

The Effects of Acetaminophen and Dexmedetomidine in Pain Threshold Sensitivity Following Temporal Traumatic Brain Injury in Rats

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Abstract

Background and Objective: High incidences of traumatic brain injury worldwide impact life outcomes beyond death, including cognitive changes, motor deficits and sensory abnormalities. TBI in rat models frequently results in heightened pain sensitivity, termed hyperalgesia or allodynia. After TBI, these animals often exhibit exaggerated responses to mild pain stimuli, mimicking chronic pain observed in human TBI patients. This study aimed to assess the effects of dexmedetomidine and acetaminophen on pain sensitivity thresholds in a rat model of traumatic brain injury and compare their analgesic efficacy with an untreated control group during the early post-injury period. Administration of dexmedetomidine or acetaminophen following traumatic brain injury would increase pain sensitivity thresholds compared with controls, restoring pain responses toward baseline levels.

Subject and Method: This animal experimental laboratory study used a pretest and posttest control group design. A TBI rat model was developed using the Feeney weight drop model with potential energy impact of 0.392 J. Samples received analgesic agents according to group intravenously every 8 hours for three days. Pain thresholds were measured before and after treatment at 1 hour, 6 hours, 24 hours, 72 hours, and 7 days after TBI.

Results: Following temporal traumatic brain injury, pain thresholds were identical at baseline and immediately post-injury (Von Frey score 6.65) but declined thereafter, indicating increased pain sensitivity. The mean score decreased to 5.91 at 1 hour and reached its lowest levels at 6–24 hours post-injury (4.47–4.56), before partially recovering at 72 hours (5.06) and approaching baseline by day 7 (5.67). Both paracetamol and dexmedetomidine significantly attenuated post-injury pain hypersensitivity compared with controls. At 24 hours, pain thresholds were markedly lower in controls (3.66 ± 0.20) than in the paracetamol (4.99 ± 0.16) and dexmedetomidine groups (5.03 ± 0.13), with this difference persisting through day 7. Overall analysis confirmed significant effects of time and treatment (Friedman $\chi^2 = 183.64$, $p < 0.001$). Post hoc testing showed that both paracetamol and dexmedetomidine increased pain thresholds compared with control ($p < 0.001$), with no significant difference between the two agents ($p = 0.58$).

Conclusion: Rats receiving dexmedetomidine or acetaminophen exhibited higher pain sensitivity thresholds than the control group at multiple post-injury time points. Pain thresholds in both treatment groups increased over time and were closer to baseline values by day 7, while thresholds in the control group remained lower. No statistically significant difference in pain sensitivity threshold was detected between the dexmedetomidine and acetaminophen groups.

Keywords: Pain sensitivity, traumatic brain injury, von frey test

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Introduction

Traumatic brain injury (TBI) defined as a change in brain function or evidence of brain pathology

caused by external mechanical trauma.¹ TBI is a major cause of disability and death worldwide. The annual incidence of TBI is estimated to vary between 27 and 69 million events globally. Based on the 2018 Basic Health Research (Riskesdas)

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report, head injury was the third most common injury with a proportion of 11.9% after lower limb and upper limb injuries.²

Survivors live with significant disability, the consequences other than death include cognitive changes, motor deficits, and sensory abnormalities making them a socioeconomic burden. Acute pain related to tissue damage lasts for several weeks and is expected to subside as healing process begins. Chronic pain, on the other hand, can persist for 3 to 6 months or longer and might not related to tissue damage as is the case with acute pain.³ A review of 23 studies involving 4,200 TBI patients found that 51% of TBI survivors experienced chronic pain, which was self-reported, suggesting that many more cases are actually occurring but not reported.⁴ Analgesic agents' mechanism of action found in various pain pathways, both in the transmission, modulation and perception phases. Acetaminophen is a weak inhibitor of COX with several receptors in the brain and spinal cord making it as the agent of choice in headache management along with its safety profile. Meanwhile, dexmedetomidine works on post-synaptic neuron terminals through α_2 receptors generating analgesic and sedative effect on the recipient. The exact mechanism of pain in TBI has not been established, while acute pain that is not handled properly will become chronic pain in the future. So that pain management in the early stages after TBI becomes mandatory. This study was aimed to assess the effects of dexmedetomidine and acetaminophen on pain sensitivity thresholds in a rat model of traumatic brain injury and to compare their analgesic efficacy with an untreated control group during the early post-injury period

Methods

This study was an experimental laboratory analytical test which allow researchers to measure the effect of treatment (intervention) on the experimental group by comparing the control group with the acetaminophen and dexmedetomidine treatment groups. At the beginning of the study, sample homogenization was carried out for 7 days and continued with randomization for the

division of the control group and the treatment groups. Measurement of pain thresholds was carried out before and after treatment in several time intervals, which were 1 hour, 6 hours, 24 hours, 72 hours, and 7 days after TBI. This research was conducted at the Experimental Animal Laboratory of the Faculty of Veterinary Medicine of Syiah Kuala University, where the ethical clearance approval also coming from the institution's ethics committee.

