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COMPARISION OF POST OPERATIVE ANALGESIC EFFECT OF NEFOPAM HYDROCHLORIDE AND DICLOFENAC SODIUM IN LAPAROSCOPIC SURGERY

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ABSTRACT **Introduction:** Pain is defined as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." Nefopam is a potent non- narcotic centrally acting analgesic with both supraspinal and spinal sites of action. Nefopam is chemically distinct and pharmacologically unrelated to any presently known analgesic. Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) used for management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics. NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 and/or COX-2). These enzymes are involved in the synthesis of key biological mediators, namely prostaglandins which are involved in inflammation, and thromboxane's which are involved in blood clotting. **Materials And Methods:** All cases of Laparoscopic surgeries of ASA grade I, II and III Patients. Pre anesthetic evaluation will be done and the techniques will be explained to patients including benefits and complications of each and written consent will be taken for the same. So, considering dropouts, total 60 patients will be enrolled, 30 patients in each group allotted as per sample size selection of cases on Randomized Controlled trial (RCT) by computer generating numbers. Patient with odd number will be assigned to group N and even number will be assigned to group D. Two investigators will participate in the study, first investigator will prepare the drugs and second investigator will be responsible for monitoring and data collection and will be blinded to the study. **Results:** In study shows Post Operative Systolic Blood Pressure. There was no significant difference in systolic blood pressure among the group at 0 min ($p>0.05$). The SBP decreased in Group N compared to Group D at rest of the intervals in Post operative period and statistically significant. In this study shows Post Operative Diastolic Blood Pressure. There was no significant difference in systolic blood pressure among the group at 0, 10, 15min and 6th hour interval($p>0.05$). The DBP decreased in Group N at 30min,1st, 2nd ,4th hour interval as compared to Group D and statistically significant ($p>0.05$). In our study shows Ramsay Sedation Score. There was significant difference in Ramsay Sedation Score among the group at 0 min interval($p>0.05$). There was no significant difference in Ramsay Sedation Score among the group in rest of the intervals. VAS Scores are comparatively less in Group N at 0 , 10 , 15 min compared to Group D and statistically significant. Mean VAS score at 6th hour in Group N is 2.85 hour and in Group D is 2.84 hour. Rescue analgesia is given when VAS score is >4. **Conclusion:** Nefopam improves the quality and duration of postoperative analgesia with better patient satisfaction in compare to diclofenac sodium. Nefopam is a centrally acting, non-opiate and non-steroidal analgesic. It is structurally not related to other analgesic drugs, has unique mechanism of action, acts by modulation of descending pain pathway by triple neurotransmitter receptor inhibition, effective for postoperative pain. It is well tolerated, without habituation or dependency and devoid of Opioids and NSAIDs side effects.

KEYWORDS : Pain, Nefopam, Diclofenac sodium

INTRODUCTION

Pain is defined by the Task force on taxonomy of the International Association for the Study of Pain (IASP) says that pain is "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." [1,2]

Although pain is a predictable part of the postoperative experience, inadequate management of pain is common and can have profound implications. Unrelieved postoperative pain may result in clinical and psychological changes that increase morbidity and mortality as well as costs and that decrease quality of life [3]. Negative clinical outcomes resulting from ineffective postoperative pain management include deep vein thrombosis, pulmonary embolism, coronary ischemia, myocardial infarction, pneumonia, poor wound healing, insomnia, and demoralization [4]. Associated with these complications are economic and medical implications, such as extended lengths of stay, readmissions, and patient dissatisfaction with medical care [5, 6].

Prevention and effective relief of acute pain may improve clinical outcomes, avoid clinical complications, save health care resources, and improve quality of life. Recognizing that some of the deleterious effects of acute pain can be avoided or minimized, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) has incorporated new standards for pain management. Effective in 2001, the JCAHO requires as one condition of accreditation adequate assessment, monitoring, and treatment of pain [7]. Pain management must become part of all patient care activities.

