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Original Article

Efficacy and Safety of Penehyclidine Hydrochloride in Postoperative Nausea and Vomiting Prevention: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Postoperative nausea and vomiting (PONV) is a common complication following anesthesia. Penehyclidine hydrochloride (PHC), an anticholinergic medication, selectively inhibits the M1 Muscarinic and M3 Muscarinic receptors involved in the nausea and vomiting pathways. This study aims to evaluate the efficacy of PHC in preventing PONV and its potential advantages over existing treatments.
Methods: This study investigated the efficacy and safety of PHC in preventing PONV by analyzing randomized controlled trials (RCTs) identified through a comprehensive search of the PubMed, Scopus, Web of Science, and Cochrane Library databases up to December 2024.
Results: Five RCTs involving 979 patients were included. Compared to the control group, PHC reduced the incidence of PONV in the first 24-72 hours after surgery (RR: 0.64, 95% CI [0.50, 0.82], p = 0.0004) and the requirement of rescue antiemetics (RR: 0.46, 95% CI [0.22, 0.96], p = 0.04). However, PHC significantly increased the incidence of dry mouth (RR: 2.64, 95% CI [1.98, 3.5], p < 0.00001). No significant differences were observed between the two groups regarding other secondary outcomes. Risk of bias assessment was done using RoB2.
Conclusions: PHC shows promising efficacy in reducing PONV and the need for antiemetic medications. Further large-scale RCTs are necessary to verify these results and determine the optimal dose.

1. Introduction

Postoperative nausea and vomiting (PONV) commonly complicates recovery, affecting about 30% of surgical patients [1, 2]. It involves nausea, retching, or vomiting within 24–72 hours after surgery in hospitalized patients [3]. PONV can cause severe health problems, including suture dehiscence in patients who cannot tolerate increased abdominal pressure or strain on suture lines, esophageal tears, postoperative bleeding, hematoma formation, dehydration, and aspiration pneumonia [4, 5]. Patients with PONV also face a higher risk of hospital readmission compared to those without these symptoms [6].

Clinicians use various medications to prevent PONV, including serotonergic (5-HT3) receptor antagonists, NK-1 receptor antagonists, corticosteroids, and anticholinergics. Gan et al. recommend using 1–2 prophylactic interventions for moderate-risk patients and at least two interventions for high-risk patients [7]. However, despite the availability of multiple anti-emetic drug classes, no single anti-emetic agent is universally effective or free from adverse effects. This highlights the need for new antiemetic agents that are both effective in preventing PONV and offer a better safety and tolerability profile for patients.

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Penehyclidine hydrochloride (PHC), chemically known as (2-hydroxyl-2-cyclopentyl-2-phenyl-ethoxy) quinuclidine, is an anticholinergic agent with antimuscarinic and antinicotinic effects. By crossing the blood-brain barrier, PHC influences both the central and peripheral nervous systems, providing strong anticholinergic effects throughout the body [8]. In China, clinicians use PHC to treat soman and organophosphorus compound toxicity. Its bronchodilatory properties also suggest potential for treating chronic obstructive pulmonary disease (COPD) [9].

Previous studies demonstrated that transdermal scopolamine, another anti-cholinergic agent, is effective in reducing the incidence of PONV [10, 11]. However, these reviews also highlighted several adverse effects associated with its use, including visual disturbances, dry mouth, agitation, and sedation [10, 11].

Several studies across various surgical settings have investigated the effectiveness and safety of PHC in preventing postoperative nausea and vomiting [12-16]. Consequently, we performed a systematic review and meta-analysis of all randomized controlled trials (RCTs) that assessed the efficacy and safety of PHC in reducing the incidence of postoperative nausea and vomiting.

