ORIGINAL ARTICLE

A study of low-dose S-ketamine infusion as "preventive" pain treatment for cesarean section with spinal anesthesia: benefits and side effects

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ABSTRACT

Background. Attenuation of central sensitization with NMDA-active drugs such as S-Ketamine may play a role in postoperative analgesia and prevention of neuropathic pain. However, during cesarean section with neuraxial block, S-Ketamine might have adverse effects on the interaction between mothers and infants, including breastfeeding.
Methods. Women undergoing elective repeat cesarean section with subarachnoid anesthesia (0.5% hyperbaric bupivacaine 8-10 mg and sufentanil 5 μg) were enrolled in a double-blind, randomized study. Patients in the S-Ketamine group (N.=28) received *i.v.* midazolam 0.02 mg/kg and S-Ketamine 0.5 mg/kg *i.m.* bolus 10 minutes after birth followed by a 2 μg/kg/min *i.v.* continuous infusion for 12 h. The control group (N.=28) received placebo. Paracetamol and patient controlled analgesia with intravenous morphine were given postoperatively. Von Frey filaments were used to assess pain threshold on the inner forearm and T10-T11 dermatomes (supposed hyperalgesic area).
Results. S-Ketamine reduced morphine consumption at 4-8, 8-12, and 12-24 hours after surgery (total 31%), even after its effect has ceased, suggesting an anti-hyperalgesic action. Mild side effects were observed in the S-Ketamine group one hour after delivery. All side effects were rated as light and there were no serious adverse events. Pain threshold was not significantly different between groups. S-Ketamine patients showed a trend towards reduced pain sensitivity at the T10 dermatome, which is involved by surgical damage. After three years, patients reported no differences in residual pain, dysesthetic symptoms, or duration of breast-feeding.
Conclusion. Preventive administration of S-Ketamine *via* 12-hour infusion was safe and may have anti-hyperalgesic action after cesarean section. *(Minerva Anestesiol 2012;78:774-81)*

Key words: Ketamine - Cesarean section - Anesthesia, spinal - Pain, postoperative - Hyperalgesia.

Persistent pain after surgery is recognized to be a prevalent healthcare problem with an incidence ranging from 10% to 80% depending on the surgical procedure,[1-4] and between 5.9% [2] and 18% [3, 4] after cesarean section, one of the commonest surgical procedures worldwide.

Poorly controlled pain in the post-operative period may contribute to the generation of persistent pain.[2-4]

It is known that tissue damage may trigger altered processing of noxious stimuli so that perception of pain persists even after cessation of nociceptive input. This is referred to as central sensitization and represent a mechanism of amplification of pain perception.[5]

Effective barrage of noxius stimuli trough regional anesthesia and perioperative administration of analgesic and anti-hyperalgesic drugs may play a significant role in attenuation of central sensitization and prevention of neuropathic persistent pain.[2-4, 6]

Due to the central role played by NMDA receptor in central sensitization,[5] NMDA-antagonists ketamine and S-ketamine may be useful

for their analgesic and anti-hyperalgesic properties. In many clinical trials [7-16] ketamine isomers showed to reduce analgesic consumption when used as adjuvant for post-operative pain treatment through various routes of administration, mostly on patients in general anesthesia.

Little information is available about ketamine isomers use in women undergoing cesarean section with neuraxial block,[11, 15, 16] in particular when they are administered not only as a preemptive (preoperatively), but as a preventive (perioperative) treatment.[17] Efficacy of these drugs in this context needs to be further investigated.

The aim of this study was to examine the benefits and side effects of preventive low dose S-Ketamine administration in cesarean section with neuraxial block, as well as its influence on breastfeeding,[6] and persistent pain generation.[12-14]

Materials and methods

Subjects

With hospital Ethics Committee approval and written informed consent from study participants, 56 women scheduled for elective repeat cesarean section with subarachnoid anesthesia were enrolled in this double-blind, randomized study. Exclusion criteria were: age <18 years or >40 years, ASA status III-IV, preexisting neurological or psychiatric illnesses, pathologic pregnancy, gestational age <37 weeks, and difficulties in cooperation between physician and patient. We also did not admit patients with history of chronic pain, assuming NSAIDs or opioids or opioids addicted.

