

Pre-Emptive Analgesic Effect of Intravenous Paracetamol In Patients Undergoing Craniotomy

Dr. Chayanika Kutum¹, Dr. Shashikant Shinde²

1- Junior resident, 2-Additional Professor, Department of Anaesthesiology, Seth GSMC and KEM hospital, Parel, Mumbai, India

Corresponding author – Dr. Chayanika Kutum

Abstract: Introduction: Within the concept of pre-emptive analgesia it is believed that suppressing the painful stimulus by giving analgesia before the stimulus will decrease the post-operative analgesic requirements. Paracetamol has a good safety profile and easily crosses the blood brain barrier and thus is an effective analgesic. In this study, craniotomy patients were given intravenous (iv) paracetamol 15 mg/kg body weight preoperatively and intraoperatively to assess its postoperative analgesic effects.

Materials and methods: 102 patients undergoing craniotomy were randomly divided into two groups: in Group I, iv paracetamol 15mg/kg body weight was given 30 minutes prior to induction. In Group II, iv paracetamol 15mg/kg body weight was given prior to skin closure. Postoperatively, pain scores, sedation scores, postoperative analgesic consumption, side effects and total hospital stay were recorded.

Results: There was no specific effect of pre-emptive intravenous paracetamol on intraoperative haemodynamics in craniotomy. Giving intravenous paracetamol prior to surgical closure than giving prior to induction for craniotomy had better results in reducing the VAS scores postoperatively for initial four hours. There was no significant beneficial effect of pre-emptive paracetamol in reducing postoperative analgesic consumption in craniotomy as compared to intraoperative paracetamol. There was no difference in incidence of side effects when pre-emptive and intraoperative paracetamol were compared. The mean length of hospital stay was shorter in craniotomy patients receiving pre-emptive paracetamol.

Key words: Pre-emptive analgesia, Craniotomy, Paracetamol

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I. Introduction

Pain is thought to be inadequately treated in one half of all surgical procedures.¹ Painful experiences can cause immediate unpleasantness, and subsequent hyperalgesia (amplified response to noxious stimuli) and allodynia (painless sensations experienced as pain). Prior painful experiences are known predictors of increased pain and analgesic use in subsequent surgery.^{2, 3} Pre-emptive analgesia is a process of prevention of establishment of altered processing of afferent signals, which amplifies postoperative pain. Because of this “protective” effect on the pain pathway, pre-emptive analgesia has the potential to be more effective than other analgesic treatments initiated after surgery. Theoretically, it can reduce immediate and chronic postoperative pain.

Surgery offers the best setting for pre-emptive analgesia because the timing of noxious stimuli is known and can be prevented. The most effective pre-emptive analgesic regimens are those that limit sensitization of the nervous system to pain all through the perioperative period.

Strategies for providing pre-emptive analgesia includes infiltration with local anaesthetics, nerve block, epidural block, subarachnoid block, intravenous analgesics, and anti-inflammatory drugs. It basically involves interventions at one or more sites along the pain pathway.

Several neurosurgical procedures can cause moderate to severe postoperative pain including craniotomies for tumour resections, epilepsy surgery, aneurysm clipping, and traumatic brain injury. Pharmacological management of post craniotomy pain can be done with anticonvulsants, dexamethasone, opioids, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and NMDA receptor antagonists. Local anaesthetic infiltration like scalp block is also helpful. Patient controlled analgesia (PCA) leads to lower opioid requirement.

Non- pharmacological treatment of chronic post craniotomy headaches includes TENS, physiotherapy, acupuncture, cognitive behaviour therapy supportive neck collars and manual neck traction.⁴

The ideal anaesthetic in craniotomies should provide fast offset to aid postoperative neurological examination as well as providing adequate analgesia.

Paracetamol has a well established safety profile relatively few side effects or contraindications. Intravenous administration of paracetamol can provide fast and predictable analgesia along with significant opioid sparing effect.^{5,6}

Hence the study was undertaken to evaluate the pre-emptive analgesic effect of intravenous paracetamol in patients undergoing craniotomy using the pain score (VAS) and postoperative other analgesic requirements.

II. Materials And Methods

The present study was conducted in KEM hospital, Parel, Mumbai, Maharashtra. The study was conducted in 102 patients posted for craniotomy under general anaesthesia (51 in each group) after obtaining Institutional ethics committee approval and written informed consent from the patients involved in the study. It was a single blind, prospective, randomized observational study of 102 cases. The patients were randomly allocated into two groups of 51 patients each.

In Group I (n=51, pre-emptive group), iv paracetamol 15 mg/kg was administered 30 minutes prior to induction and 100 ml iv normal saline was administered prior to closing of the skin incision.

In Group II (n=52, intraoperative group), 100 ml iv normal saline was given 30 minutes before induction and iv paracetamol 15 mg/kg was administered prior to closing the skin incision. Intraoperative haemodynamics, postoperative pain assessment, postoperative sedation, postoperative analgesic consumption and length of hospital stay were compared to reach a conclusion.

Inclusion criteria:

- Patients with ASA grade I and II
- Patients aged between 20 and 55 years
- Surgical duration 60-240 minutes

Exclusion criteria:

- Patients belonging to ASA grade III and IV
- Patients with medical complications like uncontrolled hypertension, severe anaemia, severe hypovolaemia, septicaemia, etc.
- Patients with abnormal bleeding time, clotting time or on anticoagulants
- Patients with severe liver, renal and pulmonary disease
- Patients with history of hypersensitivity to drugs.
- Pregnant patients
- Post operative poor GCS, patients on post-op ventilator.

Withdrawal criteria:

Severe adverse effects like:

1. Massive blood loss
2. Prolonged duration of surgery(more than 240 minutes)
3. Post-operative poor GCS
4. Post-operative ventilator requirement

By visiting the patients one day before operation, related information and training was given about the anaesthesia method to be applied and the Visual Analogue System (VAS) and patient written informed consent was taken. A detailed pre- anaesthetic evaluation comprising of history of present illness, history of previous medical and surgical illnesses, previous anaesthetic exposures, drug allergies, medications, or any addictions was taken. General physical, systemic examination and airway examination was done. Baseline investigations in the form of haemoglobin, complete blood count, liver function tests, renal function tests, chest X-ray, and electrocardiogram (ECG) were done. MRI or CT findings of the brain were recorded.

