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Research Article

Comparison of Low-Dose Naloxone with Ondansetron for Prevention of Sufentanil-Postoperative/Postdischarge Nausea and Vomiting

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ABSTRACT

Background: Sufentanil is extensively used as a powerful painkiller for both initiating and sustaining general anesthesia, thanks to its advantages like potent prolonged action, analgesic effect, and hemodynamic stability. Nonetheless, it's important to consider sufentanil's negative side effects, such as postoperative nausea and vomiting (PONV), during the surgical period. Additionally, Naloxone, an antagonist for opioid receptors, is frequently utilized to counteract the lingering effects of opioids after surgery. Hence, we examined the preventative use of low-dose naloxone on PONV and studied its potential mechanism of action.

Methods: After ethical approval and receiving IRCT code, 64 patients were evenly assigned to the naloxone and ondansetron groups prior to surgery. We also monitored the occurrence and intensity of PONV and the use of antiemetic medication within the first 24 hours after surgery. The main focus of our study was to analyze the PONV profile.

Results: The mean age was 49.8±15.5 years, the mean weight 71.8±23 kg, and the mean BMI was 23.5±5.2 kg/m2. No significant difference was detected regarding mean oxygen saturation and arterial pressure between the groups at admission, 15, 30, 60, and 90 min after surgery (p> 0.05). Adverse reactions showed no significant difference during the recovery time between the groups (p> 0.05). The PONV severity and incidence are significantly higher in the naloxone group.

Conclusion: Naloxone can be used as an antiemetic medicine, besides the ondansetron, and using this agent individually cannot prevent nausea and vomiting effectively.

Introduction

Sufentanil is frequently utilized for its potent analgesic effects in both the initiation and continuation of general anesthesia, praised for its strong pain relief capabilities, extended effectiveness, and ability to maintain hemodynamic stability [1-2]. Nonetheless, the potential adverse effects of sufentanil during the surgical period cannot be overlooked [3]. Nausea and vomiting are common side effects during the intravenous administration of sufentanil for anesthesia induction. Postoperative nausea and vomiting (PONV) as common and distressing issues often occur within the first 24 hours after general anesthesia, causing significant discomfort, disruption of water and electrolyte balance, and in severe instances, could lead to wound dehiscence [4-5]. The occurrence of PONV can reach 70%–80% in high-risk individuals, including women undergoing laparoscopic procedures, those experiencing lengthy surgeries, and the use of certain anesthetic drugs. Ondansetron, a 5HT3 receptor antagonist primarily

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utilized to prevent vomiting, has shown promising results in preventing PONV during anesthesia when administered in an 8mg IV dose without adverse effects [6]. The link between the use of sufentanil and the incidence of PONV has been well-documented, highlighting the importance for anesthesiologists to mitigate sufentanil-induced PONV [7-8].

We hypothesized that certain medications might effectively prevent PONV while maintaining their efficacy. The opioid receptor antagonist Naloxone counteracts the lingering impacts of opioids after surgery [9]. Recent findings suggest that the low dose of naloxone (approximately regaraded as 0.05 μg/kg to 1 μg/kg) can reduce opioid-induced nausea and vomiting without compromising pain relief [10]. Moreover, research by Zhang et al. demonstrated that combining intravenous sufentanil with a low dose of naloxone (0.25 μg/kg/h) preserves sufentanil's analgesic properties and also diminishes the incidence of PONV and itching in cases receiving laparoscopic gallbladder removal [11-14]. To date, there are no clinical trials specifically investigating naloxone's ability to prevent PONV. Thus, our research aims to examine the preventative use of low-dose naloxone on PONV, and its effectiveness, and to delve into the potential mechanisms involved.

Methods

This study received approval from the Ethics Committee(IR.MUI.MED.REC.1402.079) of the University, and the cases or their legal guardians signed the informed consent. It was registered on www.irct.ir under the documentation code IRCT20160307026950N52. Conducted in accordance with the Helsinki Declaration principles, the trial also followed CONSORT guidelines (Figure 1).

