Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 3, 2021, Pages. 3813 - 3828
Received 16 February 2021; Accepted 08 March 2021.

Comparitive Study of Epidural Fentanyl and Bupivacaine with Epidural Clonidine and Bupivacaine for Post Operative Pain Relief in Lower Abdominal and Lower Limb Surgeries- A Randomised Controlled Trial

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Abstract

This study was undertaken to chart and find out analgesic total time duration including the sedation and side effects of Bupivacaine (0.25%) with Fentanyl 2µg/ml and Bupivacaine (0.25%) with Clonidine 2µg/ml given via epidural route in patients post operatively who underwent lower abdominal and lower limb surgery under spinal anaesthesia.The present study includes the addition of Clonidine to 0.25% bupivacaine significantly prolonged the duration of post-operative analgesia with adding Clonidine was found to be prolonging the time duration for First Rescue Analgesia.This study focuses on the addition of Clonidine epidurally produced sedation that was easily arousable for many hours compared to Fentanyl and Occurence of adverse effects such as hypotension were found to be more in patients who got clonidine, this was not statistically significant between the groups. No episode of respiratory depression was noted in both the study groups which are more common with opioids. With regard to acceptance, the patients who received Fentanyl were highly satisfied by the study drug administration.

Keywords : Clonidine, Fentanyl, Visual Analogue Scale (VAS), anaesthetics and nausea

Introduction

Post-operative pain and discomfort are the major concerns in all patients undergoing any type of surgery. Delay of discharge is mainly due to post-operative pain. So, the Pain relief and patient ease during the initial post-operative period becomes increasingly important. Proper and uncomplicated pain management is crucial for ideal care of surgical patients. Adequate post-operative pain reduction results in earlier ambulation and cause a decrease in the onset problems

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such as infections, neurological, cardiovascular, and thrombo embolic sequelae caused by immobility. Also this further leads to short hospital stay and decreased hospital costs, better patient satisfaction, and leads to improved quality of life and health outcome.1-4 Also pain elevates the degree of the indisposition after surgeries due to a decrease in the effort to breathe and suppression of cough reflex and therefore interrupts mobility and regaining of bowel function.

Epidural analgesia is one of many recent evidence-based regimens for postoperative pain relief after surgeries particularly surgeries of abdomen.

Advantages with epidural analgesia in high risk patients were

- Significant decrease in surgical stress response
- Hemodynamic stability and reduction in cardiac and pulmonary morbidity
- Recovery of gastrointestinal function
- Early ambulation there by reduction in thromboembolic events

Local anaesthetics are useful and effective in treatment of acute & chronic post- operative pain, but the limitations like short duration of action, adverse effects on Cardio- Vascular System (CVS)and Central Nervous System (CNS) curb its use in recent times.[12] Adjuvants as well as additives are frequently used in conjunction with local anaesthetics for its combined and additive effect by extending the period of sensory-motor block and restricting the increasing dose necessity of local anaesthetics.[13] The collection of local anaesthetic adjuvants have progressed over time from opioids to a extensive collection of drugs of varying mechanisms of action. A large range of opioids from morphine, fentanyl and sufentanil to hydromorphone, buprenorphine and tramadol were used earlier which are restricted due to their severe adverse effect like respiratory depression, nausea, vomiting and pruritus, which is mainly during neuraxial use(5-11). Alpha 2 adrenoreceptor agonists including clonidine and dexmedetomidine are extensively used as a class of local anaesthetic adjuvants. Steroids, anti-inflammatory agents, midazolam, ketamine, magnesium sulphate and neostigmine have also been used with varied achievement. Success of Local Anaesthetic peripheral nerve block adjuvants for prolongation of analgesia is an extensively researched topic.[14]The apprehension concerning the safety outline of these adjuvants for prolongation of epidural analgesia demand further exploration in this track(12-14).

This study was undertaken with an aim to find out whether Clonidine and bupivacaine combination have a better efficacy in epidural analgesia compared to Fentanyl-Bupivacaine Combination.

1. MATERIALS AND METHODS

Study Subjects

Patients undergoing elective lower limb and lower abdominal surgeries in SREE BALAJI

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MEDICAL COLLEGE AND HOSPITAL, CHENNAI.

Study Design

Prospective Randomised Control Trial

Study setting

Department of Anaesthesia, SREE BALAJI MEDICAL COLLEGE AND HOSPITAL, CHENNAI

Sampling Procedure

The study was done in 50 patients who came for Elective lower limb and lower Abdominal surgeries. These 50 patients were randomly allocated to two groups using computer generated Random Number Table. Each group contained 25 subjects.

