**Propofol-Ketamine versus Propofol-Fentanyl in Outpatient Surgical Procedures: A Systematic Review**

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**Introduction:** Outpatient ambulatory surgery is the fastest growing segment of surgery and anesthesia. Propofol is a common anesthetic agent used for outpatient ambulatory surgery. Lack of analgesic property of propofol requires the use of a supplementary analgesic agent. Two of the common agents used in combination with propofol are ketamine and fentanyl.

**Materials and Methods:** A systematic search of preferably randomized controlled trials was done from January 2000 until August 2010 on ambulatory surgery using propofol-ketamine and propofol-fentanyl. Outcome measures include: post-operative analgesia, time to recovery from Post-Anesthesia Care Unit (PACU) and incidence of nausea and vomiting/emesis. Electronic databases were searched and appraised with the standardized critical appraisal tool from the JBI-MASTARI (Joanna Briggs Institute-Meta Analysis of Statistics Assessment and Review Instrument and data extracted and analyzed.

**Results:** A total of two (2) studies were found to have met the inclusion criteria. One study showed that more patients required pain medications in the group given propofol-ketamine (P value = 0.776). Data pooled from two studies reported no statistical difference in incidence of nausea (OR=2.48, 95% CI 0.81, 7.58), and no statistical difference in the incidence of vomiting/emesis between the two drug combinations (OR=2.76, 95% CI 0.62, 12.18). Furthermore, the two studies revealed a significantly faster time to recovery in patients given propofol-fentanyl (Control). The average mean difference in time to recovery between the groups is 30.77 minutes with 95% CI 22.41, 39.13.

**Conclusion:** This review concludes that propofol-ketamine caused nausea and vomiting in patients undergoing outpatient ambulatory surgery. Time to discharge was observed to be shorter in the group given propofol-fentanyl.

**Key words:** outpatient ambulatory surgery, propofol, fentanyl

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**INTRODUCTION**

Outpatient ambulatory surgery is the fastest growing segment of surgery and anesthesia. The continued growth in ambulatory surgery is related to expansion in minimally invasive surgical techniques and office-based procedures.

Procedures appropriate for ambulatory surgery are those associated with postoperative care that is easily managed at home and with low rates of postoperative complications that require intensive physician or nursing management. Patients who undergo ambulatory surgery should have someone to take them home and stay with them afterwards to provide care. Before the procedure, the patient should get information about the procedure itself, where it will be performed, laboratory studies that will be ordered, and dietary restrictions. The patient must understand that he or she will be going home on the day of surgery. The patient, or some responsible person, must ensure all instructions are followed. Once at home, the patient must be able to tolerate the pain from the procedure, assuming adequate pain therapy is provided.

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Propofol is a substituted isopropyl phenol (2,6-diisopropylphenol), short-acting, intravenously administered hypnotic agent. It is a relatively selective modulator of \( \gamma \)-aminobutyric acid (GABA\( _A \)) receptors and does not appear to modulate other ligand gated ion channels at clinically relevant concentrations. Its uses include the induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. It reduces anxiety and tension, and promotes relaxation and sleep or loss of consciousness. Propofol provides loss of awareness for short diagnostic tests and surgical procedures, sleep at the beginning of surgery, and supplements other types of general anesthetics. The prompt recovery, without residual sedation and a low incidence of nausea and vomiting, make propofol particularly well suited to ambulatory conscious sedation techniques (25 to 100 \( \mu \)g/kg per minute IV produces minimal analgesic and amnestic effects). \(^3\)

