Original Research

Comparative Assessment of Ketamine vs. Standard General Anesthesia for Analgesia in Trauma Patients: A Prospective Randomized Study

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Received: 30 August, 2020 Accepted: 17 September, 2020

Abstract

Aim: The aim of this study was to compare the analgesic effects of ketamine-based analgesia versus standard general anesthesia (GA) in trauma patients undergoing surgical interventions. The goal was to evaluate postoperative pain control, opioid consumption, and the incidence of adverse effects.

Materials and Methods: This was a prospective, randomized study involving 80 adult trauma patients (aged 18-65 years) who required surgical intervention. The patients were randomly assigned to either the Ketamine Group (Group K) or the Standard GA Group (Group GA). Group K received ketamine-based analgesia, and Group GA received standard GA. Pain scores were assessed using the Numeric Rating Scale (NRS) at 6, 12, and 24 hours postoperatively. Secondary outcomes included total opioid consumption, incidence of postoperative nausea and vomiting (PONV), sedation levels, and adverse events.

Results: The results revealed that the Ketamine Group experienced significantly lower postoperative pain scores at all time points (6, 12, and 24 hours) compared to the Standard GA Group (p-values < 0.05). Additionally, the Ketamine Group showed significantly reduced opioid consumption during the first 24 hours (12.5 mg vs. 20.4 mg morphine equivalent, $p = 0.04$). The incidence of PONV was lower in the Ketamine Group (25% vs. 45%, $p = 0.04$). Hallucinations were more common in the Ketamine Group (10% vs. 0%, $p = 0.02$), but no significant differences in delirium or respiratory depression were observed. The length of hospital stay was similar between the two groups.

Conclusion: Ketamine-based analgesia provided superior postoperative pain control and reduced opioid consumption compared to standard general anesthesia in trauma patients. Although the incidence of hallucinations was higher with ketamine, the overall safety profile was favorable, suggesting that ketamine is an effective adjunct for pain management in trauma patients.

Keywords: Ketamine, General Anesthesia, Trauma, Postoperative Pain, Opioid Consumption.

Introduction

Trauma remains one of the leading causes of morbidity and mortality worldwide, with an increasing number of patients requiring emergency care following injury. The management of trauma patients often necessitates the use of general anesthesia (GA) for surgical interventions or invasive procedures. General anesthesia serves multiple purposes in trauma care, including the maintenance of unconsciousness, muscle relaxation, and analgesia. However, the need for effective pain management and the associated risks of standard anesthetic drugs, particularly in trauma patients, has led to exploration of alternative anesthetic agents, such as ketamine. Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has garnered attention for its unique analgesic and anesthetic properties, which differ from those of traditional anesthetics.[1]

In trauma settings, managing pain and preventing its negative physiological consequences is a crucial aspect of patient care. Pain can contribute to increased sympathetic nervous system activity, resulting in adverse effects such as hypertension, tachycardia, and even worsening of injury-related complications. Effective analgesia in trauma patients is thus essential not only for comfort but also for optimizing the

physiological environment, promoting recovery, and improving overall outcomes. Traditionally, opiates and non-opioid analgesics, in combination with standard general anesthesia, are employed for pain control. However, these drugs have potential side effects such as respiratory depression, tolerance, dependence, and the exacerbation of opioid-related complications.[2]

Ketamine offers a potential alternative to traditional anesthetic agents due to its distinctive mechanism of action, which involves the blockade of NMDA receptors. This unique pharmacological action may make ketamine an attractive choice for trauma patients, particularly those with significant pain and potential for opioid-related side effects. Ketamine has been used for both induction and maintenance of anesthesia in various clinical settings, including trauma care, and it has shown promise in providing effective analgesia while minimizing some of the adverse effects associated with other anesthetic agents.[3]

The prospective randomized study design is a rigorous method for evaluating the relative efficacy and safety of different treatments. By randomizing trauma patients to receive either ketamine or standard general anesthesia, researchers can compare the two approaches in a controlled manner, reducing bias and increasing the reliability of the findings. This type of study is critical in determining whether ketamine provides superior analgesia, fewer side effects, or better outcomes in trauma patients compared to traditional anesthetic regimens.[4]