Patients were kept nil by mouth as per the recent protocols before surgery. On the day of surgery, preoperative vital parameters like heart rate, blood pressure, respiration were recorded. The 102 patients matching the working criteria were divided into two groups by randomization.(by drawing chits randomly) In Group I (n=51, pre-emptive group), iv paracetamol 15 mg/kg was administered 30 minutes prior to induction and 100 ml iv normal saline was administered prior to closing of the skin incision. In Group II (n=52, intraoperative group), 100 ml iv normal saline was given 30 minutes before induction and iv paracetamol 15 mg/kg was administered prior to closing the skin incision. Patients' age, weight, height, ASA classification and operation period were recorded. Routine monitors in the form of pulse oximetry, non invasive blood pressure, ECG, were attached. Venous access secured. The patients were pre-oxygenated for 3 minutes with 100% oxygen. For induction 1mg midazolam, 2-2.5 mg/kg propofol, 2ug/kg fentanyl citrate and 0.5 mg/kg atracurium were given. Following intubation, maintenance of general anaesthesia was accomplished by providing

isoflurane (0.8-1 MAC), propofol infusion (100-120 ug/kg), dexmedetomidine (0.3-0.7 ug/kg) and 4-8 ug/kg/hr atracurium infusion. No additional analgesics were dispensed over the entire course of the operation. Intraoperatively, mean systolic and diastolic blood pressures, heart rate (HR), peripheral oxygen saturation (SpO₂) and end tidal carbon dioxide (ETCO₂) values were recorded at 10, 20, 30, 40, 60, 90, 120, 180 and 240 minutes. For the postoperative pain assessment, VAS (Visual Analogue Scale) was used (VAS: 0-10; 0: no pain, 10: worst pain imaginable) at 1, 2, 4, 8, 12, 24 h. Post operatively, the sedation levels of the patients was defined in accordance with the Ramsay Sedation scale (RSS) at same time intervals. The total analgesic consumption during the same periods was recorded in mg. If the VAS score is above 4, 75 mg diclofenac was given intravenously. Side effects, such as nausea, vomiting, and allergic reaction were recorded. The total analgesic consumption and the side effects were recorded at 1, 2, 4, 8, 12, 24 hours post-op.

Statistical analysis: Sample size of 102 was calculated by following formula:

Mann-Whitney Test (Normal Distribution)

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1≠Mean2

The standard deviations were assumed to be known and equal.

Power	N1	N2	Allocation Ratio	Alpha	Beta	Mean1	Mean2	S1	S2
0.90168	51	51	1.000	0.05000	0.09832	4.7	5.4	1.1	1.1

Group sample sizes of 51 and 51 achieve 90% power to detect a difference of -0.7 between the null hypothesis that both group means are 4.7 and the alternative hypothesis that the mean of group 2 is 5.4 with known group standard deviations of 1.1 and 1.1 and with a significance level (alpha) of 0.05000 using a two-sided Mann-Whitney test assuming that the actual Distribution is normal. Data were statistically described in terms of mean (±SD), frequencies (number of cases) and percentages when appropriate. Data were tested first for normal distribution by Klotz-Smirnov test. Comparison of quantitative variables between the study groups was done using Student t test for independent samples if normally distributed. Mann-Whitney U test was used for non-normally distributed quantitative data. For comparing categorical data, Chi square test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2007 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 21. The observations were recorded in a proforma.

III. Results

Intraoperative parameters- Heart rate-

Figure 1: changes in heart rate

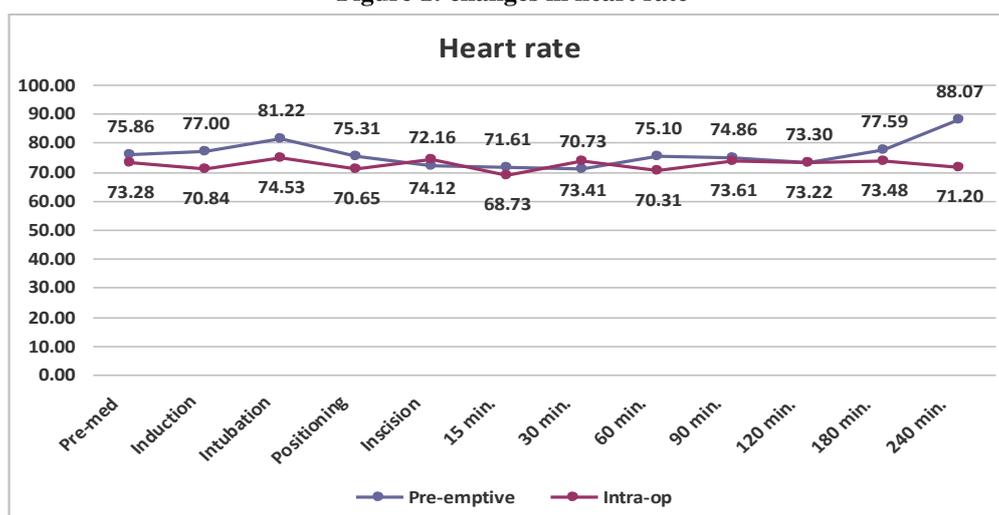


Table 1: changes in heart rate

Heart Rate	Group	N	Mean	SD	p- value	Interpretation
Pre-med	Pre-emptive	51	75.86	15.80	0.401	HR in both the groups was comparable
	Intra-op	51	73.28	15.37		
Induction	Pre-emptive	51	77.00	13.29	0.024	HR in the intraoperative group

