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Efficacy Of Low Dose Ketamine Infusion For Postoperative Analgesia In Upper Abdominal Surgeries

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Abstract

Background:

Ketamine , an NMDA antagonist blunts central pain sensitization , thereby providing pain relief in major surgeries but its optimal dosing and duration of administration is still unclear. Here we study the role of sub-anaesthetic dose of ketamine (0.2 mg/kg/hr) to provide postoperative analgesia for upper abdominal surgeries and also predict its role in reduction of the total dose of opioid consumed.

Method:

90 patients posted for upper abdominal surgeries were randomized into 2 groups of 45 each.
Group1 - postoperative analgesics were administered as per surgeon.
Group2 - an IV bolus of 0.2 mg/kg of ketamine was given at time of induction followed by an infusion of 0.2 mg/kg/ hr given for 48 hrs commencing from the end of the surgery.
VAS at 4, 6, 12, 24 and 48 hrs and total dose of opioid administered post-operatively were noted.

Results:

The VAS at varying time intervals were significantly less in Group2 with a median of 0 (at 4hrs) ,
0 (at 6 hrs) , 1 (at 12hrs), 2 (at 24hrs) and 2 (at 48hrs) when compared to Group1 which was
1(at 4hrs), 2 (6hrs) , 4(12hrs), 4(24hrs) and 5 (at 48hrs). The mean dose(mg) of opioid consumed was considerably less in Group2 (190 ± 83.09) mg compared to (620 ± 40.45) mg in Group1.

Conclusion:

An intravenous bolus of 0.2 mg/kg of ketamine given at time of induction followed by a postoperative ketamine infusion at a dose of 0.2mg/kg/hr for 48 hrs provided good analgesia and significantly reduced the dose of opioid consumed with only minimal physiological impact.

Keywords: Ketamine, opioid-free, analgesia

Introduction

For long opioids have been the keystone in alleviating post-operative pain . But since opioids are associated with side effects such as respiratory depression, urinary retention, nausea , vomiting and prolonged postoperative ileus , renewed interest has been focused on the use of opioid- free approaches to perioperative pain [1-4] . In order to reduce the incidence of opioid induced side effects, a variety of analgesic combinations have been experimented among which ketamine, a phencyclidine derivative,

has been reported to prevent opioid-induced hyperalgesia, reduce postoperative pain and opioid requirements in a variety of setting from outpatient surgery to major abdominal procedures [5-10]. Ketamine, a competitive NMDA (N-methyl-d-aspartate) receptor antagonist was synthesized in the early 1960s and since that time has been a standard anesthetic drug primarily used for induction in hemodynamically unstable patients or as an adjunct for analgesia or sedation [11] . Various studies have revealed that NMDA receptors located on both afferent somatic and visceral nerve axons are involved in pain associated with peripheral tissue or nerve .In response to such a noxious stimuli , the first order nociceptive neuron triggers release of glutamate which binds to NMDA receptors (NMDARs) on second-order neurons in the dorsal horn of spinal cord . This sets off a cascade of intracellular processes that causes continuous activation of NMDARs [12-15] . The spinal cord neurons become more responsive to inputs, leading to the central sensitization component of chronic pain . Central sensitization can progress into a pathologic chronic pain condition. By blocking the NMDA receptor, ketamine holds obvious promise for attenuating these centrally mediated pain processes, thereby reducing acute pain and potentially preventing chronic pain [16]. However, the optimal dosing and duration of ketamine administration, in order to provide adequate analgesia at the same time, cause only minimal effects on consciuosness and cognition, still remains unclear .

Material And Methods

This prospective, randomized, double-blind comparative study included 90 patients of American Society of Anaesthesiologists grade I and II, aged 18 to 70 years, body weight 40–80 kg who were posted for upper abdominal surgery under general anaesthesia. Patients excluded from the study were who refused to take part in the trial, of age <18 and >70 yrs, with history of head trauma, globe injury and psychiatric illness.

