Efficacy of Dexamethasone in Attenuation of Postinduction Hypotension in Geriatric Patients Undergoing General Anesthesia: A Randomized Controlled Trial

Original Article

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ABSTRACT

Background: Postinduction hypotension (PIH) in geriatric patients has deleterious effects. Avoidance of PIH in this group of patients should result in lower perioperative morbidity and mortality. Dexamethasone is known for its vasopressor enhancing effect. The efficacy of preoperative dexamethasone to avoid PIH in geriatric patients was tested in this study.

Results: Demographic data were comparable between both groups. The systolic blood pressure (SBP) readings at 1- and 2-minutes were lower in control (C) group ($P < 0.001$). The diastolic blood pressure (DBP) and the mean blood pressure (MBP) readings were lower in group C at 1 ,2, and 5 minutes ($P < 0.001$). The proportion of patients who suffered significant hypotension (primary outcome) was significantly higher in group C ($P = 0.009$). Patients in group C significantly needed IV fluids boluses, boluses of ephedrine, both ephedrine and IV fluids boluses more than patients in (dexamethasone (D) group) ($P = 0.039$, P = 0.009, $P = 0.031$, respectively).

Conclusions: A preemptive single dose of 8 mg dexamethasone attenuated the postinduction hypotension in geriatric patients scheduled for general anesthesia.

Key Words: Dexamethasone, general anesthesia, geriatric patients, hypotension.

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BACKGROUND

The improvement in the medical service during the few past decades was reflected by the increase in the overall population age. Consequently, anesthesiologists are increasingly being asked to anesthetize geriatric patients for surgical and other diagnostic procedures. By 2050, twenty percent of the population will be 60 years or older. That's why, the United Nations general assembly declared 2021–2030 "The decade of healthy ageing"[1,2].

Perioperative hypotension may cause perioperative morbidities especially in elderly[3–6]. In healthy young adults, cerebral autoregulation protects the brain from fluctuations of blood pressure. On the contrary, elderly has impaired cerebral autoregulation which makes them more vulnerable to cerebral hypoperfusion during hypotensive episodes[7]. Other vital organs in geriatric population are also affected during hypotension due to impaired vascular autoregulation. Acute kidney injury and myocardial ischemia are direct consequences of intraoperative hypotension with increased perioperative mortality[8]. Accordingly, all measures to avoid hypotension in geriatric patients should be taken into consideration to prevent perioperative morbidities and mortalities[5].

Perioperative hypotension can be further classified into postinduction hypotension (PIH) which is limited to twenty minutes after induction of anesthesia, early intraoperative hypotension (EIH), which is detected during the first thirty minutes of surgery and late intraoperative hypotension (LIH) which refers to hypotension occurring after 30 minutes of surgery[9]. Induction of anesthesia is usually associated with some degree of hypotension. Most induction agents exert vasodilator and negative inotropic effects[3]. The vasodilatory effect of propofol, and other opioid analgesics causes hypotension which sometimes force the anesthesiologist to use vasopressors[10]. The association of bradycardia and hypotension that frequently occur during the induction of general anesthesia could result in deleterious effects in elderly patients[11].

5-HT3 receptors antagonists have been tried with success in the management of post-spinal anesthesia hypotension which has been attributed to antagonism of Bezold-Jarisch reflex (BJR)[12]. Despite that BJR has not been clearly characterized in elderly patients, clinical perception proposes that it has a bimodal age distribution[11]. Vasopressors are widely used to elevate Mean Arterial Pressure (MAP) during hypotension. Yet

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this is accompanied by a simultaneous increase in the after load and subsequent decrease in cardiac output[13].

Dexamethasone is a synthetic glucocorticoid without mineralocorticoid activity that is used as an anti-inflammatory drug for a multitude of indications. It poses a vasopressor effect and causes systemic hypertension. The mechanism of glucocorticoid induced vasoconstriction is not yet fully understood[14] yet its pressor effect on the peripheral vascular resistance have been proposed[15]. Added to this, glucocorticoids generally inhibit 5-HT3 expression and dexamethasone specifically reduces central 5-HT3 levels in rats[15].

