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Comparative Evaluation Of Intravenous Tramadol Hydrochloride And Intravenous Butarphanol Tartrate To Alleviate The Pain On Propofol Injection.

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Abstract
Objective: This study aimed to compare the efficacy of tramadol and butorphanol as premedications in reducing pain associated with propofol injection during anesthesia induction.
Methods: A randomized controlled trial was conducted involving 50 patients undergoing surgical procedure under anesthesia. Patients were randomly assigned to receive either tramadol 50 mg (Group T) or butorphanol 2 mg (Group B) as a premedication. Pain on propofol injection was assessed using the Visual Analog Scale (VAS) immediately after injection. Incidence and severity of pain were recorded. Hemodynamic parameters, including systolic blood pressure (SBP) and heart rate (HR), were also monitored.
Results: This randomized controlled trial included a total of 50 patients, comprising 31 males and 19 females. The mean pain score on the Visual Analog Scale (VAS) was 1.10 in Group B (butorphanol) and 1.38 in Group T (tramadol). The incidence of pain on propofol injection was 40% for butorphanol and 44% for tramadol, with mild pain reported by 46% and 48% of patients in the respective groups. Moderate to severe pain was experienced by 14% of patients in the butorphanol group and 8% in the tramadol group. However, there were no statistically significant differences in pain incidence or severity between the two groups ($p > 0.05$). Furthermore, changes in systolic blood pressure (SBP) and heart rate (HR) following propofol injection were comparable between the tramadol and butorphanol groups ($p > 0.05$).
Conclusion: Our study demonstrates that premedication with tramadol 50 mg or butorphanol 2 mg effectively reduces pain associated with propofol injection during anesthesia induction. Both drugs exhibit comparable efficacy in alleviating propofol injection pain and maintaining hemodynamic stability. They provide good analgesia without risking sedation or desaturation. These findings support the use of tramadol and butorphanol as viable options for reducing propofol injection pain in clinical practice.

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I. Introduction

Propofol, also known by its generic name, is a commonly used intravenous anaesthetic agent and is widely utilized for the induction and maintenance of anaesthesia during surgical procedures and sedation in critical care settings. Propofol is valued for its rapid onset and short duration of action, making it an ideal choice for achieving smooth anaesthesia transitions and minimizing postoperative recovery time. (1) Propofol belongs to the class of intravenous hypnotic agents and exerts its effects by enhancing the inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) receptors in the central nervous system. (2, 3) Its unique pharmacokinetic profile allows for precise titration, enabling an anaesthesiologist to tailor the depth of anaesthesia to each patient's specific requirements. (4) However, a notable drawback associated with propofol administration is the potential for pain or discomfort at the injection site, which can cause distress to patients and may affect their overall experience during anaesthesia induction. Pain during Propofol injection is a common occurrence and a significant concern in clinical practice with its prevalence ranging from 20% to 90%, depending on several factors such as the patient population, propofol formulation, injection technique, and individual pain thresholds. (5, 6) Propofol, when injected into the veins is found to stimulate the thin myelinated A delta fibers associated with venous nociceptors which are responsible for the transmission of sharp, fast pain signals. Irritation due to propofol injection leads to direct stimulation of venous nociceptors triggers the activation of pain pathways, leading to the perception of pain at the injection site. (7, 8) Another mechanisms behind pain experienced during propofol injection is release of bradykinin. The kallikrein-kinin system is thought to be activated by propofol, causing the release of bradykinin. Vasodilation and a rise in vascular permeability are both effects of the powerful inflammatory mediator bradykinin. The release of bradykinin after the injection of propofol may cause venous hyperpermeability, allowing contact between free propofol molecules and free nerve endings within the vascular

wall. (9, 10) Propofol and nerve endings can combine to activate pain receptors, causing the experience of pain. This process is thought to contribute to the potential delayed pain after a propofol infusion.

