3304 secs with a 95 % confidential interval of 2793–3815 secs) compared to Keta-Race group (3570 secs with a 95 % confidential interval of 3051–4090 secs). There was also a tendency that animals in the S-Keta group attained sternal recumbency more rapidly (S-Keta 4258 secs; Keta-Race 4675 secs). Furthermore, pigs of the S-Keta group were able to stand after a mean duration of 6006 secs, approximately 8 minutes faster compared to the pigs in the Keta-Race group (6483 secs). A significant correlation between re-dosing and the recovery phase was noted: the more additional anaesthetic increments the pigs in the S-Keta group received, the faster they achieved sternal recumbency and the earlier they made their first movements or were able to stand. In contrast, the greater the number of incremental anaesthetic doses the animals in the Keta-Race group received, the later they attained sternal recumbency and the longer the time to first movement or ability to stand. There were no significant statistical differences in the recovery quality scores between the two treatments, but two pigs in the Keta-Race group showed repetitive paddling during the recovery phase; this was extreme and involved all four legs. No paddling was observed during recovery from S-Keta. A single convulsion/muscle fasciculation was noted in two animals of the S-Keta and one pig in the Keta-Race group. Repetitive convulsions were noted in one animal that received S-Keta and two animals of the Keta-Race group.

Discussion

The present study assessed the use of S-ketamine at a dose rate of 60 % of that of racemic ketamine, *versus* racemic ketamine, for castration of 9 week old pigs. In order to induce satisfactory anaesthesia, both forms of ketamine were combined with azaperone, butorphanol and meloxicam, and local anaesthesia was also administered if required. Overall, S-ketamine at the dose used induced anaesthesia comparable to racemic ketamine. The number of animals in both groups that required supplemental ketamine/S-ketamine and/or local analgesia to achieve satisfactory anaesthetic conditions was much higher than presumed. This is surprising, because the initial doses of ketamine and S-ketamine used in this study were rela-

Table 2: Number of animals and number of additional boli of racemic ketamine or S-ketamine administered to 28 pigs to achieve satisfactory anaesthesia for castration.

$\frac{1}{2}$ Ketamine bolus	Yes	No	Total	0x	1x	2x	3x	4x	Total
S-Ketamine	13	1	14	1	4	7	1	1	25
Ketamine-Racemate	10	4	14	4	3	4	2	1	21
Total of animals	23	5	28	5	7	11	3	2	28
Total of re-dosages				0	7	22	9	8	46

tively high compared to previously published data (Nussbaumer, 2011).

Most studies of S-ketamine in other species showed that 50 to 66% of the racemic ketamine dose for S-ketamine are equipotent (Deleforge et al., 1991; Larenza et al., 2008a; Larenza et al., 2009b; Jud et al., 2010). In the present study, a dose rate of 60% of S-ketamine in comparison to racemic ketamine was chosen which seemed appropriate, as the anaesthetic effects were similar and the differences between groups minimal. The need for re-dosing was unexpectedly high (23 out of 28 pigs required further doses of racemic or S-ketamine on a total of 48 occasions) but was evenly distributed throughout the two treatment groups, with a mean total dose of 13 mg/kg BW S-ketamine and 20 mg/kg racemic ketamine.

The ketamine dose, together with that of azaperone and butorphanol used in this study, were chosen based on data published by Nussbaumer et al., 2011. The dose range of racemic ketamine used in other studies varies from 8 mg/kg BW to 25 mg/kg BW (Boschert et al., 1996; Lahrman et al., 2005; Axiak, 2007; Nussbaumer et al., 2008; Heinonen et al., 2009). It is likely that, with an initially higher dose of ketamine, our pigs would have been more deeply anaesthetised; however, this would also have potentially resulted in prolonged and poorer quality recoveries, and potentially dangerous cardiopulmonary depression.

The scores used to objectively evaluate the anaesthetic and analgesic state of the tested pigs were a combination of previously described scores (Nishimura et al., 1993; Heinonen et al., 2009; Leidig et al., 2009). As only movement of legs was scored a positive response, problems arose when animals only “twitched”, but did not actually move a body part, or if they only moved their head or twitched their tongue. These observations were noted, but not included in the pre-determined scoring system. In any case, such events should not occur during a satisfactory anaesthesia state. In subsequent studies they should be included into the scoring system in order to more objectively assess the quality of anaesthesia.

Recovery of these pigs from S-ketamine was faster compared to racemic ketamine, and this has also been noted in other species due to faster elimination of the S-isomer when used as a single agent compared to its use within the R/S-ketamine (Larenza et al., 2008a; Larenza et al., 2008b; Larenza et al., 2009b). This could be of particular importance if higher dose rates of ketamine are used to improve anaesthesia quality, and if S-ketamine is used in neonatal piglets, where a quick recovery is crucial for survival. Convulsions during recovery were recorded in both groups and recovery quality was similar between groups, but two animals in the Keta-Race group showed repetitive extensive, severe paddling with all four limbs, which was not observed in the S-ketamine group. Improved recovery quality with S-ketamine has also been reported in cats, horses and syrian golden hamsters (Er-

hardt et al., 2001; Larenza et al., 2008a; Larenza et al., 2009a).

