IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 7 Ver. VII (July. 2017), PP 43-64
www.iosrjournals.org

To Study the Analgesic Effect of Transdermal Nitroglycerine with Intrathecal Clonidine in Lower Abdominal Surgeries"

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Abstract
Introduction: *Spinal anesthesia is the most preferred regional anaesthesia technique as it is easy to perform, economical and produces rapid onset of anaesthesia and complete muscle relaxation. The aim of intrathecal local anesthetic is to provide adequate sensory and motor block necessary for all lower abdominal and lower limb surgeries. The sole essence of anaesthesia is relief of pain in intra and post-operative period.*
Over the last decade, there has been considerable revival of interest in the use of adjuncts to local anaesthetic agents in central neuraxial blockswith the aim of prolonging the duration of sensory and motor block and reducing post-operative analgesic requirements.
Aims And Objectives: *This study is done to evaluate the following effects in two groups:*
- ***Group I (BC)*** *15mg of 0.5% hyperbaric bupivacaine hydrochloride with 50 mcg of clonidine hydrochloride*
- ***Group II (BCN)*** *15 mg of 0.5% hyperbaric bupivacaine hydrochloride with 50 mcg of clonidine hydrochloride with transdermal nitroglycerine patch*

- Onset and duration of sensory blockade
- Onset and duration of motor blockade
- Duration of analgesia
- Time of two segment sensory and motor block regression
- Intra operative and post-operative hemodynamic profile
-Any side effects or complications.
Materials And Methods: *We conducted this study on sixty ASA grade I and II patients undergoing elective lower abdominal and lower limb surgeries. The patients were randomly assigned to one of the two groups, each containing 30 patients, Group BC (received intrathecal clonidine with bupivacaine) and Group BCN (received transdermal nitroglycerine patch with intrathecal clonidine with bupivacaine). Parameters assessed were pulse rate, Blood Pressure, Spo2, and RR, onset of sensory and motor block, regression of two segment sensory block, and Visual analogue scale for duration of analgesia.*
Results: *The demographic profile was comparable. The hemodynamic parameters like pulse rate, Spo2 and respiratory rate did not show significant changes, it remained stable intraoperatively and postoperatively in both the study groups. Onset of sensory and motor block was seen to be similar in both the groups. In the patients receiving both the drugs showed significant prolongation in the duration of analgesia, delayed time of requirement of first rescue analgesic, decreased requirement of number of rescue analgesics, good VAS score, stable haemodynamic profile with no significant intraoperative or postoperative complications.*
Conclusion: *We have compared the drugs transdermal nitroglycerine patch with intrathecal clonidine in bupivacaine. The clinical advantage of transdermal nitroglycerine patch with intrathecal clonidine over only intrathecal clonidine in bupivacaine is that, it prolongs the duration of analgesia, delays the time of requirement of first rescue analgesic, decreases the requirement of number of rescue analgesics, with a stable haemodynamic profile and no significant intraoperative or postoperative complications.*
Keywords: *Transdermal nitroglycernine patch, Clonidine, Bupivacaine, spinal anaesthesia, lower abdominal surgeries.*

I. Introduction

The term "Spinal anaesthesia" was introduced by Leonard Corning in 1885, a neurologist in New York.[1] He was experimenting with cocaine on the spinal nerves of a dog when he accidentally pierced the dura mater; this led to administration of the first spinal analgesia. The present day spinal anaesthesia and technique of lumbar puncture was described by Quincke in 1891.The first planned spinal anaesthesia for surgery in man was administered by August Bier on 16th August 1898, in Kiel, when he injected 3ml of 0.5% cocaine solution into a 34 year old labourer. They recommended it for surgeries of legs, but gave it up due to the toxicity of

cocaine.Kries in 1900 used spinal analgesia for caesarean section; during the same year W. S. Bainbridge reported his first successful case of paediatric spinal analgesia.

Dowitz in 1903 added adrenaline to prolong the anaesthetic effect of lignocaine. Next series of studies were aimed at achieving higher levels of spinal blockade, by addition of alcohol to local anaesthetic to make it lighter than cerebrospinal fluid.Pitkin introduced Spinocaine (hypobaric) or Gravicaine (hyperbaric) in 1927. Lignocaine was synthesized by Lofgren of A.B Astra, Sweden in 1943 and used in clinical practice in 1948.Bupivacaine was synthesized by A.F.Ekenstein in 1957 and was used for regional blocks in 1966.Opiate receptors in the CNS including spinal cord were identified independently by Pert and Synder, Terrenius and Simon et al in 1973.Presence of dense collection of opiate receptors on substansia gelatinosa of spinal cord and creation of intense analgesia by direct application of narcotics to these receptors was reported by SH Snyder and TL Yaksh & TA Rudy in 1977.First description of use of intrathecal Morphine was done by Wang et al in 1979 while its first description for use of epidural morphine was done by Behar et al in 1979. 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. The aim of intrathecal local anaesthetic is to provide adequate sensory and motor block necessary for all lower abdominal and lower limb surgeries. [2] The sole essence of anaesthesia is relief of pain in the intra and post-operative period.

Post-operative pain is one of the worst types of pain a patient may suffer. With the birth of effective analgesia in the middle of 19th century, it was not long before that post-operative pain was recognized as a discipline worthy of attention in its own right. The goal of post-operative pain management is to reduce an individual patients pain considerably with minimal or no associated suffering or distress. Noxious stimuli such as surgical trauma and subsequent post-operative pain results in a broad range of endocrinological, inflammatory and immunological responses including increased release of catabolic hormones and inhibited secretion of anabolic mediators. Pathophysiologic consequences of undertreated pain may adversely influence peri-operative outcome.[3] Over the last decade, there has been considerable revival of interest in the use of adjuncts to local anaesthetic agents in central neuraxial blockswith the aim of prolonging the duration of sensory and motor block and reducing post-operative analgesic requirements.

Hyperbaric bupivacaine is the most commonly used intrathecal local anesthetic but has limited duration of action. Various adjuvants have therefore been added to bupivacaine to hasten the onset of block and prolong the duration of block. This prolongation has been tried by the addition of opioids such as morphine [4], fentanyl [5] and sufentanil [6] and other drugs such as dexmedetomidine,[7,8]clonidine[8,9,10], magnesium sulfate (MgSO4),[11] neostigmine,[11] ketamine,[12] and midazolam [13] to local anaesthetics. However each drug has its own limitations and a need for alternative method or drug always exists.

Newer adjuvants are also being investigated in an attempt to reduce the incidence of adverse effects while producing potent analgesic and anaesthetic effects.

The other newer adjuvants like, alpha2-adrenoceptor agonists are being increasingly used in anesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anesthesia and surgery, but also cause sedation and analgesia.[14] Intrathecal α2 receptors are found to have anti nociceptive action for both somatic and visceral pain.[15]

Above mentioned drugs have been used frequently as adjuvants to bupivacaine in subarachnoid block. However there are only a few studies available, on humans, upon the uses of transdermal nitroglycerine patch to prolong the duration of analgesia along with these said adjuvants; e.g.: clonidine,[16] sufentanil,[17] fentanyl,[18] ketamine [19] and neostigmine [20]. Transdermal nitroglycerine acts as an analgesic by release of nitric oxide (NO). Nitric oxide produces pain modulation via release of cyclic guanosine monophosphate (cGMP) in the central and peripheral nervous system.v Therefore we designed this study to compare the effect and side effects of the use of transdermal nitroglycerine and intrathecal clonidine with hyperbaric bupivacaine in lower abdominal surgeries.

II. Materials And Methods

Method:

Type of study: - Prospective, randomized, placebo-controlled, double blinded study

Period of study: - July 2014 to September 2016

Period requiredfor data collection: - 1.5yrs

Period required for data analysis and reporting: - 6 months

Sample size:- 66 cases

- **Group BC-** 33 cases. Group I (BC) (15mg hyperbaric bupivacaine hydrochloride with 50 mcg of clonidine hydrochloride)
- **Group II (BCN)** 33 cases (15 mg hyperbaric bupivacaine hydrochloride with 50 mcg of clonidine hydrochloride with transdermal nitroglycerine patch)

Place of study: - Department of Anaesthesiology, Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune – 411018.

Inclusion Criteria

1. ASA grade I or II fit patients.
2. Ages between 20 and 60 years of either sex
3. Patients undergoing elective lower abdominal surgeries under spinal anaesthesia.
4. Haemodynamically stable patients with all routine investigations within normal limits without any other co morbidities.
5. Patients who are not on any cardiac related drugs.
6. Availability of informed consent.

Exclusion Criteria

1. Patients with ASA physical status III or more.
2. Patients below 20 years and above 60 years of age.
3. 3 Patients posted for emergency procedures.
4. Patients with major neurological, cardiac, respiratory, metabolic, renal, hepatic disease or with coagulation abnormalities.
5. Patients contraindicated for spinal anesthesia.
6. Patients with cardiac co-morbidities.
7. Patients with known allergies to the study drugs.