Considering pilot experience, it was calculated that 23 patients per group would have been required to detect a 25% decrease in the mean 24hrs morphine consumption, assuming alpha = 5% and beta error = 20%. With use of a computer-generated randomization table, 28 patients per group were enrolled to account for dropouts.

Preoperative and intraoperative procedures

Thirty minutes before entering the operating room, all patients received normal saline 1000 mL *via* intravenous cannula and antibiotic prophylaxis. Spinal puncture was performed in the sitting position at the L3-L4 or L4-L5 interspace with a 25-gauge Whitacre spinal needle. Sterile technique was adopted and 2% lidocaine 3-5 mL was used for local anesthesia. Subarachnoid block was performed with 0.5% hyperbaric bupivacaine 8-10 mg and sufentanil 5 µg. Patients were then placed in a supine position with 15-degree left uterine displacement. Spread of sensory block level was assessed by pinprick every minute after the block until reaching the T4 dermatome and motor block was evaluated according to the Bromage scale.

Non-invasive systolic and diastolic maternal arterial pressure were recorded every three minutes and heart rate and peripheral oxygen saturation (SpO_2) were monitored continuously throughout surgery. Sixty percent oxygen via facial mask was administered until birth and after birth in case of SpO_2 <90%. Ephedrine 5 mg was administered in case of systolic pressure <100 mmHg or diastolic pressure <60 mmHg and atropine 0.04 mg *i.v.* in case of maternal heart rate <50 bpm.

Immediately after umbilical cord clamping, the infusion of oxytocin 20 UI in 500 mL 5% glucose solution infusion was started at a rate of 100 mL/h.

A person not involved in the study supplied a 50-mL syringe containing the study drug, which was either S-Ketamine diluted to 1 mg/mL or normal saline. Patients in the S-Ketamine group received 0.5 mg/kg *i.m.* S-Ketamine bolus 10 minutes after birth followed by 2 µg/kg/min. *i.v.* continuous infusion for 12 h *via* infusional pump (Fresenius Kabi AG Bad, Homburg, Germany). Patients in the control group received placebo in the same manner. In all patients *i.v.* midazolam 0.02 mg/kg was administered before *i.m.* bolus.

Study drug dosage was calculated using weight at term minus 41% of ponderal increment.[18] The dosing scheme for S-Ketamine infusion was calculated using published pharmacokinetic variables to achieve a theoretical plasma concentration of 150 ng/mL intraoperatively [19] and 60 ng/mL postoperatively.[20] These concentrations are in the range known to counteract hyperalgesia while producing minimal side effects.[21] When present, nausea and vomiting after birth and in

the postoperative period were treated with ondansetron *i.v.* 8 mg.

Postoperative analgesia

Immediately after surgery patients were connected to a patient-controlled analgesia (PCA) device set to deliver 1 mg morphine as intravenous bolus with an 8-min lock out interval and a maximum permitted volume of 30 mg/4 h. Continuous infusion was not allowed. This PCA regimen was continued for 24 h after surgery. After this, oral paracetamol 4 g/day and Ketorolac 30-90 mg/day were given for pain according to patient need.

Measurements and pain assessment

Patients demographic characteristics (age, weight, height, gestational age), duration of surgery, blood pressure (BP) and heart rate (HR) during surgery at following intervals were recorded (basal time, surgical incision, 20 min after incision, end of procedure). Time to first request of analgesia were recorded. At 1, 4, 8, 12, and 24 h from surgery the following parameters were collected:

— pain at rest and during cough using the 100-mm visual analog scale for pain (VAS) (0=no pain to 10=worst pain);

— adverse side effects including drowsiness, diplopia, nystagmus, dizziness, light-headness, dreaming, hallucinations, negative and positive dysphoria, nausea, vomiting, pruritus (rated by patients 0-3: 0=absent, 1=light, 2=disappointing, 3=severe);

— sedation using the Ramsay Sedation Scale;

— cumulative morphine consumption;

— occurrence of serious adverse events, such defined: respiratory failure needing Oxygen administration or ventilator compromise, severe hemodynamic instability (BP <80 mmHg, HR <45 bpm or cardiac arrest), severe neurological impairment (convulsions, coma).