One of the primary concerns in trauma care is the prevention of acute and chronic pain. Trauma patients are at high risk for developing pain-related complications, including post-traumatic stress disorder (PTSD), chronic pain syndromes, and long-term disability. Thus, it is essential to assess not only the immediate analgesic efficacy of anesthetic agents but also their longer-term impact on pain management and patient recovery. Ketamine has been suggested to have advantages in this area, particularly in its ability to reduce opioid consumption and prevent hyperalgesia and allodynia (conditions where normal stimuli become painful). These effects could be particularly beneficial for trauma patients, who are often exposed to high levels of pain in the acute phase following injury.[5]

Another factor influencing the choice of anesthetic in trauma patients is the potential for hemodynamic stability. Trauma patients may present with significant blood loss, hypovolemia, or other physiological disturbances. Traditional anesthetics, such as propofol or volatile anesthetic agents, can cause hypotension and compromise the patient's circulatory status. Ketamine, on the other hand, is known for its sympathomimetic effects, which can help maintain blood pressure and heart rate during anesthesia, potentially offering a safer alternative in hemodynamically unstable patients.[6]

While ketamine has demonstrated benefits in certain trauma settings, there are concerns regarding its side effects, including hallucinations, delirium, and emergence reactions. These phenomena may be of particular concern in trauma patients, who are already at risk for cognitive dysfunction and psychological stress. The prospective randomized study is essential for determining the incidence and severity of these side effects when ketamine is used as part of a general anesthetic regimen, particularly in the trauma population.[7]

In recent years, there has been growing interest in multimodal analgesia, a strategy that combines different classes of analgesic agents to provide superior pain relief while minimizing side effects. The use of ketamine as part of a multimodal approach to pain management has gained popularity, with studies suggesting that it may enhance the efficacy of other analgesics, such as opioids, while reducing the total opioid requirement. This strategy is particularly valuable in trauma care, where opioid use is often necessary but associated with significant risks, including respiratory depression, tolerance, and addiction. A study comparing ketamine with standard general anesthesia in trauma patients can provide valuable insights into whether ketamine-based multimodal analgesia offers superior pain control and fewer complications compared to traditional anesthetic techniques.

Materials and Methods

This prospective, randomized study was conducted to evaluate the comparative analgesic effects of ketamine and standard general anesthesia (GA) in trauma patients. A total of 80 adult patients, aged 18-65 years, admitted with trauma to the emergency department and requiring surgical intervention, were enrolled. The study was approved by the Institutional Review Board (IRB) and conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all patients or their legal guardians prior to participation.

Inclusion criteria:

- Patients aged 18-65 years
- Patients with moderate to severe trauma requiring surgical intervention
- Patients with an American Society of Anesthesiologists (ASA) physical status I-III
- Patients who provided informed consent

Exclusion criteria:

- Pregnancy or lactation
- Severe cardiovascular, respiratory, or hepatic impairment
- Known allergies to ketamine or components of standard anesthesia
- History of psychiatric disorders or substance abuse
- Uncontrolled bleeding or intra-abdominal trauma

Randomization and Grouping
Patients were randomly assigned to one of two groups using a computer-generated randomization table. The two groups were:

1. **Ketamine Group (Group K)**: 40 patients who received ketamine-based analgesia.
2. **Standard General Anesthesia Group (Group GA)**: 40 patients who received standard GA using a combination of inhalational agents and opioids.

Preoperative Assessment
All patients underwent a thorough preoperative assessment, including clinical evaluation, laboratory tests, and imaging as required based on their injury. Preoperative medications, including prophylactic antibiotics, were administered as per standard hospital protocol. Patients were also evaluated for any contraindications to ketamine or standard GA.

Anesthetic Protocol
For the Ketamine Group, ketamine was administered intravenously as a bolus dose of 0.5 mg/kg, followed by a continuous infusion at a rate of 0.5 mg/kg/h throughout the surgery. Analgesia was primarily maintained with ketamine, with additional supplementation from opioids and muscle relaxants as required for muscle relaxation during the procedure.
In the Standard General Anesthesia Group, general anesthesia was induced with an intravenous dose of propofol at 2-2.5 mg/kg. Anesthesia was maintained with a combination of sevoflurane (1-2%) and nitrous oxide (50%) in oxygen. Intraoperative analgesia was supplemented with opioids (fentanyl, 1-2 mcg/kg) and muscle relaxants (rocuronium) as necessary to ensure proper anesthesia depth and muscle relaxation.

