Effect of Single Compared to Repeated Doses of Intravenous S(+) Ketamine on the Release of Pro-inflammatory Cytokines in Patients Undergoing Radical Prostatectomy

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Abstract

Background: Radical prostatectomy is a major surgical procedure that is associated with marked inflammatory response and impairment of the immune system which may affect the postoperative outcome. The aim of this study was to evaluate the effect of preincision single or multiple doses of S(+) ketamine on the pro-inflammatory cytokines, namely tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).

Patients and Methods: This is a randomized controlled trial including 60 American Society of Anesthesiologists Physical Status I and II patients scheduled for radical prostatectomy under combined general-epidural anesthesia in Cairo University Teaching Hospital. Patients were randomly divided into three groups each of twenty patients: Group I received no S(+) ketamine (control group), Group II received S(+) ketamine as a single preincision dose, and Group III received preincision and repeated doses of S(+) ketamine. S(+) ketamine was injected as a single intravenous dose of 0.5 mg/kg in Group II and III, repeated as 0.2 mg/kg at 20 min interval until 30 min before the end of surgery.

Results: The three groups were comparable in age, weight, and duration of the operation. The study also revealed that a single preincision dose of S(+) ketamine decreased TNF-α to reach 1027.04 ± 50.13 μg/ml and IL-6 to reach 506.89 ± 25.35 pg/ml whereas the repeated doses of S(+) ketamine decreased TNF-α to reach 905.64 ± 35065 μg/ml and IL-6 to reach 412.79 ± 16.5 pg/ml (P < 0.05). Conclusion: S(+) ketamine suppresses pro-inflammatory cytokine production, especially when given in repeated doses.

Keywords: Cytokines, interleukin-6, prostatectomy, S(+) ketamine, tumor necrosis factor-alpha

INTRODUCTION

The stimulus of surgery leads to increase in the concentrations of pro-inflammatory cytokines and altered immune response.[1] Pro-inflammatory cytokines modulate pain indirectly through the release of certain substances such as nitric oxide, oxygen free radicals, and prostaglandins leading to peripheral and central sensitivity and hyperalgesia.[2] Excessive production of pro-inflammatory cytokines due to anesthesia and surgical trauma may provoke severe inflammatory response and postoperative complications. Radical prostatectomy is a major procedure that is associated with marked inflammatory response and derangement of the immune system which may affect the postoperative outcome with the risk of increased complications.[3]

Cytokines are low molecular weight proteins which after binding to specific receptors affect immune cell differentiation, proliferation, and activity. Pro-inflammatory cytokines comprise a number of factors such as tumor necrosis factor-alpha, interleukin-6 (IL-6), and IL-8.

S(+)-ketamine, the left-handed optical isomer of racemic ketamine, has a fourfold higher affinity for N-methyl-D-aspartate receptors than its stereoisomer R(−)-ketamine.[4] Investigational trials have reported that this results in an analgesic potency of S(+) ketamine that is approximately twice that of racemic ketamine.

The metabolism and clearance of ketamine from the plasma were found to be 4.98 h. This raises the question; is it better to give only one dose or to give multiple doses?[5,6]

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There were many trails that were using anti-inflammatory medications aiming at decrease inflammatory response by decrease cytokines or antagonize its effect; ketamine has proven to have anti-inflammatory effects and protective mechanism with great debate regarding the procedure, dose, and timing.[7-10
In this study, S(+) ketamine effect on cytokines was examined in different doses and timing in prostatectomy surgery.[8]

