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Evaluation of Effect of Low Dose Fentanyl, Dexmedetomidine and Clonidine in Spinal Anaesthesia in Hysterectomies and Lower Abdominal Surgeries

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Abstract: *In the present study effect of intrathecal hyperbaric Bupivacaine 0.5% with low doses of Clonidine or Fentanyl or Dexmedetomidine were compared in elective lower abdominal surgeries. This was a prospective randomized control trial. 90 patients belonging to ASA 1 &II, aged between 20-50 years were allocated into three groups. Group-C: Clonidine 30µg, Group-D: Dexmedetomidine 5 µg, Group-F: Fentanyl 25 µg. The onset of sensory blockade was comparable in all the three groups. The onset of motor blockade was earlier by about 1.3 mins in Dexmedetomidine group when compared to Clonidine and Fentanyl group. Duration of sensory blockade was prolonged in Dexmedetomidine group (346mins) when compared to Clonidine (300mins) and Fentanyl (302mins) group. Time duration of motor blockade was prolonged in Dexmedetomidine group (269mins) when compared to Clonidine (223mins) and Fentanyl (220mins) group. The haemodynamic parameters were clinically and statistically insignificant The time of first request for analgesics by the patients was more in Dexmedetomidine group (250mins) when compared to Clonidine (194mins) and Fentanyl (189mins) group. The use of intrathecal Dexmedetomidine as an adjuvant to Bupivacaine is an attractive alternative to Fentanyl or Clonidine for long duration surgical procedures due to its profound intrathecal anesthetic and analgesic properties combined with minimal side effects.*

Keywords: *Bupivacaine, Clonidine, Dexmeditomidine, Fentanyl, Intrathecal*

I. Introduction

Spinal anaesthesia is the most preferred regional anaesthesia technique as it is easy to perform, economical and produces rapid onset of anaesthesia and complete muscle relaxation. Hyperbaric Bupivacaine is the most commonly used intrathecal local anaesthetic.

Various adjuvants have been added to Bupivacaine to prolong the duration of block. The present study was performed to compare Fentanyl, Clonidine and Dexmedetomidine in their efficacy as adjuvants to subarachnoid block.

Fentanyl, analgesia is due to action on µ receptor at supraspinal site, is used as an adjuvant, which prolongs the duration of spinal block. The mechanism by which intrathecal α2 adrenoreceptor agonists prolong the motor and sensory block of local anesthetics is at the best, speculative. It may be an additive or synergistic effect secondary to the different mechanisms of action of the local anesthetics and intrathecal α2 adrenoreceptor agonists. Local anesthetics act by blocking sodium channels and α2 adrenoreceptor agonists act by binding to the presynaptic C-fibers and postsynaptic dorsal horn neurons. They produce analgesia by depressing release of C-fiber transmitters and by hyper-polarization of postsynaptic dorsal horn neurons. The prolongation of the motor block of spinal anesthetics may be the result of binding of α2 adrenoreceptor agonists to the motor neurons in the dorsal horn. Dexmedetomidine is eight times more specific and highly selective α2adrenoreceptor agonist compared to Clonidine, thereby making it a useful and safe adjunct in diverse clinical applications.

II. Aims And Objectives

The aim of the study was to compare the following factors in 90 patients divided into three groups of 30 each i.e.

a) 0.5%Hyperbaric Bupivacaine 15mg and Fentanyl 25µg
b) 0.5%Hyperbaric Bupivacaine 15mg and Clonidine 30µg
c) 0.5%Hyperbaric Bupivacaine 15mg and Dexmedetomidine 5µg

when given intrathecally

Onset and Duration of Sensory blockade, Onset and Duration of Motor blockade, Intraoperative Haemodynamic changes. Post operative period Analgesic requirements and post operative complications such as nausea, vomiting, hypotension, shivering, pruritus, respiratory depression
and seizures.

