Journal of Medical Sciences

ISSN 1682-4474

science alert

ANSInet
an open access publisher
http://ansinet.com

Research Paper

J. Med. Sci., 8 (2): 137-142
15th February, 2008

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued eight times per year on paper and in electronic format.

For further information about this article or if you need reprints, please contact:

Hala Mostafa
Department of Anesthesia,
Faculty of Medicine,
Cairo University,
Egypt

S (+) Ketamine Suppresses TNF-α, IL-6 and IL-8 Production in Blood in Major Abdominal Surgery under Combined Epidural-General Anesthesia

[1]Hala Mostafa, [2,3]Amr Mohamad Abo Ela and [4]Nagwa El-Tweel

It has been demonstrated that proinflammatory cytokines such as (TNF-α), interleukin (IL) 6 and IL-8 increase in patients with trauma, surgical trauma, sepsis burn 40 patients scheduled for major abdominal surgery under combined epidural general anesthesia in gynecologic Department in Kasr El-Aini Hospital were included in this study, patients age was ranged between 18-50 years, patients were ASA I and II. The patients were divided into 2 groups each group 20 patients, group 1 was received S (+) ketamine as a single preincision dose, while in II S (+) ketamine was received preincision and as a repeated doses, S (+) ketamine was injected as a single IV dose 0.5 mg kg^{-1} before incision in both groups and repeated 0.2 mg kg^{-1} doses at 20 min interval until 30 min before the end of the operation (In group 2, 20 patients only). This study reported that S (+) ketamine suppressed TNF-α production IL-6, IL-8. The study also reported that a single S (+) ketamine preincision dose decreased IL-6 to 550±20 at 30 min before end of operation while the repeated 20 min doses decreased IL-6 to 440±20 min. IL-8 when single dose of S (+) ketamine was given decreased to 850±50 at 30 min before the operation, while after repeated S (+) ketamine it was 600±40 at 30 min before operation end, about TNF-α. It decreased to reach 1110±180 in a single dose of S (+) ketamine while it decreased to 1000±120 in repeated dose of S (+) ketamine. The total dose of S (+) ketamine was 35±30 in single dose group, while it was 80±40 in repeated dose group, the dose of ropivacaine given epidurally was 148±20 in single group while it was 130±15 in repeated group. The conclusion of the study was S (+) ketamine directly suppresses proinflammatory cytokines production when given in repeated doses; it also decreased the ropivacaine dose needed more in repeated doses of S (+) ketamine.

Key words: S (+) ketamine TNF-α, IL-6 and IL-8, combined epidural-general anesthesia

[1]Department of Anesthesia,
[2]Department of Gynecology and Obesterics, Faculty of Medicine,
Cairo University, Egypt
[3]Head of Gynecology and Obesterics, 6 October University, Egypt
[4]Department of Chemical Pathology, Faculty of Medicine, Cairo University, Egypt

ANSInet
Asian Network for Scientific Information

INTRODUCTION

Ketamine was introduced approximately 30 years age to be a single anesthetic agent able to promote analgesia, amnesia unconsciousness and immobility (Kohrs *et al*., 1998) but due to its major side effects it was not widely accepted. Recent studies on mechanism of action, neuronal and analgesic effects have motivated its reevaluation to broaden its application.

In addition, the introduction of S (+) ketamine isomer, which could promote less adverse effects as compared to the racemic mixture (Pfenninger *et al*., 2002), has once more aroused the interest for these drugs.

Clinical pharmacology; major pharmacokinetic properties are short distribution and excretion half-lives alpha excretion phase take 5-15 min and β excretion phase half life is 2-3 h, S (+) ketamine is metabolized in the liver to norketamine, it has one third of the potency of original drugs the classic analgesic effects (Haas and Harper, 1992) better described as resulting form dose dependent Central Nervous System (CNS) depression determining the so called dissociative analgesia (Nagels *et al*., 2004). It has minor respiratory depression. S (+) ketamine as its isomer (Warncke *et al*., 1997) interact with multiple binding areas including NMDA and non NMDA glutamate receptors, nicotinic, cholinergic muscarinic monoaminergic and opioid receptors, S (+) ketamine has 2-4 time strongly bound to kappa opioid receptors compared to (-) ketamine. S (+) ketamine has 3-4 times more affinity to NMDA receptor than its isomer (Schmid *et al*., 1999).

