Original Research Article

Indian Journal of Anesthesia and Analgesia
July – August 2020;7(4)
DOI: http://dx.doi.org/10.21088/ijaa.2349.8471.7420.26

Evaluation of Effectivenss of Intrathecal Bupivacaine with Adjuant Fentanyl and Clonidine in Patient Undergoing Lower Segment Caesarean Section: A Randomised Control Trial

Jignesh Govindbhai Makvana[1], Sameer Parmar[2], Komal S. Shah[3]

[1]Resident, [2]Assistant Professor, [3]Associate Professor, Department of Anesthesiology, Government Medical College and Sir T. Hospital, Bhavnagar 364001, Gujarat, India.

How to cite this article:

Jignesh Govindbhai Makvana, Sameer Parmar, Komal S. Shah. Evaluation of Effectivenss of Intrathecal Bupivacaine with Adjuant Fentanyl and Clonidine in Patient Undergoing Lower Segment Caesarean Section: A Randomised Control Trial. Indian J Anesth Analg. 2020;7(4):1036–1049.

Abstract

Background and Objectives: Intrathecal opioids potentiate the analgesic property of local anesthetics. Among an alpha2 adrenergic agonist, Clonidine potentiates the effect of local anesthetics and allows decrease in required doses. Hence, this study was conducted to evaluate effectiveness of intrathecal bupivacaine with adjuvant fentanyl and clonidine in patient undergoing lower segment caesarean section.

Material and Method: 100 participants, aged 18 to 35 years, of ASA Physical status I and II, scheduled for lower segment caesarean section under subarachnoid block, were randomly divided into two groups (n=50 each); Group C (n=50) was given intrathecal inj. Bupivacaine 0.5% heavy 1.7 ml (8.5 mg)+ inj. Clonidine 0.2 ml (30 mcg)+inj. Normal saline 0.3 ml Total volume 2.2 ml and Group F (n=50) was given intrathecal inj. Bupivacaine 0.5% heavy 1.7 ml (8.5 mg) + inj. Fentanyl 0.5 ml (25 mcg) Total volume 2.2 ml. Degree of sensory and motor block, quality of intraoperative anesthesia, postoperative analgesia (VAS score), time of 1st rescue analgesia effective analgesia, hemodynamic variables and side effects were evaluated and compared. At VAS ≥4, rescue analgesic Inj. Diclofenac Sodium I.V. was given.

Results: The result of the present study shows that in group F there was significant reduction in the time for onset (1.20+0.36 min), peak of sensory blockade (1.99±0.59 min) and significant prolongation in the total duration of sensory blockade (240.40±53.45 min) extending into the postoperative period as compared to group C (2.02±0.45, 2.79±0.45 and 163±22.79 min respectively with p <0.0001, hence provided effective postoperative analgesia up to 12 hours. Complete analgesia lasted longer in group F for 11.46±1.9 hrs compared with group C for 10.96±1.9 min (p 0.19). The duration of effective analgesia was significantly prolonged in group F (14.78±2.03 min) as compared with group C (13.17±1.31 min), (p<0.0001)

Conclusion: In conclusion, addition of 25 µg Fentanyl as an adjuvant with 0.5% hyperbaric Bupivacaine, in subarachnoid block for lower segment caesarean section, has faster onset and prolongs sensory block and motor blockade; also improves postoperative analgesia with minimal side effects as compared to 30 µg clonidine.

Keywords: Subarachnoid Block; Fentanyl; Clonidine; hyperbaric Bupivacaine; Lower segment caesarean section.

Introduction

Alleviation of postsurgical pain is one of most fundamental goal in anesthesiology. Postoperative pain relief is not only desirable but also important for reduction of postoperative morbidity. Postoperative pain, apart from patients suffering, has many other adverse consequences like respiratory depression, circulatory disturbances and metabolic stress

Corresponding Author: **Sameer Parmar,** Assistant Professor, Department of Anesthesiology, Government Medical College and Sir T. Hospital, Bhavnagar 364001, Gujarat, India.

E-mail: sameerparmar87@yahoo.com

© Red Flower Publication Pvt. Ltd.

response.[1] Postoperative pain relief helps in early patient mobilization, reduction of respiratory complications, good patient's outcome, reduced morbidity and improved patient's satisfaction. And hence, its alleviation should be prime objective in anesthesia practice. Subarachnoid block being most versatile and commonly used regional block worldwide today, was introduced in 1885 by Leonard corning.[2] Most commonly used anesthetic technique for lower segment caesarian section.[2] Carl Koller's discovery of local anesthetic effects of cocaine in the 19th century heralded the birth of a new era in the field of Anesthesia. The first case of spinal Anesthesia using cocaine for surgical operation was performed by August Bier in 1898.3 In 1973, Pert and Snyder 4 identified the opiate receptors in CNS including spinal cord. Since the discovery of opioid receptors and the increase in spinal cord neuropharmacological knowledge as to transmission inhibition of nociceptive stimulation, there has been an increased interest in spinal drugs for Anesthesiology and pain relief. Advantage of simplicity of technique, rapid onset of action, reliability in producing uniform sensory and motor blockade, preservation of consciousness, thereby preventing the risk of aspiration, good postoperative analgesia, with minimal drug cost and side effects has made this method a viable alternative to general anesthesia for a variety of surgical procedure. Its main disadvantage related to its limited duration of action hence, lack of long lasting postoperative analgesia. To overcome this problem, administration of local anesthetics in combination with different adjuvants is an excellent technique which not only relieves postoperative pain but also refines the quality of sensory and motor blockade of subarachnoid block and hence, acts as synergistic to local anesthetics with lower local anesthetic requirement, decreased side effect and excellent postoperative analgesia. Growing interest in caesarean anesthesia, particularly in subarachnoid space, in the use of bupivacaine with adjuvant drugs in order to improve the quality of blockage and extend the duration of analgesia.[5] In addition, the use of adjuvants reduces the dose of bupivacaine with a lower incidence of side effects[5] and improves the quality of sensory and motor block and increased the duration of post-operative analgesia. The quality of the spinal anesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs (such as dexmedetomidine, clonidine, magnesium sulfate (Mg), neostigmine, ketamine, and midazolam).[6,7] Among an alpha2 adrenergic agonist, Clonidine potentiates the effect of local anesthetics and allows decrease in required doses.[8] Clonidine is partial alpha2 adrenergic agonist used intrathecally with well-established efficacy and safety profile with effective prolongation of both motor and sensory blockade.[9,10] Fentanyl is a synthetic lipophilic opioid with a rapid onset of action and unlike morphine, has fewer tendencies to migrate rostrally to the fourth ventricle in sufficient concentration to cause delayed respiratory depression.[11-13] When administered with bupivacaine in subarachnoid block, fentanyl by virtue of its lipophilic property like rapid onset of action and recovery, prolonged duration, reduces the need for supplements during surgery and also prolongs the postoperative analgesia.[14,15] And there are limited studies available for comparison of adjuvant with subarachnoid bupivacaine in lower segment caesarean section, which prompted us to evaluate the safety and efficacy of fentanyl and clonidine as an adjuvant to bupivacaine in patients undergoing lower segment caesarean section.

Methodology

After approval from the Institutional Review Board [(IRB No.789/2018) & (CTRI registration no. CTRI/2019/01/023468)] and informed written consent from patients, this prospective, randomized, double blind controlled study was carried out in the Govt. Medical College and Sir. T. Hospital, Bhavnagar, Gujarat. 100 patient, aged 18-35 years of ASA physical status I and II scheduled for lower segment caesarean section surgery were enrolled in this study. All the patient were subjected to detailed pre-anesthetic evaluation with clinical history and systemic examination, routine investigations like haemogram, random blood sugar, renal profile were done as per patient clinical evaluation.