Our aim was to evaluate the effectiveness of low dose ketamine infusion (0.2 mg/kg/hr) for post operative analgesia in patients undergoing upper abdominal surgery in general anaesthesia. Our secondary objective was to observe if low dose ketamine infusion can reduce the total dose of opioid analgesics. Prior ethical permission was taken from our Institutional Ethical Committee and Review Board and written informed consent were obtained from patients enrolled for the study. After shifting the patient to the operation theater, two large bore (18 G) intravenous access were obtained and pre-induction monitors like pulse oximeter, noninvasive blood pressure, 3-lead electrocardiogram were connected and heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SpO_2) were recorded at this time. Patients were premedicated with intravenous glycopyrrolate (0.005 mg/kg) and midazolam (1mg IV bolus). After preoxygenation for 3 min, patient was induced with inj. Propofol (2-2.5mg/kg) i.v followed by inj. Vecuronium bromide (0.1mg/kg) was given to facilitate direct laryngoscopy and orotracheal intubation . All the patients were mechanically ventilated and maintained with isoflurane / halothane and vecuronium (0.01 mg/kg every 30–40 min) throughout the surgical procedure. All 90 patients were randomized into 2 groups of 45 patients each , using the sealed envelope technique . GROUP 1 received postoperative analgesics as prescribed by the operating surgeon. The surgical team included in this study routinely administered IV Tramadol 100mg TDS. While GROUP 2 received an IV bolus of ketamine 0.2 mg /kg at the time of induction followed by a ketamine infusion of 0.2mg / kg / hr till 48 hrs post operatively comencing from the end of surgery. VAS (visual analogue scale) was observed in both the groups at 4, 6, 12, 24 and 48 hrs postoperatively. The time taken by the patient to request for first dose of analgesia was noted and a VAS of more than 4 called for administration of opioid analgesic.

Stastical Analysis:

The data of the present study was recorded / fed into the computers and after its proper validation, checked for error, coding & decoding and analysed with the help of STATA 14.0 software for windows. Appropriate univariate and bivariate analysis and student T test for comparing two means was carried out. All results were expressed as mean ± standard deviation and the proportion as in percentage (%). The critical value for the significance of the results will be considered at 0.05 level.

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Sample Size :

Leonid Roytblat et al reported that the requirement of opioid analgesic during the first 24 hours was 60% more in control group compared to the ketamine group. Therefore, based on the above cited study, we have taken into consideration a probability of 60% with 10 % absolute precision (marginal error) for sample size estimation .We used the following formula for calculation of sample size:

$n = z^2pq / d^2$

Final sample size was calculated as 90. These patients were divided into 2 groups of 45 patients each.

Results:

In this study the effect of a low dose (0.2 mg /kg/ hr) ketamine infusion on pain scores and opioid consumption was assessed. The 2 groups compared in this study had 45 patients each and were demographically similar in age , sex ,weight and ASA grade .

TABLE – 1 DEMOGRAPHIC DATA : AGE (YEARS)

Variables	Group	Mean	SD
Age	Group 1	51.44	10.18
	Group 2	48.98	10.01

TABLE – 2 DEMOGRAPHIC DATA : WEIGHT (KG)

Group	No.of patients	Mean
Group 1	45	65.31
Group 2	45	61.77

TABLE – 3 SEX DISTRIBUTION DATA

Sex	Group			
	Group 1		Group 2	
	Frequency	(%)	Frequency	(%)
Male	29	(64.44)	32	(71.11)
Female	16	(35.56)	13	(28.89)

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TABLE – 4 ASA GRADING DISTRIBUTION

ASA	Group			
	Group 1		Group 2	
	Frequency	(%)	Frequency	(%)
I	30	(66.67)	33	(73.33)
II	15	(33.33)	12	(26.67)

The VAS was significantly less in Group 2 with a median of 0 (at 4hrs) , 0 (at 6 hrs) , 1 (at 12hrs), 2 (at 24hrs) and 2 (at 48hrs) when compared to Group1 which was 1(at 4hrs), 2 (6hrs) , 4(12hrs), 4(24hrs) and 5 (at 48hrs) . This inferred that pain relief in patients was better with the addition of ketamine infusion in the postoperative period.

