Original Article

Intraoperative haloperidol does not improve quality of recovery and postoperative analgesia

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Abstract

Introduction: Haloperidol has an established role in nausea and vomiting prophylaxis and possible effects on multiple aspects of postoperative recovery including pain and sedation. The purpose of this study was to evaluate the effects of low-dose intraoperative intravenous haloperidol on quality of recovery (QoR) and pain control after general anesthesia and surgery.

Methods: Ninety eight American Society of Anesthesiologists (ASA) physical status I-II patients undergoing elective general, gynecologic or orthopedic surgery under general anesthesia were enrolled. Participants were randomly allocated to receive either haloperidol 2 mg or sterile water intravenously after induction of anesthesia. All patients were given elastometric morphine patient-controlled analgesia (PCA) pump for pain control after the surgery. Post-operative QoR was evaluated within 20 min in the recovery room and 6 h post-operatively. Pain intensity and demand for additional analgesic was measured in the 6th post-operative hour.

Results: The QoR score in two measurements was not statistically different between the two groups. Haloperidol significantly reduced the nausea in the recovery. The visual analog scale pain score showed that the severity of pain in the haloperidol group was more than the placebo group (4.7 ± 2.4 vs. 3.8 ± 2.5, $P = 0.05$).

Conclusion: Intraoperative small-dose IV haloperidol is effective against post-operative nausea and vomiting with no significant effect on overall QoR. It may also attenuate the analgesic effects of morphine PCA.

Key Words: Haloperidol, nausea, pain, quality of recovery, randomized clinical trial

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INTRODUCTION

Haloperidol is a dopamine D2-receptor antagonist with an established role in postoperative nausea and vomiting (PONV) prophylaxis[1] and sedation in intensive care units.[2] Although controversial, it has been suggested that haloperidol may reduce the postoperative pain and opioid consumption.[3] Considering the low cost, long duration of action and possible effects on multiple aspects of recovery, haloperidol has the potential to play a role in improving the quality of recovery (QoR). However, its effects on global QoR is not well-understood and thus, it is not routinely used in clinical practice.

The QoR score is a nine-point instrument with a simple (ordinal) scoring system that was specifically

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developed and validated to evaluate the health status of patients after anesthesia and surgery.[4] It can be particularly useful when a perioperative intervention affects various aspects of patient recovery, as is the case for haloperidol. The purpose of this study was to evaluate the effects of low-dose intravenous haloperidol on QoR and pain control after general anesthesia and surgery.

METHODS

This prospective study was approved by the regional ethics committee, and written informed consent was obtained from all patients. Ninety eight ASA physical status I-II patients, aged 21-65 years, undergoing elective general, gynecologic or orthopedic surgery under general anesthesia were enrolled. The electrocardiogram of patients was reviewed before induction of anesthesia to rule out the patients with long QT intervals.

Moreover, the patients with known electrolyte imbalance (particularly hypokalemia and hypomagnesaemia), underlying cardiac abnormalities, significant hepatic or renal dysfunction, hypothyroidism, drug abuse, familial long QT syndrome, or who are taking drugs known to prolong the QT interval were excluded.

Participants were randomly allocated to receive either haloperidol 2 mg (Halodic, Caspian Tamin Inc., Iran) diluted in sterile water to a total volume of 10 ml or sterile water 10 ml intravenously after induction of anesthesia. The randomization was performed by the hospital pharmacy using a table of random numbers, and the patients, anesthetist, and anesthetic technician who were involved in the patients' care and data recording were blinded to the nature of the assignment.

Method of anesthesia

All patients were pre-medicated with oral oxazepam 10 mg and ranitidine 150 mg 2 h before surgery. Fentanyl 3-4 μg/kg and IV lidocaine 1.5 mg/kg were administered 3-5 min before tracheal intubation. After the administration of 100% oxygen at 5l/min for several minutes, anesthesia was induced with propofol 1.5-2 mg/kg and atracurium 0.5 mg/kg. General anesthesia was maintained with propofol, fentanyl, and atracurium. Controlled mechanical ventilation with an initial tidal volume of 10 ml/kg and respiratory frequency of 10 breaths/min was adjusted to maintain normocapnia. Neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg.