Inclusion Criteria

- Age of patient- 18 to 35 years
- Gender – female
- ASA Grade I or II
- Patient undergo lower segment caesarean section.

Exclusion Criteria

- Patient refusal
- Any contraindications to spinal Anesthesia.
- Patient suffering from any valvular heart disease.
- Allergy to local anesthetic or study drug.

- Neurological disorders
- History of bleeding disorder.
- Patient on anti-coagulant therapy

In the pre anesthetic preparation room, monitoring consisting of heart rate, non-invasive blood pressure, and peripheral oxygen saturation was established and baseline vital parameters were recorded. Each patient was inform in detail regarding nature and purpose of the study and was explained 0-10 point visual analogue scale (VAS) on sheet of paper where (0) labelled as (no pain) and (10) as (worst possible pain).

Sampling Method

Patients were randomly allocated to one of the two groups of 50 patient each by computer generated randomization. One member of the team opened the envelope and filled up the drug as per the group assigned.

- Group F (n=50) was given intrathecal inj. Bupivacaine 1.7 ml (8.5 mg) + inj. Fentanyl 0.5 ml (25 mcg)= Total volume 2.2 ml
- Group C (n=50) was given intrathecal inj. Bupivacaine 1.7 ml (8.5 mg)+ inj. Clonidine 0.2 ml (30 mcg)+inj. Normal saline 0.3 ml=Total volume 2.2 ml

Each participant was informed in detail regarding the nature, purpose of the study and explained 0-10 point Visual Analog Scale (VAS) on paper sheet where zero end marked as 'no pain' while the other end marked as 'worst possible pain'. Written informed consent was obtained after explaining the procedure to the participant. Participants with inadequate sensory and motor block, who required supplementation were excluded from the study. In pre-anesthesia preparation room,

- ➢ Baseline vital parameters [heart rate, blood pressure (systolic and diastolic), respiratory rate and oxygen saturation] were recorded.
- ➢ Intravenous access was secured using 18G venous catheter and the participants were premeditated with Inj. Ondansetron 0.08 mg/kg intravenously 15 minutes prior to procedure.
- ➢ Then the participants were shifted to Operation Theatre in the operation theater, Preloading was done with Inj. Ringer Lactate 10 ml/kg.
- ➢ All equipment's and drugs necessary for resuscitation and general Anesthesia were kept ready
- ➢ Under all aseptic and antiseptic precautions, with the participant placed in left lateral position, subarachnoid block was performed with 25G spinal needle in L3-L4 intervertebral space with midline approach and the drug was injected after obtaining free and clear flow of CSF, as per the group assigned
- ➢ Principle investigator who performed the sub arachnoid block and injected the solution in the sub arachnoid space was unaware of the content of the solution injected in the subarachnoid space. All participants were given supplemental oxygen by nasal prong at the flow rate of 3L/min.
- ➢ Immediately after the block, participant was turned supine. The time of injection was noted as time "0" and participants were assessed for sensory and motor characteristics of blockade as per the grading shown in the tables (Table A) at every 30 seconds interval till peak effect was achieved.
- ➢ The primary outcomes of this randomized, double-blind clinical trial will be evaluate the time to requirement of first rescue analgesia.
- ➢ The secondary outcomes included the assessment of sensory block onset time, onset of motor block, duration of blockade, hemodynamic variables, the incidence of hypotension, ephedrine requirements, bradycardia, hypoxemia (saturation of peripheral oxygen (SpO_2) < 90), and adverse events such as dizziness, and postoperative nausea and vomiting.
- ➢ Intra operatively, Pulse rate, respiratory rate, blood pressure and oxygen saturation monitoring was done at 2,5,10 minuts, 15 minuts, 20 minuts, 30 minutes thereafter throughout the surgery and postoperative 4 hours and 8 hours
- ➢ Any supplementation required for inadequate block or side effects like hemodynamic disturbances, nausea, vomiting, shivering, pruritus and respiratory depression were recorded and managed as mentioned below.
- ➢ Bradycardia – defined as fall in pulse rate below 60 bpm and treated with bolus inj. Atropine (0.02 mg/kg) intravenously.
- ➢ Hypotension – defined as decrease in systolic or diastolic blood pressure more than 30% of baseline value and treated with IV crystalloids (200 mL bolus) or inj. Mephentermine 5 mg IV as needed.

- Nausea and vomiting- Treated with Inj. Ondansetron 4 mg IV
- After the completion of surgery, participants were shifted to Post Anesthesia Care Unit and sensory and motor block were assessed at 30 minutes interval till regression of sensory and motor blockade. Thereafter participants were monitored at 4 hourly intervals for next 24 hours for complications and adverse events if any
- Time of analgesia request was noted in post-operative period. At the time of analgesia request, the participants were asked to point out the intensity of pain on 'Visual Analog Scale' (VAS) explained to the participant preoperatively. Rescue analgesia- Inj. Diclofenac Sodium (1.5 mg/kg) intravenous was given at VAS ≥ 4.
- The duration of complete analgesia - time from subarachnoid injection to first reports of pain (pain score greater than 0) and effective analgesia - time from subarachnoid injection to first dose of rescue analgesic were recorded.

Table B: Modified Bromage Scale for Motor Block Evaluation

- The pain was scored as:

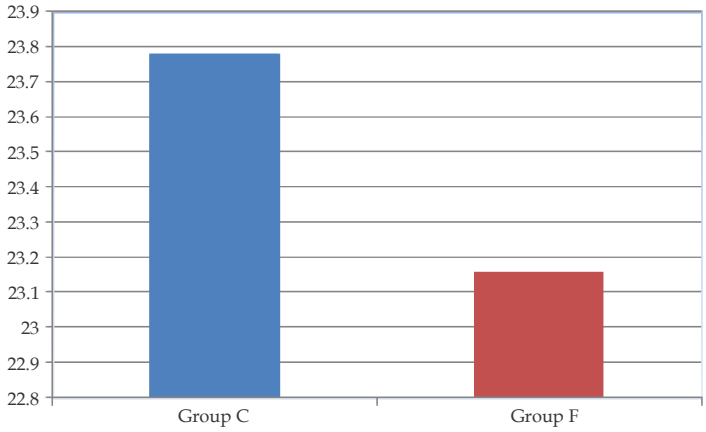
Grade 0	The patient is able to move the hip, knee and ankle
Grade 1	The patient is unable to move the hip, but is able to move the knee and ankle
Grade 2	The patient is unable to move the hip and knee but is able to move the ankle.
Grade 4	The patient is unable to move the hip, knee and ankle.

Observation and Results

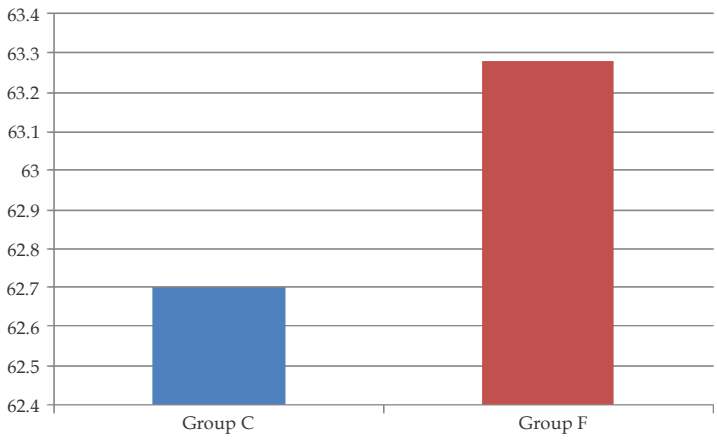
Demographic data

	Group C Mean±2SD (n=50)	Group F Mean±2SD (n=50)	P Value
Age (year)	23.78±2.61	23.16±2.77	0.25
Weight (kg)	62.7±3.66	63.28±4.34	0.47
Height (cm)	158.1±3.53	158.04±4.07	0.93

Demographic data in turns of age, sex, weight, height were comparable among both the groups.



