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Original Research Article

Prophylactic Intramuscular Mephentermine for Reduction of Spinal Anaesthesia - Induced Hypotension in Elderly Patients Undergoing Hip Fracture Surgery, is it Effective: A Randomised Double Blind Placebo - Controlled Clinical Trial

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Conflict of interest: Nil

Abstract:

Background: Spinal anesthesia - induced hypotension (SAIH) can be minimized by prophylactic intramuscular (IM) injection of mephentermine but it has not been investigated much in elderly. We aimed this study to evaluate the efficacy of prophylactic IM injection of mephentermine to prevent SAIH in elderly patients undergoing hip fracture surgery in spinal anesthesia.

Material & Methods: This randomized double blind controlled study included 130 patients ageing >60 years of both sex, American Society of Anesthesiologists grade I or II undergoing hip fracture surgery under spinal anesthesia. Patients were divided into two groups: Group M received IM mephentermine 1ml (30mg) and Group C received IM normal saline 1ml immediately after subarachnoid block and hemodynamic variables were continuously monitored. Primary outcome measured was incidence of hypotension (mean arterial pressure < 20% from baseline), secondary outcomes were rescue vasopressor requirement, hemodynamic stability and adverse effects.

Results: Hypotension was observed in 21 (32.3%) patients in Group M which was significantly less as compared to 37 (59.9%) patients in Group C, P = 0.0478. Cumulative episodes of hypotension were also significantly less in Group M (28 episodes) than in Group C (84 episodes), P = 0.038. Intra-operative vasopressor (mephentermine) requirement was significantly less in Group M as compared to Group C both in terms of number of doses (28 versus 93, P = 0.027) and dose in mg (168 versus 558, P=0.000).

Conclusion: Prophylactic use of intramuscular mephentermine is effective in reducing post-spinal hypotension and intra-operative rescue vasopressor requirement in elderly hip fracture surgery patients.

Keywords: hypotension, intramuscular, mephentermine, spinal anesthesia.

Introduction

Hip fractures are common in elderly and generally require surgical treatment. [1] Spinal anesthesia is well accepted technique for it as it is easy, economical and provides adequate sensory motor blockade with fast onset. Important concern is spinal anesthesia - induced hypotension (SAIH) which has very high incidence in elderly(30-70%) because of multiple factors such as high sympathetic tone, blunted baroreceptor reflex and impaired systolic and diastolic cardiac function.[2,3] SAIH even if it is treated can lead to critical organ hypoperfusion and deteriorate other comorbid medical illness in them. [4,5] Fluid preloading to prevent SAIH in elderly is not a preferred regime due to impending risk of cardiac failure. Therefore many researchers advocate prophylactic use of vasopressors to provide hemodynamic stability but choice of vasopressor is debatable.[6-9] Phenylephrine, a pure α1 agonist, which is preferred agent to reduce SAIH in cesarean section may lead to reflex bradycardia and decreased cardiac output, that could be concerning in geriatric patients.[10] Therefore in elderly, vasopressors which have combined α and β action like ephedrine and mephentermine take preference. Norepinephrine also has inherent β activity along

with its α1 agonistic effect so lesser incidence of bradycardia and decrease in cardiac output as compared to phenylephrine were found in elderly patients when they were administered as prophylactic infusion to prevent post-spinal hypotension.[11] However, norepinephrine infusion is mostly used to treat established hypotension which does not respond to initial rescue therapy. As a prophylactic dose it does not seem to be economical in countries like India where availability of syringe pumps is sometimes at stake in small setups where also such hip fracture surgery are commonly done.

Intramuscular (IM) administration of vasopressors has been tried in the past with good outcomes.[12] Literature have reported prophylactic intramuscular ephedrine effective in reducing SAIH in elderly undergoing hip fracture surgery[13] but such studies are not available for mephentermine, which is most common vasopressor available in Indian setups. Intramuscular mephentermine injection was found effective in reducing SAIH in cesarean section but such data are not available in elderly that prompted us to conduct this research.

We conducted the present study to evaluate the effect of prophylactic intramuscular injection of 30mg mephentermine (1 ml) to prevent spinal induced hypotension in elderly patients undergoing hip fracture surgery under spinal anesthesia. Primary objective was to assess effect on incidence of hypotension and secondary objectives were effect on rescue vasopressor requirement, hemodynamic stability and side effects as compared to saline group.

