European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 09, Issue 03, 2022

ORIGINAL RESEARCH

A comparative evaluation of post operative analgesia of two different drugs dexmedetomidine and fentanyl in combination with 0.5% levobupivacaine for surgical site infiltration in cases of open cholecystectomy under general anaesthesia, A randomized clinical study

[1]Rajat Sharma, [2]Suman Gupta, [3]Dilip Kothari, [4]Shakti Singhal

[1]RMO,[2]Associate Professor, [3]Professor and Head of Dept, [4]Assistant Professor, Dept of Anesthesiology, GRMC, Gwalior, Madhya Pradesh, India

Correspondence:
Shakti Singhal
[4]Assistant Professor, Dept of Anesthesiology, GRMC, Gwalior, Madhya Pradesh, India

ABSTRACT

Background: This Study was designed to comparatively evaluate the postoperative analgesia efficacy of levobupivacaine 0.5% in combination with dexmedetomidine and fentanyl in wound infiltration technique following open cholecystectomy surgeries.

Methodology: After ethical committee, approval, a double blind randomized controlled study was conducted on 100 patients, divided into 2 equal groups (n=50) by using computer generated random number table (considering 5% alpha error of 80% power of study), ASA grade I & II, 18 to 60 years age scheduled for open cholecystectomy surgeries over 1year duration. A standard general anaesthetic technique was used and all patients received wound infiltration at the time of wound closure. Group D received 0.5% Levobupivacaine with injection Dexmedetomidine (1mcg/Kg) and 0.9% normal saline while Group F received 0.5% Levobupivacaine with injection Fentanyl (1mcg/Kg) and 0.9% normal saline. Total volume of solution was made 25 ml. Postoperative rescue analgesia was provided with Injection Tramadol (1mg/Kg) when VAS score >3. Mean between the 2 groups were compared using independent t-test and variance between the groups by Chi-square test.

Results: The mean duration of analgesia in group D was (20.95+5.39 hours) when compared to group F (11.39+3.67 hours) which was highly significant (p=0.000). Group D patients have excellent quality of analgesia, lower VAS scores and lower rescue analgesic consumption with minimal side effects.

Conclusion: Dexmedetomidine and Fentanyl were effective adjuvants to levobupivacaine for single shot wound infiltration technique among which dexmedetomidine is found superior to fentanyl.

INTRODUCTION

The main concern of anesthesiologist with respect to major surgery is postoperative analgesia. Evidence suggests that inadequate postoperative pain relief following upper abdominal surgeries like open cholecystectomy may result in harmful physiological and psychological consequences[(1)] that many lead to significant morbidity and mortality, which may delay recovery and increase duration and cost of hospital stay. Various modalities of providing postoperative analgesia are being used such as intravenous NSAIDs or opioids, epidural analgesia, regional never blocks and wound infiltration technique as an approach to multimodal analgesia.[(2)]

As a component of multimodal analgesia, wound infiltration with local anesthetic appears to be simple less skilled and cost effective technique which can provide effective postoperative analgesia with minimal side effects.[3]