Enhanced recovery protocols to reduce length of stay in hospital after surgery are becoming more prevalent and include multimodal opioid sparing regimens as a critical component. Familiarity with the efficacy of available agents and routes of administration is important to tailor the postoperative regimen to the needs of the individual patient. This prospective study will be done to compare the effectiveness, postoperative pain and complications, safety, and patient satisfaction by using Nefopam hydrochloride and Diclofenac sodium in postoperative laparoscopic surgery patients. [8]

Nefopam is a potent non- narcotic centrally acting analgesic with both supraspinal and spinal sites of action. Nefopam is chemically distinct and pharmacologically unrelated to any presently known analgesic. Nefopam has a potent postoperative morphine sparing effect of about 30%-50%. Nefopam does not bind to opioid receptors and does not cause respiratory depression [9] No effect on platelet function, does not induce an anti-inflammatory effect & has no central nervous system depressive effect. It is generally considered safe and well tolerated. Reported adverse effects are mostly minor and include drowsiness, nausea and vomiting, sweating, tachycardia and confusion.

Diclofenac sodium is a nonsteroidal anti-inflammatory drug (NSAID) used for management of mild to moderate pain and management of moderate to severe pain alone or in combination with opioid analgesics. NSAIDs work by inhibiting the activity of cyclooxygenase enzymes (COX-1 and/or COX-2). These enzymes are involved in the synthesis of key biological mediators, namely prostaglandins which are involved in inflammation, and thromboxane's which are involved in blood clotting. Diclofenac sodium has a potent morphine sparing effect of about 30%-40% [10] It is generally considered safe and well tolerated. Most frequently encountered adverse reactions are thrombophlebitis, headache, rash, nausea, dizziness, fatigue, post-

procedural haemorrhage, infusion-related reactions.

The Major goal in postoperative pain management is to minimize the dose of medications and lessen side effects, while still providing adequate analgesia.

MATERIALS AND METHODS

All cases of Laparoscopic surgeries of ASA grade I, II and III Patients. Pre anesthetic evaluation will be done and the techniques will be explained to patients including benefits and complications of each and written consent will be taken for the same.

Inclusion Criteria

All Abdominal Laparoscopic surgeries of ASA grade I, II, III

Exclusion Criteria

- Patient Refusal
- Hepatic and Renal Insufficiency
- Patient on tricyclic antidepressants and MOA inhibitors
- Pregnancy and lactation
- Convulsive disorder

So, considering dropouts, total 60 patients will be enrolled, 30 patients in each group allotted as per sample size selection of cases on Randomized Controlled trial (RCT) by computer generating numbers.

60 Random Numbers

57161	73020	66672	80779	97022	41353
22927	53250	80903	10829	76147	33653
44503	30597	10128	76852	04481	06939
37277	51872	35011	73577	87681	74711
69351	86987	23159	66150	26404	46711
76337	34571	62280	40669	14701	83763
46858	15476	29662	45739	65349	71746
50622	38547	44859	84413	84032	49083
05950	48038	77457	40904	39205	47126
08637	87036	06789	51432	99551	27795

Specs: This table of 60 random numbers was produced according to the following specifications: Numbers were randomly selected from within the range of 0 to 99999. Duplicate numbers were allowed. This table was generated on 7/31/2019.

Patient with odd number will be assigned to group N and even number will be assigned to group D. Two investigators will participate in the study, first investigator will prepare the drugs and second investigator will be responsible for monitoring and data collection and will be blinded to the study.

Group Allocation

GROUP N: INJ NEFOPAM 0.3-0.4mg/kg TO BE GIVEN BEFORE 15- 20 MIN OF EXTUBATION IN 100ML OF NS INFUSION OVER 10-15 MIN

GROUP D: INJ DICLOFENAC SODIUM 1.5mg/kg TO BE GIVEN BEFORE 15-20 MIN OF EXTUBATION IN 100ML OF NS INFUSION OVER 10-15 MIN

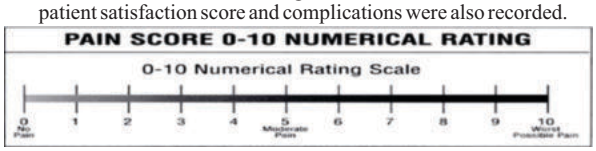
Patients will be nil per oral for 8 hours before surgery. NIBP, SpO2, ECG are applied.

