Dexamethasone Blunts Post-Spinal Hypotension in Geriatric Patients Undergoing Orthopedic Surgery: A Double Blind, Placebo-Controlled Study

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Abstract

Background. Post-spinal hypotension in elderly is challenging, correction by fluids either colloids or crystalloids or by vasoconstrictors pose the risk of volume overload or compromising cardiac conditions. Dexamethasone is used to treat conditions manifested by decrease of peripheral vascular resistance; we were the first to test the hypothesis of its role in preventing or decreasing the incidence of post-spinal hypotension.

Methods. 110 patients aged 60 years or more were recruited in the study, 55 in the Dexamethasone group (D group) were given 8 mg Dexamethasone 2 hours preoperatively, and 55 were given placebo (C group).Variations in blood pressure and heart rate and need of vasoconstrictors and/or atropine following spinal anesthesia (SA) was done. SA was done by subarachnoid injection of 3 ml of hyperbaric bupivacaine.

Results. Demographic data and the quality of sensory and motor block were comparable between groups. At 5, 10 minutes; systolic, diastolic and, mean arterial pressures were significantly higher in group D. At 20 minutes readings were non significant between groups. Heart rate changes didn't show any significance. Need for ephedrine was less in group D, side effects were less in the D group.

Conclusion. Dexamethasone may attenuate post-spinal hypotension in elderly, with a favorable response against nausea, vomiting and shivering that associate spinal anesthesia.

Background

Spinal anesthesia (SA) is preferred by anesthetists in elderly patients however, its common and sometimes dangerous complications may limit its use. Hypotension and bradycardia are the most frequent reaching up to one- third in non-obstetric populations [(1)]. The main cause of post-spinal hypotension is the decrease in the sympathetic outflow causing arterial vasodilatation, decrease in venous return and consequently the activation of the Bezold Jarish reflex (BJR) [(2)] that elicit a triad of bradycardia, vasodilatation and further hypotension [(3, 4)]. BJR is elicited by activation of 5-HT_3 receptors within the intracardiac vagal nerve endings [(5)]. Those effects are prominent in senile patients with post-spinal hypotension estimated to be over 70% [(5)]. On the other hand, methods that are used to avoid the hypotension (e.g., volume loading or vaso-pressor administration) may add the risk of hypervolemia and/or myocardial ischemia for those patients [(6)].

Dexamethasone (DEX) – a synthetic glucocorticoid- is used to abolish post-spinal nausea and vomiting [(7)] or shivering [(8)], and may increase the duration of sensory block [(9, 10)]. Dexamethasone increased tissue peripheral vascular resistance (PVR) in rats [(11)] and humans by a variety of mechanisms [(12)], and there is a plethora of studies confirming its role in maintaining the integrity of circulation in situations of intense vasodilatation like septic shock [(13)] and anaphylaxis [(14)]. Moreover, glucocorticoids in general inhibit 5-HT

expression and DEX was found to decreased the level of 5-HT in the cerebral cortex and hippocampus in developing rats [15].

This study was conducted to test the hypothesis that the prophylactic intravenous infusion of DEX attenuates post-spinal hypotension.

Methods

Approval of the ethical committee of Ain-Shams University Hospitals was obtained before commencement of the study. This randomized, prospective, double blind, study, **adheres to CONSORT guidelines** and was conducted at Ain-Shams university hospitals from the 1st of March 2018 till the 31st of August 2018 on 110 ASA I, II, III patients aged 60 years or more and scheduled for lower limb orthopedic surgeries under SA after obtaining an informed written consent. Patients with contraindication to SA (e.g. coagulopathy, thrombocytopenia, allergy to local anesthetic agent) and those on steroid or serotonin related medications (e.g. selective serotonin reuptake inhibitor) were excluded.

Randomization was done using computer-generated number table of random numbers in a 1:1 ratio in opaque and sealed envelope (SNOSE). Study medications was prepared by the hospital pharmacy and given by a resident not involved in any other part of the study. A total of 55 patients were randomly allocated to each of two groups, patient received either 8 mg of DEX in 100 ml normal saline (NSS) (D group) or an equal volume of plain NSS (C group) 2 hours preoperatively. Patients fasted 8 hours and were not intravenously hydrated before the procedure.