III. Patients And Methods

3.1 Inclusion Criteria:
Patients of either sex, with ASA Grade-I and Grade-II, Patients aged between 20-50 years.

3.2Exclusion Criteria:
Patients with ASA Grade-III, IV and V below 20 years of age and above 50 years of age, having abnormal spine, with severe systemic diseases, metabolic disorders, neurological,
congenital and cardiovascular diseases.
Mode of Selection: Randomized double blind

3.3 Equipment used:-
Disposable 25G Quincke Spinal Needle.
5ml Disposable plastic syringe.
Philips Multiparameter Monitor [SpO_2 , PR, NIBP].
Anaesthesia machine, Resuscitation Equipment (stand by)

3.4 Preoperative Period:
On the day prior to surgery all the patients were visited and detailed preanesthetic examination was carried out. The anesthetic procedure was briefly explained to the patient. An informed written consent was obtained. Patients were kept nil per oral for 6 hours before surgery.

Routine investigations like Haemoglobin, Total Leucocyte Count, Differential Leucocyte Count, ESR, Complete Urine Examination, Random Blood Sugar, Electrocardiogram, Chest X-Ray, Blood Grouping/Typing, Blood Urea, Serum Creatinine were done.

All the patients were premedicated with IM promethazine 25 mg plus pentazocine 30 mg, 1hr prior to surgery. Patient's weight and height were also recorded.

3.5 Intra operative period:
Once shifted to the operating room, the patient was connected to the routine monitors which included NIBP, SpO2 and ECG.

All emergency resuscitation equipments and emergency drugs were kept ready. The anesthesia machine was also checked along with the oxygen delivery system.

These patients were randomly assigned using sealed envelope technique to
one of the three groups in a double blind manner.viz;
Group C: 30 patients received 3ml of 15mg of hyperbaric Bupivacaine 0.5%
with 0.5 ml of 30µg of Clonidine.
Group D**:** 30 patients received 3ml of 15mg of hyperbaric Bupivacaine 0.5%
with 0.5 ml of 5µg of Dexmedetomidine.
Group F**:** 30 patients received 3ml of 15mg of hyperbaric Bupivacaine 0.5%
with 0.5 ml of 25µg of Fentanyl.

Baseline Pulse Rate, Blood Pressure, Respiratory Rate, SpO_2 were recorded.

A wide bore IV access was obtained and secured. All patients were preloaded with 500ml of Ringer's lactate prior to spinal anesthesia, and there after 10 ml/min of fluid was administered till the completion of surgery. Additional volume of fluids and vasopressor were given as per need and recorded.

The patients were then put in right lateral position. Under strict aseptic precautions, lumbar puncture was performed by midline approach by using disposable 25G Quincke spinal needle in L**3**- L**4** intervertebral space. In all the groups, the total volume administered was made up to 3.5 ml to achieve subarachnoid block.

3.5.1Assessment of Sensory blockade:
This was tested by pin-prick method. The time of onset was taken from time of injection of drug into subarachnoid space to loss of pin-prick sensation at T6 dermatomal level.

The duration of sensory blockade was recorded from time of onset to time of return of pin prick sensation to S1 dermatomal area, testing every 15 mins, postoperatively.

After spinal anesthesia, haemodynamic status was monitored by recording the patient's pulse rate and blood pressure at 0, 5 and every 5 mins up to 30 mins, every 15 mins up to 60 mins and then every 30 mins up to 120 mins.

3.5.2 Assessment of Motor Blockade:

This was assessed by Bromage scale. The time interval between injection of drug into subarachnoid space, to the patient's inability to lift the straight extended leg was taken as onset time. The time to achieve maximum motor blockade was noted from time of injection of the drug to maximum degree of motor block.

Bromage Scale:

0 - Free movement of legs and feet, with ability to raise extended leg.
1 - Inability to raise extended leg and knee flexion is decreased but full flexion of feet and ankle is present.
2 - Unable to flex knees, but some flexion of feet and ankle is possible.
3 - Unable to move feet, legs or toes.