TABLE -5 VAS SCORE

Time Hours	Group	Mean	Median	SD	Minimum	Maximum	t test	p value
4 hrs	1	1.42	1	0.50	1	2	10.58	<0.0001
	2	0.33	0	0.48	0	1		
6 hrs	1	2.20	2	0.40	2	3	19.90	<0.0001
	2	1.00	0	0.00	1	1		
12 hrs	1	4.22	4	0.42	4	5	31.03	<0.0001
	2	1.31	1	0.47	1	2		
24 hrs	1	3.98	4	0.62	3	5	16.39	<0.0001
	2	1.69	2	0.70	1	3		
48 hrs	1	4.87	5	0.73	4	6	14.87	<0.0001
	2	2.60	2	0.72	2	4		

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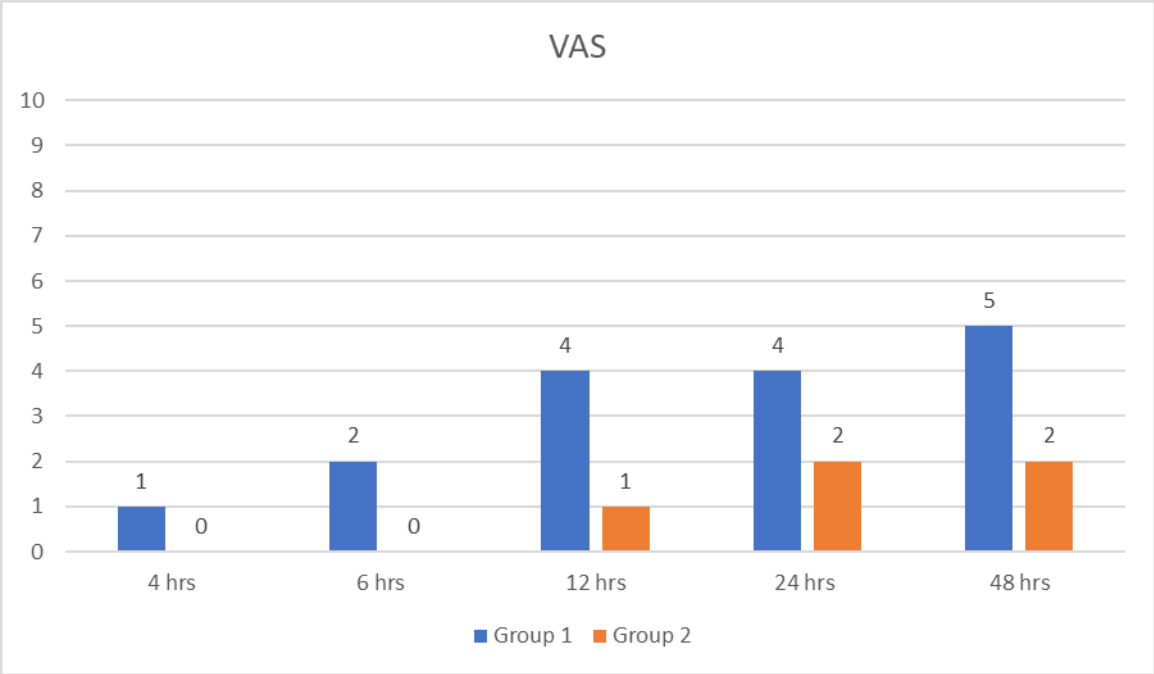
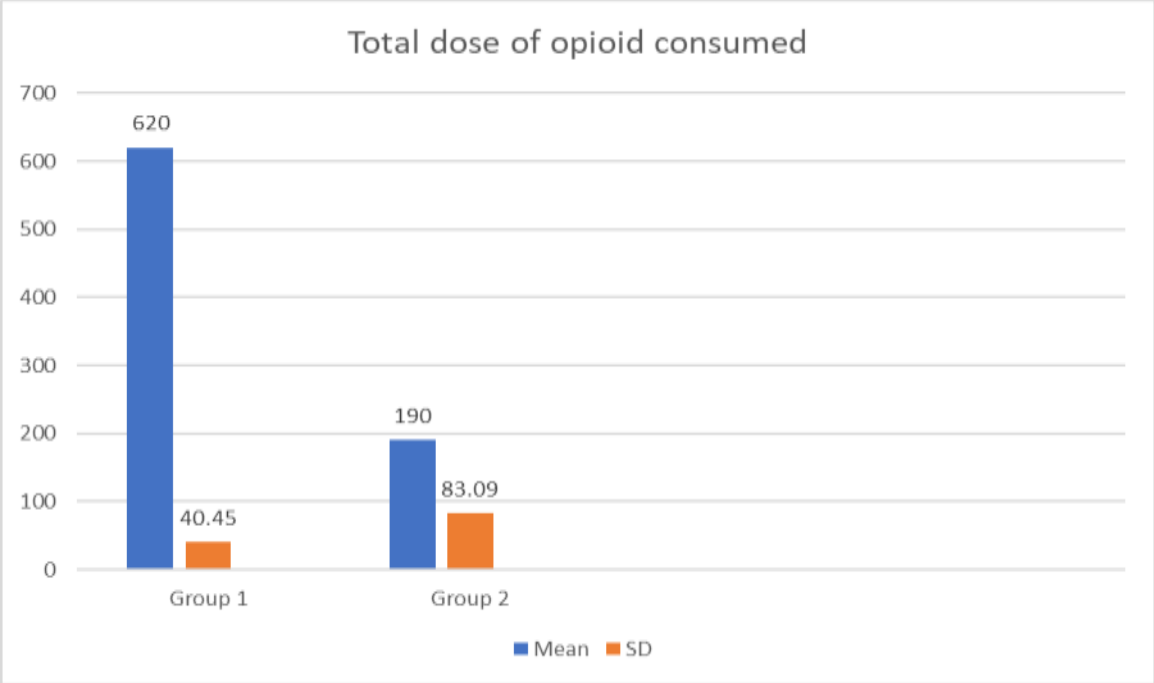


