Original Article

Effectiveness of Pre-Operative Subcutaneous Infiltration of Ketamine for Post-Operative Analgesia and Haemodynamic Attenuation

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Abstract

Background: *Ketamine is a noncompetitive antagonist of N-methyl-D-aspartate (NMDA) receptor which plays an important role in pain modulation. It decreases acute postoperative pain by inhibiting C fiber activity.* ***Objective:*** *Purpose of this study was to evaluate the effectiveness of preoperative subcutaneous infiltration of ketamine for postoperative analgesia and haemodynamic attenuation.* ***Materials and Methods:*** *This Randomized controlled trial study was conducted among the patients with ASA (Ameracin Society of Anaesthesiologist) grade I & II, planned for major abdominal surgery with upper midline incision. Total 60 patients were selected and allocated into two groups, 30 in each- group A & B. Group A - Patients received subcuteneous wound infiltration with ketamine. Group B - Patients given subcuteneous wound infiltration with bupivacaine. Then haemodynamic status and patient outcome was assessed at different point of time.* ***Results:*** *There was no significant difference between groups in respect of demographic and ASA status. Mean age was found to 38.7±8.53 years. In Group A, 63.3% were ASA I and 36.7% were ASA II. In Group B, 60% were ASA I and 40% were ASA II. It has become evident that satisfactory analgesia can be acheived by subcuteneous wound infiltration with ketamine (in Group-A).The Mean verbal pain score was 5.2±0.47 and 7.4±0.68 in group A & group B respectively. The difference was statistically significant ($p<0.05$). After 2hrs, mean sedation was found 4.38±0.57 score in group A, but in group B score is reduced and found 3.52±0.27. Mean difference was statistically significant ($p<0.05$) between two groups.* ***Conclusion:*** *Surgical site infiltration of ketamine is a promising analgesic method in reduction of postoperative pain with minimal sedation and adverse effects. There was significantly prolonged duration of analgesia and better outcome.*

Key words: *Subcutaneous Infiltration of Ketamine, Bupivacaine, Postoperative Analgesia, Haemodynamic Status.*

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Introduction

Post-operative pain has the potential for significant adverse effects on the physiology and can also drown the patient into psychological suffering. The source and degree of nociceptive stimulation differ among individuals and surgeries and hence multimodal analgesic approaches have been encouraged for pain relief.[1] Adequate pain control is essential in immediate post-operative period. Different methods are being used to provide pain management but none of these is completely effective. Regional blocks are becoming more popular then systemic opioids in all age groups due to efficacy and safety of agents used.[2]

The advantage of post-operative analgesia for procedures with small incisions such as herniotomy and herniorrhaphy is well-known.[2]

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For longer incisions; larger volumes of the drug need to be deposited subcutaneously, aided by injection in additional planes for success. A thorough understanding of the pathophysiology of the surgical wound is necessary to improve both analgesia and postoperative recovery for any given operation. Crile proposed that true peripheral afferent blockade prevents propagation of abnormal reflexes that cause major organ dysfunction and death.[3,4] Thus, postoperative complications can be minimised and recovery enhanced. Since Crile's original hypothesis, we have learnt that the major reasons for surgical morbidity and mortality are the operation itself, the surgeon's personal expertise, the stress response to that trauma and patient comorbidities.

Postoperative analgesia is a major component of perioperative care and local anaesthetic (LA) techniques are more effective than systemic analgesia regardless of the operation and mode of delivery. Until recently, research and clinical practice has focused on central neuraxial blockade and peripheral nerve blockade. These, although highly effective, are reserved for major thoracic and abdominal surgery, mainly because of high failure rates and the risks of infection and spinal haematoma. When choosing a 'procedure-specific' technique, the simplest, safest and most effective block should be employed whenever possible.[5] Thus, the meticulous direct application of LA to each identifiable layer during a surgical procedure has considerable appeal for both surgeon and anaesthetist.