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	Intra-op	51	70.84	13.90		is lower than the pre-emptive group
Intubation	Pre-emptive	51	81.22	14.26	0.018	HR in the intraoperative group is lower than the pre-emptive group
	Intra-op	51	74.53	13.80		
Positioning	Pre-emptive	51	75.31	15.00	0.132	HR in both the groups was comparable
	Intra-op	51	70.65	15.99		
Incision	Pre-emptive	51	72.16	16.88	0.549	HR in both the groups was comparable
	Intra-op	51	74.12	16.04		
15 min.	Pre-emptive	51	71.61	15.02	0.283	HR in both the groups was comparable
	Intra-op	51	68.73	11.75		
30 min.	Pre-emptive	51	70.73	15.88	0.41	HR in both the groups was comparable
	Intra-op	51	73.41	16.87		
60 min.	Pre-emptive	51	75.10	13.74	0.086	HR in both the groups was comparable
	Intra-op	51	70.31	14.15		
90 min.	Pre-emptive	51	74.86	13.75	0.671	HR in both the groups was comparable
	Intra-op	51	73.61	15.89		
120 min.	Pre-emptive	44	73.30	14.63	0.978	HR in both the groups was comparable
	Intra-op	51	73.22	13.50		
180 min.	Pre-emptive	27	77.59	13.89	0.288	HR in both the groups was comparable
	Intra-op	42	73.48	16.58		
240 min.	Pre-emptive	14	88.07	14.07	0.003	HR in the intraoperative group is lower than the pre-emptive group
	Intra-op	20	71.20	16.22		

The pre-medication heart rates in pre-emptive and intraoperative group were 75.86 and 73.28 beats per minute respectively. The pre-medication heart rate in both the groups was found to be comparable.

The heart rate during induction in pre-emptive group and intraoperative group were 77.0 and 70.84 beats per minute respectively. The heart rate during induction was found to be significantly lower in the intraoperative group with a P value of 0.024.

The heart rate during intubation in pre-emptive group and intraoperative group were 81.22 and 74.53 beats per minute respectively. The heart rate was found during intubation to be significantly lower in the intraoperative group with a P value of 0.018.

The heart rate during positioning in pre-emptive group and intraoperative group were 75.31 and 70.65 beats per minute respectively. The heart rate in both the groups was found to be comparable during positioning.

The heart rate during incision in pre-emptive group and intraoperative group were 71.61 and 68.73 beats per minute respectively. The heart rate in both the groups was found to be comparable during incision.

The heart rate at 15 minutes in pre-emptive group and intraoperative group were 71.61 and 68.73 beats per minute respectively. The heart rate at 15 minutes in both the groups was found to be comparable.

The heart rate at 30 minutes in pre-emptive group and intraoperative group were 70.73 and 73.41 beats per minute respectively. The heart rate at 30 minutes in both the groups was found to be comparable.

The heart rate at 60 minutes in pre-emptive group and intraoperative group were 75.10 and 70.31 beats per minute respectively. The heart rate at 60 minutes in both the groups was found to be comparable.

The heart rate at 90 minutes in pre-emptive group and intraoperative group were 74.86 and 73.61 beats per minute respectively. The heart rate at 90 minutes in both the groups was found to be comparable.

The heart rate at 120 minutes in pre-emptive group and intraoperative group were 73.30 and 73.22 beats per minute respectively. The heart rate at 120 minutes in both the groups was found to be comparable.

The heart rate at 240 minutes in pre-emptive group and intraoperative group were 88.07 and 71.20 beats per minute respectively. The heart rate at 240 minutes in intraoperative group was found to be significantly lower with a P value of 0.003.

Systolic blood pressure (SBP)-
Figure 2: SBP

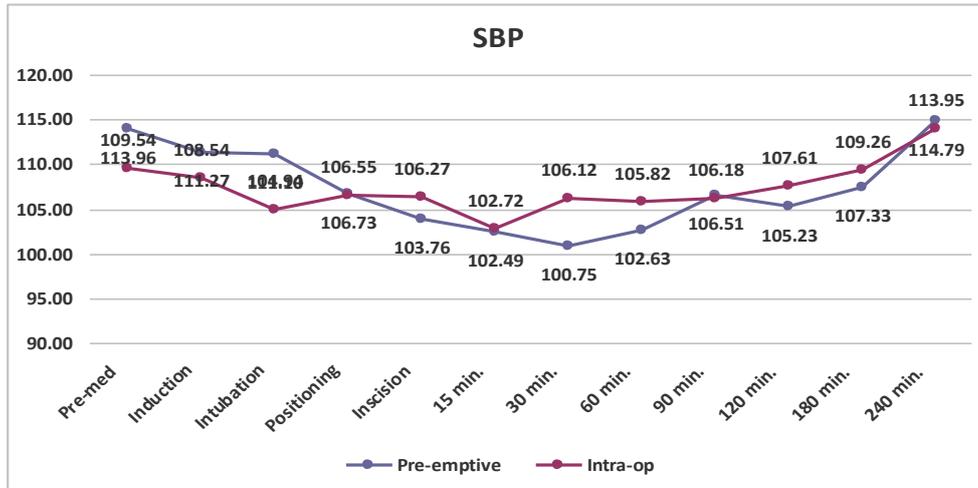


Table 2: SBP

SBP	Group	N	Mean	SD	p- value	Interpretation
Pre-med	Pre-emptive	51	113.96	16.29	0.116	SBP in both the groups was comparable
	Intra-op	51	109.54	11.30		
Induction	Pre-emptive	51	111.27	14.58	0.307	SBP in both the groups was comparable
	Intra-op	51	108.54	12.04		
Intubation	Pre-emptive	51	111.10	13.03	0.015	SBP in intra-operative group was lower
	Intra-op	51	104.94	11.88		
Positioning	Pre-emptive	51	106.73	11.90	0.948	SBP in both the groups was comparable
	Intra-op	51	106.55	15.08		
Incision	Pre-emptive	51	103.76	9.28	0.284	SBP in both the groups was comparable
	Intra-op	51	106.27	13.82		
15 min.	Pre-emptive	51	102.49	10.45	0.926	SBP in both the groups was comparable
	Intra-op	51	102.72	13.98		
30 min.	Pre-emptive	51	100.75	9.68	0.042	SBP in pre-emptive group was lower
	Intra-op	51	106.12	15.88		
60 min.	Pre-emptive	51	102.63	9.18	0.11	SBP in both the groups was comparable
	Intra-op	51	105.82	10.76		
90 min.	Pre-emptive	51	106.51	12.82	0.897	SBP in both the groups was comparable
	Intra-op	51	106.18	13.03		
120 min.	Pre-emptive	43	105.23	14.02	0.383	SBP in both the groups was comparable
	Intra-op	51	107.61	12.43		
180 min.	Pre-emptive	28	107.33	14.88	0.567	SBP in both the groups was comparable
	Intra-op	42	109.26	12.70		
240 min.	Pre-emptive	14	114.79	11.14	0.85	SBP in both the groups was comparable
	Intra-op	20	113.95	13.57		

The pre-medication systolic blood pressure in pre-emptive group and intraoperative group was 113.96 and 109.54 mmHg respectively and was comparable in both groups.