The frequent association of bradycardia with hypotension after induction of GA in elderly patients demands the updated use of prophylactic pharmacological agents that either block serotonin receptors or exert a peripheral vasoconstrictor effect or both for prevention of PIH in elderly patients. The authors hypothesized that administrating dexamethasone - with its unique pharmacological characteristics- to geriatric patients before induction of GA would decrease the episodes of PIH.

METHODS

Ethics

This study was conducted after getting the approval of the ethical committee (FMASU MS 289/ 2021) and was prospectively registered at ClinicalTrials.gov (NCT04908592). Patients were recruited into the study from 15th of June to 15th of September 2021. Every patient signed an informed consent before being enrolled in the study. This study followed the regulations of the Declaration of Helsinki-2013.

Study Population

One hundred geriatric patients, aged above 60 years, of both sexes, American Society of Anesthesiologists (ASA) physical status I or II undergoing elective surgeries under GA were recruited in the study. Patients presenting with suspected difficult airway, ischemic heart disease, uncontrolled hypertension (blood pressure above 160/90 mmHg), hypotension (blood pressure below 100/60 mmHg), heart rate below 60 beats/minute, peptic ulcer, active infection, psychiatric disorders and patients on steroid therapy or serotonin related medications were excluded from this study.

Randomization and Blinding

Patients were randomly assigned to two groups (50 each), dexamethasone (D) group and Control (C) group, using a computer-generated random numbers. Group D patients received a single dose intravenous infusion (IVI) of 8 mg dexamethasone diluted in 100 ml of 0.9 % sodium chloride (normal saline) (NS) infusion over 15 min, 2 hours before surgery. While, Group C patients (negative placebo-control) received an equal volume of plain NS as a placebo infusion. Both solutions were prepared by the hospital pharmacist who received the computer-generated allocation of each patient. The pharmacy delivered the solutions to the ward nurses to be given to patients. Follow-up notes were recorded by anesthesia residents. Patients, ward nurses, surgeons and anesthesia residents were blinded to to the solution composition and the patient's group assignment.

Study protocol

Patients were fasting for eight hours before surgery and were not intravenously hydrated. Baseline parameters such as Blood Pressure (BP) readings; systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP) and heart rate (HR) were recorded and at 1, 2, 5, 10, 15, 20 minutes post-induction. General anaesthesia was administered with 1mg/kg IV propofol, 1μg/kg IV fentanyl and 0.5 mg/kg IV atracurium and endotracheal intubation was done after 3 minutes of mask ventilation and the infusion of Ringer acetate of 100 – 150 ml/hour as a maintenance solution was initiated.

Anesthesia was maintained with isoflurane 1-1.2 % in 50 % oxygen and air to keep the bispectral index (BIS) value at 40–60 and intermittent doses of muscle relaxant if needed to maintain adequate muscle relaxation throughout the surgery. Controlled ventilation was initiated at a rate of 10 breath/min and a tidal volume of 7 ml/kg targeting end-tidal carbon dioxide (EtCO2) of 35-40 mmHg. Patients with difficult mask ventilation and/or tracheal intubation that necessitated extra doses of anesthetics or muscle relaxant were excluded from the study. Basic monitoring standards (Non-invasive blood pressure, HR, oxygen saturation, and EtCO2) were continuously monitored. Hypotension was considered if MBP drops > 25 % of base line reading and was managed by an infusion of 250 ml ringer acetate with/ without incremental doses of 5 mg ephedrine intravenously up to 50 mg and raising legs depending on the severity. In addition, inspiratory oxygen was switched to 100 % and isoflurane was discontinued during the hypotensive period. Bradycardia was defined as HR < 50 bpm and was corrected with 0.5 mg atropine intravenously. The risk of hyperglycaemia (blood glucose level > 200 mg/dL) was treated with insulin using the Insulin sliding scale. No interventions including skin incision, patient positioning or raising tourniquets were allowed till after 20 minutes of induction.