In 1992, the Food and Drug Administration has warned that the separation of stereo-isomers was not receiving adequate attention for the commercial development of drugs. Not with standing technical difficulties and high cost of, the focus on this horizon could open new therapeutic possibilities. Animal studies have shown that S (+) ketamine has approximately four times more affinity for phencyclidine binding area in NMDA receptor as compared to R (-) ketamine (McCartehy *et al*., 2004).

Increased affinity for the receptor, combined with similar pharmacokinetics, suggests that S (+) ketamine could be clinically interesting drug (Taura *et al*., 2003).

In rats and mice S (+) ketamine has 1.5-3 times higher hypnotic potency and 3 times higher analgesic potency as compared with (-) ketamine, being twice more potent than the racemic mixture (Koga *et al*., 1994).

Due to higher potency, approximately half S (+) ketamine dose should be enough to induce anesthesia and would positively affect recovery (Hae Seler *et al*., 2003).

This has been confirmed by several studies comparing S (+) to the racemic mixture In fact, in volunteers, there have been less adverse effects with S (+) ketamine as compared to R (-). Convincing evidences of low incidence of adverse events is still to be documented (Celerier *et al*., 2000).

S (+) ketamine, the left handed optical isomer of racemic ketamine, has four-fold higher affinity for NMDA receptors than its stereoisomer R (-) ketamine (Guignard *et al*., 2002). When S (+) ketamine was used at half the dose of racemic ketamine for surgical anesthesia in early studies patients who received S (+) ketamine experienced less postoperative pain and side they were in a better mood (Nagels *et al*., 2004). In healthy volunteers, half-dose S (+) ketamine induced fewer declines in intellectual capacities than racemic ketamine as aquianalgesic effect (Chen and Huang, 1992).

The aim of this study was evaluation of the effect of repeated intraoperative and preincisional IV S (+) ketamine added to combined general-epidural anesthesia on the level of blood cytokines (Il-6, IL-8 and TNF-α during abdominal surgery.

MATERIALS AND METHODS

After approval from the local Ethical Committee and after informed written consents, we conducted a computerized randomized, double-blind controlled study, 40 patients scheduled for major abdominal surgery under combined epidural general anaesthesia in Kasr, El-Aini Hospital were included in this study, patients were divided into 2 groups each group 20 patients, group 1 was received S (+) ketamine as a single preincision dose, while in II S(+) ketamine was received preincision and as a repeated doses , exclusion criteria included < 18 years or more than 65 years, weight < 45 kg or > 120 kg evidence of cardiovascular, renal, hematologic or hepatic disease, ASA physical status higher than II preexisting neurological or psychiatric illnesses, chronic pain syndromes drug abuse, or contraindication of epidural anesthesia or for any of the anesthetics or drugs used and difficulties in cooperation between physician and patients.

Patients were premedicated with midazolam 2-3 mg IV 15 min 1 h before operation. In the operating room, lactated ringer's solution 10-15 mL kg^{-1} was given before surgery, lumbar epidural catheter placement at L3-4 interspace, 10 min after, 3 mL test dose of lidocaine (20 mg mg^{-1}) ropivaciane (10 mg mL^{-1}) was titrated in 5 mL aliquots to a sensory block of dermatome T6: after epidural anesthesia was established, general anesthesia was induced with propofol (2-3 mg kg^{-1}) and fentanyl

(2-4 mic kg^{-1}) cisatracurium 0.15 mg kg^{-1} was used to facilitate tracheal intubation. For muscle relaxation, an infusion of cisatracurium at rate (1.5 mic kg^{-1} min^{-1}) was used to maintain 10-20% ratio by using train of four stimulation anesthesia was maintained with 1% isoflurane and O_2/N_2O 50%. Monitoring by E.C.G, noninvasive blood pressure, CO_2 capanogram (Critical Care 1100®; Criticare Systems, Inc, Milwaukee, WI, USA), Peripheral venous and arterial canulae were inserted.

