Descriptive Analysis of Postoperative Psychomimetic Side Effects of Subanesthetic Dose of Ketamine in Surgical Patients.

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Abstract: Objectives: Most of clinical experience gained with the use of low dose ketamine focused in its analgesic efficacy. psychomimetic side effects of ketamine were reported as secondary outcome parameters and most of studies recorded event counts rather than severity. The aim of this study was the detailed analysis of postoperative psychomimetic side effects of subanesthetic dose of ketamine. **Methods:** The study included 100 consented patients (aged 18-55 yrs), ASA I-II who were scheduled for different elective surgeries (including upper abdominal operations such as open cholecystectomy and epigastric hernia repair, thyroid, ear, nasal) under general anesthesia. Ketamine HcL (Ketalar®) 0.9mg/kg iv bolus was administered intraoperatively before skin incision. Patients were strictly observed postoperatively for occurrence of ketamine psychomimetic side effects e.g. hallucination, euphoria, excitation, agitation, illusions whether visual or auditory, fear, slurred speech, nystagmus and photophobia. The onset (time since discontinuation of anesthesia till appearance of side effect) and duration of each side effect were recorded. **Results:** 45 patients were free from ketamine side effects. Not all side effects occurred in the same patient. 12 patients had one side effect, 25 patients had two side effects, 16 patients had 3 side effects, 2 patients had 4 side effects and no patient had more than 4 side effects. The observed ketamine side effects included nystagmus (n=29), Photophobia (n=35), slurred speech (n=24), euphoria (n=3), agitation (n=2), and hallucination (n=20). Their mean onset and duration times were: nystagmus (20.55±6.9 and 4.79±2.26 min.), photophobia (39.71±8.89 and 31.03±12.57 min.), slurred speech (72.2±9.49 and 89.78±14.84 min.), euphoria (57.0±4.24 and 105.00±21.21min.), agitation (55.6±2.5 and treated with 3mg midazolam), and hallucination (70.85±10.52 and 118.45±36.18 min.). A highly significant association was recorded between the incidence and severity of recorded psychomimetic side effects of ketamine and older age, female gender, upper abdominal operations and longer surgical times. **Conclusion:** Since neuropsychiatric disturbances remain an issue with the use of ketamine, one must weigh the risks and benefits of this intervention. Outcomes other than pain and analgesic use (eg. Adverse effects, duration of hospital stay and cost-benefit analysis) should be included in future research on ketamine whenever possible.

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1. Introduction

Ketamine (CI-581, Ketalar®), was first synthesized by Stevens (1963) as a further development of phencyclidine and its congener cyclohexamine, and was approved for clinical use in 1970. Ketamine like other phencyclidines, produces undesirable psychological reactions during awakening from anesthesia that are termed emergence reactions, which vary in severity and classification such as vivid dreaming, sense of floating out of one's body, illusions, excitement, euphoria, and fear. Their clinically relevant range is probably 10%-30% of adult patients who receive ketamine as a sole or major part of the anesthetic techniques (1). These neuropsychiatric side effects have placed ketamine outside the realm of routine clinical use.

The established role of N-methyle-D-aspartate (NMDA) receptors in the processing of nociceptive input has led to renewed clinical interest in ketamine as a non-competitive NMDA receptor antagonist. Since the late 1990's, multiple studies investigated the use of subanesthetic doses of ketamine for treatment of acute and chronic pain and proved its analgesic efficacy (2-4). Low-dose ketamine is defined as a bolus dose of <2mg/kg when administered intramuscularly or <1mg/kg when administered via intravenous or epidural route (5).

Most of clinical experience gained with the use of low dose ketamine focused in its analgesic efficacy. psychomimetic side effects of ketamine were reported as secondary outcome parameters and most of studies recorded event counts rather than severity (6).

The aim of this study was to investigate the psychomimetic side effects of ketamine iv bolus dose of 0.9mg/kg in patients undergoing different surgical procedures. A detailed analysis was performed including the incidence, onset and duration of each side effect, in addition to its close association to age, weight, gender, surgical site and surgical time.

2. Patients and Methods:

This descriptive analytic prospective study was approved from the local research Ethics Committee in the Faculty of Medicine, Assiut University, Egypt. The study included 100 consented patients (aged 18-55 yrs), ASA I-II who were scheduled for different elective surgeries including upper abdominal operations such as open cholecystectomy and epigastric hernia repair, thyroid, ear exploration, nasal polypi removal or turbinectomy. Excluded from the study patients with:

- Increased intracranial pressure, head injury or intracranial mass lesions.
- Open eye injury or other ophthalmic disorders.
- Ischaemic heart disease or vascular aneurysms.
- History of psychiatric illness, drug or alcohol dependence, patients with increased propensity of postoperative delirium (e.g. elderly, head trauma, delirium tremens), and patients who normally dream.