Materials and Methods:

After taking approval from institutional ethics committee ((RNT/Stat./IEC/2020/07)) and informed written consent from patients for participation, this prospective randomized, placebo-controlled, double blind clinical study was carried out in the department of anesthesia in orthopedic operation theatre in a tertiary care centre over a period of one year. The study was registered under Clinical Trial Registry of India (CTRI/2021/09/036268) and codes of Helsinki declaration were followed. Sample size was calculated using power analysis based on the previous study by Yadav et al [12]. To detect minimum difference of 37% in incidence of post spinal hypotension between mephentermine and control groups in elderly patients, sample size of 127 was required in the present study with type 1 error of 5% and power of 80%. To compensate for dropouts we included 130 patients in our study.

The study was carried out in 130 patients of age>60 years of both sex, American Society of Anesthesiologists (ASA) grade I or II having surgeries for hip fracture like proximal femur nail, dynamic compression plating, dynamic hip screw, hemiarthroplasty etc under spinal anesthesia. Exclusion criteria were patient refusal, ASA III or more, drug hypersensitivity, morbid obesity, contraindication to subarachnoid block, coexisting severe medical illness like severe respiratory disease (SpO2< 94% on air), severe cardiac disease (congestive heart failure, valvular dysfunction, ejection fraction <45%, history of myocardial infarction), uncontrolled hypertension, neurological disease, psychiatric disease, uncontrolled endocrine disorder and coagulation abnormalities.

Patients were randomly allocated in two groups of 65 each using computer generated table of random numbers and sealed envelope technique as follows:

- Group M (Mephentermine) - received 1 ml (30 mg) mephentermine IM inj. after subarachnoid block. Injection Termin^{TM} (Mephentermine sulphate injection 30 mg/ml;10 ml vial) Neon Laboratories Ltd Mumbai was used.
- Group C (Control Placebo) - received 1 ml 0.9% normal saline IM inj. after subarachnoid block

To ensure double blindness, the anesthesiologist who prepared study drugs as per group allocation was not further involved in the study. Another anesthesiologist, who was not aware of the group allocation, performed subarachnoid block, administered IM drugs provided in identical syringes, conducted perioperative management and data recording. Patient and surgeon were also unaware of group allocation.

After thorough pre-anesthetic evaluation and routine investigations, patients were explained about the study protocol. On arrival in operating room, multi-paramonitor involving non-invasive blood pressure, electrocardiography and pulse-oximetry was attached to patient. Baseline vital parameters like systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO2) were recorded. Two 20 gauge intravenous (IV) cannula were inserted to administer Ringer Lactate (RL) 8 ml/kg as co-load. Taking all aseptic precautions lumbar puncture was done in sitting position using 25-gauge Quincke spinal needle via median/paramedian approach and 2ml of 0.5% hyperbaric bupivacaine (10mg) with 25µg fentanyl (0.5 ml) was injected in subarachnoid space. End of spinal injection was noted as time zero for all further data recording. At this time intramuscular injection of the study drug as per group allocation was administered.

Sensory block was assessed using pinprick method. Motor block was assessed using Modified Bromage score [14] [0=Able to lift lower limb against gravity