Wound infiltration with local anaesthetics is a simple, effective and inexpensive means of providing good analgesia for a variety of surgical procedures without any major side-effects. In particular, local anaesthetic toxicity, wound infection and healing do not appear to be major considerations.[3] Local anaesthetic infiltration for surgery itself has largely been confined to small superficial procedures. However, performed well, this is a logical means of preventing pain and other noxious stimuli from reaching the spinal cord. When combined with specific nerve blockade, e.g. ilio-inguinal nerve block or transversusabdominis plane (TAP) block during hernia repair, this allows a 'multimodal local anaesthetic' means of combating pain and anoci-association. By allowing patients to mobilise more quickly, wound infiltration may be as effective as central and proximal peripheral blocks in ensuring a safe postoperative recovery.

Recently several studies have proven success of subcuteneous wound infiltration in attenuation of post-operative pain. In a study 48 patients randomized into two equal groups; Group K received subcutaneous infiltration of 20 ml containing ketamine 2 mg/kg and Group L received subcutaneous infiltration of 20 ml of levobupivacaine 0.25% along the Pfannenstiel incision 5 min before incision. Postoperative pain was assessed using visual analog scale (VAS). VAS score decreased significantly in Group L from 10 to 24 h and in Group K from 8 to 24 h as compared to the immediate postoperative reading. VAS score in ketamine group was significantly lower than that in the levobupivacaine group 8, 10, and 24 h postoperatively. Surgical site infiltration of ketamine is a promising preemptive analgesic method in the lower abdominal surgery with minimal sedation and adverse effects.[6] In another trial, 98 patients, eligible for elective C/S under general anesthesia, were randomly allocated to 2 groups (e.g., 20 cc of 0.025% bupivacaine and 2 mg/kg of tramadol). Local infiltration of tramadol (2 mg/kg) at the incision site of C/S was found effective in somatic wound pain relief without significant complications.[7]

Local anesthetics have been used in surgery for a long time to reduce postoperative pain and the need for analgesics. Bupivacaine is a long-acting local anesthetic that effectively reduces postoperative pain. In practice, bupivacaine is used for infiltration anesthesia, nerve blocks, epidural, and caudal anesthesia. It has a more selective effect on sensory nerve fibers as compared to motor nerve fibers. Bupivacaine has been used for preoperative wound infiltration and study reported intraoperative local bupivacaine application is effective in decreasing postoperative pain.[8] Instillation of Bupivacaine hydrochloride into the surgical incision is a safe, well-tolerated treatment and it is superior to traditional systemic pain medication in both self-reported and clinical outcomes.[9]

Ketamine is by far the most versatile drug available in anesthesia and possibly in all of medicine. Although this drug was designed over 50 years ago as a replacement for phencyclidine as a dissociate anesthetic, in recent years various new indications for ketamine have been discovered across multiple clinical settings, including anesthesia, pain medicine.[6] Ketamine is a lipophilic compound that easily crosses the blood-brain barrier. This results in a rapid onset of action of acute pain relief with an estimated blood-effect site equilibration half-life of close to 1 minute. Randomized control trial demonastrated that Ketamine treatment is most effective for relief of postoperative pain, causing reduced opioid consumption.[10]

Ketamine is a drug that acts at multiple targets; most importantly, it blocks the N-methyl-D-aspartate receptor (NMDAR). The excitatory glutamatergic NMDAR is ubiquitously distributed throughout the brain and spinal cord and plays an important role in the development and chronification of pain. However, ketamine's molecular mechanism is not restricted to the NMDAR, and several studies indicate interactions with a series of receptor systems, including agonism at the opioid, AMPA, GABA, cholinergic, dopaminergic and innate repair receptors, and antagonism at HCN1, potassium, calcium, and sodium channels. Previous study reported that surgical site infiltration of ketamine is a promising preemptive analgesic method in the lower abdominal surgery with minimal sedation and adverse effects.[11] Therefore aim of this study was to assess the analgesic effectiveness of wound infiltration of ketamine.

Materials and Methods

This study was conducted to evaluate the effectiveness of subcuteneous wound infiltration with ketamine for postoperative pain control. Patients scheduled for major abdominal surgeries with upper midline incision under G/A were selected. Total 60 patients, ASA (Ameracin Society of Anaesthesiologist) physical status I and II, were recruited according to inclusion, criteria and randomised into two groups of 30 each. Group A (ketamine n = 30) plan to subcutaneous infiltration of ketamine 2 mg/kg and Group B (bupivacaine n =30) given subcutaneous infiltration of 20 ml of bupivacaine 0.25%. Ketamine was diluted with sterile 0.9% saline solution to 20 ml volume and similar syringes and will be infiltrated subcutaneously along the skin wound edges (along the incision) before reversal.