2. Methods

2.1. Data collection and extraction

We searched the Medline/PubMed, Web of Science, Scopus, and Cochrane Library databases from inception up to December 2024 using the following search terms: ((“Penehyclidine” OR “Penehyclidine hydrochloride raceme” OR “Penehyclidine hydrochloride”) AND (“Nausea” OR “Vomiting” OR “PONV” OR “Emesis” OR “Emeses”))

We removed duplicates with EndNote 20.5 software (Clarivate Analytics, PA, USA). Reference screening followed two phases: first, three authors independently reviewed titles and abstracts to assess relevance, and then they examined the full-text articles to confirm eligibility for quantitative analysis. A fourth author helped resolve any disagreements through discussion. We used the Rayyan website to facilitate the screening process [17]. The protocol for this systematic review and meta-analysis was registered on PROSPERO (CRD42025605004) on 02 January 2025.

We included RCTs that assessed the efficacy and safety of PHC in preventing PONV in patients undergoing any type of surgical procedure and receiving PHC. Included studies reported at least one of the following outcomes: incidence of PONV, time to first vomit, or incidence of adverse events. The control group in all included studies received 0.9% normal saline as a placebo. We excluded non-RCT studies, studies with insufficient reporting of relevant outcomes, studies where PHC was not the primary intervention for PONV prevention, animal studies, and any study not published in English. For overlapping study populations, the most recent publication was chosen for inclusion. Four co-authors independently extracted the data to an MS Excel sheet, with any conflicts regarding study inclusion resolved by E.A. Extracted data were organized into two domains: (1) Baseline characteristics of the study population, and (2) Study outcomes.

In the included studies, the dosage of PHC varied but remained within a similar range. Lu et al., Wang et al., and Ding et al. administered a fixed intravenous dose of 0.5 mg while Sun et al. and Zhao et al. used a weight-based approach, with a dose of 10 μg/kg, capped at a maximum of 0.5 mg. Additionally, Zhao et al. employed a continuous infusion of PHC at 10 μg/kg at a fixed rate of 2.0 mL/h over 48 hours in a postoperative analgesia pump.

2.2. outcomes

The primary endpoint is the Incidence of PONV, defined as the development of any nausea, retching, or vomiting at any time within the 72-hour postoperative period, and requirement of rescue anti-emetics. Secondary outcomes included the incidence of dry mouth, the incidence of dizziness, the requirement of rescue analgesics, and the incidence of headache. We analyzed the overall rate of incidence of PONV regardless of time.

2.3. Risk of Bias Assessment

We used the revised Cochrane risk-of-bias tool (RoB2) for RCTs to evaluate the risk of bias in the included clinical trials [18]. This assessment included the randomization process, concealment of the allocation sequence, deviations from intended interventions, use of appropriate analysis to estimate the effect of the assigned intervention, outcome measurement, selection of reported results, and overall risk of bias. The methodological quality of the studies was categorized as either low risk, some concerns, or high risk of bias. Two independent co-authors (AM, IT) assessed the risk of bias, and disagreements were resolved through discussion with a third author (EA).

2.4. Statistical Analysis

We used RevMan (Version 5.3 for Windows) for statistical analysis [19]. Heterogeneity was assessed through visual inspection of forest plots and statistically using the I-squared and Chi-squared tests. When significant heterogeneity was detected (Chi-squared $p < 0.1$), we applied a random-effects model, which assigns relatively greater weight to smaller studies to account for heterogeneity. Otherwise, a fixed-effects model was employed. To address heterogeneity, we conducted sensitivity analyses systematically excluding one study at a time. The pooled effect size (risk ratio) and its corresponding 95% confidence interval were calculated using the Mantel-Haenszel method. Extracted data were entered into a spreadsheet and carefully checked for accuracy.

3. Results

3.1. Literature search

The search strategy yielded 58 relevant articles. Of these, 23 duplicate articles were removed, and 35 were included in the title and abstract screening phase. Ultimately, six articles were selected for full-text review, resulting in the exclusion of one article. Finally, five eligible RCTs comprising 979 patients were included in the final meta-analysis [12-16] (**Table 1 and Table 2**). The screening process is illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (**Figure 1**). According to the Cochrane RoB 2 assessment, one study had an overall low risk of bias, whereas the other four studies had some concerns (**Supplementary Figure 1**).

