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Original Research Article

Efficiency of IV Ketamine in Preventing Pain

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Abstract:

Introduction: ketamine have an effective usage in medical field as an analgesic. It is used in case of pain management, helps to get relief from both chronic and acute level of pain after surgery. For the quick mode of action of ketamine it is used as pain reliever. Various researchers are still cultivating other importance of ketamine. It is also used as a supplement of curing severe depression condition also.

Aims and Objective: To evaluate the efficacy of pain prevention with intravenous Ketamine administration.

Method: The observational study was done for the determination of the potentiality of ketamine as a pain reliever among 80 patients, divided 40 in each group. Ketamine was given to the Group 1 while Normal Saline was given to Group 2. For the measurement of pain, Visual Analog Scale (VAS) was utilized. Different parameters and side effects were considered and compared among patients. Student's t test used for statistical analysis with p value <0.05.

Result: The comparative study of pain after surgery between two groups was studied with ketamine and saline for the two groups. Different parameters like duration of surgery, side effects and time of recovery was similar for both groups. The study found significant differences in post-operative outcomes between the IV Ketamine and Normal Saline groups. Group 2 had a higher incidence of nausea/vomiting ($p=0.0498$) and required significantly more analgesia within 24 hours (TFA: 4.2±0.9 hours vs. 22.05±0.15 hours, $p<0.05$). Additionally, Group 2 needed more additional doses of anesthetic (19.5±1.8 vs. 5.9±1.55, $p<0.05$), indicating a more challenging recovery.

Conclusion: The study concluded that ketamine has significant positive impact on the post-operative pain and there was negligible adverse effects among the patients.

Keywords: Ketamine, Anaesthesia, Post-Operative Pain, Surgical Pain.

Introduction

Efficient pain management is crucial in therapeutic treatment and, similarly, it is necessary to discover safe and effective alternatives for pain alleviation. The latest progress in research and technology is crucial in the creation of pharmaceuticals and therapies that effectively address the ailments experienced by individuals. Ketamine remains a potential medication for several clinical reasons, even years after its early discovery. It has become widely identified and has emerged as a potent analgesic, especially when taken intravenously [1]. Ketamine provides a spectrum of pharmacological effects, operating as an anaesthetic for induction and maintenance, as well as producing analgesic and sedative effects depending on the dosage. According to the previous research primarily ketamine was created as an anaesthetic, but later, it was revealed that it exhibits special features that make it a valuable choice for reducing pain, that too at lower levels than those required for anaesthesia for therapy. Ketamine can be administered alone or in combination with other drugs to boost their efficacy [2].

Ketamine functions as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, which acts as a key pain regulator and helps in heightened sensitivity. Through its blockage of the NMDA receptor, ketamine deters the action of the key excitatory neurotransmitter glutamate, which leads to lower neural excitability and, therefore the experience of pain lightens. In addition to this ketamine also affects opioid receptors, mono aminergic pathways, and voltage-gated calcium channels, contributing to its broad pain-relieving properties. These rare properties make ketamine very efficient in mending both short-term and long-term pain disorders [3]. It is frequently used to alleviate acute pain, particularly in surgery and urgent situations. A recent study indicates that low-dose IV ketamine can dramatically reduce postoperative pain and opioid intake, with lower

pain scores and relatively fewer opioid-related adverse effects. Ketamine works as a beneficial tool for acute pain management as its rapid onset and brief duration make it valuable for routine sedation, fracture, and pain relief in emergency medicine [4].

Ketamine has demonstrated good outcomes not just for acute pain, but also for chronic pain syndromes such as neuropathic pain, complex regional pain syndrome (CRPS), and fibromyalgia. The underlying process functions by lowering central sensitization through its antagonistic impact on NMDA receptors [5]. Likewise, ketamine infusions have shown potential in remedying refractory neuropathic pain, where traditional analgesics fail to offer enough relief. The use of sub-anaesthetic dosages of ketamine is vital in pain management to enhance its analgesic properties while reducing the side effects. At these lower levels, ketamine can give efficient pain treatment without generating anaesthesia or severe psychotropic effects. Ongoing research has been focused on improving ketamine dosage to balance efficacy and safety [6]. New research has broadened the use of ketamine beyond pain management, indicating its potential in treating depression and PTSD. This underlines the necessity for more research into ketamine's various pharmacological characteristics. Medical practices are adding ketamine into comprehensive pain regimens, exclusively for patients with significant opioid tolerance or at risk of opioid-related problems. The objective is to improve patient outcomes, decrease opiate dependency, and enhance the quality of life for patients who face acute and excruciating pain [7]. This study will explore the importance of ketamine and its exploitation as a pain reliever, the underlying complex mechanism by which it acts and its effectiveness and utility in the clinical context.