Heart rate (HR), noninvasive arterial blood pressure (systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure (MAP) and peripheral oxygen saturation level were monitored in the operating room. Anesthesia was induced by 1% propofol 2mg/kg, fentanyl 1µg/kg and suxamethonium 1.5 mg/kg for facilitation of tracheal intubations. Anesthesia was maintained by 0.6% halothane, nitrous oxide in oxygen (2:1). The study drugs was infiltrated subcutaneously by a surgeon who not involved in group assignment into the incisional site region before reversal. At the end of surgery, volatile anesthetics was discontinued, neuromuscular blockade reversed by intravenous (IV) neostigmine 0.05mg/kg and IV atropine 0.02 mg/kg, and extubation was performed when airway reflexes has returned.

During the postoperative period, pain was assessed at baseline, 2, 6, 12, 24 h using visual analog scale (VAS) where 0 = no pain and 10 = the worst pain possible. In addition, the patients will be assessed for level of sedation using Ramsay sedation scale (1 = patient anxious and agitated or restless or both, 2 = patient cooperative, orientated and tranquildrowsy 3 = patient responds to command only, 4 = brisk response, 5= sluggish response, 6= no response), HR, and MAP. The time from induction of anesthesia to discontinuation of anesthesia was considered as the anesthetic time and the time from the first surgical incision till the last skin suture was considered the operative time. Finally, occurrence of adverse effects such as nausea, vomiting, dizziness, hallucination, and allergic reactions was recorded in the postoperative period. In case of vomiting, ondansetron 4 mg was given intravenously.

Statistical analysis of the data was done using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) software version 22. Qualitative data such as sex, ASA physical status, adverse effects was compared using Chi-square test. Quantitative data such as age, numeric rating scales, time to first analgesic request and total analgesic requirement in 24 h was compared using independent t-test. $P < 0.05$ was taken as statistically significant.

Results

Total of 60 patients fulfilling inclusion criteria were studied.

Table I: Age distribution of Study population (n=60)

Age (years)	**Number of patients**		**Total & Percentage**
	Group A (n=30)	**Group B (n=30)**	
18-39	21(70.0%)	18(60.0%)	39(65.0%)
40-60	9(30.0%)	12(40.0%)	21(35.0%)
Mean ± S.D.	38.7±8.53		

While studying the distribution of cases by age it was found that majority of the patients i.e. 65.0% (n=39) were between 18-39 years, 35.0% (n=21) were between 40-60 years. Mean age was found to 38.7±8.53 years. Comparison was done by Chi-Square (x^2) test. No significant differences were found between groups with respect to age. (Table-I)

Table II: American Society of Anesthesiologist (ASA) physical status (n=60)

Status	**Number of Patient**		**P value**
	Group A	Group B	
ASA I	19(63.3%)	18(60%)	0.790
ASA II	11(36.6%)	12(40%)	

There were no significant difference between the groups (p=0.790). Comparison was done by Chi-Square (x^2) test. All 60 enrolled patients were randomized to groups, 30 patients of each. In Group A, 63.3% were ASA I and 36.6% were ASA II. In Group B, 60% were ASA I and 40% were ASA II (Table-II).

Common indication of surgery was gastric surgery (gastrectomy), gynaecological surgery (TAH), intestinal surgery (hemicolectomy, Intestinal resection and anastomosis) and orthopaedic surgery (Hemiarthoplasty), 35.0%, 23.0%, 30.0%, 7.0% and 5.0% of patients respectively.

Postoperative heart rate and other haemodynamic status were evaluated at 2h, 6h, 12h after surgery. Present study shows that, at 2 hr after mean heart rate was 87.7±11.2 beat/min and 92.0±11.9 beat/min in group A and group B respectively. At 6 hr after, mean heart rate was 90.7±8.2 beat/min in group A and 98.5±7.7 beat/min in group B. At 12 hr after surgery, mean heart rate was 94.2±7.8 beat/min and 96.9±7.4 beat/min in group A and group B respectively. At after 6 hr difference was statistically significant ($p<0.05$) between two groups. So it is found that heart rate was more stabilize those patients getting subcuteneous wound infiltration with ketamine than others. SBP and DBP was non-significant in between groups (Table-III).

