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Comparison of hemodynamic changes between intrathecal dexzmedetomidine 5µg and Fentanyl 25µg as adjuvants to 12.5mg of 0.5% hyperbaric bupivacaine for spinal anesthesia

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Abstract
The application of a single high dose of Dexmedetomidine reduced norepinephrine release by as much as 92% in young healthy volunteers. The release of epinephrine is also reduced by the same amount [51]. The baroreceptor reflex is well preserved in patients who received Dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented. These results illustrate that cardiovascular response is evoked mainly by decrease in central sympathetic outflow. After clinical approval of Institutional Ethical Committee Clearance and informed written consent of 90 patients of ASA physical class I and II who were posted for elective Total Abdominal Hysterectomy (TAH). The study population was randomly selected based on the closed sealed opaque envelope technique. The mean duration of surgery in Group-B was 61.00±13.60min, Group-D was 66.33±12.79min and Group-F was 67.33±10.72min. There was no statistically significant difference in the mean duration of surgery among three groups (P>0.05). Statistically there was no significant difference in DBP (mm of Hg) measured at various intervals throughout the surgery among the groups (P>0.05).

Keywords: Hemodynamic changes, intrathecal dexmedetomidine, fentanyl

Introduction
Hypotension during spinal anaesthesia is due to the exaggerated physiologic effects of central neuraxial blockade with two major alterations in cardiovascular systems. First is blockade of sympathetic vasoconstrictor fibers of the arterioles. Arteriolar dilatation results in a decrease in peripheral vascular resistance. Second is actual dilatation of peripheral veins and venules with pooling of blood. This combined with paralysis of skeletal muscle and the loss of muscular milking action plus interference with thoracic respiratory pump decreases venous return. Symptoms are related to the tissue hypoxia that results from diminished blood pressure.

Adequate hydration that is replacement of fluid deficit prior to induction of spinal anaesthesia and proper positioning of the patient after spinal anaesthesia will improve venous return, cardiac output and blood pressure. Once the diagnosis of hypotension is established four procedures are of practical importance [1, 2].

- Intravenous fluid: Rapid administration of fluid increases the blood volume and improves circulation.
- Administration of oxygen by simple facemask or nasal catheter will increase oxygen content of blood. This will minimize hypoxia and at the same time relieve dyspnoea and ameliorate nausea and vomiting. Occasionally, despite the above measures blood pressure will need to be supported with vasopressors.
- Vasopressors that constrict veins in preference to arterioles provide a more rational method for treating the hypotension. Drugs commonly used are ephedrine, mephenteramine, and phenylephrine. The former two have mixed α and β receptor agonist activity and are potent vasoconstrictor whereas the latter is an α receptor agonist and a more potent arteriolar vasoconstrictor.
- Head down position: About 5-8° of head low position will increase venous refilling of the heart and the pulmonary blood volume. The result is an increase in stroke volume and cardiac output with a rise in blood pressure. This can only be done after fixation of local anaesthetic.

Respiratory impairment is related to high spinal anaesthetic levels with ascending blockade of the thoracic and the cervical segments, a progressive ascending paralysis of the intercostal muscles and diaphragm ensues. This leads to respiratory insufficiency and apnoea. Respiratory arrest may be due to hypoperfusion of respiratory centre in brainstem following hypotension.

Nausea and vomiting are often the results of sudden changes in perfusion found along with hypotension. They are related to hypoxia or excessive rise in blood pressure following administration of a vasopressor.

Repeated attempts to achieve a spinal tap may result in direct trauma to nerves, to periosteum of vertebra, to intervertebral discs and to spearing of spinal nerves. Bloody tap tends to neutralize the effectiveness of local anaesthetics while blood in the sub arachnoid space may produce arachnoiditis.

Post spinal anaesthesia headache was first documented by August Bier in 1899. Classically, the spinal headache appears on the second or third post operative day. It is postural in nature, aggravated or appearing with assumption of the erect position and relieved by recumbency. Terms used to describe the headache include the following, roughly in order of frequency: constricting weight of the head, pressure in the head, throbbing sensation; top blowing off; and occasionally a vacuum-like sense [3, 4].