TABLE -6 DOSE OF OPIOID CONSUMED(mg)

Variables	Group	Mean	SD	P value
Total dose of opioid (mg)	Group 1	620	40.45	<0.0001
	Group 2	190.48	83.09	



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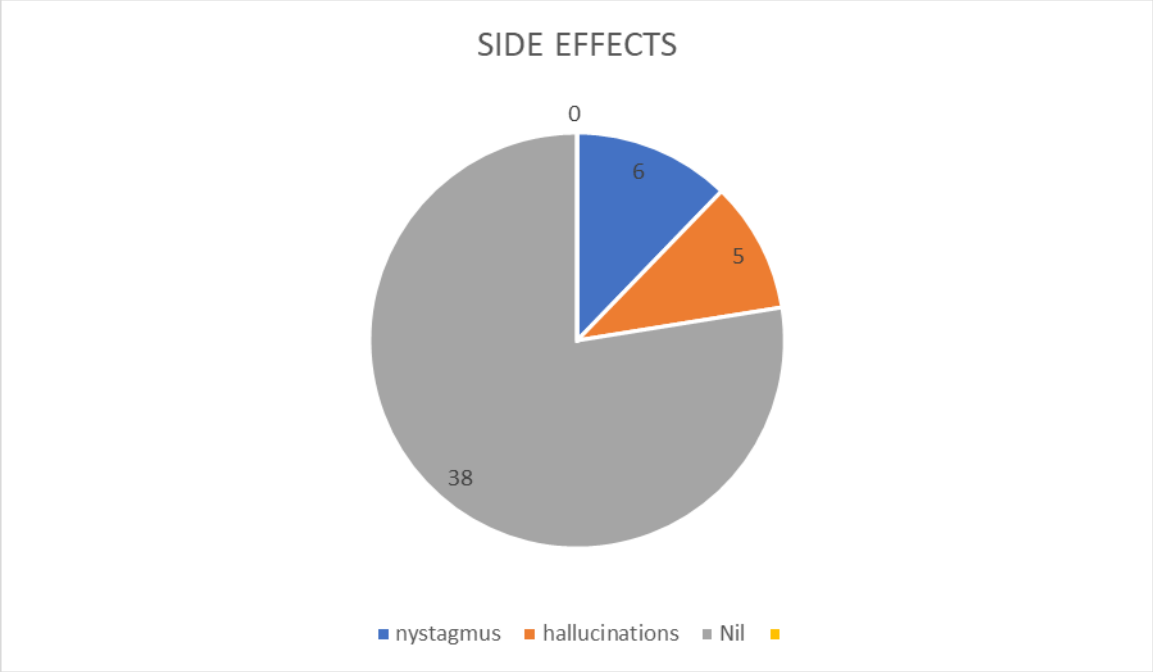
In patients whom ketamine infusion was administered the mean time taken for them to request for analgesia was 29.81 (± 5.4)hrs inferring that ketamine provided analgesia for a prolonged duration .