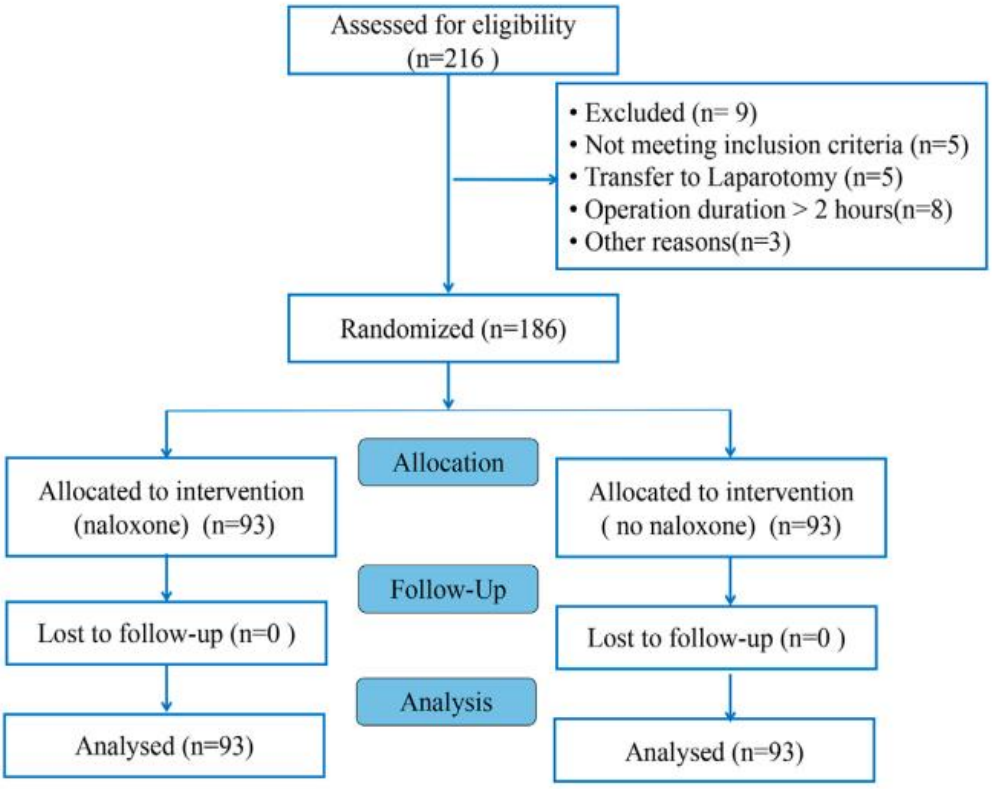

Figure 1- Flowchart study

Sixty-four adult patients who had an ASA physical status of I or II were assessed and received elective surgeries under general anesthesia at the hospital associated with Isfahan University from May 10 to May 25, 2023. Exclusion criteria included a history of chronic cough, gastroesophageal reflux disease (GERD), asthma, and upper respiratory tract infections two weeks before enrollment, heart disease, peptic ulcers or bleeding, aneurysms, and gastric retention that causes vomiting and nausea. Those who had taken antiemetic medications or analgesics before surgery were excluded.

Consequently, 64 patients were randomly assigned (1:1 ratio) to the naloxone (Group N) and control (Group O) groups each with 32 cases using a computer-generated randomization sequence, with an assurance of no premedication. Pulse oxygen saturation (SpO2) and Noninvasive blood pressure (NBP) were consistently checked in the suregery room. Patients had a 20G venous trocar needle inserted into the forearm median cubital

vein for cannulation. Then, 5 minutes before general anesthesia, Group N received an intravenous injection of naloxone at 1.25 μg/kg (diluted to 20 μg/ml with normal saline (NS) over 3 seconds. Concurrently, Group C received NS (5 ml). An anesthesia nurse prepared the saline or naloxone solution and a skilled anesthesiologist administrated them and they were unaware of the group assignments. Before anesthesia, all patients received 100% oxygen through a face mask at 6 L/min for 2 minutes. Using a sufentanil bolus intravenouse injection at 0.1 μg/kg (diluted to 5 μg/ml with NS) over 5 seconds, general anesthesia was initiated, which followed one minute later by sequential infusions of cis-atracurium (0.25 mg/kg), propofol (2.5 mg/kg), and midazolam (0.04 mg/kg). A GlideScope facilitated Endotracheal intubation. The continuation of general anesthesia utilized propofol (4–6 mg/kg/h), cis-atracurium (0.2 mg/kg/h) and remifentanil (0.1–0.3 μg/kg/min) for maintenance. Anesthesia depth was regulated to keep the Bispectral Index within the range of 40 to 60. Throughout the surgery, Group N patients were administered naloxone intravenously at 1.25 μg/kg/h, whereas Group O patients were given a matching placebo and utilized ondansetron for antiemetic purposes. Upon completion of the surgery, all maintenance medications were discontinued. Subsequently, patients received tracheal extubation in the anesthesia recovery room and were then transferred to the ward as deemed suitable. The SPO2, heart rate (HR), and mean arterial pressure (MAP) were meticulously documented at predetermined intervals: before the intervention, and 15, 30, 60, and 90 minutes post-intervention. Additionally, the group receiving ondansetron was administered NS as a placebo.