Plan Of Study

Institutional ethics committee approval was taken prior to the commencement of the study. 66 patients undergoing elective lower abdominal surgeries under spinal anesthesia were selected randomly after applying already mentioned stringent inclusion and exclusion criteria. The patients were divided into two groups of 33 each, namely Group BC and Group BCN.

An informed and written consent was taken from every case selected for the study, patients were randomly allocated to one of the two groups according to the drug used:

- Group I (BC) 33 cases (Inj. 15mg hyperbaric bupivacaine hydrochloride with 50 mcg of Inj. clonidine hydrochloride)
- Group II (BCN) 33 cases (Inj. 15mg hyperbaric bupivacaine with inj. 50 mcg of intrathecal clonidine hydrochloride and transdermal nitroglycerine patch)
-

Material Required

- Standard anaesthesia machine (Boyle's apparatus)
- Intravenous cannula 20 G
- Intravenous fluids – Crystalloids and colloids
- Monitoring equipments such as pulse oximeter, ECG monitor, non-invasive blood pressure apparatus
- 26 G Quincke's spinal need
- Disposable syringe
- Drugs for spinal anaesthesia: 0.5% hyperbaric Bupivacaine hydrochloride , Inj. Clonidine hydrochloride 150mcg/ml ampoule, Transdermal NTG patch(Novartis Pharma, Basel, Switzerland)
- Drugs and equipments necessary for resuscitation

Pre Operative Evaluation

All patients were thoroughly evaluated pre-operatively, one day prior to surgery. It comprised of detailed history (including history of ischemic heart disease, hypertension, bronchial asthma, allergy to any of the drug used), general, physical and systemic examination was done. The necessary and relevant laboratory investigations, like complete haemogram, urine routine, renal function tests, random blood sugar, chest X-ray and electrocardiogram (ECG) were done prior to surgery and proper written consent was confirmed.

In the pre-operative room, the patient's pulse, blood pressure and heart rate was taken, with the patient lying comfortably in supine position.

All the patients were kept nil per oral (NPO) for a period of at least 6 hours prior to the surgery to avoid the risk of aspiration and other anesthesia related complications.

Pre-Anaesthetic Medication And Administration Of Study Drug

The patients were brought into the operation theatre. After shifting the patient on the operating table, all the monitors such as non-invasive blood pressure (NIBP), pulse oximeter, electrocardiogram (ECG), were connected to the patients. Base line vital parameters such as pulse rate (PR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SPO_2, respiratory rate (RR) and ECG was recorded (T_0) .A good and secure intravenous line was obtained using a 20 G i.v. cannula and an infusion of ringer lactate solution (RL) was started slowly. The drug to be given intrathecally was prepared by one anaesthesiologist. However observations were made by the second anaesthesiologist.

The two groups were as under:

- Group I (BC) 33 cases (Inj. 15mg hyperbaric bupivacaine hydrochloride with 50 mcg of Inj. clonidine hydrochloride)

Group II (BCN) 33 cases (Inj. 15mg hyperbaric bupivacaine with inj. 50 mcg of clonidine hydrochloride and transdermal nitroglycerine patch).

Spinal anaesthesia technique:

Administration Of Study Drug-

The patients were administered subarachnoid block under all aseptic precautions in sitting position, the drug to be studied was administered intrathecally. A 26-gauge Quincke spinal needle was introduced into subarachnoid space at the L_{2-3} or L_{3-4} vertebral level after local infiltration of the interspace with 2 ml of 2% lignocaine. With the needle orifice cephalad and after confirmation of free flow of CSF, the prepared drug solution was injected through the spinal needle. The spinal needle was withdrawn and patients were repositioned supine.

An ECG electrode cut into the shape of an NTG patch was then put on the unanaesthetised area, over left infraclavicular region of patients in Group I (BC) while an NTG patch (Nitroderm TTS, Novartis Pharma, Global headquarters, Basel, Switzerland, 25 mg/ patch) was put on patients of Group II (BCN); in the unanaesthetized area similar to the placebo that is the cut ECG patch. The anaesthesiologist inducing the patient did not know about the contents of the intrathecal agent and also the type of the patch put. The monitoring was done by the second anaesthesiologist.
No additional analgesic was administered unless requested by the patient.

Clinical Parameters Studied

During the surgery, monitoring was done as follows:

- Continuous pulse rate monitoring
- Continuous blood pressure monitoring (S.B.P, D.B.P, Mean B.P)
- Oxygen Saturation

- Respiratory Rate

These parameters were monitored in following time pattern:
T0- baseline (before induction of drug)
T1-after induction of drug
T2-onset of sensory block
T3-onset of motor block
T4-time of two segment motor regression
T5-time of two segment sensory regression
T6-time of first rescue analgesia given
Patients were also monitored for side effects like nausea, vomiting, restlessness, pruritus and sedation.

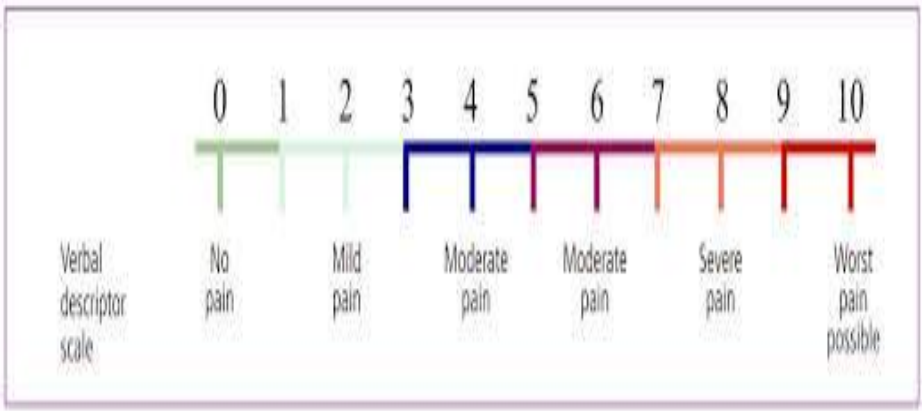
Intraoperatively pulse rate, non-invasive blood pressure, electrocardiogram, SpO_2 was recorded, every 2 minutes for the first 10 minutes, every 10 minutes for the next 50 minutes and every 15 minutes till the end of surgery.

- Time of onset of sensory block was noted using pin prick method.
- Time of onset of motor block using modified Bromage scale [66]was noted as follows.

Bromage 0 – free movement of legs and feet, with ability to raise extended leg
Bromage 1 – inability to raise extended leg and knee flexion is decreased, but full flexion of feet and ankles is present
Bromage 2 – inability to raise leg or flex knees, flexion of ankle and feet present
Bromage 3 – inability to raise leg, flex knee or ankle or move toes.

- Hypotension defined as > 20 % fall of baseline blood pressure was treated with bolus dose of 6 mg mephenteramine i.v.
- Bradycardia defined as pulse rate < 50 bpm , was treated with 0.6 mg atropine.iv
- Post operatively regression of the sensory block and the motor blockade to reach modified Bromage scale 0 was noted.
- Visual analogue scale[67,68] was used to assess post-operative pain.

0 = no pain
1-2= Mild pain
3-7= Moderate pain
>7= Severe pain
10 = Maximum pain.



When patient complained of moderate to severe pain, with VAS score of 7 or more, it was taken as time for first rescue analgesia and total duration of analgesia was calculated from time of induction till time of first rescue analgesia was given. Inj. Diclofenac 75 mg. was given intramuscularly in the gluteal region on demand for rescue analgesia by the patient. Subsequent rescue analgesics were given if the patient had a pain score of 5 or more than 5. Time of administration and the total requirement of rescue analgesics were noted and chart was maintained. The nitroglycerine patch or the placebo patch was subsequently removed after 24 hours. Replacement of fluid loss was done with crystalloids or colloids and no extensive blood loss was seen in study

cases. Sedation in the patients was also noted in patients of both the groups throughout the surgery using the following sedation score: [62]

Sedation Score

0	Awake, alert
1	Mild Sedation, easy to arouse
1S	Asleep, easy to arouse
2	Moderate sedation, unable to remain awake
3	Difficult to arouse

III. Observations And Results

Table 1: Comparison of age in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Age (Yrs)	39.42	11.36	40.42	9.35	0.39	0.70

Bar diagram showing comparison of age in Group I (BC) and Group II (BCN)