The samples were white rats (*Rattus norvegicus*) Wistar strain aged 4–8 weeks, with a body weight of 100–250 grams in healthy condition. TBI treatment used a modification of the Feeney Traumatic Brain Injury (TBI) weight drop model⁵ method, by dropping a 100-g weight with a 1.0-cm diameter from a height of 40 cm with potential energy impact 0,392 J onto the right frontoparietal region of the rat's head once. Before TBI induction, the rats were given a topical anesthetic ointment containing lidocaine HCl to reduce pain. Experimental animals were considered to have mild TBI (the desired level) based on clinical observation and palpation revealing head swelling, followed by incoordination and purposeless walking. Moderate TBI was indicated by seizures progressing to immobility or death (severe TBI). Study doses were determined using the Animal Equivalent Dose (AED) based on body weight and species-specific correction factors for rats, resulting in doses of acetaminophen 62 mg/kg and dexmedetomidine 3.1 mcg/kg. Examination of pain threshold sensitivity using the Von Frey Test.⁶

There were 3 groups in this study; group 1 as a negative control which is TBI rat model without any drug intervention; group 2 was TBI rat model which were given acetaminophen at a dose of 62 mg/kg with an interval of 8 hours for 3 days after injury; group 3 was TBI rat model that were given dexmedetomidine at a dose of 3.1 mcg/kg with an interval of 8 hours for 3 days after injury. Administration of analgesic agents was carried out intravenously. Data normality was tested with Shapiro-Wilk test and homogeneity with Levene test. If the data was normally distributed, then it was analyzed using the repeated ANOVA test, if the data was not normally

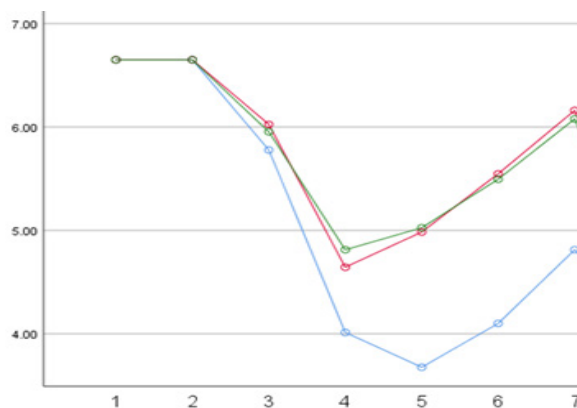
distributed, then to see the differences between treatments, needed to be seen, the Friedman test was carried out. In this study, all research data were analyzed using the SPSS program.

Results

Each Von Frey evaluator size has different compressive energy to the rat's plantar. The smaller the size causing plantar withdrawal reaction (paw withdrawal) indicates the more sensitive the rat's sensory assessment result, in

Table 1. Descriptive Statistics

Assessment timing	Mean	Confidence Interval 95%	
		Minimum value	Maximum value
Baseline	6.65	6.65	6.65
Post TBI	6.65	6.65	6.65
1 hour	5.91	5.46	6.45
6 hours	4.47	3.84	4.93
24 hours	4.56	3.22	5.18
72 hours	5.06	3.84	5.88
7 days	5.67	4.56	6.45



Information:

1 = baseline
2 = post TBI

3 = 1 hour post TBI

4 = 6 hours post TBI

5 = 24 hours post TBI

6 = 72 hours post TBI

7 = 7 days post TBI

Blue line = control group

Red line = acetaminophen group

Green line = dexmedetomidine group

other words, a low pain threshold. Conversely, the larger the evaluator size that causes paw withdrawal indicates a high pain threshold. Following temporal traumatic brain injury (TBI), baseline and immediate post-injury pain thresholds were identical across all groups, with a mean Von Frey score of 6.65. After injury, a clear reduction in pain threshold was observed, indicating increased pain sensitivity. The mean Von Frey score decreased to 5.91 at 1 hour post-injury, followed by a marked decline at 6 hours (4.47) and reaching its lowest level at 24 hours (4.56). Thereafter, partial recovery was noted at 72 hours (5.06), and by 7 days post-injury the pain threshold had nearly returned to baseline values (5.67), suggesting resolution of the acute pain-sensitive phase of TBI.