Dexmedetomidine does not appear to have any direct effects on the heart. A biphasic cardiovascular response has been described after the application of Dexmedetomidine. The administration of a bolus of 1µg/kg body weight, initially results in a transient increase of the blood pressure and a reflex decrease in heart rate, especially in young healthy patients. The initial reaction can be explained by the peripheral alpha 2B adrenoceptors stimulation of vascular smooth muscles and "can be attenuated by a slow infusion over 10 or more minutes". Even at slower infusion rates however the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7% with a decrease in heart rate between 16% and 18%.The initial response lasts for 5-10 minutes and is followed by a decrease in blood pressure of approximately 10%-20% below baseline values; both these effects are caused by the inhibition of the central sympathetic outflow overriding the direct stimulant effects. Another possible explanation for the subsequent heart rate decrease is the stimulation of presynaptic alpha-2 adrenoceptors, leading to a decrease in norepinephrine release [5].

The application of a single high dose of Dexmedetomidine reduced norepinephrine release by as much as 92% in young healthy volunteers. The release of epinephrine is also reduced by the same amount. The baroreceptor reflex is well preserved in patients who received Dexmedetomidine, and the reflex heart rate response to a pressor stimulus is augmented. These results illustrate that cardiovascular response is evoked mainly by decrease in central sympathetic outflow [6].

Dexmedetomidine could result in cardiovascular depression i.e. bradycardia and hypotension. The incidence of postoperative bradycardia has been reported as high as 40% in healthy surgical patients who received Dexmedetomidine, especially high doses. Usually these temporary effects were successfully treated with atropine or ephedrine and volume infusions.

Methodology

Data was collected from 90 patients in the age group of 30-60 years of ASA class I & II, posted for elective TAH without any co-morbid diseases were grouped randomly by using closed sealed opaque envelope technique. The study drug was prepared by an anaesthesiologist, who was not involved with the study. All spinal blocks were given by the same anaesthesiologist who also was the observer. Hence the patient and the observer were blinded for the study drug.

After clinical approval of Institutional Ethical Committee Clearance and informed written consent of 90 patients of ASA physical class I and II who were posted for elective Total Abdominal Hysterectomy(TAH). The study population was randomly selected based on the closed sealed opaque envelope technique.

Group-B: Received 12.5mg (2.5ml) of 0.5% hyperbaric Bupivacaine with 0.5ml normal saline.

Group-D: Received 12.5mg (2.5ml) of 0.5% hyperbaric Bupivacaine with 5µg of Dexmedetomidine in (0.5ml normal saline).

Group-F: Received 12.5mg (2.5ml) of 0.5% hyperbaric Bupivacaine with 25µg Fentanyl in (0.5ml normal saline).

Inclusion criteria

Patients aged between 30 – 60 years belonging to ASA class I & II without any co-morbid disease admitted for elective TAH were included in the study.

Exclusion criteria

1. Patients with co-morbid conditions like diabetes mellitus, asthma, hypertension, cardiac disease, haematological disease etc.
2. Allergy to local anaesthetics.
3. Patients belonging to ASA class III, IV and V.
4. Patients posted for emergency surgeries.
5. Patients with body mass index more than 28kg/m^2.
6. Patients having absolute contraindication for spinal anaesthesia like raised intracranial pressure, severe hypovolaemia, bleeding diathesis and local infection.
7. Patient's refusal.

Results

Table 1: Diagnosis

Diagnosis	Groups					
	Group-B		Group-D		Group-F	
	No of patients	%	No of patients	%	No of patients	%
Fibroid uterus	21	70	21	70	22	73.3
DUB	9	30	9	30	8	26.7
Total	30		30		30	

P= 0.947

There was no statistically significant difference in the diagnosis of the patients among three groups (p=0.947).

Table 2: Duration of surgery in minutes

Duration of surgery in minutes	Group-B	Group-D	Group-F	P value B vs F	P value B vs D	P value F vs D
Mean±SD	61.00±13.60	66.33±12.79	67.33±10.72	0.051	0.123	0.744
Minimum	45	45	45			
Maximum	90	90	90			

The mean duration of surgery in Group-B was 61.00±13.60min, Group-D was 66.33±12.79min and Group-F was 67.33±10.72min. There was no statistically significant difference in the mean duration of surgery among three groups (P>0.05).