Table III: Evaluation of heart rate amongst the study subjects (n=60)

Heart rate (beat/min)	Group A n(%) Mean ±SD	Group B n(%) Mean ±SD	Pvalue
Baseline	86.7 ±9.4	85.9 ±7.1	0.258ns
2 hr after	87.7 ±11.2	92.0 ±11.9	0.074ns
6 hr after	90.7 ±8.2	98.5 ±7.7	0.001s
12 hr after	94.2 ±7.8	96.9 ±7.4	0.206ns
24 hr after	82.7 ±8.4	84.9 ±7.1	0.871ns

The day before surgery patients were instructed about the Visual Analog Scale (VAS) in which 0=no pain and 10=worst pain imaginable. Patients in the group-B had higher VAS, during the second hours (P = 0.0001), compared with the group-A. Mean verbal pain score was 5.2±0.47 and 7.4±0.68 in group A & group B respectively. The difference was statistically significant. Six hours after the surgery, both groups showed downward trends of the pain VAS, but significantly in group A. Mean score was 3.1±0.32 and 5.2±0.51 in group A & group B respectively. At the 12th hour, almost all patients had no pain. So overall finding suggested that, subcuteneous wound infiltration with ketamine reduced the postoperative pain significantly (Table-IV).

Table IV: Assessment of pain sensation using Visual Analogue Score (VAS) (n=60)

VAS score	Group A n(%)		Group B n(%)		P value
	n	%	n	%	
2 hr After surgery					
0 - 2	5	16.6	1	3.3	
3 - 6	16	53.3	14	46.7	
7 - 10	9	30.0	15	50.0	
Mean±SD	5.2 **±0.47**		7.4 **±0.68**		**0.001s**
6 hr after surgery					
0 - 2	12	40.0	5	16.7	
3 - 6	18	60.0	21	70.0	
7 - 10	0	0	4	13.3	
Mean±SD	**3.1 ±0.32**		**5.2 ±0.51**		**0.001s**
12 hr after surgery					
0 - 2	19	63.3	12	40.0	
3 - 6	11	36.7	18	60.0	
7 - 10	0	0	0	0	
Mean±SD	**2.1 ±0.23**		**2.8 ±0.27**		**0.091ns**

On evaluation of sedation score, after 2hrs, mean sedation was found 4.38±0.57 score in group A, but in group B score is reduced and found 3.52±0.27. Mean difference was statistically significant ($p<0.05$) between two groups. After 6 hrs, mean sedation was found 4.13±0.32 score in group A and 3.89±0.51 score in group B. The quality of pleasant and adequate sedation varied between groups, and it was maintained properly in group A in whole time. But after 12 hrs of surgery sedation level gradually impaired in both groups. After 12 hrs, mean sedation score between groups almost similar and was found 1.39±0.47 score in group A and 1.46±0.51 score in group B. So precise control of the depth of sedation was maintained in group A than group-B (Table-V).

Table V: Assessment of sedation according to Ramsay Sedation Scale (n=60)

RSS	Group A n(%)		Group B n(%)		P value
	n	%	n	%	
2 hr After surgery					
1	0	0	0	0	
2	0	0	4	13.3	
3	0	0	9	30.0	
4	12	40.0	6	20.0	
5	9	30.0	6	20.0	
6	9	30.0	5	16.6	
Mean±SD	4.38	±0.57	3.52	±0.27	0.001 s
6 hr after surgery					
1	0	0	0	0	
2	0	0	2	6.6	
3	3	10.0	9	30.0	
4	10	33.3	7	23.3	
5	8	26.6	8	26.6	
6	9	30.0	4	13.3	
Mean±SD	4.13	±0.32	3.89	±0.51	0.001 s
12 hr after surgery					
1	18	60.0	19	63.3	
2	9	30.0	7	23.3	
3	3	10.0	4	13.3	
4	0	0	0	0	
5	0	0	0	0	
6	0	0	0	0	
Mean±SD	1.39	±0.47	1.46	±0.51	0.131 ns