Pulse oximetry, electrocardiogram monitoring, and non-invasive arterial pressure measurement were hooked, and patients were sedated by 1 mg of IV midazolam. NSS infusion was commenced not to exceed 400 mL during SA and for 20 minutes thereafter. SA was performed by injecting 3 ml of 0.5% hyperbaric bupivacaine solution (Marcaine® Spinal 0.5% Heavy; Sunny pivacaine, Manufactured by Sunny Pharmaceutical - Cairo - Egypt) at L3-L4 or L4-L5 level using 25gauge Quincke spinal needle.

After completing the subarachnoid injection, patients were positioned supine. Sensory level (by alcohol swab) and motor block (Modified Bromage Score [16]) was assessed every 5 minutes. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) were recorded before giving the study medication (base line) and then during SA every 5 minutes for 4 readings.

Hypotension was considered if there was 25% decrease below the baseline for MAP and was managed by 300 ml of NSS with incremental intravenous 5 mg doses of ephedrine. Bradycardia was considered if the heart rate was less than 50 beats/min and was treated with IV atropine (0.01 mg/kg), only data before giving ephedrine and/or atropine were analyzed if they were given.

Analysis was done by comparing the obtained c values at each study time point and comparing the minimal values recorded within the 20 minutes following the blockade. Surgical procedure, positioning

the patient or application of tourniquet was not allowed during the study period. Changes in the MAP, SAP, and DAP were set to be the primary outcome, while the pattern of motor and sensory block, number of patients who needed atropine and/or ephedrine and, changes in heart rate were considered as secondary outcomes.

Statistical analysis

Depending on **Baig et al.,2017** [17] who found that the hypotension rate in ondansetron and normal saline groups 7.5% and 28.3% respectively, and assuming the power = 0.80 and α = 0.05 and by using PASS 11th release the minimal sample size for an equal size controlled clinical trial is 50 in each group. We recruited 55 in each group for possible attrition [18].

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 18.0, IBM Corp., Chicago, USA, 2009.

Descriptive statistics were done for quantitative data as minimum& maximum of the range as well as mean (SD) (standard deviation) for quantitative normally distributed data, while it was done for qualitative data as number and percentage.

Inferential analyses were done for quantitative variables using Shapiro-Wilk test for normality testing, independent t-test in cases of two independent groups and paired t-test in cases of paired data. In qualitative data, inferential analyses for independent variables were done using Chi square test for differences between proportions and Fisher's Exact test for variables with small expected numbers. The level of significance was taken at P value < 0.050 is significant, otherwise is non-significant.

Results

Out of 136 patients who were assessed for eligibility, 110 patients were analyzed, 55 in the D group and 55 placebo one. Demographic data in the study population were comparable between groups with no significant differences between them. **(Table 1)**

Assessment was done after subarachnoid block and ended 20 minutes later. Number of segments above S1 was non-significantly lower in group-C than in group-D from minute-5 afterwards. Number of segments above S1 significantly increased in both groups beginning from minute-5 afterwards. Time to complete motor block was non-significantly shorter in group-D than in group-C. **(Table 2)**

SBP at 5 and 10 minutes was significantly higher among group-D, while DBP and MBP at 5,10 and 15 minutes were significantly higher among group-D **(Table 3)**, on the other hand there were non-significant changes between groups in HR. **(**Fig. 2**)**

Minimum readings in SBP, DBP and MBP were significantly lower among group-D, while the minimum reading in HR shows non-significant differences between groups. **(**Fig. 3**)**

The need of ephedrine was significantly less in group D (P = 0.025), while there were no significant changes in the need of atropine (P = 0.0303) or those who needed atropine and ephedrine (P = 0.429). The time to ephedrine and/or atropine need was non significant between groups. Nausea, vomiting and shivering were less in group D. **(Table 4)**

Discussion

The main value of this study is that pre-spinal administration of dexamethasone 8 mg intravenously in geriatric patients may attenuate post-spinal hypotension. The research team observed higher minimal values of systolic, diastolic and mean arterial pressures in dexamethasone group, with minimal effects on heart rate. As far as the authors know, we were the first to raise that observation and proposed that theory.

The investigators observed that patients who were on steroids for different reasons and had spinal anesthesia had favorable post spinal hemodynamic outcome with minimal hypotension and accordingly minimal need for vasoconstrictors. This proposed the theory of the value of steroids in obtunding the post-spinal hypotension.

SA is considered safe for elderly patients undergoing orthopedic surgeries however, the associated hypotension and/or bradycardia may have detrimental consequences on their cardiac and mental compromised condition [19]. Morbidity associated with hypotension includes but is not limited to a higher incidence of nausea, vomiting, dizziness, aspiration, syncope and cardiac arrhythmias[20].

