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ORIGINAL ARTICLE

IMPACT OF PREEMPTIVE ANALGESIC REGIME ON THE RATS' ANESTHETIC RECOVERY PERIOD IN SOMATIC PAIN MODEL

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ABSTRACT

Background: Preemptive analgesia refers to the beginning of an analgesic intervention to block peripheral and central nociception before the noxious stimuli manifests. The aim of this study was to evaluate the effectiveness of preemptive regime on smooth recovery of rat undergoing somatic surgical pain model.

Materials & Method: This Experiment lab based study was conducted at Khyber Medical University Peshawar for one year from January 2022 to January 2023. Thirty five female Sprague-Dawley rats were divided into five distinct research groups, with each group consisting of seven rats. Group A treated with tramadol+lidocain, while group B experienced the administration of buprenorphine+lidocain before surgery. On the other hand, group C had received only saline injections. In order to simulate a realistic minor surgical scenario, each group underwent a lower transverse skin incision right above the pubic symphysis under general anesthesia. Meanwhile, the sham groups, D and E, were treated with injections of tramadol+lidocain and buprenorphine+lidocain respectively, without surgery but following the protocol of general anesthesia.

Results: The implementation of preemptive therapy with either tramadol or buprenorphine significantly shortened the time it took for recovery from the anesthesia ($p < 0.001$), Furthermore, the time for the pedal withdrawal reflex and righting reflex return was significantly reduced compared to the saline group ($p < 0.001$ for both measures). These improvements in recovery by preemptive groups were comparable to those observed in the sham group, with no significant differences observed ($p \geq 0.05$).

Conclusion: The implementation of a preemptive regime significantly reduced the recovery period and accelerated the overall recovery process in the somatic surgical pain model.

KEY WORD: Preemptive regime; Skin Incision; postoperative pain; recovery from anesthesia; pedal withdrawal reflex; righting reflex.

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INTRODUCTION

Preemptive analgesia refers to the beginning of an analgesic intervention to block peripheral and central nociception before the noxious stimuli manifests. In animal surgical models, the preemptive regime has been shown to be an effective component of well-adjusted anesthesia for pain-free postoperative recovery.[1-3] Preventive measures during general anesthesia in animal models are chosen based on a variety of variables, including the animal's species, strain, gender, the recovery period from anesthesia etc.[4] The smooth, pain-free post-operative recovery is still a nightmare, though, not just for patients but also for their carers given and medical professionals.[5,6] Researchers are now trying to develop 'animal pain models' to imitate distinct clinical diseases as well as surgical procedures, and understand underlying

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mechanisms of sympathetic stimulation in the CNS and its possible improvement with a preemptive regime.[5]

Clinical studies comparing preemptive versus no treatment were strongly suggestive of a positive outcome in pretreated individuals, but the value of preemptive treatment was less clear when compared to the same treatment started after surgery.[7,8] A suitable preemptive regimen improves the cardiovascular response after surgery, minimizing complications both during the recovery phase and after waking from anesthesia.[9] Anesthetic reflexes, particularly the righting reflex, the pedal withdrawal reflex, recovery from anesthesia, and cardiovascular monitoring, are typically used in animal models to assess post-operative recovery.[8]

Moreover, there is disagreement over the best analgesic for rats or the ideal timing to provide it.[10] Thus it is decided to use either buprenorphine or tramadol (analgesia) with lidocain and isoflurane before creating a somatic pain model. The aim of this study is to determine whether, the preemptive regimen could facilitate a smooth recovery from anesthesia. Furthermore, these substances affect the central and peripheral nerve systems at various locations. This regimen, when used prior to surgery in human, may help to lessen the side effects of general anesthetic (GA) dose, which is important for older, hypertensive individuals who are unfit for lengthy induction of GA, as highlighted in our previous article.[11]

MATERIALS AND METHODS

This Experiment lab based study was conducted at Khyber Medical University Peshawar for one year from January 2022 to January 2023. Institutional Ethical Committee gave its approval to this study protocol (No. DIR/KMU-EB/MB/000755). Thirty five Sprague-Dawley adult female rats were used in the experiments. Their weight ranged from 150 to 250gm, and they were kept in the main animal facility in cages (n=7) with free access to food and tap water. At 22 °C, a 12:12-h light-dark cycle was employed. The entire surgical research was carried out between 0900 and 1400 hours. All surgical procedures were conducted between 0900 and 1400 hours, adhering to ethical investigational guidelines and the 3R animal research ethics principles.[12] A random sample methodology was employed in this investigation; with the sample size determined using the "resource equation approach".[13] The study participants were assigned to the following groups:

- Group A: Received tramadol as part of the preemptive regimen (along with lidocain + isoflurane).
- Group B: Received buprenorphine + lidocain +isoflurane.
- Group C: only received saline injection + isoflurane.
- Group D: Sham group that received tramadol, without surgical intervention (along with lidocain + isoflurane).
- Group E: Sham group that received buprenorphine, without surgical intervention (along with lidocain + isoflurane).

The rats were anesthetized using a general anesthesia machine and inhaled isoflurane (5% for induction and 2% for maintenance with oxygen). Intramuscular penicillin was administered to each rat. Prior to surgery, preventive regimens were administered to Group A and Group B. Group A received intraperitoneal tramadol (12.5mg/kg/IP), and Group B received subcutaneous buprenorphine (0.05-0.1mg/kg/SC) paired with lidocain (7mg/SC) at the incision site. The control group (Group C) received only a saline injection subcutaneously. The incision site was shaved and cleansed with a 10% Povidone-iodine solution. A 2 cm transverse incision was made in the lower abdomen (Figure I) and closed with vieryl 2/0. Rats were housed individually in cages after recovery. Sham groups (Groups D and E) followed the same protocol, excluding the skin incision.

During the recuperation, a variety of anesthetic parameters were evaluated. The time between the end of the surgical procedure and the time it takes the rat to right itself was used to calculate the time for reinstatement of the righting reflex. The pedal withdrawal reflex was measured after the conclusion of the surgical process to the return of this reflex, whereas the recovery time was calculated as the time between the end of the surgical procedure and return of normal activity (Figure I). At 1 and 10 minutes, abdominal excursion was used to record heart rate and breathing rate as heart rate/min and breaths/min, respectively. Following surgery, oxygen saturation was measured at 1 and 10 minutes using pulse oximeter.

By using ANOVA, post hoc analysis, Bonferroni and Holm correction, and post hoc analysis, type I and type II errors were avoided.[14] Mean and standard deviation were analyzed for numerical variables such as oxygen saturation, heart rate, and breathing rate. The 95% confidence interval corresponded to a standard deviation of 1.96. Statistical analysis was conducted using SPSS version 22 and MS Excel.

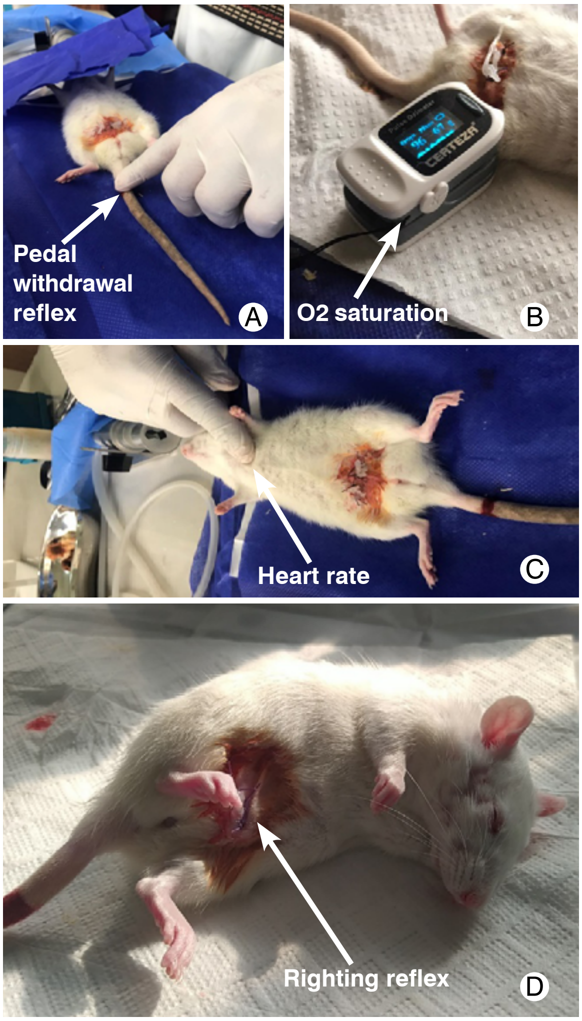

Figure 3. Monitoring of reflexes and vital signs to assess the effect of a preemptive regimen under general anesthesia in a minor surgical pain model. **Figure "A"** shows the pedal withdrawal reflex by applying pressure on the tail of rat. **"B"** showed oxygen saturation by pulse oximeter**.** **Figure C** depicted manual heart rate monitoring, and **Figure D** depicted the righting reflex.

