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Original Research Article

Comparison of Opioid Free Versus Opioid Based General Anesthesia on Post Operative Pain Intensity for Laparoscopic Surgeries: A Double Blinded RCT from A Tertiary Care Centre from Andhra Pradesh

N Syama Kumar[1], Y Nicolas Israel[2], Gantela Vijaya[2], G. Chandra Sekhar[1], Naveen[3], Anant A. Takalkar[4]

[1]Associate Professor, Department of Anaesthesiology, Guntur Medical College, Guntur, Andhra Pradesh
[2]Assistant Professor, Department of Anaesthesiology, Guntur Medical College, Guntur, Andhra Pradesh
[3]Senior resident, Department of Anaesthesiology, Guntur Medical College, Guntur, Andhra Pradesh
[4]Professor, Department of Community Medicine, MIMSR Medical College, Latur, Maharashtra

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Corresponding author: Dr. G. Chandra Sekhar
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Abstract:

Introduction: Efficacious multimodal analgesia and anaesthesia are basis of successful fast-track surgery. These multidrug regimens aim at decreasing postoperative pain, intraoperative and post operative opioid requirements, and subsequently, opioid related adverse effects and hastening recovery.

Objective: Our study objective was to compare opioid free versus opioid based general anesthesia on post operative pain intensity for laparoscopic surgeries.

Methodology: This is a prospective double blinded, RCT study design using simple random sampling and shuffled closed sealed envelope technique. Patients were randomly allocated into 2 groups;

DK group: Receiving Dexmedetomidine 1µg/kg body weight & ketamine 25 mg intravenously before induction.

F group: Receiving Fentanyl 1µg/kg/body weight intravenously before induction.

Results: Mean VAS Score at these intervals was significantly low in Group DK compared to Group Fentanyl. There was a significant difference in usage of Inj Diclofenac 75mg distribution between two groups at 2nd hour post operatively (a greater number of patients were required rescue analgesic doses in group F). At other intervals there was no significant difference. There was significant difference in No of Doses of Diclofenac Distribution between two groups.

Conclusion: Pain intensity was less in patients receiving Dexmedetomidine & ketamine as compared to that receiving Fentanyl. A greater number of patients were required rescue analgesic doses in group receiving Fentanyl.

Keywords: Dexmedetomidine, Ketamine, Fentanyl, Laparoscopic Surgeries.

Introduction

Since the 1960s, intra operative administration of opioids was considered a keystone of anaesthesia as well as hypnotics and muscle relaxants. Synthetic opioids were introduced to achieve haemodynamic stability during anaesthesia. They allow an inhibition of the sympathetic system without inhibition of cardiovascular system and histamine release. Since then, anaesthesia has changed from inhalational to multimodal anaesthesia with lower doses of hypnotics. In 2017, it was shown that the intraoperative objectives of hypnosis, hemodynamic stability, immobility and anticipation of postoperative analgesia can be achieved without opioids.[1]

Perioperative opioids are associated with nausea and vomiting, sedation, ileus, confusion, delirium, respiratory depression, increased post-operative pain and morphine consumption, immunodepression, hyperalgesia and chronic postoperative pain. They are associated with a significant morbidity, can increase the length of stay and slow post-operative rehabilitation.[1]

Efficacious multimodal analgesia and anaesthesia are basis of successful fast-track surgery. These multidrug regimens aim at decreasing postoperative pain, intraoperative and post operative opioid requirements, and subsequently, opioid related adverse effects and hastening recovery. Opioids free postoperative analgesia has therefore been recommended for >10years. Based on the same principle of opioid sparing, opioid free anaesthesia (OFA) has been introduced which is a multimodal anaesthesia associating hypnotics, N-methyl-D-aspartate (NMDA) antagonists, local anaesthetics, anti-inflammatory drugs and alpha 2 agonists [2].

OFA was initially introduced for bariatric surgeries.[2]

Multimodal analgesic techniques such as use of acetaminophen, pregabalin, cyclooxygenase-II inhibitors, nonsteroidal anti-inflammatory drugs, local anaesthetics, beta-blockers, dexamethasone either alone or in combination, have been shown to decrease the requirement of opioids intra-operatively and postoperatively. However, none of these drugs are efficacious as the sole analgesic, and thus need for evaluating newer drugs as replacement of opioids in the intraoperative period is continuing. Alpha 2 receptors agonists such as clonidine and dexmedetomidine have shown promising results in this context [3]. Dexmedetomidine is highly selective to alpha 2 receptors with a ratio alpha 1: alpha 2 of 1:1600. It has been found that use of this drug in the dose of 1mcg/kg as a bolus premedicant; maintains the perioperative haemodynamic stability, decreases requirement of intra and perioperative analgesics, and hypnotics. It also decreases the postoperative nausea and vomiting and does not produce respiratory depression unlike opioids.[3]

Beloeil H et al [4] showed that balanced opioid-free anesthesia with dexmedetomidine was associated with intra-operative bradycardia, delayed extubation, post-operative hypoxemia, increased length of PACU stay.

