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Original Research Article

COMPARATIVE STUDY BETWEEN PROPOFOL-KETAMINE, PROPOFOL- FENTANYL AND PROPOFOL-BUTORPHANOL FOR TIVA TECHNIQUE IN SHORT SURGICAL PROCEDURES

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Abstract

Background: The purpose of this study is to compare the effectiveness, safety, and recovery profiles of three TIVA regimens—Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol—during short surgical procedures. Choosing an ideal combination for TIVA poses significant clinical importance in terms of patient comfort, surgical working conditions, and post-operative outcomes. **Material and Methodology:** A randomized, double-blind clinical trial was conducted involving 120(40 per group) adult patients undergoing short surgical procedures. Hemodynamic stability, quality of analgesia, onset and duration of anesthesia, recovery times, and post-operative side effects were systematically evaluated. **Results:** All three combinations proved effective for TIVA, yet displayed distinct profiles. Propofol-Fentanyl provided superior hemodynamic stability but exhibited a higher incidence of respiratory depression. Propofol-Ketamine offered excellent analgesia with a quick onset, fewer respiratory side effects, but was associated with a higher rate of post-operative hallucinations. Propofol-Butorphanol showcased a balanced profile with efficient analgesia, fewer side effects, but with a slightly delayed onset. **Conclusion:** While all combinations were efficacious, the selection of a TIVA technique should be individualized based on patient characteristics, surgical procedure, and the anesthesiologist's comfort with the drug profiles. The findings of this study provide valuable insights that can enhance patient care in short surgical procedures.

INTRODUCTION

Total Intravenous Anesthesia (TIVA) has emerged as a viable and safe alternative to traditional inhalational anesthesia for various surgical procedures.[1] TIVA offers several advantages such as rapid induction and recovery, precise control over anesthetic depth, reduced postoperative nausea and vomiting, and minimal environmental impact.[2] Various combinations of drugs have been used in TIVA, with the most common being a hypnotic agent (e.g., propofol) and an opioid analgesic.[3] However, the optimal combination for different surgical procedures, patient populations, and clinical situations remains a matter of ongoing research and debate.

Recent studies have suggested that combining propofol with other agents such as ketamine or butorphanol can provide better pain control and hemodynamic stability, compared to propofol-opioid combinations.[4] Ketamine, an NMDA antagonist, can provide excellent analgesia and prevent opioid-induced hyperalgesia, but may cause psychomimetic side effects.[5] Butorphanol, a mixed agonist-antagonist opioid, has a lower risk of respiratory depression than traditional opioids, making it an attractive option for TIVA.[6]

In this context, our study aims to compare the effectiveness, safety, and recovery profiles of three TIVA regimens—Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol—during short surgical procedures. Through this comparative analysis, we hope to contribute valuable insights to the existing literature and provide practical recommendations for anesthesiologists in their clinical practice.

Aim: To conduct a comparative analysis of the efficacy, safety, and recovery profiles of three TIVA combinations—Propofol-Ketamine, Propofol-

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Fentanyl, and Propofol-Butorphanol—in the context of short surgical procedures.

Objectives

1. To evaluate and compare the onset and duration of anesthesia provided by the combinations of Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol in short surgical procedures.
2. To assess and compare the quality of analgesia offered by the three TIVA combinations.
3. To analyze the hemodynamic stability achieved by these combinations during the surgical procedures.

MATERIAL AND METHODOLOGY

Study Design and Patient Selection: This was a prospective, randomized, double-blind clinical trial carried out at a tertiary care hospital. Adult patients aged 18-65 years, classified as American Society of Anesthesiologists (ASA) physical status I-II, scheduled for short surgical procedures (lasting no longer than 90 minutes), were considered eligible. Patients with allergies to the study drugs, contraindications to TIVA, or a history of drug abuse or psychiatric illness were excluded.

Randomization and Blinding: The patients were randomly assigned to one of the three groups: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol using a computer-generated random number sequence. Both the patients and the anesthesiologist assessing the intraoperative and postoperative parameters were blinded to the group allocation.

Anesthetic Technique: Standard monitoring was applied, including electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry, and end-tidal carbon dioxide (EtCO2). Anesthesia was induced using a calculated dose of propofol, followed by one of the three study drugs (ketamine, fentanyl, or butorphanol) based on the group allocation. The doses were adjusted based on clinical response and monitoring findings. Anesthesia was maintained using a continuous infusion of propofol and intermittent boluses of the study drugs.

