Effect of ondansetron on prevention of post-induction hypotension in elderly patients undergoing general anesthesia: A randomized, double-blind placebo-controlled clinical trial

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ABSTRACT

Background: Elderly patients are susceptible to post-induction hypotension. Volume loading and vasopressors for prevention of hypotension in elderly patients may increase perioperative cardiovascular risks. Ondansetron by blocking Bezold–Jarisch reflex (BJR) through inhibition of serotonin receptors has been effective in the prevention of post-spinal hypotension, and bradycardia. Bradycardia frequently accompanies post-induction hypotension in elderly patients, which signifies a possible preventing role for ondansetron. No previous study has evaluated the prophylactic effects of ondansetron for the prevention of post-induction hypotension. **Materials and Methods:** In this randomized placebo-controlled clinical trial, ondansetron 4 mg was given intravenously to 65 elderly patients, 20 min before induction of general anesthesia, and the rate of post-induction hypotension defined as 25% or more reduction in mean arterial blood pressure, compared with a placebo groups. **Results:** A total of 114 patients completed the study (58 in ondansetron and 56 in the placebo group). Proportions of post-induction hypotension were 9 (16%) and 25 (45%) in ondansetron and placebo groups, respectively, (P = 0.001). Forty-five patients (40%) developed bradycardia. Rates of bradycardia were not significantly different between two groups. **Conclusions:** The results of this study show the effectiveness of intravenous ondansetron for prevention of post-induction hypotension in elderly patients. The mechanism of this effect largely is unknown. Role of ondansetron for prevention of post-induction hypotension may not fully understandable by its interaction with BJR, as has been shown in post-spinal hypotension.

Key words: *Elderly patients, general anesthesia, hypotension, ondansetron*

INTRODUCTION

Nearly all intravenous anesthetics may produce arterial hypotension. Hence, the induction of general anesthesia may result in decreased systemic vascular resistance and depression of cardiac function, which result in arterial hypotension, particularly in elderly patients.[1] Since cardiovascular reserves diminishes with increasing ages, elderly patients are particularly prone to the development of post-induction hypotension.[2] Intraoperative hypotension may have serious effects on postoperative outcome in terms of vital organ system functions.[3] Although vasopressors, inotropes, and intravenous fluid loading have established places in the treatment of intraoperative hypotension, they have questionable efficiency and safety for prophylactic use, and their benefits may be offset by unnecessary increase in myocardial work particularly in an aged heart.[4-9] Ondansetron, a serotonin receptor antagonist, has been used effectively for prevention of post-spinal hypotension.[10-13] The effect has been attributed to blocking Bezold–Jarisch reflex (BJR) by the inhibitory effects of ondansetron on serotonin receptors.[14] Though the incidence of BJR has not clearly been defined in elderly patients, recent observation denotes a bimodal age distribution of BJR.[15] Frequent association of bradycardia and hypotension after induction of general anesthesia in elderly patients warrants exploring prophylactic effects of

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blocking serotonin receptors on preventing post-induction hypotension in this age group. This clinical trial was designed to investigate prophylactic effects of intravenous ondansetron on preventing post-induction hypotension in a sample of elderly patients undergoing general anesthesia for elective operations.

MATERIALS AND METHODS

Ethics sub-committee of research department, faculty of medicine, Isfahan University of Medical Sciences, Isfahan, Iran (Chairman Dr. Siavash) approved this study on January 16, 2014 (proposal number 393598).

After written informed consent 120 American Society of Anesthesiology I or II patients 65 years of age or older scheduled for elective surgery enrolled prospectively in a double-blind, parallel groups clinical trial. Patients with a history of cardiorespiratory or renal disorders, those with preoperative bradycardia, tachycardia, hypo or hypertension and hyperglycemia were excluded from the study. The study was performed on spring 2014 at Al-Zahra Medical Center, a university teaching hospital located in Isfahan, central area of Iran. Preoperatively patients received 2 ml/kg of a 2/3 dextrose 5%-1/3 normal saline (0.9%) during fasting period. After recording baseline vital signs, patients were randomly divided into two groups to receive either intravenous ondansetron 4 mg in 10 ml normal saline or equal volume of normal saline as placebo. Twenty minutes after administration of ondansetron or placebo, anesthesia was induced with thiopental up to 5 mg/kg in divided dose until loss of consciousness, atracurium 0.5 mg/kg and fentanyl 1 μg/kg. After 3 min of mask ventilation, 50 mg of thiopental was administered, and trachea was intubated. Anesthesia maintained with isoflurane 1-1.2% in 50% N_2O plus 50% oxygen. Controlled ventilation continued with a rate of 10 breath/min and a tidal volume of 7-10 ml/kg aiming for an end-tidal carbon dioxide ($EtCO_2$) of 35-40 mmHg. Patients in whom mask ventilation or tracheal intubation proved difficult and those needed extra doses of anesthetics or muscle relaxant more than specified in the protocol, excluded from the study. Throughout the procedure blood pressure, heart rate (HR), oxygen saturation, and $EtCO_2$ were monitored noninvasively. Hypotension was treated with intravenous crystalloid (Ringer solution), incremental 5 mg doses of ephedrine and raising legs depending on the severity. In addition, inspiratory oxygen switched to 100% and isoflurane was discontinued during the hypotensive period.