Ketamine is an NMDA receptor antagonist. At high, fully anesthetic level doses, ketamine has also been found to bind to opioid mu and sigma receptors. Ketamine has a wide range of effects in humans, including analgesia, anesthesia, hallucinations, elevated blood pressure, and bronchodilation. Ketamine is primarily used for the induction and maintenance of general anesthesia, usually in combination with some sedative drug. Other uses include sedation in intensive care, analgesia (particularly in emergency medicine), and treatment of bronchospasm profound bradycardia and asystole after the administration of propofol have been described in healthy adult patients, despite prophylactic anticholinergics. Intense analgesia can be achieved with subanesthetic doses of ketamine, 0.2 to 0.5 \( \mu \)g/kg IV. \(^3\)

Fentanyl, a phenyl piperidine-derivative synthetic opioid agonist analgesic, is 75 to 125 times more potent than morphine. Opioids, in general, act as agonists on those stereospecific opioid receptors occurring at presynaptic and postsynaptic sites within the central nervous system (CNS) (principally the brainstem and spinal cord) and outside the CNS in peripheral tissues. They mimic the actions of endogenous ligands by binding to opioid receptors, thus resulting in the activation of pain-modulating (antinoceptive) systems. Opioid receptors are located in those areas of the brain (periaqueductal gray matter of the brain stem, amygdala, corpus striatum, and hypothalamus) and spinal cord (substantia gelatinosa) that are involved with pain perception, integration of pain impulses, and responses to pain. It is speculated that endorphins inhibit the release of excitatory neurotransmitters from the terminals of nerves carrying nociceptive impulses. As a result, neurons are hyperpolarized, which suppresses spontaneous discharges and evoked responses. Low doses of fentanyl, 1 to 2 \( \mu \)g/kg IV, are injected to provide analgesia. Large doses of fentanyl, 50 to 150 \( \mu \)g/kg IV, have been used alone to produce surgical anesthesia. \(^3\)

Anesthetic drugs are often combined to enhance their therapeutic effect while minimizing toxicity. Propofol is an IV anesthetic that is often used as an adjuvant during monitored anesthesia care. It produces dose-related sedation, amnesia and anxiolysis. However, propofol is a poor analgesic, thus requiring the use of an adjunct analgesic agent. Ketamine is an IV anesthetic that produces minimal cardiovascular or respiratory depression. Earlier studies suggested that the analgesic effects of small-dose ketamine complement the sedation provided by propofol during monitored anesthesia care thus, the combination of propofol and ketamine has the potential to provide better sedation with less toxicity than either drug alone. Propofol is also combined with opioids to achieve better analgesia and cause less PONV.

**RESEARCH QUESTION**

The authors aimed to answer the following research question: What is the effectiveness of using propofol-ketamine versus propofol-fentanyl in outpatient surgical procedures?

**OBJECTIVE OF THE STUDY**

The objective of this review was to present the best available evidence on the effectiveness of using propofol-ketamine versus propofol-fentanyl in outpatient surgical procedures.
METHODOLOGY

Criteria for Considering Studies for this Review

Randomized controlled clinical trials (RCTs) were the study design of choice. Clinical controlled trials (CCTs) and quasi experimental trials were also considered in the absence of RCTs. This review included trials with adults both males and females, ASA I or II, undergoing outpatient ambulatory surgery. Patients with mental disease, neurologic disease or those receiving treatment with sedatives were excluded. The intervention of interest of this review is the use of propofol-ketamine or propofol-fentanyl in outpatient surgical procedures. Post-operative analgesia, incidence of nausea and vomiting, and the time to discharge from the post-anesthesia care unit (PACU) were determined.

Search Strategy

Language

Both published and unpublished English language studies were sought. Assessment for inclusion of foreign language publications was based on the English language extract, and if considered appropriate, an English translation of the study was sought.

Bibliographic Databases and Key Words

The keywords used to search for studies included in this review are presented in Table I. Studies from January 2000 up to present were identified during the database searches and assessed for relevance from a review of the title, abstract and descriptors of the study. A full text report was obtained for all the studies deemed relevant for this review. The following databases were searched: Cochrane library, OVID, Google scholar, Science Direct and PubMed.

Unpublished Literature

To minimize publication bias, unpublished studies were identified using dissertations abstracts international and proceedings first.