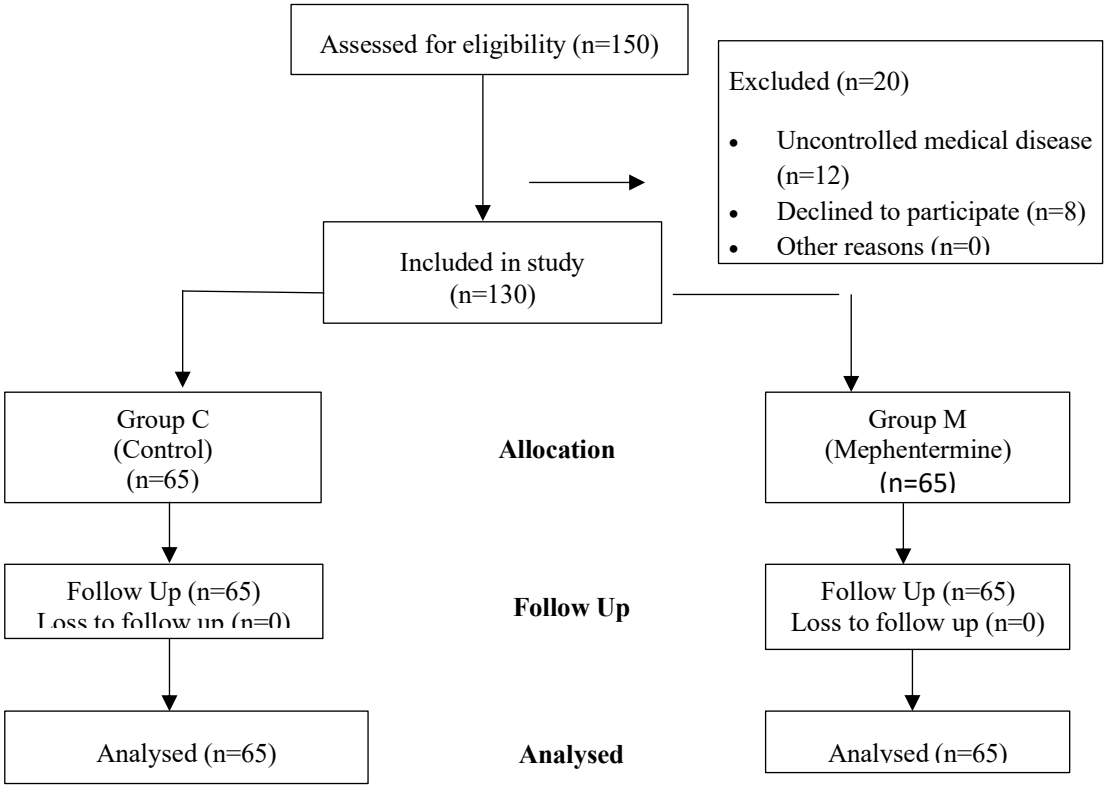
by hip flexion, 1=Able to flex knee but unable to flex hip , 2=Able to move feet by flexion of ankle, but unable to flex knee , 3=Unable to move any joints, hip, knee or ankle]. Sensory and motor block was assessed after subarachnoid block at every 5 min till 15 min to record peak sensory level (PSL) and maximum Bromage score (MBS). Surgery was allowed to start if L1 sensory level or above and Bromage score of 2 or 3 was achieved.

Hemodynamic data (SBP, DBP, MAP, HR, SpO_2) were recorded at baseline and after subarachnoid block (every 5 min till 30 min), thereafter every 15 min till the end of the surgery. However, patients were continuously monitored for SpO_2, HR by ECG and BP every 5 min to observe any episode of hypotension and bradycardia. Hypotension episode was defined as fall in MAP >20% of baseline and/or an absolute value of MAP less than 65mm Hg and was treated with rescue vasopressor as mephentermine 6mg intermittent IV bolus administerd every 2 minutes (maximum 30mg) till achievement of MAP within 20% of baseline. The time interval from subarachnoid injection to first episode of hypotension was recorded as onset of hypotension. If MAP falls again it was counted as next episode, and total episodes of hypotension were recorded. For persistent hypotension, norepinephrine infusion 2-10 µg/min was administered. Bradycardia was defined as fall in heart rate < 55 beats per min and treated with atropine 0.6 mg IV. Other intraoperative complications like nausea, vomiting, pruritus, shivering, hypertension (MAP > 25% of baseline), tachycardia (HR > 25% of baseline), arrythmia, headache etc were recorded and treated accordingly. During surgery additional fluid as RL, colloid and blood were given as per intraoperative losses. Intraoperative urine output was recorded.

Primary outcome measured was incidence of hypotension (number of patients as well as number of episodes). Secondary outcomes were rescue vasopressor requirement, onset of hypotension, hemodynamic parameters and complications.

Statistical analysis: Data were entered in Microsoft excel no.10 and analyzed using Statistical Package of Social Sciences version 20. Categorical data was presented as number (proportion) and compared with Chi-square test. Continuous variables were presented as mean±S.D. and compared using t-test. Ordinal data was noted as Median (Range) and compared with Mann Whitney U test. $P<0.05$ was considered statistically significant.