S(+) ketamine (Pfizer, karlsruhe, Germany) was injected as a single IV dose 0.5 mg kg^{-1} before incision in both groups and repeated 0.2 mg kg^{-1} doses at 20 min interval until 30 min before the end of the operation (In group 2, 20 patients only). The blood samples were taken after induction of anesthesia, before incision and every 20 min until the last 30 min. Blood samples were taken as 3 mL into tubes containing heparin and diluted with 5 vol of RPMI 1640 (Ogata *et al*., 1997).

The blood samples was centrifuged at 700 g for 10 min to remove blood cells the supernatants was collected and stored at -80°C until assay.

If heart rate or arterial blood pressure exceeded 20% of baseline values, another aliquot of ropivacaine was provided as considered necessary by the attending anesthesiologist cisatracurium was stopped at the beginning of abdominal skin closure, if T1/T4 ratio was 90% at completion of skin closure muscle relaxation was reversed with atropine (0.01 mg kg^{-1} and neostigmine 0.05 mg kg^{-1}). Spontaneously breathing patients were tracheal extubated in the absence of hypercapnia and decreased respiratory rate, when they were able to follow command.

The L929 cell cytotoxic assay was used to determine the plasma TNF-α activity (De Forge *et al*., 1992). Briefly, L929 cells in RPMI 1640 medium containing 5% fetal calf serum seeded at 3×10^5 cell/well in 96-well flat bottomed micro titer plates (Becton, Dickinson, Lincoln park, NI) and incubated over night at 37°C in an at atmosphere of 5% CO_2 in air, serial 1:2 dilutions of samples were made in this medium containing 1 mg mL^{-1} actinomycin D (Banyu Pharmaceutical Co, Tokyo, Japan) and 0.1 mL of each dilution was added to different tubes, on the following day the cells with crystal violet (0.20 in 20% methanol and 1% sodium dodecyl sulfate added to each tube to solubilize the stained cells. The absorbance of each well was determined at 490 nm using a micro plate reader (Bio-Read Laboratories, Richmond, (A) TNF activity was expressed in units per milliliter, which is the reciprocal of dilution necessary for 50% lysis of the cells (Kawasaki *et al*., 1995).

The plasma IL-6 concentration was measured in duplicate using a commercially available enzyme linked immunoassay (IL-6 enzyme immunoassay kit advanced magnetic, Inc., Cambridge, MA). The intra-and interassay precision was 9 and 6%, respectively, at an IL-6 concentration of 88 pg mL^{-1}. The plasma IL-8 concentration was measured in duplicate using the same enzyme in linked immunoassay. The intra and interassay precision was 7 and 4% respectively, at an IL-8 concentration of 76% pg mL^{-1}. According to manufacture, cross reactivity with other cytokines is negligible in both assays.

Data are presented as mean±SD, paired two tailed student t-test was used to compare between groups and continuous variables were evaluated with analysis of variance (ANOVA). Ordinal data were analyzed using contingency table and the Chi-square test with appropriate correction (SPSS. Inc, Chicago, IL) software, categorical variables were analyzed by using Fisher's exact test or χ^2 tests, as appropriate. A p-value <0.05 was considered statistically significant.

RESULTS

Table 1 shows the demographic data of the patients in the study the age was 30±20 and 32±18 (year) in both groups. The weight was 79±10 and 68±14 kg 14/6 , ASAI/ ASA II was 16/4 and 15/5 in both groups.

Table 2 shows the duration of surgery in both groups and anesthesia duration in both groups, the total dose of ropivacaine was 148±20 mg in group 1 while it was 130±15 mg group 2, which was significantly lower.