The systolic blood pressure at induction in pre-emptive group and intraoperative group was 111.27 and 108.54 mmHg respectively and was comparable in both groups.

The systolic blood pressure during intubation in pre-emptive group and intraoperative group was 111.10 and 104.94mmHg respectively. The systolic blood pressure at intubation was lower in the intraoperative group with a P value of 0.015.

The systolic blood pressure at positioning in pre-emptive group and intraoperative group was 106.73 and 106.55 mmHg respectively and was comparable in both groups.

The systolic blood pressure at incision in pre-emptive group and intraoperative group was 103.76 and 106.27 mmHg respectively and was comparable in both groups.

The systolic blood pressure at 15 minutes in pre-emptive group and intraoperative group was 102.49 and 102.72 mmHg respectively and was comparable in both groups.

The systolic blood pressure during 30 minutes in pre-emptive group and intraoperative group was 100.75 and 106.12 mmHg respectively. The systolic blood pressure at 30 minutes was lower in the intraoperative group with a P value of 0.042.

The systolic blood pressure at 60 minutes in pre-emptive group and intraoperative group was 102.63 and 105.82mmHg respectively and was comparable in both groups.

The systolic blood pressure at 90 minutes in pre-emptive group and intraoperative group was 106.51 and 106.18mmHg respectively and was comparable in both groups.

The systolic blood pressure at 120 minutes in pre-emptive group and intraoperative group was 105.23 and 107.61mmHg respectively and was comparable in both groups.

The systolic blood pressure at 180 minutes in pre-emptive group and intraoperative group was 107.33 and 109.26mmHg respectively and was comparable in both groups.

The systolic blood pressure at 240 minutes in pre-emptive group and intraoperative group was 114.79 and 113.95mmHg respectively and was comparable in both groups.

Diastolic blood pressure-

Fig 3- DBP

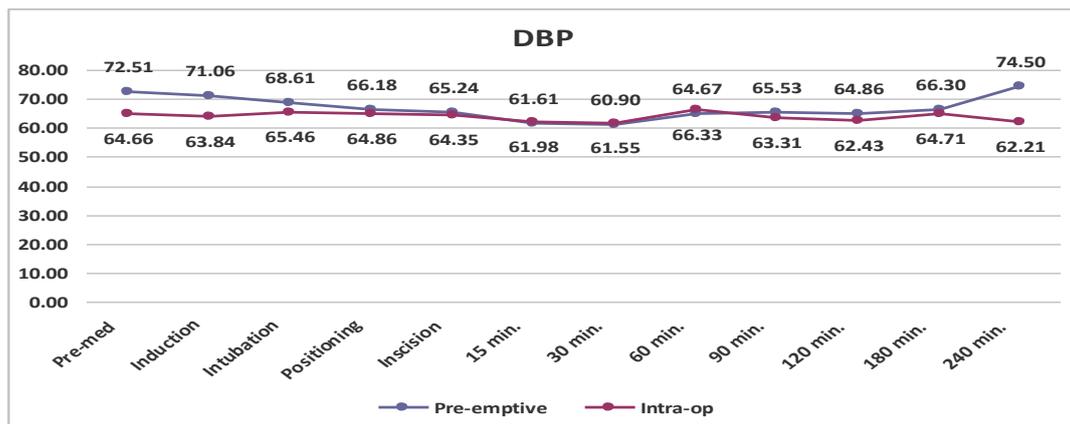


Table 3: DBP

DBP	Group	N	Mean	SD	p- value	Interpretation
Pre-med	Pre-emptive	51	72.51	12.13	0.003	DBP in intraoperative group was lower
	Intra-op	51	64.66	13.37		
Induction	Pre-emptive	51	71.06	11.83	0.006	DBP in intraoperative group was lower
	Intra-op	51	63.84	14.10		
Intubation	Pre-emptive	51	68.61	13.08	0.218	DBP in both the groups was comparable
	Intra-op	51	65.46	12.44		
Positioning	Pre-emptive	51	66.18	7.85	0.555	DBP in both the groups was comparable
	Intra-op	51	64.86	13.75		
Incision	Pre-emptive	51	65.24	9.19	0.701	DBP in both the groups was comparable
	Intra-op	51	64.35	13.56		
15 min.	Pre-emptive	51	61.61	8.95	0.865	DBP in both the groups was comparable
	Intra-op	51	61.98	12.76		
30 min.	Pre-emptive	51	60.90	8.12	0.761	DBP in both the groups

	Intra-op	51	61.55	12.78		was comparable
60 min.	Pre-emptive	51	64.67	9.31	0.459	DBP in both the groups was comparable
	Intra-op	51	66.33	13.04		
90 min.	Pre-emptive	51	65.53	13.77	0.422	DBP in both the groups was comparable
	Intra-op	51	63.31	13.99		
120 min.	Pre-emptive	43	64.86	10.99	0.318	DBP in both the groups was comparable
	Intra-op	51	62.43	12.40		
180 min.	Pre-emptive	28	66.30	11.17	0.619	DBP in both the groups was comparable
	Intra-op	42	64.71	13.79		
240 min.	Pre-emptive	14	74.50	11.23	0.01	DBP in intraoperative group was lower
	Intra-op	20	62.21	13.47		

The pre-medication diastolic blood pressure in pre-emptive group and intraoperative group was 72.51 and 64.66 mmHg respectively. The diastolic blood pressure at induction was significantly lower in the intraoperative group with a P value of 0.003.

The diastolic blood pressure at induction in pre-emptive group and intraoperative group was 71.06 and 63.84 mmHg respectively. The diastolic blood pressure at induction was significantly lower in the intraoperative group with P value of 0.006.

The diastolic blood pressure during intubation in pre-emptive group and intraoperative group was 68.61 and 65.46mmHg respectively and was comparable in both groups.

The diastolic blood pressure at positioning in pre-emptive group and intraoperative group was 66.18 and 64.86 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at incision in pre-emptive group and intraoperative group was 65.24 and 64.35 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 15 minutes in pre-emptive group and intraoperative group was 61.61 and 61.98 mmHg respectively and was comparable in both groups.