Table 3: Mean heart rate in bpm at various intervals in minutes

HR in bpm at various intervals (minutes)	Group-B	Group-F	Group-D	P value B vs F	P value B vs D	P value F vs D
Basal	84.23± 3.8	82.23±4.03	82.10±5.95	0.053	0.104	0.919
0	80.16±3.4	79.20±4.3	78.4±5.34	0.343	0.142	0.543
2	77.26±4.77	76.66±4.83	76.46±5.92	0.631	0.567	0.887
4	74.73±7.01	73.86±6.08	74.16±6.79	0.611	0.752	0.858
6	73.16±9.12	73.23±8.02	72.76±10.49	0.976	0.875	0.847
8	74.66±9.13	74.53±9.43	73.10±11.42	0.956	0.560	0.598
10	74.66±7.79	73.90±6.83	71.83±8.14	0.700	0.179	0.292
15	75.36±8.26	74.10±6.64	75.36±8.26	0.515	0.210	0.469
20	75.93±6.51	74.43±6.91	72.43±7.9	0.391	0.067	0.302
25	75.43±5.94	74.80±6.83	73.00±7.55	0.704	0.171	0.339
30	76.23±5.88	75.13±6.54	72.76±7.65	0.496	0.054	0.203
45	76.33±5.98	75.46±6.98	73.03±7.4	0.608	0.064	0.197
60	77.56±7.00	75.36±6.45	75.50±7.72	0.211	0.282	0.942
75	76.80±6.97	75.80±6.07	73.43±6.89	0.556	0.065	0.163

Statistically there was no significant difference in HR measured at various intervals throughout the surgery among the groups (P>0.05).

Table 4: Mean systolic blood pressure at various interval in mm of Hg

SBP at various intervals	Group-B	Group-D	Group-F	P value B vs F	P value B vs D	P value F vs D
Basal	126.80±6.18	125.33±5.67	126.03±5.35	0.610	0.342	0.625
0	122.56±5.37	121.66±4.75	122.23±4.85	0.802	0.495	0.650
2	117.06±6.43	115.26±5.34	115.70±5.53	0.382	0.243	0.759
4	110.90±10.31	110.00±7.40	107.60±10.94	0.234	0.699	0.324
6	111.40±6.47	106.70±17.70	107.73±11.035	0.122	0.177	0.787
8	112.73±7.22	113.46±4.71	112.96±5.43	0.888	0.643	0.705
10	115.43±6.92	115.86±3.91	116.06±4.24	0.671	0.766	0.850
15	119.13±6.67	117.73±4.10	118.70±6.26	0.796	0.332	0.483
20	119.50±5.13	118.93±3.83	118.91±4.45	0.333	0.630	0.552
25	119.76±5.51	118.96±3.7	118.16±4.04	0.205	0.514	0.429
30	118.73±3.66	118.36±2.74	118.20±3.30	0.556	0.663	0.833
45	119.70±5.65	118.70±4.50	118.40±4.44	0.326	0.452	0.796
60	118.40±5.79	117.63±4.82	117.90±4.35	0.707	0.580	0.823
75	118.30±5.02	118.20±4.14	117.96±4.25	0.783	0.933	0.830

Statistically there was no significant difference in SBP (mm of Hg) measured at various intervals throughout the surgery among the groups (P>0.05).

Table 5: Mean diastolic blood pressure at various intervals in mm of Hg

DBP in mm of Hg at various intervals in minutes	Group-B	Group-D	Group-F	P value B vs F	P value B vs D	P value F vs D
Basal	81.80±3.12	80.63±3.26	80.50±3.22	0.118	0.163	0.874
0	79.73±3.81	78.46±4.01	78.84±3.96	0.174	0.215	0.899
2	76.43±3.90	75.56±4.31	75.03±3.50	0.149	0.418	0.601
4	72.26±3.17	71.30±5.94	70.16±6.18	0.103	0.435	0.472
6	70.50±3.97	69.16±6.62	69.26±4.67	0.275	0.349	0.946
8	71.40±3.86	71.26±3.61	71.36±3.69	0.973	0.891	0.916
10	70.43±5.51	71.33±3.72	71.13±3.14	0.548	0.462	0.823
15	72.33±4.90	72.13±4.23	72.40±4.08	0.955	0.866	0.805
20	73.20±5.33	72.46±4.72	72.40±4.59	0.536	0.575	0.956
25	73.93±5.74	73.26±5.74	73.13±5.00	0.567	0.638	0.919

30	75.56±5.29	74.56±4.77	74.96±5.01	0.654	0.446	0.753
45	75.70±5.98	74.86±5.59	75.33±5.55	0.807	0.580	0.747
60	76.63±5.18	75.70±4.85	76.13±4.87	0.702	0.474	0.731
75	76.23±4.88	75.96±4.03	75.96±4.37	0.172	0.819	1

Statistically there was no significant difference in DBP (mm of Hg) measured at various intervals throughout the surgery among the groups (P>0.05).