Allocation list was produced using random allocation software,[16] with equal blocked design and 10 subjects per block. Ondansetron and placebo were prepared in similar syringes each labeled with a unique code according to the allocation list. The person responsible for administering syringes, anesthesia care, and data acquisition were not aware of the allocation list and contents of syringes.

Statistical analysis

Based on previous studies on the effect of ondansetron for prevention of post-spinal hypotension, and a pilot study on a sample of 30 subjects, a medium effect size was selected for ondansetron, and sample size was estimated as 50 subjects in each groups (total 100), considering a study power of 80% and a 0.05 significance level for difference between proportions.[17] Final sample size was selected as 120 subjects (60 in each groups) to compensate for possible drop outs.

Data were reported as mean (standard deviation) or *n* (%) where appropriate. Primary outcome variable in this study was proportions of patients with marked hypotension defined as a mean arterial blood pressure (MAP) at least 25% less than the basal value at any time during the first 20 min after induction of anesthesia before start of surgical procedure. Other outcomes of interest were proportions of patients with marked hypertension (at least 25% rise in MAP), bradycardia (HR <60 or >25% drop) and tachycardia (HR >100 or >25% rise). Frequency data like proportions of hypotension were compared between two groups using Fisher's exact test. Repeatedly measured data like blood pressure were compared between two groups using repeated measures analysis of variances. Other numerical data were compared between two groups using Student's *t*-test. $P < 0.05$ was considered as statistically significant. Decimal fractions rounded to the nearest integer. Statistical analysis was performed using R statistical software.[18]

RESULTS

A total of 130 eligible subjects from 261 subjects were enrolled in the study from February to May 2014 [Figure 1]. Sixteen patients were excluded from the study due to difficult airway (6 in ondansetron and 5 placebo) and need for higher anesthetic than scheduled (1 in ondansetron and 4 in the placebo group). Final analysis run on 114 subjects (58 in ondansetron and 56 in the placebo group). Baseline hemodynamic data were comparable between two groups [Table 1]. MAP significantly reduced after induction of anesthesia in both group ($P < 0.001$). Although the reduction of MAP was more pronounce in the placebo group, but was not significantly different from ondansetron group [Figure 2]. Thirty-four (30%) patients developed marked hypotension (22-39%, 95% confidence intervals) in both groups (9 in ondansetron and 25 in the placebo group). Systolic blood pressure was

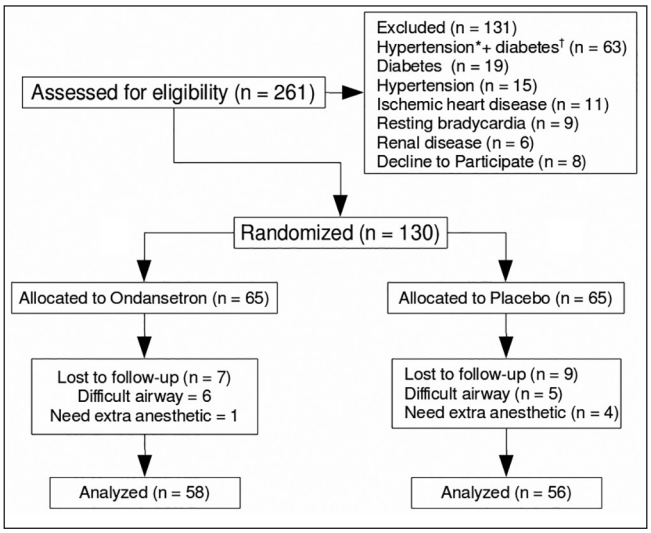

Figure 1: Subject enrollment, randomization, follow-up and final analysis. *Uncontrolled preoperative hypertension denoted by systolic and diastolic blood pressure >160 and 90 mmHg respectively. †preoperative hyperglycemia evidenced by fasting blood sugar higher than 250 mg/dl