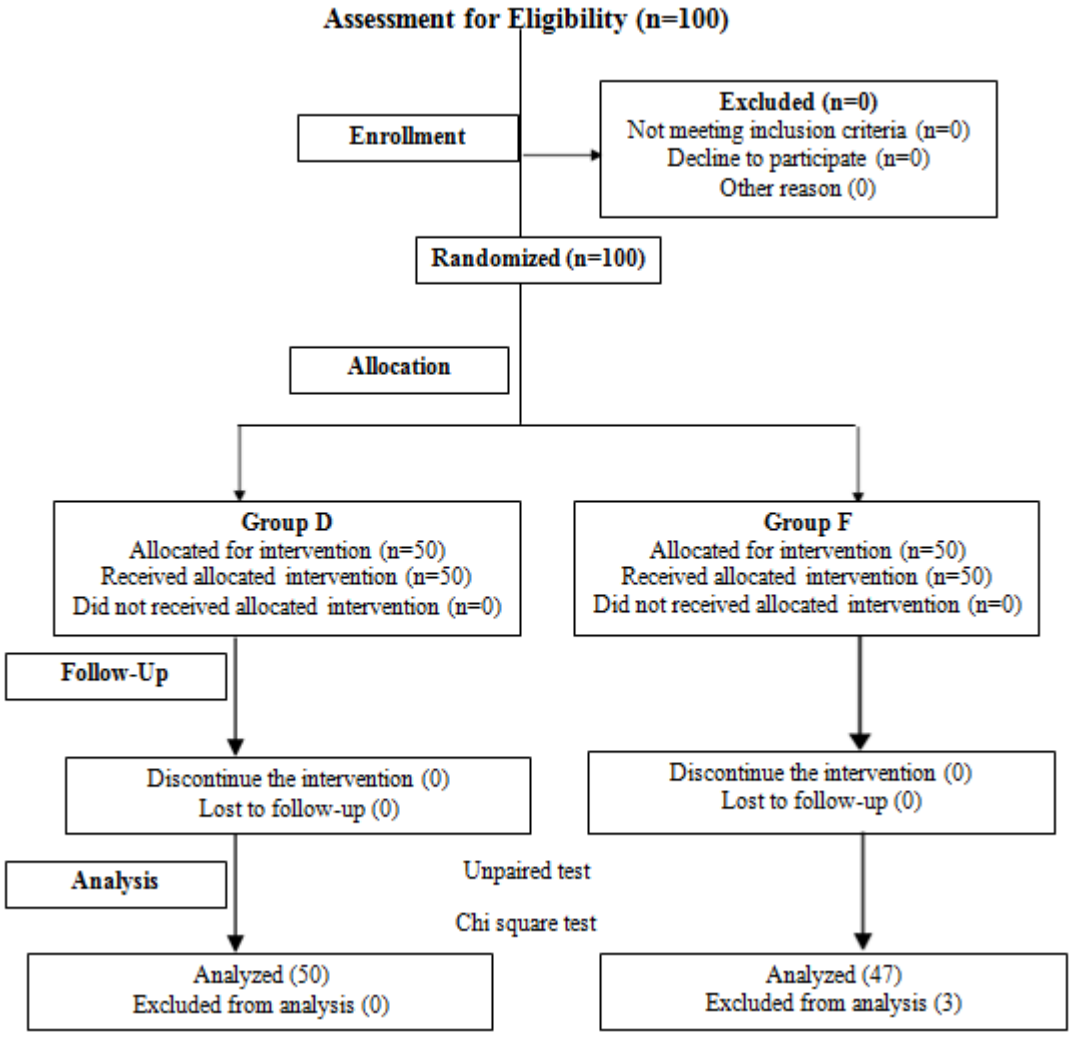
Various studies have shown that local anesthetic when used alone for wound infiltration do not to provide satisfactory postoperative analgesia.[5,6] Therefore various adjuvants Opioids, alpha-2 agonists, epinephrine, tramadol, has been used with local anesthetic for increasing their duration of analgesia.[7]

Levobupivacaine is the local anesthetic being used in the former study as it has less depressant effects on myocardium and central nervous system pharmacodynamically, and a superior pharmacokinetic profile.[4]

Fentanyl, a mu- receptor agonist have peripheral anti-nociceptive effect, less histamine releasing and advantage of inflammatory anti-nociceptive at wound site makes it a far better drug than other opioids.[8,9]

Another promising adjuvant which can improve quality and duration of analgesia is Dexmedetomidine which a superior to clonidine in having 8 times more affinity to alpha2-receptor and dual mechanism for peripheral anti-nociception with opioids sparing effect.[10]

Therefore we are hypothesizing that both fentanyl and dexmedetomidine are effective adjuvants to levobupivacaine for wound infiltration analgesic technique in patients undergoing open cholecystectomy surgeries and may reduce opioids requirements in postoperative period with prolonged postoperative analgesia with minimal side effects, faster recovery with early ambulation.