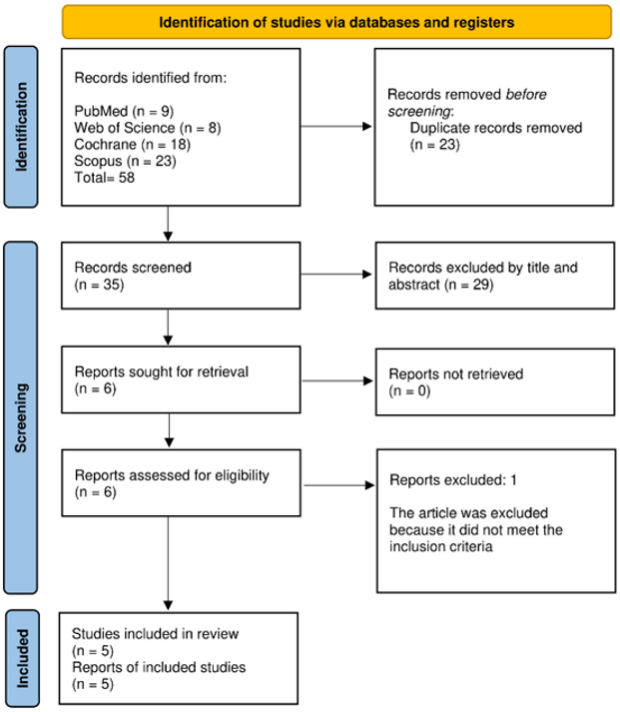

Figure 1: PRISMA flow diagram of the study

Table 1: Baseline Characteristics of Included Studies

Study ID[i]	Type of Study	Groups	Sample Size	Age (years), Mean (SD)	Females, n (%)	BMI, kg/m², Mean (SD)
Zhao 2024 [16]	RCT	PHC	46	44.1 (11)	46 (100%)	23.8 (4.1)
		Placebo	46	48.8 (12)	46 (100%)	24.9 (4.8)
Ding 2023 [12]	RCT	Placebo	113	34 (9)	88 (77.8%)	38 (7)
		PHC	221	33 (8)	153 (69.2%)	38 (7)
Wang 2022 [15]	RCT	Placebo	118	25 (4.50)	81 (68.6%)	20.5 (2.93)
		PHC bolus	117	24.33 (5.25)	82 (70.1%)	20.37 (2.40)
		PHC bolus + infusion	118	25.33 (5.25)	81 (68.6%)	21.2 (3.08)
Lu 2022 [13]	RCT	TIVA + PHC	50	42.8 (9.6)	37 (74%)	-
		TIVA only	50	43.6 (10.1)	33 (66%)	-
Sun 2021 [14]	RCT	PHC	114	11 (14)	57 (50%)	-
		Placebo	104	10 (11)	43 (41.3%)	-

PHC: Penehyclidine Hydrochloride; RCT: Randomized Controlled Trial; BMI: Body Mass Index; SD: Standard Deviation

Table 2: Surgical and Anesthetic Characteristics of Included Studies

Study ID[ii]	Groups	ASA		Apfel Risk Score			Duration of Surgery, Mean (SD)	Duration of anesthesia, Mean (SD)	Length of stay in PACU, Mean (SD)
		ASA 2/3	ASA 1/2	2	3	4			
Zhao 2024 [16]	PHC	27/19	-	1 (2.2%)	25 (54.3%)	20 (43.5%)	120.5 (60.6)	147.1 (63.1)	-
	Placebo	28/18	-	2 (4.3%)	22 (47.8%)	22 (47.8%)	105.7 (55.3)	132.2 (58.5)	-
Ding 2023 [12]	Placebo	49/64	-	48 (42%)	46 (41%)	4 (4%)	77 (22)	93 (22)	66 (23)
	PHC	103/118	-	97 (44%)	67 (30%)	6 (3%)	76 (22)	92 (23)	66 (27)
Wang 2022 [15]	Placebo	-	-	-	-	-	201.33 (59.29)	252 (69.05)	-
	PHC bolus	-	-	-	-	-	209.67 (51.79)	262.67 (56.30)	-
	PHC bolus + infusion	-	-	30 (25.4%)	71 (60.2%)	11 (9.3%)	204.33 (49.53)	254.33 (52.54)	83 (53.29)
Lu 2022 [13]	TIVA + PHC	-	97/20	32 (27.4%)	66 (56.4%)	16 (13.7%)	76.6 (13.9)	95.9 (14.5)	76 (58.55)
	TIVA only	-	91/27	28 (23.7%)	61 (51.7%)	20 (16.9%)	75.5 (15.5)	95.9 (16.7)	76.67 (60.04)
Sun 2021 [14]	PHC	-	-	-	-	-	30 (16)	63.5 (20)	60 (30)
	Placebo	-	-	-	-	-	28 (16)	64 (17.3)	59 (30)