Preoperatively, patients were screened to exclude major mental illness e.g. schizophrenia, bipolar disorder or major depression in first or second degree relatives.

The attending anesthesiologist, surgeon and data collection personell were blinded to the nature of the study medication.

The anesthetic technique was standardized. Induction started with iv propofol 2-3mg/kg, fentanyl 1µg/kg, and cisatracurium 0.15mg/kg to facilitate endotracheal intubation. Anesthesia and muscle relaxation were maintained by isoflurane 1-1.5 MAC in 50% oxygen/air mixture and cis-atracurium 0.03 mg/kg, respectively. Monitoring included electrocardiography (ECG), non-invasive blood pressure, peripheral arterial oxygen saturation and end-tidal carbon dioxide. Ketamine 0.9mg/kg iv bolus was administered intraoperatively before the skin incision. All patients received intraoperative 100mg tramadol for analgesia to exclude any pain associated change in postoperative psychological behavior. At end of surgery, anesthesia was discontinued and neuromuscular relaxation was reversed using neostigmine 40 µg/kg and atropine 20 µg/kg slowly intravenous, and patients were extubated and transported to PACU, where they discharged to the ward after attaining an Aldrete & Kroulik (7) score > 9.

Patients were strictly observed in the first 6hrs postoperative for the occurrence of ketamine neuropsychiatric side effects e.g. hallucination, euphoria, excitation, agitation, illusions whether visual or auditory, fear, slurred speech in addition to nystagmus and photophobia. The onset (time since discontinuation of anesthesia till appearance of side effect) and duration of each side effect were recorded. 24 hrs postoperative, patients were asked about history of vivid dreaming in the night before or any other side effect.

Definition of outcome parameters:

- *Hallucination:* False or distorted sensory experiences that appear to be real perceptions.
- *Disorientation:* mental confusion or impaired awareness especially regarding place, time, or personal identity.
- *Euphoria:* a feeling of great happiness or well being, commonly exaggerated and not necessarily well founded.
- *Excitation:* the state of being emotionally aroused and worked up.
- *Agitation:* restlessness and increased psychomotor activity.
- *Illusions:* false interpretation of a real external stimulus e.g. rustling of leaves interpreted as sound of voices.
- *Slurred speech:* abnormal speech in which words are not enunciated clearly or completely but are run together or partially eliminated.
- *Nystagmus:* small involuntary tremors of the eyeballs.
- *Photophobia:* an abnormal sensitivity to or intolerance of light.
- *Dreaming:* a mental phenomenon occurring during rapid eye movement (REM) sleep in which images, emotions, and thoughts are experienced with a sense of reality.

Statistical analysis:

Analysis was performed using SPSS version 17 (Chicago-USA). Data were presented as mean ± SD for quantitative variables and numbers. Frequency distribution for each side effect, surgical site, and gender were analyzed using Chi square tests. Age, weight, surgery time, onset and duration of each side effect were analyzed using Student's t-test. A P value<0.05 was considered statistically significant.

3. Results:

One hundred patients were randomly screened to participate in this study, 43 men and 57 women, aged 18-55 years, and were scheduled to different surgical operations. The detailed analysis of patients characteristics including age, weight, gender, ASA class, surgical site and surgical time are presented in table1.

Forty five patients were free from ketamine side effects. Not all side effects occurred in the same patient, 12 patients had one side effect, 25 patients had two side effects, 16 patients had 3 side effects, 2 patients had 4 side effects and no patient had more than 4 side effects (Figure.1). There was a significant association between the number of side effects and the surgical site (P<0.05). The observed ketamine side effects included nystagmus (n=29), Photophobia (n=35), slurred speech (n=24), euphoria (n=3), agitation (n=2), and hallucination (n=20) (Figure.2).

The mean onset and duration times for each observed side effect were, nystagmus (20.55±6.9 and 4.79±2.26 min.), photophobia (39.71±8.89 and 31.03±12.57 min.), slurred speech (72.2±9.49 and 89.78±14.84 min.), euphoria (57.0±4.24 and 105.00±21.21min.), agitation (55.6±2.5 and treated with 3mg midazolam), and hallucination (70.85±10.52 and 118.45±36.18 min.), respectively (Table. 2).