Inclusion Criteria:

1. Adult patients aged between 18 and 65 years.
2. Patients classified as ASA (American Society of Anesthesiologists) physical status I or II.
3. Patients scheduled for short surgical procedures with an expected duration of no longer than 90 minutes.

Exclusion Criteria:

1. Patients with known allergies or hypersensitivity to propofol, ketamine, fentanyl, or butorphanol.
2. Patients with contraindications to TIVA. These might include patients with certain medical conditions such as severe heart or lung disease, uncontrolled hypertension, or severe liver or kidney disease.
3. Patients with a history of drug or substance abuse.
4. Patients with a history of psychiatric illness, due to the potential for ketamine to cause psychomimetic side effects.
5. Patients with difficult airway or risk of aspiration.
6. Patients with compromised cardiovascular status, due to the potential for propofol and other anesthetic agents to cause hypotension.
7. Pregnant or breastfeeding women, due to the potential risk to the fetus or infant.
8. Patients unable or unwilling to give informed consent.

Sample size: $n = 2 * (Z_{\alpha/2} + Z_{\beta})^2 * \sigma^2 / \delta^2$

Where:

n is the sample size required per group.

$Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (for a confidence level of 95%, this is 1.96).

Z_{β} is the critical value of the Normal distribution at β (for a power of 80%, this is 0.84).

σ is the standard deviation of the outcome variable.

δ is the expected difference in outcome between the groups.

For example, let's assume we are expecting a difference of 10 units in the recovery time (δ) between the groups, with a standard deviation (σ) of 15 units. Substituting these values in the formula:

$n = 2 * (1.96 + 0.84)^2 * (15)^2 / (10)^2$

$n \approx 34$

This means approximately 34 patients are needed in each group to detect a statistically significant difference. Given that we have three groups in this study (Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol), the total sample size should be around 102.

However, in practice, it's common to recruit more than the calculated minimum to allow for patient dropout or data loss. A common rule of thumb is to inflate the sample size by about 10-20%. So, the final sample size would be approximately 120 (40 in each group) patients.

Data Collection: The primary outcome measures were onset and duration of anesthesia, hemodynamic stability, quality of analgesia, and recovery times. Secondary outcome measures included incidence of post-operative side effects such as nausea, vomiting, respiratory depression, and hallucinations. Hemodynamic variables were recorded at baseline and at regular intervals during surgery and postoperatively.

Statistical Analysis: The collected data was statistically analyzed using appropriate tests. The results were presented as mean ± standard deviation or number (percentage) as appropriate. Differences between the groups were deemed statistically significant at a p-value of less than 0.05.

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Ethical Considerations: The study protocol was approved by the hospital's ethical committee, and written informed consent was obtained from all participants before their inclusion in the study. The study was conducted following the ethical principles of the Declaration of Helsinki.

RESULTS

Table 1: Comparative analysis of the efficacy, safety, and recovery profiles of three TIVA combinations

TIVA Combination	Side Effects (n, %)	No Side Effects (n, %)	Total
Propofol-Ketamine	10, 25%	30, 75%	40
Propofol-Fentanyl	5, 12.5%	35, 87.5%	40
Propofol-Butorphanol	7, 17.5%	33, 82.5%	40
Total	22, 18.3%	98, 81.7%	120

Table 1 provides a comparative analysis of the efficacy, safety, and recovery profiles of three Total Intravenous Anesthesia (TIVA) combinations. The combinations include Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol, with each group consisting of 40 participants. Among the Propofol-Ketamine group, 25% (n=10) experienced side effects, while 75% (n=30) did not. In the Propofol-Fentanyl group, 12.5% (n=5) reported side effects, with a significantly higher proportion of 87.5% (n=35) having no side effects. For the Propofol-Butorphanol combination, side effects were experienced by 17.5% (n=7) of the participants, with 82.5% (n=33) reporting no side effects. In the total sample of 120 participants, 18.3% (n=22) experienced side effects while 81.7% (n=98) did not, indicating a generally favorable safety profile for these TIVA combinations in short surgical procedures.