Bar Diagram 1A: Distribution of participants with respect to age.



Bar Diagram 1B: Distribution of participants with respect toweight.

Sensory blockage

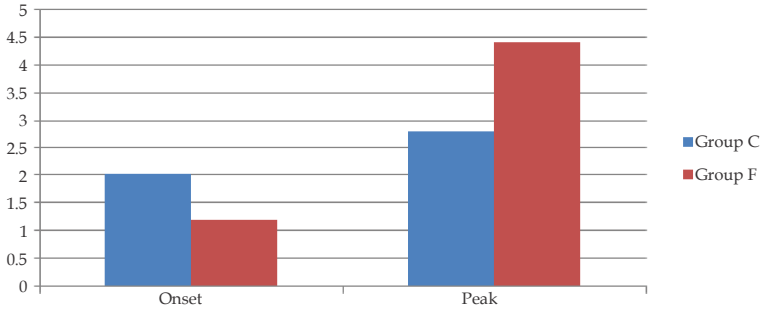
	Group C Mean±2SD	Group F Mean±2SD	P value
Onset (minutes)	2.02±0.45	1.20±0.36	<0.0001
Peak (minutes)	2.79±0.45	1.99±0.59	<0.0001
Duration (minutes)	163±22.79	240.40±53.45	<0.0001

The mean onset of sensory block in group C was 2.02±0.45 minutes and in group F was 1.20±0.36 minutes. There is statistically significant difference in mean time of onset and peak of sensory block in both the group. There was early onset and peak achieved in group F as Compared to group C. Duration of sensory block was prolonged in group F as compared to group C difference was statistically significant.

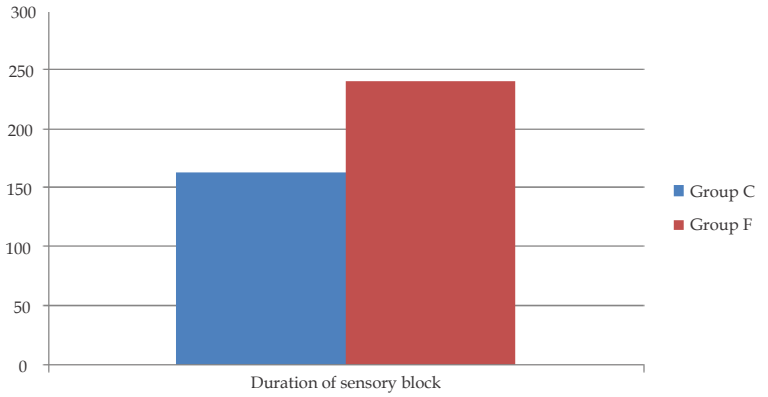
Motor block

	Group C Mean±2SD	Group F Mean±2SD	P value
Onset (minutes)	2.20±0.47	1.43±0.40	<0.0001
Peak (minutes)	2.87±0.61	2.22±0.62	<0.0001
Duration (minutes)	144.6±21.20	223±53.93	<0.0001

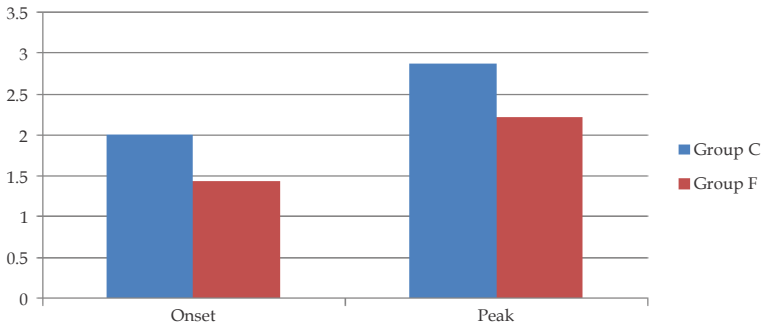
There were statistically significant difference in mean time of onset peak and duration of motor block in both the groups. There was faster onset and peak of motor block in group F as compared to group C. duration of motor block were longer significantly in group F as compared to group C.



Bar Diagram 2A: Onset and peak of sensory block



Bar Diagram 2B: Duration of sensory block



Bar Diagram 3A: Onset and peak of motor block

Heart rate

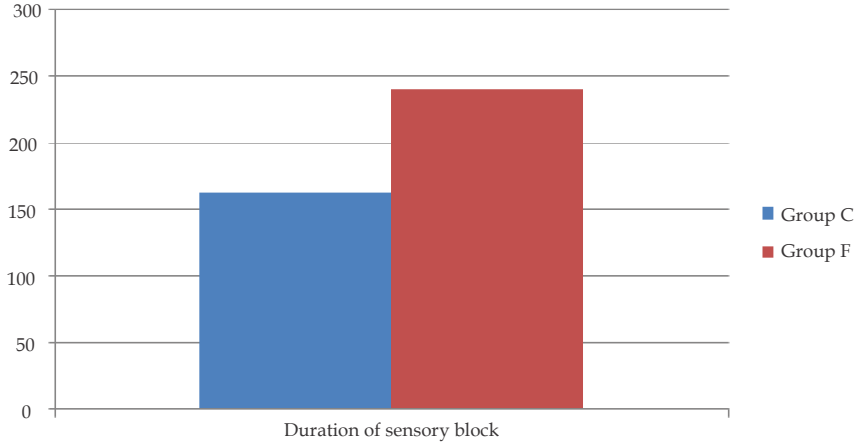
	Group C Mean±2SD	Group F Mean±2SD	P value
Base line	88.3±7.48	89.64±8.51	0.40
Before block	89.56±8.43	88.3±7.43	0.43
After block	87.66±9.78	91.32±10.34	0.07
1 min	91.32±10.34	89.8±10.71	0.47
3 min	88.14±10.8	85.52±10.8	0.91
5 min	88.14±10.8	85.52±10.8	0.23
10 min	87.2±11.08	83.6±10.07	0.08
15 min	86.1±10.84	82.3±10.11	0.07
20 min	86.1±10.22	80.54±9.9	0.006
30 min	86.6±10.62	78.36±9.6	<0.0001
45 min	86.54±10.62	78.36±9.6	<0.0001

There were statistically significant difference in fall in heart rate in group C as compared to group F. At 30 minutes and 45 minutes significant fall in heart rate in group C. Which was corrected by injection atropine 0.6 mg

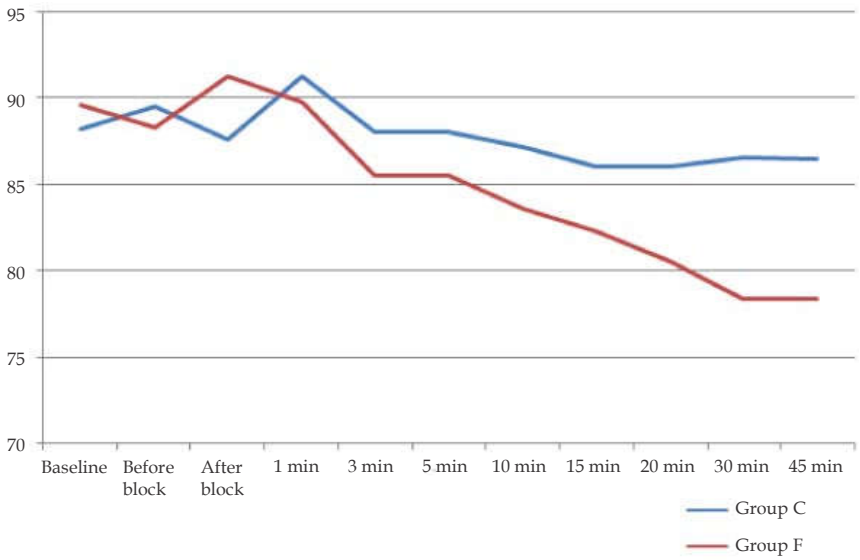
Arterial Blood Pressure

	Group C Mean±2SD	Group F Mean±2SD	P value
Base line	88.87±6.1	90.78±6.9	0.54
Before block	87.40±7.5	89.7±5.9	0.81
After block	85.30±6.2	87±5.3	0.51
1 min	84.20±5.53	85.95±5.4	0.72
3 min	82.40±4.8	84.82±5.05	0.20
5 min	74.67±12.85	81.5±7.3	<0.0001
10 min	89.06±10.5	76.68±12.5	<0.0001
15 min	75.38±10.70	77.54±7.67	0.0002
20 min	74.81±11.42	76.64±9.78	0.0077
30 min	73.24±11.37	76.46±10.32	0.0145
45 min	74.22±11.50	77.06±8.2	0.0001

There were statistically significant difference in fall in mean arterial blood pressure at 5, 10 and 15, 45 min after subarachnoid block in group C as compared to group F. Which was corrected by injection Mephentermine 5 mg i.v.