MATERIAL AND METHOD

A prospective randomized controlled and double blinded study was done with well informed and written consent on 100 patients (ASA I & II) for open cholecystectomy surgery in the Department of Anaesthesiology of G.R Medical college & J.A. Group of Hospitals, Gwalior (M.P) after approval of our institutional ethics committee with certificate number 16/IEC-GRMC/2018.

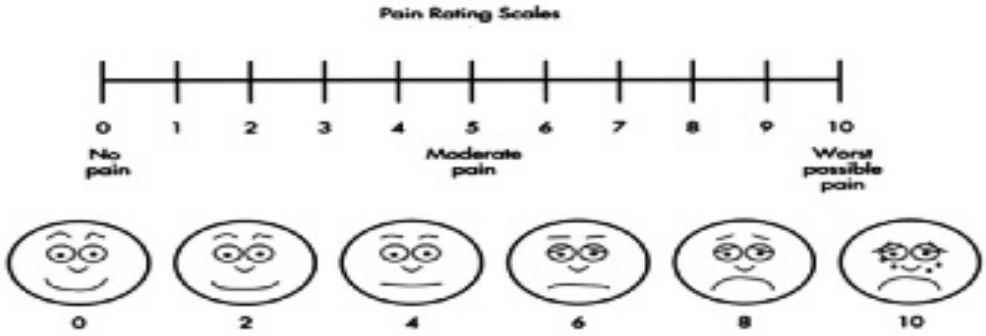
All patients of either gender, aged between 18 to 60 years, BMI 18.5-24.9, with no history of allergy to drugs such as local anesthetics, alpha 2 agonists and opioids were included in the study. Patients with morbid obesity, thromboangitis obliterans, Raynauds disease, pregnancy, on narcotics and corticosteroids, who already have chronic pain and on treatment; pregnancy were excluded from the study.

All patients were evaluated a day before surgery with Routine basic laboratory investigations being done and procedure of general anesthesia explained to all patients. All vital monitors in the operating room such as ECG, noninvasive blood pressure (NIBP), pulse oximetry (SPO_2), and end-tidal carbon dioxide ($EtCO_2$) were connected. For intraoperative monitoring, patient was premedicated with injection Ranitidine 50 mg IV, injection Ondansetron 4 mg IV were given, IV injection midazolam 0.05 mg/kg and injection glycopyrrolate 0.004 mg/kg. The patient was preoxygenated with 100% oxygen for 3 min and induced with Injection Fentanyl 2mcg/kg IV, Injection Propofol 2 mg/kg IV and injection succinylcholine 2 mg/kg IV and intubated using appropriate-sized endotracheal tube and bilateral equal air entry was confirmed by auscultation and $EtCO_2$ monitoring. Anesthesia was maintained with nitrous oxide: oxygen 5:3, sevoflurane 1-2 volume% and injection atracurium 0.1 mg/kg IV. This standard general anesthetic technique was used for all patients. Anesthesiologist which is not a part of study prepared the drug solution where total volume was standarlizedto 25 ml for every patient.

Postoperative analgesia was assessed via VAS score & rescue analgesic was given with injection Tramadol 1mg/kg on demand or whenever VAS >3 over 24 hour period.

Groups	Local anesthetic	Adjuvants	Total drug volume
GROUP D(n=50)	0.5%LEVOBUPIVACAINE (20ml)	DEXMEDETOMIDINE (1mcg/kg) + 0.9 % normal saline	25 ml
GROUP F(n=50)	0.5%LEVOBUPIVACAINE (20ml)	FENTANYL (1mcg/kg) + 0.9 % normal saline	25 ml

At the end of procedure, operating surgeon was requested to infiltrate the study drug at the wound site subcutaneously and patients were reversed with injection neostigmine 0.08 mg/kg and injection glycopyrrolate 0.01 mg/kg IV and extubated on meeting the standard extubation criteria. The following parameters were noted by a third anesthesiologist who had not participated in preparing the drug.