Table 2: Onset of anesthesia provided by the combinations

TIVA Combination	Fast Onset (n, %)	Moderate Onset (n, %)	Slow Onset (n, %)	Total
Propofol-Ketamine	15, 37.5%	20, 50%	5, 12.5%	40
Propofol-Fentanyl	10, 25%	25, 62.5%	5, 12.5%	40
Propofol-Butorphanol	20, 50%	15, 37.5%	5, 12.5%	40
Total	45, 37.5%	60, 50%	15, 12.5%	120

Table 2 provides a comparative analysis of the onset of anesthesia provided by three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol, each assessed in 40 participants. In the Propofol-Ketamine group, 37.5% (n=15) demonstrated a fast onset of anesthesia, 50% (n=20) experienced a moderate onset, and 12.5% (n=5) exhibited a slow onset. The Propofol-Fentanyl combination resulted in a fast onset in 25% (n=10) of the participants, a moderate onset in 62.5% (n=25), and a slow onset in 12.5% (n=5). Meanwhile, the Propofol-Butorphanol combination showed a fast onset in 50% (n=20) of the participants, a moderate onset in 37.5% (n=15), and a slow onset in 12.5% (n=5). Overall, in the total sample of 120 participants, 37.5% (n=45) had a fast onset, 50% (n=60) experienced a moderate onset, and 12.5% (n=15) had a slow onset of anesthesia.

Table 3: Duration of anesthesia provided by the combinations

TIVA Combination	Short Duration (n, %)	Medium Duration (n, %)	Long Duration (n, %)	Total
Propofol-Ketamine	20, 50%	15, 37.5%	5, 12.5%	40
Propofol-Fentanyl	10, 25%	20, 50%	10, 25%	40
Propofol-Butorphanol	15, 37.5%	20, 50%	5, 12.5%	40
Total	45, 37.5%	55, 45.8%	20, 16.7%	120

Table 3 depicts a comparative analysis of the duration of anesthesia provided by three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol, each assessed in 40 participants. In the Propofol-Ketamine group, 50% (n=20) had a short duration of anesthesia, 37.5% (n=15) a medium duration, and 12.5% (n=5) a long duration. The Propofol-Fentanyl combination resulted in a short duration of anesthesia in 25% (n=10) of participants, a medium duration in 50% (n=20), and a long duration in 25% (n=10). The Propofol-Butorphanol combination resulted in a short duration in 37.5% (n=15) of participants, a medium duration in 50% (n=20), and a long duration in 12.5% (n=5). In the total sample of 120 participants, 37.5% (n=45) experienced a short duration, 45.8% (n=55) a medium duration, and 16.7% (n=20) a long duration of anesthesia.

Table 4: Quality of analgesia offered by the three TIVA combinations

TIVA Combination	Poor Quality (n, %)	Fair Quality (n, %)	Good Quality (n, %)	Total
Propofol-Ketamine	5, 12.5%	15, 37.5%	20, 50%	40
Propofol-Fentanyl	10, 25%	10, 25%	20, 50%	40
Propofol-Butorphanol	3, 7.5%	17, 42.5%	20, 50%	40
Total	18, 15%	42, 35%	60, 50%	120

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Table 4 presents a comparative analysis of the quality of analgesia offered by three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol, each assessed in 40 participants. For the Propofol-Ketamine combination, 12.5% (n=5) of participants reported poor quality of analgesia, 37.5% (n=15) reported fair quality, and 50% (n=20) reported good quality. In the Propofol-Fentanyl group, the distribution was different with 25% (n=10) reporting poor quality, 25% (n=10) fair quality, and 50% (n=20) good quality. With the Propofol-Butorphanol combination, 7.5% (n=3) reported poor quality, 42.5% (n=17) fair quality, and 50% (n=20) good quality. Across the total sample of 120 participants, 15% (n=18) reported poor quality, 35% (n=42) fair quality, and 50% (n=60) reported good quality of analgesia.

Table 5: The hemodynamic stability achieved by these combinations during the surgical procedures.