Bar Diagram 3B: Duration of motor block

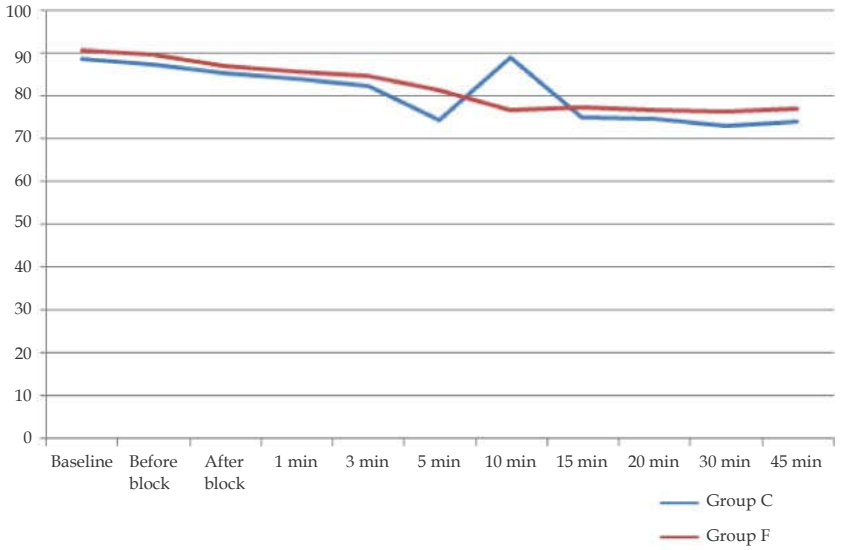


Bar Diagram 4: Heart rate

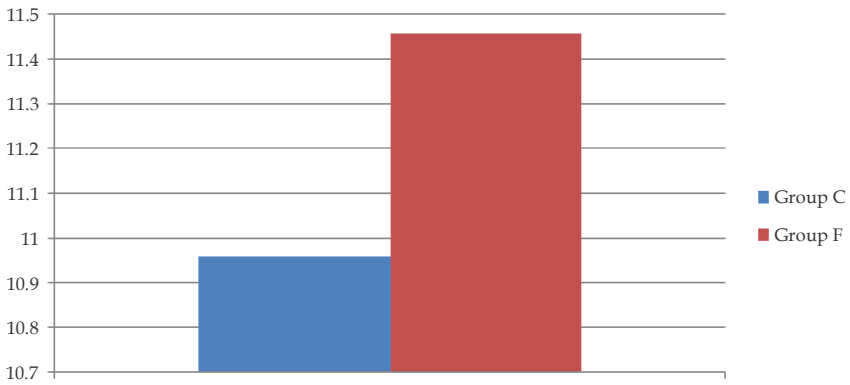
Duration of post-operative analgesia

	Group C Mean±2SD	Group F Mean±2SD	P value
Duration of Postoperative Analgesia	10.96±1.9	11.46±1.9	0.19

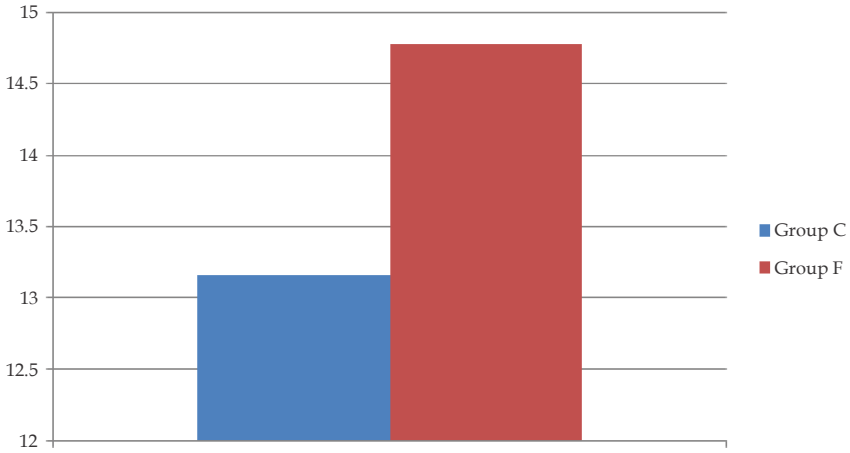
There is no statistically significant difference in duration of post-operative analgesia in both group. Duration of post-operative analgesia is prolong in group F as compare to group C but p value 0.19 is statistically insignificant.



Bar Diagram 5: Mean Arterial Blood Pressure



Bar Diagram 6: Duration of postoperative analgesia



Bar Diagram 7: Rescue Analgesia

Rescue Analgesia

	Group C Mean±2SD	Group F Mean±2SD	P value
Rescue Analgesia	13.17±1.31	14.78±2.03	0.0018

There was significant prolong postoperative analgesia in group F as compared to group C.

1st rescue analgesic requirement

Post Op Duration	Group C	Group F
10 Hours	01	03
12 Hours	21	03
14 Hours	25	21
16 Hours	03	15
18 Hours	00	06
20 Hours	00	01
24 Hours	00	00

Postoperative analgesic requirement in fentanyl group maximum around 18 hours in 6 patient. Postoperative analgesic requirement in clonidine group maximum around 14 hours in 25 patients.

Discussion

Both fentanyl and clonidine if used in low doses are safe and prolongs postoperative analgesia of intrathecal bupivacaine. Thorough literature search revealed paucity of studies directly comparing these two drugs for their efficacy and safety. Present study was designed to directly compare these two drugs. To compare the efficacy we used the duration of effective analgesia measured by time in hours for requirement of rescue analgesia. In consistency to results of several other studies.[53-58] We found both drugs to be effective as adjuvants to intrathecal bupivacaine prolonging the duration of analgesia.

Fentanyl citrate, a synthetic amine opioid from the class of pure μ opioid receptor agonist, is structurally related to the phenylpiperidine nucleus and 100 times more potent than morphine[59] as an analgesic in equivalent doses. Fentanyl is a very important drug in anesthetic practice because of its relatively shorter time to peak analgesic effect,[60] rapid termination of effect after small bolus doses, minimal direct depressant effects on the myocardium, and their ability to significantly reduce the dosing requirement for the volatile action.

Fentanyl was first introduced for widespread palliative use with the clinical introduction of the Duragesic patch in clinical practice in mid 1960s. Availability of fentanyl in a wide range of preparations like, intravenous, buccal tablets or patches, nasal sprays, inhalers, and active transdermal patches made it a recreational drug. Nowadays it is popularly used as an I.V. analgesic supplement, component of inhalational Anesthesia, balanced Anesthesia, neuroleptic analgesia and also a sole anesthetic in intensive care unit and in the management of severe pain states.