Method

Research Design: This is a prospective, observational study of determining the efficiency of ketamine for prevention of pain in case of operative processes. The study was conducted in a multispeciality hospital in India from February 2023 to January 2024. The selected patients for the study were total 80 and were divided into two groups, group 1 and group 2 having 40 patients in each group. Selected patients were made aware about the utilization of visual analog scale (VAS) which is of 100 cm where 0 level denoted no pain and the highest level of unbearable pain is 100. In case of group 2 which is the control group, normal saline of 10 ml and group 1 patients received intravenous ketamine (1mg/ml) of 10 ml were used. This is made for the bolus dose. Whereas normal saline of 50ml and ketamine of 50 ml were prepared for group 2 and group 1 respectively, this is for the infusion.

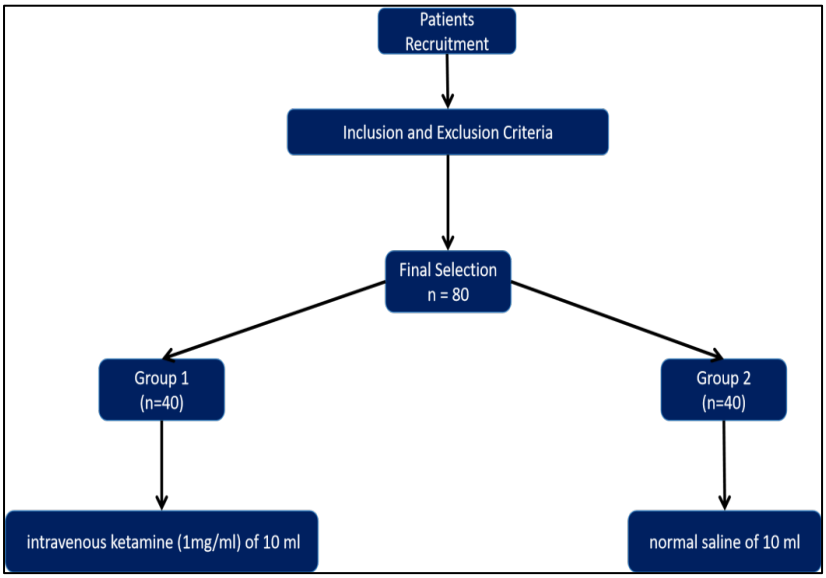

Figure 1: Grouping and Intervention of this study

Firstly patients under surgical processes were given medication with ranitidine 5omg, fentanyl 2ug/kg, metoclopramide 10mg and glycopyrrolate 0.004mg/kg were given intravenously (IV). This step is followed by anesthesia along with Injection Propofol 2mg/kg. Basic maintenance of patients was done under O_2, N_2O, isoflurane and Atracurium and was under observation. Then the bolus dose was administered containing ketamine and normal saline solution of 0.15ml/kg and infusion of 0.12ml/kg/hour was done continuously containing 2ug/kg/min ketamine for group 1 and saline for the group 2. Various parameters like heart rate, noninvasive blood pressure, saturation of oxygen level were continuously under observation. By altering the Isoflurane concentration, variance in the surgical stimulus can be controlled. Assessment of VAS score at different time intervals like 15 min, 30 min,

45 min then 4 hour, 8hr, 12 hour, 16 hour and lastly at 24 hour were taken, in the post-surgery condition. Also noted that post-operative processes include various side effects such as diplopia, pruritus, nausea, vomiting, seadation and various other respiratory problems (RR <10 breaths/min).

Inclusion Criteria

The criteria to include patient for the study are as follows

- The age of patient should be between 20- 65 years of age.
- Renal surgery patients with anesthesia will be included for the study

Exclusion Criteria

The factors which should be considered for the exclusion of patients includes –

- Patients those who are under some regular medication like analgesics and are suffering from chronic pain were not included for the study.
- Psychiatric patients are not allowed
- Extreme drug/alcohol addicted patients were excluded from study
- Both written and verbal consent should be taken from the patients before selection.

Statistical analysis

The study has used SPSS 27 for effective analysis. The ordinal values were expressed in frequencies and percentage while the continuous data were expressed in mean value and standard deviation. The study used students 't' test. The study considered P <0.05 as statistically significant.