The duration of motor block was recorded from onset time to time when the patient was able to lift the extended leg, noted every 15 minutes, postoperatively.

3.5.3Adverse effects:

The adverse effects like nausea and vomiting, hypotension, respiratory depression, shivering, pruritus, motor weakness and seizures are noted in both groups
.

3.5.4Statistical analysis:

The data was analyzed using one-way analysis of variance (ANOVA). All values were expressed as mean ± standard deviation. $P < 0.05$ was considered statistically significant.

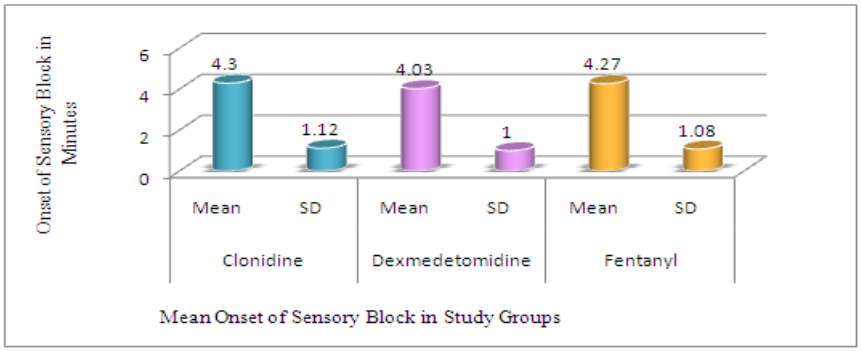
IV. Observations And Results

The results are as follows :

Demographic profiles of the patients scheduled for study were comparable

The onset of sensory blockade was 4.3 +/- 1.12 minutes in Group C, 4.03 +/- 1.00 in Group D and in Group F was 4.27 +/- 1.08 minutes.

The difference between the groups was statistically not significant.



The onset of motor blockade was 6.57 +/- 1.48 minutes in Group C, 5.27 +/- 1.25 in Group D and in Group F was 6.53 +/- 1.31 minutes. The difference between groups was statistically highly significant and earlier in Group D.

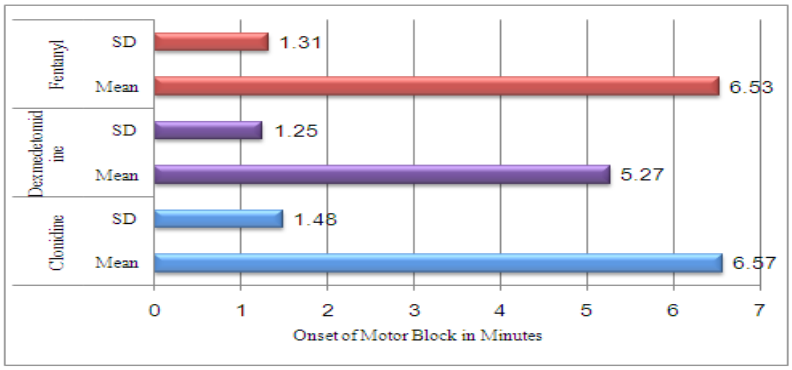


Table: Duration of Sensory Blockade(Minutes)

	Group C		Group D		Group F			
Duration of Sensory Block (Minutes)	Clonidine		Dexmedetomidine		Fentanyl		Total	
	No.	%	No.	%	No.	%	No.	%
230-289	10	33.33%	2	6.67%	9	30.00%	21	23.33%
290-349	19	63.33%	14	46.67%	20	66.67%	53	58.89%
350-409	1	3.33%	10	33.33%	1	3.33%	12	13.33%
410-469	0	0.00%	4	13.33%	0	0.00%	4	4.44%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Mean +/- SD	300.83 +/- 35.06		345.93 +/- 45.9		301.7 +/- 35.35			
ANOVA 'F'-statistic	13.05							
P-Value	< 0.001							
Inference	Highly Significant							

The time for complete sensory recovery was 300.83 +/- 35.06 in Group C, 345.93 +/- 45.9 minutes in Group D and in Group F was 301.7 +/- 35.35 minutes. The duration of sensory blockade was longer in Group D. The difference was statistically highly significant.