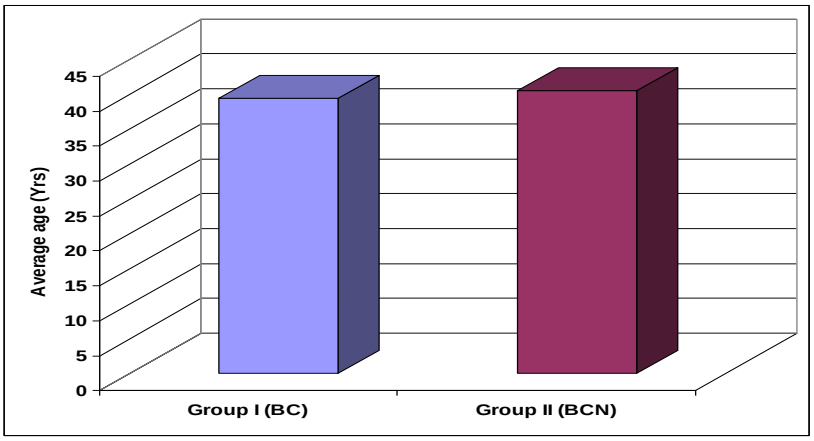
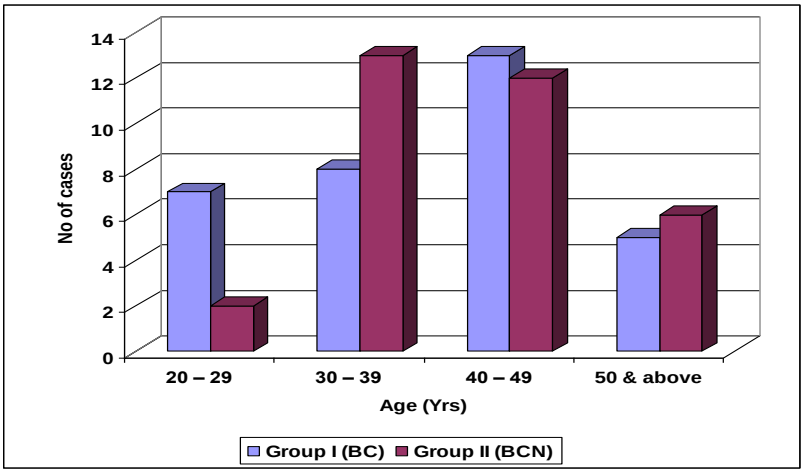


Table 1: Age wise distribution of cases in Group I (BC) and Group II (BCN)

Age (Yrs)	Group I (BC)	Group II (BCN)	Total
20 – 29	7	2	9
30 – 39	8	13	21
40 – 49	13	12	25
50 & above	5	6	11
Total	33	33	66

Chi-square =4.10, P=0.25

Bar diagram showing age wise distribution of cases in Group I (BC) and Group II (BCN)



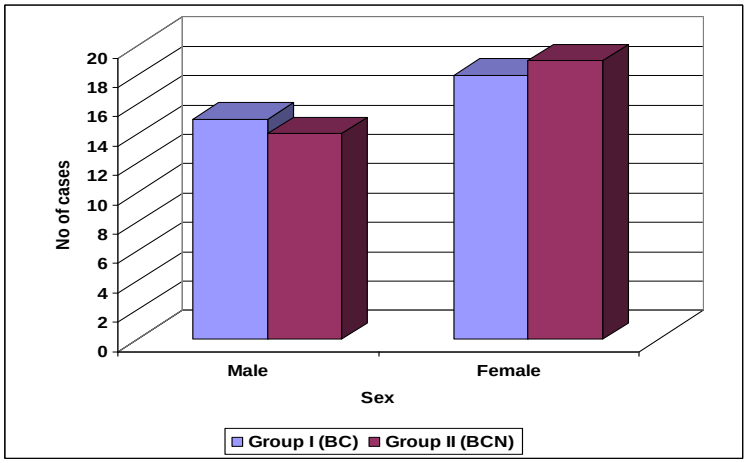
The table no.1 shows age wise distribution of cases in study group. Mean age in group BC was 39.42+-11.36 and in group BCN was also 40.42+-9.35. This was statistically not significant.

Table 2: Sex wise distribution of cases in Group I (BC) and Group II (BCN)

Sex	Group I (BC)	Group II (BCN)	Total
Male	15	14	29
Female	18	19	37
Total	33	33	66

Chi-square =0.06, P=0.80

Bar diagram showing sex wise distribution of cases in Group I (BC) and Group II (BCN)



The table no.2 shows gender wise distribution of cases in study group. Out of total 60 cases there were more females than males. Within group comparison showed that numbers of females were more in group BC than compared to group BCN and numbers of male were more in group BC than BCN.

Table 3: Type of surgery wise distribution of cases in Group I (BC) and Group II (BCN)

Type of surgery	Group I (BC)	Group II (BCN)	Total
Open appendicectomy	7	7	14
Total abdominal Hysterectomy	8	9	14
Meshplasty	7	7	13
VH	7	6	12
Haemorrhoidectomy	2	2	4
Myomectomy	1	1	2
Sling surgery	1	1	2
Total	33	33	66

Bar diagram showing type of surgery wise distribution of cases in Group I (BC) and Group II (BCN)

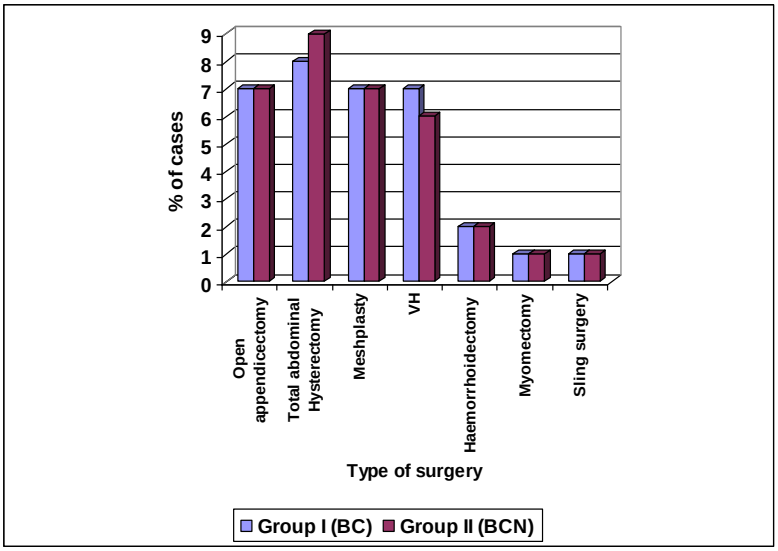


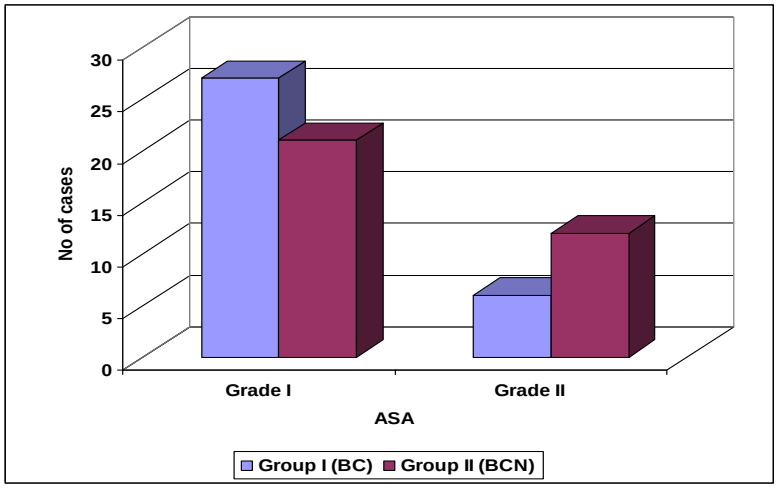
Table No.3 shows distribution of patients on basis of type of surgery. Types of surgeries were similar in both the groups.

Table 4: ASA grade wise distribution of cases in Group I (BC) and Group II (BCN)

ASA	Group I (BC)	Group II (BCN)	Total
Grade I	27	21	48
Grade II	6	12	18
Total	33	33	66

Chi-square =2.75, P=0.097

Bar diagram showing ASA grade wise distribution of cases in Group I (BC) and Group II (BCN)



The table no.4 shows ASA grade wise distribution of cases in study group. Out of 66 cases 48 (72%) were in grade I ASA and 18 (29%) were in Grade II ASA. Within group comparison shows that Group BC as well as Group BCN are having similar no. of cases under ASA I, ASA II.

Table 5: Comparison of duration of surgery in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Duration (min)	141.97	6.92	144.24	6.72	1.35	0.18

Bar diagram showing comparison of duration of surgery in Group I (BC) and Group II (BCN)

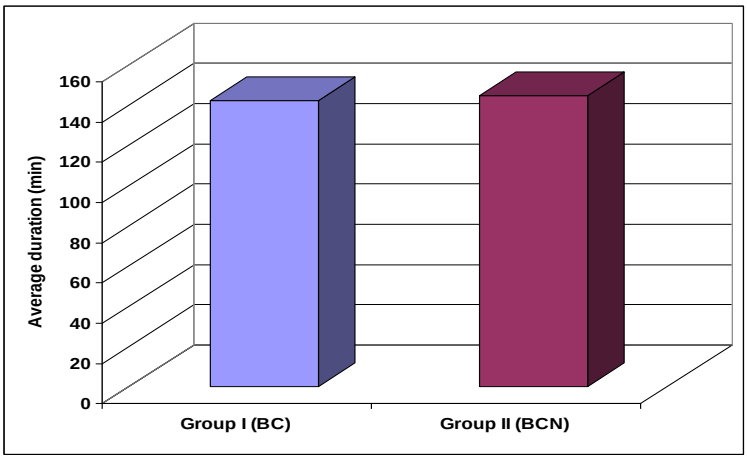


Table No. 5 shows comparison of duration of surgery. It was 141.97+-6.92 in BC and 144.24+-6.72 in group BCN. This was statistically insignificant.