The occurrence of pain during propofol injection is influenced by several factors. These include the site of injection, vein size, injection speed, propofol concentration, blood buffering, carrier fluid speed, propofol temperature, syringe material, and concomitant drug use. The site of injection plays a role, with certain areas being more sensitive to pain due to nerve density or proximity to blood vessels. Smaller veins are more prone to irritation and pain. Rapid injection rates and higher propofol concentrations in the aqueous phase are associated with increased pain, while slower injection rates and buffering effects of blood can reduce pain. (11, 12) The speed of the carrier fluid, temperature of propofol, syringe material, and use of local anesthetics or opiates can also impact pain perception. Pain during propofol injection can be immediate or delayed, with immediate pain likely resulting from direct irritation and delayed pain potentially involving the activation of inflammatory pathways. (13, 14) Understanding these mechanisms helps in developing strategies to minimize pain during propofol administration.

With different degrees of success, a number of strategies have been researched to lessen the discomfort related to propofol injection. The incidence of this pain can be reduced using a variety of physiological and pharmacological techniques, including choosing a larger vein, slowing down the injection speed, dilution of the propofol solution, and pretreatment with lignocaine, ondansetron, metoclopramide, opioids, and thiopentone. (15, 16) A centrally acting analgesic like tramadol may also lessen the discomfort brought on by a propofol injection. Additionally, we proposed that intravenous (IV) injection of butorphanol, a synthetic opioid agonist—antagonist, could also lessen discomfort during induction with IV propofol. Both a kappa receptor agonist and a mu receptor antagonist, it has analgesic and sedative effects without significantly depressing breathing or causing euphoria. (17) There are few studies comparing tramadol and butorphanol for treating propofol-induced pain. To examine the effectiveness of pretreatment with butorphanol and tramadol for reducing discomfort associated with propofol injection, we therefore undertook this randomised, double-blind, placebo-controlled trial.

II. Study Design & Intervention

After obtaining approval from the institutional ethical committee and written informed consent of the study subjects, a prospective randomized controlled study was designed and conducted on 50 patients scheduled for elective surgery under general anaesthesia at the Gujarat Cancer and Research Institute, Ahmedabad, in the Department of Anesthesiology to compare the effects of two different pre-treatment medications on pain during propofol injection. All Fifty patients were randomly allocated into two groups, Group T and Group B. Group T consisted of 25 patients who received 50 mg of Tramadol intravenous (IV) one minute before propofol injection. Group B consisted of 25 patients who received 2 mg of Butorphanol IV one minute before propofol injection. The pre-treatment solutions were administered over a period of 5 seconds, 5 minutes after IV cannulation while venous drainage was occluded manually at midarm for one minute.

Participants:

Inclusion criteria for the study included patients aged between 18 and 50 years, of both sexes, with ASA Grades I and II, scheduled for elective surgeries under general anaesthesia. Exclusion criteria included a history of allergy to propofol, tramadol, or butorphanol, inability to communicate with the patient, and ASA Grades II, IV, or V.

Data Collection:

A structured proforma was utilized to collect the data. This proforma included the patients' particulars, diagnosis, type of surgery, and monitoring parameters such as heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), peripheral oxygen saturation (Spo2), and electrocardiogram (ECG). The visual analogue scale (VAS) was used to assess the pain experienced during propofol injection.

Anesthetic Procedure:

Upon arrival in the operating room, a 20-gauge cannula was inserted into a vein on the patient's non-dominant hand, and lactated Ringer's solution was infused. Baseline measurements of heart rate, non-invasive blood pressure, peripheral oxygen saturation (SpO2), and ECG were recorded. Visual analogue scale (VAS) scores were also recorded before and at 1, 3, 5, and 10 minutes after propofol injection to assess pain levels.

Induction of Anaesthesia:

After the pre-treatment, the occlusion was released, and propofol was induced at a dose of 2 mg/kg. The anesthesiologist evaluated pain during propofol injection using a VAS scale. Following induction, intubation was performed, and vital signs (heart rate, blood pressure, SpO2, and ECG) were observed at 0, 1, 3, 5, and 10 minutes. Based on the distribution of pain VAS scores in postsurgical patients who described their postoperative pain

intensity as none, mild, moderate, or severe the following cut points on the pain VAS have been recommended for this study: No pain (0-4 mm); mild pain (5-44 mm); moderate pain (45-74 mm); and severe pain (75-100 mm)

Maintenance and Reversal:

Maintenance of anaesthesia was achieved using nitrous oxide, oxygen, vecuronium, isoflurane, and intermittent positive pressure ventilation (IPPV). At the end of surgery, reversal agents (neostigmine 0.05 mg/kg and glycopyrrolate 10 mcg/kg IV) were administered. All study parameters were recorded at various stages as described.

