ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 05 | May - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A COMPARISON OF POST-OPERATIVE ANALGESIC EFFICACY OF OPIOID FREE ANAESTHESIA USING INTRAVENOUS PARACETAMOL (15mg/kg), LIGNOCAINE (2mg/kg) AND MAGNESIUM SULPHATE (20mg/kg) VERSUS STANDARD OPIOID ANAESTHESIA USING INTRAVENOUS TRAMADOL (2mg/kg) FOR PREEMPTIVE ANALGESIA IN ENT SURGERIES UNDER GENERAL ANAESTHESIA

Anaesthesiology

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KEYWORDS

INTRODUCTION

Goal for peri-operative pain management : reduce or eliminate pain and discomfort with a minimum of side effects.

Traditionally: Opioids are used.

The most important side effects of Opioid Analgesics are:-

- Respiratory depression.
- Post-operative nausea, vomiting (PONV)
- ileus and constipation
- dependence and addiction.
- Pruritus
- Delayed emergence, somnolence, dizziness
- Acute tolerance and hyperalgesia

Multimodal Opioid Sparing Analgesia

- Evidence based multimodal opioid sparing analgesia has become an alternative to managing post-surgical pain in the last two decades
- Intraoperative use of agents that can lead to opioid sparing effects are
- via sodium channel blockade of G protein coupled receptors,
- NMDA blockade,
- central alpha-2 agonists and
- anti-inflammatory effects can make opioid free anesthesia (OFA) possible.

Hypothesis

- Adequate post-operative pain relief and decreased in 24-hour analgesic consumption can be achieved with the use of opioid free multimodal anaesthesia regimen using paracetamol, lignocaine and magnesium sulphate, when compared to a standard opioid based anaesthesia protocol.
- In this study we investigated the 24-hours post-surgical analgesia and analgesic consumption with use of OFA vs opioid anaesthesia (standard regimen) in patients undergoing ENT surgery under general anesthesia.

AIMS AND OBJECTIVES

PRIMARY OBJECTIVE:

- 24hour post-operative analgesic consumption

SECONDARY OBJECTIVES:

- Quality of analgesia using (numeric rating scale NRS)
- Duration of post-operative analgesia (time for demand of rescue analgesic)

MATERIAL & METHODS

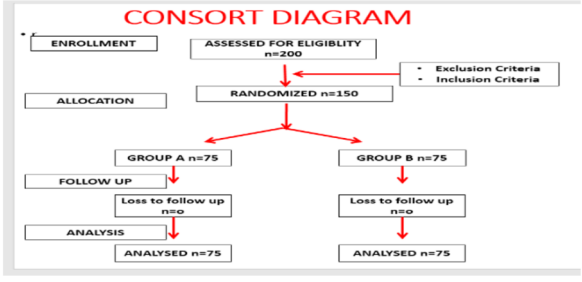
This hospital based prospective, randomized, double blind clinical study. Permission of college Ethical Committee and an informed consent from patient was obtained. The study was conducted on patients undergoing ENT surgeries under General anaesthesia in Department of ANAESTHESIA at Jawahar Lal Nehru Medical College and Hospital. Ajmer. Study period between June 2018 to July 2019

INCLUSION CRITERIA

- Patients posted for elective ENT surgery under general anaesthesia.
- Age between 18 to 65 years.
- ASA physical status I and II

EXCLUSION CRITERIA:

- Pregnant or Breastfeeding women
- Emergency surgery
- Patients refusal.
- Patient sensitive / allergic to any of the study drugs.
- Patients with neuro-psychiatric illness.
- Cardiovascular disease patients (I and II degree heart block)
- Patients on beta blockers.
- Severe bradycardia (HR<50bpm) or left- ventricular failure.
- Severe hepatic and renal disease.



Sample size calculation :

Proposed study was done to have a 80% statistical power, at two-sided alpha level of .05 (95% confidence level) 1.96 was used as critical value of Z at 95% confidence level, outcome rate in the study is based on previous study of *Samuels D. et al*.

Randomization technique:

computer generated table of random numbers.