Figure 1: Consort Flow Chart



Results

Total 150 patients were assessed for eligibility and 20 were excluded (12 for uncontrolled medical illness, and 8 declined to participate), remaining 130 patients received allocated intervention and completed the study with no loss to follow up. (Figure 1)

Both groups were comparable regarding mean age, height, weight, sex, ASA grade, coexisting medical illness, type of surgery and its duration. Peak sensory level (Median T10) and Maximum Modified Bromage score (Median B3) were comparable in two groups and none of the patients required anesthetic supplementation. There was no significant difference in two groups regarding fluid received, blood transfusion and urine output ,P>0.05. (Table 1)

Hypotension was observed in 21 (32.3%) patients in Group M which was significantly less as compared to 37 (59.9%) patients in Group C, P = 0.004. Onset of hypotension after SAB was also significantly earlier in Group C (21.86±22.61min) than in Group M (36.05±20.56 min); P = 0.021. Cumulative number of episodes of hypotension were also significantly less in Group M (28 episodes) than in Group C (84 episodes), P = 0.000, (Table 2) .Patient distribution showed significantly greater number of patients in Group C had 3 or 4 episodes as compared to very few in Group M, P=0.038. (Figure 2)

Cumulative rescue vasopressor (mephentermine) requirement was significantly less in Group M as compared to in Group C both in terms of number of doses (28 versus 93, P = 0.027) and dose in mg (168 versus 558, P=0.000). There were 8 (12.3%) patients in Group C who required norepinephrine infusion as compared to only 1 (1.5%) patient in Group M, the difference was statistically significant, P=0.015. However there was no significant difference in the dose of norepinephrine infusion in two groups (2-5 mcg/kg/min) and was tapered postoperatively. (Table 2)

Mean value of SBP, DBP and MAP were significantly less in Group C as compared to Group M at 10 min after subarachnoid block, remained so till 30 min for SBP and MAP and till 20 min for DBP, P< 0.05.Thereafter also they were comparatively low in Group C but the difference could not reach statistical significance, P>0.05. (Figure 3)

The lowest value of SBP, DBP and MAP were significantly less in Group C as compared to Group M, and their % fall from baseline was also significantly more in Group C than in Group M,P<0.05(Table 3).Mean HR and SpO2 were comparable in two groups at all-time intervals, P>0.05.

In our study adverse effects were minimal and comparable; P=0.403. In Group C, 1(1.5%) patient had ventricular premature beats and 2(3.07%) had nausea, which coincided with timing of hypotension episode and recovered as BP normalized. In Group M, 1 (1.5%) patient had hypertension (160/95 mmHg) and 1 (1.5%) had tachycardia (100 bpm) after 15 min which returned to baseline without any treatment. None of our study patient had postoperative adverse outcome.

Table 1: Comparison of baseline, preoperative and intraoperative characteristics

Variable	Group C (n=65)	Group M (n=65)	P value
Age (years)	72.55±10.50	70.80±9.43	0.318
Weight (kg)	71.71±12.32	70.42±12.65	0.556
Height (cm)	166.31±8.81	164.50±8.80	0.240
Gender (M/F)	38/27	37/28	0.859
ASA (I/II)	50/15	49/16	0.670
Comorbidity n (%)	17 (26%)	15 (23%)	0.723
Hypertension	9 (13.8%)	7 (10.7%)	
Diabetes mellitus	4 (6%)	5 (7.6%)	
Hypothyroidism	2 (3%)	1 (1.5%)	
COPD	2(3%)	2(3%)	
Baseline Hemoglobin (g/dl)	11.32±1.19	11.11±0.97	0.277
Prior Blood Transfusion n(%)	5 (3.25%)	4 (2.6%)	0.843
Type of Surgery n (%)			0.375
Bipolar prosthesis	13 (16.9%)	17 (24.6%)	
Proximal femur nail	39 (60.0%)	41 (63.1%)	
Dynamic hip screw	13 (20.0%)	7 (10.8%)	
Duration of Surgery (min)	73.56±22.14	77.38±23.60	0.343
Peak Sensory Level	T 9.57±0.90 Median T10 (T8-T12)	T9.88±1.32 Median T10 (T8-T12)	0.122
Maximum Bromage Score	B 2.83±0.38	B 2.92±0.37	0.111

	Median B3 (3-3)	Median B3 (3-3)	
Intraoperative fluid input(litre)	1.7±0.4	1.8±0.4	0.403
Urine output (ml)	232.31±120.69	273.38±287.47	0.290