I.V. line will be secured and patient will be premedicated with:

- Inj Glycopyrrolate 0.2 mg,
- Inj Ondansetron 4 mg i.v.
- Inj Ranitidine 50 mg i.v.
- Inj Tramadol 1.5mg/kg i.v. slowly.

Anaesthesia Technique

- All the patients will be pre-oxygenated with 100% O2 for 3 minutes.
- General anaesthesia induced with Inj. Sodium thiopentone 5-6mg/kg, Inj. succinyl choline 1.5-2mg/kg,
- Anaesthesia will be maintained with a mixture of 50% N2O in O2 and Sevoflurane and Inj.vecuronium
- Intra-operatively patient will on volume-controlled ventilation and normocapnia will be maintained.
- Intra-operative hemodynamic changes will continuously monitor including: heart rate, mean arterial blood pressure every 5 mins, oxygen saturation and end tidal CO2
- INJ NEFOPAM 0.3-0.4mg/kg TO BE GIVEN BEFORE 15- 20 MIN OF EXTUBATION IN 100ML OF NS INFUSION OVER 10-15 MIN
- Post operative hemodynamic changes will be monitored including: heart rate, mean arterial blood pressure for every 10 min in first two hours and hourly till the need for first rescue analgesia
- Intensity of post-operative pain will be evaluated using VAS (Visual analogue score) with grade 0 (no pain) to 10 (worst pain). Pain score will be noted every 10 minutes initially then hourly till the patient VAS Score>4. When VAS score>4 rescue analgesia will be given inj. Paracetamol 15mg /kg. (Maximum 1gm) and time for need of rescue analgesia was noted. Sedation scores, patient satisfaction score and complications were also recorded.



Ramsay Sedation Score (evaluated At Every 15 Minutes)

1. Anxious, agitated, restless
2. Co-operative, oriented, tranquilated
3. Responds to commands only
4. Brisk response to glabellar taps
5. Sluggish response to glabellar taps
6. No response to glabellar taps

Patient Satisfaction (evan Scale)

- GRADE 1. VERY GOOD
- GRADE 2. GOOD
- GRADE 3. NEITHER GOOD NOR BAD
- GRADE 4. BAD
- GRADE 5. VERY BAD

Analysis Of Data (statistics)

Quantitative data will be expressed as mean +SD while qualitative data will be expressed as numbers and percentages (%). Student t test will be used to test significances of difference for quantitative variables (HR. BP) that follow normal distribution and Chi square test will be used to test the significance of difference for qualitative variables. A probability value (P-value) <0.05 will be considered statistically significant.

RESULTS

Table 1: Demographic Data

	Group N Mean±SD	Group D Mean±SD	Student t test	p value	Inference	CI 95%
Age	32.33± 13.47	33.56± 14.46	0.3409	0.7344	NS	-8.45 to 5.99
Sex(M/F)*	(16/14)	(9/21)	-	-	-	
ASA Grade (1/2/3)*	(0/17/13)	(0/4/26)	-	-	-	

Values are represented as mean ± SD except marked * which is expressed as number of patients.

Table 1 shows demographic data of two groups. The groups were comparable with respect to age, sex, ASA grading. Mean age in Group N years and Group D years is comparable and not statistically not significant (P value >0.05).

Table 2: Post Operative Systolic Blood Pressure

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	126.1±7.3	126.7±6.6	0.3339	0.7396	NS	-4.19 to 2.99
30 min	117.9±6.7	126.7±5.8	5.4391	<0.0001	HS	-12.03 to -5.56
1 hr	117.8±6.7	127.2±5.7	5.8529	<0.0001	HS	-12.61 to-6.18
6 hr	118.9±7.2	126.1±7.8	3.7151	<0.0001	HS	-13.14 to -1.25

Table 2 shows Post Operative Systolic Blood Pressure. There was no significant difference in systolic blood pressure among the group at 0 min (p>0.05). The SBP decreased in Group N compared to Group D at rest of the intervals in Post operative period and statistically significant.