Group I- Received Bupivacaine (0.25%) with Fentanyl 2mcg/ml Group II- Received Bupivacaine (0.25%) with Clonidine 2mcg/ml

Inclusion Criteria

ASA I & II Patients Age 20- 70 years
Patient undergoing elective lower limb and lower abdominal surgery

Exclusion criteria

Refusal to participate in the study ASA III&IV
Morbidly Obese Patients
Patients with neurological disease Spinal deformity
Patient having drug allergy to local anaesthetics Patients with mental illness
Patient having coagulative disorders Patient with infection in injection site

Sample Size: 50

STUDY PROCEDURE

Ethical committee approval was obtained before the commencement of the study. Following the pre-anaesthetic assessment, patients were admitted the day before the surgery. After obtaining informed consent patients were shifted to OT. All patients fasted for 8 hours. Routine pre-anaesthetic assessment was done. In all patients, age, body weight and baseline vital parameters were recorded. History regarding previous anaesthesia, surgery and significant other co-morbid illness, medications and allergy was recorded. Complete physical examination and airway assessment were done.

In the preoperative period all patients were instructed about the benefits of epidural analgesia and 10-point visual analogue scale. And also informed consent form obtained from all the study group patients.

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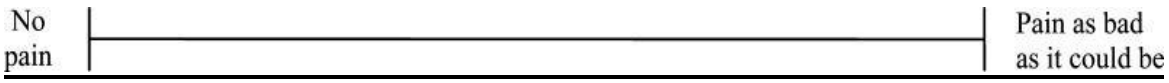
Premedication:

All patients were given T.Alprazolam 0.5mg(previos night),Inj.Ondansetron 4mg(IV) Inj.Ranitidine 150 mg(IV) before anesthesia. Anesthesia work station check list done,emergency trolley was kept ready .Standard monitors like ECG, Non-invasive BP, SpO2 and temperature probe were connected to the patient and baseline values recorded.18G IV Cannula inserted under aseptic precaution and Ringers lactate is the fluid of choice which was started.

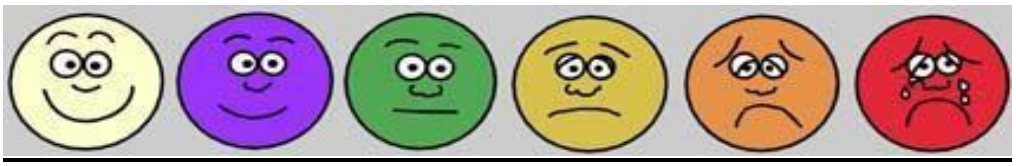
Epidural block was performed in sitting position in T11-T12/T12-L1 interspace with 18-gauge Tuohy needle. After ensuring epidural space by LOR Technique, catheter is placed at 10 cm and test dose with 3 ml lignocaine (2%0 with adrenaline (1 in lakh) was given. Spinal sub arachnoid block given with 0.5% Bupivacaine heavy without any adjuvant. After injection, patient was put back in supine position. 3L/min of O2 was given by mask. After ensuring attainment of adequate level of sensory block, the surgeons proceeded with surgery.

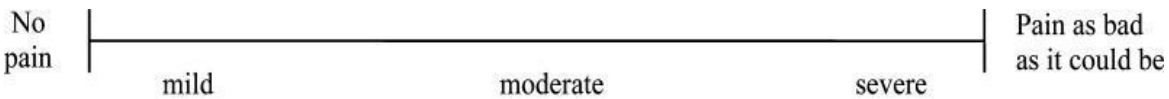
VISUAL ANALOGUE SCALE (VAS) [12]

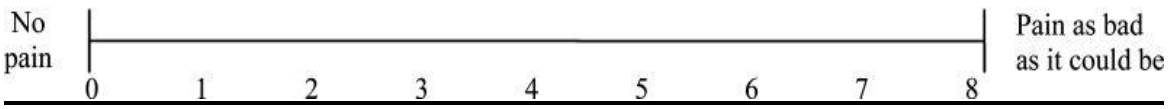
The Visual Analogue Scale (VAS) consists of a straight line with the endpoints defining extreme limits such as 'no pain at all' and 'pain as bad as it could be'.Sensitive to small changes in pain intensity. Not suitable for use in visually impaired patients or small children. It consists of a 100 mm line anchored at one end with 'no pain' and at the other end with 'worst pain imaginable'. The patient is asked to place a mark on the line that best represents their pain intensity.
The distance between 'no pain at all' and the mark then defines the subject's pain. This tool was first used in psychology by Freyd in 1923. If descriptive terms like 'mild', 'moderate', 'severe' or a numerical scale is added to the VAS, one speaks of a Graphic Rating Scale (GRS).



VAS







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GRS

ASSESSMENT OF SEDATION USING RAMSAY SEDATION SCORE[13]

Awake levels

- Anxious, agitated or both
- Co-operative oriented, tranquil
- Response to commands only

Asleep levels

- Brisk response to loud auditory stimulus.
- Sluggish response to loud auditory stimulus
- No response to loud auditory stimulus

Vital parameters were monitored continuously and recordings were made every 15 minutes until 30 minutes and at 120 minutes interval for next 24 hours. Hypotension (defined as systolic arterial pressure falling less than 90mmHg) was treated with I V Ephedrine 6mg and bradycardia (heart rate <50 beats/min) was treated with 0.3mg of I V Atropine.