DEX is a potent synthetic glucocorticoid that has pure glucocorticoid activity [12]. It increases PVR by a variety of mechanisms i.e. decrease vasodilator nitric oxide (NO), increase sympathetic activity and elevate plasma dopamine and epinephrine. It also increases the sensitivity of vascular endothelium to different vasoconstrictors. [12] Moreover, it has an anti $5HT_3$ effects which might influence BJR [12]. Those two effects hit exactly the two pathophysiologic effects incriminated in eliciting post-spinal hypotension [2], and explain our results and confirm our conclusion. (Fig. 4)

Methods to alleviate post-spinal hypotension either physical e.g. leg wrapping, elastic stockings, optimizing patient's position, or pharmacological e.g. intravenous fluids and vasopressors have been used with varying degree of success [20]. The usual measures of pre-load or co-load of either crystalloid or colloid remain controversial with many studies that confirm that post-spinal hypotension remain significant regardless of the type or timing of the given fluids [20], and may cause hypervolemia [6]. Crystalloids infusion, results in its redistribution to extravascular compartment and induce atrial natriuretic peptide secretion which might augment lowering blood pressure because of its natriuretic, diuretic, and vasodilatory effects. [21] Colloids on the other hand, despite remaining in intravascular space for a longer duration it is not popular routinely due to its increased cost, possibility of derangement of coagulation, suppression of platelet activity and risk of anaphylaxis. [22] When it comes to

vasoconstrictors, they cause tachycardia and hypertension which may worsens associated myocardial ischemia [23].

Recently, $5HT_3$ blockers (Ondansetron) have been proposed as a method of preventing post-spinal hypotension on the basis of inhibiting BJR.[5] concluding that the incidence of hypotension and bradycardia after spinal anesthesia was decreased following the use of ondansetron. However, meta-analysis studies fail to confirm the validity of those conclusions based on low quality of evidence and insufficient evidence. [24]. Moreover, ondansetron might be responsible for lower spinal block level and early recovery from spinal anesthesia. [25]

DEX also has a bundle of collateral benefits in spinal anesthesia having anti-emetic [7] and anti-shivering [8] effects. Adding to this, it was proposed to increase the duration of sensory block in spinal anesthesia. [9]

This study had some limitation namely; relatively small sample size and restricting the study duration to 20 minutes post-spinal, however. The investigators research chose to restrict the time of study to the time of maximum hemodynamic instability and before other influences e.g. tourniquet, skin incision or, bleeding occur.

The study however had many merits; the most important of which is to redirect medical society toward using a relatively well known, cheep and available DEX in spinal anesthesia to alleviate post-spinal hypotension and to get use of its collateral benefits.

Conclusion

Preoperative dexamethasone 8 mg infusion may attenuate post-spinal hypotension in geriatric patients undergoing orthopedic surgeries.

Abbreviations

SA
spinal anesthesia; BJR:Bezold Jarish reflex; $5HT_3$:5-hydroxytryptamine receptor type 3; DEX:Dexamethasone; PVR:peripheral vascular resistance; ASA:American Society of Anesthesiologists; SNOSE:ratio in opaque and sealed envelope; NSS:normal saline; I.V.:Intravenous; HR:Heart rate; SBP:systolic blood pressure, DBP:diastolic blood pressure; MBP:mean blood pressure; SD:standard deviation; NO:nitric oxide.

Declarations

Ethics approval and consent to participate

Ethical approval from Ain Shams University hospitals research committee was obtained (FMASU R 46/ 2018). Written informed consent was taken from all the patients, their parents or their guardians before any study procedure was conducted.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ain Shams university hospitals and they are not publicly available. Data are however available from the corresponding author on reasonable request after permission of Ain Shams university.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors' contributions

T.A and I.E. were responsible for the conception and design of the study, analysis of the data, writing the manuscript and revising the manuscript. N.H. and S.A were responsible for clinical cases handling, collect the data and search the database. All authors have read and approved the manuscript.

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Implication statement: The research team validated the efficacy of pre-operative dexamethasone infusion in attenuating post-spinal anesthesia hypotension in geriatric patients.