There was a significant association between the recorded psychomimetic side effects of ketamine and the older age, female gender, upper abdominal operations and longer surgical times (Table. 3). No patient in the study reported a dreaming event.

Table (1): Patient characteristics (n=100).

Age(years)	28.23±9.84 (range:18-55yr)
Weight (kilogram)	74.17±12.59 (range:50-100kg)
ASA class (ASA I/II)	99/1
Sex (Male/Female)	43/57
Surgical Site: ***Upper abdominal*** ***Non abdominal*** ***(e.g,Thyroid, breast..)*** ***Nasal*** ***Ear***	 27(M/F=2/25) 25(M/F=7/18) 21(M/F=14/7) 27(M/F=20/7) ***Total = 100***
Surgical time (min.)	95.08±35.79 (range: 35-180min.)

Data are *expressed* as mean ±SD, and number.

Table (2): Descriptive analysis of ketamine adverse effects:

	Nystagmus	**Photophobia**	**Slurred speech**	**Euphoria**	**Agitation**	**Halucination**
Frequency (total=100 M/F: 43/57)	**N=29** M/F: 12/17	**N=35** M/F: 8/27	**N=24** M/F: 7/17	**N=3** M/F:0/3	**N=2** M/F:0/2	**N=20** M/F:4/16
Distribution						
Abdominal	13	**9**	**14**	**3**	**2**	**13**
Non-abdominal	**10**	**19**	**4**	**--**	**--**	**4**
Nasal	**---**	**---**	**3**	**--**	**---**	**3**
Ear	**6**	**7**	**3**	**--**	**--**	**--**
Onset (min.)	20.55±6.9	39.71±8.89	72.2±9.49	57.0±4.24	55.6±2.5	70.85±10.52
Duration (min.)	4.79±2.26	31.03±12.57	89.78±14.84	105.00± 21.21	Treated with 3mg midazolam	118.45±36.18

Data are expressed as mean ± SD and number (n).

Table (3): Significance levels for ketamine adverse effects in relation to age, weight, sex, surgical site, and surgical time.

	Nystagmus N=29	**Photophobia N=35**	**Slurred Speech N=24**	**Euphoria N=2**	**Agitation N=2**	**Halucination N=20**
Age	0.001	0.000	0.000	NS (0.368)	NS (0.702)	0.04
Weight	NS (0.202)	NS (0.06)	NS (0.107)	NS (0.341)	NS (0.644)	NS (0.181)
Sex	NS (0.335)	0.014	0.027	NS (0.322)	NS 0.570	0.05
Surgical site	0.000	0.000	0.02	NS (0.175)	NS (0.579)	0.01
Surgical time	0.01	0.01	0.009	NS (0.195)	NS (0.575)	0.02

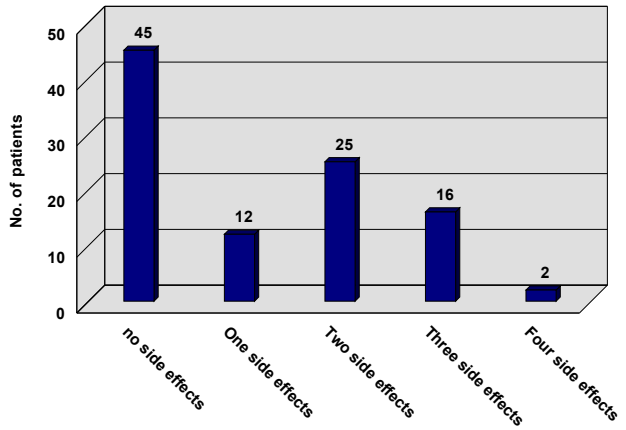

Figure.1: Number of ketamine psychomimetic side effects recorded in each patient in the study.

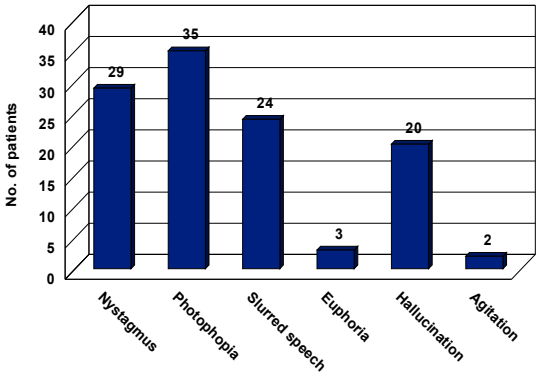

Figure.2: Frequency of ketamine psychomimetic side effects recorded in the study.