When analyzed by treatment group, both paracetamol and dexmedetomidine consistently demonstrated higher pain thresholds compared with the control group from 6 hours onward. At 6 hours post-injury, mean pain thresholds were 3.99 ± 0.15 in controls, 4.63 ± 0.20 in the paracetamol group, and 4.80 ± 0.13 in the dexmedetomidine group. This difference persisted at 24 hours (3.66 ± 0.20 vs 4.99 ± 0.16 and 5.03 ± 0.13 , respectively) and at 72 hours (4.12 ± 0.18 vs 5.53 ± 0.28 in both intervention groups). By day 7, the paracetamol (6.15 ± 0.18) and dexmedetomidine (6.08 ± 0.23) groups showed pain thresholds approaching baseline, whereas the control group remained lower (4.80 ± 0.13). This indicates that an increase in pain threshold sensitivity occurred in the intervention group. To determine the significant differences across groups, a post hoc test was conducted.

In table 3, the control group compared with acetaminophen and dexmedetomidine has lower sensory measurement results which means that the pain threshold sensitivity of the control group is significantly lower in all measurement values compared to the acetaminophen group and the dexmedetomidine group. Then the acetaminophen group is compared with the control and dexmedetomidine. It appears that the sensory measurement results of the acetaminophen group are 0.6227 higher at the lower limit and

Table 2. Descriptive Statistics Based on Intervention's Groups

Sensory Assessment	Groups	Mean	Deviation standart	N
Baseline	Control (K1)	6.65	0.000	9
	Acetaminophen (K2)	6.65	0.000	9
	Dexmedetomidine (K3)	6.65	0.000	9
Post TBI	Control (K1)	6.65	0.000	9
	Acetaminophen (K2)	6.65	0.000	9
	Dexmedetomidine (K3)	6.65	0.000	9
1 hour post TBI	Control (K1)	5.81	0.281	9
	Acetaminophen (K2)	5.96	0.360	9
	Dexmedetomidine (K3)	5.97	0.267	9
6 hours post TBI	Control (K1)	3.99	0.149	9
	Acetaminophen (K2)	4.63	0.199	9
	Dexmedetomidine (K3)	4.80	0.132	9
24 hours post TBI	Control (K1)	3.66	0.203	9
	Acetaminophen (K2)	4.99	0.156	9
	Dexmedetomidine (K3)	5.03	0.125	9
72 hours post TBI	Control (K1)	4.12	0.184	9
	Acetaminophen (K2)	5.53	0.280	9
	Dexmedetomidine (K3)	5.53	0.280	9
7 days post TBI	Control (K1)	4.80	0.132	9
	Acetaminophen (K2)	6.15	0.182	9
	Dexmedetomidine (K3)	6.08	0.233	9

Table 3. Post Hoc Test

Groups	Groups	95% Confidence Interval				
		Mean Difference	Std. Error	Sig.	Lower Bound	Upper Bound
K1 (control)	K2 (acetaminophen)	-.6968	.03590	.000	-.7709	-.6227
	K3 (dexmedetomidine)	-.7170	.03590	.000	-.7911	-.6429
K2 (acetaminophen)	K1 (control)	.6968	.03590	.000	.6227	.7709
	K3 (dexmedetomidine)	-.0202	.03590	.580	-.0942	.0539
K3 (dexmedetomidine)	K1 (control)	.7170	.03590	.000	.6429	.7911
	K2 (acetaminophen)	.0202	.03590	.580	-.0539	.0942

0.7709 higher at the upper limit compared to the control group. However, the acetaminophen group compared with dexmedetomidine showed results that acetaminophen is lower by 0.0942 at the lower limit but higher by 0.0539 at the upper limit compared to dexmedetomidine, where the p value showed the difference was not statistically

significant. Finally, the dexmedetomidine group showed higher sensory measurement results of 0.6429 at the lower limit and 0.7911 higher at the upper limit compared to the control. However, the dexmedetomidine group had lower sensory measurement results of 0.0539 at the lower limit and 0.0942 higher at the upper limit compared

to the acetaminophen group, where the *p* value showed the difference was not statistically significant. Statistical analysis confirmed a significant effect of time and treatment on pain sensitivity. The Friedman test demonstrated a highly significant difference in pain thresholds across groups and time points ($\chi^2 = 183.64$, *df* = 7, *p* < 0.001). Post hoc analysis revealed that both paracetamol and dexmedetomidine significantly increased pain thresholds compared with the control group (mean differences -0.70 and -0.72 , respectively; both *p* < 0.001). In contrast, no statistically significant difference was found between paracetamol and dexmedetomidine (mean difference -0.02 , *p* = 0.58). Overall, these findings indicate that both paracetamol and dexmedetomidine effectively attenuate post-TBI pain hypersensitivity, with comparable analgesic efficacy.