Table 6: Comparison of Heart rate in Group I (BC) and Group II (BCN)

HR at	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
To	82.79	9.542	75.12	5.360	4.02	<0.0001
T1	76.85	8.668	75.91	7.860	0.46	0.65

T2	75.12	5.360	75.12	5.360	0	1
T3	75.12	5.360	76.15	6.315	0.72	0.48
T4	75.12	5.360	75.27	5.569	0.11	0.91
T5	75.12	5.360	76.42	4.542	1.06	0.29
T6	75.12	5.360	76.64	5.968	1.08	0.28
T7	75.12	5.360	76.85	8.668	0.97	0.33
T8	75.12	5.360	76.24	6.519	0.76	0.45

Line diagram showing comparison of heart rate in Group I (BC) and Group II (BCN)

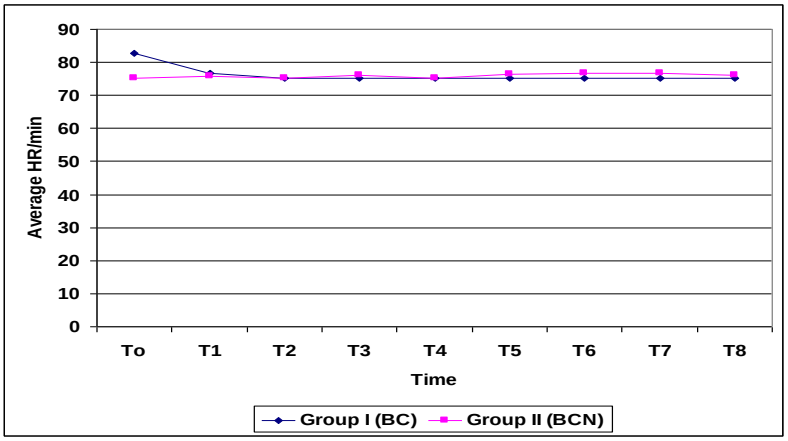


Table No. 6 shows comparison between heart rates in the two groups from subarachnoid block o demand of first rescue analgesic. It was not significant statistically

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Table 7: Comparison of Systolic Blood Pressure in Group I (BC) and Group II (BCN)

SBP at	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
To	124.36	11.059	115.27	1.973	4.65	<0.0001
T1	116.09	3.458	116.09	3.458	0	1
T2	115.27	1.973	115.39	1.731	0.26	0.79
T3	115.64	2.826	115.82	2.417	0.28	0.78
T4	118.00	1.803	115.39	2.015	5.54	<0.0001
T5	117.06	2.207	115.39	1.836	3.33	0.001
T6	117.73	1.737	115.15	1.938	5.68	<0.0001
T7	116.18	2.555	116.09	3.458	0.12	0.90
T8	115.64	2.510	115.18	2.200	0.78	0.44

Line diagram showing comparison of SBP in Group I (BC) and Group II (BCN)

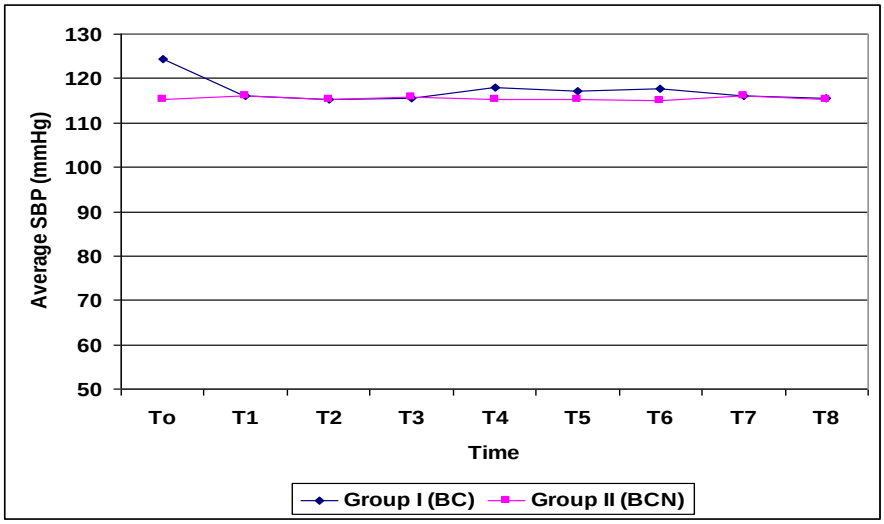

Table No. 7 shows comparison between systolic blood pressures in the two groups from subarachnoid block to demand of first rescue analgesic. It was not significant statistically.

Table 8: Comparison of Diastolic Blood Pressure in Group I (BC) and Group II (BCN)

DBP at	Group I (BC) (n=33)		Group II (BCN) (n=33)		Z Value	P Value
	Mean	**SD**	**Mean**	**SD**		
To	78.33	7.016	73.39	7.822	2.70	0.009
T1	75.24	5.579	75.06	5.690	0.13	0.90
T2	73.39	7.822	74.36	6.950	0.53	0.60
T3	78.18	5.790	76.24	12.298	0.82	0.41
T4	72.97	9.606	73.39	7.822	0.19	0.84
T5	75.52	6.104	72.30	8.421	1.77	0.081
T6	74.12	9.707	73.06	7.361	0.50	0.62
T7	75.52	9.798	75.06	5.690	0.23	0.82
T8	77.45	11.270	72.03	8.727	2.19	0.032

Line diagram showing comparison of DBP in Group I (BC) and Group II (BCN)

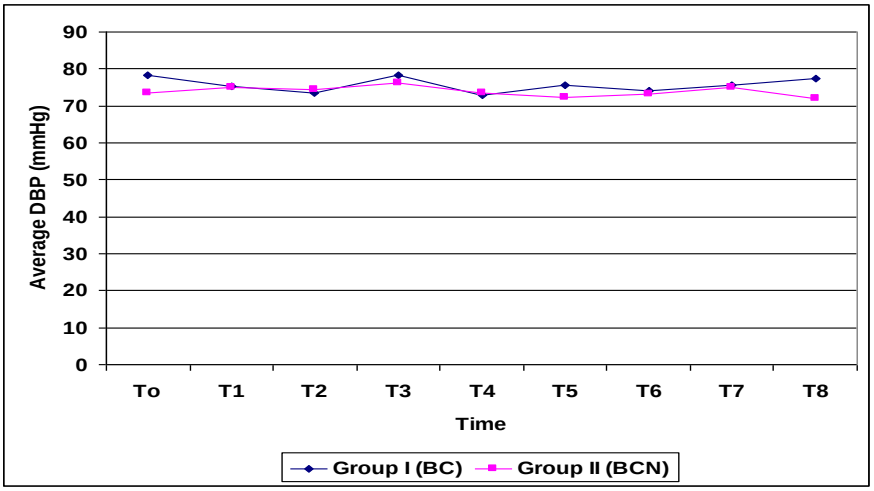

Table No. 8 shows comparison between diastolic blood pressures in the two groups from subarachnoid block to demand of first rescue analgesic. It was not significant statistically.

Table 9: Comparison of Mean Arterial Pressure in Group I (BC) and Group II (BCN)

MAP at	Group I (BC) (n=33)		Group II (BCN) (n=33)		Z Value	P Value
	Mean	**SD**	**Mean**	**SD**		
To	93.68	5.34	65.52	4.21	23.79	<0.0001
T1	88.86	4.19	66.55	3.18	24.36	<0.0001
T2	87.35	5.56	88.04	4.88	0.53	0.60
T3	90.67	4.08	89.43	8.78	0.73	0.47
T4	87.98	6.58	87.39	5.50	0.39	0.70
T5	89.36	4.15	86.67	6.04	2.12	0.038
T6	88.66	6.59	87.09	5.27	1.07	0.29
T7	89.07	6.56	88.74	4.24	0.25	0.81
T8	90.18	8.02	86.41	6.36	2.12	0.038

Line diagram showing comparison of MAP in Group I (BC) and Group II (BCN)

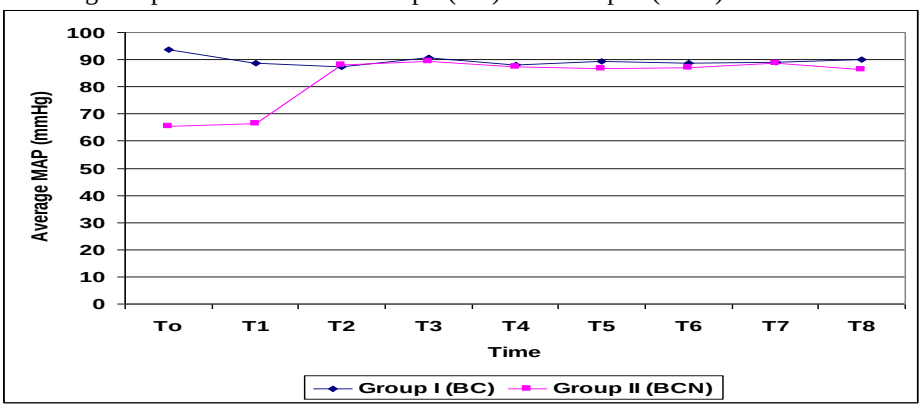

Table No. 9 shows comparison between mean arterial pressures in the two groups from subarachnoid block to demand of first rescue analgesic. It was not significant statistically.