Not only balanced anesthesia with dexmedetomidine, using magnesium sulphate, lidocaine and dexamethasone intra-operatively also decreased the opioid related side effects. Magnesium sulphate acts through the NMDA receptors, by blocking the entry of Calcium and Sodium through the receptors there by decreasing the transmission of pain.[5] We hypothesized that opioid free anesthesia using dexmedetomidine and ketamine is equally effective in providing balanced intra-operative anesthesia and post-operative analgesia with minimal incidence of opioid related side effects.

Objective: Our study objective was to compare opioid free versus opioid based general anesthesia on post operative pain intensity for laparoscopic surgeries.

Materials and Methods

Material source

Patients of (ASA) Physical status Class I/II scheduled to undergo elective laparoscopic surgeries lasting for <2 hours who full fill the inclusion criteria mentioned hereafter, at Guntur Medical College, Guntur

Inclusion Criteria: Patients of ASA Physical status class I/II aged 20-60 years undergoing elective laparoscopic surgeries lasting for < 2 hours.

Exclusion Criteria

1. Pregnant, breast-feeding women.
2. Hepatic, renal or cardiac insufficiency.
3. Psychiatric disease.
4. Allergy or contraindication to study drugs.
5. BMI >30Kg/m^2.
6. Obstructive sleep apnoea (OSA) syndrome.

Type of Study

This is a prospective double blinded, RCT study design using simple random sampling and shuffled closed sealed envelope technique.

Method of Collection of Data

$$n = \frac{2\{(a + b)\}^2 \, \upsilon^2}{(\mu 1 - \mu 2)^2}$$

- n = Sample size in each of the groups
- μ1 = Population mean in treatment Group 1
- μ2 = Population mean in treatment Group 2
- μ1−μ2 = The difference the investigator wishes to detect i.e. 15% in our study.
- ʊ= Population variance (SD)
- If a difference of 15% i.e. (μ1− μ2) between two groups is considered clinically significant
- Power = 80%, significance level alpha of 0.05.
- a = Conventional multiplier for alpha = 0.05,
- b = Conventional multiplier for power=0.80
- Value of a = 1.96, b = 0.842
- n = 2 × ([1.96 + 0.842]^2× 20^2)/15^2= 27.9

28 patients per group will be needed, at a two-sided alpha level 0.05, to show a relative group difference of 15% in the composite of primary outcome i.e in order to find a post-operative pain intensity and need of rescue analgesics for laparoscopic surgeries; keeping the confidence interval of 95% and to achieve a power of 80%. Total of 70 patients; 35 in each group to compensate for drop-outs.

Chemicals Used: Dexmedetomidine, Fentanyl, Ketamine, Diclofenac

Methodology

Following approval from institutional ethical committee, informed consent and written consent was taken from 70 patients of American Society of Anaesthesiologist (ASA) physical status class I/II undergoing laparoscopic surgeries under general anaesthesia.

Patients were randomly allocated into 2 groups;

DK group: Receiving Dexmedetomidine 1μg/kg body weight& ketamine 25mg intravenously before induction.

F group: Receiving Fentanyl 1μg/kg/body weight intravenously before induction.

Randomisation was done by another anaesthesiologist (who did not take part further in the study) using shuffled sealed envelope technique.