Of all the 45 patients who received the low dose ketamine infusion , 38 patients did not had any side effects , 6 (13.33%) of them had nystagmus and 5 (11.11%) had hallucinations. All of which resolved without requiring any active intervention. Hence we could prove that ketamine at this low dose caused very minimal side effects.



Discussion

It is well known that patients undergoing major abdominal surgeries experience severe pain in the postoperative period, which increases the incidence of postoperative morbidity and mortality. There is abundant evidence available indicating that noxious stimulation may have profound effects on the central neural processes which is involved in pain transmission, including the establishment of central sensitisation and the transition of acute, time-limited pain to chronic, pathological pain . It has been shown that opioids activate not only antinociceptive systems but also pronociceptive systems, causing acute opioid tolerance and opioid-induced hyperalgesia . Hence alternative adjuvants for analgesia in order to reduce opioid consumption are being researched extensively .

One such drug with pain relieving properties is ketamine which is an N-methyl-D-aspartate (NMDA) receptor–ion channel inhibitor and thereby plays a critical role in the development of central sensitisation [17,18] .The current model of pain processing consists of 3 primary sites of neural modulation which includes the peripheral nociceptor, the dorsal horn of the spinal cord, and the brainstem [19] . The NMDA receptor probably acts at the dorsal horn of the spinal cord. In response to tissue injury , the primary nociceptive neuron triggers release of glutamate in the dorsal horn of the spinal cord, which binds to NMDA receptors on the second-order neurons.

Once triggered , the NMDA receptor activates a cascade of intracellular processes that culminates in the altered expression of NMDA receptors which are responsible for the development of central sensitization. In addition to this, the NMDA receptor is intimately involved in the development of opioid tolerance and opioid-induced hyperalgesia, processes which can occur in parallel with central sensitization when patients are being treated with opioids [20]. By blocking the NMDA receptor, ketamine holds obvious promise for attenuating these centrally

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mediated pain processes, thereby reducing acute pain and potentially

preventing chronic pain [21,22,23] . Bushra A. Hadi et al studied forty-five patients undergoing microdiscectomy surgery in three groups: Group1 received normal saline, Group 2 ketamine (1 mcg/kg/min) intra-operatively and Group 3 ketamine (1 mcg/kg/min) both intra and postoperatively. Morphine consumption, pain scores, nausea and vomiting, CNS disorders were recorded for 24 h post surgery. The results showed that the time for the first analgesia demand dose was significantly shorter ($P < 0.05$) in G117 ± 1.7 min than for G2 and G3. In G3 morphine consumption 6, 12, and 24 h after surgery was 3 ± 2.26, 9.2 ± 2.11 and 26.9 ± 2.71 mg. Total morphine consumption was lower for G3 than for G1 or G2 ($P < 0.05$). The visual analog scale score (VAS) values were lower in G3 ($P < 0.05$) than for the other groups during the first 24 h. The rate of nausea and vomiting was higher in G1 vs G3 ($P < 0.05$). No difference in drug induced CNS disturbances was observed among the groups.This proved that using 1 mcg/kg/min of ketamine hydrochloride intra- operatively and post-operatively for microdiscectomy surgery could be an adjunct therapy to reduce postoperative morphine consumption minimizing its side effects [24] .