After surgery, the occurrences of adverse effects were documented and analyzed, which included issues such as depressed breathing, dizziness and lethargy, delayed recovery, and agitation during the recovery phase. The frequency and intensity of PONV were measured by the Visual Analogue Scale (VAS) and the nausea and vomiting rating scale, and the use of antiemetic medication within the first 24 hours post-surgery was also tracked. The primary focus was on assessing the PONV profile.

For statistical analysis, SPSS 26 software was utilized. The Kolmogorov-Smirnov test tested the normal distribution of data. Quantitative data are reported as mean ± standard deviation, and between-group differences were assessed by Student's t-test. The Mann-Whitney U test was applied to check differences in ordinal data. The chi-square or Fisher's exact tests were applied for analyzing differences in categorical data, which are reported as either absolute numbers or percentages. P-values of < 0.05 were considered significant.

Results

In our study, 64 adult patients with ASA physical status I or II who had an average age of 49.8±15.5 years, an average weight of 71.8±23 kg, and an average BMI of 23.5±5.2 kg/m2 were assessed.

The consort fellow diagram is shown in (Figure 1). The groups were homogenous regarding surgery, characteristics of patients, and anesthesia profiles ($p> 0.05$) (Table 1).

The two groups indicted no significant differences in the dosage of any used medicine ($p > 0.05$). We observed no significant differences in HR, SPO2 and MAP between the two groups at admission, 15, 30, 60, and 90 min following operation. ($p > 0.05$) (Table 2).

Differ significantly during the recovery time between the groups N and O. ($p > 0.05$) (Table 3).

The PONV severity and incidence are shown in (Table 4).

Table 1- The Characteristics of patients and surgery

Variable	N	O	P
Age	52.1±15.5	47.5±15.3	0.2
Height	175±7.2	178±7.9	0.4
Weight	72.7±7.7	70.8±12.1	0.2
BMI	23.7±2.4	23.3±7	0.7
ASA I/II)	10/22	9/23	0.21
Medical condition	17(53)	15(46)	0.24
PONV	4(12)	3(9)	0.1
Duration of surgery	106.5±14.8	105±13.4	0.37
Duration of anesthesia	130±16	135±13.6	0.11

The p-values are not significant with the level of > 0.05.

Table 2- The vital signs of patients during the surgery

Variable	Group	before	15min	30min	60min	90min
MAP	N	98±10.9	90±7.8	99±6.9	104±9	102±6.3
	O	101±10	100±9	100±8.3	101±5.2	101±6.1
HR	N	83.7±10.7	80±8.7	78±7.1	81.6±8.9	82.3±7.5
	O	79±6.5	82±5.7	83±6.4	83.3±6.6	83.7±5.9
RR	N	12.1±1.1	12.4±1.6	13.1±1.9	13.1±1.6	13.1±1.8

	O	12.1±2.3	11.9±1.5	12.5±1.6	13.4±1.2	13.4±1.2
SPo2	N	97±0.8	96.7±0.6	96.7±1.1	96.3±0.9	96±0.8
	O	96±1	96.3±1	96.6±1.3	95.8±1	96±1.2

Table 3- Adverse reactions during the recovery period between the groups.

Variable	N	O	P value
Depressed respiration	1	1	0.1
Dizziness and drowsiness	2	3	0.2
Delay of recovery	2	1	0.12
Restlessness in the recovery period	3	1	0.2

the variables are not significant with the level of > 0.05.

