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ORIGINAL RESEARCH PAIN MANAGEMENT

A comparative prospective study on efficacy of premedication with intravenous paracetamol vs 6% hydroxy ethyl starch for reduction of propofol induced local pain

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ABSTRACT

Background & objective: A wide variety of approaches have been tried to reduce propofol-induced pain including physical and pharmacological methods. As there are very few studies on this topic, we decided to conduct a study to compare the effectiveness of pretreatment with i.v. paracetamol with that of 6% hydroxy ethyl starch (HES) to reduce pain induced by propofol injection.

Methodology: The prospective comparative observational study was conducted on patients who belonged to American Society of Anesthesiologists (ASA) class I and II and were to undergo general anesthesia. A total of 60 patients were distributed into two groups; Group HES patients received 100 mL hydroxy ethyl starch (HES) intravenously, and Group P received 100 mL inj. paracetamol IV before the propofol injection. We evaluated the pain on the injection of propofol using verbal rating scale (VRS) and noticed any associated behavioral signs. Hemodynamix parameters and the Perfusion Index (PI) were monitored.

Results: Pain experienced by the HES group expressed in terms of VRS score was comparatively higher with early onset of pain (at 1 sec) whereas participants in IV paracetamol started experiencing pain at 4 sec. There was no significant difference between both groups in terms of Heart Rate (HR) Systolic Blood Pressure (SBP), Mean Arterial Pressure (MAP), and Perfusion Index (PI).

Conclusion: The present study found that IV paracetamol is more effective in reducing the propofol-induced local pain compared to hydroxy ethyl starch solution IV. Hence it is preferable as a pretreatment to provide pain relief to the patients.

Abbreviations: COX: cyclooxygenase , HES: hydroxy ethyl starch, MAP: Mean Arterial Pressure, PI: Perfusion Index, VRS: verbal rating scale

Keywords: Analgesia; Injection; Propofol; Paracetamol; Premedication; Pain Management

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1. INTRODUCTION

Propofol is the most widely used intravenous anesthetic induction agent. But injection of propofol is associated with local pain in30-90% of the cases.[1] Most patients remember it as one of the unpleasant encounters during the operation. Propofol injection pain ranks seventh among common postoperative problems after anesthesia.[2] The irritating property of phenol moiety present in propofol is responsible for producing pain.[3] The immediate pain (on starting of propofol injection) is due to the irritation of the veins and delayed pain (after 10-20 sec) is due to kinin release.[4] Various techniques like choosing a larger vein, pre-administration of opioids, pre-mixing with lignocaine, using sub-anesthetic doses of ketamine, and using a mixture of medium and long-chain triglycerides in the carrier emulsion can decrease the pain.[5]

Colloids are used for intraoperative fluid therapy in anesthesia and are considered to be safe. They are macromolecules that have the capacity to modify endothelial cell junctions and permeability of the vascular endothelium and inhibit endothelial activation by various substances and molecules.[6] Thus, pre-administration of colloids may prevent contact activation by propofol, which may in turn lead to reduced or no pain during injection.[7]

Paracetamol is a synthetic, non-opiate, centrally-acting analgesic derived from p-aminophenol. Paracetamol is used as preoperative co-analgesia for pain management.[8] The mechanism of paracetamol is that it acts through cyclooxygenase (COX) inhibition, peripherally and serotonergic descending neuronal pathway centrally. Recently, it has been demonstrated to have a weak peripheral effect by blocking impulse generation within the bradykinin-sensitive chemoreceptors responsible for the generation of nociceptive impulses.[9]

We aimed to compare the effect of premedication with i.v. paracetamol with that of 6% hydroxy ethyl starch (HES) regarding reduction of propofol-induced pain during induction of general anesthesia.

2. METHODOLOGY

The prospective comparative observational study was conducted on patients undergoing elective surgeries under general anesthesia and meeting inclusion criteria over 12 month period. Patients aged between 18 to 60 y who belong to ASA I and II category patients and are posted under general anesthesia and patients who are willing to give informed consent to participate in the study were included in the study. The patients with a history of anaphylaxis to the study drugs(6% HES and paracetamol), Chronic alcoholics and nicotine addiction, and patients with opioid drug intake for other comorbid conditions were excluded from the study. Sample size is calculated by using the formula, based on one of the previous studies.[10]

$N = [(Z\alpha/2 + Z\beta)^2(p1q1)+(p2q2)]/(p1-p2)^2$

$Z\alpha/2=1.96$

$Z\beta=0.84$

p1=97.3 q1=2.7 (p1 is the percentage of the study population having an analgesic effect with the study drug)

p2=64.9 q2=35.1 (p2 is the percentage of the study population having analgesic effect without the study drug)

p1-p2= 32.4

N=18.97 approximately 19

So, we included 30 patients in each group. Convenience sampling was used for the distribution of patients in two groups.