All the patients were evaluated on the previous day of surgery& on the morning of the surgery. Patients were shifted to operation theatre and connected with multiparameter monitor (PHILIPS intellivue MP-20) and baseline parameters like systolic blood pressure (SBP); diastolic blood pressure (DBP); mean arterial pressure (MAP) &heart rate (HR), saturation of O_2 were noted. Patients belonging to DK group received dexmedetomidine 1µg/kg diluted to100ml NS and infused over 10-15min before induction. Inj. Ketamine 25mg diluted to 2ml with NS was injected IV before induction. Patients belonging to F group received 100 ml of NS over 10-15 min before induction and Inj fentanyl 1µg/kg diluted to 2 ml was administrated IV before induction. The study drugs were prepared by the same anaesthesiologist involved with randomisation who did not take part further in the study and thus the observer and patient were blinded to study. All the patients were given 1.5mg/kg/body weight of IV lidocaine (preservative free) after pre-oxygenation for 3min, followed by 1% propofol till the loss of eye lash reflexes and total dose of used propofol was also noted. All the patients were intubated with appropriately sized ET tubes using 0.1mg/kg of vecuronium. Patients were maintained using O_2+ N_2O (30:70) and isoflurane 0.5%. Intraoperative blood pressure (BP) and heart rate (HR) were monitored and any increase in either BP or HR more than 20% of baseline were managed by increasing the isoflurane to 1% and if not controlled additional boluses of 20mg of propofol was given and number of doses of propofol were also noted. Any fall in SBP more than 30% was treated with IV fluids and if required 6mg of ephedrine boluses & number of doses of ephedrine were noted. Any decrease in heart rate less than 50/min was treated with Inj. Atropine 0.6mg IV. Patients of both the groups were given Inj. Dexamethasone 8mg IV after induction and Inj. Ondansetron 4mg IV just before extubation. Patients were administered with inj. paracetamol 1gm IV and Inj. diclofenac 75mg iv intraoperatively. At end of surgery patients were reversed with 0.05mg/kg neostigmine and glycopyrrolate 0.01mg/kg. Time of recovery was noted from the time of administrating reversal drugs and patients satisfying the extubation criteria were extubated. All the patients were shifted to post anaesthetic care unit (PACU) and monitored for post-operative pain using VAS score at the interval of immediate post-operative and 2nd hourly for 6 hours and every 6th hourly for 24 hours. Any patient with VAS score >4 had received rescue analgesic Inj. Diclofenac 75mg and number of doses in 24 hours were

Statistical Analysis

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions.

Chi-square test was used as test of significance for qualitative data. Continuous data was represented as mean and standard deviation.

Independent t test or Mann Whitney U test was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

Graphical representation of data

MS Excel and MS word was used to obtain various types of graphs such as bar diagram and line diagram.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software

MS Excel, SPSS version 22 (IBM SPSS Statistics, Somers NY, USA) was used to analyse data.

Results

Table 1: Mean Age (in years) Comparison between group DK and group F

	Group				p value
	Group DK		Group Fentanyl		
	Mean	SD	Mean	SD	
Age in years	39.77	12.27	41.91	12.65	0.474

Mean Age in Group DK was 39.77 ± 12.27years and in Group Fentanyl was 41.91 ± 12.65yeras. There was no significant difference in mean Age comparison between two groups.

Table 2: Gender Distribution between two groups

		Group			
		Group DK		Group Fentanyl	
		Count	Column N %	Count	Column N %
Gender	Female	23	65.71%	20	57.14%
	Male	12	34.29%	15	42.86%

$\chi 2 = 0.543$, df = 1, p = 0.461

There was no significant difference in Gender Distribution between two groups.

Table 3: Mean BMI (Kg/M2) Comparison between group DK and group F

	Group				p value
	Group DK		Group Fentanyl		
	Mean	SD	Mean	SD	
BMI (Kg/M2)	24.21	2.77	24.64	2.91	0.527

Mean BMI (Kg/M2) in Group DK was 24.21 ± 2.77 and in Group Fentanyl was 24.64 ± 2.91. There was no significant difference in mean BMI (Kg/M2) comparison between two groups.

Table 4: Mean Dose of Study drugs Comparison (in Micrograms (µgms) between group DK and group F

Group	Study Drug	Mean dosage in micrograms	SD	p value
Group DK	Dexmedetomidine	60.29	8.13	
Group F	Fentanyl	61.14	7.68	0.652

Mean Dose of Dexmedetomidine in Group DK was 60.29 ± 8.13µgms and in Group Fentanyl was 61.14 ± 7.68µgms. There was no significant difference in mean Dose of study drug comparison between two groups.

Table 4: VAS Score Comparison between two groups

VAS SCORE	Group						P value
	Group DK			Group Fentanyl			
	Mean	SD	Median	Mean	SD	Median	
@0hrs	1.69	4.7	2	2.49	5.1	2	<0.001*
@2hrs	2.54	7.8	2	3.26	10.4	3	0.002*
@4hrs	3.29	9.6	3	3.43	11.7	3	0.578
@6hrs	2.49	10.9	2	2.49	8.5	2	1
@12hrs	2.31	10.2	2	2.71	9.3	2	0.091
@18hrs	1.86	3.6	2	2.34	5.9	2	<0.001*
@24hrs	1.71	4.6	2	2.17	4.5	2	<0.001*

In the study there was significant difference in mean VAS Score between two groups at baseline, 2 hrs, 18 hrs and 24 hrs. Mean VAS Score at these intervals was significantly low in Group DK compared to Group Fentanyl.