Discussion

This study demonstrated that traumatic brain injury (TBI) lead to a significant decrease in pain threshold sensitivity in rats, as measured by the Von Frey filament test. Following TBI induction, the average pain threshold decreased markedly within the first 6–24 hours and gradually improved by 72 hours, approaching baseline values. Administration of acetaminophen or dexmedetomidine significantly increased pain threshold sensitivity compared with untreated controls (*p* < 0.05). At 7 days post-TBI, animals receiving either analgesic showed pain thresholds close to baseline, whereas reduced pain thresholds persisted in untreated animals. No significant difference was observed between acetaminophen and dexmedetomidine in their analgesic efficacy (*p* > 0.05).

These findings are consistent with prior animal and clinical studies reporting increased mechanical allodynia and sensory hypersensitivity following TBI. Approximately 40% of TBI patients experience heightened cutaneous sensitivity to mechanical stimuli, a phenomenon not observed under normal conditions. Experimental rat studies demonstrated reduced tactile pain thresholds that began to recover two weeks after injury, while

Fernando et al. reported early periorbital allodynia associated with TRPV1 pathway activation.^{7,8}

Additionally, perfusion studies in humans have identified the thalamus as a highly vulnerable structure in TBI, with damage contributing to persistent post-traumatic pain. Altered dopamine signaling, synaptic dysfunction, and hyperexcitability in pain-related brain regions such as the hippocampus, amygdala, and cortex further support the development of chronic pain following TBI.⁹ TBI triggers a strong neuroinflammatory response characterized by activation of NF- κ B, increased levels of TNF- α , IL-1 β , IL-6, iNOS, and nitric oxide, which contribute to secondary injury and pain sensitization.¹⁰ Inflammatory mediators peak within the first 24 hours post-injury and gradually decline thereafter, paralleling changes in pain threshold sensitivity observed in this study.¹¹ Dexmedetomidine, a highly selective α_2 -adrenergic agonist, exerts sedative, analgesic, anxiolytic, anti-inflammatory, and neuroprotective effects. It inhibits NF- κ B activation, reduces pro-inflammatory cytokines (TNF- α , IL-6, IL-8), suppresses ERK1/2 signaling, inhibits iNOS expression, preserves blood–brain barrier integrity, and reduces cerebral edema and apoptosis.¹² Acetaminophen produces central analgesia, in part through its metabolite AM404, which modulates TRPV1 receptors in the dorsal horn of the spinal cord. TRPV1 and TRPA1 receptors play a key role in TBI-related neurogenic inflammation by increasing microvascular permeability and edema.¹³ Experimental evidence shows that reduced TRPV1 signaling decreases inflammatory markers, astrocyte activation, and blood–brain barrier disruption, thereby reducing post-traumatic pain. The analgesic effects of acetaminophen via TRPV1 modulation are therefore particularly relevant in the context of TBI-induced inflammatory sensitization.¹⁴

The results suggest that early administration of acetaminophen or dexmedetomidine after TBI can effectively attenuate pain hypersensitivity and facilitate recovery of pain thresholds, potentially reducing the risk of chronic post-traumatic pain. Given their comparable efficacy,

both agents represent viable analgesic options in the management of TBI-associated pain. Dexmedetomidine may offer additional benefits due to its neuroprotective and anti-inflammatory properties, while acetaminophen provides effective central analgesia through TRPV1-mediated mechanisms. These findings support the importance of early analgesic intervention as part of a comprehensive strategy to prevent long-term pain complications following traumatic brain injury. There are limitations related to this study. Sensory pain threshold assessment after traumatic brain injury was not accompanied by serum biomarker measurements that could strengthen the sensory findings, nor by post-injury motor and behavioral evaluations that could be correlated with overall quality-of-life outcomes in patients with traumatic brain injury.

Conclusion

Traumatic brain injury treatment decreased pain threshold sensitivity in all groups, with the lowest decrease seen at 6 hours and 24 hours post-trauma. There was no significant difference in the increase in pain threshold sensitivity between the dexmedetomidine group when compared with the acetaminophen group. The control group had a pain threshold that did not approach the baseline value on the 7th day before traumatic brain injury treatment was carried out, resulting in a mechanical allodynia response.

Conflict of Interest

The author declared no conflict of interest.

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