Von Frey filaments were used to assess pain threshold for mechanical static stimuli. Two sites were analyzed: a 2 cm^2 area on the inner forearm (FA site: C6-C7 dermatomes, no supposed hyperalgesic area), and a 2 cm^2 area on the umbilical-pubic line, 5 cm under the umbilicus (T10 site: T10-T11 dermatomes, supposed hyperalgesic area). Filaments were applied on the chosen areas for approximately 1 s, applying only a pressure stimulus without scrubbing the skin.

Von Frey filaments were applied from thinner to thicker (0.057-178 g/mm^2), each for three times, separated by 30 seconds to reduce the likelihood of anticipatory responses. Patients were instructed to describe each sensation in the following way: no touch (score 1), light touch (score 2), strong touch (score 3), sharp touch with no pain (score 4), light prick (score 5), strong prick (score 6). A mean of the three determinations was calculated. The first force (g/mm^2) sufficient to elicit pain (mean score 5) was the tactile pain threshold.[22] Measurements were performed before surgery (basal time) and at 4, 12, and 24 h after surgery.

In order to reduce the influence of intra-individual and inter-individual variability in pain perception and to maximize study sensitivity, the following methodology was adopted.

At each time, pain thresholds at FA and T10 sites were compared in each patient and their difference was termed FA-T10.

In each patient, FA-T10 obtained at 4, 12, and 24 hours after surgery was compared with FA-T10 at basal time. Their difference was termed Δ4, Δ12, and Δ24, respectively (*i.e.* Δ4 = [FA-T10]4 h- [FA-T10] basal). A positive Δ value indicated a relative increase in pain sensitivity at the T10 site respective to FA site. A negative Δ value indicated a relative decrease in pain sensitivity in T10 site respective to FA site. Δ values were compared between Ketamine-treated patients and controls.

The incidence of postoperative residual pain was evaluated at 6 and 36 months after surgery using the following questions:

1) Do you feel any pain at the scar area? Do you take medication to alleviate it? Do you have any particular sensations from the scar area (itching, burning, sensitivity, etc.)?

2) Do you feel pain at any other place? If yes: where? Do you take analgesics?

3) Which unpleasant manifestation have you experienced since your operation?[12]

4) How long did you breastfeed your child?

Table I.—*Demographic variables.*

	CONTROLS	KETAMINE Patients	P-value
Age (yrs)	33.54	34.00	0.357
Weight (kg)	75.04	73.22	0.315
Gestation age (wks)	38.05	38.44	0.004
Surgery duration (min)	51.07	53.04	0.271
Parity (N.)	2.46	2.33	0.249

Data are presented as mean (SD).

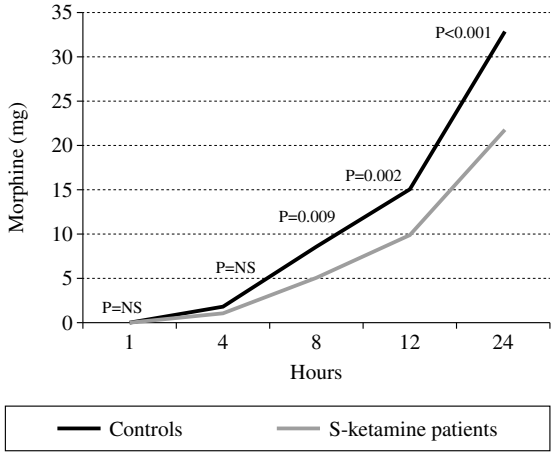

Figure 1.—Morphine consumption.