PHC: Penehyclidine Hydrochloride; RCT: Randomized Controlled Trial; TIVA: Total Intravenous Anesthesia; ASA: American Society of Anesthesiologists Physical Status Classification; SD: Standard Deviation; PACU: Post-Anesthesia Care Unit

3.2. Primary outcomes

PHC was associated with a significant decrease in the incidence of PONV (RR: 0.64, 95% CI [0.50, 0.82], p = 0.0004) compared to normal saline (Figure 2). However, the pooled studies were heterogeneous (p = 0.04, I2 = 61%). We conducted a sensitivity analysis in multiple scenarios. Heterogeneity was best resolved by excluding the study by Ding 2023 (p = 0.46, I-square = 0%). In the meta-analysis model, the overall risk ratio was still in favor of PHC (RR = 0.59, 95% CI [0.50 to 0.71], p < 0.00001) (**Figure 3**). PHC significantly reduced the need for rescue anti-emetics compared to normal saline (RR: 0.46; 95% CI [0.22, 0.96]; p = 0.04) as shown in (**Figure 4**). However, the pooled studies showed considerable heterogeneity (p = 0.002, I² = 76%). We conducted a sensitivity analysis. Excluding the study by Ding et al., 2023, most effectively resolved the heterogeneity (p = 0.77, I² = 0%). After this adjustment, the meta-analysis still favored PHC, with an overall RR of 0.36 (95% CI [0.24, 0.55], p < 0.00001) (**Figure 5**).

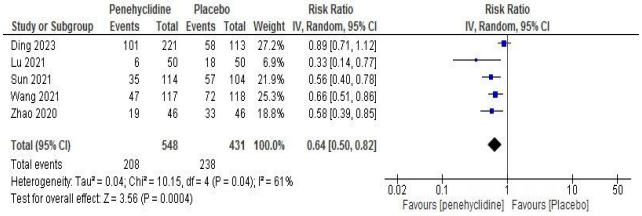

Figure 2: Forest plot of postoperative nausea and vomiting (PONV)

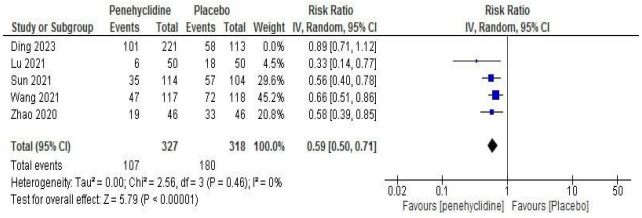

Figure 3: Forest plot of sensitivity analysis for PONV

3.3. Secondary Outcomes

PHC showed no significant difference from normal saline in the requirement for rescue analgesics (RR: 0.93; 95% CI [0.67, 1.28], p = 0.64). The pooled studies were homogeneous (p = 0.60, I² = 0%) as illustrated in **Supplementary Figure 2**.

The use of PHC did not demonstrate a statistically significant difference in dizziness occurrence when compared to normal saline (RR: 1.38; 95% CI [0.90, 2.14], p = 0.14). The combined studies exhibited homogeneity (p = 0.62, I² = 0%) (**Supplementary Figure 3**).