During the first 24 hours of postoperative period, adverse events like nausea, vomiting, dizziness, hypotension, dizziness, dry mouth, pruritus and respiratory depression were noted. Nausea and vomiting were treated with 4mg of intravenous Ondansetron.

2. Results

Results of this study are described under the following headings:

a. Comparison of basic characteristics

i. Age distribution of study population

ii. Weight distribution of study population

iii. Gender distribution of study population

iv. ASA-PS distribution of study subjects

v. Distribution of surgery done among subjects

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b. Inferential Statistics:

i. Comparison of duration of analgesia between two groups

ii. Comparison of time for First Rescue Analgesia between two groups

iii. Comparison of time for Second Rescue Analgesia between two groups

iv. Comparison of Visual Analogue Scale between two groups

v. Comparison of Ramsay Sedation Score between two groups

vi. Comparison of variables of Hemodynamic Stability like SBP, DBP, Pulse Rate between two groups

vii. Comparison of side effects between two groups

viii. Comparison of patient acceptance between two groups The study was done among 50 subjects.

AGE DISTRIBUTION OF STUDY POPULATION AMONG TWO GROUPS

Age in years	**CLONIDINE**	**FENTANYL**
Mean	53.36	58.84
Median	53	60
Mode	43	60
Std. Deviation	8.611	6.067
Minimum	37	46
Maximum	69	70

The mean (SD) age of subjects who used clonidine is 53.36 (8.61) compared to those who used fentanyl 58.84(6.07).

The histogram with normal curve for age among the two groups are represented below

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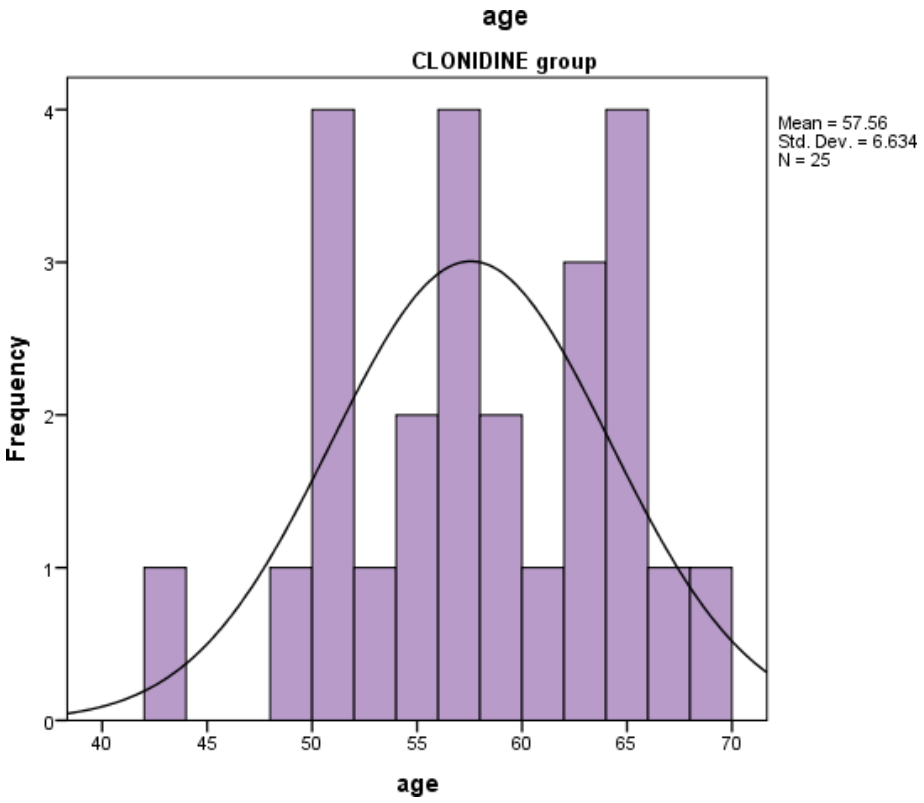