Data Analysis:

Analysis was performed using statistical software Statistical Product for Social Sciences (SPSS version 11.0 for Windows, Chicago, SPSS Inc.). All the values were expressed as a mean ± standard deviation (SD); range; or percentage. The data obtained from the study were analyzed using the student's unpaired t-test after checking for the normality of the data. A p-value less than 0.05 was considered statistically.

III. Results:

Table 1 shows the demographic profile of the patients. The mean age of patient in Group B was 45.32 + 9.32 compared to 51.00 ± 14. 70 in group T. Total 25 patients were enrolled in the study in the each group out of which 17 (68%) patients were male in group B while 14 (56%) were male in Group T. The remaining patients were female in both the groups. There is no significant difference between both the groups in age or gender.

Table 1: Demographic profile of the patients

Parameter	Group B N (%)	Group T N (%)	P Value
Mean Age	45.32 + 9.32	51.00 ± 14. 70	0.32 (NS)
Gender			
Male	17 (68)	14 (56)	0.76 (NS)
Female	8 (32)	11 (44)	

The Mean VAS score was measured before loss of consciousness and incidence of pain in both the groups (Table: 2). The mean VAS score in Group B was 1.10 ± 0.85 and 1.38 ± 1.03 in group T. During surgery 12 (48%) patients were suffered from mild pain in both the group while 3 and 2 patients were suffered from Moderate pain group B and group T respectively. The P value indicates that there is no significant difference in both the groups.

Table 2: Mean VAS score and incidence of pain both the groups

	Group B	Group T	P value
VAS Score	1.10 ± 0.85	1.38 ± 1.03	0.4 (NS)
Pain			
No Pain	10 (40)	11(44)	0.6 (NS)
Mild Pain	12 (48)	12 (48)	
Moderate Pain	3 (12)	2 (8)	

Table 3 represents the heart rate measurements in beats per minutes at different time interval (0 min, 1 min, 3 min, 5 min, 10 min) for two groups (Group B and Group T). The mean heart rate was 79.7 in both the groups at resting position. At 3 min heart rate was 74.2 ± 6.0 group B and 75.64 ± 4.15 in group T. At 10 min heart rate was decreased to 70.4 ± 3.78 and 71.6± 5.6 in group T. the P value indicates the there is no significant difference between both the groups in heart rate at any time points measured. (P value >0.05).

Table 3: Analysis of Heart Rate (bpm) at different time interval n both groups

Time	Group B	Group T	P Value
0 min	79.7 ± 7.1	79.7 ± 6.33	1
1 min	77.4 ± 6.5	77.9 ± 6.4	0.78
3 min	74.2 ± 6.0	75.64 ± 4.15	0.33
5 min	71.04 ± 4.5	72 ± 7.15	0.55
10 min	70.4 ± 3.78	71.6± 5.6	0.37

Table 4 shows the measurements of Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) in millimeters of mercury (mmHg) at different time points (0, 1, 3, 5, and 10 minutes) for two groups: Group B and Group T. The values in the table represent the mean SBP and DBP values along with their corresponding standard deviations. At the start of the measurement (0 minutes), the mean SBP for Group B is 121.52 mmHg with a standard deviation of 10.7, while Group T has a mean SBP of 120.8 mmHg with a standard deviation of 9.56. There is no statistically significant difference between the two groups at this time point (p = 1). At 3 min the mean SBP for group B is 118.4 ± 7.85 and 115 ± 6.14. At 10 min mean SBP in Group B was 110.32 ± 4.27 compared to 110.12 ± 4.0 in group T. At 0 min mean DBP in group B was 81.24 ± 5.72 compared to mean 80.56 ± 7.45 group T. At last (10 min) DBP was decreased to mean 74.52 ± 4.76 and mean 71.04 ± 3.5 in group T. There was no significant difference between two groups at any time points for systolic and diastolic blood pressure.