The total dose of S (+) ketamine was 35±30 mg in group 1 and 80±40 mg in group 2, which was significantly higher in group 2.

Table 3 shows the IL-6 level in group 1 (single) S (+) ketamine dose as mean±SD. Before IV injection of S (+) ketamine it was 1190±50 pg mL^{-1}, which was significantly decreased to 550±30 in repeated 20 min samples and 550±20 pg mL^{-1} at 30 min before end of operation.

Table 1: Patients demographic data

The demographic parameter	Single S (+) ketamine group 1	Repeated S (+) ketamine group 2
No.	20	20
Age (year)	30±20	32±18
Weight (kg)	79±10	68±14
ASA (1/II) (n)	16/4	15/5

Table 2: Comparison between Single S (+) ketamine dose group and repeated S (+) ketamine doses group as regard intraoperative data

Parameters	Single S (+) ketamine dose	Repeated S (+) ketamine doses
Surgery duration (min)	180±30	190.0±40
Anesthesia duration (min)	250±10	240.0±30
Total dose of ropivacaine (mg)	148±20	130.0±15*
Total dose of S (+) ketamine (mg)	35±30	80.0±40*

*p<0.05 significant

Table 3: Cytokines levels in S (+) ketamine single dose group

Cytokines	After induction before S (+) ketamine	20 min repeated samples	30 min before end of operation
IL-6 (pg mL^{-1})	1190±50	550.0±30	550.0±20
IL-8 (pg mL^{-1})	1502±160	900.0±50*	850.0±50*
TNF-α (μ mL^{-1})	2170±160	1110.0±180*	1110.0±180*

*p<0.05 significant

Table 4: Cytokines levels in repeated dose of S (+) ketamine group

Cytokines	After induction before S (+) ketamine	20 min repeated samples	30 min before end of operation
IL-6 (pg mL^{-1})	1180±55	440±20*	380.0±30*
Il-8 (pg mL^{-1})	1500±167	800±25*	600.0±40*
TNF-α (μ mL^{-1})	2176±170	1015±160	1000.0±120*

*p<0.05 significant

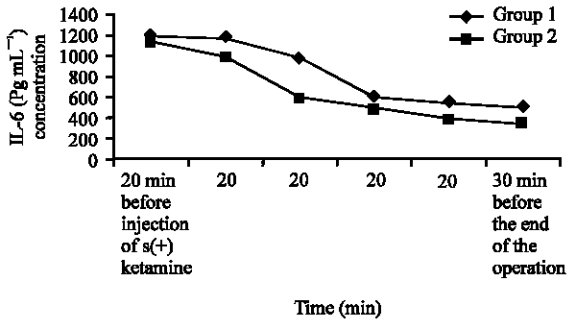

Fig. 1: IL-6 α (u mL^{-1}) in both groups

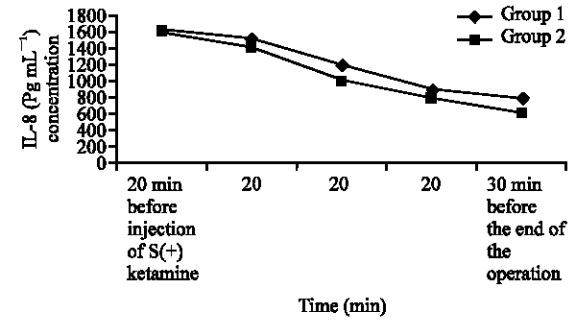

Fig. 2: Concentration of IL-8 in both groups

IL-8 (pg mL^{-1}) was 1502±160 before S (+) ketamine which was significantly decreased to 900±50 in repeated 20 min samples and 850±50, 30 min before end of operation.

TNF-α (u mL^{-1}) was 2170±160 before S (+) ketamine and then significantly decreased to 1110±180 in repeated 20 min samples and 1110±180, 30 min before end of operation.