Table 6: Mean arterial pressure at various intervals in mm of Hg

MAP at various intervals in minutes	Group-B	Group-D	Group-F	P value B vs F	P value B vs D	P value F vs D
Basal	96.90±3.43	95.53±3.17	95.73±3.09	0.172	0.115	0.806
0	93.93±3.18	92.80±3.34	92.93±3.44	0.248	0.184	0.880
2	89.86±3.42	89.03±3.37	88.60±2.96	0.131	0.346	0.600
4	85.10±4.71	83.23±.75	82.60±7.17	0.116	0.175	0.707
6	84.10±4.02	80.56±8.54	82.00±6.36	0.132	0.045	0.464
8	85.16±3.74	85.33±3.28	85.20±3.38	0.971	0.855	0.878
10	85.50±5.25	86.23±2.93	86.16±2.71	0.540	0.507	0.928
15	87.93±4.35	87.33±3.56	87.86±3.85	0.950	0.562	0.580
20	88.63±4.35	87.93±3.59	87.70±3.69	0.375	0.500	0.805
25	89.23±4.50	88.56±3.9	88.13±3.75	0.308	0.546	0.667
30	89.93±3.77	89.93±3.55	89.43±3.68	0.606	0.421	0.776
45	90.36±4.45	89.50±4.18	89.63±4.24	0.516	0.440	0.903
60	90.60±4.53	89.73±4.20	90.06±4.19	0.638	0.445	0.759
75	90.30±4.01	90.03±3.36	90.03±3.69	0.790	0.819	1.00

Statistically there was no significant difference in MAP (mm of Hg) measured at various intervals throughout the surgery among the groups (P>0.05).

Discussion

The most common anesthetic technique used in our institution for TAH is spinal anaesthesia. Hyperbaric Bupivacaine 0.5% is extensively used in India for spinal anaesthesia for its long duration of action and minimal incidence of transient neurological symptoms. In our institution 12.5mg of hyperbaric Bupivacaine is the dose that is regularly used for TAH. Bupivacaine alone will produce duration of sensory block up to 90-100 minutes. Hence it is understood that Bupivacaine alone may not be sufficient to provide post-operative analgesia for these patients. Hence, commonly adjuvants are added along with Bupivacaine for prolonging the post-operative analgesia. Opioids are the most popular adjuvants used for this purpose. Other than morphine, Fentanyl is the most common opioid used for prolonging the duration of intrathecal Bupivacaine. Addition of various doses of Fentanyl intrathecally as an adjuvant to spinal anaesthesia produces faster onset time, decreases the visceral pain, somatic pain, improved intra-operative analgesia and excellent quality of peri-operative analgesia. Fentanyl 25µg as an adjuvant to Bupivacaine is the usual dose administered by various authors and in our institution. But drawback of Fentanyl is its short duration of post-operative analgesia, side effects like pruritus, respiratory depression, increased incidence of post-operative nausea and vomiting. Because of these draw backs of Fentanyl there is requirement of a suitable adjuvant which could produce prolonged duration of postoperative analgesia with minimal side effects [7].

α2 agonists like Clonidine and Dexmedetomidine have been used as adjuvants along with 0.5% hyperbaric Bupivacaine for spinal anaesthesia. Dexmedetomidine has been used as an intrathecal adjuvant for spinal anaesthesia in various doses from 3 to 15µg. Although Dexmedetomidine has been approved by the US food and drug administration as an intravenous sedative for mechanically ventilated adult intensive care unit patients. Its intrathecal use is off label. Various clinical studies using Dexmedetomidine as an adjuvant by intrathecal route with Bupivacaine have found to be safe without producing any neurological deficit on short term followup. Dexmedetomidine is more specific to α 2 adrenergic receptor and recently introduced in India. Dexmedetomidine 5µg has been used in more number of studies. Its use in human studies has also shown promising results in terms of early sensory and motor blocks and enhanced post-operative analgesic effects. Not many studies have been done comparing the usefulness of Dexmedetomidine with commonly used Fentanyl [8].

In our study there was no statistically significant difference in the haemodynamic parameters like heart rate, systolic blood pressure, and diastolic blood pressure, mean arterial blood pressure throughout the surgery when Group-D and Group-F was compared with group-B and also there is no statistical significant difference when Group-D compared with Group-F. In our study 2 patients each in Group-B and Group-F, 4 patients in Group-F developed significant bradycardia, which was statistically not significant. In our study 4 patients in Group-B, 7 patients in Group-F and 11 patients in Group-D developed significant hypotension, which was statistically not significant. Our study compares with the studies conducted by Al Ghanem S M *et al*. [9] Kanazi *et al*. [10], Tarbeeh G A [11] and Gupta R *et al*. [12] who also did not find significant difference statistically.

Conclusion

Both Fentanyl and Dexmedetomidine as adjuvants do not produce significant haemodynamic changes, with minimal effects on ventilation and oxygenation.

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