Intraoperative Monitoring
During the procedure, all patients were monitored using standard monitoring techniques to ensure safety and optimal anesthetic management. These included electrocardiogram (ECG) to monitor cardiac rhythm, non-invasive blood pressure (NIBP) to assess hemodynamics, pulse oximetry to track oxygen saturation, and end-tidal carbon dioxide ($ETCO_2$) to monitor ventilation status. The patient's temperature was also continuously measured. Additionally, the depth of anesthesia was carefully monitored using a Bispectral Index (BIS) monitor, which helps ensure adequate anesthesia levels and prevent intraoperative awareness.

Postoperative Analgesia
Postoperative pain management was standardized across both groups. Intravenous analgesics such as morphine or fentanyl were administered on-demand based on the patient's pain score. The Numeric Rating Scale (NRS) was used to assess pain levels, with a score of 0 indicating no pain and a score of 10 indicating the worst pain imaginable. In addition to monitoring pain, postoperative nausea and vomiting (PONV), sedation levels, and any adverse events such as hallucinations, delirium, or respiratory depression were carefully documented and managed as necessary.

Outcome Measures
The primary outcome of the study was the level of postoperative pain, measured using the Numeric Rating Scale (NRS) at 6, 12, and 24 hours following surgery. Secondary outcomes included the total opioid consumption during the first 24 hours postoperatively, the incidence of postoperative nausea and vomiting (PONV), and sedation levels as assessed using the Ramsay Sedation Scale. Additional secondary outcomes included the occurrence of any adverse effects such as hallucinations, delirium, or respiratory depression, as well as the length of hospital stay after the surgery. These outcomes were analyzed to compare the effectiveness and safety of ketamine-based analgesia versus standard general anesthesia in trauma patients.

Statistical Analysis
Data were analyzed using SPSS (version 22, IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as frequencies and percentages. Comparisons between the two groups were made using independent t-tests for continuous data and Chi-square tests for categorical data. A p-value of <0.05 was considered statistically significant.

Results

Table 1: Demographic and Baseline Characteristics
The demographic and baseline characteristics of the two groups (Ketamine and Standard GA) were comparable, indicating that the randomization process was successful in balancing these variables. The average age of patients in the Ketamine Group was 34.2 ± 8.7 years, while the Standard GA Group had an average age of 33.9 ± 9.2 years. This difference was not statistically significant, with a p-value of 0.82, indicating that age distribution between the two groups was nearly identical.
Regarding gender distribution, the Ketamine Group consisted of 24 males and 16 females, while the Standard GA Group had 25 males and 15 females. The difference in gender between the two groups was also not significant, with a p-value of 0.85.
In terms of ASA physical status, which assesses the overall fitness of patients for surgery, both groups were similar. The majority of patients in both groups had ASA status I, representing patients with no systemic disease (28 in the Ketamine Group vs. 27 in the Standard GA Group). A smaller proportion of patients had ASA status II, representing patients with mild systemic disease (12 in the Ketamine Group vs.

13 in the Standard GA Group). The difference in ASA status was not significant (p-value = 0.84).

The Mean Injury Severity Score (ISS), which quantifies the severity of trauma, was also comparable between the two groups. The Ketamine Group had a mean ISS of 18.5 ± 4.3, while the Standard GA Group had a mean ISS of 17.9 ± 4.6. This slight difference was not statistically significant (p-value = 0.65).

Finally, the types of surgery performed were evenly distributed between the two groups, with no significant difference in the type of surgery performed. Both groups had 15 patients undergoing musculoskeletal surgery, 15 patients undergoing abdominal surgery in the Ketamine Group vs. 14 in the Standard GA Group, and 10 thoracic surgeries in the Ketamine Group vs. 11 in the Standard GA Group. This was confirmed by a p-value of 0.92.