Morphine is a forerunner as an opioid adjuvant added to local anesthetic for spinal Anesthesia and causes delayed respiratory depression (>2 hours after administration) which is to some extent dose-related[61] and believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), seen more commonly with hydrophilic opioids. Hence, the lipophilic drugs like fentanyl, sufentanil, remifentanil, alfentanil, methadone are more logical choice.

The safety of fentanyl regarding neurotoxicity has been demonstrated in animal studies and it has been proved safest among all opioids.[62,63] Yaksh et al.[64] in 1988, found that intrathecal administration of opioids can produce profound segmental analgesia without causing significant alteration of motor or sensory function or subjective effects.

Epidural use of fentanyl citrate for postoperative pain or labor analgesia has significant popularity. A combination of intrathecal opioids with local anesthetics permits reduction in the dosage of both components, minimizing the side effects of the local anesthetic (motor blockade) and the opioid (i.e. urinary retention, itching and delayed respiratory depression in the case of morphine). An important caveat to their spinal use is that, because of their rapid clearance, these agents at analgesic spinal doses can produce blood levels that are similar to those producing effects after systemic administration.[65,66]

The synergistic effect of opioid combined with local anesthetic can be explained by virtue of their different mechanism of action. Intrathecal opioids inhibit nociceptive afferent synaptic transmission via Aδ and C fibers by opening presynaptic K^+ channels to inhibit transmitter release and thus reduce calcium influx. There is also a direct postsynaptic effect with hyperpolarization and reduced neuronal activity evoked by glutamate.

Local anesthetic, bupivacaine, works primarily by causing blockade of voltage-gated Na^+ channels in the axonal membrane and, possibly, a further effect on presynaptic inhibition of Ca^{2+} channels. The results of our study are consistent with experimental evidence of synergistic interaction between spinal opioids and local anesthetics, which are characterized by enhanced somatic analgesia without effect on the degree or level of the local anesthetic induced sympathetic or motor blockade.[67-70]

Clonidine is an α2–agonist which block the conduction of Aδ and C fibers, thereby prolongs the action of local anesthetics. When used intrathecally, it activates the postsynaptic α2–receptors in Substantia gelatinosa of spinal cord and produces analgesia.[71,72] Analgesic properties of clonidine have been shown to depend on the activation of $\alpha 2$ receptors located in the dorsal horn. Presynaptic stimulation of $\alpha 2$ receptors inhibits neurotransmitter release and postsynaptic stimulation prevents neuronal transmission through hyperpolarization[73.s1] Bhure et al. demonstrated that addition of clonidine, fentanyl, and midazolam to bupivacaine significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability, prolongs the duration of analgesia, and reduces the consumption of systemic analgesics in comparison to bupivacaine alone. They concluded that clonidine is an excellent additive to bupivacaine in spinal anesthesia and provides prolonged duration of analgesiawithout any deleterious effects on the mother and baby.[74 AE]

With this background, present study was carried out in the Dept. of Anesthesiology, Government medical college & Sir T General Hospital, Bhavnagar to evaluate the effects of fentanyl in subarachnoid block in patients undergoing lower segment caesarean section.

Morphine is a forerunner as an opioid adjuvant added to local anesthetic for spinal Anesthesia and causes delayed respiratory depression (>2 hours after administration) which is to some extent dose-related[61] and believed to be a result of the cephalad spread of opioids to the medulla within the cerebrospinal fluid (CSF), seen more commonly with hydrophilic opioids. Hence, the lipophilic drugs like fentanyl, sufentanil, remifentanil, alfentanil, methadone are more logical choice.

The safety of fentanyl regarding neurotoxicity has been demonstrated in animal studies and it has been proved safest among all opioids.[62,63] Yaksh et al.[64] in 1988, found that intrathecal administration of opioids can produce profound segmental analgesia without causing significant alteration of motor or sensory function or subjective effects.

Epidural use of fentanyl citrate for postoperative pain or labor analgesia has significant popularity. A combination of intrathecal opioids with local anesthetics permits reduction in the dosage of both components, minimizing the side effects of the local anesthetic (motor blockade) and the opioid (i.e. urinary retention, itching and delayed respiratory depression in the case of morphine). An important caveat to their spinal use is that, because of their rapid clearance, these agents at analgesic spinal doses can produce blood levels that are similar to those producing effects after systemic administration.[65,66]

The synergistic effect of opioid combined with local anesthetic can be explained by virtue of their different mechanism of action. Intrathecal opioids inhibit nociceptive afferent synaptic transmission via Aδ and C fibers by opening presynaptic K^+ channels to inhibit transmitter release and thus reduce calcium influx. There is also a direct postsynaptic effect with hyperpolarization and reduced neuronal activity evoked by glutamate. Local anesthetic, bupivacaine, works primarily by causing blockade of voltage-gated Na^+ channels in the axonal membrane and, possibly, a further effect on presynaptic inhibition of Ca^{2+} channels. The results of our study are consistent with experimental evidence of synergistic interaction between spinal opioids and local anesthetics, which are characterized by enhanced somatic analgesia without effect on the degree or level of the local anesthetic induced sympathetic or motor blockade.[67-70]

Clonidine is an α2–agonist which block the conduction of Aδ and C fibers, thereby prolongs the action of local anesthetics. When used intrathecally, it activates the postsynaptic α2–receptors in Substantia gelatinosa of spinal cord and produces analgesia.[71,72 AE] Analgesic properties of clonidine have been shown to depend on the activation of $\alpha 2$ receptors located in the dorsal horn. Presynaptic stimulation of $\alpha 2$ receptors inhibits neurotransmitter release and postsynaptic stimulation prevents neuronal transmission through hyperpolarization[73.s1] Bhure et al. demonstrated that addition of clonidine, fentanyl, and midazolam to bupivacaine significantly improves the onset and duration of sensory and motor block with relative hemodynamic stability, prolongs the duration of analgesia, and reduces the consumption of systemic analgesics in comparison to bupivacaine alone. They concluded that clonidine is an excellent additive to bupivacaine in spinal anesthesia and provides prolonged duration of analgesia without any deleterious effects on the mother and baby.[74 AE]

With this background, present study was carried out in the Dept. of Anesthesiology, Government medical college & Sir T General Hospital Bhavnagar to evaluate the effects of fentanyl in subarachnoid block in patients undergoing lower segment caesarean section.

The result of our study shows that demographic data (age, weight, height, and duration of surgery) was comparable in both the groups ($p > 0.05$).

In our study, in group F significantly reduced the time for onset (1.43+0.40 min), peak of motor blockade (2.22±0.62 min) and significantly prolonged the total duration of motor blockade (223±53.93 min) extending into the postoperative period as compared to group C (2.02±0.45, 2.79±0.61 and 144.6±21.20 min respectively with p<0.0001).

In other study there were faster onset and prolong duration of both sensory and motor block in clonidine group as compare to fentanyl group but they used more than 30µg clonidine which was higher than taken in our study.[75-77]

Complete analgesia lasted longer in group F for 11.46±1.9 hr compared with group C for 10.96±1.9 min (p 0.19). The duration of effective analgesia was significantly prolonged in group F (14.78±2.03 min) as compared with group C (13.17 ±1.31 min), (p<0.0001).

To compare the efficacy we used the duration of effective analgesia measured by time in hours for requirement of rescue analgesia. In consistency to results of several other studies.[53-58] We found both drugs to be effective as adjuvants to intrathecal bupivacaine prolonging the duration of analgesia). The duration of effective analgesia was significantly prolonged in group F (14.78±2.03 min) as compared with group C (13.17±1.31 min), (p<0.0001).

Another study by Bathari et al. concluded that intrathecal fentanyl was superior to intrathecal clonidine in knee arthroscopy.[78] this is in agreement in our study.