RESULTS

In this study, total sample was 35, among them 7 rats were included in each intervention arm and study groups were divided into five groups; Buprenorphine + lidocain group (A), Tramadol +lidocain group (B), and Saline group (C), tramadol+ lidocain without surgery (sham group) (D), Buprenorphine+ lidocain sham group (E). Various parameters were evaluated to assess the smooth recovery from anesthesia, and the findings are as follows:

Reflexes

Significant variation was observed in the timing of righting reflex ($p = 0.001$), the pedal withdrawal reflex ($p=0.001$) and recovery from anesthesia ($p=0.0001$), when comparing the five groups using one way ANOVA test. (Fig 2).

The saline group (C) exhibited a longer return of the righting reflex compared to the tramadol group (A), buprenorphine group (B), tramadol sham group (D), and buprenorphine sham group (E), ($p = 0.0004$, $p=0.001$, $p=0.001$, $p=0.007$ respectively) (table 1). These findings suggest that the preemptive regime significantly reduces the timing of the righting reflex and aids in the recovery of rats from anesthesia following minor surgery without pain.

Similarly, the saline group demonstrate longer time for the pedal withdrawal reflex when compared to rest of groups ($p < 0.001$ figure I). In comparison, the timing of the pedal withdrawal reflex was increased in saline group compared to the tramadol surgical group and tramadol sham group ($p=0.004$, $p=0.001$ respectively). Similarly, the return of the pedal withdrawal reflex is higher in the saline group than in the buprenorphine (B) and buprenorphine sham group (E) with statistically significant ($p=0.006$, $p=0.007$ respectively). However, no significant differences were observed when comparing the preemptive groups A and B ($p=0.9$), the preemptive sham groups D and E ($p=0.3$), the tramadol groups A and D ($p=0.08$), and the buprenorphine groups B and E ($p=0.7$) in terms of pedal withdrawal reflex (Table I).

Similarly, the recovery time from anesthesia was longer in the saline group than in the tramadol, buprenorphine, tramadol sham, and buprenorphine sham groups ($p = 0.006$, $p<0.001$,$p<0.0001$), $p<0.007$) respectively (table I). Although the average mean recovery time was shorter in the tramadol groups compared to the buprenorphine groups, no statistically significant variation was observed between groups A versus B, D versus E, A versus D, A versus E, B versus D, and B versus E ($p =0.7$, $p=0.2$, $p=0.2$, $p=0.8$, $p=0.2$ and $p=1$).

Therefore, no significant difference was found between the preemptive regime given in minor surgery and the preemptive sham groups in terms of the time to return to the spontaneous righting reflex, the pedal withdrawal reflex, and the recovery time from anesthesia. However, a statistically significant difference was noted between the saline group and the preemptive groups during recovery phase.

Vital signs

The breathing rate in rats from the saline group appeared slightly higher than those in the Buprenorphine and Tramadol groups at 1 and 10 minutes, but the difference was not statistically significant ($p \geq 0.05$) (Table 1).

No significant variation was observed in the heart rate between groups at 1 and 10 minutes ($p \geq 0.05$), and the oxygen saturation levels were similar across all groups at both time points ($p \geq 0.05$) (Table 2).