Table 10: Comparison of SPO2 in Group I (BC) and Group II (BCN)

SPO2 at	Group I (BC) (n=33)		Group II (BCN) (n=33)		Z Value	P Value
	Mean	SD	Mean	SD		
To	99.42	0.830	99.79	0.415	2.25	0.028
T1	99.79	0.415	99.79	0.415	0	1
T2	99.79	0.415	99.79	0.415	0	1
T3	99.79	0.415	99.79	0.415	0	1
T4	99.79	0.415	99.79	0.415	0	1
T5	99.79	0.415	99.79	0.415	0	1
T6	99.79	0.415	99.79	0.415	0	1
T7	99.79	0.415	99.79	0.415	0	1
T8	99.79	0.415	99.79	0.415	0	1

Line diagram showing comparison of SPO2 in Group I (BC) and Group II (BCN)

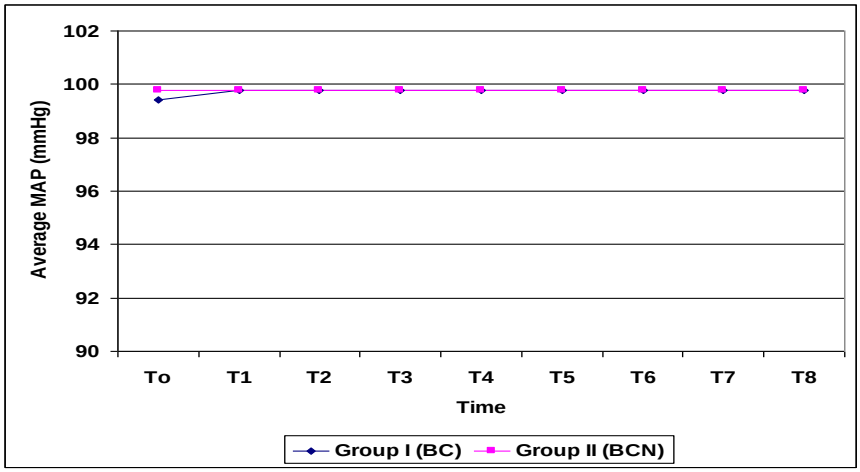

Table No. 10 shows comparison between oxygen saturations in the two groups from subarachnoid block to demand of first rescue analgesic. It was not significant statistically.

Table 11: Comparison of respiratory rate in Group I (BC) and Group II (BCN)

RR at	Group I (BC) (n=33)		Group II (BCN) (n=33)		Z Value	P Value
	Mean	SD	Mean	SD		
To	13.12	1.219	13.36	0.895	0.92	0.36
T1	12.52	0.939	12.52	0.939	0	1
T2	13.36	0.895	13.36	0.895	0	1
T3	13.36	0.895	13.36	0.895	0	1
T4	13.36	0.895	13.36	0.895	0	1
T5	13.36	0.895	13.36	0.895	0	1
T6	13.36	0.895	13.36	0.895	0	1
T7	13.36	0.895	13.36	0.895	0	1
T8	13.36	0.895	13.36	0.895	0	1

Line diagram showing comparison of RR in Group I (BC) and Group II (BCN)

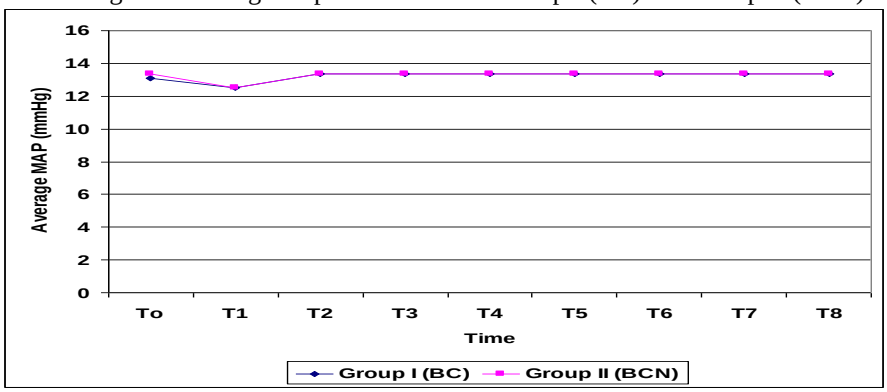

Table No. 11 shows comparison between systolic respiratory rates in the two groups from subarachnoid block to demand of first rescue analgesic. It was not significant statistically.

Table 12: Comparison of VAS score in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
VAS score	9.42	0.61	4.55	1.15	21.53	<0.0001

Bar diagram showing comparison of VAS score in Group I (BC) and Group II (BCN)

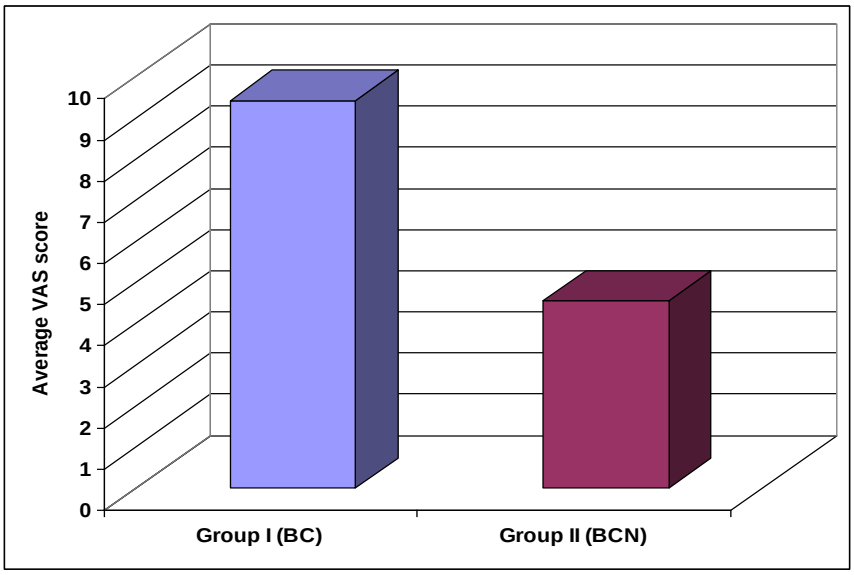

Table no. 12 shows the comparison between VAS scores of the two groups. It was 9.42+-0.61 in group BC and 4.55+-1.15 in group BCN. It was highly statistically significant.

Table 13: Comparison of number of time rescue analgesia taken in Group I (BC) and Group II (BCN)

No. of times	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
rescue analgesia taken	1.39	0.49	1.24	0.44	1.32	0.19

Bar diagram showing comparison of total doses of rescue analgesia taken in 24 hours in Group I (BC) and Group II (BCN)

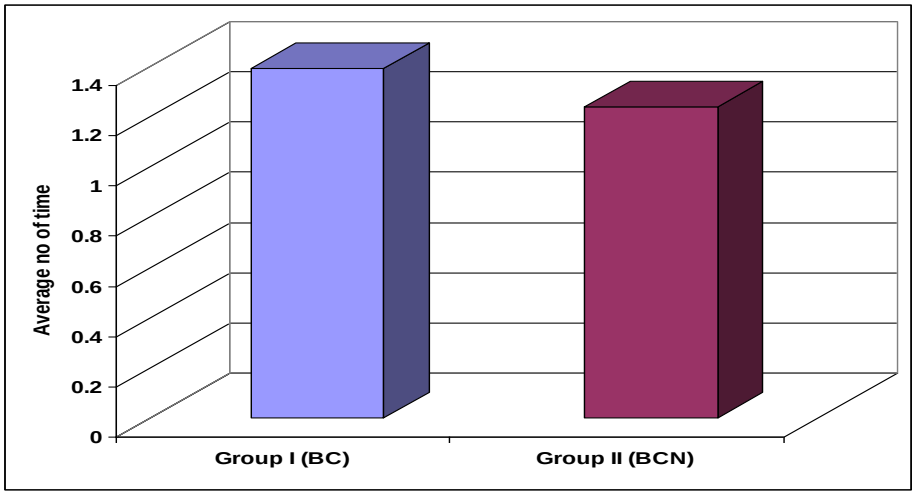

Table No. 13 shows comparison between no. of times of taking rescue analgesics in the two groups. It was not significant statistically.