After approval of the Institutional Ethics Committee (No. MIMS/IEC/676) and obtaining the informed consent orally as well as in written form after explaining the procedure to the patient in their understandable language. The data was recorded using a semi-structured questionnaire which contains 2 parts. The first part collects the details regarding socio-demographic characteristics like name, age, sex, etc. The second part included monitoring vital parameters like HR, MAP, SBP, Perfusion Index and behavioral changes, unlike infusion 1/4th induction dose of propofol.

We included 60 patients, ASA I or II status, scheduled for general anesthesia for elective surgery. Patients were observed throughout the procedure patients receiving 100 mL HES intravenously (IV) were considered Group HES and those who received 100 mL paracetamol IV were considered Group P. After routine monitoring, the superficial radial vein was cannulated using an 18-gauge catheter, and the upper arm was inflated using a pneumatic tourniquet (pressure inflated to 70 mmHg) to occlude the venous drainage. The patients were pretreated over 10 min, with one of the pretreatment solutions: 100 mL HES 6% IV (Group HES) and 100 mL of paracetamol IV (1000 mg) (Group P). The upper arm is kept inflated for 12 min (10 min for infusion of the test drug and 2 min for its time to act). The occlusion was released after 2 min and 1/4th of the total calculated dose of propofol was administered through the i.v. line over 20 sec. During the injection of propofol, we evaluated the pain using a four-point Verbal Rating Scale (VRS) (none = 0, mild = 1, moderate = 2, and severe = 3) and noticed any associated behavioral signs. Behavioral

signs were considered as VRS = 3 when the patient showed tears, arm withdrawal, strong vocal response, or responses accompanied by facial grimacing. Changes in the vital parameters such as heart rate SBP, MAP, and perfusion index were monitored and documented during the propofol infusion. After that induction of anesthesia with the remaining dose of propofol was continued. Postoperatively within 24 h, the injection site was checked for pain, edema, allergic reaction, etc.

Statistical Analysis

Statistical analysis of the data was done using SPSS 20.0. Categorical variables were presented using frequency and percentage. Descriptive statistics were expressed using mean ± SD. Categorical variables were analyzed using the chi-square test. An unpaired t-test was done to compare parametric variables such as age, height, Blood pressure, and perfusion index. A p-value <0.05 was considered statistically significant.

Table 1: Comparative demographic and hemodynamic parameters between Group HES and Group P

Parameters		Group HES (n=30)	Group P (n=30)	P value
Age (y)		25.00 ± 4.17	22.50 ± 2.16	0.005
Height (inches)		64.13 ± 9.24	61.80 ± 5.38	0.237
ASA	Class I	21	20	0.068
	Class II	09	10	0.065
Heart Rate (/min)	Pre	91.63 ± 7.33	86.7 ± 7.73	0.084
	Post	98.10 ± 11.56	95.77 ± 7.53	0.358
Systolic Blood Pressure (mmHg)	Pre	116.6 ± 10.81	116.3 ± 11.19	0.192
	Post	107.5 ± 12.39	110.3 ± 9.36	0.358
Mean Arterial Pressure (mmHg)	Pre	76.33 ± 9.41	77.07 ± 5.74	0.717
	Post	68.33 ± 9.24	73.57 ± 13.37	0.083
Perfusion Index (%)	Pre	5.60 ± 0.81	3.97 ± 1.30	0.537
	Post	5.63 ± 0.67	5.77 ± 0.77	0.478
SpO_2	Pre	99.23 ± 0.63	98.73 ± 0.87	0.063
	Post	98.90 ± 0.84	99.37 ± 0.72	0.025

Data presented as mean ± SD; P < 0.05 consided as significant

Table 2: Comparison of Verbal Rating Scale score at different times between two group

Time (sec)	Group HES (n=30)	Group P (n=30)	Chi-square	P-value
0	25 (83.3)	17 (53.3)	6.858	0.032
1	24 (80.0)	3 (10.0)	30.667	0.000
2	18 (60.0)	1 (3.3)	33.256	0.000
3	21 (70.0)	0 (0.0)	43	0.000
4	15 (50.0)	0 (0.0)	37.522	0.000
5	9 (30.0)	0 (0.0)	38.376	0.000
10	7 (23.3)	0 (0.0)	27.643	0.000
15	7 (23.3)	0 (0.0)	16.681	0.001
20	7 (23.3)	0 (0.0)	26.908	0.000

Data presented as n (%); P < 0.05 consided as significant

3. RESULTS

Around 30 patients with ASA I or II status, were included in each group. The average age of patients in Group HES was 25.00 ± 4.17 y and in Group P was 22.50 ± 2.16 y. Both groups had a significant difference in age. Other baseline parameters such as height, ASA class did not have significant difference in both groups **(**Table 1).

The average pre-induction heart rates did not vary significantly between the two groups. Even at 20 sec, no significant difference was found in HR between the groups. At pre-induction and second 20, there was no significant difference found in systolic blood pressure between the groups.