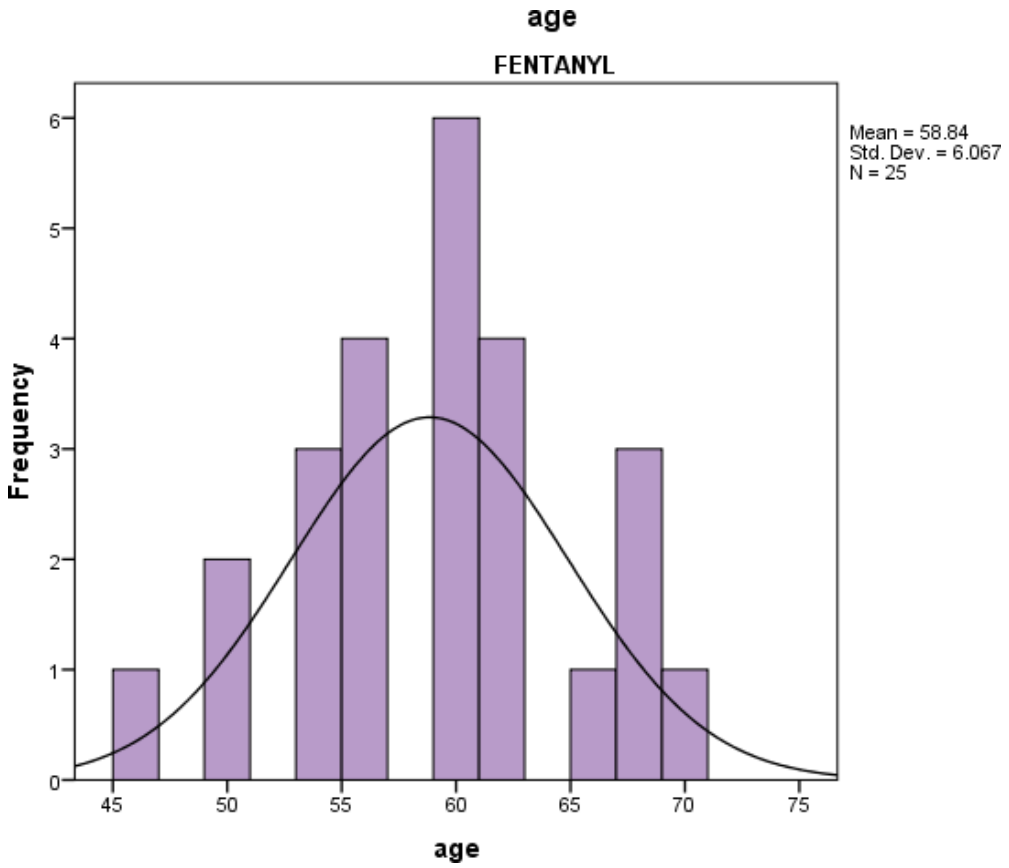

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AGE DISTRIBUTION BETWEEN THE GROUPS

	No. of cases	Mean ±S. D	t value	p value*
Group C	25	57.56± 6.634	.712	0.480
Group F	25	58.84 ± 6.067		

*p value calculated by independent sample t test, p value<0.05 is significant

This study found that mean age of participants in Clonidine group (57.56± 6.634 years) was comparable to that of Fentanyl group (58.84±8.067yrs) t value= .712, p value:
0.48. No significant difference between two groups with respect to age.

Table: Categorisation of age between two Clonidine and Fentanyl groups

Age categorisation	DRUG GROUP		Total
	CLONIDINE	FENTANYL	
<50 YEARS	5 62.5%	3 37.5%	14 100.0%
51-60 YEARS	11 45.8%	13 54.2%	21 100.0%
61-70 YEARS	9 50.0%	9 50.0%	15 100.0%
Total	25	25	50
	50.0%	50.0%	100.0%

Among 60 subjects, 8 belonged to <50 years of age group,24 belonged to 51-60 years of age group, 18 belonged to 61-70 years of age group. 5(62.5%) of <50 years were in clonidine group.13(54.2%) of 51-60 years in fentanyl group. Clonidine and Fentanyl group had equal number of persons in 61-70 years of age group.