At the entrance of patients to the recovery, the patients were given a 100 ml elastometric PCA pump (BOT-802, Nanchang Biotek Medical Device Co, China) containing 20 mg morphine sulfate diluted in sterile water with the infusion rate of 5 ml/h and a bolus volume of 0.5 ml with the lockout period of 15 min. Additional analgesics were not administered until completion of the first evaluation in the recovery. If the patients required additional analgesic in the post-operative period, a nurse blinded to the assignments administered incremental doses of morphine sulfate and documented it in the patient record.

Outcome measures

Post-operative QoR [Table 1] was evaluated within 20 min in the recovery room and 6 h post-operatively. Pain intensity was measured in the 6th post-operative hour with a visual analog scale (VAS), a 100-mm horizontal line with anchors of no pain and worst possible pain. All scales were completed by a nurse blinded to the study groups.

Statistical analysis

Calculation of required sample size was performed with respect to VAS pain intensity score. From the literature, a standard deviation of 20 mm was expected, and the analysis was carried out with respect to detecting a difference of at least 13 mm for this parameter. Based on 0.9 power to detect a significant difference and α level of 0.05, 36 patients are required for each group.

Results are presented as either mean (SD), median (25,75 percentile) or percentages, as appropriate. The QoR as well as its questions was compared between the two groups with the Mann–Whitney *U* test. Pain intensity in the 6th h post-operatively was analyzed with independent two-sample *t*-test. Qualitative comparisons between two groups were made with Chi-square test. All comparisons were two-tailed. *P* values < 0.05 were considered statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) version 11.0 software (SPSS, Chicago, IL, USA).

RESULTS

Baseline characteristics and covariates of surgery in the haloperidol and placebo groups were comparable [Table 2]. The QoR score in two measurements was not statistically different between the two groups. Haloperidol significantly reduced the nausea in the recovery (Q8) but in the 6th h post-operatively the beneficial effect of haloperidol on nausea was attenuated. In both measurements, pain score (Q9) in haloperidol-treated patients was higher than

Table 1: The QoR score

Questions	Not at all	Some of the time	Most of the time	Always
Had a feeling of general well-being	1	2	3	4
Hatd support from others	1	2	3	4
Been able to understand instructions and advice	1	2	3	4
Been able to look after personal toilet and hygiene unaided	1	2	3	4
Been able to pass urine and having no trouble with bowel function	1	2	3	4
Been able to breath easily	1	2	3	4
Been free from headache, backache, and muscle pain	1	2	3	4
Been free from nausea, dry-retching, or vomiting	1	2	3	4
Been free from experiencing severe pain, or constant moderate pain	1	2	3	4

QoR: Quality of recovery

Table 2: Baseline characteristics and covariates of surgery

Variables	Haloperidol (*n*=49)	Placebo (*n*=50)
Age (y)#	36 (8)	33 (9)
Male sex*	22 (44.9)	26 (52.0)
Duration of surgery (min)#	79 (26)	67 (24)
Duration of recovery (min)#	41 (11)	37 (12)
Type of surgery*		
Laparotomy	8 (16.3)	7 (14.0)
Orthopedic	24 (48.9)	21 (42.0)
Gynecologic	13 (26.6)	17 (34.0)
Urologic	4 (8.2)	5 (10.0)

#Data are presented as mean (SD),*Data are presented as *N* (%)

the placebo group, however, the difference was not statistically significant [Table 3]. The VAS pain score showed that the severity of pain in the haloperidol group was more than the placebo group (4.7 ± 2.4 vs. 3.8 ± 2.5, $P = 0.05$). Assessment of other components of the QoR score showed comparable results in the two groups. None of the patients showed psychomotor or extrapyramidal complications attributable to the use of haloperidol.

DISCUSSION

The results of this study show that intraoperative small-dose IV haloperidol is effective against PONV with no significant effect on overall QoR. It may also attenuate the analgesic effects of morphine PCA.

Haloperidol has been used extensively as a first line antiemetic treatment, especially after the Food and Drug Administration "black box" warning for droperidol.[5] In this study, the use of haloperidol 2 mg significantly reduced PONV. A systematic review using data from 1962 to 1988 suggested that haloperidol 1-2 mg is effective for the prophylaxis and treatment of PONV.[1] Similarly, a recent study reported that the combination of haloperidol 2 mg with dexamethasone 5 mg was more effective than either drug alone.[6] Collectively, it seems reasonable to consider the low-dose of haloperidol as a safe and cost-effective choice in the prophylaxis and treatment of PONV.