Number of patients requiring rescue analgesia during the first 24 h after surgery was recorded. PR, NIBP, and RR were recorded at baseline, intraoperatively, just before wound

infiltration and postoperatively at PACU arrival and then at 30 min, 1, 2, 3, 4, 6, 12, and 24 hr. Other drug related side effects were also assessed postoperatively.

Depending on the subjective response, quality of analgesia was assessed using 4-point categorical scale by asking patients about "How effective was your medication in relieving your pain over the last 24 h?" with responses: 1 = excellent, 2 = good, 3 = satisfactory, 4 = poor, and 5 = very poor.All the observations and particulars of each patient were recorded in a proforma.

For sample size calculation, we conducted a pilot study on 10 patient in each group for the drug Dexmedetomidine and Fentanyl. We found that Mean Time for Rescue Analgesia for Group D is 24.8 hours with Standard Deviation 0.98 hours while for the Group F Mean Time for Rescue Analgesia was 11.2 hours with Standard Deviation 2.7 hours. Considering 5% alpha error and 80% power of test using formula

$n = (Z_{\alpha/2} + Z1 - \beta)^2 2S^2 / d^2$

where, $Z_{\alpha/2} = 1.96$

$Z1 - \beta = 0.84$

$S^2 = 74.2536$

d = 13.6

n = 49.35 approx. 50

So in each group 50 patients were taken. Total sample size for the study is 100 patients.

Mean and Standard Deviation were calculated in each group. Mean between the 2 groups were compared using independent t-test. To see the association for the variables in Group D and Group F with sex and ASA grade chi-square test were applied.

Bar diagram were prepared to show the graphical representation of the data. P- value was calculated at 5% level of significance.

The information collected on the study was recorded in a schedule and computerized in Microsoft Excel 2007 software according to defined variables. Data analysis was done by SPSS-26 statistical software and results were transferred on predesigned classified tables

RESULTS

The characteristics of the two groups were comparable with respect to age, weight, height, ASAclassification, and gender. The mean PR, DBP, SBP and MAP at different time intervals showed no significant difference among the two groups ($p>0.05$). In our study mean duration of analgesia (mean **± SD)** among the two groups were (**20.95 ± 5.39 hours)** in Group D as compared to (**11.39 ± 3.67 hours**) in Group F over 24 hour period postoperatively. Among both the adjuvants Dexmedetomidine is found superior to Fentanyl and this difference was highly significant (**p=0.000**). Mean VAS Scores of Group D were lower than Group F at all specified time intervals (1,2,3,4,6,12,24 hours) and this difference was significant at 1 hr (**p=0.022**) and highly significant (**p=0.000**) at 2,3,4,6,12,24 hours respectively mean time to first rescue analgesia was significantly higher in Group D (**20.95 ± 5.39 hr**) as compared to Group F (**11.39 ± 3.67 hr**) which was highly significant (**p=0.000**). Total dose of rescue analgesic consumed in the postoperative period in our study was significantly higher in Group F (**65.26± 18.01mg**) in comparison to Group D (**76.60± 25.14 mg**) with (**p=0.011**). In our study Quality of Analgesia Score was significantly lower in Group D (MEAN±**SD**=1.54±**0.50)** in comparison to Group F (MEAN±**SD**=2.56±**0.64)** (**p=0.000**). No opioid related side effects were noted in our study.

DISCUSSION

In wound infiltration technique our goal is to prevent origin of pain at surgical site and administration of intravenous analgesics or opioids that produce multiple side effects.

The major drawback of using local anesthetics alone for infiltration is their limited duration of analgesia and as open cholecystectomy is upper abdominal surgery so local anesthetic alone does not provide satisfactory analgesia which can hamper lung function postoperatively. Therefore various adjuvants have been studied with local anesthetics for increasing their duration of analgesia.