The diastolic blood pressure during 30 minutes in pre-emptive group and intraoperative group was 60.90 and 61.55 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 60 minutes in pre-emptive group and intraoperative group was 64.67 and 66.33 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 90 minutes in pre-emptive group and intraoperative group was 65.53 and 63.31 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 120 minutes in pre-emptive group and intraoperative group was 64.86 and 62.43 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 180 minutes in pre-emptive group and intraoperative group was 66.30 and 64.71 mmHg respectively and was comparable in both groups.

The diastolic blood pressure at 240 minutes in pre-emptive group and intraoperative group was 74.50 and 62.21mmHg respectively. The diastolic blood pressure at 240 minutes was significantly lower in the intraoperative group with P value of 0.01.

Post-operative parameters-

Visual Analogue Scale- VAS Score

Figure 4: Visual Analogue Scale

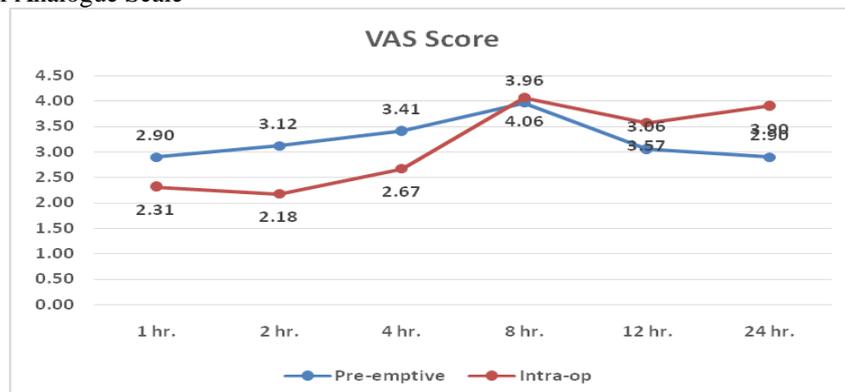


Table 4: Visual Analogue Scale

VAS	Group	N	Mean	SD	p- value	Interpretation
1 hr.	Pre-emptive	51	2.90	1.08	0.008	VAS score is lower in the intraoperative group
	Intra-op	51	2.31	1.10		
2 hr.	Pre-emptive	51	3.12	1.11	<0.001	VAS score is lower in the intraoperative group
	Intra-op	51	2.18	0.95		
4 hr.	Pre-emptive	51	3.41	1.15	0.003	VAS score is lower in the intraoperative group
	Intra-op	51	2.67	1.29		
8 hr.	Pre-emptive	51	3.96	1.93	0.798	VAS score is comparable in both the groups
	Intra-op	51	4.06	1.93		
12 hr.	Pre-emptive	51	3.06	1.17	0.109	VAS score is comparable in both the groups
	Intra-op	51	3.57	1.92		
24 hr.	Pre-emptive	51	2.90	1.30	<0.001	VAS score is lower in the pre-emptive group
	Intra-op	51	3.90	1.42		

VAS score at 1 hour post operatively was 2.90 and 2.31 in pre-emptive and intraoperative group respectively. VAS score in 1 hour postoperatively was significantly lower in the intraoperative group with a P value of 0.008. VAS score at 2 hours post operatively was 3.12 and 2.18 in pre-emptive and intraoperative group respectively. VAS score in 2 hours was significantly lower in intraoperative group in 2 hours postoperatively with a P value of <0.001.

VAS score at 4 hours post operatively was 3.41 and 2.67 in pre-emptive and intraoperative group respectively. VAS score in both groups was significantly lower in intraoperative group in 4 hours postoperatively with a P value of 0.003.

VAS score at 8 hours post operatively was 3.96 and 4.06 in pre-emptive and intraoperative group respectively and was comparable in 8 hours postoperatively.

VAS score at 12 hours post operatively was 3.06 and 3.57 in pre-emptive and intraoperative group respectively and was comparable in 12 hours postoperatively.

VAS score at 24 hours post operatively was 2.90 and 3.90 in pre-emptive and intraoperative group respectively. VAS score in both groups was significantly lower in pre-emptive group in 24hours postoperatively with a P value of <0.001.

Ramsay sedation score- RSS

Figure 5: RSS

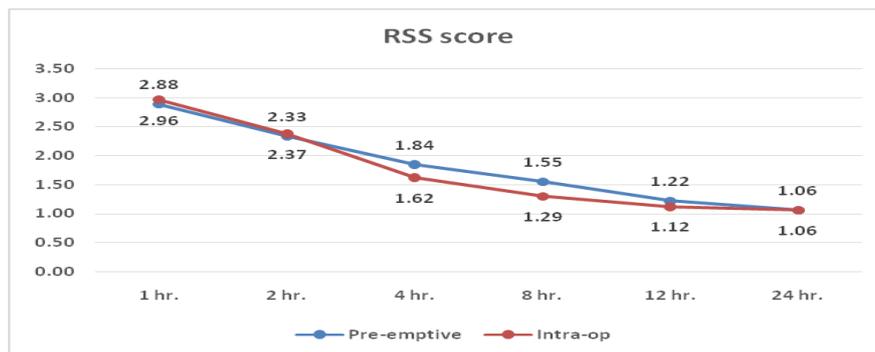


Table 5: RSS

RSS	Group	N	Mean	SD	p- value	Interpretation
1 hr.	Pre-emptive	51	2.88	0.55	0.342	RSS in both the groups are comparable
	Intra-op	51	2.96	0.20		
2 hr.	Pre-emptive	51	2.33	0.52	0.694	RSS in both the groups are comparable
	Intra-op	51	2.37	0.49		
4 hr.	Pre-emptive	51	1.84	0.50	0.046	RSS is lower in the intraoperative group
	Intra-op	51	1.62	0.60		

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8 hr.	Pre-emptive	51	1.55	0.50	0.012	VAS score is lower in the intraoperative group
	Intra-op	51	1.29	0.50		
12 hr.	Pre-emptive	51	1.22	0.42	0.186	RSS in both the groups are comparable
	Intra-op	51	1.12	0.33		
24 hr.	Pre-emptive	51	1.06	0.24	1.00	RSS in both the groups are comparable
	Intra-op	51	1.06	0.24		

RSS at 1 hour post operatively was 2.88 and 2.96 in pre-emptive and intraoperative group respectively and was comparable in 1 hour postoperatively.