Table 5: Comparison of Number of patients receiving inj. diclofenac 75mg as rescue analgesics post operatively

Time post operatively in hours (hrs)		Group				p value
		Group DK		Group Fentanyl		
		Count	Column N %	Count	Column N %	
0 hrs	No	35	100.00%	35	100.00%	
2 hrs	No	32	91.43%	25	71.43%	0.031*
	Yes	3	8.57%	10	28.57%	
4 hrs	No	24	62.86%	18	51.43%	0.334
	Yes	11	37.14%	17	48.57%	
6 hrs	No	31	85.71%	31	88.57%	0.721
	Yes	4	14.29%	4	11.43%	
12 hrs	No	31	85.71%	30	85.71%	1.000
	Yes	4	14.29%	5	14.29%	
18 hrs	No	35	100.00%	33	94.29%	0.151
	Yes	0	0.00%	2	5.71%	
24 hrs	No	35	100.00%	35	100.00%	

There was a significant difference in Usage of Inj Diclofenac 75mgdistribution between two groups at 2nd hour post operatively (a greater number of patients were required rescue analgesic doses in group F). At other intervals there was no significant difference.

Table 6: No of Doses of Diclofenac Distribution between two groups

		Group				P value
		Group DK		Group Fentanyl		
		Count	%	Count	%	
No of Doses of Diclofenac	0	16	45.7%	5	14.29%	0.0041*
	1	16	45.7%	23	65.71%	0.092
	2	3	8.6%	6	17.14%	0.2854
	3	0	0.0%	1	2.86%	0.3159

$\chi 2 = 9.018$, df = 3, p = 0.029*

In Group DK, majority (45.7%) of them required 0 or 1 dose of diclofenac. In Group Fentanyl, majority required 1 dose of diclofenac (65.71%), 17.14% required 2 doses and 2.86% required 3 doses. There was significant difference in No of Doses of Diclofenac Distribution between two groups.

Discussion

VAS Score

The mean VAS score immediate post operative was 1.69 (median 2) in group DK vs 2.49 (median 2) in group F (p = 0.001) respectively, at 2hrs in group DK mean VAS was 2.54 vs 3.26 in group F (Median 2 vs 3, P = 0.002) respectively, at 18 hrs in group DK mean VAS was 1.86 vs 2.34 in group F(median VAS 3 vs 3, p = 0.001) respectively, at 24 hrs mean VAS was 1.71 in group DK vs 2.17 in group F(median VAS 2 vs 2, p = 0.001) respectively. maximum VAS score observed in group DK was 4 and in group F was 5 at rest.

At 6th hours, 12th hours there was no statistically significant difference between group DK and group F.

Bakan M. et al [6] showed that mean post-operative pain till 6 hours of surgery was less in opioid free group in terms of NRS (numeric rating scale) scale. The maximum NRS observed in opioid free group was with a mean of 3 (2-4) when compared with opioid group, with mean NRS of 4(2-6) at rest (p = 0.028). Max NRS while coughing was also less in opioid free group (4 vs 5.5 in RF group, p =0.015). These results are consistent with our study.

Kataria et al [7] had showed that mean VAS score was less in opioid free group when compared with fentanyl group during the 1st hour of surgery at 15min, 30min, 45min, 60 min post-surgery. These results are consistent with our study.

Toleska et al [5] showed that opioid free anesthesia (OFA) had less post-operative VAS scores at 1st hour (3.27 ±1.7 vs 5.13± 2.7) and 24th hour (1.90 ±1.7 vs 3.67 ±2.3) at rest and while coughing at 1st hour 4.17 ±1.5 vs 6.03 ±2.5 and at 24 hrs 2.67 ±1.9 vs 4.57 ±2.5. These results are consistent with our study.

Farran H A et al [8] showed that mean VAS score was significantly less in opioid free group in post-operative period at 0 hrs (2 vs 4, p = <0.001), 2 hrs (3 vs 5, p = <0.001), 4 hrs (2 vs 3, p = 0.044), 8 hrs (2 vs 3, p= 0.025), 12 hrs (1 vs 2, p = 0.027), 24 hrs (1 vs 2, p = 0.001). The maximum VAS score observed in opioid group was 5, and in Opioid free group was 3 at 2 hours post operatively.