In our study, we compared the postoperative analgesic effects of 0.5% Levobupivacaine with adjuvants Dexmedetomidine and Fentanyl as single shot wound infiltration following open cholecystectomy surgery.

Athar M. et al performed a review study to assess Levobupivacaine (S-) efficacy and found that it has decreased toxicity profile, less myocardial and CNS depressant effect with superior pharmacokinetic profile than Bupivacaine. In our study dose of 0.5% Levobupivacaine used is 100mg as we did not measure plasma concentration of given local anesthetic and keeping in view the probability of higher concentration reaching systemically toxic levels and lower concentration being ineffective.

Various studies such as Arora R. et al suggests that opioids have peripheral anti-nociceptive effect and advantage of inflammatory anti-nociception at wound site which is also supported by a study conducted by Bhandari G. et al. In our study Fentanyl(1mcg/kg) is used as an adjuvant as it has less histamine releasing property, cardiostable and independent peripheral antinociception effect.

Another adjuvant which we used in our study is Dexmedetomidine (1mcg/kg) an alpha-2 agonist due to its more alpha-2 selectivity than clonidine and dual mechanism for peripheral antinociception which is also supported by Luan H. et al and Agrawal N. et al. Peripherally it primarily acts by inducing vasoconstriction at infiltration site which delays absorption of local anesthetic thereby prolonging its effect and secondly by direct inhibition of peripheral nerve activity and thus inhibiting transmission of pain.

One of the major limitations of our study was that the follow up of patients was only till 24 hours postoperatively. Therefore we have excluded 3 patients from Group D in final analysis of the result.

Other limitation of our study is investigator's inability to objectively quantify and evaluate postoperative pain, which being a subjective experience. There was no group receiving Dexmedetomidine and Fentanyl by intravenous administration for the evaluation of central action of these drugs.

Our study also had few advantages which are worth mentioning. First, only elective open cholecystectomy surgeries and same operating team of surgeons were included in our study to avoid various confounders like type, nature and duration of pain associated with different type of surgery and different incision size of surgeons.

CONCLUSION

Both Dexmedetomidine and Fentanyl can be effectively used as an adjuvant to produce desired results. However, mean duration of analgesia in Group D is found superior to Group F with significantly less mean rescue analgesic requirement and better patient satisfaction with no incidence of any serious/life threatening adverse effect reported in any of the groups.