Table 2: Postoperative Pain Scores at 6, 12, and 24 Hours

Postoperative pain scores, measured using the Numeric Rating Scale (NRS), showed significant differences between the two groups at all timepoints. At 6 hours after surgery, the Ketamine Group reported a mean pain score of 3.4 ± 1.2, while the Standard GA Group had a higher pain score of 4.6 ± 1.3. The difference was statistically significant, with a p-value of 0.002, indicating better pain control in the Ketamine Group.

At 12 hours postoperatively, the Ketamine Group's mean pain score was 2.1 ± 1.0, while the Standard GA Group's mean pain score was 3.3 ± 1.1. This difference was again statistically significant, with a p-value of 0.001, suggesting superior pain relief in the Ketamine Group at this timepoint.

The difference between the two groups remained significant at 24 hours, where the Ketamine Group reported a mean pain score of 1.6 ± 0.8, compared to 2.9 ± 1.2 in the Standard GA Group. The p-value of 0.001 confirms that the Ketamine Group had significantly lower pain scores at all postoperative timepoints, suggesting that ketamine provided better postoperative analgesia than standard general anesthesia.

Table 3: Total Opioid Consumption (Morphine Equivalent) in the First 24 Hours

Total opioid consumption during the first 24 hours postoperatively was significantly lower in the Ketamine Group compared to the Standard GA Group. The Ketamine Group required an average of 12.5 ± 4.3 mg of morphine equivalent, while the Standard GA Group required 20.4 ± 6.1 mg. The difference in opioid consumption was statistically significant with a p-value of 0.04, indicating that the Ketamine Group needed less opioid analgesia, likely due to the effectiveness of ketamine in providing adequate pain relief. This suggests that ketamine may help reduce the reliance on opioids for pain management in trauma patients.

Table 4: Incidence of Postoperative Adverse Events

In terms of adverse events, the Ketamine Group exhibited a significantly lower incidence of postoperative nausea and vomiting (PONV) compared to the Standard GA Group. Specifically, 25% of patients in the Ketamine Group experienced PONV, compared to 45% in the Standard GA Group, with a p-value of 0.04, indicating a statistically significant difference.

The incidence of hallucinations was higher in the Ketamine Group, with 10% of patients reporting hallucinations, compared to none in the Standard GA Group (p-value = 0.02). Although hallucinations are a known side effect of ketamine, this difference should be interpreted with caution, as the incidence was still relatively low.

No significant differences were found in the incidence of delirium or respiratory depression. The Ketamine Group had 5% of patients experiencing delirium and 2.5% experiencing respiratory depression, while the Standard GA Group had 7.5% and 5%, respectively. These differences were not statistically significant (p-value = 0.61 for delirium and p-value = 0.64 for respiratory depression).

Table 5: Length of Hospital Stay (Days)

The length of hospital stay was similar between the two groups, with the Ketamine Group having an average stay of 5.2 ± 1.3 days and the Standard GA Group having an average stay of 5.6 ± 1.2 days. The difference in length of stay was not statistically significant, with a p-value of 0.12. This suggests that while ketamine may offer advantages in terms of analgesia and opioid sparing, it does not appear to have a significant impact on the length of hospital stay.

Table 1: Demographic and Baseline Characteristics

Characteristic	Ketamine Group (n=40)	Standard GA Group (n=40)	p-value
Age (years)	34.2 ± 8.7	33.9 ± 9.2	0.82
Gender			
Male	24	25	
Female	16	15	0.85
ASA Physical Status			
I	28	27	0.84
II	12	13	

Mean Injury Severity Score (ISS)	18.5 ± 4.3	17.9 ± 4.6	0.65
Type of Surgery			
Abdominal,	15	14	
Thoracic	10	11	
Musculoskeletal	15	15	0.92

Table 2: Postoperative Pain Scores at 6, 12, and 24 Hours

Timepoint	Ketamine Group (n=40)	Standard GA Group (n=40)	p-value
6 hours	3.4 ± 1.2	4.6 ± 1.3	0.002
12 hours	2.1 ± 1.0	3.3 ± 1.1	0.001
24 hours	1.6 ± 0.8	2.9 ± 1.2	0.001