The administration of PHC showed no significant effect on headache incidence in comparison to normal saline (RR: 1.00; 95% CI [0.53, 1.88], p = 1.00). The aggregated studies demonstrated homogeneity (p = 0.70, I² = 0%), as shown in **Supplementary Figure 4**.

PHC was linked to a significantly higher occurrence of dry mouth when compared to normal saline (RR: 2.64; 95% CI [1.98, 3.50], p < 0.00001). The pooled studies were homogeneous (p = 0.50, I² = 0%), as presented in **Supplementary Figure 5**.

4. Discussion

This study aimed to investigate the effectiveness and safety of the novel anti-cholinergic drug PHC in preventing PONV. Our findings revealed that PHC significantly lowered the incidence of PONV while maintaining a commendable safety profile. Notably, PHC substantially reduced the need for rescue anti-emetics, though it came with a marked increase in dry mouth incidence. In contrast, PHC had no meaningful impact on headache, dizziness, or the requirement for rescue analgesics.

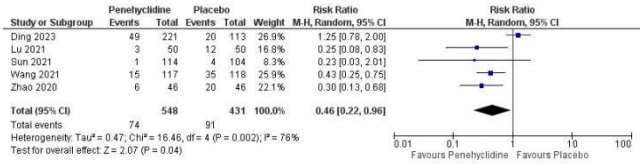

Figure 4: Forest plot of the requirement of rescue anti-emetics

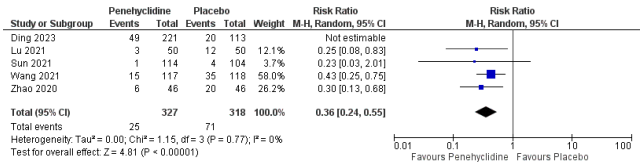

Figure 5: Forest plot of sensitivity analysis of the requirement of rescue anti-emetics

PONV demonstrates a critical challenge for surgeons and anesthesiologists, significantly affecting patient outcomes. It can lead to severe complications such as aspiration of gastric contents, which may result in aspiration pneumonitis and wound dehiscence [20]. Moreover, PONV heightens the risk of postoperative bleeding and airway obstruction caused by hematoma formation, further worsening wound complications and intensifying postoperative pain. These complications collectively hinder recovery, extend hospital stays, and diminish patient satisfaction [4].

Vomiting is a complex neural reflex driven by five main afferent pathways: the chemoreceptor trigger zone (CTZ), the vagal mucosal pathway in the gastrointestinal tract, neuronal pathways from the vestibular system, reflex pathways from the cerebral cortex, and midbrain afferents [21]. Activation of any of these pathways can trigger the vomiting response, mediated by various receptors, including cholinergic, dopaminergic, histaminergic, and serotonergic (5-HT3) receptors [22].

Type 1 muscarinic acetylcholine receptors, predominantly expressed in the vestibular system, play a key role in cholinergic transmission. Anticholinergic drugs block this transmission from the vestibular nuclei to the higher CNS and from the medullary reticular formation to the vomiting center [10]. Nonselective muscarinic receptor antagonists like scopolamine and atropine are widely used to prevent nausea and vomiting linked to motion sickness [23].

PHC, an anti-cholinergic drug, selectively targets muscarinic 1 (M1) and muscarinic 3 (M3) acetylcholine receptor subtypes. This mechanism of action aligns with its observed effectiveness in reducing the incidence of PONV. Beyond its antiemetic properties, PHC provides organ protection, benefiting the heart and lungs through its antioxidant, antiapoptotic, and anti-inflammatory effects. Administering PHC prior to surgery enhances the depth of anesthetic sedation and prolongs the inhibition of respiratory secretions, making it particularly advantageous in surgical settings [26-24]. Additionally. Liang et al. found that PHC administration at a dose of 0.012mg/kg could reduce propofol dosage for anesthesia induction without effect on Bispectral index (BIS) values [27].