Bhattacharjee et al. concluded from their study that perioperative analgesia for cesarean section was prolonged by the addition of 75 µg of clonidine and 25 µg fentanyl to bupivacaine. However, prolongation of postoperative analgesia was more with fentanyl compared to clonidine, and side effects such as nausea, vomiting, and Hypotension were more with clonidine.[79] This study is in agreement with our study.

Prolonged duration of analgesia due to fentanyl in our study was different to other studies.[80,81] In other study duration of analgesia was significantly higher in BC60 group (598.7±140.47 min) than in BF25 (417.75±108.76) group, (p<0.01). But in their study 2.0 ml of hyperbaric bupivacaine 0.5% with either 60 µg of clonidine (BC 60) or 25 µg of fentanyl (BF25) intrathecally. However intrathecal addition of 60 µg clonidine to bupivacaine provides longer duration of postoperative analgesia than 25 µg of fentanyl and is a preferred option when sedation is acceptable or required. Chhabra et al. in their study concluded that clonidine 60 µg has advantage over fentanyl and it prolonged the duration of the subarachnoid block and postoperative analgesia.[82]

Lavand'homme et al. showed higher incidence of hypotension and sedation with intrathecal clonidine 150 µg than clonidine 75 µg.[83] but its increase the duration of post-operative analgesia as compared to 25 µg fentanyl.

But in our study we used 30 µg clonidine and 25 µg of fentanyl so prolong analgesia in fentanyl group as compared to clonidine group. To minimize the side effects like bradycardia and hypotension due to high dose clonidine we take 30 µg clonidine.

Singh et al. evaluated the effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after caesarean section and has shown that the duration of postoperative analgesia increases significantly on adding 75 µgclonidine to 2 ml of hyperbaric bupivacaine without any increase in maternal side effects. There was no effect on neonatal outcome.[84] Shidhaye et al. concluded that intrathecal addition of 25 µg fentanyl to bupivacaine provides good analgesia with less sedation and is a better option when sedation is not desirable. However, intrathecal addition of 60 µg clonidine to bupivacaine provides longer duration of postoperative analgesia than 25 µg of fentanyl and is a preferred option when sedation is acceptable.[85] In our study fentanyl group give prolong analgesia but dose of clonidine was 30 µg.

Based on the data found in Marzieh Beigom Khezri, 1, it was concluded that Administration of intrathecal clonidine 75 µg with bupivacaine prolonged intraoperative anesthesia and the time to first analgesic request after cesarean delivery compared to fentanyl and control groups. This is not in agreement in our study.

The result of the present study shows that in group F significantly reduced the time for onset (1.20+0.36 min), peak of sensory blockade (1.99 ± 0.59 min) and significantly prolonged the total duration of sensory blockade (240.40±53.45 min) extending into the postoperative period as compared to group C (2.02±0.45, 2.79±0.45 and 163±22.79 min respectively with p<0.0001), hence provided effective postoperative analgesia up to 12 hours.

In other study[75-77] there was faster onset, peak and prolong duration of sensory blockade in clonidine group as compared to fentanyl group. But they use higher dose of clonidine than our study.

However, Mahendru et al. in their study opined that intrathecal 30 µg clonidine is comparable to 25 µg fentanyl regarding sensory and motor block

characteristics which was not in agreement with our study.[11 AE]

There is statistically significant difference in fall in heart rate in group C as compared to group F, at 30 minutes and 45 minutes significant fall in heart rate in group C.

There is statistically significant difference in fall in mean arterial blood pressure at 5, 10 and 15, 45 min after subarachnoid block in group C as compared to group F. The finding in Marzieh Beigom Khezri,[86] which should be taken into account is that transient hypotension episodes and vasopressor requirementin clonidine group were significantly greater than fentanyl group a finding in agreement with our studies.

Side effects observed in our study were nausea, vomiting, hypotension, bradycardia and shivering. The total number of participants who experienced side effects were significantly less in group F. Twelve participants (24%) in the group C and three participants (6%) in the group F had hypotension in our study, requiring treatment with intravenous Inj. Mephentermine (5mg) in addition to crystalloid bolus.

Two participants (4%) in group C experienced nausea and vomiting as compared to group F, which was statistically not significant.

In present study, 25 µg fentanyl and 30 µg clonidine was used and no participant in either group experienced respiratory depression. Reuben SS et al.[87] and Varrasi G et al.[88] found that although no patient developed respiratory depression.

Late rostral spread with small dose intrathecal fentanyl is less and studied by Neil Roy et al.[89], Echevarria et al.[90], Singh H et al.[91], Dalhgren G et al.[92] and Olofsson et al.[93] and they concluded that 25 µg fentanyl is the safest dose. In our study no patient in fentanyl group developed respiratory depression.

References

1. Cervero F, Laird JMA. One pain or many pains? A new look at pain mechanisms. NIPS 1991;6:268–73.
2. Corning JLNY Med J. 1885;42:483 (reprinted in classical file, Survey of Anesthesiology 1960;4:332)
3. Richard Brull, Alan JR Macfarlane, Vincent WS Chan. Miller's Anesthesia. 8th ed. Ch. 56, Elsevier, 1685.
4. Pert CB and Snyder SH. Opiate receptors: Demonstration in nervous tissue. Science 1973;179:1011–4.
5. Hunt CO. Spinal anesthesia for obstetrics. International Anesthesiology, Clinics 1989;27:26–30.
6. M–B Khezri, S Yaghobi, M Hajikhani, et al. "Comparison of postoperative analgesic effect of intrathecal magnesium and fentanyl added to bupivacaine in patients undergoing lower limb orthopedic surgery," Acta Anesthesiologica Taiwanica 2012;50(1):19–24.
7. F. Safari, A. Dabbagh, and M. Sharifnia, "The effect of adjuvant midazolam compared with fentanyl on the duration of spinal anesthesia with 0.5% bupivacaine in opium abusers," KoreanJournal of Anesthesiology 2012;63(6):521–26.
8. JC Eisenach, M de Kock, and W Klimscha. "α2–adrenergic agonists for regional anesthesia: A clinical review of clonidine (1984–1995)," Anesthesiology 1996;85(3):655–74.
9. JC Eisenach, DD Hood, and R Curry. "Relative potency of epidural to intrathecal clonidine differs between acute thermal pain and capsaicin–induced allodynia," Pain 2000;84(1):57–64.
10. PM Lavand'Homme, F Roelants, H Waterloos, et al. "An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery," Anesthesia and Analgesia 2008;107(3):948–55.
11. Akerman B, Arwestrom E, Post C. Local anesthetics potentiate spinal morphine antinociception. Anesth Analg 1988 Oct;67(10):943–8.
12. Wang C, Chakrabarti MK, Whitwam JG. Specific enhancement by fentanyl on the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. Anesthesiology 1993 Oct;79(4):766–73.
13. Tejwani GA, Rattan AK, Macdonald JS. Role of spinal opioid receptors in the antinociceptive interaction between intrathecal morphine and bupivacaine. Anesth Analg 1992 may;74(5):726–34.
14. Olanrewaju N Akanmu, Olaitan A Soyannwo, Patience T Sotunmbi, et al. Analgesic Effects of Intrathecally Administered Fentanyl in Spinal Anesthesia for Lower Limb Surgery. Maced J Med Sci. 2013 Sep 15;6(3):255–60.
15. Ben–David B, Solomon E, Levin H, et al. Intrathecal fentanyl with small–dose dilute bupivacaine: Better anesthesia without prolonging recovery. Anesth Analg, 1997 Sept;85(3):560–5.
16. Y harada, K Nishioka, LM Kitahata, et al. Visceral antinocipceptive effect of spinal clonidine combined with morphine, [D– pen2, D– pen5] encephalin, or U50, 488H. Anesthesiology 1995;83;344–52.
17. H Buerkle and TL Yakas. Pharmacological evidence for α2 adrenergic receptor sites mediating analgesia and sedation in rat BJA 1998;81;208–15.