Table 2: Comparison of hypotension and vasopressor requirement in two groups

Variables	Group C (n=65)	Group M (n =65)	P value
Occurrence of Hypotension			
Incidence of patients who had hypotension n (%)	37 (59.9%)	21 (32.3%)	**0.004**
Cumulative hypotension episodes (n)	84	28	**0.000**
No. of hypotension episodes per patient (mean±SD)	1.29±1.49	0.43±.770	**0.000**
Onset of hypotension (mean±SD)	21.86±22.61	36.05±20.56	**0.021**
Vasopressor Requirement			
Cumulative number of Mephentermine doses (n)	93	28	**0.000**
Cumulative amount of Mephentermine (mg)	558	168	**0.000**
Number of Mephentermine doses per patient (mean±SD)	1.43±1.81	0.43±.77	**0.000**
Amount of Mephentermine (mg) per patient (mean±SD)	8.53±10.8	2.58±4.62	**0.000**
Incidence of Noradrenaline Requirement n (%)	8 (12.3%)	1 (1.5%)	**0.015**

Table 3 : Comparison of baseline and lowest value of SBP, DBP and MAP and maximum percentage fall from baseline in two groups

Blood pressure (mmHg)	Group C (n=65)	Group M (n=65)	P value
Systolic Blood Pressure (SBP)			
Baseline	136.38±18.70	135.88±16.20	0.869
Lowest	101.43±12.29	108.69±13.64	**0.002**
Maximum % fall from baseline	24.64±11.02	19.29±10.66	**0.006**
Diastolic Blood Pressure (DBP)			
Baseline	77.46±10.53	79.52±10.80	0.273
Lowest	60.92±9.49	65.09±8.75	**0.010**
Maximum % fall from baseline	20.63±12.88	17.34±11.43	0.125
Mean Arterial Pressure (MAP)			
Baseline	96.88±11.89	97.22±11.56	0.870
Lowest	73.33±8.90	78.15±13.69	**0.019**
Maximum % fall from baseline	23.49±11.30	18.60±15.64	**0.043**