Table 14: Comparison of total duration of analgesia in Group I (BC) and Group II (BCN)

Analgesia	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Total duration	304.39	25.06	466.79	9.31	34.89	<0.0001

Bar diagram showing comparison of total duration of analgesia in Group I (BC) and Group II (BCN)

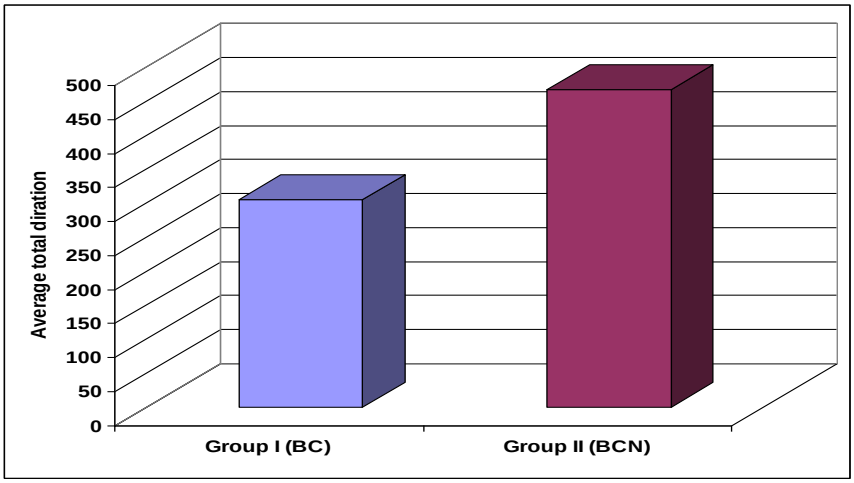

Table No. 14 compares the total duration of analgesia in the two groups. In group BC it wa 304.39+-25.06 and in group BCN it was 466.79+-34.89. The comparison was highly significant statistically in group BCN.

Table 15: Comparison of time of 1st rescue analgesia in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Time of 1st rescue analgesia	5.05	0.42	7.75	0.17	34.57	<0.0001

Bar diagram showing comparison of time of 1st rescue analgesia in Group I (BC) and Group II (BCN)

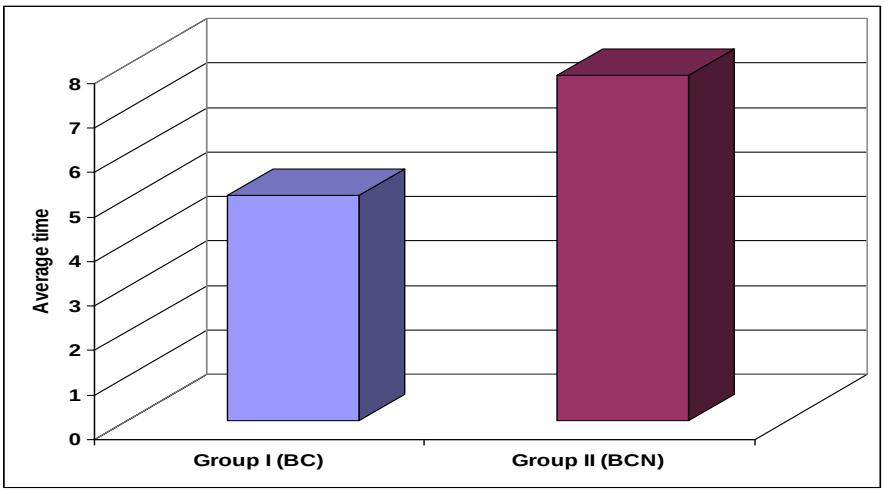

Table No. 15compares the time of first rescue analgesic in the two groups. In group BC it was 5.05+-0.42 and in group BCN it was 7.75+-0.17. The comparison was highly significant statistically in group BCN.

Table 16: Comparison of onset of motor block (T2-T7) in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Onset of motor block (T2 -T7) (min)	8.02	0.58	8.25	0.65	1.53	0.13

Bar diagram showing comparison of onset of motor block in Group I (BC) and Group II (BCN)

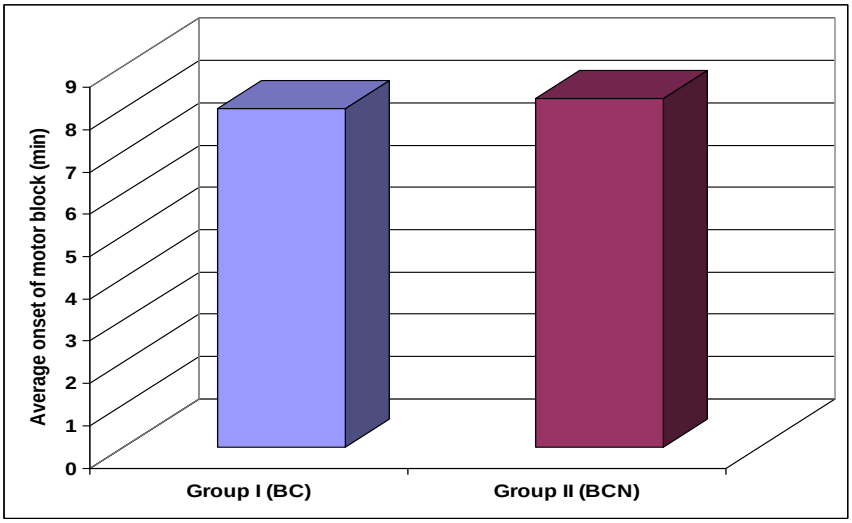

Table No. 16compares the onset of motor block in the two groups. In group BC it was 8.02+-0.58 and in group BCN it was 8.25+-0.65. The comparison was not significant statistically.

Table 17: Comparison of total duration of motor block in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Total duration of motor block (min)	150.06	3.34	174.36	19.96	6.89	<0.0001

Bar diagram showing comparison of total duration of motor block in Group I (BC) and Group II (BCN)

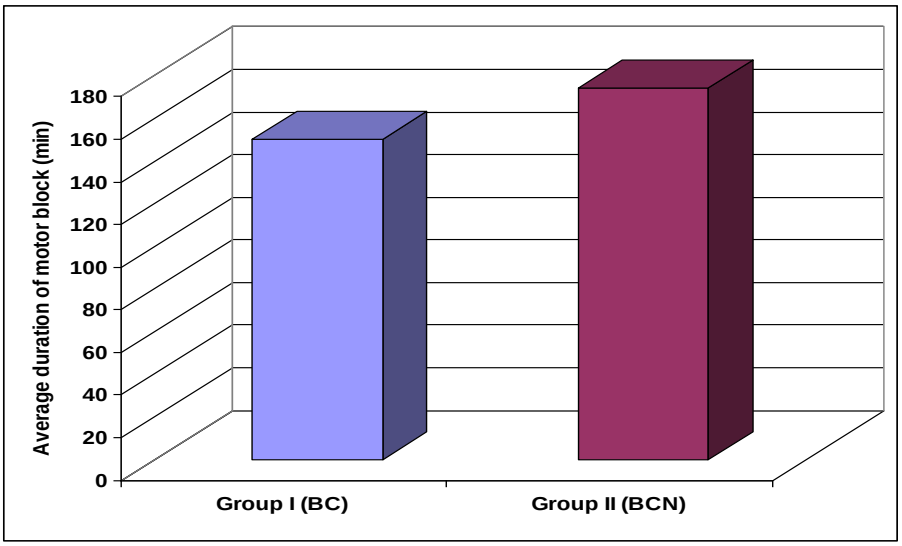

Table No. 17 compares the total duration of motor block in the two groups. In group BC it was 150.06+-3.34 and in group BCN it was 174.36+-19.96. The comparison was highly significant statistically in group BCN.

Table 18: Comparison of time for regression of sensory block (T1-T6) in Group I (BC) and Group II (BCN)

Parameters	Group I (BC) (n=33)		Group II (BCN) (n=33)		**Z Value**	**P Value**
	Mean	**SD**	**Mean**	**SD**		
Time for regression of sensory block (T1-T6)(min)	136.88	10.57	139.55	25.08	0.56	0.58

Bar diagram showing comparison of time for regression of sensory block in Group I (BC) and Group II (BCN)

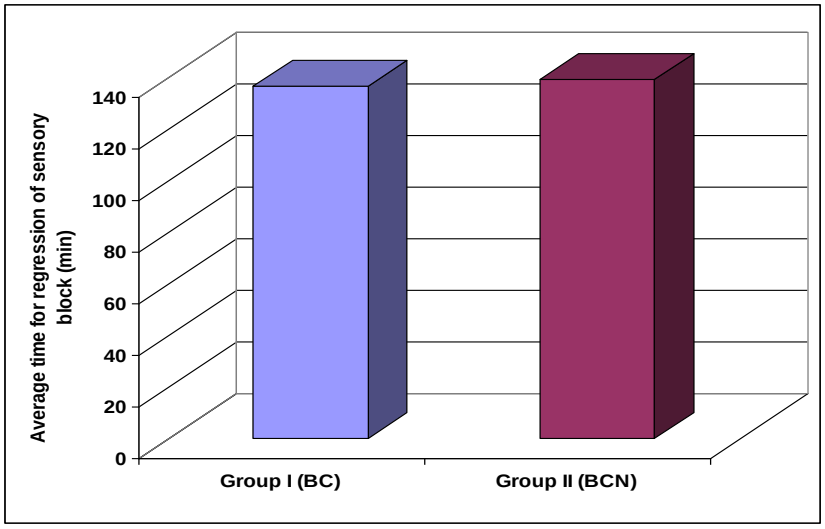

Table No. 18 compares the time for regression of sensory block (T1-T6) in the two groups. In group BC it was 136.88+-10.57 and in group BCN it was 139.55+-25.08. The comparison was not significant statistically.