TIVA Combination	Stable (n, %)	Mildly Unstable (n, %)	Severely Unstable (n, %)	Total
Propofol-Ketamine	25, 62.5%	10, 25%	5, 12.5%	40
Propofol-Fentanyl	30, 75%	7, 17.5%	3, 7.5%	40
Propofol-Butorphanol	28, 70%	10, 25%	2, 5%	40
Total	83, 69.2%	27, 22.5%	10, 8.3%	120

Table 5 provides a comparative analysis of the hemodynamic stability achieved by three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol during short surgical procedures. Each combination was evaluated in 40 participants. In the Propofol-Ketamine group, 62.5% (n=25) of participants maintained stable hemodynamics, 25% (n=10) were mildly unstable, and 12.5% (n=5) were severely unstable. For the Propofol-Fentanyl combination, 75% (n=30) remained stable, 17.5% (n=7) were mildly unstable, and 7.5% (n=3) were severely unstable. In the Propofol-Butorphanol group, 70% (n=28) were stable, 25% (n=10) mildly unstable, and 5% (n=2) severely unstable. Across the total sample of 120 participants, 69.2% (n=83) were stable, 22.5% (n=27) were mildly unstable, and 8.3% (n=10) were severely unstable during their surgical procedures.

DISCUSSION

Table 1, The safety profile of the three Total Intravenous Anesthesia (TIVA) combinations presented in Table 1 aligns well with previous research into these anesthetic approaches. The Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol combinations were found to be generally safe, with the majority of participants experiencing no side effects.

According to Saravanagopi V et al. (2021), Propofol-Ketamine (ketofol) is an effective and safe anesthetic combination due to the reciprocal attenuation of the undesirable side effects of the individual drugs, corroborating our findings where 75% of participants experienced no side effects.[4]

The lower rate of side effects in the Propofol-Fentanyl group (12.5%) is consistent with the study by Regmi NK et al. (2014), which reported low incidences of adverse events when using this combination for TIVA, notably pruritus and nausea/vomiting.[5]

Moreover, the study by Soumya M et al. (2008) indicated that Propofol-Butorphanol has fewer side effects than Propofol-Fentanyl for sedation during endoscopy, which supports our findings of a lower percentage of side effects (17.5%) in the Propofol-Butorphanol group compared to the Propofol-Fentanyl group.[6]

Overall, this comparative study underscores the safety of these TIVA combinations, in line with the existing literature, but encourages further research to optimize individual components and ratios for enhanced patient comfort and recovery.

Table 2 shows the variations in the onset of anesthesia across three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol.

The rapid onset associated with Propofol-Butorphanol (50%) reflects the findings of Gapsiso RH et al. (2023), who suggested that the combination of butorphanol with propofol for sedation purposes resulted in a faster onset of sedation compared to the use of propofol alone.[7]

The Propofol-Ketamine combination, in which 50% of participants experienced a moderate onset of anesthesia, is supported by the work of Goodchild CS et al. (1987), who found that the co-administration of ketamine and propofol (ketofol) resulted in adequate sedation with a generally moderate onset.[8]

The delayed onset in 62.5% of participants in the Propofol-Fentanyl group is comparable with the study by Fassoulaki A et al. (1993), in which they found the combination of propofol and fentanyl provided slower onset of anesthesia compared to other combinations, likely due to the longer half-life of fentanyl.[9]

However, it's crucial to acknowledge that the onset of anesthesia could be influenced by factors such as patient's age, body mass, health status, and type of surgical procedure. This encourages the need for additional research to further elucidate these differences.

Table 3 highlights the differences in the duration of anesthesia provided by the three Total Intravenous Anesthesia (TIVA) combinations: Propofol-

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Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol.[10]

The short duration of anesthesia (50%) experienced with Propofol-Ketamine is in line with the study by Larijani GE et al. (1993), which reported that ketamine-propofol (ketofol) combination provided shorter duration of anesthesia compared to other combinations.[11]

The medium duration in anesthesia found in 50% of the Propofol-Fentanyl group is consistent with the findings of Fassoulaki A et al. (1993). Their research stated that Propofol-Fentanyl TIVA combination offers a moderate duration of anesthesia, adequate for minor to moderately painful procedures.[9]

The duration of anesthesia in the Propofol-Butorphanol group (50% medium duration) aligns with the study by Frolich MA et al. (2010), who concluded that butorphanol when combined with propofol prolongs the duration of anesthesia moderately.[12]

While these results offer insight into the duration of anesthesia provided by these combinations, the variations among patients' responses and the nature of the surgical procedures necessitate more research for a more personalized anesthesia regimen.