Tests of comparison : Unpaired t test and chi square test

Version of software used : Graphpad prism 6, 2015.

PROCEDURE

The study population was randomly divided into two groups with 75 patients each.

Group A (n = 75) (OFA group)	**Opiate free anaesthesia (OFA) =** injection Lignocaine(2mg/kg)+ injection MgSO4(20mg/kg)+ injection Paracetamol (15mg/kg) in 100 ml NS
Group B (n =75) (OA group)	**Opiate anaesthesia (OA) =** injection Tramadol(2mg/kg)+ injection Midazolam (0.02mg/kg) in 100 ml NS

Patients were followed up to 24 hour in postoperative period.

They were assessed for-

- 24 hour post- operative analgesic consumption
- Assessment of pain was done by NRS (Neumaric rating scale) score
- Duration of analgesia– time to NRS >3 or when patient demanded for rescue analgesia.
- Vital parameters (PR, NIBP, SpO_2),side effects like, post operative nausea, vomiting, sedation, post- operative hypoxia, post operative ileus.

RESULTS

The present study was conducted on patients undergoing ENT surgery

under general anaesthesia in Department of Anaesthesiology at Jawaharlal Nehru Medical College, Ajmer. In this study, two study groups (The case or OFA group A and the control or OA group B) were studied.

Table 1: Age distribution of study subjects

Age Group (in Year)	Group A		Group B		Total	
	N	%	N	%	N	%
10-19	31	41.33	38	50.67	69	46
20-29	24	32	13	17.33	37	24.67
30-39	4	5.33	6	8	10	6.66
40-59	11	14.67	13	17.33	24	16
>60	5	6.67	5	6.67	10	6.66
Total	**75**	**100**	**75**	**100**	**150**	**100**

In our study 31 patients in case and 38 patients in control age group of 10-19 Years, and 24 patients in case and 13 patients in control age group of 20-29 Years, and 4 patients in case and 6 patients in control age group of 30-39 Years, and 11 patients in case and 13 patients in control age group of 40-59 Years, and 5 patients in case and 5 patients in control age group of >60 Years.

Table 2: Gender distribution of study subjects

Gender	Group A		Group B		Total	
	N	%	N	%	N	%
Female	33	44%	40	53.3%	73	48.7%
Male	42	56%	35	46.7%	77	51.3%
Total	**75**	**100%**	**75**	**100%**	**150**	**100%**

Chi square test=1.308, d.f=1, p value=0.25

There were 44.00 per cent female and 56.00 per cent male in the case group while in the control group, there were 53.30 per cent female and 46.70 per cent male. Overall there were 48.70 per cent female and 51.30 per cent male in the studied population (Table 2).

Table 3: Comparison of mean duration of Surgery (Min) & Anaesthesia (Min) among study groups

	Group A (n=75)	Group B (n=75)	T Value	P value
Duration of Surgery (Minutes) Mean±SD	95.66 ± 53.60	92.86 ± 48.54	11.29	0.001
Duration of Anaesthesia (minutes) Mean±SD	96.93 ± 52.05	98.36 ± 48.21	11.26	0.001

The mean value of Duration of surgery was 95.66 ± 53.60 in Case group and 92.86 ± 48.54 in Control group. The mean value of Duration of anaesthesia was 96.93 ± 52.05 in Case group and 98.36 ± 48.21 in Control group. Both of these values were very significantly different between groups (P<0.01) .

Table 4: Comparison of post-operative Ramsey Sedation score among study groups

Time Interval	Group A	Group B	T	P value
0 hour	1.39±0.4	1.32±0.4	0.85	0.39
2 hours	1.41±0.4	1.36±0.4	0.66	0.5
4 hours	1.64±0.4	1.48±0.5	1.98	0.04 (S)
6 hours	1.87±0.3	1.88±0.3	0.24	0.8
8 hours	1.95±0.2	1.99±0.11	1.36	0.17
12 hours	1.97±0.1	2±0	1.42	0.15
16 hours	1.97±0.1	2±0	1.42	0.15
20 hours	1.97±0.1	2±0	1.42	0.15
24 hours	1.97±0.1	2±0	1.42	0.15

Mean post-operative Ramsey Sedation Score was compared in between the study groups at various time intervals, as shown in the above table. Statistically significant difference was observed between the groups for mean values of Ramsey score only at 4 hrs (P<0.05).