RSS at 2 hours post operatively was 2.33 and 2.37 in pre-emptive and intraoperative group respectively and was comparable in 2 hours postoperatively.

RSS at 4 hours post operatively was 1.84 and 1.62 in pre-emptive and intraoperative group respectively. RSS score at 4 hours postoperatively was significantly lower in the intraoperative group with P value of 0.046.

RSS at 8 hours post operatively was 1.55 and 1.29 in pre-emptive and intraoperative group respectively. RSS score at 8 hours postoperatively was significantly lower in the intraoperative group with P value of 0.012.

RSS at 12 hours post operatively was 1.22 and 1.12 in pre-emptive and intraoperative group respectively and was comparable in 12 hours postoperatively.

RSS at 24 hours post operatively was 1.06 and 1.06 in pre-emptive and intraoperative group respectively and was comparable in 24 hours postoperatively.

Analgesic requirements-

Figure 6: Analgesic requirements

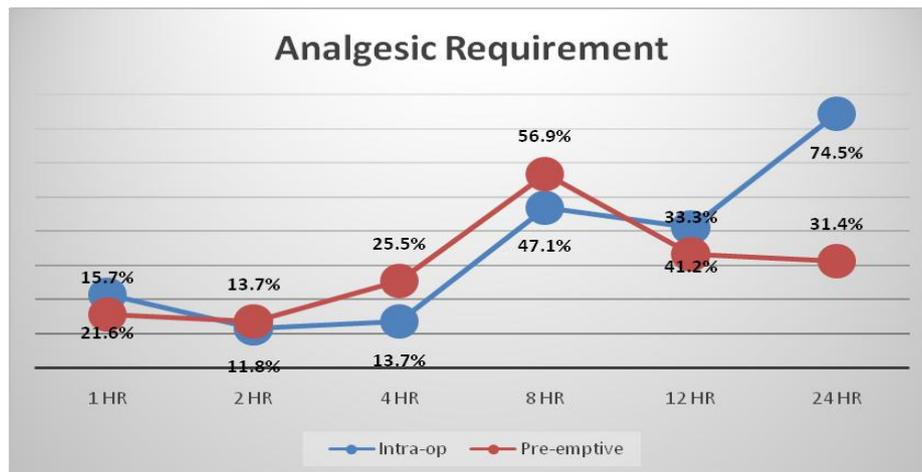


Table 6: Analgesic requirements

Analgesic Consumption	Group		Total	p- value	Interpretation
Analgesic Consumption	Intra-op	Pre-emptive			
1 hr	11	8	19	0.612	Analgesic consumption in both groups are comparable
1 hr	21.6%	15.7%	18.6%		
2 hr	6	7	13	1.00	Analgesic consumption in both groups are comparable
2 hr	11.8%	13.7%	12.7%		
4 hr	7	13	20	0.21	Analgesic consumption in both groups are comparable
4 hr	13.7%	25.5%	19.6%		
8 hr	24	29	53	0.43	Analgesic consumption in both groups are comparable
8 hr	47.1%	56.9%	52.0%		
12 hr	21	17	38	0.54	Analgesic consumption in both groups are comparable
12 hr	41.2%	33.3%	37.3%		

24 hr	38	16	54	<0.01	Analgesic requirement in pre-emptive group is lower
24 hr	74.5%	31.4%	52.9%		

Analgesic requirement at 1 hour post operatively was 21.6% and 15.7% in intraoperative and pre-emptive group respectively and was comparable in 1 hour postoperatively.

Analgesic requirement at 2 hours post operatively was 11.8% and 13.7% in intraoperative and pre-emptive group respectively and was comparable in 2 hours postoperatively.

Analgesic requirement at 4 hours post operatively was 13.7% and 25.5% in intraoperative and pre-emptive group respectively and was comparable in both groups.

Analgesic requirement at 8 hours post operatively was 47.1% and 56.9% in intraoperative and pre-emptive group respectively and was comparable in both groups.

Analgesic requirement at 12 hours post operatively was 41.2% and 33.3% in intraoperative and pre-emptive group respectively and was comparable in 12 hours postoperatively.

Analgesic requirement at 24 hours post operatively was 74.5% 31.4% in intraoperative and pre-emptive group respectively. Analgesic requirement in 24 hours postoperatively was significantly lower in the pre-emptive group with P value of <0.01.

Adverse events-

Figure 7: Adverse events

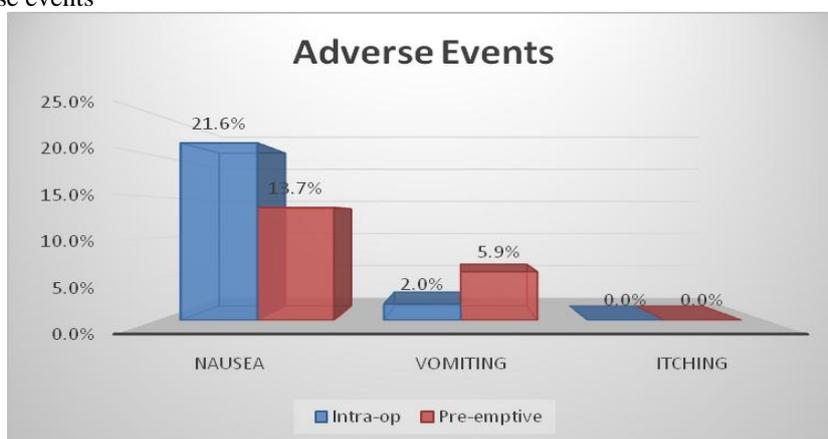


Table 7: Adverse events

Adverse Events	Group		Total	p- value	Interpretation
	Intra-op	Pre-emptive			
Nausea	11	7	18	0.44	Adverse events of both groups are comparable
Nausea	21.6%	13.7%	17.6%		
Vomiting	1	3	4	0.62	Adverse events of both groups are comparable
Vomiting	2.0%	5.9%	3.9%		
Itching	0	0	0	NA	This adverse event was not found in both groups
Itching	0.0%	0.0%	0.0%		

All the adverse events of both the groups were comparable.