4. Discussion:

The current study demonstrated that the incidence of psychomimetic side effects of ketamine analgesic dose is still high with a significant association between the incidence and severity of each side effect and the older age, female gender, upper abdominal operations and longer surgical time. Most studies reported neuropsychiatric side effects of ketamine as event counts rather than severity. To our knowledge this is the first study to investigate ketamine side effects in surgical patients in detail.

Intravenous low dose ketamine given at an infusion rate < 2.5µg/kg/min (estimated plasma levels <50ng/ml) does not cause hallucinations (8, 9) or impairment of cognitive functioning (8,10). Other adverse effects such as a sense of intoxication, dizziness, blurred vision, itching, or nausea and vomiting occur more commonly but the incidence of these adverse effects does not appear to differ from that of opioids (10). At higher doses and plasma levels (200ng/ml), incidence of cognitive and memory impairments, psychiatric symptoms, illusory experiences and other adverse effects increases (8-14). Most of the above studies were undertaken on healthy volunteers. However, postoperative settings differ as many anesthetic and surgical factors can modulate the postoperative psychomimetic side effects of intravenous ketamine. The results of this study conflict with the above studies as although the dose used was fixed, the incidence, severity and type of ketamine psychomimetic side effects significantly differed among the patient subgroups. Serum levels if present could have enabled the interpretation of these results. Further studies are needed in such topic. The psychomimetic side effects of subanesthetic dose of intravenous ketamine should be investigated in a graded dose manner starting from 1mg/kg down to 0.25mg/kg supplemented with serum levels and correlated with incidence, duration and severity for each side effect in detail.

Despite the clear opioid-reducing effect of ketamine in clinical scenarios, ketamine was not efficacious for tonsillectomy, dental, or head and neck surgery, but it had significant analgesic benefit for those procedures involving the upper abdomen and thorax (6). The site of surgery and possibly the extent of the incision have an impact on the efficacy of ketamine as a perioperative adjuvant drug (6). Laskowski *et al.,* in their systemic meta-analysis on perioperative intravenous ketamine analgesia, concluded that there was an increase in neuropsychiatric side effects with the treatment of ketamine (P=0.018), which becomes more prevalent with treatment efficacy (P<0.001) (6). Whenever ketamine becomes more effective, its neuropsychiatric side effects become more prevalent. These conclusions explain why in this study we observed an increased incidence of neuropsychiatric side effects in patients undergoing upper abdominal surgery. Pain severity was not measured in this study. Postoperative pain scores if present: First, could have assessed the analgesic efficacy of intravenous ketamine in different surgical operations. Second, might have confirmed the positive correlation between the analgesic efficacy of intravenous ketamine and the incidence of its neuropsychiatric side effects.

The increase in neuropsychiatric side effects with increased surgical time may be a product of the type of surgery. This is because the longest surgical times observed in this study were recorded in abdominal operations. In this study, the mean age in patients who developed neuropsychiatric side effects and patients who did not was 35.12±12.15 *vs*. 24.68±5.89 years, respectively. This age difference is small though statistically significant.

Many studies commented that the psychological side effects of ketamine were well tolerated and could be decreased by a benzodiazepine. We also report that these side effects were moderate in severity and subsided within the first 3hours postoperative.

However, the patients and their relatives did not accept this type of side effects. It is the quality of such adverse effects rather than severity. For example, postoperative nausea and vomiting (PONV) and pain though annoying are much accepted as a postoperative complication than the neuropsychiatric side effects of ketamine.

This study can be criticized for its small sample size and the unequal distribution of male/female gender within the patient subgroups. Further studies with larger patient groups in different surgical populations should be conducted.

In conclusion, Perioperative intravenous ketamine may be a useful addition in pain management regimens. The optimal dose of ketamine remains unclear as there appeared to be no correlation between dose and efficacy. Ketamine has a clinical benefit when used perioperatively in certain clinical circumstances while potentially causing harm in others. Since neuropsychiatric disturbances remain an issue with the use of ketamine, one must weigh the risks and benefits of this intervention. Out comes other than pain and analgesic use (e.g. Adverse effects, duration of hospital stay and cost-benefit analysis) should be included in future research on ketamine whenever possible.

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Conflict of interest:

There were no conflicts of interest.

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