Table 4 shows the cytokines level in repeated S (+) ketamine doses IL-6 (pg m^{-1}) was 1180 before starting S (+) ketamine, which was significantly decreased to 440±20 in repeated 20 min samples and significantly decreased to 380±30, 30 min before the end of operation, IL 8 (pg mL^{-1}) was 1500±167, significantly decreased to 800±25 in repeated 20 min samples, to reach 600±40, 30 min before end of operation. TNF-α was 2176±170, was significantly decreased to 1015±160 and then to 1000±120, 30 min before end of the operation.

Figure 1 and 2 compare the cytokines level in group 1 and group 2 and shows that the repeated injection of S (+) ketamine significantly decreased the cytokines levels more than in single S (+) ketamine

DISCUSSION

It is known that nociceptive afference triggered by surgery and inflammation may develop peripheral sensitization and primary hyperalgesia, increasing medullary response to stimulations, noxious or not, due to the wind-up phenomenon and other mechanisms, with central sensitization induction and long-term potentiation (Woolf and Salter, 2000). Blocking these mechanisms, before they developed may prevent central sensitization (Schmid *et al*., 1999).

When pre-incision administration was compared to administration at the end of surgery, the former has provided better analgesia as compared with the latter (Dickenson, 2003).

It is how well established that the N-methyl D-aspartate (NMDA) receptor-ion channel complex plays a critical role in the development of central sensitization. This has led to renewed interest in the pain-relieving properties of clinically available NMDA antagonists such a S (+) ketamine for use in humans undergoing major surgery.

More recently, NMDA receptor activation has also been linked to the development of acute opioid tolerance and opioid induced hyperalgesia Furthermore it is now recognized that the process of central sensitization is induced not only during surgery but also postoperatively by inflammatory injuries (Katz, 2003). In the clinical setting this suggests that for optimal effects NMDA receptor antagonists need to be administrated before induction of anaesthesia (before opioid are given) and continued during surgery and into postoperative period (Hollmann *et al*., 2005). Cytokines are essential for hematopoiesis and immune responses and they play a key role in the defense against infection. It has been demonstrated that proinflammatory cytokines, such as tumour necrosis factor (TNF-α), interleukin (IL-6) and IL-8, increase in patients with sepsis trauma, burns (Engelhard *et al*., 2003). IL-6 mediates acute phase response and IL-8 is potent chemotactic agent for neutrophils. These cytokines are associated with

development of septic shock and organs dysfunction. S (+) ketamine the left handed optical isomer of racemic ketamine, has fourfold higher affinity for NMDA receptors than its isomer R (-) ketamine that approximately twice that of racemic ketamine. This study shows the effect of S (+) ketamine in decreasing the cytokines and that leads to less noxious stimulation less hyperalgesia and subsequent decreases the dose of opioid needs and the dose of anesthetics, this has may be the following advantages, first decrease pain postoperatively, decreased dose of opioid analgesia, intraoperative, deceases the doses of anesthetics used, the cost of anesthetic also decreased this study revealed that, when S (+) ketamine used as single dose before incision, it decreased the level of cytokines, but when it used as repeated IV dose the cytokines decreased more and there was significantly difference between single and repeated doses, the dose of ropivacaine is significantly lower in the repeated dose S (+) ketamine this results was in agreement of the results of Snijdelaar *et al*. (2004). He found that the low dose of S (+) ketamine given during and after radical prostatectomy reduces PCA morphine consumption by 34 at 48 h after surgery and lower pain scores at rest compared with standard treatment control group, that did not receive S (+) ketamine.

In a study of healthy volunteers, ketamine isomers induced less fatigue and cognitive impairment than aquianalgesic low-dose racemic ketamine. In addition, S (+) ketamine produced less of a decline in concentration capacity and primary memory (Jaksch *et al*., 2000). Because of its higher potency (about twice that racemic ketamine) and more favorable adverse-effect profile, S (+) ketamine is an attractive alternative to race- mate for peri-operative use in humans.