The primary outcome of this study was the proportion of patients who suffered significant hypotension "defined as a (MAP) at least 25 % less than the basal value" at any time during the first 20 minutes after induction of general anaesthesia and before starting the surgical procedure. The need for IV fluid bolus infusion and IV atropine, the postoperative nausea and vomiting (PONV) and the postoperative shivering were secondary outcomes. The need for ephedrine including the dose, time of need and rate of need for IV ephedrine boluses were also secondary outcomes.

Statistical analysis

Power of the Study

Based on similar previous research, a minimal sample size of 38 patients in each group was appropriate to keep a statistical significance when the assumed marked post-induction hypotension between the ondansetron group and the placebo group was 16.0 % and 45 % respectively[11] with setting the power = 0.80 and α=0.05 and using PASS 11th release[16]. The investigators enrolled 50 cases per group to compensate for possible attrition and finding possible adverse events.

Data Analysis

IBM Statistical Package for Social Sciences (SPSS) version 22.0, IBM Corp., Chicago, USA, 2013 was used for data management and analysis. Normal quantitative distributed data were described as mean ± SD (standard deviation) after testing for normality using Shapiro-Wilk test, then were compared using independent t-test (two independent groups) and paired t-test (paired data). Qualitative data were described as number and percentage and were compared using Chi square test and Fisher's Exact test for variables with small expected numbers. Log rank test was used to compare rates. Relative effects were presented as relative risk and its 95 % confidence interval for qualitative outcomes as well as mean ± SE and its 95 % confidence interval for quantitative outcomes. A *p-value* < 0.050 was used as a significance cut point.

RESULTS

Among 126 eligible patients, 26 patients were excluded. 100 patients were enrolled in the study and randomly allocated (50 each) into group D and group C. Statistical analysis was performed for data of 43 patients in group D and 44 patients in group C. This was attributed to unanticipated difficult airway and need of extra anesthetics in some cases Figure 1. Patient characteristics were comparable in both groups, as regards the demographic data, comorbidities, preoperative medications, and type of surgeries Table 1.