Table 3: Total Opioid Consumption (Morphine Equivalent) in the First 24 Hours

Group	Opioid Consumption (mg)	p-value
Ketamine Group (n=40)	12.5 ± 4.3	0.04
Standard GA Group (n=40)	20.4 ± 6.1	

Table 4: Incidence of Postoperative Adverse Events

Adverse Event	Ketamine Group (n=40)	Standard GA Group (n=40)	p-value
Postoperative Nausea and Vomiting (PONV)	10 (25%)	18 (45%)	0.04
Hallucinations	4 (10%)	0 (0%)	0.02
Delirium	2 (5%)	3 (7.5%)	0.61
Respiratory Depression	1 (2.5%)	2 (5%)	0.64

Table 5: Length of Hospital Stay (Days)

Group	Length of Stay (Days)	p-value
Ketamine Group (n=40)	5.2 ± 1.3	0.12
Standard GA Group (n=40)	5.6 ± 1.2	

Discussion

The results of this study show that ketamine-based analgesia provides superior postoperative pain control compared to standard general anesthesia (GA) in trauma patients.

Our findings align with previous studies that have demonstrated the effectiveness of ketamine in controlling postoperative pain in trauma patients. In this study, the Ketamine Group had significantly lower pain scores at 6, 12, and 24 hours postoperatively compared to the Standard GA Group. At 6 hours, the Ketamine Group reported a pain score of 3.4 ± 1.2, while the Standard GA Group had a score of 4.6 ± 1.3, with a p-value of 0.002. This result is consistent with the study by Larsen et al. (2017), which found that ketamine was more effective than standard GA in providing postoperative analgesia, with lower pain scores at similar timepoints.[9]Moreover, Yoon et al. (2018) also noted that ketamine significantly reduced pain scores in trauma patients post-surgery, supporting the effectiveness of ketamine in acute pain management. At 12 and 24 hours postoperatively, the Ketamine Group continued to report significantly lower pain scores, confirming that ketamine provides superior long-lasting analgesia.[10]

Another major benefit of ketamine is its ability to reduce opioid consumption. In this study, the Ketamine Group required significantly less opioid analgesia in the first 24 hours post-surgery (12.5 ± 4.3 mg morphine equivalent) compared to the Standard GA Group (20.4 ± 6.1 mg) with a p-value of 0.04. This result supports findings from Haack and Howland (2018), who conducted a systematic review and concluded that ketamine, when used as part of multimodal analgesia, significantly reduces opioid use in trauma patients.[8] The opioid-sparing effect of ketamine is particularly important given the ongoing concerns over opioid use and abuse in trauma care.

In terms of adverse events, the Ketamine Group demonstrated a lower incidence of postoperative nausea and vomiting (PONV), a common complication associated with opioid use, compared to the Standard GA Group (25% vs. 45%, p-value = 0.04). This result is consistent with Chambers and Owens (2019), who found that ketamine, through its opioid-sparing effects, can reduce the incidence of PONV in trauma patients.[7] However, it is worth noting that the incidence of hallucinations was higher in the Ketamine Group (10% vs. 0%, p-value = 0.02), which aligns with known side effects of ketamine, as reported by Penner and Johnson (2019), who reviewed the safety profile of ketamine in trauma patients.[11] Despite this, the overall incidence of hallucinations was low and may be managed with proper monitoring and dose adjustments.

The incidence of delirium and respiratory depression did not differ significantly between the two groups,

suggesting that ketamine does not lead to higher rates of these serious adverse effects, which aligns with the findings of Goldstein and Brown (2017), who demonstrated that ketamine was safe for trauma patients in terms of respiratory depression and delirium.[12]

In terms of the length of hospital stay, no significant difference was observed between the Ketamine and Standard GA groups. The Ketamine Group had an average length of stay of 5.2 ± 1.3 days, compared to 5.6 ± 1.2 days in the Standard GA Group (p-value = 0.12). This result is consistent with De la Torre and Briones (2018), who found that while ketamine provided superior analgesia, it did not significantly impact the length of hospital stay in trauma patients .[13] Although ketamine improved pain management, the overall recovery time and hospital discharge did not differ significantly, which suggests that other factors, such as the severity of trauma and complications, may influence the duration of stay more than the type of analgesia used.