Table 4- The incidence of post-operative nausea and vomiting and the severity.

	Incidence of PONV	Severity of PONV		
		II	III	IV
Group N	30	8	12	10
Group O	24	14	10	0
P -values	0.03	0.02	0.1	0.000

Discussion

Opioid receptor agonists are considered top-choice medications for perioperative pain relief, capable of significantly reducing patient stress levels, enhancing comfort, and facilitating quicker recovery. Nevertheless, their associated side effects, including coughing, respiratory depression, nausea, and vomiting, can negatively impact the patients' recovery after surgery and quality of life. Intravenous administration of Fentanyl, sufentanil, and similar opioid painkillers during the clinical anesthesia induction phase are likely contributors to PONV.

PONV is a significant adverse effect during the perioperative time, and using opioid receptors during this time increases its risk. Sufentanil causes PONV by three mechanism [15-17]: (1) Sufentanil serves as an excitatory mediator for the chemoreceptor trigger zone (CTZ), directly stimulating the CTZ and activating the vomiting center in the medulla oblongata, leading to vomiting and nausea; (2) Sufentanil delays gastric emptying, relaxes the lower esophageal sphincter, diminishes gastrointestinal peristalsis, and heightens the vestibulocochlear nerve sensitivity, causing gastrointestinal discomfort; (3) Sufentanil can trigger the 5-hydroxytryptamine (5-HT) release in the intestines or stimulates the vagus nerve, causing digestive issues. Current medications for preventing and treating PONV target blocking one or several receptors [18]. It was hypothesized that PONV may activate central mechanism in the medulla oblongata through sufentanil's μ receptors, which then provoke coughing, nausea, and vomiting. Our goal is to explore a medication counteracting this side effect to inhibit and treat PONV, with opioid receptor antagonists being potential candidates. Naloxone as a classic antagonist of the μ opioid receptor neutralizes the effects of residual opioids post-general anesthesia during the perioperative period [19-20]. In treating PONV using naloxone, analgesia using epidural naloxone at a low dose successfully reduced PONV following intravenous sufentanil administration after operation [21]. Moreover, a naloxone dose of 5 μg/ml could also improve sufentanil's analgesic effect [22]. Through competing with agonists for opioid receptors, naloxone quickly begins to work approximately 2 minutes after intravenous administration, although its effect often lasts only a short duration.

In our research, we administered naloxone at a dose of 1.25 μg/kg before the anesthesia induction period, and then a 0.1 μg/kg dose of sufentanil was administered for 5 seconds during the induction. This approach was compared to another group. We observed that the occurrence and intensity of PONV were notably higher 24 hours after surgery in patients from Group N. Consequently, we deduced that while low-dose naloxone could mitigate PONV, the effectiveness of ondansetron was significantly superior. Therefore, based on existing literature, naloxone should not replace ondansetron; instead, their combined use may yield improved outcomes. Our hypothesis regarding naloxone's mechanism in preventing nausea and vomiting is that opioids exhibit a dual mode of action, involving both excitability and inhibition. In terms of excitability, opioids may interact with Gs protein, leading to opioid side effects, whereas for inhibition, they bind to Gi/Go protein, facilitating their analgesic impact. Naloxone at low-dose could potentially diminish Gs protein coupling in the medulla oblongata, thereby reducing nausea and vomiting. However, a more detailed understanding of this mechanism requires further investigation through animal studies. Moreover, as this was a single-center investigation, its findings are limited by the research duration and the sample size. We encourage future studies with larger sample sizes and longer durations to

explore these findings more deeply and provide more detailed and comprehensive insights.

Do not use splitting words with hyphens at the end of lines. Use bold typeface for symbols representing vectors and matrices, while scalar variables should be in italics. Utilize SI units for all weights and measures. Define all non-standard abbreviations and symbols clearly.

Conclusion

Our findings demonstrated that administering a single low-dose naloxone bolus before anesthesia induction significantly reduced the occurrence of sufentanil-related postoperative/postdischarge nausea and vomiting. These findings not only offer clinical strategies for preventing PONV but also suggest that opioids play a crucial role in PONV, whereas opioid antagonists could serve a dual purpose. Further research is needed to explore the specific mechanisms underlying PONV.

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