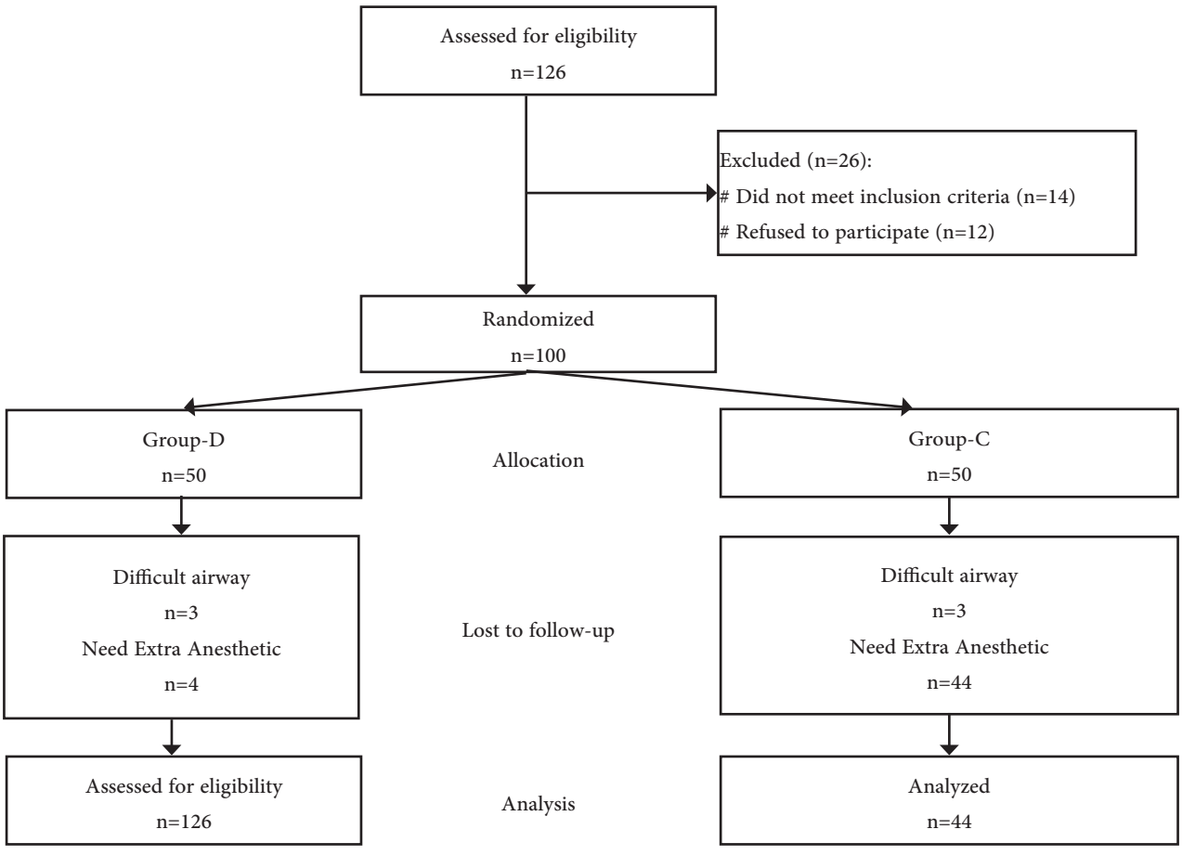

Figure 1: Flow chart of the studied cases

Table 1: Baseline characteristics between the study groups:

Variables	Measures		Group-D (n=43)	Group-C (n=44)	*p-value*
	Age (years)		67.5±3.7	66.6±4.5	^0.326
Sex, (n, %)	Male		27 (62.8%)	29 (65.9%)	#0.761
	Female	16 (37.2%)	15 (34.1%)		
	BMI (kg/m^2)		30.8±2.3	31.1±2.1	^0.584
ASA, (n, %)	II		43 (100.0%)	44 (100.0%)	NA
	Diabetes mellitus, (n, %)		23 (53.5%)	25 (56.8%)	#0.755
	Renal impairment, (n, %)		14 (32.6%)	12 (27.3%)	§0.590
	Hypertension, (n, %)		41 (95.3%)	40 (90.9%)	§0.676
	Antihypertensive medications	Beta blockers	39 (90.7%)	37 (84.1%)	#0.354
	ACEI 22 (51.2%)	24 (54.5%)	#0.752		
	ARBs 12 (27.9%)	10 (22.7%)	#0.578		
	CCBs 16 (37.2%)	14 (31.8%)	#0.597		
Operation Types	Arm and Forearm Fractures		19 (44.2%)	16 (36.4%)	§0.968
	Shoulder Arthroscopy		4 (9.3%)	5 (11.4%)	
	Posterior Approach Spinal Surgery		6 (14.0%)	7 (15.9%)	
	Modified Radical Mastectomy (MRM)		9 (20.9%)	10 (22.7%)	
	Percutaneous Nephrolithotripsy		5 (11.6%)	6 (13.6%)	

Data are presented as mean ± SD or number of patients and (%). ^Independent t-test. #Chi square test. §Fisher's Exact. NA: Not applicable. ASA: American Society of Anesthesiologists.

The HR readings were comparable among both groups Figure 2. The SBP readings were comparable for both groups except at 1- and 2-minutes at which the readings were significantly lower in group C compared with group D ($P < 0.001$) Figure 2. The DBP and MBP readings were also significantly lower in group C compared to group D only at 1- ,2-, and 5-minutes ($P < 0.001$) Figure 2. The SBP, DBP and MBP readings at follow up throughout the study interval were significantly lower than baseline reading at both groups (*P value* < 0.001) Figure 2.