IV. Discussion

As the awareness of the pathophysiology of postoperative pain increases, a new analgesic concept has been developed and applied for the prevention of pain in which analgesic treatment is started prior to surgical intervention. Within this concept, known as pre-emptive analgesia, it is believed that pain will either subside or be prevented prior to the painful stimulus by suppressing central or peripheral sensitization. Pre-emptive analgesia gives rise to a decrease in analgesic requirements, a decline in morbidity, and shortening of stay in the hospital.

Paracetamol is a non-opioid agent, and it primarily acts upon the central nervous system by way of central cyclooxygenase inhibition, and probably has an indirect effect on the serotonergic system. Paracetamol

has a good safety profile and easily passes through the blood brain barrier, which makes it an effective analgesic.

In this study we aimed to compare the analgesic effects of intravenous paracetamol given pre-emptively with that of given intraoperatively in patients undergoing craniotomy. We studied the intraoperative haemodynamics, postoperative VAS score, RSS, analgesic requirements and side effects in both groups.

Haemodynamic parameters-

Heart rate: (fig 1, table 1)

The mean premedication heart rate was 75.86 beats per minute in the pre-emptive group vs. 73.28 beats per minute in the intraoperative group and was found to be comparable in both the groups.

The mean heart rate at induction was 77.0 beats per minute in the pre-emptive group vs. 70.84 beats per minute in the intraoperative group. The mean heart rate during induction was found to be significantly lower in the intraoperative group with a P value of 0.024.

The mean heart rate during intubation in the pre-emptive group and the intraoperative group was 81.22 and 74.53 beats per minute respectively and it was found that heart rate was significantly lower in the intraoperative group with a P value of 0.018.

The mean heart rate during positioning in the pre-emptive group and the intraoperative group was 75.31 and 70.65 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate during incision in the pre-emptive group and the intraoperative group was 72.16 and 74.12 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 15 minutes in the pre-emptive group and the intraoperative group was 71.61 and 68.72 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 30 minutes in the pre-emptive group and the intraoperative group was 70.72 and 73.41 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 60 minutes in the pre-emptive group and the intraoperative group was 75.10 and 70.31 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 90 minutes in the pre-emptive group and the intraoperative group was 74.86 and 73.61 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 120 minutes in the pre-emptive group and the intraoperative group was 73.30 and 73.22 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 180 minutes in the pre-emptive group and the intraoperative group was 77.59 and 73.48 beats per minute respectively and was found to be comparable in both the groups.

The mean heart rate at 240 minutes in the pre-emptive group and the intraoperative group was 88.07 and 71.20 beats per minute respectively and it was found the heart rate was significantly lower in the intraoperative group with a P value of 0.003.

The heart rate was found to be lower during induction and at 240 minutes of surgery in the group not receiving pre-emptive paracetamol. Otherwise it was comparable throughout the study. So, it can be derived that there is no significant effect of pre-emptive paracetamol on heart rate during craniotomy.

Systolic blood pressure (SBP) - (fig 2, table 2)

The premedication systolic blood pressure in the pre-emptive group was 113.96 mmHg and 109.54 mmHg in the intraoperative group and was found to be comparable in both the groups.

The mean systolic blood pressure during induction in the pre-emptive and the intraoperative group was 111.27 and 108.54 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure during intubation in the pre-emptive and the intraoperative group was 111.10 and 104.94 mmHg respectively and was found to be lower in the intraoperative group with a P value of 0.015.

The mean systolic blood pressure during positioning in the pre-emptive and the intraoperative group was 106.73 and 106.55 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure during incision in the pre-emptive and the intraoperative group was 103.76 and 106.27 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 15 minutes in the pre-emptive and the intraoperative group was 102.49 and 102.72 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 30 minutes in the pre-emptive and the intraoperative group was 100.75 and 106.12 mmHg respectively and was found to be lower in the pre-emptive group significantly with a P value of 0.042.

The mean systolic blood pressure at 60 minutes in the pre-emptive and the intraoperative group was 102.63 and 105.82 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 90 minutes in the pre-emptive and the intraoperative group was 106.51 and 105.23 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 120 minutes in the pre-emptive and the intraoperative group was 105.23 and 107.61 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 180 minutes in the pre-emptive and the intraoperative group was 107.33 and 109.26 mmHg respectively and was found to be comparable in both the groups.

The mean systolic blood pressure at 240 minutes in the pre-emptive and the intraoperative group was 114.79 and 113.95 mmHg respectively and was found to be comparable in both the groups.

Thus, we can see that the mean systolic blood pressure was found to be lower in the patients not receiving pre-emptive paracetamol during intubation but it was significantly lower in the pre-emptive group in the 30 minutes of surgery.

So, it can be derived that there is no specific effect of pre-emptive paracetamol on systolic blood pressure during craniotomy.

Diastolic blood pressure (DBP): (fig 3, table 3)

The premedication diastolic blood pressure in the pre-emptive group was 72.51 mmHg and 64.66 mmHg in the intraoperative group and was found to be lower in the intraoperative group with a P value of 0.003

The mean diastolic blood pressure during induction in the pre-emptive and the intraoperative group was 71.06 and 63.84 mmHg respectively and was found to be lower in the intraoperative group with a P value of 0.006.

The mean diastolic blood pressure during intubation in the pre-emptive and the intraoperative group was 68.61 and 65.46 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure during positioning in the pre-emptive and the intraoperative group was 66.18 and 64.86 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure during incision in the pre-emptive and the intraoperative group was 66.24 and 64.35 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 15 minutes in the pre-emptive and the intraoperative group was 61.61 and 61.98 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 30 minutes in the pre-emptive and the intraoperative group was 60.90 and 61.55 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 60 minutes in the pre-emptive and the intraoperative group was 64.67 and 66.33 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 90 minutes in the pre-emptive and the intraoperative group was 65.53 and 63.31 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 120 minutes in the pre-emptive and the intraoperative group was 64.86 and 62.43 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 180 minutes in the pre-emptive and the intraoperative group was 66.30 and 64.71 mmHg respectively and was found to be comparable in both the groups.

The mean diastolic blood pressure at 240 minutes in the pre-emptive and the intraoperative group was 74.50 and 62.21 mmHg respectively and was found to be lower in the intraoperative group with a P value of 0.01.