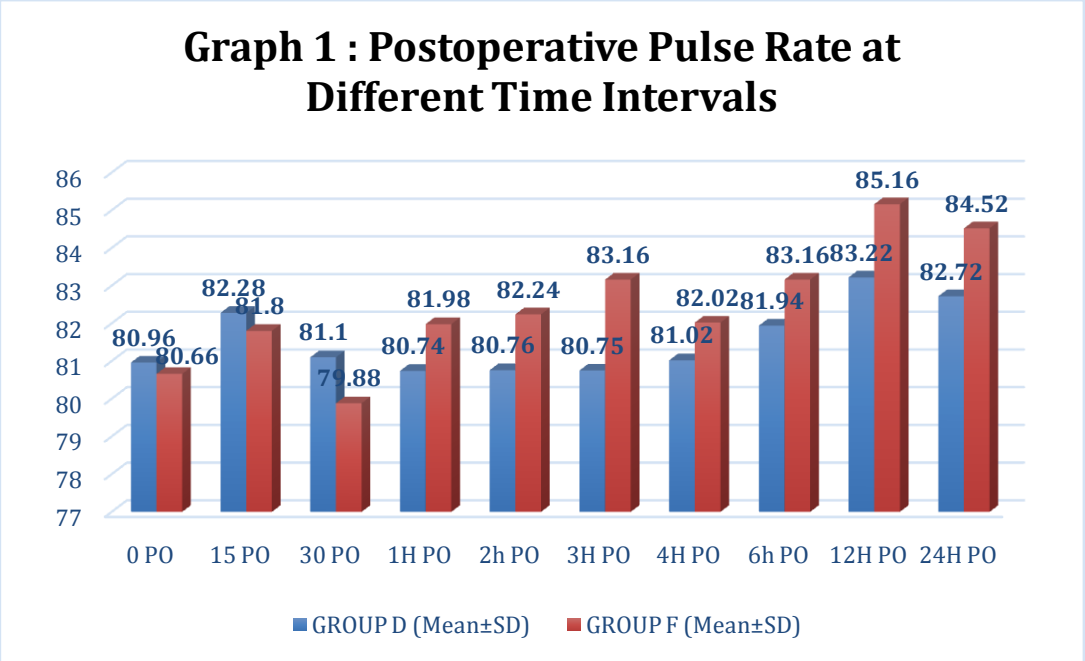
OBSERVATION AND RESULTS

Table 1: Demographic Profile

Variable	Group D N – 50 (Mean±SD)	Group F N – 50 (Mean±SD)	P value
Age (Years)	41.76±12.70	41.64±11.31	P=0.960
Sex (Male/Female)	13/37	12/38	P=0.817

ASA Grade (I/II)	25/25	27/23	P=0.688
BMI	20.81±1.77	20.54±1.83	P=0.447
Duration of Surgery (Min)	47.52±8.27	44.94±7.87	P=0.113

Table 1 shows the demographic profile of study participants according to Age, Sex, ASA Grade, BMI and Duration of surgery. Both the groups were comparable in terms of demographic profile with female preponderance and was statistically insignificant (p>0.05).