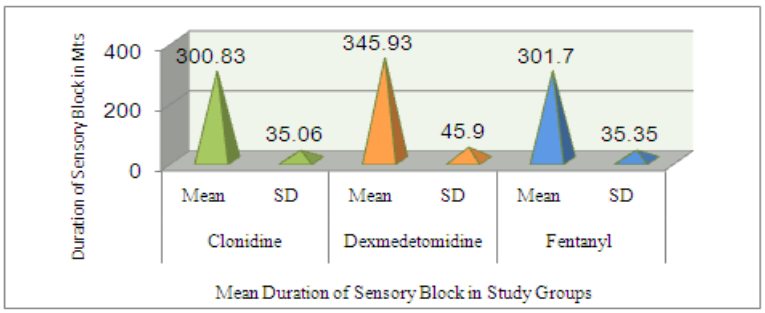


Table : Duration Of Motor Blockade (Minutes).

	Group C		Group D		Group F			
Duration of Motor Block (Minutes)	Clonidine		Dexmedetomidine		Fentanyl		Total	
	No.	%	No.	%	No.	%	No.	%
121-180	5	16.67%	1	3.33%	5	16.67%	11	12.22%
181-240	13	43.33%	3	10.00%	13	43.33%	29	32.22%
241-300	10	33.33%	20	66.67%	10	33.33%	40	44.44%
301-360	2	6.67%	5	16.67%	2	6.67%	9	10.00%
361-420	0	0.00%	1	3.33%	0	0.00%	1	1.11%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Mean +/- SD	223.03 +/- 45.35		269.6 +/- 45.05		220.93 +/- 41.7			
ANOVA'F'-statistic	10.55							
P-Value	< 0.001							
Inference	Highly Significant							

The time for complete motor recovery was 223.03 +/- 45.35 in Group C, 269.6 +/- 45.05 minutes in Group D and in Group F was 220.93 +/- 41.7 minutes. The duration of motor blockade was longer in Group D. The difference was statistically highly significant.

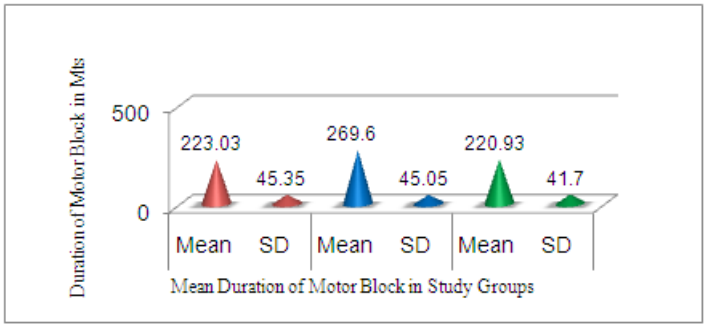
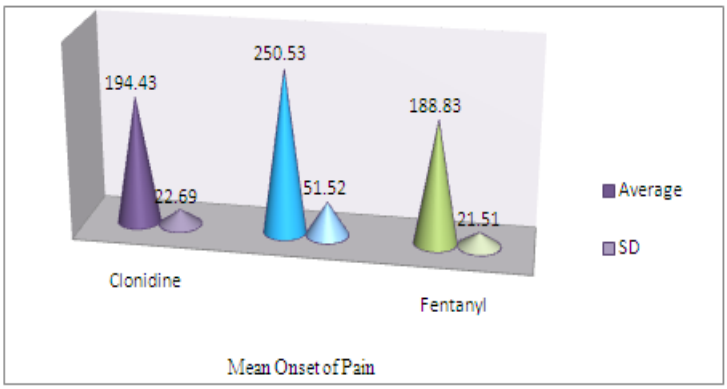


Table Time of first request of analgesic by the patients in three groups in minutes.