PHC demonstrates a longer half-life (10.35 hours) compared to scopolamine (1.35 hours), another anti-cholinergic drug commonly used for PONV prophylaxis [28]. While scopolamine significantly influences

autonomic cardiovascular regulation by increasing vagal cardiac inhibition and lowering blood pressure in healthy young individuals, it can also cause postoperative tachycardia when administered transdermally [30 ,29]. In contrast, Penehyclidine's selective antagonism of M1 and M3 receptors allows it to inhibit vagal reflexes without affecting heart rate [26].

Wang et al., who found that PHC did not increase cardiovascular side effects compared to placebo, confirmed these cardiovascular safety benefits [15]. These findings, though not based on direct comparisons, suggest that PHC may be an equally effective alternative to scopolamine for PONV prevention but with fewer unwanted cardiovascular side effects. Future head-to-head trials comparing Penehyclidine and scopolamine are warranted to validate these observations.

Additionally, PHC boasts a more favorable side-effect profile than other antiemetics commonly used for PONV prevention. While dry mouth remains its most frequent adverse effect, it avoids the complications associated with drugs like dexamethasone, such as delayed wound healing, hyperglycemia, and heightened infection risks, particularly in vulnerable patients like those with diabetes [32 ,31]. Ondansetron, another widely used 5-HT3 antagonist, has well-established efficacy and safety in preventing nausea and vomiting. However, it may cause headaches and a slight prolongation of the QT interval, warranting cautious use in at-risk patients [33].

Our analysis included studies with different patient populations, surgical procedures, and anesthesia techniques, leading to some variability. Some studies used a combination of intravenous and inhalational anesthesia, while others used total intravenous anesthesia (TIVA), which is generally associated with a lower risk of PONV [34]. This difference in anesthesia methods is important because inhalational agents can increase PONV risk, while TIVA has a protective effect [36 ,35]. Additionally, the included studies assessed PHC across a range of surgical procedures, including gynecological laparoscopy, thyroidectomy, orthognathic surgery, strabismus surgery, and bariatric surgery, each of which carries a different baseline risk for PONV. Notably, PHC did not significantly decrease the incidence of PONV in bariatric surgery, suggesting that its efficacy may depend on specific surgical and patient-related factors. However, the overall trend across studies demonstrated a reduction in PONV incidence with PHC, supporting its potential as an effective antiemetic in most surgical settings.

Our study constitutes the first comprehensive systematic review and meta-analysis assessing the efficacy and safety profile of the anti-cholinergic agent PHC in alleviating the incidence of PONV. However, this study exhibits certain limitations. The patient cohort was relatively small and derived from a single center. Moreover, all of the studies included in our meta-analysis enrolled participants of Chinese descent, which may influence the external validity and potentially introduce selection bias. Furthermore, the types of surgical procedures across the analyzed studies displayed varied heterogeneity. Additionally, the included studies varied in anesthetic protocols, with some using inhalational anesthesia and others employing total intravenous anesthesia (TIVA), which has a lower baseline risk of PONV.

5. Conclusion

Our meta-analysis indicated that PHC significantly reduced the incidence of PONV compared to placebo. The most commonly reported adverse effect was dry mouth, while other side effects, such as dizziness and headache, were less frequent. The overall safety profile suggests that PHC-related adverse effects are generally mild and tolerable. However, further large-scale randomized controlled trials are needed to confirm these findings, explore optimal dosing strategies, and compare PHC with other antiemetic agents.

Conflicts of Interest:

The authors declare no competing interests that could have influenced the objectivity or outcome of this research.

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Authors Contribution Statement:

A.M.H. and E.A. contributed equally to this work and were responsible for study conceptualization, data curation, formal analysis, and visualization. M.W., K.O., A.T.S., I.T., M.A., and A.A. assisted with methodology development, data validation, and critical review. M.S., S.E., and A.H. contributed to manuscript review and editing. A.H. supervised the project. All authors reviewed and approved the final version of the manuscript. A.M.H. serves as the corresponding author and is responsible for all communication regarding this work.

Data Availability Statement:

Data Availability Statement: This review article does not contain any new primary data. All information discussed is derived from previously published sources and publicly available databases, as cited in the manuscript.

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