Meta-analysis conducted by Grape S. et al [9] showed that dexmedetomidine group has lower VAS scores when compared with opioid groups post-operatively at 2 hours (mean VAS of 3.3{2.7-3.9} vs 4.0 {3.2-4.8}, p = 0.004) respectively. These results are comparable with our study.

Usage of post operative rescue analgesics

Immediate post operative none of the patients received rescue analgesics either in group DK or in group F.

At 2nd hour 3 patients required rescue analgesics in group DK and 10 patients required in group F (p = 0.031), which was statistically significant. At 4th hour (group DK-11 vs group F-17), 12th hour (group DK-4 vs group F-5), 18th hour (group DK-0 vs group F-2) there was a reduction in overall in the number of patients receiving rescue analgesics in both the groups which was not statistically significant. Total number of rescue analgesics doses in group DK was 22 vs in group F was 37.

In group DK, majority (45.7%) of patients required 0 or 1 dose of diclofenac. In Group Fentanyl, majority required 1 dose of diclofenac (65.71%), 17.14% required 2 doses and 2.86% required 3 doses. There was significant difference in the number of doses of Diclofenac Distribution between two groups.

Beloeil H et al [4] showed that mean post-operative morphine consumption was less in opioid free group (6mg vs 11 mg) over 48 hrs. number of patients experiencing NRS of ≥ 3 was equal in dexmedetomidine and remifentanil group. Patients were given paracetamol 1gm IV at 6th hour followed by orally 6th hourly, and nefopam 20mg IV at 6th hour followed by orally 6th hourly along with lidocaine infusion (1.5mg/kg/hr) for 12 hours with morphine PCA pump.

Farran H A et al [8] showed that consumption of post operative pethidine was also less in opioid free group (450.32 ± 50.32 mg vs 1300.85 ± 123.5 mg in opioid group). 20 % of the patients needed post-operative opioids in opioid free group, and in opioid group it was 68%. This was consistent with our results in terms of post operative analgesics consumption and number of patients requiring post operative analgesics.

Bakman M. et al [6] showed that in the immediate post-operative period up to 2 hours there was a significant reduction in the fentanyl consumption in the opioid free group (75 ±59 µg vs 120 ±94µg, p = 0.04), consistent results were obtained in our study.

Soffin E M. et al [10] showed that mean opioid consumption post-operatively in opioid free group was significantly less (2.43 ± 0.86 mg in OFA vs 38.13 ± 6.11mg in OCA group). This was consistent with our results in terms of total rescue analgesic doses post-operatively. In this study the authors

followed ERAS pathway and multimodal analgesia (acetaminophen and gabapentin in all patients). In our study we used dexmedetomidine in opioid free group along with multimodal analgesia (paracetamol 1gm and diclofenac 75mg intra-operatively).

Meta analysis conducted by Grape S et al [11] showed that in dexmedetomidine group at 12 hours post-operatively morphine consumption was less when compared with opioid group with high quality evidence.

Siddiqui T H et al [12] showed that TIVA with opioids had better analgesia when compared with TIVA with non-opioids (dexmedetomidine) in terms of total number of patients requiring analgesics 1st hour post-operatively. The results of this study were not consistent with the results of our study. This is because the authors have used 2 micro gm/ kg as premedication and infusion of 1micro gm /kg/hour of intra operative of fentanyl unlike our study where we have used only 1 micro gm/ kg of fentanyl as premedicant without intra operative infusion.

Massoth C et al [13] showed that there was no significant difference in the mean NRS scores in the immediate post-operative period, 15 minutes, 30 minutes, during time of discharge from PACU and post-operative day one. Morphine consumption was also not significant between opioid and opioid free group. This was not consistent with our results. This is probably because in this study the authors have used in the opioid group, repetitive bolus administrations of sufentanil of 0.15 µg/kg as required intraoperatively at the discretion of the attending anesthesiologist. They have also not specified the total mean dose of sufentanyl used throughout the study. Sufentanyl is also 8 times more potent than fentanyl.

Conclusion

- Mean VAS Score at different intervals was significantly low in Group DK compared to Group Fentanyl. It means pain intensity was less in patients rreceiving Dexmedetomidine & ketamine as compared to thatreceiving Fentanyl.
- A greater number of patients were required rescue analgesic doses in group receiving Fentanyl.
- In Group DK, majority (45.7%) of them required 0 or 1 dose of diclofenac. In Group Fentanyl, majority required 1 dose of diclofenac (65.71%), 17.14% required 2 doses and 2.86% required 3 doses. There was significant difference in No of Doses of Diclofenac Distribution between two groups. It means rescue analgesic was required in greater amount in group receiving Fentanyl.

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