Patients in group C significantly needed IV fluids boluses, boluses of ephedrine, both ephedrine and IV fluids boluses more than patients in group D ($P = 0.039$, $P = 0.009$, $P = 0.031$, respectively) Table 2. The Rate of need for ephedrine was significantly lower in group D patients in comparison to group C patients ($P = 0.006$) Figure 3. The time of need for ephedrine was significantly shorter in group C patients compared with group D patients ($P= 0.020$) Table 2. The need of atropine was comparable between the study groups. Patients in group D significantly developed less postoperative nausea, vomiting and shivering than those in group C ($P = 0.007$, $P = 0.031$, $P = 0.001$, respectively) Table 2.

Table 2: Side effects and treatments between the study groups:

Findings	Group-D (n=43)	Group-C (n=44)	*p-value*	Relative effect Relative risk (95% CI)
Nausea	5 (11.6%)	16 (36.4%)	#0.007*	0.32 (0.13 – 0.80)
Vomiting	4 (9.3%)	12 (27.3%)	#0.031*	0.34 (0.12 – 0.98)
Shivering	6 (14.0%)	20 (45.5%)	#0.001*	0.31 (0.14 – 0.69)
Post-induction hypotension	6 (14.0%)	17 (38.6%)	#0.009*	0.36 (0.16 – 0.83)
Boluses of IV fluids	5 (11.6%)	13 (29.5%)	#0.039*	0.39 (0.15 – 1.01)
Ephedrine	6 (14.0%)	17 (38.6%)	#0.009*	0.36 (0.16 – 0.83)
Boluses of IV fluids and Ephedrine	4 (9.3%)	12 (27.3%)	#0.031*	0.34 (0.12 – 0.98)
Atropine	10 (23.3%)	9 (20.5%)	#0.752	1.14 (0.51– 2.52)
Atropine and Ephedrine	5 (11.6%)	8 (18.2%)	#0.391	0.64 (0.23 – 1.80)
				Mean ± SE 95% CI
¤Time of need for Ephedrine (min)	4.0±1.3	2.4±1.4	*0.020^	1.6 ± 0.7 (0.3 – 3.0)

Data are presented as mean ± SD or number of patients and (%). ^ Independent t-test. # Chi square test. § Fisher's Exact test. ¤ In cases needed ephedrine (n=6, 17 respectively) . CI: confidence interval. Relative effect: effect of group-D relative to group-C. * Significant.