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Tables

Table (1): Demographic characteristics among the studied cases

	Group-D N=55	Group-C N=55	P
Age; years	75.8 (5.4)	75.6 (5.0)	^0.826
Sex; male/female	22/33	25/30	#0.563
Weight ; kg	67.7 (3.8)	66.8 (3.2)	^0.217
Height ; cm	167.3 (4.3)	166.4 (4.9)	^0.316
ASA; I, II, III; n	4 /38/13	7/33/15	#0.519
Ischemic heart disease; n	33	39	#0.229
Hypertension; n	42	45	#0.482
Diabetes Mellitus; n	20	21	#0.844
Renal impairment; n	11	10	#0.808

^Independent t-test. #Chi square test

Table (2): Sensory and motor block among the studied cases

	Group-D (N=55)	Group-C (N=55)	Difference(D-C)		^P (groups)	#P (versus minute-5
			Mean (SE)	95% CI		
Number of segments above S1						
Minute-5	4.0 (0.8)	3.8 (0.7)	0.2 (0.2)	-0.1–0.5	0.174	–
Minute-10	5.5 (0.8)	5.2 (1.0)	0.3 (0.2)	0.0–0.7	0.056	**<0.001***
Minute-15	6.7 (0.9)	6.4 (0.9)	0.2 (0.2)	0.0–0.6	0.167	**<0.001***
Minute-20	7.0 (0.8)	6.7 (0.6)	0.2 (0.1)	0.0–0.5	0.097	**<0.001***
Time to complete motor block						
Time (minutes)	7.1 (0.8)	7.4 (0.9)	-0.3 (0.2)	-0.6–0.1	0.126	–

^Independent t-test. #Paired t-test. *Significant

Table (3): Blood pressure changes among the studied cases

	Group-D (N=55)	Group-C (N=55)	Difference (D-C)		^P (groups)	#P (versus baseline)
			Mean (SE)	95% CI		
SBP (mmHg)						
Baseline	147.9 (7.5)	147.9 (8.0)	0.1 (1.5)	-2.9–3.0	0.951	–
Minute-5,	142.3 (10.2)	133.7 (15.2)	8.6 (2.5)	3.7–13.5	**0.001***	**<0.001***
Minute-10, (N=52, 47)	139.8 (9.5)	134.7 (9.9)	5.1 (1.9)	1.3–9.0	**0.009***	**<0.001***
Minute-15, (N=50, 41)	137.2 (9.3)	135.0 (8.2)	2.2 (1.9)	-1.5–5.9	0.246	**<0.001***
Minute-20, (N=48, 38)	134.1 (8.3)	132.1 (6.9)	2.0 (1.7)	-1.3–5.3	0.236	**<0.001***
Minimum	131.4 (10.6)	125.2 (13.3)	6.2 (2.3)	1.7–10.8	**0.008***	**<0.001***
DBP (mmHg)						
Baseline	86.8 (6.1)	86.5 (6.6)	0.4 (1.2)	-2.0–2.8	0.753	–
Minute-5,	77.8 (7.5)	72.6 (9.2)	5.1 (1.6)	2.0–8.3	**0.002***	**<0.001***
Minute-10, (N=52, 47)	75.4 (6.7)	70.5 (7.6)	4.9 (1.4)	2.0–7.7	**0.001***	**<0.001***
Minute-15, (N=50,41)	72.5 (7.7)	67.8 (8.1)	4.7 (1.7)	1.4–8.0	**0.006***	**<0.001***
Minute-20, (N=48, 38)	67.8 (6.9)	65.7 (7.1)	2.1 (1.5)	-0.9–5.1	0.174	**<0.001***
Minimum	66.6 (7.3)	63.0 (7.9)	3.6 (1.5)	0.7–6.5	**0.015***	**<0.001***

MBP (mmHg)						
Baseline	107.2 (6.5)	106.9 (7.0)	0.3 (1.3)	-2.3–2.8	0.826	–
Minute-5,	99.3 (8.3)	93.0 (11.1)	6.3 (1.9)	2.6–10.0	**0.001***	**<0.001***
Minute-10, (N=52, 47)	96.9 (7.4)	91.9 (8.2)	5.0 (1.6)	1.8–8.1	**0.002***	**<0.001***
Minute-15, (N=50, 41)	94.0 (8.1)	90.2 (8.0)	3.8 (1.7)	0.5–7.2	**0.026***	**<0.001***
Minute-20, (N=48, 38)	89.9 (7.0)	87.8 (6.9)	2.1 (1.5)	-1.0–5.1	0.178	**<0.001***
Minimum	88.2 (8.0)	83.7 (9.2)	4.5 (1.6)	1.2–7.7	**0.008***	**<0.001***