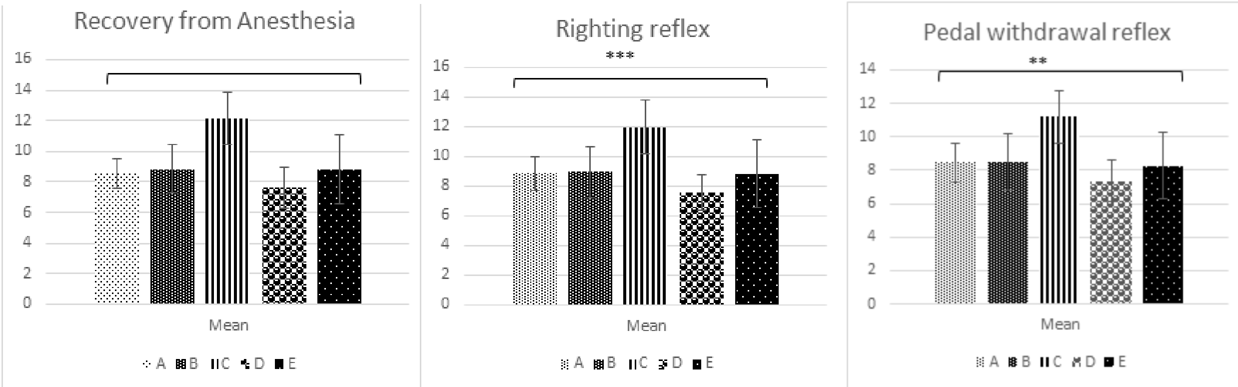

Figure 2: Comparison of mean righting reflex, Pedal withdrawal reflex and recovery timing (in minutes) between the study groups.

Table 1: Post hoc analysis with Bonferroni and holms correction for anesthetic reflexes within sub-groups of superficial pain and control group. Bonferroni correction is taken as 0.005.

Intergroup comparison	Righting reflex		Pedal withdrawal reflex		Recovery from anesthesia	
	p-value	Holm	P-value	Holm	p-value	Holm
B Vs C	0.01	0.006	0.01	0.006	0.006	0.006
A Vs C	0.004	0.006	0.004	0.006	<0.001	0.006
C Vs D	<0.001	0.005	<0.001	0.005	<0.001	0.005
C Vs E	0.007	0.007	0.007	0.007	0.007	0.007
A Vs B	0.9	0.02	1	0.05	0.7	0.02
B Vs D	0.1	0.01	0.2	0.01	0.2	0.008
B Vs E	0.7	0.025	0.8	0.02	1	0.05
A Vs D	0.08	0.008	0.1	0.008	0.2	0.01
A Vs E	0.8	0.05	0.8	0.025	0.8	0.025
D Vs E	0.3	0.0125	0.4	0.0125	0.2	0.0125

Figure 2: Comparison of above bars shows time (in minutes) of righting reflex (**p <0.00l), pedal withdrawal reflex (**p <0.00l) and recovery from anesthesia (***p <0.000l) in five study groups by using one way ANOVA. The data were shown as mean ± standard error of the mean with $p \leq 0.05$. A: Tramadol+ Lidocain, B: Buprenorphine +lidocain, C: Saline, D: Tramadol +lidocain sham group, E: Buprenorphine +lidocain sham group.

Table 2: Comparison of Oxygen saturation, breathing and heart rate between groups.

	Breathing at 1 min			Breathing at 10 min		
Group	**Average**	**Standard deviation**	**P- value**	**Average**	**Standard deviation**	**P- Value**
A	86	±2.5	0.6	86	±1.4	0.07
B	85	±1.03		87.6	±1.03	
C	86.6	±1.18		86.6	±1.18	
D	87	±1.4		86.28	±1.3	
E	84	±1.4		87.28	± 0.7	
	Heart rate at 1 min			**Heart rate at 10 min**		
A	374.9	±12	0.45	385	±6	0.23
B	376.3	±8.6		380	±12.6	
C	368.6	±12.5		375	±11.99	
D	364.3	±21.9		371	±10.4	
E	365.7	±8.63		368	±28.22	
	Oxygen saturation at 1 min			**Oxygen saturation at 10 min**		
A	95	±0.9	0.23	97	±0.7	0.57
B	94.6	±1.4		97	±0.8	
C	95.6	±0.8		97	±9.8	
D	96	±0.8		96.6	±0.78	
E	96.14	±0.9		96.6	±0.98	

Table 2: Comparison of Oxygen saturation, breathing, and heart rate between groups. Group A: tramadol group, Group B: buprenorphine group, and C: Saline group, D: tramadol+ lidocaine sham group, and group E: buprenorphine +lidocaine sham group**.** The data were shown as the mean ±standard deviation. Saline was used as the internal control group (C), while sham groups D and E were the external control group. There was no statistical variation noted in all groups at 1 min and at 10 min with $p>0.05$.