The findings of this study are consistent with a body of literature supporting the use of ketamine for trauma analgesia. Larsen et al. (2017) in their randomized controlled trial compared ketamine and standard GA in trauma patients and found that ketamine significantly improved postoperative analgesia without increasing adverse effects.[9] Similarly, Wilson and Smith (2019) reviewed the role of ketamine in pain management and confirmed that ketamine offers significant advantages in terms of pain relief and opioid reduction in trauma settings.[14] These studies, along with ours, suggest that ketamine is a valuable component of multimodal analgesia in trauma care.

Moreover, the Haack and Howland (2018) systematic review of ketamine for induction and maintenance of anesthesia in trauma patients also concluded that ketamine is a safe and effective option, providing significant analgesia with a reduced need for opioids.[8] This supports our findings of reduced opioid consumption in the Ketamine Group and highlights ketamine's potential to mitigate the risks associated with opioid use in trauma patients.

Conclusion

In conclusion, this study demonstrates that ketamine-based analgesia provides superior postoperative pain control compared to standard general anesthesia in trauma patients, with significantly lower pain scores at 6, 12, and 24 hours. Additionally, ketamine reduced opioid consumption in the first 24 hours post-surgery, potentially minimizing the risk of opioid-related complications. While the incidence of hallucinations was higher in the Ketamine Group, the overall safety profile was favorable, with fewer cases of postoperative nausea and vomiting. These findings suggest that ketamine is a promising adjunct for pain management in trauma patients, offering effective analgesia with reduced opioid requirements.

References

1. White BP, L.L. L. Ketamine as an Anesthetic and Analgesic Agent in Trauma Patients. J Trauma Acute Care Surg. 2015;78(4):234-238.
2. Candiotti MA, Gan AD. Analgesic Effectiveness of Ketamine in Trauma Patients: A Prospective Study. J Clin Anesth. 2013;25(1):48-53.
3. Lee DM, Buchanan TW. Comparative Analysis of Ketamine and Propofol for General Anesthesia in Trauma. Trauma Surg Acute Care Open. 2016;1(1):e000003.
4. Doyle SM, Jones AR. Safety of Ketamine in Trauma Patients: A Review of Current Literature. Emerg Med J. 2017;34(12):817-822.
5. Schmidt TM, Hunt PD. Ketamine and General Anesthesia in Trauma: A Meta-Analysis of Efficacy and Safety. J Trauma Inj. 2018;84(3):463-469.
6. McCormick LF, Charles SJ. A Randomized Trial Comparing Ketamine and Standard Anesthesia for Major Trauma Surgery. Ann Surg. 2019;269(6):1163-1171.
7. Chambers MA, Owens DK. Multimodal Analgesia and Ketamine in Trauma: Efficacy and Safety. J Pain Res. 2019;12:1077-1087.
8. Haack ET, Howland SR. Ketamine for Induction and Maintenance of Anesthesia in Trauma: A Systematic Review. Br J Anaesth. 2018;121(5):979-987.
9. Larsen SD, Larsen AL. Ketamine versus Standard General Anesthesia in Trauma Patients: A Randomized Controlled Trial. J Trauma Acute Care Surg. 2017;82(5):924-929.
10. Yoon MS, Beauchamp DJ. Effects of Ketamine on Post-Trauma Pain and Recovery: A Randomized Controlled Study. Pain Med. 2018;19(7):1414-1421.
11. Penner SL, Johnson MP. Ketamine for Trauma-Induced Analgesia: A Review of Current Literature. Can J Anesth. 2019;66(4):383-391.
12. Goldstein SM, Brown RA. Evaluation of Ketamine as a Sole Anesthetic Agent in Trauma Care: A Pilot Study. Anesthesiology. 2017;126(4):730-735.
13. De la Torre E, Briones J. Ketamine in Trauma Surgery: The Balance Between Analgesia and Sedation. Anaesthesia. 2018;73(3):288-293.
14. Wilson GR, Smith T. Ketamine for Pain Management in Trauma: A Review of Its Role and Mechanisms. J Pain Res. 2019;12:1485-1494.