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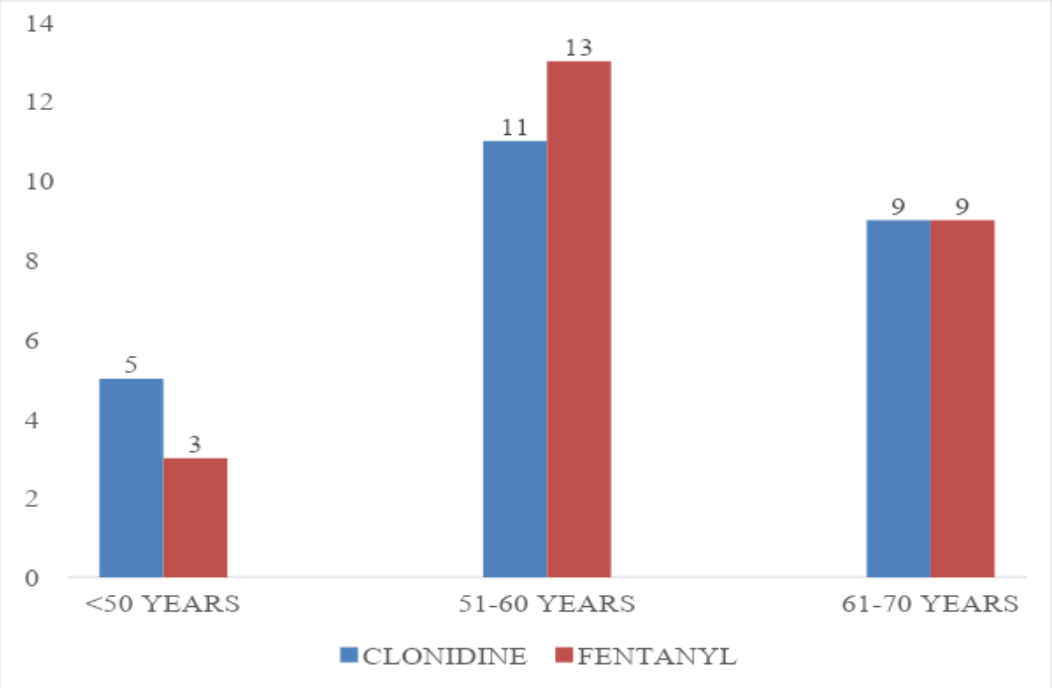
Figure: Categorisation of age between two Clonidine and Fentanyl groups



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WEIGHT DISTRIBUTION OF STUDY POPULATION AMONG TWO GROUPS

Weight (Kg)	CLONIDINE	FENTANYL
Mean	65.36	61.68
Median	67	58
Mode	60	56
Std. Deviation	6.975	9.949
Minimum	53	43
Maximum	78	90

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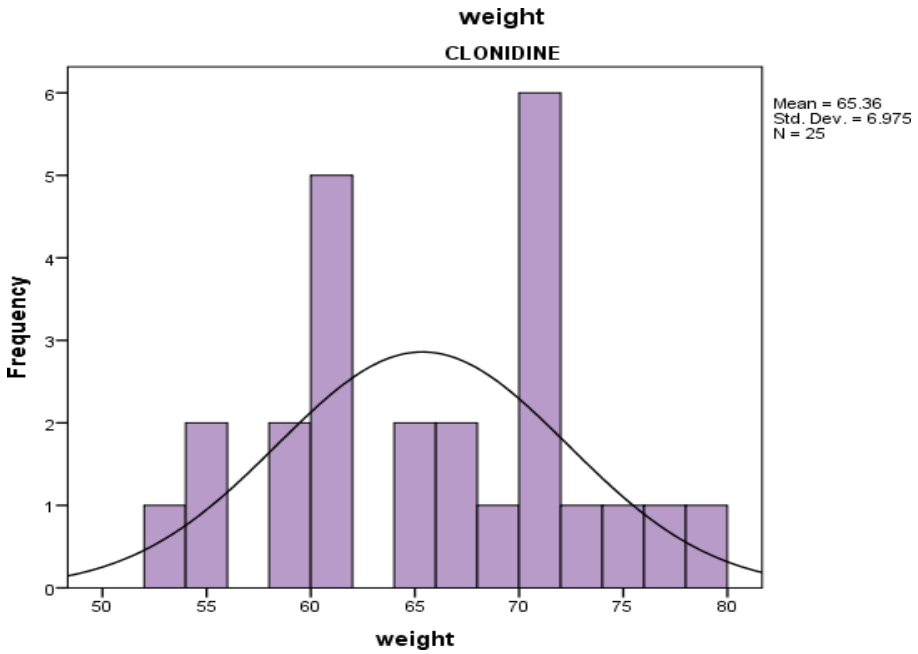
The mean (SD) weight of subjects who used clonidine is 65.36 (6.975) compared to those who used fentanyl 61.68(9.949). The histogram with normal curve for age among the two groups are represented
below