Hand Searching

The reference lists of all identified publications (both included and excluded), were searched for additional studies. Hand searching of relevant conference proceedings was included as well.

Validity Assessment

The evidence of the retrieved studies were assessed using the Joanna Briggs Institute (JBI) levels of evidence (Table II).

Table 1. Keywords used to search relevant studies for the review.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Participants</th>
<th>Outcomes of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol and ketamine</td>
<td>Adults</td>
<td>Post-op analgesia</td>
</tr>
<tr>
<td>Propofol and fentanyl</td>
<td>Ambulatory surgery</td>
<td>Incidence of nausea</td>
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<tr>
<td></td>
<td></td>
<td>Incidence of vomiting</td>
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<td></td>
<td></td>
<td>Time to discharge from PACU</td>
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</table>

Table 2. The Joanna Briggs Institute levels of evidence.

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Effectiveness E (1-4)</th>
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<tbody>
<tr>
<td>I</td>
<td>Systematic review (with homogeneity) of experimental studies (eg RCT with concealed allocation)</td>
</tr>
<tr>
<td>II</td>
<td>Quasi experimental studies (eg., without randomisation)</td>
</tr>
<tr>
<td>III</td>
<td>3a Cohort studies (with control group)</td>
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<tr>
<td></td>
<td>3b Case controlled</td>
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<td></td>
<td>3c Observational studies without control groups</td>
</tr>
<tr>
<td>IV</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or consensus</td>
</tr>
</tbody>
</table>
Assessment of Methodological Quality

Two independent reviewers critically appraised each study. A third reviewer was consulted if a disagreement between reviewers was encountered.

The methodological quality of each of the RCTs was assessed by two authors using the Joanna Briggs Institute’s Critical Appraisal of Evidence of Effectiveness. Each author evaluated the 2 journals independently.

Joanna Briggs Institute Critical Appraisal of Evidence of Effectiveness

1. Was the assignment to treatment groups random?
2. Were participants blinded to treatment allocation?
3. Was allocation to treatment groups concealed from the allocator?
4. Were the outcomes of people who withdrew described and included in the analysis?
5. Were those assessing the outcomes blind to the treatment allocation?
6. Were control and treatment groups comparable at entry?
7. Were groups treated identically other than for the named interventions?
8. Were outcomes measured in the same way for all groups?
9. Were outcomes measured in a reliable way?
10. Was there adequate follow-up of participants?
11. Was appropriate statistical analysis used?

Each number is answerable by a yes or a no. All yes answers were tallied. A score of 1-4 is given a rating of low quality paper; 5-8 is classified as moderate quality; and a score of 9-11 as high quality study.

Data Analysis

Data were pooled statistically if they were sufficiently similar in terms of extract dose and formulation, patient demographics and disease activity, and if they were of adequate quality. Pooling was done using Review Manager (Revman) software. Weighted mean differences and 95% confidence intervals (CI) were calculated for continuous data to analyze the size of the effects of the interventions.

For the trials in which statistical pooling of results was inappropriate, findings were summarized in narrative form.

RESULTS

A total of 383 citations were obtained from electronic search of databases using the key terms presented. From this number, 137 articles were identified to have the most potential to qualify for this review. After reviewing the full texts of the papers obtained, 2 articles satisfied the inclusion criteria for this review.

Evaluation of the methodological quality by two evaluators was then done; a consensus between the two evaluators was immediately met. Both articles were rated as of high methodological quality.