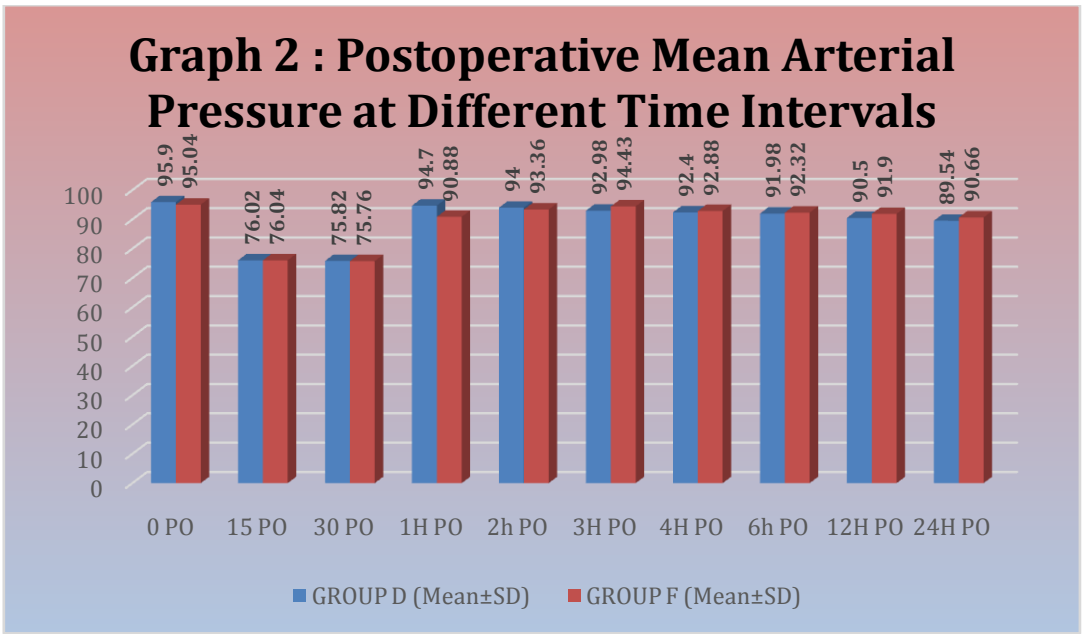
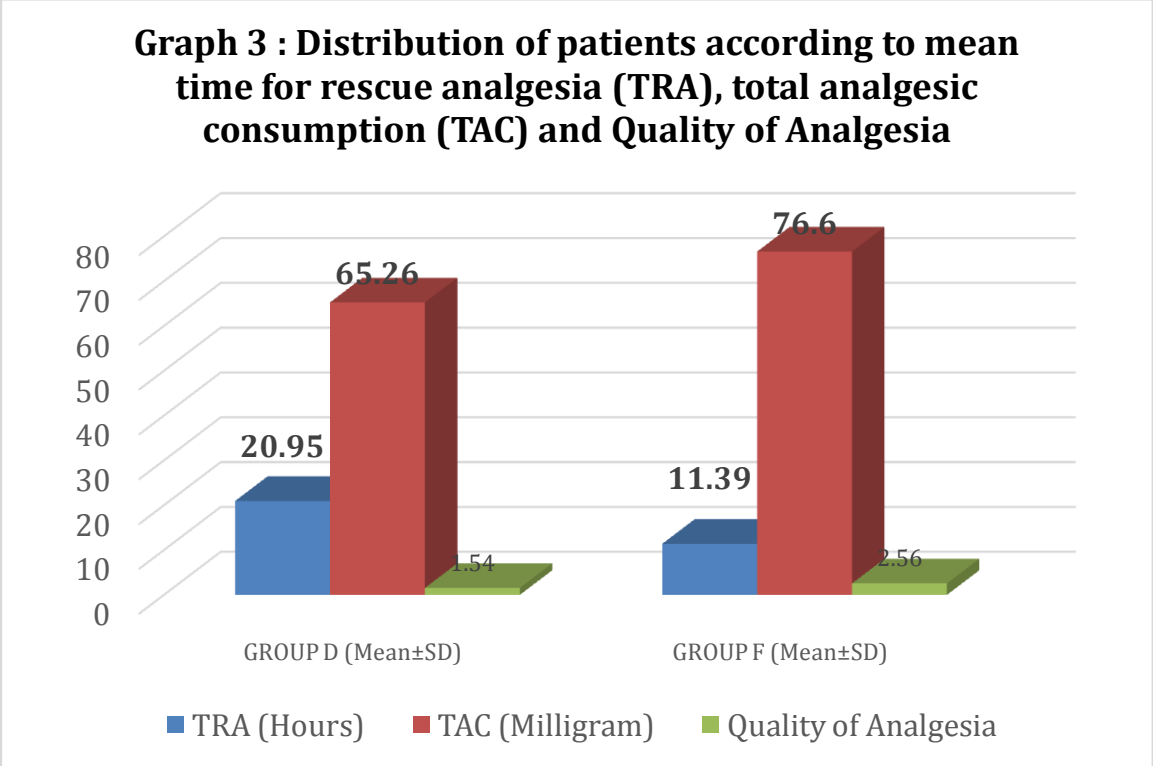


Table:2 Postoperative VAS Score at Different Time Intervals in both the Study Groups

S.NO	TIME (HOURS)	Group D (MEAN±SD)	Group F (MEAN±SD)	P VALUE
1	0 PO	0.00±0.00	0.00±0.00	NA
2	15 PO	0.00±0.00	0.00±0.00	NA
3	30 PO	0.00±0.00	0.00±0.00	NA

4	1H PO	0.00±0.00	0.10±0.30	0.022
5	2H PO	0.00±0.00	0.64±0.52	0.000
6	3H PO	0.06±0.24	1.44±0.50	0.000
7	4H PO	0.10±0.41	2.18±0.38	0.000
8	6H PO	0.56±0.61	2.98±0.42	0.000
9	12H PO	2.14±0.75	3.84±0.37	0.000
10	24H PO	1.86±0.67	2.62±0.63	0.000