^Independent t-test. #Paired t-test. *Significant

Table (4): Atropine and ephedrine need and associated side effects among groups

Variables	Group-D (N=55)	Group-C (N=55)	p	RR (95% CI)
Hemodynamic supports				
Atropine; N,%	7 (12.7%)	11 (20.0%)	#0.303	0.64 (0.27–1.52)
Ephedrine; N,%	8 (14.5%)	18 (32.7%)	**#0.025***	0.44 (0.21–0.94)
Atropine and Ephedrine; N,%	7 (12.7%)	10 (18.2%)	#0.429	0.70 (0.29–1.71)
Time of atropine need (minute), (N=7,11)	8.6 (3.8)	7.7 (3.4)	^0.631	
Time of ephedrine need (minute), (N=8,18)	10.6 (5.6)	9.2 (4.6)	^0.493	
Associated side effects				
Nausea; N,%	7 (12.7%)	18 (32.7%)	**#0.012***	0.39 (0.18–0.86)
Vomiting; N,%	1 (1.8%)	8 (14.5%)	**§0.032***	0.13 (0.02–0.97)
Shivering; N,%	7 (12.7%)	25 (45.5%)	**#<0.001***	0.28 (0.13–0.59)

Figures

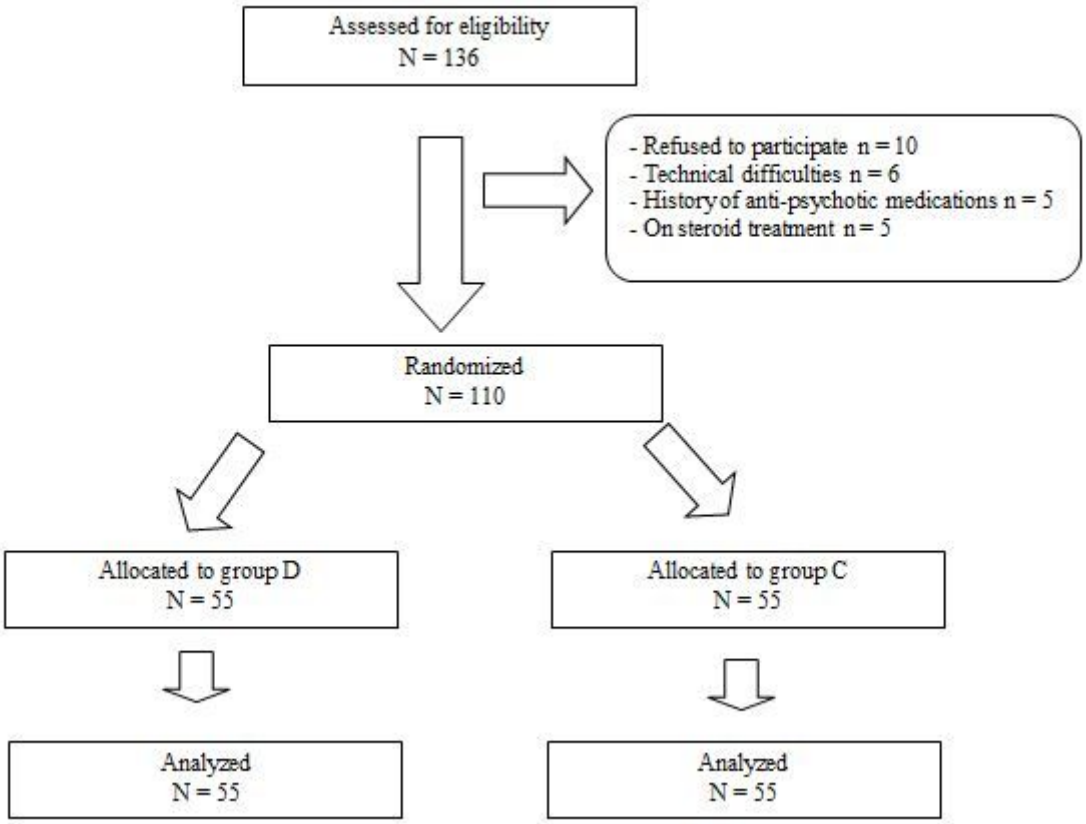

Figure 1

Flow chart of the study.