According to the animal protection law in Switzerland, since January 2010 every animal must be anaesthetized for castration. Previously, the Swiss College of Agriculture (SHL) launched a project called ProSchwein, which investigated all the possible methods of anaesthesia for castration in pigs, in addition to assessing the degree of acceptance or otherwise – by farmers and consumers – of raising this species for food production without castration, including the potential economical impacts and international developments. Client acceptance for surgical castration compared to vaccination against boar taint was shown to be better (Kupper et al., 2008; de Roest et al., 2009). The use of local anaesthesia alone was found not to achieve complete analgesia and therefore did not accomplish Swiss standards for pain relief for castration (Jäggin et al., 2008; Kupper et al., 2008). Further studies even concluded that castration solely under local anaesthesia caused pain comparable to that of castration without local anaesthesia (Zols et al., 2006).

Even though isoflurane inhalation anaesthesia for piglet castration carries the risk of incorrect use of the anaesthetic machine, causes pollution of the environment, is not analgesic and potentially poses a health risk for the operator (Jäggin and Burren, 2008; Kupper et al., 2008; Jäggin and Burren, 2009), it is in widespread use by Swiss farmers. The only alternative recommendation, so far, is the use of azaperone/butorphanol/ketamine intramuscularly (Burren et al., 2008). The idea of using S-ketamine instead of racemic ketamine was to further improve the applicability of the protocol by shortening recovery times and quality. We tested the current protocols in 9 week old pigs and not in neonates in order to have the possibility for IV intervention in case of unsatisfactory anaesthesia with S-ketamine, as this drug had not been used previously in pigs.

The present study tested S-ketamine at 60% dose rate in comparison to racemic ketamine, in combination with azaperone, butorphanol and meloxicam. As expected, the differences between the groups were minimal but recovery was shorter with S-ketamine. The overall incidence of unsatisfactory anaesthesia quality was high for both treatments, and trials with higher ketamine dose rates have to be performed in order to optimize the dose for castration of pigs.

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674 Originalarbeiten/Original contributions**Comparaison entre la kétamine racémique et la S-kétamine combinées à l'azaperon et au butorphanol pour la castration des porcs.**

Pour cette étude prospective, randomisée et en aveugle, on a castré 28 porcs mâles âgés de 9 semaines et d'un poids estimé de 25 kg en utilisant soit 15 mg/kg de kétamine racémique soit 9 mg/kg de S-kétamine, en combinaison avec 5mg/kg d'azaperon, 0.2 mg/kg de butorphanol et 0.4 mg/kg de meloxicam, administrés par voie intramusculaire. L'induction et l'anesthésie elle-même ainsi que la phase de réveil ont été estimées qualitativement et leurs durées mesurées. Si la profondeur de l'anesthésie était insuffisante, on a injecté par voie intraveineuse $\frac{1}{4}$ de la dose initiale de kétamine. On a estimé les durées par T-test et ANOVA et la qualité de l'anesthésie par «two sample Wilcoxon rank-sum test». Chez 23 animaux, il a été nécessaire de rajouter 46 fois de la kétamine (de façon égale dans les deux groupes). Les seules différences entre les deux groupes ont été observées lors de la phase de réveil. Avec la S-kétamine, on observe plus rapidement des mouvements, une position sternale et un relevé. Trois animaux de chaque groupe ont présenté des fasciculations musculaires et deux, après application de kétamine racémique, des mouvements de pédalage importants durant la phase de réveil. En résumé, l'application de S-kétamine à un dosage correspondant à 60% de celui de la kétamine racémique produit une anesthésie similaire. Aucun des porcs anesthésiés avec de la S-kétamine n'a montré une phase de réveil inacceptable.

Ketamina racemica paragonata alla S-ketamina combinata con azaperone e butorfanolo per la castrazione dei suini

In questo studio prospettivo, a cieco e randomizzato sono stati castrati per via intramuscolare 28 suini maschi, di 9 settimane di un peso di ca. 25 kg, con 15 mg/kg di Ketamina racemica oppure con 9 mg/kg di S-ketamina in combinazione con 5 mg/kg di azaperone, 0.2 mg/kg di butorfanolo e 0.4 mg/kg di meloxicam. L'introduzione, l'anestesia di fatto e la fase di recupero sono state valutate qualitativamente e misurate sulla durata. In caso di insufficiente profondità dell'anestesia è stato successivamente somministrato per via endovenosa $\frac{1}{4}$ della dose iniziale di ketamina. Con l'utilizzo di T-test e ANOVA è stata misurata la durata e tramite il test «due Wilcoxon rank-sum test» è stata valutata la qualità. In 23 animali per ben 46 volte si è dovuto somministrare la ketamina in più (allo stesso modo in entrambi i gruppi). Le uniche differenze tra i gruppi si sono osservate durante la fase di recupero. Con la S-ketamina, i movimenti, il decubito sternale e la posizione in piedi sono sopravvenuti prima. Tre animali di ogni gruppo hanno mostrato contrazioni muscolari e 2, con ketamina racemica, hanno reagito con movimenti a remi frenetici durante la fase di recupero. In sintesi, la S-ketamina in dosi del 60% della ketamina racemica conduce ad un'anestesia comparabile. Nessun suino trattato con S-ketamina ha mostrato una fase di recupero inaccettabile.

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