5) How long did you breastfeed after the previous cesarean section? What kind of anesthesia did you receive then?

The enquiry was performed by the researcher via phone call and was confirmed by mail.

Statistical analysis

Student's t test for continuous data with Satterthwaite method for equality of variance was applied to compare groups for morphine consumption at 24 hours and in the first and second 12 hours and for duration of breastfeeding.

Groups were compared with Student's *t* test for demographic variables, time for first morphine bolus request, basal FA-T10, Δ4, Δ12, and Δ24. Chi square test was used for side effect analysis.

A repeated measurements model was also used to describe morphine consumption in relation to time and von Frey diameters, using the MANOVA model with four classical indexes (Wilks, Pillai, Hotelling, and Roy) to calculate a Fischer's F for model evaluation. A logistic model was used to compare groups for follow-up data.

Results

There were no differences in groups regarding patient demographics (age, weight, number of pregnancies, and number of previous cesarean sections) (Table I). Incidentally, we found a slight but significant difference in gestational age (P=0.004). No difference in hemodynamics between groups was observed throughout the procedure. VAS scores at rest and during cough were not statistically different in S-ketamine and control patients at any interval. There was no difference between groups concerning use of other medications (ondansetron, paracetamol, ketorolac).

Morphine consumption was significantly reduced in the S-Ketamine group at 4-8, 8-12, and 12-24 hours after surgery (Figure 1). Additionally, S-Ketamine treated patients showed an approximately 31% reduction in total morphine consumption (P=0.0005) (Table II).

MANOVA confirmed that increased morphine consumption was linked both to time (P value <0.001) and absence of exposure to S-Ketamine (P value=0.019). Additionally, time to first morphine bolus administration was significantly longer in S-Ketamine treated patients (190 min ±81.48 SD *vs.* 268 min ±158 SD, P=0.013).

Several side effects were observed in the S-Ketamine group and not in controls: drowsiness, diplopia, nystagmus, dizziness, light-headness, positive dysphoria, and vomiting. (P<0.05); dreaming, negative dysphoria, hallucinations (P=NS) (Table III). None of them were considered disappointing (rating 1). All side effects were short-lived and resolution time was less

Table II.—*Cumulative morphine consumption, mg.*

Time	Control patients (mean values)	Controls (SD)	Ketamine patients (mean value)	Ketamine (SD)	P value
1 h	0.03	0.18	0.00	0.00	0.165
4 h	3.03	3.93	1.88	2.69	0.107
8 h	11.17	8.52	6.48	5.62	0.009
12 h	18.21	9.78	11.29	6.01	0.002
24 h	37.00	11.57	25.33	11.76	<0.001

Table III.—*Side effects.*

	Controls (N.=28)	Ketamine (N.=28)	P
Drowsiness*	0	14	<0.001
Diplopia*	0	11	<0.001
Nystagmus*	0	14	<0.001
Dizziness*	0	23	<0.001
Light-headness*	0	6	0.009
Dreaming	0	3	0.075
Negative dysphoria	0	2	0.149
Positive dysphoria*	0	7	0.005
Nausea	4	7	0.313
Vomiting*	0	5	0.019
Pruritus	25	23	0.445
Hallucinations	0	2	0.150

rating=1 when present, * =significant difference.

Table IV.—*Follow-up data.*

	Control patients N.=13/28 (46%)	Ketamine patients N.=13/28 (46%)	P value
Residual wound pain	1	0	NS
Analgesic drugs use for wound pain	0	0	NS
Wound dysesthesia	8	5	NS
Pain in other sites	8	5	NS
Analgesic drugs for pain in other sites	8	4	NS
Improved experience	4	6	NS
Breastfeeding duration (months)	10.53	8.03	NS

NS: non significant.

than 1 hour after the end of surgery. Exceptions were: 1 patient with diplopia lasting 8 hours, 1 patient with dizziness lasting 4 hours, and 1 patient with vomiting 4 hours after surgery.