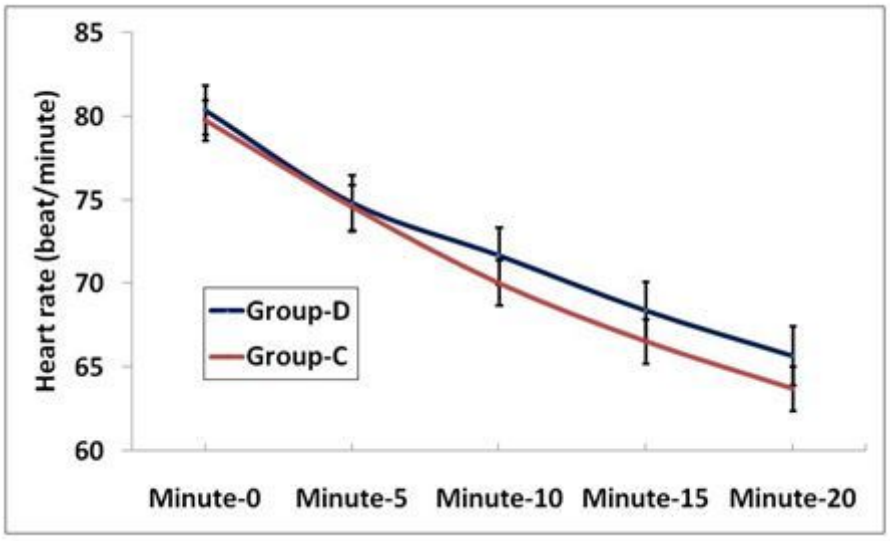

Figure 2

Changes in HR among groups.

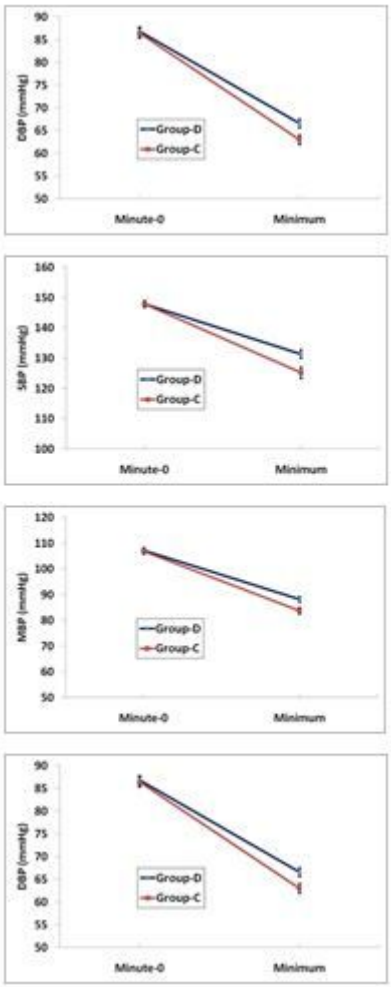

Figure 3

a) Minimum HR, b) Minimum SBP, c) Minimum DBP, d) Minimum MBP changes between groups.

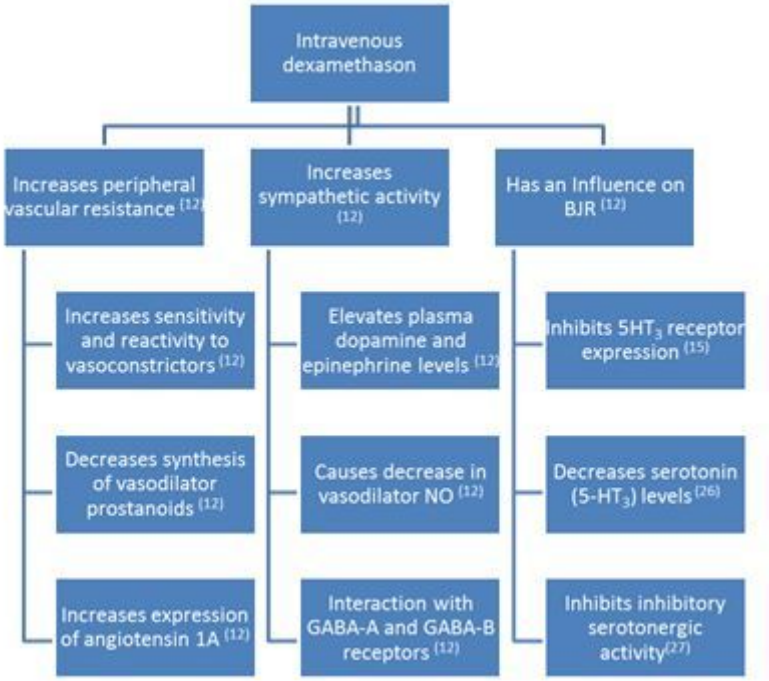

Figure 4

Possible mechanisms of Dexamethasone in alleviating spinal anesthesia induced hypotension.

Supplementary Files

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- CONSORTChecklist.docx