Table 19: Comparison of complications in Group I (BC) and Group II (BCN)

Complications	Group I (BC) (n=33)	Group II (BCN) (n=33)	P Value
Headache	1	2	>0.05
PONV	1	1	>0.05

Bar diagram showing comparison of complications in Group I (BC) and Group II (BCN)

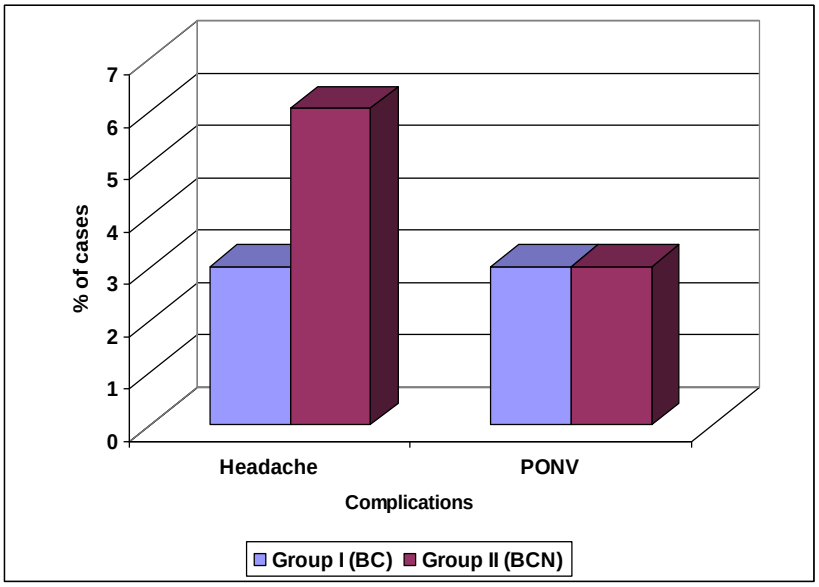

Table No.19 compares the complications between two groups. Headache is seen to be more in group BCN. This was not significant statistically.

Table no. 20: Comparison of Sedation score in group BC and group BCN

GROUP	Group I (BC) (n=33)	Group II (BCN) (n=33)
MEAN	1	1
SD	0	0
P value	Insignificant	

Bar diagram showing comparison of sedation score between group BC and group BCN.

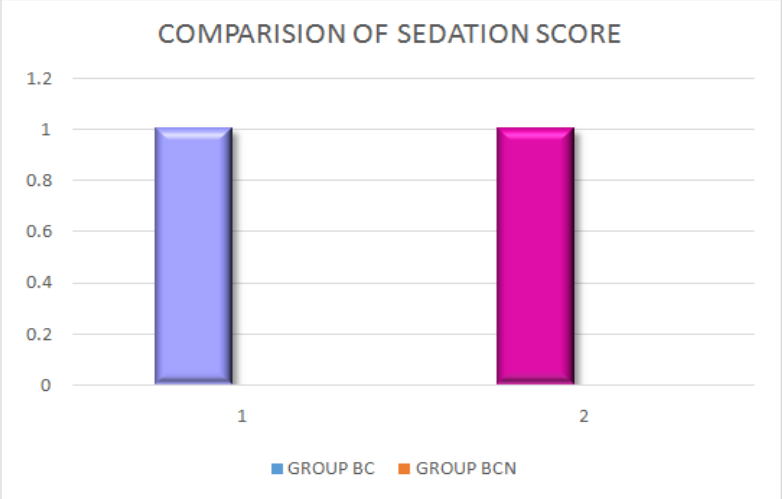

Table no. 20 compares sedation score between the two groups throughout the surgery. This was not statistically significant.

IV. Discussion

Subarachnoid block with bupivacaine has been most extensively used for lower abdominal and lower limb surgeries because of its simplicity, speed, reliability and minimal exposure to cardiac depressant drugs. It reduces stress response to surgery and improves post-operative pain relief. Intrathecal local anaesthetics work by inhibiting voltage gated sodium channels in spinal cord, which interferes with afferent and efferent sensory and motor impulses. But bupivacaine given alone intrathecally does not prolong the analgesic effects in post-operative period because of its short duration of action. [26]

Surgical incision leads to cell disruption and subsequent intracellular release of phospholipids and a state of widespread inflammation depending on the degree of surgical trauma. A vast number of chemical mediators such as prostanoids, bradykinin and nerve growth factor are released during the perioperative period. The chemical mediators lead to central pain sensitization, necessitating a multitude of pharmacological agents to treat postoperative pain.Uncontrolled post-operative pain may produce a range of detrimental acute and chronic effects. Reduction of nociceptive input to the CNS and optimization of perioperative analgesia may decrease complications and facilitate recovery during the immediate post-operative period.[69]

To enhance the quality of the spinal anesthesia and provide post-operative pain relief, addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs (such as dexmedetomidine, clonidine, magnesium sulfate (MgSO4), neostigmine, ketamine, and midazolam) have been tried. This technique of adding adjuvants to local anaesthetics is simple and less cumbersome and has gained a worldwide acceptability by anaesthesiologists. Adjuvants are the drugs that increase the efficacy or potency of other drugs when given concurrently. Neuraxial adjuvants are used to improve and prolong analgesia and decrease the adverse effects associated with high doses of a single local anaesthetic agent. In addition to their dose sparing effects, neuraxial adjuvants are also utilized to increase the speed of onset of neural blockade (reduce latency), improve the quality and prolong the duration of neural blockade.

Most commonly used adjuvants to local anesthetics for spinal anaesthesia are opioids and they have formed a cornerstone option for the treatment of post-operative pain. These agents exert their analgesic effects through μ-receptors at spinal and supraspinal level.Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as a forerunner. Neuraxial administration of opioids along with local anaesthetics improves the quality of intraoperative analgesia and also provides postoperative pain relief for longer duration. Animal studies have also demonstrated antinociceptive synergism between intrathecal opioids and local anaesthetics during visceral and somatic nociception.[70, 71]

The other newer adjuvants like, alpha2-adrenoceptor agonists are being increasingly used in anaesthesia and critical care as they not only decrease sympathetic tone and attenuate the stress responses to anaesthesia and surgery, but also cause sedation and analgesia. Various adjuvants have therefore been added to bupivacaine to hasten the onset of block and prolong the duration of block. This prolongation has been tried by the addition of opioids such as morphine[4], fentanyl[5]and sufentanil[6] and other drugs such as dexmedetomidine,[7, 8]clonidine[8,9,10], magnesium sulfate (MgSO4),[11] neostigmine,[11] ketamine,[12] and midazolam [13] to local anaesthetics. However each drug has its own limitations and a need for alternative method or drug always exists. There have been a few studies done showing that transdermal nitroglycerine patch further enhances the

analgesic effect of these adjuvants. Transdermal nitroglycerine acts as an analgesic by release of nitric oxide (NO). Nitric oxide produces pain modulation via release of cyclic guanosine monophosphate (cGMP). [21, 22]
In this study, we aimed to find out whether quality of anaesthesia and post-operative analgesia is better when clonidine is used along with an additional transdermal nitroglycerine patch. We also studied the onset, quality and duration of sensory and motor blockade produced in the above said groups.
Total 66 patients were enrolled belonging to ASA I and II, of either sex, belonging to 20-60 years age group undergoing elective lower abdominal under spinal anesthesia. After taking Institutional Ethics committee approval study was conducted.
All patients were equally divided into two groups randomly.

- **Group I (BC)** 33 cases : 15mg hyperbaric bupivacaine hydrochloride with 50 mcg of intrathecal clonidine hydrochloride
- **Group II (BCN)** 33 cases: 15mg hyperbaric bupivacaine hydrochloride with 50 mcg of intrathecal clonidine hydrochloride with transdermal nitroglycerine patch.

Sterile water was used to make intrathecal drug volume equal to 3.5ml. The density of the solution was thus maintained in both the groups. The density of compounds is a major determinant in controlling the extent of neural block.