D. G. Snijdelaar et al conducted a randomised, double-blind prospective study in which they compared the effects on postoperative pain and analgesic consumption of intra-operative s(+)-ketamine (100 mcg/kg) bolus and a continuous infusion of (2 mcg/kg/min) followed by postoperative patient- controlled analgesia with morphine (1 mg per bolus) plus s(+)-ketamine (0.5 mg per bolus), or intra-operative saline followed by postoperative patient-controlled analgesia morphine (1 mg per bolus) alone. A total of 28 male patients undergoing radical prostatectomy were studied. Morphine consumption, pain scores, pressure algometry and adverse effects were recorded for 48 h after surgery. Cumulative morphine consumption was lower in the keta mine ⁄ morphine group (47.9 ± 26.2 mg) than in the saline ⁄ morphine group (73.4 ± 34.8 mg; $p = 0.049$). Pain scores at rest were significantly lower in the ketamine ⁄ morphine group across the 48-h study period ($p = 0.01$). No significant differences were found in pressure algometry measurements or the occurrence of adverse effects. The results of this study showed that low-dose 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 a standard treatment control group that did not receive s(+)-ketamine [25] .

Leonid Roytblat et al carried out a study to prove that postoperative pain can be decreased when ketamine in low doses is added to general anesthesia before surgical stimulation. In a randomized, double-blind study done by him postoperative pain was assessed in 22 patients undergoing elective open cholecystectomy with two types of anesthesia: standardized general anesthesia (control group), and low-dose ketamine as an addition to the same method of general anesthesia, before surgical incision (ketamine group). After the operation we found that the time from the end of surgery to the first request for analgesic was longer in the ketamine group. Postoperatively, patients in both groups were treated with patient-controlled analgesia (PCA) in exactly the same way. The major difference in the study was the reduced dose requirement of morphine in the ketamine group compared with the control group after the operation. The mean dose of morphine given in patients of the control group during the first 24 h was 48.7 mg vs 29.5 mg in the ketamine group. Mean visual analog scale (VAS) and verbal rating scale (VRS) were higher in patients in the control group during the first 5 h after surgery ($P < 0.021$), but between 5 and 24 h after surgery VAS and VRS were not significantly different ($P > 0.05$) [26] .

G. Adriaenssens et al studied the effect of adding ketamine to i.v. morphine patient-controlled analgesia (PCA) for the treatment of pain after laparotomy. Thirty patients were allocated randomly to receive PCA with saline or ketamine in a double-blind, randomized study. Analgesia was started in the recovery room when visual analogue scale (VAS) scores were 4. A bolus dose of morphine 3 mg was given to all the patients followed by i.v. PCA. Simultaneously, an infusion of ketamine 2.5 mcg/ kg /min or saline was started. Pain scores, morphine consumption and side effects were noted for up to 48 h after the start of PCA. VAS scores decreased significantly with time ($P= 0.0001$) and