18. Toshio Ashno, Shuji, Shuichiro, Hiroyuki Shimonaka and Hiokilida Antinociception by epidural and systemic aα adrenoceptor agonist and their binding affinity in rat spinal cord and brain. Anesth Analg 2000;90:400–07.

19. Gyongyi Howawath, Gabriella Joo, Ildiko Dobos. The synergistic antinociceptive interaction of endorphins with dexmedetomidine and ketamine in rats. Anesthesia Anal 2001;93:1018–24.

20. Katsauki Tanaka, Yutaka Oda, Tomoharu Funao, et al. Dexmedetomidine decreases the convulsive potency of bupivacaine and levobupivacaine in rats: Involvement of aα adrenoceptor for controlling convulsions. Anesth Analg 2005:100:687–96.

21. Robert D. Eric Evans, Laura A. Renee G. Spinal clonidine prolongslabor analgesia from spinal sufentanil and bupivacaine. Anesh Analg 1999; 88:573–76.

22. Dobrydnjov K, Axelsson J, Samarutel B. holmstrom. Postoperative pain relief following intrathecal bupivacaine combined with intrathecalor oral clonidine. Acta Anesthesiologica Scandinavica 2002;46(7):806.

23. AM Hennaway, AM Abd–Elwahab, AM Elmaksoud, et al. Addition of clonidine or dexmedetomidine to bupivacaine prolongs caudal analgesia in children. BJA 2009;103:268–74.

24. Mausami Neogi, Dhurjati Prasad Bhattacharjee, Satrajit Dawn, et al. A comparative study between clonidine and dexmedetomidine used as adjuncts to ropivacaine for caudal analgesia in paediatric patients. J Anesth Clin pharmacol 2010;26:149–53.

25. Sukhminder jitsingh Bajawa, Sukhwinder Kaur Bajawa, Jasbir Kaur, et al. Dexmedetomidine and clonidine in epidural Anesthesia: A Comparative evaluation. Indian Journal of Anesthesia 2011;55: 116–21.

26. GE Kanazi, MT Aouad, SI Jabbour–Khoury, et al. Effect of low–dose dexmedetomidine or clonidine on the characteristics of bupivacaine spinal block. Acta anesthesiol Scand 2006;50:222–27.

27. Rajani Gupta, Jaishi Bogra, Reetu Verma, et al. Dexmedetomidine as an intrathecal adjuvant for postoperative analgesia. IJA 2011;55:347–51.

28. Ibrahim F, A Khalifa. A comparative study of adding intrathecal dexmedetomidine versus sufentanil to heavy bupivacaine for postoperative analgesia in patients undergoing inguinal hernia repair. Benha Medical journal 2009;26;207–19.

29. Rajani Gupta, Jaishi Bogra, Reetu Verma, et al. A comparative study of intrathecal dexmedetomidine and fentanyl as adjuvant to bupivacaine. JOACP 2011;339–43.

30. Gray's Anatomy of the Human Body, 40th edition.

31. Barash Paul G, Cullen Bruce F, Stoelting Robert K, et al. Clinical Anesthesia, 6th Edition; Chapter 37: Epidural and spinal Anesthesia; 925–45.

32. Agur Anne MR, Dalley Arthur F. Grants atlas of anatomy; Edition 12: Chapter 4–Back; 558–66.

33. David L Brown: Miller's Anesthesia: 7th Edition; Spinal, epidural and caudal Anesthesia; 1611–20.

34. International Association for the Study of Pain: Taxonomy: International Association for the Study of Pain, 2012 http://www.iasppain.org/Content/NavigationMenu/GeneralResourceLinks/PainDefinitions/default.htm/.

35. Ganong's Review of Medical Physiology. 23rd Edition; chap 10:168–71.

36. Wylie: Textbook of Anesthesia.

37. Charles B Berde, Gray R Strichartz. Local anesthetics; Ronald D. Miller's Anesthesia 7th edition: 913–41.

38. Opioid agonist and antagonist: Robert K Stoelting, MD., Simon C. Hillier, M.B. Ch. B, FRCL, Pharmacology and Physiology in Anesthetic practice 4th ed. USA: Lippincott Williams and Wilkins 2006;87–122.

39. LE. Mather Clinical Pharmacokinetics of Fentanyl and its Newer Derivatives. Clinical Pharmacokinetics. 1983; 8:422–46.

40. Roerig DL, Kortly KJ, Vucins ET, et al. First pass uptake of fentanyl, meperidine and morphine in human lung. Anesthesiology 1987;67:466.

41. John B Bentley, James D Borel, Robert E Nenad, et al. Age and fentanyl pharmacokinetics. Anesth Analg 1982;61:968–71.

42. KD Tripathi. Essential of Medical Pharmacology 6th ed. Chapter;34–459.

43. Atcheson R, Lambert DG. Update on opioid receptors. Editorial II, Br. J Anesth 1994;73:132–34.

44. Atcheson R, Rowbotham DJ, Lambert DG. Fentanyl inhibits the uptake of (3H) noradrenaline in cultured neuronal cell. Br J Anesth 1993;71:540–43.

45. McEwen AI, Smith C, Dyaro O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology.1993;78:864–9.

46. Hickay PR, Hanson DD, Wessel DL. Blunting the stress response in pulmonary circulation in infants by fentanyl. Anesth Analgesia 1985;64–1137.

47. Giesckek K, Hambergerb, Jarnberg et al. High and Low dose fentanyl Anesthesia: Hormonal and metabolic response during cholecystectomy. Br J Anesth 1988;61–575.

48. Miller"s Anesthesia–Ronald D. Miller. 7th edition.

49. KD Tripathi. Essential of Medical Pharmacology 6th ed. Antihypertensive drugs Clonidine in peadiatrics–Sujathabasker et al. Indian joural of Anesthesia 2009;53(3):270–80.

50. Addition of clonidine or dexmedetomidine to bupivacaine prolonged in caudal analgesia for children. AM Abd Elwahab, et al. British journal of Anesthesia 2009;103(2):268–74.

51. Epidural Analgesia–philip R. Bromage: 258–82.

52. Benhamou D, Thorin D, Brichant JF, et al. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesth Analg 1998;87(3):609–13.

53. Van Tuijl I, Van Klei WA, Van der Werff DB, et al. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain and morphine requirements after Caesarean section: A randomized controlled trial. Br J Anesth 2006;97(3):365–70. http://dx.doi.org/10.1093/bja/ael182PMid:16861258.

54. Kothari N, Bogra J, Chaudhary AK. Evaluation of analgesic effects of intrathecal clonidine along with bupivacaine in cesarean section. Saudi J Anesth 2011;5(1):31–5.
http://dx.doi.org/10.4103/1658–354X.76499PMid:21655013 PMCid:PMC3101750

55. Bajwa SJ, Bajwa SK, Kaur J, et al. Prevention of hypotension and prolongation of postoperative analgesia in emergency cesarean sections: A randomized study with intrathecal clonidine. Int J CritIllnInj Sci 2012;2(2):63–9.

56. Breen TW, Shapiro T, Glass B, et al. Epidural anesthesia for labor in an ambulatory patient. Anesth Analg 1993;77:919–24.
http://dx.doi.org/10.1213/00000539–199311000–00008 PMid:8214727.

57. Agrawal A, Agrawal S, Asthana V, et al. Comparison of intrathecal fentanyl and Sufentanil in addition to bupivacaine for caesarean section under spinal Anesthesia. J Anesth Clin Pharmacol 2009;25(2):154–56.

58. LE Mather Clinical Pharmacokinetics of Fentanyl and its Newer Derivatives. Clinical Pharmacokinetics 1983;8:422–46.

59. McEwen AI, Smith C, Dyaro O, et al. Isoflurane minimum alveolar concentration reduction by fentanyl. Anesthesiology 1993;78:864–9.