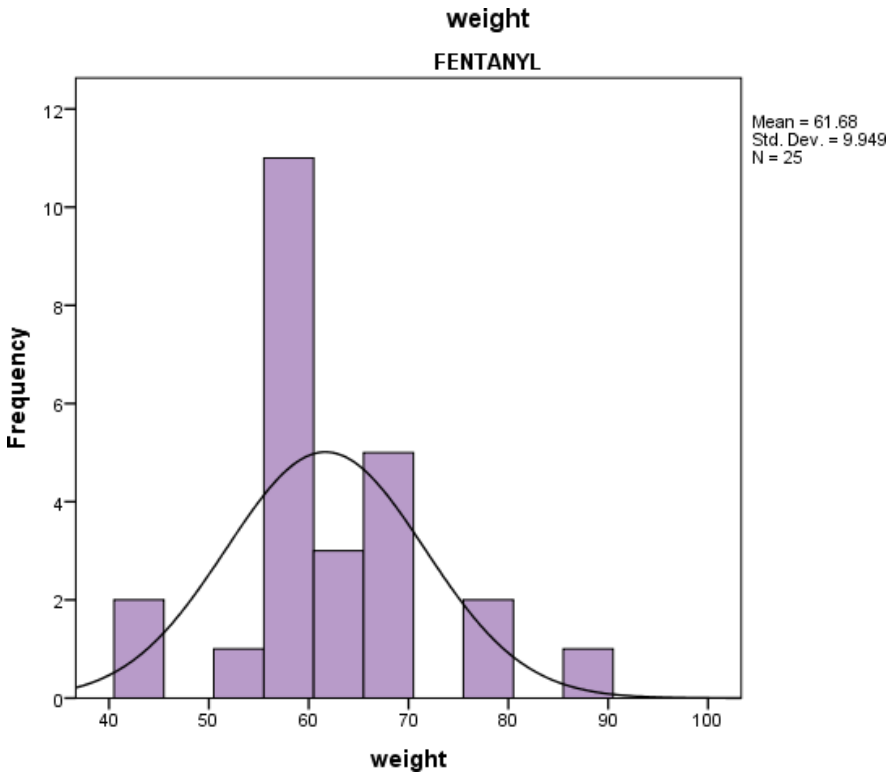


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Table: Weight distribution between the groups

	No. of cases	Mean ±S. D	t value	p value*
Group C	25	65.36± 6.975	1.51	0.13
Group F	25	61.68 ± 9.949		

*p value calculated by independent sample t test, p value<0.05 is significant

This study found that mean age of participants in Clonidine group (65.36± 6.975 Kg) was comparable to that of Fentanyl group (61.68 ± 9.949 Kg) t value= 1.51, p value: 0.13. No significant difference between two groups with respect to age.

GENDER DISTRIBUTION AMONG STUDY SUBJECTS

	MALE	FEMALE	Chisquare value	p value
Group C	14(56%)	11(44%)	0.081	1.00
Group F	13(52%)	12(48%)		
Total	27 (54%)	23(46%)		

*p value calculated by Chi-square test. P value<0.05 is significant

Among 50 subjects, 27(54%) of subjects were males and 23(46%) were females. Out of 27 males 14 were in Clonidine group and 13 in Fentanyl group. Among 23 females, 11 were in Clonidine group and 12 in Fentanyl group. Both groups were comparable according to gender side effects were not found in 22(88%), 2(8%) had vomiting.

Discussion

Our study was done with an aim to find out whether Clonidine and bupivacaine combination have a better efficacy in epidural analgesia compared to Fentanyl- Bupivacaine Combination

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(15-18).

In human beings, many studies using epidural α-2 agonists like clonidine & dexmedetomidine have been showed absence of any neurological discrepancy. 38,41Clonidine is an alph-2 agonist, which gives a synergistic additive effect on both sensory & motor blockade of local anaesthetics. The analgesic effect succeeding intrathecal administration is facilitated via the stimulation of postsynaptic alpha 2 receptors in the substantia gelatinosa of the spinal cord. Mechanism of action is blockade of conduction of the Aδ and C fibres. These drugs reduce sympathetic central nervous system outflow and exert tranquillizing, anxiolytic, hypnotic effects, analgesic effects.54Clonidine has been used effectively over the last decade and the introduction of dexmedetomidine has further expanded the opportunity of α-2 agonists in post-operative epidural analgesia. Quicker onset of action of local anaesthetics, protracted duration of post-operative analgesia and steady hemodynamic parameters makes these agents very useful and successful adjuvants in post-operative analgesia. [13,18]

The other drug is fentanyl that is an opioid, given epidurally helps in early extubation and provides longer duration of analgesia. Fentanyl acts as an agonist at μ- opioid receptors to enhance the analgesia, it is 100 times more potent than morphine.55 But occurrence of side effects such as respiratory depression, pruritus, nausea and vomiting, and urinary retention may occur which reduce its usage and coverage.[16–18]

In our study, one group received Bupivacaine (0.25%) with Fentanyl 2mcg/ml and the second group received Bupivacaine (0.25%) with Clonidine 2mcg/ml. We studied effectiveness of these as an adjuvant in post-operative epidural analgesia in 50 patients who underwent elective lower limb and abdominal surgery. Each group consisted of 25 members who were comparable according to age, gender, weight and ASA-PS. The demographic profile was comparable between two groups (19-20).