Nausea and pruritus were observed in both groups with no significant differences (Table III). No serious adverse events were observed.

At 3 years follow-up, 13 women per group (46%) completed the telephone survey. Groups did not show any significant differences in terms of residual pain and other dysesthetic symptoms (pruritus, tension, hypoesthesia, other), incidence of other pain syndromes, memory of perceived postoperative pain with respect to other caesarean sections, or duration of breastfeeding (Table IV).

S-Ketamine treated patients showed negative Δ values and controls showed positive Δ values at each interval (Figure 2). Δ4, Δ12, and Δ24 were not significantly different between groups.

Discussion

The main result of this study was that low-dose preventive S-ketamine 12-hour infusion

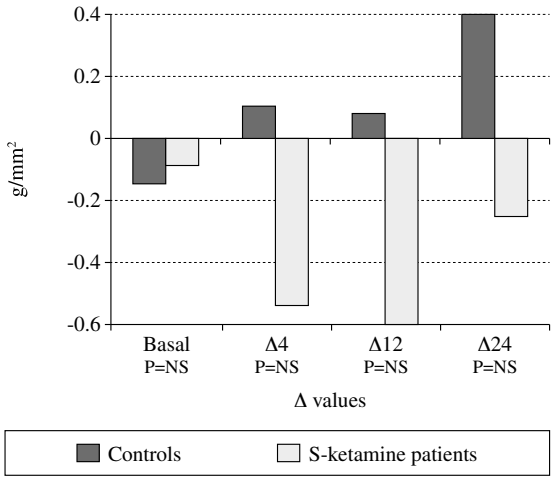

Figure 2.—Δ values (pain thresholds on abdominal skin *vs.* forearm skin at set time intervals).

reduced total morphine consumption approximately by 31% and prolonged time to first request of analgesia without harmful side effects or influence on breastfeeding in obstetric patients undergoing cesarean section with subarachnoid anesthesia

In previous studies,[2, 7, 11, 15, 16] ketamine after cesarean section prolonged analgesia and reduced analgesic consumption when administered intravenously soon after initiating spinal anesthesia [11] and not when administered intravenously but in association with general anesthesia [7] or intrathecally.[16]

Systemic route seems to be the most effective for S-Ketamine administration as adjuvant therapy for perioperative analgesia and in reducing wound hyperalgesia.[23] This could be due to peripheral and supraspinal effects predominance.[11]

Also, persistent pain incidence after cesarean section was found to be higher with general than with spinal anesthesia [1-4] and in patients with recall of severe pain in the immediate postoperative period.[4] It must be considered that most cesarean sections with general anesthesia are performed for urgent conditions and these may be associated with higher pain scores.[2] Anyway, it can be argued that a combination of regional block and systemic anti-hyperalgesic drug (ketamine) may allow better analgesia and reduce persistent pain occurrence, acting at peripheral and central level.[6] In fact, if noxious input is only partially blocked, it may determine prolonged and repetitive activation of first (by tissue damage and inflammation) and second order neuron, which could represent the pathophysiological basis for altered processing of noxious stimuli and peripheral and central sensitization, respectively.

Differently from previous studies, in which ketamine was administered as a single dose, we adopted a perioperative administration of S-ketamine in order to better prevent sensitization to pain. In fact, both timing and duration of analgesic treatments can be important in this modulation. As pain hypersensitivity is initially triggered by neurophysiologic mechanisms due to incisional injury but perpetuated by inflammatory phenomena, a treatment aimed to prevent sensitization should not only start preoperatively (preemptive treatment) but should cover the entire perioperative period (preventive treatment).[17]

In our study nociceptive input induced by surgical trauma was initially blocked by spinal anesthesia. In addition, systemic S-Ketamine administration was begun in order to take advantage of its NMDA and non-NMDA effects at supraspinal and peripheral sites.[23, 24] S-Ketamine bolus was delayed just after delivery to avoid any fetal exposure to drugs active on the central nervous system.