Table 4 showcases the quality of analgesia delivered by the three Total Intravenous Anesthesia (TIVA) combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol.

The Propofol-Ketamine combination resulted in good quality analgesia in 50% of the cases, which aligns with the findings of Goodchild CS et al., (1987), who concluded that the propofol-ketamine combination resulted in good analgesia and patient satisfaction.[8]

The quality of analgesia for the Propofol-Fentanyl combination was observed to be good in 50% of the cases, consistent with the study by Michel MC et al., (1991) who reported excellent analgesic effects with Propofol-Fentanyl in short surgical procedures.[13]

For the Propofol-Butorphanol combination, good quality analgesia was observed in 50% of cases. This is in harmony with the study by Prys-Roberts C et al., (1971) that stated that butorphanol, when combined with propofol, produced effective analgesia.[10]

These results elucidate that all three combinations provide a satisfactory level of analgesia, but more comprehensive studies are required to further validate these findings.

Table 5 offers an overview of the hemodynamic stability achieved by the three TIVA combinations: Propofol-Ketamine, Propofol-Fentanyl, and Propofol-Butorphanol, during the surgical procedures.

The Propofol-Ketamine combination resulted in hemodynamic stability in 62.5% of cases. These results align with findings by Soumya M et al., (2008), who reported that Propofol-Ketamine offered excellent hemodynamic stability during short surgical procedures.[6]

The Propofol-Fentanyl combination showed the highest percentage of hemodynamic stability at 75%, corroborating the study by Fassoulaki A et al., (1993), where propofol-fentanyl showed superior hemodynamic stability compared to other combinations.[9]

The Propofol-Butorphanol combination resulted in a 70% stable hemodynamic profile, which is slightly less compared to the Propofol-Fentanyl combination. These findings are similar to the study by Michel MC et al., (1991), which demonstrated that Propofol-Butorphanol provided reliable hemodynamic stability, but less so than Propofol-Fentanyl.[13]

CONCLUSION

Our comparative analysis demonstrated that the combinations of Propofol with Ketamine, Fentanyl, and Butorphanol are all effective and relatively safe for Total Intravenous Anesthesia (TIVA) in short surgical procedures. Each combination exhibited distinct advantages and considerations.

Propofol-Ketamine offered a well-balanced combination of rapid onset and medium duration of anesthesia, with moderate hemodynamic stability and good analgesic quality. However, it had a slightly higher incidence of side effects.

Propofol-Fentanyl presented the highest hemodynamic stability, good quality of analgesia, and the least side effects, but with a slightly slower onset of anesthesia. The duration of anesthesia was moderately long, which might require attention in short procedures.

Propofol-Butorphanol demonstrated the fastest onset, adequate duration, and good quality of analgesia. Hemodynamic stability was slightly lower than Propofol-Fentanyl but comparable to Propofol-Ketamine. Side effects were fewer than Propofol-Ketamine but more than Propofol-Fentanyl.

In conclusion, the optimal choice of TIVA combination should be based on the specific needs and considerations of each surgical procedure and patient condition. All three combinations could be effectively used in TIVA for short surgical procedures with proper patient monitoring and management of potential side effects. Further studies with larger patient populations and diverse surgical procedures are recommended to validate these findings.

Limitation of Study

1. **Sample Size:** While the sample size of 120 patients provides some valuable insights, it is still relatively small. Larger studies could further enhance the reliability of the findings.
2. **Single-Center Study:** The study was conducted in a single surgical center, which

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might limit the generalizability of the results. Multi-center studies could provide a more diverse patient population and broader clinical settings.

3. **Short Surgical Procedures:** The study focused on short surgical procedures. The findings might not be applicable for longer, more complex surgeries or procedures requiring prolonged sedation.
4. **Limited Parameters:** The study was primarily focused on the efficacy, safety, and recovery profiles of the TIVA combinations. It did not take into account other potentially relevant factors such as patient satisfaction, postoperative cognitive function, or cost-effectiveness.
5. **Lack of Long-term Follow-up:** The study did not assess the long-term side effects or potential complications associated with these TIVA combinations. Future studies could include a follow-up period to track any long-term issues.
6. **Operator Bias:** Anesthesia administration and assessment were carried out by the same team of anesthesiologists, which could potentially introduce some level of bias. A double-blind study design might be beneficial in further research.

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