In our study, the mean duration of analgesia was 415 ± 63.7 minutes in Group Clonidine and 231.00 ± 30.754 minutes in Group Fentanyl. There was statistically significant difference among two groups in the mean duration of analgesia ($P<0.05$). Higher duration of analgesia was observed in group who received Clonidine. The addition of clonidine as adjuvants promotes faster onset and longer duration of action similar to other studies (21-24). The dermatomal effect of clonidine may be the reason for this. Another study by Dobrydnjov et al also had similar findings.[10] Another study by Pooja Chopra et al[11] where by adding 30 μg of clonidine to the mixture of 0.5% hyperbaric bupivacaine and 15 μg fentanyl significantly enhances the duration of adequate analgesia. They also showed that intraoperative pain and requirement of postoperative analgesics and duration of analgesia are significantly lesser when clonidine was added to bupivacaine 0.5% or in mixture of bupivacaine and fentanyl, in comparison with the group which did not receive clonidine.[21]

The faster action may be due to the spinal cholinergic activation of clonidine. Cholinergic interaction in spinal α-2 adrenergic receptors which are situated on downward route of nor-adrenergic pathways produces nor-adrenaline release that causes analgesia directly and also it releases acetyl choline (Ach) to produce analgesia. Clonidine also blocks A delta and C-fibres at

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lamina V, thereby producing analgesia. This was similar to studies by Van Suijl et al61 and Strebel et al.[12]

The mean time for 1st rescue analgesia (defined as the time at which patient demands some mode of pain relief i.e. when VAS score more than 4) was 427.6 ± 62.168 minutes in Group Clonidine and 240.4 ± 32.143 minutes in Group Fentanyl and this difference was significant. Other studies also showed similar studies declaring the longer duration of action of clonidine.[10,12,13,16]

There was no statistical significance in Ramsay Sedation score at 0 minutes and 60 minutes. The mean Ramsay sedation scores of Clonidine group is gradually decreasing starting from 60 minutes. The mean score of Clonidine group at 120 minutes was 2.72±.458 and that of Fentanyl group 3±0 which was statistically significant. The mean scores of Clonidine group at 180,240,300 and 360 minutes were lower compared to Fentanyl group where the scores and this was statistically significant (25-26). The results of our study clearly indicates the sedation score between the two groups was similar in the first two hours after study drug administration and they had profound sedation but arousable by gentle tactile stimulation- Ramsay sedation score-3. After 2 hours the mean Ramsay score in clonidine group decreased compared to fentanyl rate at a faster rate. Over all decrease in clonidine group is statistically significant showing a faster onset of anaesthesia in clonidine group, which was similar to another study done by Yoganarasimha et al and Celleno et al respectively. [13,17]

There was no difference in pain score at 15 and 30 minutes and was found to be statistically not significant ($p>0.05$).At 240 minutes, the mean VAS score in Group C was 2.44±1.19 and in Group F was 4 ± 0; there was statistically significant difference in both groups ($p<0.05$).At 1080,1200,1320 minutes the mean VAS score between Clonidine

group and Fentanyl group were statistically significant. Pain scores in clonidine group is significantly lower compared to fentanyl group reinforcing the higher analgesic aspect of clonidine. The cause being attributed to the stimulation of post-synaptic α-2 receptors in substantia gelatinosa of the spinal cord.[13,18]

Hypotension were observed more in 16% of clonidine group patients corrected with bolus of IV fluids and ephedrine. None of patients in either groups had excessive sedation,vomiting, pruritus, post dural puncture headache or transient neurological symptoms at intraoperative period or during post-operative follow up (27).

The post-op hemodynamic variables between the groups were comparable and were statistically significant. The results of our observations show that in addition to prolonged analgesia, and less pain scores clonidine has a favorable safety profile and stable hemodynamics over fentanyl, which correlates with the reports published by other authors.

All the above results conclude that the addition of Clonidine to Bupivacaine epidurally lengthens motor and sensory block and analgesia, without an amplified frequency of side effects which was estimated by study done by Gupta et al.[15]

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3. CONCLUSION

To conclude that 2 µg/ml of Clonidine was found to be a better adjuvant to epidural bupivacaine (0.25%) in post-operative analgesia. The post-operative analgesic effect as well as the arousal sedation was excellent with lowest side effects. The hemodynamic stability was well maintained with fentanyl.

Clonidine has proved to be very efficient in contrast to fentanyl in regard to the increased sedative property that is easily arousal, longer duration of analgesia, anxiolytic properties and patient comfort ability.

Funding: No funding sources

Ethical approval: The study was approved by the Institutional Ethics Committee

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The encouragement and support from Bharath University, Chennai is gratefully acknowledged. For provided the laboratory facilities to carry out the research work.