Reduction in morphine consumption confirms opioid sparing effect of ketamine,[25-27] expression of analgesic activity. This effect persisted even after S-Ketamine infusion had stopped and its action could be considered to be ceased that is, in the second 12-hour period after surgery (Figure 1). As S-Ketamine context-sensitive half-life is less than 2 hours,[28, 29] this may be consistent with anti-hyperalgesic properties of the drug, rather than simple additive analgesic effect.

In order to look for S-Ketamine antihyperalgesic utility, subjective neurophysiological pain threshold evaluation was performed with Von Frey filaments. With this technique, no statistically significant difference between groups was found. However, compared to controls, S-Ketamine treated patients showed a trend to a relative reduction in pain sensitivity in the T10 dermatome, which was involved by surgical damage (Figure 2).

Pain threshold evaluation was easily approached through von Frey's filaments subjective technique, but newer methods, such cold-heat passive threshold evaluation, laser-evoked potentials, or cold-heat evoked potentials (CHEPS) [30, 31] are less operator-dependent and could offer greater sensitivity in showing variation in these biological phenomena, which are difficult to objectify.

S-Ketamine administration to awake mothers could raise safety concerns. Mild neurologic side effects were associated with S-Ketamine, while discomfort due to nausea, pruritus, hallucinations, or negative dysphoria were not more frequent in the study group than in controls. We conclude that no serious (life-threatening or severely uncomfortable) side effects were observed in mothers and newborns with the dosage used in this study.

Pain following cesarean section has some peculiarities. First, as cesarean section is one of the most commonly performed surgical procedures, the development of persistent pain after cesarean section may represent an important and very diffuse health problem.[1] Therefore, its prevention could afford a significant improvement in women's health. A few studies investigated chronic pain after cesarean section.[2-4] Pain was found to represent a significant daily problem in 5.9% of all women who underwent cesarean section.[4] A high pain score after surgery has shown to be an independent risk factor.[2]

In the present study, follow-up evaluation after 36 months showed no significant difference in residual pain or dysesthetic symptoms between ketamine treated patients and controls.

It is difficult to draw conclusions because just 46% of study population answered the questionnaire.

Group numerosity was calculated for the primary endpoint of morphine consumption and larger, appropriately powered studies should be specifically performed for chronic pain evaluation.

Also, a more prolonged S-ketamine infusion (*i.e.*, 12 to 24 or 48 h postoperatively) could have been more effective but was avoided in our obstetric population, in which early mobilization is encouraged.

A second most peculiar aspect of obstetric patients is that exposure of the newborn to analgesic drugs and maternal functional limitations associated with postoperative discomfort and pain or its treatment may interfere with the mother-child relationship and breastfeeding. S-Ketamine induced minor adverse effects but never produced a significant risk for patient safety or for postoperative recovery (feeding, deambulation, global wellbeing) (Table III) nor were its effects considered unpleasant. S-Ketamine exposure did not reduce womens' ability to breastfeed or breastfeeding duration, which appears very important for child health and development.[32]

Conclusions

Preventive S-Ketamine, administered by i.m. bolus and continuous i.v. infusion, enhanced the analgesic effect of morphine even after Ketamine effect had ceased, suggesting anti-hyperalgesic action of the drug. S-Ketamine administration in obstetric patients after cesarean section was safe and did not affect breastfeeding. A benefit of S-Ketamine on prevention of postoperative hyperalgesia remains to be demonstrated, probably through studies on larger populations with objective methods of pain and hyperalgesia assessment.

Key messages

— Perioperative systemic low-dose S-Ketamine administration is safe in obstetric patients.

— It reduces morphine consumption and prolongs time to first morphine bolus after cesarean section with spinal anesthesia.

— Neuraxial anesthesia may be combined with systemic S-Ketamine to allow a better control of nociceptive input after cesarean section.

— S-Ketamine effect on persistent pain should be demonstrated in specifically addressed studies.

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