Some earlier studies have suggested that droperidol and metoclopramide, dopaminergic D2 receptor antagonists, may have analgesic effects[7-9] and haloperidol may modify pain behavior in animals[10] and humans.[3,11] However, our findings as well as the results of some earlier studies[12] do not support the analgesic effects of dopaminergic D2 receptor antagonists or even propose the anti-analgesic properties of haloperidol.[13] The mechanism by which haloperidol may influence the threshold of pain perception is not clear, but it possibly includes the effects of haloperidol on the receptors of dopamine, norepinephrine and serotonin. These receptors interact with each other, and modify pain perception. The controversial findings may be due to different doses of administered drugs or variable adjunct opioids in different studies which may affect the role of dominant receptor and subsequent clinical effect.

Haloperidol has been used extensively for the purpose of sedation in the intensive care units. Considering the long half-life of 18 h,[14] it is reasonable to assume that an intraoperative dose of haloperidol may prolong the recovery period or over-sedate the patients in the intermediate recovery period. However, the recovery period was not prolonged in the haloperidol group. Analyses in the recovery room and 6 h post-operatively showed that the other components of QoR score including feeling of general well-being, ability to understand instructions and look after personal hygiene, ability to breathe easily and pass urine were also comparable between two groups. Collectively, the sedative effects of haloperidol would not impair the recovery of patients.

Haloperidol has a number of potential side effects namely akathesia, extrapyramidal symptoms, neuroleptic malignant syndrome, and cardiac arrhythmias.[15] The risk of developing Torsades de Pointes is increased in patients receiving doses of 35 mg/d or higher.[16] Haloperidol at doses 1-2 mg showed no significant effect of QT interval.[17,18] In this

Table 3: The QoR score in the haloperidol and placebo groups

Questions	Within 20 min of recovery			6th h postoperatively		
	Haloperidol	Placebo	*P* value	Haloperidol	Placebo	*P* value
Q1	2 (1, 3)	2 (1, 4)	0.64	2 (2, 4)	2 (2, 4)	0.83
Q2	4 (4, 4)	4 (4, 4)	0.52	4 (4, 4)	4 (4, 4)	0.49
Q3	2 (1, 2)	2 (1, 3)	0.39	3 (2, 4)	3 (2, 4)	0.36
Q4	4 (4, 4)	4 (4, 4)	0.88	4 (4, 4)	4 (4, 4)	0.62
Q5	4 (2.5, 4)	4 (2, 4)	0.87	4 (4, 4)	4 (4, 4)	0.90
Q6	4 (4, 4)	4 (4, 4)	0.55	4 (4, 4)	4 (4, 4)	0.77
Q7	4 (3, 4)	4 (2.5, 4)	0.76	4 (3, 4)	4 (3, 4)	0.62
Q8	4 (4, 4)	4 (2.5, 4)	0.001	4 (4, 4)	4 (2, 4)	0.16
Q9	2 (1, 3)	2.5 (2, 4)	0.11	2 (2, 3)	3 (2, 4)	0.09
QoR score	3.1 (2.8, 3.4)	3.0 (2.6, 3.4)	0.59	3.3 (3.1, 3.6)	3.3 (2.8, 3.6)	0.65

QoR: Quality of recovery

study, none of the patients showed extrapyramidal or psychomotor side effects attributable to the use of haloperidol. Noteworthy, the dose of administered haloperidol in this study was small, considerably lower than those used for the management of agitation and psychosis. Moreover, we used the medication intra-operatively under the impact of anesthetics, which might blunt the extrapyramidal side effects of haloperidol.

Study limitations

We included a variety of surgeries in this study, which may induce different levels of pain, nausea and disability post-operatively. Another limitation of this study was short duration of follow-up being limited to the post-anesthesia care unit and 6 h post-operatively, while the half-life of haloperidol is approximately 18 h.

CONCLUSION

The available evidence suggests that a single dose of haloperidol 2 mg appears to be safe and effective when given as PONV prophylaxis. However, it may not improve the analgesic efficacy of morphine PCA and overall QoR. Further studies are required to better understand the mechanism of the analgesic interaction between intraoperative haloperidol and opioids.

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