	Group C		Group D		Group F			
Onset of Pain (Minutes)	Clonidine		Dexmedetomidine		Fentanyl		Total	
	No.	%	No.	%	No.	%	No.	%
141-200	24	80.00%	6	20.00%	25	83.33%	55	61.11%
201-260	6	20.00%	13	43.33%	5	16.67%	24	26.67%
261-320	0	0.00%	9	30.00%	0	0.00%	9	10.00%
321-380	0	0.00%	1	3.33%	0	0.00%	1	1.11%
381-440	0	0.00%	1	3.33%	0	0.00%	1	1.11%
Total	30	100.00%	30	100.00%	30	100.00%	90	100.00%
Mean +/- SD	194.43 +/- 22.69		250.53 +/- 51.52		188.83 +/- 21.51			
ANOVA 'F'-statistic	28.85							
P-Value	< 0.001							
Inference	Highly Significant							

The time for first request analgesic by the patient was 144.65 ±26.39 in Group C, 250.53 +/- 51.52 minutes in Group D and in Group F was 188.83 +/- 21.51minutes .The time for first request analgesics was longer in Group D. The difference was statistically highly significant

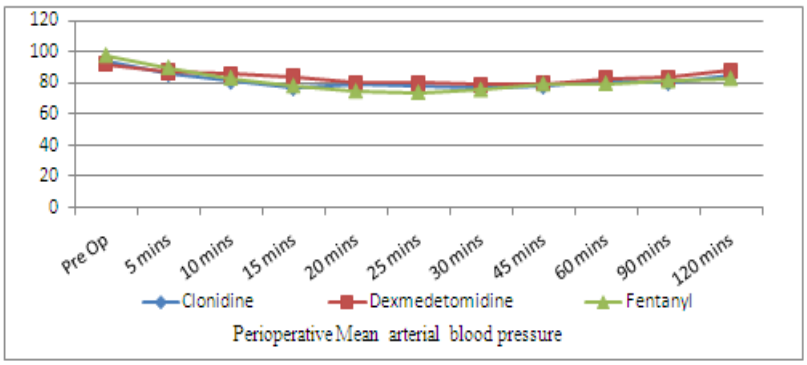


Incidence of side effects:

Bradycardia was observed in 2 patients in Group C, 1 patient in Group D and 1 patient in Group F and Vomiting was observed in 1 patient in the Group D and 1 patient in the Group F without any significant difference

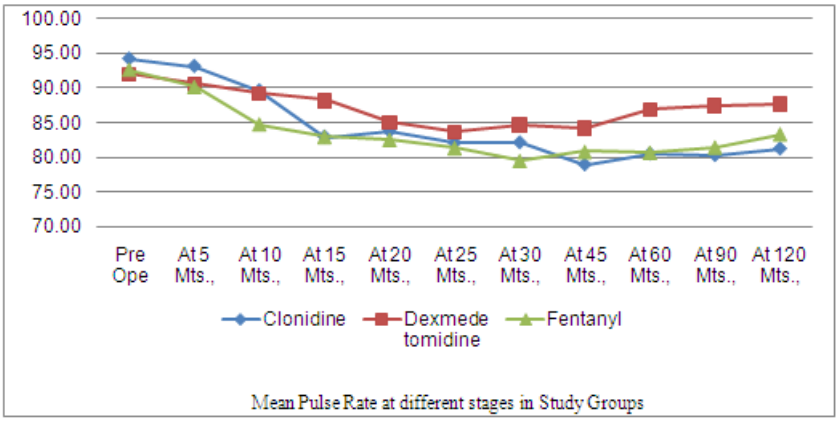
Incidence of hypotension and requirement of mephenteramine was comparable in all the groups with no significant difference among them

The difference of fall in SBP between the groups at different time intervals studied was statistically insignificant (P>0.05).