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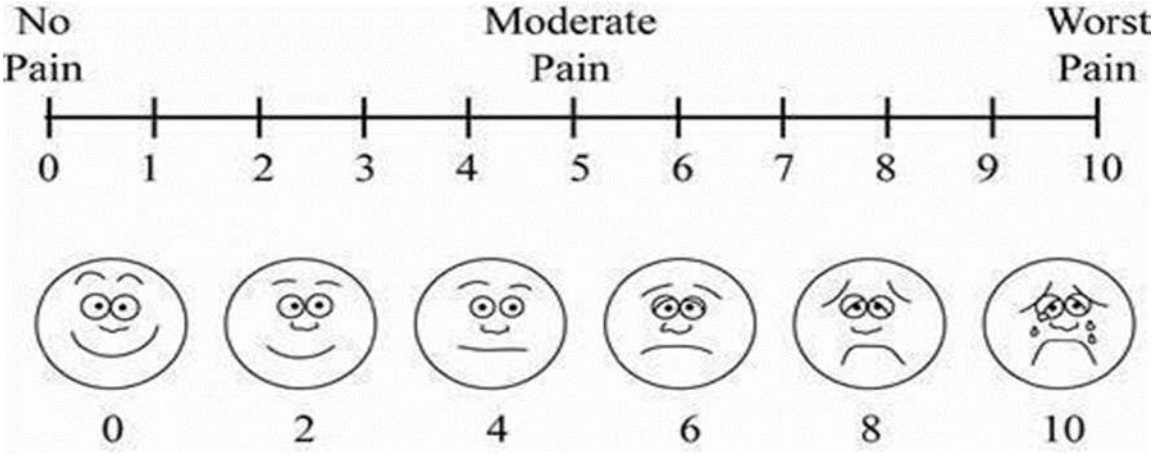
were similar (P= 0.3083) in both groups. Cumulative morphine consumption at 48 h was significantly lower in the ketamine group (28 mg) than in the control group (54 mg) (P= 0.0003). Nausea was less frequent in the ketamine group (P=0.03). Thus he successfully demonstrated that postoperative pain after laparotomy can be treated successfully with a low-dose continuous infusion of ketamine supplemented with i.v. morphine PCA. The combination of ketamine and morphine allowed a significant reduction in morphine consumption and decreased incidence of nausea. The dose of ketamine was low enough to avoid its psychomimetic effects [27].

Kevin Laskowski et al conducted a meta analysis in which Ninety-one comparisons in seventy studies involving 4,701 patients met the inclusion criteria (2,652 in ketamine groups and 2,049 in placebo groups). Forty-seven of these studies were appropriate for evaluation in the core meta-analysis, and the remaining 23 studies were used to corroborate the results. A reduction in total opioid consumption and an increase in the time to first analgesic were observed across all studies ($P < 0.001$). The greatest efficacy was found for thoracic, upper abdominal, and major orthopedic surgical subgroups. Despite using less opioid, 25 out of 32 treatment groups (78%) experienced less pain than the placebo groups at some point postoperatively when ketamine was efficacious. This finding implies an improved quality of pain control in addition to decreased opioid consumption. Hallucinations and nightmares were more common with ketamine but sedation was not. When ketamine was efficacious for pain, postoperative nausea and vomiting was less frequent in the ketamine group [28].

The pain measurement instrument used was Visual Analogue Scale (VAS) which is a simple and quick scale numbered from 1 to 10 on which patients can describe their postoperative pain intensity as no pain (0–4), moderate pain (5-7), and worst pain (7–10).



Limitation Of The Study

There were a few limitations to the present study. The first concern was that the patients in this study were only followed for up to 48 h after surgery. The study could not address the question of whether perioperative ketamine influences chronic pain and analgesic consumption in the longer term. Second, although we did not find differences in psychomimetic side-effects, a larger study is needed to assess this properly. A larger study is also needed to assess whether the favourable postoperative effects of ketamine make a difference in clinical outcomes such as time to ambulation, resumption of dietary intake and discharge from hospital.

Conclusion

Our study concluded that an IV bolus of 0.2 mg/kg of ketamine given at time of induction followed by a postoperative infusion of sub anaesthetic ketamine dose of 0.2mg/kg/hr for 48 hrs provided good analgesia by improving pain scores and significantly reduced the dose of opioid administered. At sub-anesthetic doses, ketamine was associated only with a low incidence of mild side effects like nystagmus and hallucination.

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Thus, ketamine at sub anaesthetic doses can be used as an ideal and safe analgesic in the perioperative setting in patients undergoing major upper abdominal surgeries .

Declaration of patient consent :

The authors certify that they have obtained appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

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