Table 3: Post Operative Diastolic Blood Pressure

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	81.9±6.2	81±4.6	0.6385	0.5256	NS	-1.92 to 3.72
30 min	78.7±5.7	81.9±4.5	2.4135	0.0190	S	-5.85 to -0.54
1 hr	78.9±5.6	81.6±4.8	2.0050	0.0496	S	-5.39 to -0.004
6 hr	78.1±6.3	79.4±4.4	0.6169	0.5429	NS	-5.64 to 3.04

Table 3 shows Post Operative Diastolic Blood Pressure. There was no significant difference in systolic blood pressure among the group at 0, 10, 15min and 6th hour interval(p>0.05). The DBP decreased in Group N at 30min,1st, 2nd ,4th hour interval as compared to Group D and statistically significant (p>0.05).

Table 4: Post Operative SPO_2

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	97.1±0.9	97.1±0.5	0.0000	1.0000	NS	-0.37 to 0.37
30 min	98±0.4	97.5±0.6	3.7978	0.0004	S	0.23 to 0.76
1 hr	98.1±0.6	97.9±0.4	1.5191	0.1342	NS	-0.06 to 0.46
6 hr	98.1±0.4	98.3±0.5	1.1519	0.2603	NS	-0.55 to 0.15

Table 4 shows Post Operative SPO_2. There was no significant difference in SPO_2 among the group at 0min 1st, 2nd ,4th and 6th hour interval(p>0.05). There was fall in SPO_2 in Group D at 10, 15 30min interval as compared to Group N and statistically significant (p>0.05).

Table 5: Ramsay Sedation Score

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	1.6± 0.5	1.9± 0.2	3.0513	0.0034	S	-0.49 to -0.10
30 min	2±0	2±0	-	-	-	
1 hr	2±0	2±0	-	-	-	
6 hr	2±0	2±0	-	-	-	

Table 5 shows Ramsay Sedation Score. There was significant difference in Ramsay Sedation Score among the group at 0 min interval(p>0.05). There was no significant difference in Ramsay Sedation Score among the group in rest of the intervals.

Table 6: VAS Score

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	0.16±0.5	1±0.26	8.1639	<0.0001	HS	-1.04 to -0.63
30 min	1.03±0.4	1.1±0.3	0.7668	0.4463	NS	-0.25 to 0.11
1 hr	1.43±0.56	1.5±0.5	0.5107	0.6115	NS	-0.34 to 0.20
6 hr	2.85±0.77	2.84±0.38	0.0422	0.9666	NS	-0.47 to 0.49

Table 6 shows VAS score. VAS Scores are comparatively less in Group N at 0 , 10 , 15 min compared to Group D and statistically significant. Mean VAS score at 6th hour in Group N is 2.85 hour and in Group D is 2.84 hour . Rescue analgesia is given when VAS score is >4.

Table 7: Evans Scale

	Group N	Group D	Student t test	p value	Inference	CI 95%
Time	Mean ±SD	Mean ±SD				
0 min	1.7±0.5	2±0	3.2863	0.0017	S	-0.48 to -0.11
30 min	1.7±0.4	1.9±0.2	2.4495	0.0173	S	-0.36 to -0.03
1 hr	1.7±0.4	1.9±0.2	2.4495	0.0173	S	-0.36 to -0.03
6 hr	2.4±0.6	2.9±0.3	2.7045	0.0121	S	-0.88 to -0.11

Table 7 shows EVANS scale. Patients satisfaction is assessed on EVANS scale.

Patient satisfaction is better in Group N compare to Group D and is statistically significant.

Table 8: Total Duration Of Analgesia

	Group N	Group D	Student T Test	P value	Inference	CI 95%
	Mean ±SD	Mean ±SD				
Time	6.7±2.7	5.4 ±1	2.4730	0.0163	S	0.24 to 2.35

Table 8 shows Total Duration of Analgesia. Mean duration of analgesia in Group N is 6.7 hours and in Group D is 5.4 hours and are statistically significant.