In the first 15min the drop in mean arterial pressure in Group C is more than in Group D. The difference is statistically significant.(P<0.05)
In the first 15min the drop in diastolic pressure in Group C and Group F is more than in Group D. The difference is statistically significant.(P<0.05)

The difference between the pulse rates in three groups was statistically not significant(P>0.05)



V. Discussion

Opioid receptors were found to be precisely localized in the posterior horn of the spinal cord in 1977. The effectiveness of intrathecal opioids depends on their bioavailability. Penetration into medullary tissue is influenced by their molecular weight, degree of ionization, and lipophilicity.

Fentanyl and meperidine are absorbed more rapidly than morphine for these reasons. They bind more solidly to neural tissue. The more lipophilic products are reabsorbed at the site through spinal vasculature. Neuraxial administration of opioids along with local anaesthetics improves quality of intraoperative analgesia and also provides postoperative pain relief for longer duration.[68] Highly hydrophilic opioids such as morphine, though provides very good intra and postoperative analgesia, its use becomes limited because of delayed respiratory depression that it causes due to rostral spread in intrathecal space.[68]

Fentanyl, a highly lipophilic opioid, has rapid onset of action following intrathecal administration. It is associated with fewer side effects compared to morphine. It has become very popular additive to hyperbaric Bupivacaine in recent times. However, fentanyl has side effects like pruritus, nausea and vomiting and even a possible serotonin syndrome related to intrathecal fentanyl has been reported.

Harbhej singh et al [1] in 1995, BN Biswas et al [2] in 2002, Khanna MS et al [3] in 2002 have chosen 25 micrograms of fentanyl as an additive to intrathecal hyperbaric Bupivacaine in their studies. Hence in this study, 25 micrograms of fentanyl was chosen as an additive to hyperbaric Bupivacaine.

In this study, the intrathecal dose of Dexmedetomidine selected was based on previous human studies wherein no neurotoxic effects have been observed.

Kanazi et al.[4] found that 3µg Dexmedetomidine or 30 µg Clonidine produced the same duration of sensory and motor block with minimal side effects in urologic surgical patients. From Kanazi study and animal studies, we assumed that 3-5 µg Dexmedetomidine would be equipotent to 30-45 µg Clonidine when used for supplementation of spinal bupivaciane..

Al-Mustafa MM et al.[5] in their study used intravenous Dexmedetomidine and found that it prolonged isobaric Bupivacaine spinal anaesthesia. However the dose required was 1µg/kg Dexmedetomidine bolus and an infusion of 0.5µg/kg/hr. whereas, when Dexmedetomidine has been used intrathecally by various authors the total dose used is from 3 µg to 15 µg. So intrathecal route is more specific and low doses can be used.

The onset of sensory blockade was 4.3 +/- 1.12 minutes in Group C, 4.03 +/- 1.00 in Group D and was 4.27 +/- 1.08 minutes. The difference between the groups was statistically not significant.

The onset of motor blockade was 6.57 +/- 1.48 minutes in Group C, 5.27 +/- 1.25 in Group D and in Group F was 6.53 +/- 1.31 minutes. The difference between groups was statistically highly significant.

Duration of sensory and motor blockade - In the present study, the time for complete sensory recovery was 300.83 +/- 35.06 minutes in Group C, 345.93 +/- 45.9 minutes in Group D and in Group F was 301.7 +/- 35.35 minutes. The duration of sensory blockade was longer in Group D. The difference was statistically highly significant. This shows addition of Dexmedetomidine to intrathecal Bupivacaine increases the duration of sensory blockade more than that with Clonidine and Fentanyl . Both Clonidine and Fentanyl were however comparable producing almost similar duration of sensory blockade.

The time for complete motor recovery was 223.03 +/- 45.35 minutes in Group C, 269.6 +/- 45.05 minutes in Group D and in Group F was 220.93 +/- 41.7 minutes. The duration of motor blockade was longer in Group D. The difference was statistically highly significant. This shows addition of Dexmedetomidine to intrathecal Bupivacaine increases the duration of motor blockade more than that with Clonidine and Fentanyl.