Monitoring of the pulse rate, blood pressure (SBP, DBP and MBP), oxygen saturation (Spo2) and respiratory rate was done throughout the surgery. Onset of sensory block was assessed using pin prick method and onset and quality of motor block was assessed using Bromage scale. Duration of analgesia was assessed using visual analogue scale, when patient's pain scale showed score 7 or more, it was taken as time for rescue analgesia. Following are the observations from our study.

Demographic data across the groups:
There were no statistically significant differences in patient's age, gender, type of surgery and ASA status between the groups.

The age wise distribution of cases in our study group showed mean age in group BC was 39.42 (S.D.± 11.36) and in group BCN was 40.42 (S.D.± 9.35), which was statistically not significant ($p > 0.05$). The gender wise distribution of cases in the study group showed that, out of total 60 cases maximum number were of females (56.06%) and remaining (43.94%) were males. Within group comparison showed that number of females were more in group BCN than compared to group BC and number of male were more in group BC than BCN. The comparison between the two groups on the basis of type of surgery shows that type of surgeries were same in both the groups. The ASA grade wise distribution of cases in study group showed that out of 66 cases 48 (72%) were in ASA grade I and 18 (29%) were in ASA Grade II. Between the group comparison shows that Group BC as well as Group BCN are having similar no. of cases under ASA I, ASA II.

Duration Of Surgery
The comparison of the duration of surgery in the two groups shows that in group BC the surgery lasted for 141.97 min (SD: 6.92) while in group BCN it lasted for 144.24 min (SD: 6.72). The duration of surgery was more in group BCN but is neither statistically ($p>0.05$) nor clinically significant.

Vital Parameters

In our study we compared the variation in heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate and spO2. In both the groups vital parameters were compared using Z test at various time intervals from the time of subarachnoid block to the time of first rescue analgesic. At all the times the changes in the heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate and oxygen saturation were within the normal physiological limits, hence were clinically insignificant and did not require any clinical intervention.

Khandelwal M et.al[62] conducted a study to see whether transdermal nitroglycerine enhances the post-operative analgesic effect of intrathecal clonidine in abdominal hysterectomies. In this study,they found that tNTG has enhanced the post-operative analgesic effect of IT clonidine without any significant alteration of haemodynamics and increase in incidence of nausea and vomiting. This finding is consistent with the findings in our study.

Post-Operative Analgesia

The duration of effective analgesia was defined as the time from the intathecal injection to the time of the first request of rescue analgesia. The demand of rescue analgesia was measured on the basis of the visual analog scale (VAS Score).

We observed the following:

The comparison of **VAS** score in both groups suggested that mean score was 9.42 (SD: 0.61) in group BC while in group BCN it was 4.55 (S.D.: 1.15).This result was highly statistically significant. On comparing the **time of the first rescue analgesia** taken, it was delayed in group BCN (5.05+-0.42) than in group BC (7.75+-0.17). This value was highly statistically significant suggesting that the time of 1st rescue analgesic demanded in the group BCN was delayed as compared to group BC.

The comparison between the **number of times rescue analgesia** was taken revealed that in group BC it was 1.39+-0.49 and in group BCN it was 1.24+-0.44 times. However this comparison was not statistically significant but clinically the patients in group BCN required less number of rescue analgesics than patients in group BC.

The **total duration of analgesia** was 304.39+-25.06 min in group BC and 466.79+-9.31 min in group BCN. This comparison was highly significant statistically and clinically both. Thus the duration of analgesia was more in group BCN than in group BC. Lauretti GR[17] studied to find out whether Transdermal nitroglycerine enhances spinal sufentanil postoperative analgesia following orthopedic surgery, in 1999. They found that transdermal nitroglycerine alone (5 mg/day), did not result in postoperative analgesia itself, but it prolonged the analgesic effect of spinal sufentanil (10 microg) and provided 13 h of effective postoperative analgesia after knee surgery.

In 2000, Lauretti GR[20] again studied the effect of transdermal nitroglycerine with spinal neostigmine for postoperative analgesia following gynaecological surgery. They found that although neither intrathecal 5 microgram neostigmine alone nor transdermal nitroglycerine alone (5 mg/day) delayed the time to administration of first rescue analgesics, the combination of both provided an average of 14 h of effective postoperative analgesia after vaginoplasty, suggesting that transdermal nitroglycerin and the central cholinergic agent neostigmine may enhance each other's antinociceptive effects at the dose studied.In 2001, Lauretti GR[19] studied the effect of transdermal nitroglycerin on spinal S (+)-ketamine antinociception following orthopedic surgery and concluded that epidural S(+)- ketamine resulted in antinociception, which was enhanced by transdermal nitroglycerine.

In 2010 Ahmed F et.al[59] studied the effect of Transdermal nitroglycerine for postoperative analgesia with intrathecal neostigmine following abdominal hysterectomies. They concluded that transdermal nitroglycerine itself does not show any analgesic potential but it enhances the analgesic potential of intrathecal neostigmine. In 2010, Agreta Gecaj-Gashi et.al [60] studied whether intrathecal clonidine added to small-dose bupivacaine prolongs postoperative analgesia in patients undergoing transurethral surgery. The aim of this prospective, double-blinded study was to investigate the effects of clonidine in co-administration with bupivacaine during spinal anesthesia, regarding the onset and regression of motor and sensory block, postoperative analgesia and possible side effects. They concluded that intrathecal application of clonidine in combination with bupivacaine not only improves the duration and quality of spinal anesthesia but it also provides longer duration of postoperative analgesia, without significant side effects. In 2011, Manal Mohamed Elgohary[61] studied that transdermal nitroglycerine potentiates the analgesic effect of patient controlled epidural analgesia after lower abdominal surgery. He concluded that pre-emptive application of 5 mg transdermal nitroglycerine patch as adjuvant to CGEA provided significant prolongation of the postoperative analgesia and reduction of the postoperative bupivacaine and fentanyl consumption.

In 2012 Khandelwal et.al [62] studied whether transdermal nitroglcerine enhances the post-operative analgesic effect of intrathecal clonidine in abdominal hysterectomies. They concluded that transdermal nitroglycerine enhances the post-operative analgesic effect of intrathecal clonidine without any significant changes in the haemodynamics and increase in the incidence of nausea and vomiting. It increases the time required for rescue analgesia.

In 2016, effect of transdermal nitroglycerine patch on intrathecal neostigmine with bupivacaine for post-operative analgesia was studied by Viralben P. Patel e. al. [65] . The study was conducted by taking 50 randomly selected patients for various surgeries. Patients belonged to ASA Grade I/II aged 18 to 60 years were included. Patients were divided into 2 groups. Group - A: 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg. Group - B: 0.5% heavy bupivacaine 3 ml (15 mg) + preservative free neostigmine 5 mcg + transdermal nitroglycerine patch (5 mg/24 hours), applied on a non-anaesthetised area after 20 minutes. It was concluded that transdermal nitroglycerine patch increases post-operative analgesia of low dose intrathecal neostigmine with bupivacaine in spinal aneesthesia with less side effects

Effect On Motor Block (T2-T7)

The comparison between the two groups for onset of motor block show that it was 8.02+-0.58 in group BC and 8.25+-0.65 in group BCN. This comparison was statistically not significant.

However the comparison between the two groups for the total duration of motor block revealed that it was more in group BCN (174.36+-19.96) than in group BC (150.06+-3.34). This comparison was highly significant both statistically and clinically.

Comparison Of Complications

Complications like headache and post-operative nausea and vomiting (PONV) were noticed in some patients of both the groups. Headache was seen more in group BCN than in group BC while PONV was seen equally in both groups. The comparison was not statistically significant. But anticipation of complications and adverse effects of the drugs have to be anticipated and treated whenever needed in the clinical setting.

Comparison Of Sedation

Patients in both the groups were mild to moderately sedated throughout the surgery. This was both statistically and clinically insignificant as clonidine was a common drug in both the groups and sedation is known to be associated with clonidine. We felt that this was a beneficial side effect as patients were both calm and pain free.

V. Conclusion

The patients in the two groups were comparable with regards to age, gender, type of surgery and ASA physical status. The study shows that there is not only significant delay in time of the first rescue analgesia required but also decreased requirement of total number of rescue analgesics in the patients who received both clonidine and the nitroglycerine patch than in patients who received only intrathecal clonidine.There is also prolonged duration of analgesia, increased duration of motor blockade and decreased number in the patients who received both clonidine and the nitroglycerine patch than in patients who received only intrathecal clonidine.To conclude, our study validates the use of transdermal nitroglycerine patch with intrathecal clonidine as an adjuvant to bupivacaine (0.5 % heavy) as there was:

Significant prolongation in the duration of analgesia
Delayed time of requirement of first rescue analgesic
Decreased requirement of number of rescue analgesics
Good VAS score
Stable haemodynamic profile
No significant complications

Thus, in our study transdermal nitroglycerine enhanced the post-operative analgesic effect of intrathecal clonidine without any significant alteration of haemodynamics and increase in incidence of nausea and vomiting. The effect was synergistic and possibly mediated through nitric oxide.

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