DISCUSSION

In our study shows post operative SBP. compared to Group D, Group N shows no statistical difference at 0 min but has highly significant thereafter till 6 hours. In our study shows post operative DBP. compared to Group D, Group N shows no statistical difference up to 15 min but has statistically significant up to 4 hours. **Heel et al** [11] in 1980 in his study stated that, nefopam has slight Inotropic and Chronotropic effect. **Chanques et al** [12] in 2011 showed, nefopam infusion causes an increase in heart rate and cardiac output and decrease in mean arterial pressure.

In our study shows Ramsay sedation score, Group N has slight sedation in early 10 minutes of the post operative period compared to Group D. **Sung kwan choi et al** [13] in 2016 Compared the effects of intraoperative nefopam and ketamine infusion on managing postoperative pain after laparoscopic cholecystectomy administered remifentanil in 54 patients and concluded Both nefopam and ketamine infusion may be useful in managing in postoperative pain control under concomitant infusion of remifentanil. However, nefopam may be preferred to ketamine in terms of sedation. **Heel et al** [11] in 1980 in his study noticed the sedation caused by nefopam. **Aymard et al** [14] in 2003 observed the sedative effect of nefopam. The oral route seems to induce more drowsiness than intravenous route

In this study shows VAS score. Group N has statistically significant VAS score in early postoperative period up to 30min in compared to Group D. Visual Analogue Scale (VAS) is widely used scale for measurement of pain intensity across diverse patient populations and pain disorders. The VAS scale used for assessment of pain is a continuous scale which consists of a line usually of 10 centimetres (or 100 mm) in length. It is a single item, one-dimensional scale with two

verbal descriptions one on each side describing extreme of the symptom. The extremes are usually marked as "no pain" indicating score of "0" and "worst imaginable pain" indicating score of 10 (100 in 100 mm scale). The timing for assessment and period of reporting may differ from study to study. It is easy to use and administer scale for assessment of pain intensity," **Eun Mi Kim et al** [15] in 2017 concluded intraoperative nefopam infusion during laparoscopic cholecystectomy reduced opioid requirements and pain scores (VAS) during the early postoperative period. **Jin hyun seung et al** [16] in 2016. pain scores were significantly lower in nefopam plus fentanyl group than nefopam group. **Tiancheng Zhao et al** [17] in their meta-analysis concluded intravenous nefopam infusion resulted in significant reduction in postoperative pain scores and opioid requirements

In this study shows EVANS scale, used for assessing the patient satisfaction. Patient satisfaction was statistically significant in the nefopam group compared to diclofenac group. **Jin Hyun Seung et al** [16] in 2016 conducted A double-blind randomised study to evaluate the opioid sparing effect and safety of nefopam when administered via intravenous patient-controlled analgesia (PCA) with fentanyl in patients undergoing elective open laparotomy. groups were assigned into fentanyl 25 mg/ml (SF group) and nefopam 2.4 mg/ml plus fentanyl 25 mg/ml (NF group). Pain scores were significantly lower and patients' satisfaction with treatment significantly better in the NF group than the SF group.

In this study shows the duration of analgesia. Group N has mean duration of 6.7±2.7hour while Group D has mean duration of 5. 4±1hour.with p value of 0.016 implies statistically significant. **Aymard et al** [14] in his studied observed half-life of Nefopam is of 5.1±0.6hr but the half-life of desmethyl-nefofam, the active metabolite is 15±2.4hr. **Christensen et al** [18] in 2011. The median times to rescue medication for recipients of HPβCD diclofenac 3.75, 9.4, 18.75, 37.5 and 75 mg were 3.0, 4.0, 4.1, 6.2 and 6.0 hours, respectively, compared with 1.2 hours for placebo and >8 hours for ketorolac

CONCLUSION

Intravenous Nefopam 20 microgram can be used as an analgesic for postoperative pain after laparoscopic surgeries similar to that of intravenous diclofenac sodium 75mg. Nefopam improves the quality and duration of postoperative analgesia with better patient satisfaction in compare to diclofenac sodium. Nefopam is a centrally acting, non-opiate and non-steroidal analgesic. It is structurally not related to other analgesic drugs, has unique mechanism of action, acts by modulation of descending pain pathway by triple neurotransmitter receptor inhibition, effective for postoperative pain. It is well tolerated, without habituation or dependency and devoid of Opioids and NSAIDs side effects.

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