Table 5: Comparison of NRS score among study groups

Time Interval	Group A	Group B	T	P value
0 hour	2.93±1.03	3.45±0.622	3.74	0.001 (S)
2 hours	2.67±0.905	3.29±0.65	4.86	0.001 (S)
4 hours	2.49±0.79	2.69±0.69	1.63	0.1
6 hours	2.24±0.76	2.4±0.76	1.37	0.16
8 hours	2.08±1.19	2.25±0.71	1.07	0.28
12 hours	1.81±0.56	1.95±0.69	1.29	0.19
16 hours	1.45±0.52	1.77±0.68	3.19	0.002 (S)
20 hours	1.39±0.51	1.61±0.67	2.307	0.02 (S)
24 hours	1.29±0.48	1.49±0.55	2.34	0.02 (S)

Comparison of NRS score in between the study groups showed statistically significant difference at 0hr, 2hr, 16hr, 20hr and 24hr, as shown in the above table (P<0.05).

Table 6: Comparison of mean duration of analgesia (hours) among study groups

	Mean ± S.D.	P value
Group A	6.38 ± 2.81	0.04 (S)
Group B	5.09 ± 3.57	

Mean duration of analgesia (in hours) was compared in between the study groups. Statistically significant difference was observed between the groups for mean duration of Analgesia (P<0.05), mean duration being significantly higher among the group A (6.34±2.81 hrs) as compared to the group B (5.09±3.57), as tabulated above.

DISCUSSION

Intraoperative nociception is the consequence of the interactions of multiple noxious stimuli that promote peripheral and central sensitisation. Pre-incisional analgesic drug administration showed more effectiveness in decrease the postoperative pain by protecting the CNS from noxious stimuli induced deleterious effect, and which may lead to increased pain and hyperalgesia.

The aim of perioperative pain control is to minimize delays in recovery, postoperative delirium, and pain-related stress responses that can lead to serious morbidity and poor outcomes. Numerous approaches to effectively control postoperative pain in ENT surgical patients have been evaluated, as poorly controlled acute postoperative pain can be associated with persistent pain most commonly used is preemptive opioid administration.

In present study, a combination of drugs was given to allow for total opioid-free anaesthesia with the same hemodynamic stability and rapid recovery as opioid anaesthesia. The drugs paracetamol, lignocaine and magnesium sulfate used to replace opioids during anaesthesia were previously shown to reduce intraoperative opioids and to reduce the adverse effects associated with opioid use such as somnolence, dizziness, constipation, nausea and vomiting, respiratory depression, itching, urinary retention, short muscular stiffness, weak pharyngeal musculature (hence breathing problems) as well as hyperalgesia and opioid tolerance.

Demography:

In our study, group A (OFA) and group B (control group) patients were comparable with respect to gender distribution, age, weight, ASA physical status, types of surgery performed and pre-op hemodynamic parameters (Pulse, SBP, DBP, RR and Saturation) as no significant difference as observed between groups.

Duration of surgery:

Duration of surgery was slightly longer in group A and likewise duration of anesthesia was also longer in this group in comparison to group B.

Post-op analgesia/duration/degree/analgesic consumption:

Regarding demand of rescue analgesic, significant differences were found between groups in this study. In group OFA, 46.70% did not require any rescue analgesic during 24 hour postoperative period while this percentage was quite low in group OA (4.00%). Among the rest, 32.00% were given Tab. PCM 500 mg and 20.00% were given Tab. Ibuprofen 400 mg in group OFA while 38.70% were given Inj diclofenac 75 mg and 34.70% were given Tab. PCM 500 mg in group OA. In group OA 10.70% were given a combination of Inj diclofenac 75 mg and Tab PCM 500 mg. This shows the importance of avoiding all opioids intra operative instead of only reducing the amounts by adding additives. Samuels et al.(2017) found in a retrospective analysis that opioid free anaesthesia needed 50 % less opioids post-operative while opioid sparing anaesthesia did not make any difference. His observation suggests that exposure to even marginal amounts of opioids intra operatively increases the need for opioids in the post-operative course. Estebe JP et. al. in their retrospective, non-interventional observational study of all consecutive patients who received a total intravenous (IV)-OFA protocol for the surgical