Above results conclude that supplementation of intrathecal Bupivacaine with Dexmedetomidine increases the duration of sensory as well as motor block than Clonidine and Fentanyl.

Duration of Post operative analgesia In this study: the time for first request of analgesics by the patient was 144.65 ±26.39 in Group C, 250.53 +/- 51.52 minutes in Group D and in Group F was 188.83 +/- 21.51minutes .The time for first request analgesics was longer in Group D. The difference was statistically highly significant.

van Tuijl I, van Klei WA et al [6] (2006) have demonstrated that addition of 75µg Clonidine to hyperbaric Bupivacaine prolongs spinal analgesia and the motor block after caesarean section and improves early analgesia.

Nayagam HA, Singh NR, Singh HS.,[7](2014) concluded that Dexmedetomidine is superior to Fentanyl since it facilitates the spread of the block and offers longer postoperative analgesic duration.

In the present study also addition of Dexmedetomidine to intrathecal Bupivacaine increases the duration of postoperative analgesia and the duration of postoperative analgesia is longer than that with Clonidine and Fentanyl.

Regarding Haemodynamic stability, in the present study, the incidence of hypotension and requirement of mephenteramine with comparable in all the groups with no significant difference among them

In the first 15min the drop in mean arterial pressure in Bupivacaine + Clonidine is more than Bupivacaine + Dexmedetomidine group and the difference is statistically significant. Bradycardia was observed in 2 patients in Group C, 1 patient in Group D and 1 patient in Group F, without any significant difference.

G.E.Kanazi, M.T.Aouad et al (2006) found that Dexmedetomidine 3µg and Clonidine 30µg have an equipotent effect on the characteristics of the block without any significant hemodynamic instability or sedation.

H. Singh . et al[1] 1995 in their study administered Fentanyl 25 µg with Bupivacaine 13.5 mg in patients undergoing urological procedures. They observed that cardiovascular profile of their patients were stable.

Above studies conclude that addition of low doses of Clonidine, Dexmedetomidine or Fentanyl to intrathecal Bupivacaine causes no gross hemodynamic changes .Our present study also confirmed the same probably because small doses of intrathecal Dexmedetomidine, Clonidine, and Fentanyl were used. These doses of adjuvants used in this study did not affect the near maximal sympatholysis caused by local anesthetics.

Vomiting was observed in 1 patient in the Dexmedetomidine group and 1 patient in the Fentanyl group without any statistical significance. Respiratory depression is one of the major side effect of intrathecal opioids. None of our patients experienced respiratory depression and maintained SpO_2 of 98-100% in all the groups.

Pruritus is a frequent complication (49-100%) of intrathecal Fentanyl but it was not observed in the present study

Buvanendran et al[8] found that addition of small dose of Bupivacaine to intrathecal Fentanyl reduces the incidence of prurities from 95% to 36%, on all parts of body except the face.

The mechanism by which the combination of local anesthetic with opioid may result in a reduced incidence of pruritus may be either due to neuronal blockade or direct modulation of opioid receptors, probably inhibiting receptor action and increasing opioid binding to delta and kappa receptors. The α-2 adrenergic agents also have antishivering property as observed by Talke et al [9] and Maroof M et al [10] . no incidence of shivering was found in this study.

VI. Conclusion

In the present study use of intrathecal Dexmedetomidine as an adjuvant to Bupivacaine seems to be an attractive alternative to Fentanyl and Clonidine for long duration surgical procedures due to its profound intrathecal anesthetic and analgesic properties combined with minimal side effects.

- Addition of Dexmedetomidine to intrathecal Bupivacaine will prolong the duration of sensory and motor blockade when compared to Clonidine and Fentanyl, with stable hemodynamics and no significant side effects.
- Onset of motor blockade is earlier with Dexmedetomidine.
- Dexmedetomidine provides prolonged postoperative analgesia.

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