It is seen from the above results that the mean diastolic blood pressure was lower in the group receiving paracetamol before closure, during induction and 240 minutes of surgery.

Thus it is derived that there is no effect of pre-emptive intravenous paracetamol on mean diastolic blood pressure in patients undergoing craniotomy.

VAS score (Visual Analogue Scale) - fig 4, table 4

VAS score at postoperative 1 hour in the pre-emptive and intraoperative group was 2.90 and 2.31 respectively and was found to be significantly lower in the intraoperative group with a P value of 0.008.

VAS score at postoperative 2 hours in the pre-emptive and intraoperative group was 3.12 and 2.18 respectively and was found to be significantly lower in the intraoperative group with a P value of <0.001.

VAS score at postoperative 4 hours in the pre-emptive and intraoperative group was 3.41 and 2.67 respectively and was found to be significantly lower in the intraoperative group with a P value of 0.003.

VAS score at postoperative 8 hours in the pre-emptive and intraoperative group was 3.96 and 4.06 respectively and was found to be comparable in both groups.

VAS score at postoperative 12 hours in the pre-emptive and intraoperative group was 3.06 and 3.57 respectively and was found to be comparable in both groups.

VAS score at postoperative 24 hours in the pre-emptive and intraoperative group was 2.90 and 3.90 respectively and was found to be significantly lower in the pre-emptive group with a P value of <0.001.

From the above results it is observed that the postoperative VAS scores were significantly lower in the group receiving paracetamol before closure at 1st, 2nd and 4th hours after surgery. At 24 hours postoperatively the VAS score was significantly lower in the group receiving paracetamol pre-emptively. Hence, we can say that giving

paracetamol prior to surgical closure than giving prior to induction has better results in reducing the VAS scores postoperatively for initial four hours.

All the mean VAS scores in the group receiving pre-emptive paracetamol was <4 that is indicating minor pain. In one study done to compare the pre-emptive analgesic effects of diflunisal, naproxen, meloxicam, paracetamol, and rofecoxib in ambulatory surgeries it was found that all mean VAS scores indicated minor pain⁷.

Another study was done by Mustafa et al⁸ compared the efficacy of pre-emptive intravenous paracetamol in patients undergoing cholecystectomy. They found that VAS scores were significantly reduced in patients receiving pre-emptive paracetamol.

Ramsey sedation scale score (RSS) - fig 5, table 5

RSS score at postoperative 1 hour in the pre-emptive and intraoperative group was 2.88 and 2.96 respectively and was comparable in both the groups.

RSS score at postoperative 2 hours in the pre-emptive and intraoperative group was 2.33 and 2.37 respectively and was comparable in both the groups.

RSS score at postoperative 4 hours in the pre-emptive and intraoperative group was 1.84 and 1.62 respectively and was found to be significantly lower in the pre-emptive group with a P value of 0.046.

RSS score at postoperative 8 hours in the pre-emptive and intraoperative group was 1.55 and 1.29 respectively and was found to be significantly lower in the pre-emptive group with a P value of 0.012.

RSS score at postoperative 12 hours in the pre-emptive and intraoperative group was 1.22 and 1.12 respectively and was found to be comparable in both groups.

RSS score at postoperative 24 hours in the pre-emptive and intraoperative group was 1.06 and 1.06 respectively and was found to be comparable in both the groups.

From above findings it is seen that the RSS in the initial postoperative hours was comparable in both the groups. At 4th and 8th postoperative hours RSS was lower in the pre-emptive group. After that it was comparable.

Analgesic requirements: (fig 6, table 6)

Analgesic requirement at postoperative 1 hour in the pre-emptive and intraoperative group was 8(15.7%) and 11(21.6%) respectively and was comparable in both the groups.

Analgesic requirement at postoperative 2 hours in the pre-emptive and intraoperative group was 7(13.7%) and 6(11.8%) respectively and was comparable in both the groups.

Analgesic requirement at postoperative 4 hours in the pre-emptive and intraoperative group was 13(25.5%) and 7(13.7%) respectively and was comparable in both the groups.

Analgesic requirement at postoperative 8 hours in the pre-emptive and intraoperative group was 29(56.9%) and 24(47%) respectively and was found to be comparable in both the groups.

Analgesic requirement at postoperative 12 hours in the pre-emptive and intraoperative group was 17(33.3%) and 21(41.2%) respectively and was found to be comparable in both groups.

Analgesic requirement at postoperative 24 hours in the pre-emptive and intraoperative group was 16(31.4%) and 38(74.5%) respectively and was found to be lower in the pre-emptive group with a P value of <0.01.

In our study the analgesic requirements was recorded in the form of consumption of intravenous diclofenac based on the VAS score. There were no significant differences in the analgesic requirement in both the group except for the 24 postoperative hours where it was significantly lower in the pre-emptive group.

In one study involving 60 patients posted for elective caesarean section to compare pre-emptive versus preventive analgesia with intravenous paracetamol it was found that pre-emptive group had longer time for next analgesia⁹.

Another study involving comparison of postoperative analgesia after laparoscopic cholecystectomy by pre-emptive administration of intravenous paracetamol or ketorolac showed that the total postoperative rescue analgesic consumption was higher in the paracetamol group¹⁰.

Side effects- (fig 7, table 7)

Nausea was found in 7(13.7%) cases in the pre-emptive group and 11(21.6%) cases in the intraoperative group which was comparable in both the groups.

Vomiting was found in 3(5.9%) cases in the pre-emptive group and 1(2.0%) case in the intraoperative group which was comparable in both the groups.

There was no incidence of itching in both the groups.

Thus, it is observed that the side effects like nausea, vomiting, or itching are comparable in both the pre-emptive and intraoperative group.

V. Conclusion

The consensus of our study are as follows:

- There is no specific effect of pre-emptive intravenous paracetamol on intraoperative haemodynamics in craniotomy.
- Giving intravenous paracetamol prior to surgical closure than giving prior to induction for craniotomy has better results in reducing the VAS scores postoperatively for initial four hours.
- There is no significant beneficial effect of pre-emptive paracetamol in reducing postoperative analgesic consumption in craniotomy as compared to intraoperative paracetamol.
- There is no difference in incidence of side effects when pre-emptive and intraoperative paracetamol are compared.

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