**Patients and Methods**

This study was a prospective, randomized, controlled, double-blinded trial. After approval of Local Ethical Committee in Anesthesia Department, Faculty of Medicine, Cairo university, informed written consent was obtained from all patients. Sixty patients’ physical status American Society of Anesthesiologists (ASA) classes I–II, aged over 45 years old scheduled for radical prostatectomy under combined epidural-general anesthesia were included in this study. All cases were done in Urology Theater in Kasr Alaini hospital (Cairo university teaching hospital). The exclusion criteria included Physical Status ASA classes III or more, morbid obesity (body mass index >35), preexisting neurological or psychiatric disorders, chronic drug abuse, the use of drugs affecting immunity as chemotherapy or hormonal therapy, uncontrolled diabetes, renal, hepatic, hypertensive patients, contraindication for epidural catheter insertion, and hypersensitivity for any anesthetics or drug used. Patients were randomly divided into three groups according to randomized sequences without duplicates, twenty patients in each group. Group I received combined epidural-general anesthesia without S(+) ketamine (control group), Group II received combined epidural-general anesthesia and S(+) ketamine as a single preincision dose, and Group III received combined epidural-general anesthesia and S(+) ketamine as preincision and repeated doses up to 4 h of surgery. In the preparation room under local anesthesia intravenous cannula was inserted, midazolam 1 mg and ranitidine 50 mg were given to all patients. Then, the patient was transferred to the operating room, standard monitors were applied, and then epidural catheter was inserted under complete aseptic technique to supplement general anesthesia and to control postoperative pain. Then, general anesthesia was induced with propofol (2 mg/kg), fentanyl (1 μg/kg), and atracurium (0.5 mg/kg) to facilitate tracheal intubation. For maintenance of anesthesia, an infusion of atracurium at rate of 8 μg/kg/min and 1%–1.5% isoflurane, ventilator parameter was adjusted to keep EtCO$_2$ between 30 and 35 mmHg, 5 ml of levobupivacaine 0.25% was administrated in the epidural catheter and repeated according to the hemodynamic variables. Blood samples were drawn immediately after induction of anesthesia and before S(+) ketamine injection to determine the baseline of cytokines that were measured (tumor necrosis factor-alpha [TNF-α] and IL-6); then, S(+) ketamine (Pfizer, Karlsruhe, Germany) was injected as a single IV dose 0.5 mg/kg before incision in Group II and III and repeated 0.2 mg/kg doses at 20 min intervals till the end of surgery (in Group III only). The blood samples were taken after 1 h and then hourly after S(+) ketamine injection till 4 h. Blood was collected in ethylenediaminetetraacetic acid tubes and centrifuged at 3,000 rpm for 15 min. Plasma was stored at −80°C until the moment of analysis. TNF-α and IL-6 levels were measured using The RayBio® Human TNF-α Enzyme-Linked Immunosorbent Assay kits.

Although ketamine has well-known complications such as tachycardia, hypertension, and delirium, it will be obscured by prolonged surgery under general anesthesia. Consequently, these complications will not be monitored in this study.

The study was blinded to patients and laboratory technician but not anesthetist.

**Statistical methods**

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) version 22. Data were summarized using mean ± standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between groups were done ANOVA with post hoc test. For comparison of serial measurements within each group, repeated measures ANOVA was used. For comparing categorical data, Chi-square test was performed. The exact test was used instead when the expected frequency is <5. P < 0.05 was considered statistically significant.

**Sample size**

Sample size was calculated based on hypothesis that the difference in cytokine concentration in the groups that receiving ketamine would be at least 25%. To have a 95% chance to detect this difference at a level of significance (P < 0.05), the number of patients calculated by the group was 18 we added two patients for dropouts. P ≤0.05 was considered statistically significant.

**Results**

Patients were recruited over a period of 6 months; 74 patients were indicated for radical prostatectomy, 4 of them were excluded as per exclusion criteria while 9 refused and one neglected (more than sample size).

Every patient was randomly allocated in one of the three groups using computer randomization program (e.g., number 1 in Group III and number 2 in Group I); fortunately, there was no dropout, and consequently, every group was composed of twenty patients [Figure 1].

The study was blinded to patients and laboratory team but not to anesthetist who conducted anesthesia and collected samples.

There was no statistically significant difference between the three groups as regarding demographic data (age, weight, and height), duration of surgery and anesthesia, a number of intravenous fluids, transfused packed red blood cells, and baseline serum TNF-α and IL-6 [Table 1]. No serious adverse effects were recorded in all groups.
Regarding TNF-α serum level, there were no statistical differences among the three groups at 0 h (1988.27 ± 38.58 μ/ml, 2053.07 ± 58.98 μ/ml, and 2001.16 ± 30.14 μ/ml in Groups I, II, and III, respectively). Likewise, there was a marked decrease in the serum level with statistical significance (value < 0.05) during the consequent readings in hours 1, 2, 3, and 4 [Table 2 and Figure 2].

In comparing TNF-α serum level between Groups II and III, although both groups show a significant decrease in serum level, decrease in TNF-α serum level in Group III was much more than in Group II with \( P < 0.05 \). Furthermore, it shows a steady decline over time in comparison to Group II which start to rise again after 3 h [Figure 3]. These conclude that repeated ketamine boluses are more effective than a single shot.

Regarding serum levels of IL-6, there was a marked drop in both Groups II and III after 1 h (from 1089.54 ± 85.54 to 506.890 ± 25.34 pg/ml in Group II and from 1150.27 ± 65.74 μ/ml to 586.09 ± 5.45 phb/ml in Group III) with \( P < 0.05 \). Furthermore, serum level was kept low over the next 3 h in both Groups II and III in comparison to the Group I with values showed to be statistically significant [Figure 4].

In between Groups II and III, the serum level of IL-6 was lower in Group III with \( P < 0.05 \). Despite there was a significant decrease in serum level in Group II at the 1st h, it started to increase again slightly over the consequent hours. On the other hand, it kept on decreasing in Group III over the same time [Figure 5].