Result

Table 1 shows the mean age of Group 1 was 40.25 years with a standard deviation of 15.25, while Group 2 had a slightly higher mean age of 43.52 years and a standard deviation of 12.56. Both groups had an equal gender distribution, with 20 males and 20 females in each. The average surgery time for Group 1 was 3.65 hours with a standard deviation of 0.44, and for Group 2, it was 3.56 hours with a standard deviation of 0.07, showing minimal difference between the two. The duration of recovery was also comparable, with Group 1 averaging 8.45 hours (standard deviation of 1.79) and Group 2 averaging 8.5 hours (standard deviation of 0.8). Regarding the type of surgery, Group 1 had 27 nephrectomies, 2 pyelolithotomies, and 1 pyeloplasty, whereas Group 2 had 30 nephrectomies, indicating a slight variation in surgical procedures between the groups.

Table 1: Study of different parameters for both the study groups

Parameters	Group 1 (n=40)	Group 2 (n=40)
Age (year)	40.25±15.25	43.52±12.56
Sex M/F	20/20	20/20
Surgery time (hours)	3.65±0.44	3.56±0.07
Duration of recovery (hours)	8.45±1.79	8.5±0.8
Surgery type	27 nephrectomy 2 pyelolithotomy 1 pyeloplasty	30 nephrectomy

Table 2 shows the incidence of side effects post-operation was recorded for both groups, and statistical analysis was performed to determine significance. In both groups, there were no cases of hypotension/hypertension, hyperalgesia, pruritis, emergence reaction, or respiratory problems, leading to no significant p-values for these side effects. However, for tachycardia/bradycardia, Group 1 had 1 case (2.5%), while Group 2 had none, with a p-value of 0.0887, indicating no significant difference. Nausea/vomiting was noted in 4 participants (10%) in Group 2, but none in Group 1, yielding a p-value of 0.0498, which is statistically significant and suggests that Group 2 had a higher incidence of nausea/vomiting post-operation.

Table 2: Side effects related to post operation

Side effects	Group 1(n=40)	Group 2(n=40)	P-value
Hypotension/hypertension	0	0	-
Tachycardia /Bradycardia	1 (2.5%)	0	0.0887
Nausea /vomiting	0	4 (10%)	0.0498
Hyperalgesia	0	0	-
Pruritis	0	0	-
Emergence reaction	0	0	-
Respiratory problems	0	0	-

The study shows the requirement for analgesia within the first 24 hours post-operation was significantly different between the two groups. The total fentanyl administered (TFA) in hours had a mean of 22.05 hours (standard deviation of 0.15) in Group 1, compared to 4.2 hours (standard deviation of 0.9) in Group 2, with a p-value of less than 0.05, indicating a highly significant difference. Additionally, the number of additional doses required for anesthetic patients was also significantly different, with Group 1 needing an average of 5.9 doses (standard deviation of 1.55) compared to Group 2's 19.5 doses (standard deviation of 1.8), again with a p-value of less than 0.05. This data suggests that Group 2 required significantly more analgesia and additional doses compared to Group 1 within the first 24 hours post-operation.

Table 3: Need for the analgesia after operation for 24 hours

	Group 1	Group 2	P value
TFA (hours) mean±SD	22.05±0.15	4.2±0.9	<0.05
Additional doses for anesthetic patient	5.9±1.55	19.5±1.8	<0.05

P <0.05

Discussion

Ketamine, an uncompetitive antagonist of the NMDA receptor, is thought to largely exert its analgesic effects by counteracting certain pathways, notably in the context of neuropathic pain, which is the main area of investigation for this medication. Ketamine has a broad spectrum of receptor affinities, encompassing opioid (mu, kappa, and sigma), dopaminergic, serotonergic, monoaminergic, anticholinergic, muscarinic, gamma-aminobutyric acid (GABA), and other receptors. This diverse receptor profile enables ketamine to have antidepressant, analgesic, and psychomimetic effects. Thus, ketamine has demonstrated its efficacy in both nociceptive and nociplastic pain settings, suggesting that the analgesic mechanism of ketamine cannot be only attributed to NMDA receptor blocking, as this explanation is too naive [8, 5].