Discussion

Findings were accordance with result of other studies. In a study mean age was 48.4±5.6 year.[12] Similar study reported mean age of 90 patients included in the study was 44.37±13.42 years (range 18-67 years), and the female:male ratio was 62:28 (females, 68.9%; males, 31.1%).[13]

The results of this study indicate that preincisional surgical site infiltration using both ketamine and bupivacaine can provide adequate postoperative pain relief up to 12 h postoperatively following abdominal surgery under general anesthesia. Both drugs were safe with minimal sedation and limited adverse events. Ketamine appeared to have a longer analgesic duration compared to bupivacaine. It delayed requesting and decreased consumption of additional analgesia.

The concept of preemptive or preincisional analgesia focuses on prevention of central sensitization triggered by surgical incision; however, other factors have been advocated to exaggerate acute and long?term postoperative pain as a result of central sensitization. These include noxious intraoperative stimuli as retraction, postoperative inflammatory processes, and ectopic neural activity.[12]

In the current study, we tested the hypothesis that ketamine, having multiple mechanisms of action, may be effective when administered by subcutaneous injection at the surgical site before incision. The analgesic effect of ketamine may involve the block of other sources of pain. It is a NMDA receptor antagonist that can reverse central sensitization and reduce wind?up and consequently decreases postoperative pain.[14] It has been shown to have a local anesthetic effect mediated by a depression of sodium?channel function.[15] The analgesic effect of ketamine may be increased due to its anti?proinflammatory effect. It interacts with inflammatory cells recruitment, cytokines production, and inflammatory mediator regulation.

Investigators were concerned whether the analgesic effect of ketamine is mainly a result of an antihyperalgesia, or specific analgesia.[16] Pain level appears to reflect an increased nociceptive input in addition to pain sensitization process. Glutamate through the NMDA receptors plays a major role in this phenomenon of neuronal plasticity that leads to pain hypersensitivity that could facilitate chronic pain development. By an action on NMDA receptors, opioids also induce, in a dose dependent manner, an enhancement of this postoperative hypersensitivity. Thus, ketamine the NMDA receptors antagonist can exert its antihyperalgesic effect to decrease this central sensitization in the postoperative period.[17]

On the other hand, the action of local anesthetic is restricted to block of nerve impulse conduction by inhibition of sodium channels at the nerve endings and along the axon. In a study, compared ketamine with levobupivacaine owing to its longer duration of action (approximately 14-16 h) which diminishes the clinical importance of adding epinephrine.[12]

Ketamine has the additional advantage of being inexpensive, widely available, noninvasive and does not require additional laboratory work.

In a recent randomized trial, surgical site infiltration with liposomal bupivacaine was compared to transverses abdominis plane blocks for pain relief after total abdominal hysterectomy through a Pfannenstiel incision. Surgical site infiltration provided superior pain relief at rest and on coughing and reduced opioid consumption for up to 48 h.[18] Other studies did not find any advantage of local infiltration in many types of surgery.

Postoperative analgesic efficacy of surgical site infiltration of ketamine has been demonstrated in few previous studies, mostly in pediatric population. In a group of fifty children undergoing palatoplasty, ketamine produced similar analgesic effect compared to bupivacaine up to 12h; then pain intensity was lower with ketamine 24h postoperatively with reduction of requirement of rescue analgesic.[19] A prospective, randomized, double blind study compared postoperative analgesic efficacy of preincisionalperitonsillar infiltration of ketamine and ropivacaine in children undergoing tonsillectomy. Ketamine was as effective as ropivacaine in pain relief, but ropivacaine was superior in reduction of time to first analgesic demand.[20] In a similar study, ketamine was equivalent to tramadol in pain reduction. It was safe with limited instances of postoperative nausea, vomiting, and dysphagia.[21] These results confirmed the findings of prior systematic review that ketamin is a superior than others.

Conclusion

Subcutaneous infiltration of ketamine appears to be a promising analgesic through surgical site infiltration in major abdominal surgery. It has comparable effect to bupivacaine with longer duration of action and minimal adverse effects. Thus, the local infiltration of ketamine in incision is proposed as a safe and effective analgesic after general anesthesia.

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