For the repeated dose of S (+) ketamine to be an effective (CO) analgesics and morphine-sparing agent in surgical patient, recently evolved concept is of a major importance, it has been shown that opioid activate not only antinociceptive system, but also pronociceptive systems, causing acute opioid tolerance and opioid induced hyperalgesia (Laulin *et al*., 2002). These phenomena seem to stem from a common NMDA receptor-dependent mechanism; use of M-opioid receptor agonists causes a sustained increase in NMDA-activated currents by activating intra cellular protein kinase C. In turn protein kinase C potentiates the NMDA response by reducing the voltage-dependent Mg+ block of NMDA-receptor channels (Tverskoy *et al*., 1994).

It is now recognized that central sensitization is not only induced during surgery by incision at injury by also postoperatively by inflammatory injuries. The practical consequences of these concepts are that S (+) ketamine when administered before incision and continued during surgery and into postoperative period. It decreases the intraoperative anesthetic dose and postoperative opioid dose 0.4 mg kg^{-1} of S (+) ketamine administered over 20 min was capable of inhibiting the development of secondary hyperalgesia in experimental electrically pain (Koppert *et al*., 2001). The use of higher dose of S (+) ketamine might have yield more significant differences in sensitivity to mechanical pressure around the surgical wound in that study, in contrast to the results of the present study, Jaksch *et al*. (2000) did not find evidence for improved postoperative analgesia when S (+) ketamine was used in patients underwent arthroscopic anterior cruciate ligament repair. There are several limitation to the present study, the first concerns the relatively small number of patients studied.

Second, the study cannot address the question of whether perioperative S (+) ketamine influences pain and analgesic consumption in longer term. Third we did not found differences in psychomimetic side effects; a larger study is needed to assess this properly. So a larger study is needed to complete these items. This study concluded that S (+) ketamine when used intraoperative it decreased level of cytokines in blood, it decreases the anesthetic doses used, which may decreased the cost of anesthetic drugs used intraoperative.

REFERENCES

Celerier, E., C. Rivat and Y. Juny, 2000. Long-lasting hyperalgesia induced by fentanyl in rat: Preventive effect of ketamine. Anesthesiology, 92 (2): 465-472.

Chen, L. and L.Y. Huang, 1992. Protein kinase C reduces Mg^{2+} block of NMDA-receptor channel as a mechanism of modulation nature. J. Nature, 356: 521-523.

De Forge, L.E., J.S. Kenncy and M.L. Jones, 1992. Biphasic production of IL-8 in LPS stimulated human blood. J. Immunol., 148: 2133-2141.

Dickenson, A.H., S.L. Flatters and A.J. Fox, 2003. Spinal interlevkin-6 (IL-6) inhibits nociceptive transmission following neuropathy. Brain Res., 984 (1-2): 54-62.

Engelhard, K., C. Werner and E. Eberspacher, 2003. The effect of the $\alpha 2$ agonist dexmedetomidine and the NMDA antagonist S (+) ketamine on the expression of apoptosis-regulating proteins after incomplete cerebral ischemic, reperfusion in rats. Anesth. Analg., 96: 524-531.

Guignard, B., C. Gostes and H. Costes, 2002. Supplementing desflurane-remifentanyl anesthesia with small ketamine reduces preoperative opioid analgesic requirements. Anesth. Analg., 95: 103-108.

Haas, D.A. and D.G. Harper, 1992. Ketamine a review of its pharmacologic properties and use in ambulatory anesthesia. Anesth. Prog., 39: 61-68.

Hae Seler, G., D. Tetzlaff and J. Bufler, 2003. Blockade of voltage-operated neuronal and skeletal muscle sodium channels by S (+) and R (-) ketamine. Anesth. Analg., 96: 1019-1026.

Hollmann, M.W., H.T. Liu and N.C. Hoenemon, 2005. Modulation of NMDA receptor function by ketamine and magnesium Part II: Interactions with volatile anesthetics. Anesth. Analg., 92: 1182-1191.