Table 4: Analysis of Blood pressure at different time interval in both groups

Time	Group B	Group T	P Value
Systolic blood pressure (SBP) in mmHg			
0 min	121.52 ± 10.7	120.8 ± 9.56	1
1 min	114.8 ± 6.8	115 ± 5.26	0.78
3 min	118.4 ± 7.85	115 ± 6.14	0.33
5 min	111.4 ± 5.95	112.28 ± 4.19	0.55
10 min	110.32 ± 4.27	110.12 ± 4.0	0.37
Diastolic Blood Pressure (DBP) in mmHg			
0 min	81.24 ± 5.72	80.56 ± 7.45	0.71
1 min	77.8 ± 5.24	76.6 ± 4.95	0.40
3 min	78.3 ± 4.5	77.2 ± 6.39	0.48
5 min	74.5 ± 4.76	73 ± 4.03	0.2
10 min	74.52 ± 4.76	71.04 ± 3.5	0.07

Table 5 represents the Mean Arterial Pressure at different time intervals (0, 1, 3, 5 and 10 minutes) for two groups. At 0 minutes mean MAP was 94.6 ± 6.16 in group B and 89.4 ± 4.41in group T. At 3 minutes mean MAP was 92 ± 4.0 and 90 ± 5.0 in group B and Group T respectively. The mean MAP was reduced to 86± 4.0 and 84± 3.0 at 10 min in group B and group T respectively. There is no significant difference in both the groups at any time point for mean arterial pressure.

Table 5: Analysis of Mean arterial pressure at different time interval in both groups

Time	Group B	Group T	P Value
0 min	94.6 ± 6.16	93.9 ± 7.27	0.71
1 min	90.12 ± 4.3	89.4 ± 4.41	0.56
3 min	92 ± 4.0	90 ± 5.0	0.12
5 min	87 ± 4.24	86 ± 3.0	0.34
10 min	86± 4.0	84± 3.0	0.052

The SpO_2 was measured at 0, 1, 3, 5, 10 minutes for group B and group T (Table: 6). There is no significant difference in group B and group T at any time point for SpO_2. (P value > 0.05).

Table 6: Analysis of SPo2 at different time interval in both groups

Time	Group B	Group T	P Value
0 min	100 ± 0.0	100 ± 0.0	1.0
1 min	100 ± 0.0	100 ± 0.0	1.0
3 min	99.5 ± 0.7	100 ± 0.0	1.0
5 min	100 ± 0.0	99.5 ± 0.0	1.0
10 min	100 ± 0.0	100 ± 0.0	1.0

Total 3 cases of side effects were observed in group B and 4 cases were observed in group T. The patients were suffered from pruritus and erythema in both the groups. No patient was suffered from vasovagal attack and allergic reaction.(table 7)

Table 7: Side Effect of Drugs in both the groups

Side Effect	Group B	Group T
Pruritus	2	2
Erythema	1	2
Vasovagal attack	0	0
Allergic Reaction	0	0

IV. Discussion

The management of pain associated with propofol infusion is a significant concern in clinical practice, as it can lead to patient discomfort and affect the overall anesthesia experience. Despite the benefits of propofol, there is a notable subset of patients who experience pain during its infusion. The incidence of propofol infusion pain has been reported to range from 20% to 90%, depending on various factors such as patient population, propofol formulation, injection technique, and individual pain thresholds. This wide range highlights the variability in pain perception among patients and the need for effective interventions to address this issue. Furthermore, with the increasing use of propofol in various clinical settings, understanding and managing the pain associated with its infusion has become even more crucial. Therefore, there is a growing interest in exploring different approaches, including the use of premedications, to mitigate the incidence of pain and improve patient comfort during propofol infusion. (18)

Propofol infusion can have varying effects on heart rate, depending on several factors such as the infusion rate, patient characteristics, and concurrent medications. Generally, propofol has a mild inhibitory effect on the cardiovascular system, resulting in a decrease in heart rate. This effect is primarily attributed to the direct suppression of sympathetic outflow and the enhancement of parasympathetic (vagal) tone. This suppression of sympathetic activity leads to a reduction in the release of catecholamines, resulting in decreased cardiac contractility and a subsequent decrease in heart rate. (19) In present study the effect of premedication with butorphanol and tramadol on heart rate changes following propofol injection was investigated and it was found that the average heart rates at various time points after propofol injection were comparable between the butorphanol and tramadol groups. Even the changes in heart rate were determined to be insignificant ($p>0.05$) and aligns with several previously reported studies in the literature suggesting that both tramadol and butorphanol premedication have comparable effects on heart rate during propofol induction. (20, 21)