The studies included were prospective, randomized double-blind controlled trials with level I evidence. Akin and colleagues (2005) studied the comparison of fentanyl-propofol with a ketamine-propofol combination during an endometrial biopsy. Vallejo and associates (2002) studied the effects of propofol-ketamine and propofol-fentanyl on postoperative

![Figure 1. Flow diagram of article inclusion in the Review.](image)
<table>
<thead>
<tr>
<th>Title</th>
<th>No. and Characteristics of Patients</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Post-op analgesia</strong> (median range)</td>
<td><strong>Time to recovery from anesthesia</strong></td>
<td><strong>Nausea</strong></td>
<td><strong>Vomiting</strong></td>
</tr>
<tr>
<td>Propofol- ketamine Versus propofol-fentanyl for Outpatient Laparoscopy: Comparison of Postoperative Nausea, Emesis, Analgesia, and Recovery</td>
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<td>Vallejo MC, Romeo RC, Davis DJ, and Ramanathan S</td>
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<td>Akin A, Guler G, Esmaoglu A, Bedirli N, and Boyaci A</td>
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<td>Journal of Clinical Anesthesia June 2005</td>
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**Table I. Demographic characteristics and results in studies included for review**
nausea, emesis analgesia and recovery. The studies included 159 adult females. Subjects had similar baseline characteristics, in terms of age, sex and weight. (Table 1).

Based on demographic data, all patients were comparable at entry in the two studies. These two studies compared the effectiveness of propofol-ketamine versus propofol-fentanyl in out patient ambulatory surgery using the following outcomes: post-op analgesia, time to recovery to anesthesia, and incidence of nausea and vomiting.

**Post-operative Analgesia**

The study done by Vallejo, et. al showed that more patients required pain medications in the group given propofol-ketamine. Eight patients from propofol-ketamine group and 6 patients from the propofol-fentanyl group required pain medication while at the PACU ($P = 0.776$).

**Incidence of Nausea**

Two RCTs reported on the incidence of nausea. There was no statistical difference between the two drug combinations when the data from the studies were pooled. OR and 95% CI is 2.48 (0.81, 7.58).

**Incidence of Vomiting/ Emesis**

Two RCTs reported on the incidence of vomiting/ emesis. Data summarized from the two trials reported no statistical difference between the two drug combinations (OR=2.76, 95% CI= 0.62-12.18).

**Time to Recovery from Post Anesthesia Care Unit (PACU)**

Two RCTs reported on the time to recovery from PACU. Data summarized from the two trials report a significantly faster time to recovery in patients given Propofol - Fentanyl (Control). The average mean difference is 30.77 minutes with 95% CI 22.41-39.13.

**DISCUSSION**

In this era of health care cost containment, it is important to reduce the cost without compromising patient care. The goals of outpatient ambulatory anesthesia include a rapid and smooth induction, effective intraoperative anesthesia, and a smooth and
prompt recovery with minimal, if any, postoperative side effects, leading to a quicker return to "home readiness" and an overall shorter outpatient stay. Propofol is a common anesthetic agent used for outpatient ambulatory surgery. Lack of analgesic property of propofol requires the use of a supplementary analgesic agent. Two of the common agents used in combination with propofol are ketamine and fentanyl.

Fentanyl is used as a part of balanced anesthesia. Opioids are used to provide analgesia but are associated with a 15% to 40% incidence of PONV. In the study done by Vallejo, et al. hypnotic-anesthetic doses of propofol-ketamine combination do not improve postoperative nausea, emesis, analgesia and recovery compared with the propofol-fentanyl combination.

Ketamine has been used in combination with propofol for both general and IV sedation and to supplement general anesthesia. Preliminary studies indicate that ketamine may be a useful alternative to opioid adjuncts during propofol sedation and that the sympathomimetic effects of ketamine may be effective in counteracting the hemodynamic depression of propofol. Subhypnotic dosages of ketamine coadministered with propofol for sedation during MAC exert an opioid-sparing effect with no clinically significant respiratory depression and a low incidence of psychotomimetic effects.

**CONCLUSION**

This review concludes that propofol-ketamine caused nausea and vomiting in patients undergoing outpatient ambulatory surgery. Time to discharge was observed to be shorter in the group given propofol-fentanyl.
REFERENCES