REFERENCES

1. Singh M, Singh R, Jain A. An observational study to evaluate the effect of different epidural analgesia regimens on dynamic pain scores in patients receiving epidural analgesia for postoperative pain relief after elective gynecological surgery. J Anaesthesiol Clin Pharmacol. 2018 Jul 1;34(3):362.
2. Kehlet H. Effect of postoperative pain treatment on outcome-current status and future strategies. Langenbecks Arch Surg. 2004 Aug;389(4):244–9.
3. Ahmed A, Latif N, Khan R. Post-operative analgesia for major abdominal surgery and its effectiveness in a tertiary care hospital. J Anaesthesiol Clin Pharmacol. 2013;29(4):472–7.
4. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg. 2003 Aug;97(2):534–40, table of contents.
5. G B, C V, Sc S, S BA, Vs K, N RK, et al. Postoperative analgesia following elective abdominal surgery: a prospective observational study. Int Surg J. 2017 Jul 24;4(8):2710–6.
6. Garimella V, Cellini C. Postoperative Pain Control. Clin Colon Rectal Surg. 2013 Sep;26(3):191–6.
7. Ezra Y, Hammerman O, Shahar G. The Four-Cluster Spectrum of Mind-Body Interrelationships: An Integrative Model. Front Psychiatry [Internet]. 2019 Mar 1[cited 2019 Oct 14]; 10. Available from: https://www.ncbi.nlm.nih.gov/pm c/articles/PMC6405696.

8. Mehta S, Gajbhare MN, Kamble NP. Comparison of epidural analgesia using 0.2% bupivacaine and 0.2% ropivacaine for the management of postoperative pain in major orthopedic surgery. Anesth Essays Res. 2018 Apr 1;12(2):586.
9. Centre ND. Epidural anaesthesia helps return of bowel function after abdominal surgery [Internet]. 2016 [cited 2019 Oct 14]. Available from: epidural-anaesthesia- helps-return-of-bowel-function-after-abdominal-surgery
10. Congedo E, Sgreccia M, De Cosmo G. New drugs for epidural analgesia. Curr Drug Targets. 2009 Aug;10(8):696–706.
11. Wheatley RG, Schug SA, Watson D. Safety and efficacy of postoperative epidural analgesia. BJA Br J Anaesth. 2001 Jun 1;87(1):47–61.
12. Bagshaw KR, Hanenbaum CL, Carbone EJ, Lo KW, Laurencin CT, Walker J, et al. Pain management via local anesthetics and responsive hydrogels. Ther Deliv. 2015 Feb;6(2):165–76.
13. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases. 2017 Aug 16;5(8):307–23.
14. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local Anesthetic Peripheral Nerve Block Adjuvants for Prolongation of Analgesia: A Systematic Qualitative Review. PLOS ONE. 2015 Sep 10;10(9):e0137312.
15. Joy L. Hawkins MD,. Epidural Space - an overview | ScienceDirect Topics Epidural Analgesia and Anesthesia in Anesthesia Secrets (Fourth Edition), 2011 [Internet]. 4th ed. 2011 [cited 2019 Oct 16]. Available from: https://www.sciencedirect.com/topics/neuroscience/epidural-space
16. Jonathan Richardson, MD MRCP FRCA FIPP, Gerbrand J Groen, MD PhD. Applied epidural anatomy | BJA Education | Oxford Academic. Continuing Education in Anaesthesia Critical Care & Pain,. 2005 Jun;5(3):198–200.
17 . nTech-Anatomy_and_clinical_importance_of_the_epidural_space.pdf [Internet].[cited 2019Oct16 Availablefrom:http://cdn.intechopen.com/pdfs/32648/InTech-_of_the_epidural_space.pdf
18. Maria Bauer John E. George II John Seif, and Ehab Farag. Recent Advances in Epidural Analgesia. [cited 2019 Oct 16]; Available from: https://www.hindawi.com/journals/arp/2012/309219/
19. Clemente A1, Carli F. The physiological effects of thoracic epidural anesthesia and

analgesia on the cardiovascular, respiratory and gastrointestinal systems. - PubMed - NCBI. Minerva Anestesiol. 2008 Oct;74(10):549–63.

20. O'Donohoe PB, Pandit JJ. Physiology and pharmacology of spinal and epidural anaesthesia. Surg Oxf. 2012 Jul 1;30(7):317–9.
21. Strandness T, Wiktor M, Varadarajan J, Weisman S. Migration of pediatric epidural catheters. Paediatr Anaesth. 2015 Jun;25(6):610–3.
22. Moriarty A. Pediatric epidural analgesia (PEA). Paediatr Anaesth. 2012 Jan;22(1):51–5.
23. Triffterer L, Marhofer P, Lechner G, Marksz TC, Kimberger O, Schmid W, et al.
24. An observational study of the macro- and micro-haemodynamic implications of epidural anaesthesia in children. Anaesthesia. 2017 Apr;72(4):488–95.
25. Stacey Kast RN,BSN staceykast@yahoo.com. Spinal Block Versus Epidural Block. RN Journal [Internet]. [cited 2019 Oct 16]; Available from: https://rn- journal.com/journal-of-nursing/spinal-block-versus-epidural-block
26. Avila-Hernandez AN, Singh P. Epidural Anesthesia. In: StatPearls [Internet].
27. Treasure Island (FL): StatPearls Publishing; 2019 [cited 2019 Oct 16]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK542219.