Comparison of MAP between the groups shows, there was no significant difference found at pre-induction. At 20 sec, MAP was relatively less in 6% HES group (68.33

Table 3: Median and IQR of Verbal Rating Scale score between both groups

Groups	Level	Median	Interquartile range (IQR)
6% HES	Pre	0	-
	Sec 20	2	(1.75−3)
Paracetamol	Pre	0	-
	Sec 20	1	(0.75−1)

± 9.24) than in Group P (73.57 ± 13.37), but the difference was statistically not significant as the p-value is at 0.08.

Comparison of the PI between the groups shows that at pre-induction and at 20 sec, there was no significant difference found in PI between the groups.

A comparison of SpO_2 between the groups shows that at pre-induction, and after 5 sec there was no significant difference found between the groups. At 20 sec, SpO_2 was significantly less in Group HES (98.9 ± 0.84) than in Group P (99.37 ± 0.72) (Table 1).

Table 2 shows the comparison of VRS scores between the HES Group and the Paracetamol group. In HES group, 83.3% of the patients experienced pain at 0 sec and in the Paracetamol group, 53.3% of the patients

experienced pain at 0 sec with a statistical P = 0.032. At 1 sec, 2 sec time interval 80% and 60% of patients experienced pain in HES Group and only 10% and 3.3% of patients experienced pain in the Paracetamol group. At 3, 4, and 10 sec intervals of time, patients with HES were still experiencing pain (70%, 50%, 30%, and 23.3% of patients respectively); whereas, in the Paracetamol group none of the patients experienced pain. From 3 sec onwards we found statistically significant results with a P = 0.000 (<0.005).

At the 20th sec, the median VRS score in Group HES was 2 with the interquartile range (1.75-3) and in Group P median was 1 with the interquartile range (0.75-1). The comparison of the VRS score at the 20th-sec shows Mann-Whitney U value=124.5 with P < 0.001. The analysis reports VRS score was significantly higher with 6% HES when compared to paracetamol (Table 3).

4. DISCUSSION

In 2020, Hayat et al ., conducted a double-blind, randomized controlled trial on 74 patients, and participants were placed into two equal groups: group A received IV paracetamol (1 g) in combination with lidocaine pretreatment before the injection of propofol, and group B received lidocaine pretreatment alone before propofol injection. As per their study result, there was no significant difference in the values of vital parameters of both groups. These study findings are comparable to the present study.[10] Hayat et al, in their study, found the significant difference in pain free responses between groap A (Lidocaine+Paracetamol) and group B (Lidocaine alone). From their study it was concluded that pretreatment with Lidocaine+Paracetamol is greatly effective than Lidocaine alone in propofol induced pain. These findings are again supportive to the present study where we also found that pretreatment with i.v. paracetamol reduces pain after propofol injection.[10]

In 2022, Misra et al, conducted comparative study between 0.9% Normal saline and HES for minimazing the propofol induced pain. They found that Pre-treatment of HES significantly reduced propofol injection pain. These findings were different from the present study, where HES group showed little higher VRS score than paracetamol.[11]

Khouadja H et al, carried out a comparartive study between three groups to find out the analgesic efficacy of i.v. paracetamol, placebo, and lidocaine. Among the three, Group with pretreatment of I.V Paracetamol showed more pain free responses than the other two groups.[12] This was one more study which was supportive to the present study findings.

In 2019, Nimmaanrat et al., from their study concluded that propofol injection induced pain can be reduced by dose-dependent paracetamol.[13] From the above studies it can be stated that Paracetmol is effective in reducing the propofol induced pain. The strength of the present study is that it is a single randomized controlled trial.

5. LIMITATIONS

The limitation of the study is that it is a single-center study. And we did not compare it with lidocaine as many studies have shown the analgesic efficacy of lidocaine in the reduction of propofol-induced pain. The minimal sample size is one more drawback of the study. The depth of the pain could not be assessed and we did not include open-ended questions to assess the pain among the patients. We suggest a multicentre study to be conducted on a larger sample size to evaluate the analgesic efficacy of paracetamol and lidocaine.

6. CONCLUSION

Paracetamol can be used both Intravenously and orally to minimize the pain that occurs during the propofol injection. The present study found that IV Paracetamol effectively reduces the injection propofol-induced pain

compared to HES. Hence it can be used as a pretreatment to provide better health to patients.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Declaration of patient consent

The authors certify that we have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

9. Conflict of interest

The authors declare no conflict of interest. The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

SG: Designed the work, contributed in collection of the data and software resources and manuscript writing.

KAV: Designing the work, methodology, collecting the data, analysing the results and manuscript writing.

DSR: Methodology, collecting the data, analysing the results, drafting the data and manuscript writing.

CH: Methodology, collecting the data, drafting the data and manuscript writing.

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