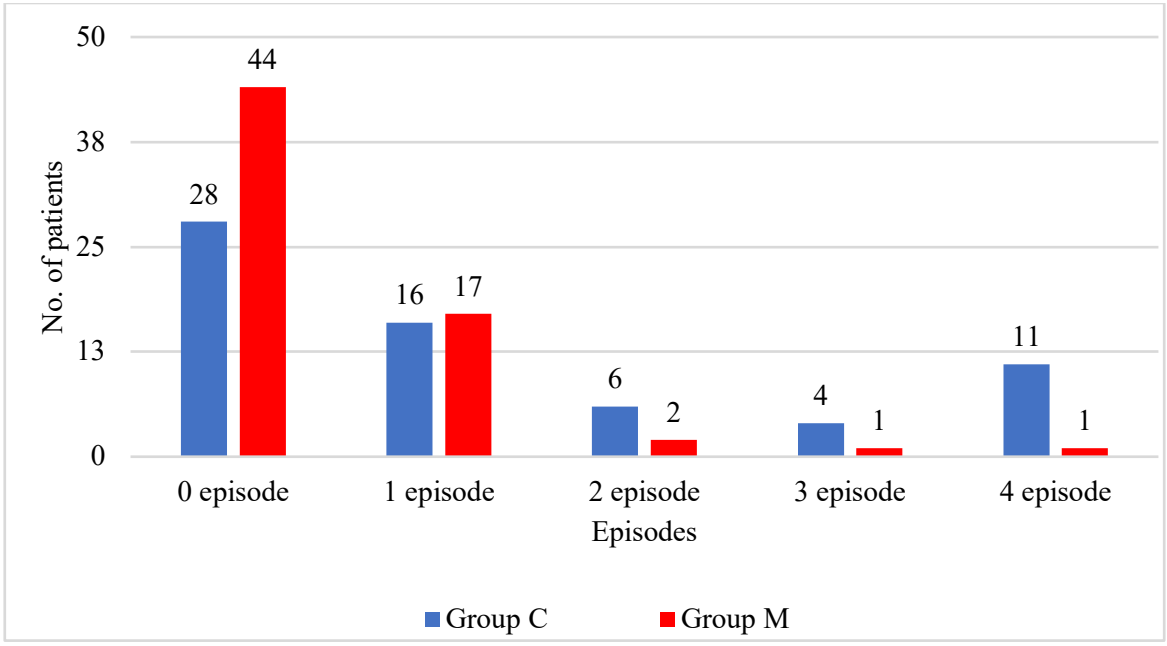


Figure 2: Comparison of episodes of hypotension in two groups

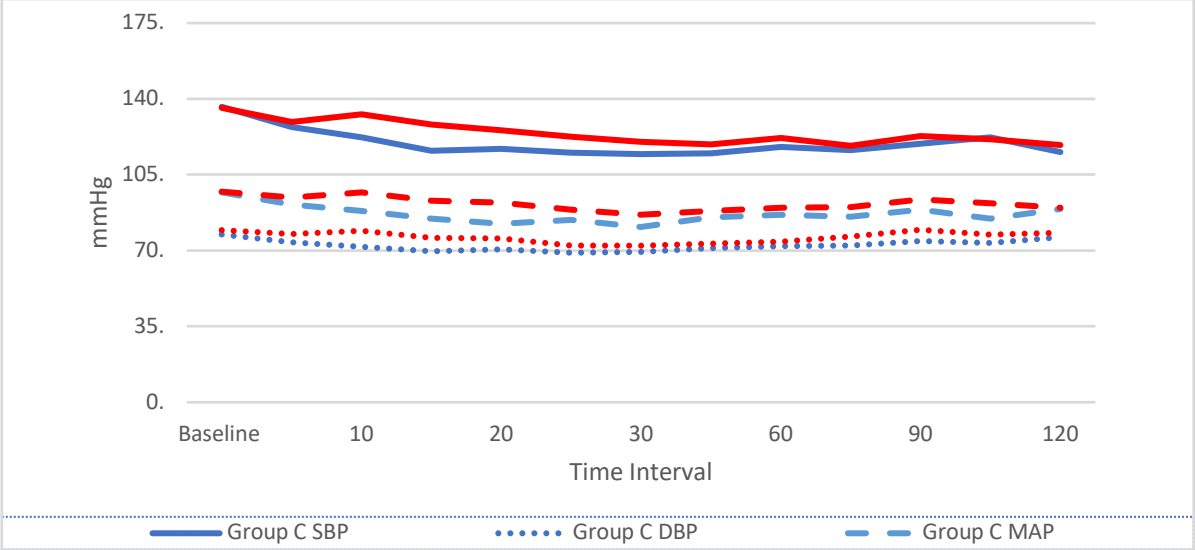


Figure 3: Comparison of changes in Systolic, Diastolic, Mean Arterial blood pressure at various time intervals in two groups

Discussion

We evaluated the effect of prophylactic use of injection mephentermine 30 mg given intramuscularly immediately after spinal injection of local anesthetic (2 ml of 0.5% hyperbaric bupivacaine + 25 µg fentanyl) for hip fracture surgeries in elderly patients and observed that IM mephentermine was effective in preventing post spinal hypotension in terms of reduction in incidence of hypotension (number of patients as well as total episodes), and rescue vasopressor requirement leading to better hemodynamic stability without producing significant adverse effects.

Intraoperative hypotension is an independent risk factor for postoperative 5- and 30-day mortality in patients undergoing hip surgery.[15] Spinal anesthesia, the most common anesthetic technique used in hip surgery, is usually associated with hypotension, whose risk is increased in elderly patients due to age-related cardiovascular changes, such as decreased baroreceptor sensitivity and higher basal sympathetic activity. Furthermore, spinal anesthesia-induced hypotension can occur even in adequately hydrated elderly patients.[16] Hence, the use of prophylactic vasopressors for preventing hypotension is increasingly recommended in elderly population.[17]

Mephentermine and ephedrine are indirectly acting synthetic catecholamines which stimulate α and β adrenergic receptors. These drugs raise the blood pressure in two ways, firstly by increasing the force of the heart's contraction; and secondly by causing peripheral vasoconstriction. Hence these drugs counteract effects of spinal induced sympathetic blockade, thereby reducing hypotension episodes. [12,13] In elderly patients maintenance of blood pressure and prevention of hypotension is of utmost importance because it reduces critical organ ischemia. It is well known that association of medical illness is common in geriatric patients, as observed in our study also, where 25 percent patients had coexisting medical morbidities and stable hemodynamics would be beneficial in preventing further end organ damage in such patients. We included medically controlled co-morbid patients so that our study sample can reflect actual population, to increase external validity of research.