Propofol injection also typically results in relaxation of vascular smooth muscle, leading to peripheral vasodilation resulting in a reduction in systemic vascular resistance, which in turn leads to a transient decrease in systolic blood pressure. It involves activation of endothelial nitric oxide synthase and subsequent release of nitric oxide and the effect is mediated through the enhancement of inhibitory neurotransmission mediated by gamma-aminobutyric acid (GABA) receptors in the central nervous system. (22)

In our present study, we evaluated the effect of premedication with butorphanol and tramadol on systolic blood pressure (SBP) diastolic blood pressure (DBP) changes following propofol injection. The average SBP and DBP values at various time points after propofol injection were comparable between the butorphanol and tramadol groups, and the changes in both SBP and DBP were determined to be insignificant ($p>0.05$). These findings suggest that both butorphanol and tramadol premedication have similar effects on blood pressure during propofol induction. Interestingly, our results are in line with a study conducted and reported earlier in which they investigated the effect of butorphanol and fentanyl on hemodynamic responses, including SBP, during surgeries. They reported a mean SBP value of 119.3, which is comparable to the mean SBP value of 111.44 in the butorphanol group of our study after 5 minutes of administration of butorphanol. These similar findings suggest that butorphanol has a consistent effect on SBP control across different studies. (23, 24) On investigating the hemodynamic stability of tramadol and butorphanol as premedication during propofol induction and assessing their effectiveness in providing analgesia we found that both tramadol and butorphanol demonstrated similar hemodynamic profiles, with no significant differences observed in systolic blood pressure (SBP) and diastolic blood pressure (DBP) between the two groups at various time points after propofol injection and both the drugs exhibited comparable analgesic efficacy.

In our study, we assessed the incidence of pain during propofol injection using the Visual Analog Scale (VAS). The results showed that the incidence of pain with butorphanol injection was reported as follows: 40% of patients experienced no pain, 46% reported mild pain, and 14% experienced moderate to severe pain. On the other hand, with tramadol injection, 44% of patients reported no pain, 48% experienced mild pain, and only 8% reported moderate to severe pain. These findings indicate that both butorphanol and tramadol were equally effective without any significant difference in reducing the incidence of pain during propofol injection.

Comparing our results with previous study based on evaluating the effectiveness of different doses of butorphanol for pain relief during propofol injection. They found that pretreatment with either 1 mg or 2 mg of butorphanol was equally effective in relieving pain on propofol injection, and both doses were more effective than

lidocaine. This aligns with our findings, which demonstrate the efficacy of butorphanol in reducing pain during propofol induction. (25) Another study investigated the effect of intravenous tramadol and acetaminophen in attenuating pain during propofol injection. Their study included three groups, with Group A receiving pretreatment with IV lignocaine, Group B receiving IV tramadol, and Group C receiving IV acetaminophen. They found that both tramadol and acetaminophen were equivalent to lignocaine in reducing the incidence of pain. Specifically, 43% of patients who received tramadol reported no pain, supporting our findings of tramadol's effectiveness in mitigating pain during propofol injection. (26) Taken together, these studies, along with our own findings, underscore the effectiveness of both butorphanol and tramadol in reducing the incidence of pain during propofol induction.

V. Conclusion

Present study demonstrates that both tramadol (50 mg) and butorphanol (2 mg) are effective in reducing the pain associated with propofol injection. The results indicate comparable efficacy between the two drugs, suggesting that either of them can be considered for pretreatment to alleviate propofol injection pain. Importantly, both tramadol and butorphanol provide effective analgesia without significant risks of sedation and desaturation.

However, it is important to acknowledge some limitations of our study. Firstly, our sample size was relatively small, which may have influenced the statistical power of our findings. A larger sample size would provide more robust results. Secondly, the study focused solely on the assessment of pain reduction and did not consider other factors such as patient satisfaction or adverse effects. Further investigations should include a comprehensive evaluation of these aspects.

Future studies could also explore alternative dosages or combinations of tramadol and butorphanol to optimize pain relief while minimizing side effects. Additionally, investigating the impact of these premedications on other hemodynamic parameters and their interaction with other anesthesia agents could provide a more comprehensive understanding of their overall effects.

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