A recent study has raised attention to the possibility of intravenous (IV) ketamine in alleviating different forms of pain. The trials illustrate the adaptability and efficacy of low-dose ketamine in treating pain through multiple routes and clinical settings [9]. Ketamine has proven usefulness in preventing acute pain, such as that after Propofol injections, as well as in managing persistent post-surgical pain syndromes. These results show that low-dose ketamine may be a good alternative for managing several pain-related problems [10]. Administering low-dose IV ketamine is well-known for its effectiveness in decreasing pain induced by Propofol injections. Sangawar et al. observed that providing 100 mcg/kg of IV ketamine before Propofol dramatically decreased the frequency and severity of pain, with no patients in the ketamine group experiencing moderate or severe pain. The study also featured that ketamine pre-treatment was well-abided and did not cause any harmful effects on cardiac function or safety concerns [11]. Researchers are vigorously investigating the possibility of ketamine in inhibiting persistent post-surgical pain syndromes, adding to its role in controlling acute pain. The Ketamine analgesia for long-lasting pain relief after surgery (KALPAS) is a double-blind, multi-centre, randomized trial with a placebo control in phase 3 trial which is a part of the NIH's Helping to End Addiction Long-term (HEAL) Initiative, that is being implemented across the country, which focused on evaluating the effectiveness of ketamine in lowering post-mastectomy pain syndrome (PMPS), a persistent disease that impacts a considerable part of mastectomy patients. By focusing on issues such as acute pain and poor temperament, the researchers are hoping that ketamine could potentially slow the development from acute to chronic pain. If successful, this research could lead to improved long-term results and less reliance on opioids for the administration of enduring post-surgical pain [12].

Another undertaken by Polomano et al. has revealed that ketamine, when administered in low dosages either as a single injection or continuous infusion, has proven to be beneficial in lowering both peripheral and central pain in persons with serious limb injuries acquired in combat. This is a noteworthy result as battle injuries sometimes include sophisticated pain systems that are tough to treat. By treating diverse pain pathways, ketamine could offer a helpful option for opioid-based pain management, which typically has limited effectiveness and significant bad effects, especially in cases of severe trauma [13]. Interestingly, Ketamine has also shown a potential to lower shivering, a typical adverse effect of spinal anaesthesia. A study undertaken by Avais et al. discovered that IV ketamine (0.5 mg/kg) significantly decreased shivering compared to placebo (p=0.006) but was no more effective than IV tramadol (0.5 mg/kg). On the contrary, the ketamine group displayed a considerable rate of nystagmus (eye movement irregularities), a serious adverse consequence. While ketamine may assist cure shivering, its potential side repercussions necessary to be studied. Further explicit research is required to increase the dose and distribution of

ketamine in order to maximize its advantages and minimize any negative effects [14].

Recent breakthroughs in ketamine research have increased its clinical utility beyond the traditional administration of pain, indicating its potential in the treatment of depression and post-traumatic stress disorder (PTSD). These insightful findings emphasised the broad pharmacological profile of ketamine and underlined the necessity for continuing study into its many therapeutic applications [15]. The rapid antidepressant properties of ketamine have been a significant area of focus in recent studies. Several research have revealed that ketamine infusions can instantly reduce depressive symptoms and suicidal thoughts in patients with treatment-resistant depression. Also, ketamine has exhibited possibilities for the management of PTSD, offering instant relief for patients who do not react to traditional therapies [16]. Ketamine is valuable in reducing both acute and chronic pain as it helps to lower surgical pain, reduce opioid use, and give relief for long-lasting chronic pain making it a substantial adjunct to the pain management regimens [1,17]. Constant research is seeking novel medical applications for ketamine and its varied applications. As guidelines evolved, ketamine's role in multimodal pain therapy is anticipated to rise , leading to improved patient outcomes and less opioid dependence [18].

Conclusion

The study concluded that ketamine has significant positive impact on the post-operative pain and there was negligible adverse effects among the patients. Although the demographic and surgical parameters between the IV Ketamine group and the Normal Saline group were similar, significant differences were observed in post-operative outcomes. The Normal Saline group experienced a higher incidence of nausea and vomiting, requiring significantly more analgesia within the first 24 hours post-operation compared to the IV Ketamine group. The mean total fentanyl administered was substantially lower in the Normal Saline group, and they required more additional doses of anesthetic. These findings suggest that the Normal Saline group had a more challenging post-operative recovery, with an increased need for pain management interventions. The study concluded that despite similar demographic and surgical parameters, the post-operative outcomes differed significantly between the IV Ketamine and Normal Saline groups. The Normal Saline group exhibited a higher incidence of nausea and vomiting and required significantly more analgesia within the first 24 hours post-operation compared to the IV Ketamine group. The mean total fentanyl administered was substantially lower in the Normal Saline group, and they required more additional doses of anesthetic. These findings indicate that the Normal Saline group faced a more challenging post-operative recovery, with a heightened need for pain management interventions, suggesting that IV Ketamine may offer advantages in managing post-operative pain and reducing associated side effects.