In conclusion, S(+) ketamine will reduce the release of IL-6 and TNF-α significantly during radical prostatectomy surgery. S(+) ketamine boluses are more effective than S(+) ketamine single shot.

**Limitations**

the follow-up was only intraoperatively; it is questionable if this effect will be sustained later on, and if this effect will reduce mortality and morbidity.

**Discussion**

Radical prostatectomy is a major surgical procedure associated with marked surgical trauma and release of pro-inflammatory cytokines. S(+) ketamine was chosen as it has better recovery profile with less hallucination or mood changes.
This study shows the effect of S(+) ketamine in decreasing the level of cytokines, and that leads to less noxious stimulation. Furthermore, this study revealed that when S(+) ketamine used as a single dose before the incision, it decreased the level of cytokines, but when used as repeated intravenous doses, the cytokine levels decreased more and there was a significant difference between single and repeated doses. Roytblat et al.\(^\text{[11]}\) reported that a single dose of ketamine 0.25 mg/kg administered before cardiopulmonary bypass suppressed the increase in serum IL-6 during and after coronary artery bypass surgery,\(^\text{[12]}\) and that a subanesthetic dose of ketamine suppressed IL-6 production in women undergoing a hysterectomy. In contrast, Cho et al.\(^\text{[13]}\) found that low-dose ketamine with anesthesia induction will not show any anti-inflammatory effect in the low-risk patient going for off-pump coronary bypass graft surgery. The author of this study used a single shot of ketamine 0.5 mg/kg and measured its effect on IL-6 and TNF-\(\alpha\) after 4 h and once after 1 and 2 days. There was no continuous measurement over the early hours which may explain the differences between his study and this one.

Wang et al.\(^\text{[14]}\) have tried ketamine in another nonconventional route; their study has examined ketamine through both inhalational and intravenous routes in the patient going for esophagectomy with one lung ventilation. The study demonstrated that ketamine has succeeded to lower serum level of cytokines.

### Table 1: Comparison among groups regarding demographic data and baselines

|                      | Mean±SD | P     |
|----------------------|---------|-------|
| **Group I, control** |         |       |
| Age                  | 64.15±5.03 |       |
| Weight (kg)          | 74.24±3.01  |       |
| Height (cm)          | 175.02±3.25 |       |
| Duration of procedure (min) | 180.47±29.98 |       |
| Duration of anesthesia (min) | 251.52±8.23   |       |
| Amount of IV crystalloid (ml) | 3155.40±152.35 |       |
| Amount of IV colloid (ml) | 532.35±25.49   |       |
| Amount of transfused pRBC (ml) | 354.72±152.80 |       |
| TNF-\(\alpha\) baseline (µ/ml) | 1988.27±38.58 |       |
| IL-6 baseline (pg/ml) | 1108.54±43.01 |       |

Data are expressed as mean±SD.

### Table 2: Cytokines serum level among the three groups

|                      | Mean±SD | P     |
|----------------------|---------|-------|
| **Group I**          |         |       |
| TNF-\(\alpha\)       | 1988.27±38.58 |       |
| IL-6 baseline (pg/ml)| 1108.54±43.01 |       |

**Group II, single dose S(+) ketamine**

|                      | Mean±SD | P     |
|----------------------|---------|-------|
| TNF-\(\alpha\)       | 2053.07±58.98 | 0.974 |
| IL-6 baseline (pg/ml)| 1089.02±85.54 | 0.865 |

**Group III, repeated doses S(+) ketamine**

|                      | Mean±SD | P     |
|----------------------|---------|-------|
| TNF-\(\alpha\)       | 2001.16±30.14 | <0.001 |
| IL-6 baseline (pg/ml)| 1150.27±65.74 | <0.001 |

Values are represented as mean±SD. *Statistically significant compared to corresponding value in control group (\(P<0.05\)). **Statistically significant compared to corresponding value in single dose ketamine group (\(P<0.05\)). TNF-\(\alpha\)=Tumor necrosis factor \(\alpha\), IL-6=Interleukin 6, SD=Standard deviation

**Figure 5:** Graph shows levels of interleukin-6 in both Groups II and III
of IL-6, IL-8, and soluble intercellular adhesion molecule-1. Furthermore, it has resulted in decreasing airway pressure.

Kawasaki et al.\(^{[15]}\) had carried out \textit{in vitro} studies with human whole blood and reported a suppressive effect of ketamine on lipopolysaccharide-induced TNF-\(\alpha\), IL-6, and IL-8 production. TNF-\(\alpha\) is the first cytokine which stimulates IL-6 and IL-8 production by macrophages.

**Conclusion**

Preincisional and repeated use of intraoperative S(+) ketamine significantly decreased the level of pro-inflammatory cytokines.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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