Jaksch, W., S. Lang, R. Reichhalter, G. Raab, K. Dann and S. Fitzal, 2000. Preoperative small S (+) ketamine has no incremental beneficial effects on postoperative pain when standard practice opioid infusions are used. Anesth. Analg., 94: 981-986.

Katz, J., 2003. Timing of Treatment and Pre-Emptive Analgesia in Rice. Warfield, A.S., C.A. Justins and D. Ecclestion (Eds.). Clinical Management of Pain-London Arnold, pp: 113-162.

Kawasaki, T., M. Ogata, Ch. Kawasaki, J. Ogata, T. Inoue and A. Shigemitsu, 1995. Ketamine suppress proinflammatory cytokines in human blood *in vitro*. Anesth. Analg., 89: 665-669.

Koga, K., M. Ogata and Takenka, 1994. Ketamine Suppresses tumour necrosis factor-α activity and mortality in sensitized end toxin shock model. Circ. Shock. Nov., 44 (3): 160-168.

Kohrs, R., M.E. Durieux and Ketamine, 1998. Teaching old drug new tricks. Anesth. Analg., 87: 1186-1193.

Koppert, W., S.K. Dern, A. Schattler and M. Schmelz, 2001. A new model of electronically evoked pain and hyper algesiain human skin: The effect of intravenous alfentanil ketamine and lidocaine. Anesthesiology, 95: 395-402.

Laulin, J.P., P. Maurette, J.B. Coruff, M. Rivatc Chauvin and G. Simonnet, 2002. The role of ketamine in preventing fentanyl induced hyperalgesia and subsequent acute morphine tolerance. Anesth. Analg., 94: 1263-1269.

McCartehy, C., A. Sinha and J. Katz, 2004. A qualitative systematic review of the role of N-methyl aspartate receptor antagonists in preventive analgesia. Anesth. Analg., 98: 1385-1400.

Nagels, W., R. Demeyere and C.H. Van Hemelrij, 2004. Evaluation of the neuroprotective effect of S (+) ketamine during open heart surgery. Anesth. Analg., 98: 1595-1603.

Ogata, M., M.F. Flecher and M. Kloezewiak, 1997. Effects of anticoagulants on binding and neutralization of lipopolysaccharide by peptide immunoglobulin conjugate, CAP 18 immunoglobulin G in whole blood. Infect. Immunol., 65: 2160-2167.

Pfenninger, E.G., M.E. Duripux and S. Himelseher, 2002. Cognitive impairment after small dose of ketamine isomers in comparison to aquianalgesic racemic ketamine in human volunteers. Anesthesiology, 96: 357-366.

Schmid, R.L., A.N. Sandler and J. Katz, 1999. Used and efficacy of low-dose ketamine in management of acute postoperative pain: A review of current technique and outcomes. Pain, 82: 111-125.

Snijdelaar, H.B., R. Corneslise, C. Schmidt and L. Katz, 2004. A randomized, Controlled study of preoperative low dose S (+) ketamine in combination with postoperative patient controlled S (+)- ketamine and morphine after radical prostatectomy. Anesthesia, 98: 1385-1400.

Taura, P., J. Fuster and A. Blasi, 2003. Postoperative pain relief after hepatic resection in cirrhotic patients: The efficacy of a single dose of ketamine plus morphine epidurally. Anesth. Analg., 96: 475-480.

Tverskoy, M., Y. OZ, A. Isakson, J. Finger, E.L. Bradley Jr. and I. Kissin, 1994. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth. Analg., 78: 205-209.

Warncke, T., E. Jorum and A. Stubhaung, 1997. Local treatment with the N-methyl-D aspartate receptor antagonist ketamine, inhibit development of secondary hyperalgesia in man by a peripheral action. Neurosci. Lett., 227: 1-4.

Woolf, C.J. and M.W. Salter, 2000. Neuronal plasticity increasing the gain in pain. Science, 288: 1765-1769.