References

1. Abdollahpour A, Saffarieh E, Zoroufchi BH. A review on the recent application of ketamine in management of anesthesia, pain, and health care. J Family Med Prim Care. 2020 Mar 26;9 (3):1317–24.
2. Savić Vujović K, Jotić A, Medić B, Srebro D, Vujović A, Žujović J, et al. Ketamine, an Old-New Drug: Uses and Abuses. Pharmaceuticals (Basel). 2023 Dec 21;17(1).
3. Zorumski CF, Izumi Y, Mennerick S. Ketamine: NMDA receptors and beyond. J Neurosci. 2016 Nov 2;36(44):11158–64.
4. Riccardi A, Guarino M, Serra S, Spampinato MD, Vanni S, Shiffer D, et al. Narrative Review: Low-Dose Ketamine for Pain Management. J Clin Med. 2023 May 2;12(9).
5. Griffiths HM. Low-dose ketamine infusions for chronic pain management: Does this qualify as evidence-based practice? Br J Pain. 2023 Oct;17(5):457–67.
6. Guimarães Pereira JE, Ferreira Gomes Pereira L, Mercante Linhares R, Darcy Alves Bersot C, Aslanidis T, Ashmawi HA. Efficacy and Safety of Ketamine in the Treatment of Neuropathic Pain: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Pain Res. 2022 Apr 9;15:1011–37.
7. Azari L, Saleh Anaraki K, Hemati H, Tavasolian R, Shahdab S, Tomlinson SM, et al. The efficacy of ketamine for pain management in patients with cancer: A systematic review. JCO. 2024 Jun 1;42(16_suppl):e24069–e2406 9.
8. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013 Jun;19(6):370–80.
9. Dutton M, Can AT, Lagopoulos J, Hermens DF. Oral ketamine may offer a solution to the ketamine conundrum. Psychopharmacology (Berl). 2023 Dec;240(12):2483–97.
10. Alaa Ahmed Whied Mohamed NM. Low dose ketamine in prevention of propofol injection pain. EJHM. 2018 Jul 1;72(3):4189–93.
11. Shewalkar MS, Sangawar MA, Shinde PM, Cham SC, Shende AN. Evaluation of efficacy of low dose IV ketamine for prevention of pain associated with IV propofol injection. IJCA. 2023 Sep 28;10(3):235–41.
12. Wang J, Doan LV, Axelrod D, Rotrosen J, Wang B, Park HG, et al. Optimizing the use of ketamine to reduce chronic postsurgical pain in women undergoing mastectomy for oncologic indication: study protocol for the KALPAS multicenter randomized controlled trial. Trials. 2024 Jan 19;25(1):67.
13. Polomano RC, Buckenmaier CC, Kwon KH, Hanlon AL, Rupprecht C, Goldberg C, et al.

Effects of low-dose IV ketamine on peripheral and central pain from major limb injuries sustained in combat. Pain Med. 2013 Jul;14(7): 10 88–100.
14. Avais B, Javed HM, Sheikh NG, Sheikh MG, Jamshaid B, Butt Z. Comparison of ketamine and tramadol for prevention of shivering during spinal anesthesia. Biol Clin Sci Res J. 2022 Dec 12;2022(1).
15. Sachdeva B, Sachdeva P, Ghosh S, Ahmad F, Sinha JK. Ketamine as a therapeutic agent in major depressive disorder and posttraumatic stress disorder: Potential medicinal and deleterious effects. Ibrain. 2023 Feb 20;9(1):90–101.
16. Krystal JH, Kavalali ET, Monteggia LM. Ketamine and rapid antidepressant action: new treatments and novel synaptic signaling mechanisms. Neuropsychopharmacology. 2024 Jan; 49(1):41–50.
17. Kohtala S. Ketamine-50 years in use: from anesthesia to rapid antidepressant effects and neurobiological mechanisms. Pharmacol Rep. 2021 Apr;73(2):323–45.
18. Schwenk ES, Pradhan B, Nalamasu R, Stolle L, Wainer IW, Cirullo M, et al. Ketamine in the past, present, and future: mechanisms, metabolites, and toxicity. Curr Pain Headache Rep. 2021 Jul 16;25(9):57.