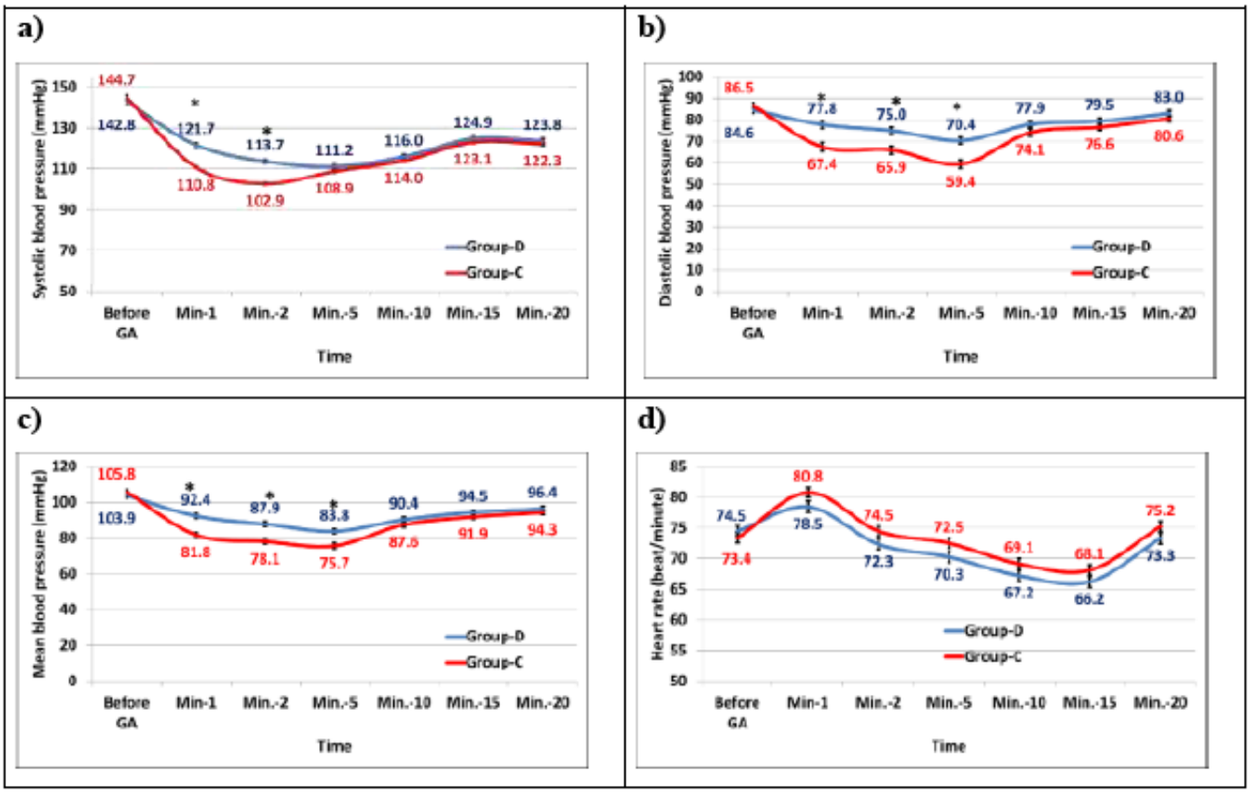

Figure 2: Hemodynamic variables between the study groups, a; Systolic blood pressure, b; Diastolic blood pressure, c; Mean blood pressure, d; Heart rate. (* denotes significant difference between groups at the that time point)

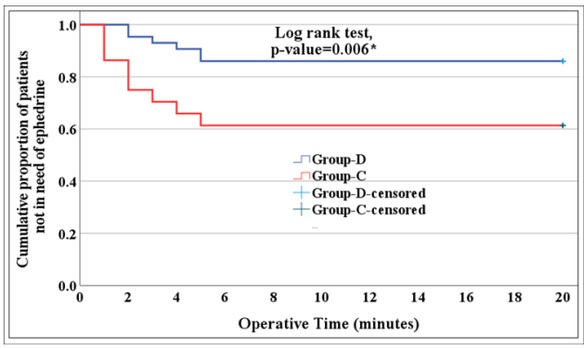

Figure 3: Kaplan-Meier curve for rate of need to ephedrine between the study groups (*Significant)

DISCUSSION

Results of this study showed superior hemodynamics in the group D compared to group C during the postinduction period in geriatric patients undergoing GA. Concomitant with the lower incidence of PIH in the group D, these patients required less interventions to keep within the normal blood pressure. This was evident by the fact that they needed less boluses of IV fluid, IV ephedrine or both when compared with the group C. A prior study also proved the effectiveness of a single dose of preemptive 8 mg dexamethasone to avoid post spinal anesthesia hypotension with significantly lower needs to administer boluses of IV ephedrine. The effect of preoperative dexamethasone described by the previous research resembles that recorded in our current study, despite the difference in the anesthetic technique[15].

PIH is common especially in elderly patients receiving propofol as an induction anesthetic agent. The concomitant usage of high doses of fentanyl is also associated with PIH even in ASA I and II patients[17]. Incidence of Cerebrovascular stroke and early postoperative mortality is increased with perioperative hypotension and bradycardia[18]. Even transient episodes of hypotension during anesthesia can be associated with postoperative cardiovascular morbidities[19]. Geriatric patients are frequently encountered for surgeries and other diagnostic procedures requiring GA. They are at more risk of PIH and perioperative morbidities[20].

Here came the importance to tackle any episode of hypotension, especially in this group of patients. Dexamethasone is a synthetic steroid that poses intense glucocorticoid activity with a half-life of 36 to 54 hours. It is used in a multitude of diseases, one of which is its use as a vasoconstricting agent in shock states[21]. The side effects of steroid therapy are dose and duration dependent. Hence, the authors assumed that a single dose of dexamethasone preoperatively will help to maintain adequate systemic blood pressure during the post-induction period without expected major side effects[22].