Table 1: Comparing baseline data between ondansetron and placebo groups

Parameter	Ondansetron (*n* = 58)	Placebo (*n* = 56)
Age (year)	72 (6.2)	74 (5.9)
Weight (kg)	68 (9.3)	67 (8.3)
Height (cm)	163 (7.4)	164 (6.1)
Systolic blood pressure (mmHg)	138 (16.5)	143 (15.8)
Diastolic blood pressure (mmHg)	84 (11.0)	87 (10.2)
Mean blood pressure (mmHg)	103 (13.5)	107 (14.3)
HR (min^{-1})	77 (9.0)	79 (9.8)
Gender		
Female	26 (45)	21 (38)
Male	32 (55)	35 (62)
ASA		
I	27 (47)	19 (34)
II	31 (53)	37 (66)

Data are mean (SD) or *n* (%). No significant difference between two groups. HR: Heart rate; SD: Standard deviation; ASA: American Society of Anesthesiologists

<90 mmHg in all hypotensive cases. Proportion of patients with marked hypotension after induction was significantly lower in the ondansetron group compared with the placebo group, but association of hypotension with bradycardia or tachycardia was not significantly different in two groups [Table 2]. There was no significant difference between two groups with respect to the proportions of post-induction bradycardia, tachycardia and hypertension [Table 2].

DISCUSSION

Results of this study shows that prophylactic ondansetron before induction of general anesthesia lowers the incidence of post-induction hypotension in elderly patients. This is evident from 65% reduction in relative risk for post-induction hypotension by prophylactic administration of ondansetron. This effect is not associated with an accompanying inhibition of bradycardia, which is evident from a relative independence of bradycardia and hypotension in both groups.

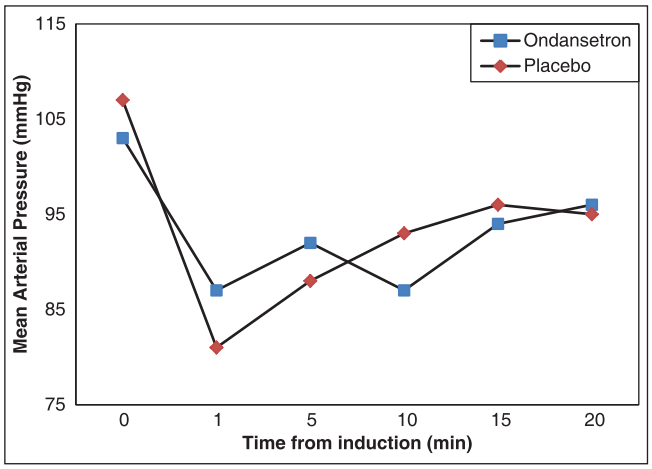

Figure 2: Mean arterial blood pressure before induction and up to 20 min after induction in ondansetron (solid line) and placebo (dashed line) groups. Data points are mean (standard deviation of the mean). Blood pressure significantly decreased after induction of anesthesia ($P < 0.001$), but the drop was not significantly different between two groups (repeated measure analysis of variance)

Previous researches into the effects of intravenous ondansetron on prevention of post-spinal hypotension differ from the present study with respect to the cause of hypotension. Spinal anesthesia invariably is associated with arterial hypotension, while general anesthesia is associated with both hypotension and hypertension. Most anesthetics cause vasodilation and decrease in myocardial contractility while airway manipulation after induction of anesthesia tends to increase the blood pressure. The net effect may be a wider spectrum of arterial blood pressure variation, which invalidate using central tendency statistics such as mean, as a reliable surrogate for studying prophylactic effect of drugs on post-induction hypotension. This may be the reason behind nonsignificance of differences in blood pressure means between two groups, while they were significantly different with respect to proportions of hypotensive subjects.