60. Jacobson L, Chabal C, Brody MC. A dose–response study of Intrathecal morphine: Efficacy, duration, optimal dose and side effects. Anesth Analg. 1988; 67:1082–8.

61. Gissen AJ, Gugino LD, Datta S, et al. Effects of Fentanyl and Sufentanil on Peripheral Mammalian Nerves. Anesth Analg 1987 Dec;66:1272–6.

62. Gielen MJM. Spinal Anesthesia. Current opinion in Anesthesiology 1993;6:803–7.

63. Yaksh TL, Gaumann DM and Stevens CW. Receptors in the Dorsal Horn and Intrathecal Drug Administration. Annals of the New York Academy of Sciences 531:90–107. doi: 10.1111/j.1749–6632.1988.tb31816.x[TL Yaksh, DM Gaumann, CW Stevens. Receptors in the Dorsal Horn and Intrathecal Drug Administration. Annals of the New York Academy of Sciences. 1988 June;531(1):90–107.

64. Bernards CM. Understanding the physiology and pharmacology of epidural and intrathecal opioids. Best Pract Res Clin Anesthesiol 2002;16:489–505.

65. Bernards CM. Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. Curr Opin Anesthesiol 2004;17:441–7.

66. Akerman B, Arwestrom E, Post C. Local anesthetics potentiate spinal morphine antinociception. Anesth Analg 1988 Oct;67(10):943-8.

67. Wang C, Chakrabarti MK, Whitwam JG. Specific enhancement by fentanyl on the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. Anesthesiology 1993 Oct;79(4):766–73.

68. Tejwani GA, Rattan AK, Macdonald JS. Role of spinal opioid receptors in the antinociceptive interaction between intrathecal morphine and bupivacaine. Anesth Analg 1992 may;74(5):726–34.

69. Ben–David B, Solomon E, Levin H, et al. Intrathecal fentanyl with small–dose dilute bupivacaine: Better anesthesia without prolonging recovery. Anesth Analg, 1997 Sept;85(3):560–5.

70. Giovannitti JA, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: A review of current clinical applications. Anesth Prog 2015;62:31-8.

71. Sethi BS, Samuel M, Sreevastava D. Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian J Anesth 2007;51:415-9.

72. M. Yoshimura and H. Furue, "Mechanisms for the anti–nociceptive actions of the descending noradrenergic and serotonergic systems in the spinal cord," Journal of Pharmacological Sciences, 2006;101(2):107–17.

73. Bhure A, Kalita N, Ingley P, et al. Comparative study of intrathecal hyperbaric bupivacaine with clonidine, fentanyl and midazolam for quality of Anesthesia and duration of postoperative pain relief in patients undergoing elective caesarean section. Peoples J Sci Res 2012;5:19-23.

74. Benhamou D, Thorin D, Brichant JF, et al. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesthesia and Analgesia 1998;87(3):609–13. https://doi.org/10.1213/00000539–199809000–00022.

75. Khezri MB, Tahaei E, Atlasbaf AH. Comparison of postoperative analgesic effect of intrathecal Ketamine and fentanyl added to bupivacaine in patients undergoing cesarean section: A prospective randomized double–blind study. Middle East Journal of Anesthesiology 2016;23(4):427–36. https://doi.org/10.1155/2014/513628.

76. Trial to Evaluate the Effectiveness of Intrathecal Bupivacaine Combined with Different Adjuvants (Fentanyl, Clonidine and Dexmedetomidine) in Caesarean Section. Drug Research 65(11):581–86. Li, Z., Tian, M., Zhang, C. Y., Li, A. Z., Huang, A. J., Shi, C. X., … Li, K. Z. (2014). A Randomised Controlled https://doi.org/10.1055/s–0034–1395614.

77. Bathari R, Bhalotra A, Anand R, et al. A randomized trial tocompare the effect of addition of clonidine and fentanyl to hyperbaric ropivacaine for spinal Anesthesia for knee arthroscopy. S Afr J Anesth Analg 2016;22:14–8.

78. Bhattacharjee A, Singh NR, Singh SS, et al. A comparative study of Intrathecal clonidine and fentanyl along with bupivacaine in spinal anesthesia for caesarean section. J Med Soc 2015;29:145–9.

79. Breen TW, Shapiro T, Glass B, et al. Epidural anesthesia for labor in an Ambulatory patient. Anesth Analg. 1993; 77:919–24. http://dx.doi.org/10.1213/00000539–199311000–00008PMid:8214727.

80. Agrawal A, Agrawal S, Asthana V, et al. Comparison of intrathecalfentanyl and Sufentanil in addition to bupivacaine for caesarean section under spinal Anesthesia. J Anesth Clin Pharmacol 2009;25(2):154–56.

81. Chhabra AR, Jagtap SR, Dawoodi SF. Comparison of clonidine versus fentanyl as an adjuvant to intrathecal ropivacaine for major lower limb surgeries: A randomized double blind prospective study. Indian J Pain 2013;27:170–4.

82. Lavand'homme PM, Roelants F, Waterloos H, et al. An evaluation of the postoperative antihyperalgesic and analgesic effects of intrathecal clonidine administered during elective cesarean delivery. Anesth Analg 2008;107:948–55.

83. Singh R, Gupta D, Jain A. The effect of addition of intrathecal clonidine to hyperbaric bupivacaine on postoperative pain after lower segment caesarean section: A randomized control trial. Saudi J Anesth 2013;7:283–90.

84. Shidhaye RV, Shah BB, Joshi SS, et al. Comparison of clonidine and fentanyl as adjuvant to intrathecal bupivacaine for spinal Anesthesia and postoperative analgesia in patients undergoing caesarean section. Sri Lankan J Anesthesiol 2013;22:15–20.

85. Benhamou D, Thorin D, Brichant JF, et al. Intrathecal clonidine and fentanyl with hyperbaric bupivacaine improves analgesia during cesarean section. Anesthesia and Analgesia 1998;87(3):609–13. https://doi.org/10.1213/00000539–199809000–00022

86. Reuben SS, Dunn SM, Duprat KM, et al. An intrathecal fentanyl dose response study in lower revascularization procedures. Anesthesiology. 1994 Dec;81(6):1371–5.

87. Varrassi G, Celleno D, Capogna G, et al. Ventilatory effects of subarachnoid fentanyl in the elderly. Anesthesia 1992;47:558–62.

88. Neil Roy Connelly, Steven M. Dunn, Venesa Ingold, et al. The use of fentanyl added to morphinelodocaine– epinephrine spinal solution in patients undergoing cesarean section. Anesthesia Analgesia 1994;78:918–20.

89. Echevarria M, Caba F, Olmenda L, et al. Comparative study of single dose intradural anesthesia and continuous intradural anesthesia with or without fentanyl. Rev ESP Anestesiol Reanim. 1995 Apr; 42(4):115–8.

90. Gissen AJ, Gugino LD, Datta S, et al. Effects of Fentanyl and Sufentanil on Peripheral Mammalian Nerves. Anesth Analg. 1987 Dec;66:1272–6.

91. Yaksh TL, Gaumann DM and Stevens CW, Receptors in the Dorsal Horn and Intrathecal Drug Administration. Annals of the New York Academy of Sciences 1988;531:90–107. doi: 10.1111/j.1749–6632.1988.tb31816.x[TL Yaksh, DM Gaumann, CW stevens. Receptors in the Dorsal Horn and Intrathecal Drug Administration. Annals of the New York Academy of Sciences 1988 June;531(1): 90–107.

92. Olofssan C, Ekblom A, Skoldefors E, et al. Anesthetic quality during cesarean section following subarachnoid or epidural administration of bupivacaine with or without fentanyl. Acta Anesthesiol Scand 1997 Mar ; 41(3): 332–8.