Use of prophylactic IM mephentermine (30mg) to prevent spinal induced hypotension had been studied in cesarean section previously by Yadav et al [12] and Somayaji et al[18] and found it as effective regime. There is paucity of data in which IM mephentermine has been investigated in the elderly patients. However, use of intramuscular ephedrine had been studied by Sterno et al [13](0.6 mg/kg) and Singh et al [2] (30 mg) for hip fracture surgeries in elderly population and it was found to reduce incidence of hypotension.

Onset of action of IM mephentermine is 5–15 min and duration is 4 hours. This gradual onset buys enough time to counteract effects of spinal induced sympathetic blockade and persistent action maintains hemodynamic stability, which makes IM mephentermine a good choice for prophylaxis to prevent post spinal hypotension. On the contrary, by IV route it has immediate onset of action and duration is 30 min, hence IV mephentermine is preferred as a rescue vasopressor to treat the hypotension once it occurs. [19] In our study, when prophylactic IM mephentermine was used in Group M, incidence of hypotension was significantly less which occurred in 21 (32.3%) patients and cumulative hypotension episodes were 28, as compared to control Group C in which hypotension

occurred in 37 (59.9%) patients and cumulative hypotension episodes were 84, P = 0.004 and P=0.000 respectively. Blood pressure was also better maintained intraoperatively in Group M than in control Group C and the difference was significant during first 30 min. Similar to our study, Yadav et al compared prophylactic IM normal saline (Group I), mephentermine (30 mg) (Group II) and ephedrine (30 mg) in Group III given 5 min before spinal anesthesia in cesarean section.

They reported that incidence of hypotension was 60% (18 patients) in control Group I, which was significantly higher than observed in 23.33% (7 patients) in mephentermine Group II and 26.66% (8 patients) in ephedrine Group III, P < 0.05. SBP and DBP were also significantly lower in control Group I as compared to Group II and Group III; P<0.05. This difference was observed from 5 min to 30 min after spinal anesthesia. [12]

We found that hypotension occurred significantly earlier in Group C because it was due to initial spinal induced vasodilatation which was countered by IM mephentermine received in Group M patients, whereas hypotension occurred later in Group M and coincided with start of surgical bleeding. In Group C as number of episodes of hypotension were more so the number of rescue vasopressor (mephentermine) doses were also significantly more in Group C (93 doses) as compared to Group M (28 doses); P = 0.027. There were 8 (12.3%) patients in Group C who required norepinephrine infusion as compared to only 1 (1.5%) patient in Group M, the difference was statistically significant; P=0.015.

Somayaji et al[18] and Singh et al[2] also reported that requirement of rescue IV ephedrine was significantly less in mephentermine and ephedrine groups respectively (P<0.05) as compared to saline group. Though intraoperative rescue vasopressor requirement was significantly more in control groups in above mentioned studies including ours, but we should remember that all study group patients already received 30 mg mephentermine or ephedrine IM.

However,this regime offered advantage of better maintenance of SBP, DBP and MAP, ultimately improving the end organ perfusion in elderly. Apart from this, prophylactic IM injection is easy, yet effective regime which does not require any advanced devices for administration and also avoids undue wastage of drugs which may occur in infusion of drugs.

Our study had few limitations, firstly we did not use invasive blood pressure monitoring that would have shown beat to beat variability of hemodynamic changes and could be more authentic than non-invasive blood pressure monitoring. But its use was not justifiable in short duration surgeries just for the sake of the study and could also be associated with risk of thromboembolism and bleeding. Small number of patients and single centre study are other limitations of our work. Large-scale, multicentric studies and comparison with other agents is required to confirm our observations in further studies.

Conclusion

We conclude that administration of intramuscular injection of mephentermine (30mg) just after subarachnoid block is simple and effective regime in reducing incidence of hypotension and rescue vasopressor requirement in patients undergoing hip fracture surgery in spinal anesthesia thereby providing hemodynamic stability without any significant adverse effects.

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