The results of this study show that hypotension irrespective of prophylactic ondansetron, are not necessarily associated with bradycardia in elderly patients. Only half of hypotensive subjects exhibit accompanying bradycardia while the rest may have tachycardia or have relatively normal HRs. It is worth emphasizing that, similar to blood pressure, the effects of various mechanisms contributed

Table 2: Proportions of patients with marked hypotension, hypertension, bradycardia and tachycardia after induction of anesthesia in ondansetron and placebo groups

Parameter	Ondansetron (*n* = 58)	Placebo (*n* = 56)	Risk ratio (95% CI)	Risk difference (95% CI)
Hypotension	9 (16)*	25 (45)	0.35 (0.18-0.68)	−29 (−45-13)
Hypertension	15 (26)	17 (30)	0.85 (0.47-1.54)	−4.5 (−21-11)
Bradycardia	21 (36)	24 (43)	0.85 (0.54-1.33)	−6.7 (−25-11)
Tachycardia	14 (24)	20 (36)	0.68 (0.38-1.2)	−11.6 (−28-5)
Hypotension and bradycardia	6 (10)	11 (20)	—	—
Hypotension and tachycardia	2 (3)	10 (18)	—	—

*P = 0.001 compared to placebo group, relative risk = 0.35 (0.18-0.68 95% CI). Data are *n* (%). Hypotension, hypertension, bradycardia and tachycardia were defined as a change of at least 25% in MAP or HR, compared to basal values at any time during the first 20 min after induction of anesthesia and before start of surgical procedure. Bradycardia and tachycardia were also defined as a HR <60 or higher than 100 respectively. CI: Confidence interval; HR: Heart rate; MAP: Mean arterial pressure

in post-induction changes in HR may be different. For example tachycardia during anesthesia could be associated with hypotension, hypovolemia or an inflammatory response, however, other mechanisms such as negative inotropy of induction agents, BJR and an increase in baroreflex activity prone patients to bradycardia.[10,11,19] Therefore, HR may change differently in response to induction among patients, which can justify independence of bradycardia and hypotension in both groups of our study. This is in accordance with previous studies, which showed different chronotropic response in hypotensive elderly patients compared to younger subjects.[20-22] Owczuk *et al*. also declared the predictable blockade of the BJR reflex by ondansetron did not result in significant changes in HR after spinal anesthesia.[10]

The exact mechanism by which ondansetron prevents hypotension after induction of general anesthesia in elderly patients is unknown and cannot be sufficiently defined by the role of BJZ reflex via 5-HT3 receptors located in intracardiac vagal nerve endings which has been described for post-spinal hypotension.[10,11,13] Perhaps factors other than the serotonin receptors may have roles in ondansetron-induced prevention of post-induction hypotension particularly in elderly subjects. In addition prevention of serotonin-induced tachycardia by ondansetron may prevent shortening of diastolic period and enhance contractility by improving coronary perfusion in an aged heart.[23] A recent study on prophylactic effect of ondansetron in elderly patients after spinal anesthesia, has shown the effectiveness of ondansetron for preventing diastolic (and MAP) hypotension, but prophylaxis against bradycardia and systolic hypotension was not effective.[24]

To our best knowledge, this study is the first one studying effect of prophylactic ondansetron for prevention of post-induction hypotension in elderly patients. There is no clear guideline for the best time interval from intravenous ondansetron administration to the induction of anesthesia for this particular application of ondansetron. The selected interval of 20 min was chosen based on the previous studies, which given ondansetron 5 min before induction of spinal anesthesia, which roughly equals 20 min before occurrence of anticipated post-spinal hypotension.

Selecting a proper induction agent in elderly patients may present a clinical challenge, which needs proper assessment of myocardial and circulatory function. Most intravenous anesthetics may produce systemic vasodilatation and depressed myocardial function. Midazolam though produce less severe circulatory depression, in geriatric patients, it may prolong postoperative recovery period and increase rates of oxygen desaturation.[25] Etomidate has the lowest depressant effect on myocardial function, but it is associated with a high prevalence of seizure activity.[26] Thiopental and propofol are the commonest induction agents. Again their usage in elderly patients is associated with hypotension and bradycardia. The rational behind choosing thiopental in this study was the result of previous studies, which showed a greater incidence of hypotension with propofol compared to thiopental.[27,28] Based on the result of the current study we can recommend using thiopental for induction of anesthesia in elderly patients, provided an intravenous dose of ondansetron is given 20 min earlier. Weather ondansetron can prevent hypotensive effects of propofol need to be answered in future studies.

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