REFERENCES

1. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiology Clinics of North America. 2005 Mar;23(1):21-36. DOI: 10.1016/j.atc.2004.11.013.
2. Postoperative pain management in pediatric patients by Dr R P Ghedoo
3. Scott NB Wound infiltration for surgery, Anaesthesia, 2010, vol. 65 Suppl.1(pg. 67-75)
4. Athar M, Ahmed SM, Ali S, Siddiqi OA. Levobupivacaine: A safer alternative. J Curr Res Sci Med 2016;2:3-9
5. Abigail Whiteman, MA MB BChir FRCA, Sanjay Bajaj, MD DNB FRCA, Maan Hasan, MB ChB DA FRCA, Novel techniques of local anaesthetic infiltration, Continuing Education in Anaesthesia Critical Care & Pain, Volume 11, Issue 5, October 2011, Pages 167–171
6. Jyothi, B & Govindaraj, Kirthiha & Pratishruthi, & Shaikh, SafiyaI. (2017). Comparison of analgesic efficacy of levobupivacaine, levobupivacaine and clonidine, and levobupivacaine and dexmedetomidine in wound infiltration technique for abdominal surgeries: A prospective randomized controlled study. Indian Journal of Pain. 31. 127. 10.4103/ijpn.ijpn_20_17
7. 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;10(9):e0137312. Published 2015 Sep 10. doi:10.1371/journal.pone.0137312

8. Barbara A. Dodson, Keith W. Miller; Evidence for a Dual Mechanism in the Anesthetic Action of an Opioid Peptide. Anesthesiology 1985;62(5):615-620
9. Chander R, Liddle D, Kaur B, Varghese M. Wound infiltration with plain bupivacaine as compared with bupivacaine fentanyl mixture for postoperative pain relief after abdominal surgery. Anesth Essays Res. 2011;5(2):142–146. doi:10.4103/0259-1162.94753
10. Ralph Gertler, H. Cleighton Brown, Donald H. Mitchell & Erin N. Silvius (2001) Dexmedetomidine: A Novel Sedative-Analgesic Agent, Baylor University Medical Center Proceedings, 14:1, 13-21, DOI: 10.1080/08998280.2001.11927725
11. Kadyan, Neha and Mishri Lal Khatri. "Comparison of Dexmedetomidine And Fentanyl As Adjuvant for Wound Infiltration To Bupivacaine for Postoperative Pain Relief After Abdominal Hysterectomy." (2017).
12. Athar, M., Ahmed, S.M., Ali, S. and Siddiqi, O.A., 2016. Levobupivacaine: A safer alternative. Journal of Current Research in Scientific Medicine, 2(1), p.3
13. Arora, R., Zuberi, A., Rastogi, B., Singh, V.P., Trivedi, A. and Noorani, S., 2019. COMPARATIVE EVALUATION OF CLINICAL EFFICACY OF INTRAPERITONEAL ROPIVACAINE WITH AND WITHOUT FENTANYL FOR POST-OPERATIVE ANALGESIA AFTER LAPAROSCOPIC CHOLECYSTECTOMY. Global Journal For Research Analysis, 8(03).
14. Bhandari, G., Shahi, K.S., Parmar, N.K., Asad, M., Joshi, H.K. and Bhakuni, R., 2013. Evaluation of analgesic effect of two different doses of fentanyl in combination with bupivacaine for surgical site infiltration in cases of modified radical mastoidectomy: A double blind randomized study. Anesthesia, essays and researches, 7(2), p.243.
15. Luan, H., Zhu, P., Zhang, X., Tian, L., Feng, J., Wu, Y., Yan, Y., Zhao, Z. and Gu, X., 2017. Effect of dexmedetomidine as an adjuvant to ropivacaine for wound infiltration in patients undergoing open gastrectomy: A prospective randomized controlled trial. Medicine, 96(38).
16. Agrawal, N. and Singh, S., To Evaluate the Analgesic Efficacy of Port Site Infiltration of Dexmedetomidine for Postoperative Pain Relief after Laproscopic Procedure in Comparison with Bupivacaine.