The obtained results in this study denoted that dexamethasone abolished the vasodilatory effects of the used anesthetics, which were clearly reflected on the hemodynamics in the postinduction period. Dexamethasone could have done this increase in BP via two mechanisms; The first one is the inhibitory effect on nitric oxide (NO) through the glucocorticoid induced increase in the reactive oxygen species (ROS) which hinder the action of NO on vascular smooth muscle cells (VSMCs). It also decreases the endothelial nitric oxide synthetase which lowers the NO available for vasodilation. In addition to inhibiting NO, glucocorticoids also inhibit the prostacyclin (PGI2) which is the other vasodilator mediator in VSMCs[23]. The other mechanism is through the potentiating effect on both endothelin-I and angiotensin II, the well-known vasoconstricting mediators in VSMCs[24].

Acute effects of glucocorticoids are protective whereas the long-term use can cause severe adverse events. The protective effects include better regulation of metabolism, homeostasis and maintenance of the vasomotor tone whereas the harmful effects include all the known side effects of glucocorticoids, as hyperglycemia, dyslipidemia and hypertension[21,22,25].

While maintaining adequate perfusion pressure, avoidance of sympathomimetics is beneficial in these vulnerable group of patients. This can be attributed to the fact that these drugs pose sometimes deleterious effects on the cardiovascular system. Sympathomimetic drugs can directly cause tachycardia, arrhythmias and electrolyte imbalance especially in elderly[26]. Phenylephrine can indirectly cause severe reflex bradycardia which may not be tolerated in such patients[27].

Results of this study revealed lower incidence of nausea, vomiting and shivering in group D in comparison to group C. Dexamethasone is already known with its antiemetic effect[28,29]. Moreover, prior studies documented that dexamethasone reduced postanesthetic shivering[29,30].

The authors of this study concluded that a single dose of 8 mg dexamethasone given preoperatively protected geriatric patients from PIH. In addition, preemptive dexamethasone limited the use of sympathomimetic drugs which can have unfavorable side effects on such group of patients. It also had an added benefit to reduce postoperative nausea, vomiting and shivering.

This study had some limitations: First, this research did not include other adverse events of using dexamethasone, as hyperglycemia and wound infection. This was attributed to previous studies which did not report such adverse events with a single dose of preemptive dexamethasone [29]. Second, the conduct of this clinical research in resource-poor and constrained settings in a developing country like Egypt necessitated a cost-effectiveness analysis of the study drugs including vasopressor medications. Third, this study was conducted in a single center. However, double-blind randomization prevented selection bias and increased objectivity among researchers.

If there's one thing that everybody knows it's: 'prevention is better than cure'. It holds true for prevention of PIH also and it should be practiced. Since the proposed protocol is efficacious, inexpensive and relatively safe, the research team recommends to focus more on prevention of PIH in geriatric patients undergoing GA. Moreover, this protocol diminished volume loading or vasopressor use which might increase the risk of hypervolemia as well as myocardial ischemia. Further studies are needed to confirm our findings in more invasive operations and in patients with cardiovascular instability.

CONCLUSION

A preemptive single dose of 8 mg dexamethasone attenuated the postinduction hypotension in geriatric patients scheduled for general anesthesia.

ABBREVIATIONS

ASA: American Society of Anesthesiologists; **BP:** Blood Pressure; **DBP:** diastolic blood pressure; **EIH:** early intraoperative hypotension; **HR:** heart rate; **IVI:** intravenous infusion; **LIH:** late intraoperative hypotension; **MAP:** Mean Arterial Pressure; **MBP:** mean blood pressure; **NO:** Nitric oxide; **NS:** Normal saline; **PIH:** postinduction hypotension; **PONV:** postoperative nausea and vomiting; **PGI2:** prostacyclin; **ROS:** reactive oxygen species; **SBP:** systolic blood pressure; **SD:** Standard deviation; **VSMCs:** vascular smooth muscle cells.

CONFLICT OF INTERESTS

There are no conflicts of interest

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