DISCUSSION

In the present study, we investigated the smooth recovery of Sprague Dawley rats from anesthesia, by utilizing balanced anesthesia approach, comprising isoflurane along with a preemptive regimen of tramadol+ lidocain and buprenorphine + lidocain for somatic surgical pain procedures in rats. Pain management in such surgeries is often overlooked due to their short duration and minor nature. In our previous study, we employed the same preemptive regimen in a novel uterine surgical model (a major surgery).[11] In the current study, we examined the improvement in vital signs and anesthetic reflexes in the preemptive groups compared to the saline group but for minor surgery. We not only applied the same regimen to surgical procedures but also included two additional sham groups without surgery. We meticulously evaluated the presence or absence of reflexes and vital sign responses, including heart rate and respiratory rate, during the recovery period after a transverse abdominal skin incision extending to the subcutaneous tissue. We had previously observed these parameters in a novel uterine surgical pain model (for visceral pain) in our previous study. We evaluated the combination of analgesia with local and general anesthesia, aiming to identify a protocol that would result in better surgical outcomes and smoother patient recovery from general anesthesia.

Several studies, such as those conducted by Salam A and Chan G et al., have reported the use of buprenorphine and tramadol as commonly employed analgesics in the post-operative period to alleviate patient pain.[4,15,16] These analgesics are readily available and have been found to offer advantages over other forms of pain management. However, in our study, tramadol and buprenorphine were administered prior to the surgery, along with local and general anesthesia, and their effectiveness was assessed during the recovery phase of anesthesia. Our findings indicated that they were equally effective compared to the sham group.

In our study, we observed that the pedal withdrawal reflex, righting reflex, and recovery from anesthesia were significantly improved in the preemptive groups compared to the saline group in minor surgical model. This finding suggests that the preemptive regimen successfully reduces the duration of the recovery period, further supporting the results of our previous study on the novel uterine surgical model published in.[11] Additionally, Vincent et al. and Molina AM emphasized the importance of pedal withdrawal test and righting reflex in assessing smooth recovery from anesthesia after surgery.[17,18] Adetola RA. et al, indicated that the disappearance of the pedal withdrawal reflex reflects the depth of anesthesia, and that the combined use of analgesia with local and general anesthesia is more effective than without analgesia and local anesthesia.[19] While these findings align with previous studies, they warrant further validation, especially considering that only female rats were used in our study.

Maintaining an optimum temperature is necessary during and after the surgery because it affects the quality and speed of recovery from anesthesia.[20] Keeping this in mind, we kept the temperature at 22 ±2 °C. Furthermore, proper anesthetic machine was used for the delivery of 2% Isoflurane to avoid the buildup of carbon dioxide, which may also affect the recovery period, pedal withdrawal reflex, righting reflex, and even vital signs.

Suzanne M reported no difference in heart rate, return of spontaneous breathing, extubation time, or respiratory rate between animals treated with medetomidine or xylazine and romifidine, which is consistent with our study.[4] Laporte JA, et al. also reported that although anesthesia prevents conscious perception of pain, surgical manipulations serve as stimuli that induce changes in vital signs, such as increased blood pressure, heart rate, and brain activity changes.[21,22] Moreover, anesthetics effectively induce unconsciousness, but their analgesic effect during the recovery period is not widely reported. Our research endorses the potential of analgesics in combination with anesthetics to optimize peri-anesthetic stability. Moreover, Metry, et al. stated that cardiopulmonary function monitoring in animal models during and after surgery in the postoperative period is crucial for assessing the effectiveness of balanced anesthesia.[23]

In conclusion, the administration of a preemptive regimen effectively reduces the recovery time and facilitates a seamless recovery from general anesthesia in the somatic surgical pain model. We encourage the replication of this surgical model in different settings to corroborate our findings. Moreover, a preemptive regime should be investigated in human to reduce the hazards and side effect of anesthesia and for smooth recovery of patients post-surgery especially in elder and hypertensive patients.

Limitation of our study: Male rats were not part of this study, and manual monitoring of heart rate and breathing rate was done due to limited resources.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	SM, NB
Acquisition, Analysis or Interpretation of Data:	SM, NB, SHH, NW, SS, SM
Manuscript Writing & Approval:	SM, NB, SHH, NW, SS, SM

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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