management of major open abdominal and urological surgery found that The maximal pain (max. NRS) recorded in the PACU was 2.1 ± 2.7 (0: 0–4; 0–9). Only 38.3% of the patients required morphine IV titration (Fig. 2). The mean total morphine consumption in the PACU was 1.9 ± 2.9 mg (0 mg: 0–3 mg; 0–15 mg). No patient required IV-PCA morphine to be started in the PACU.

This is in similar to our study where we observed mean NRS score in OFA group remained in the range of 1.29 ± 0.48 and 2.93 ± 1.03 , whereas in OA group it was 1.49 ± 0.55 and 3.45 ± 0.62.

Mann GE et. al. in their hypothesis generating study, evaluated safety and efficacy of stand-alone opioid free analgesia for adenotonsillectomy and tonsillectomy in children. They found that 102 patients (73.4%) in the intraoperative opioid-free group and 184 patients (83.2%) in the intraoperative opioid group did not receive any postoperative opioids (p = 0.033). They concluded that American Society of Anesthesiologists I- II pediatric patients undergoing adenotonsillectomy and tonsillectomy can be efficiently and safely managed with an opioid-free intraoperative and postoperative analgesic regimen.

The findings of present study are in conformity with the findings of Sun et al. (2012) who published a systematic review which confirmed that for abdominal surgery, IV lidocaine consistently reduces analgesic consumption, pain scores, and side-effects. When subgroup analysis compared laparoscopic procedures with open surgery, systemic lidocaine significantly improved return of bowel function and shortened hospital stay in the open surgery group. The concepts of multimodal analgesia and its therapeutic options in the management of acute postoperative pain are still evolving. Identification of acute hyperalgesia is an important concept that improves the safety and efficacy of acute pain management. Rimbäck and colleagues published one of the earliest clinical trials with IV lidocaine. They observed that the patients randomized to IV lidocaine treatment (100 mg bolus followed by 3 mg min−1 for 24 h) showed these patients had less pain, opioid requirements, and recovered faster. Groudine and colleagues randomized patients undergoing open radical prostatectomy to receive placebo or lidocaine (bolus 1.5 mg kg−1 followed by 3 mg min−1 continued until 60 min after skin closure), they reported a significant reduction in opioid analgesic requirements and decreased pain scores with greater satisfaction in the patients receiving lidocaine. The effect of intraoperative lidocaine administration is sustained beyond its infusion period and continues into the postoperative period as was observed in our study. Kaba and colleagues' randomized 45 patients undergoing laparoscopic colon resections to receive placebo or IV lidocaine (bolus of 1.5 mg kg−1 followed by 2 mg kg−1 h−1 for 24 h). Lidocaine decreased pain scores, analgesic consumption, and side-effects well beyond the duration of lidocaine infusion. Until this date, there have been at least six published systematic reviews with meta-analyses (Level 1 evidence) for the perioperative use of IV lidocaine. Sun and colleagues published a systematic review which confirms that for abdominal surgery, IV lidocaine consistently reduces analgesic consumption, pain scores, and side-effects.

Similarly, Eipe et al. (2016) found that lidocaine was a useful option in the prevention and/or treatment of acute hyperalgesia. The benefits of perioperative IV lidocaine infusions have been confirmed with good quality evidence; these include decreases in pain scores, analgesic consumption, and side-effects with improvements in ERAS outcomes. They were also able to attest to the safety of IV lidocaine infusions for postoperative pain on standard surgical wards, provided a well-established APS protocol is followed. Similarly, White (2017) also advocated for non opioid and non pharmacological approaches towards treatment of pain. Carr and Cohen (2017) reported that longer hospitalization and slower recovery are adverse effects of opioids which may overcome by using a multimodal approach.

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