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ORIGINAL ARTICLE

COMPARISON BETWEEN THE ANALGESIC EFFECT OF TIZANIDINE, DICLOFENAC AND GABAPBENTIN ON EXPERIMENTALLY INDUCED ACUTE AND CHRONIC PAIN IN MALE ALBINO RATS

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ABSTRACT

Background: Pain is an unpleasant sensation experienced when tissues are damaged. Therapeutic management of pain requires consideration of many factors due multiplicity of etiopathogenesis.
Objectives: The present study was designed to assess and compare the analgesic effects of gabapentin, diclofenac and tizanidine as well as their combinations in acute and chronic pain.
Methods: 128 rats were randomly allocated into two main equal categories; one for acute inflammatory and other for chronic neuropathic pain study. The acute category was divided into 8 equal groups**;** control, carrageenan, diclofenac, gabapentin, tizanidine, gabapentin-diclofenac, gabapentin-tizanidine and tizanidine-diclofenac groups. Acute inflammatory pain was induced by carrageenan injection in the animals paw. In the chronic category neuropathic pain was induced by right sciatic nerve ligation except for control and sham groups. This category was divided into; control, sham, gabapentin, tizanidine, gabapentin-diclofenac, gabapentin-tizanidine and tizanidine-diclofenac groups. The mean reaction time was assessed in all groups.
Results: In acute pain the three drugs and their combinations had significant analgesic effects. Tizanidine potentiated the analgesic effects of diclofenac and gabapentin. In chronic neuropathic pain diclofenac and gabapentin had significant analgesic action while, tizanidine had no analgesic effect.
Conclusion: Tizanidine didn't show analgesic effect on chronic pain but potentiated the analgesic effect of gabapentin and diclofenac in acute pain model.
Key words: Acute pain, Neuropathic pain, Diclofenac, Gabapentin, Tizanidine.

INTRODUCTION

Pain is an unpleasant sensation but may protect body from imminent threat or injury [(1)]. Acute pain has sudden onset, with severe intensity, but short-lasting (less than 30 days) [(2)]. Chronic pain was defined as persistent or recurrent pain lasting longer than 3 months or past the time of normal healing [(3)]**.** The cause of pain is irritation of nociceptors. Nociceptors are free nerve endings that respond to painful stimuli. Nociceptors are highly found in skin called exteroceptors. Also they are found in organ of motion, cornea of the eye and dental pulp, also abundant in the meninges, pleura, peritoneum and organ capsule and are called interoceptors [(4)]. Nociceptors are stimulated by biological, electrical, thermal, mechanical, and chemical stimuli. They transmit information to the central areas of the brain and pain perception occurs [(5)].

Diclofenac, a member of non-steroidal anti-inflammatory drugs (NSAIDs), is the most

extensively used for inflammatory conditions as the drug affords quick relief of pain [6].

Gabapentin, analog of gamma amino butyric acid GABA is used for the treatment of seizures and postherpetic neuralgia as well as acute and neuropathic pain [7].

Tizanidine, a centrally acting skeletal muscle relaxant is an α_2-agonist that acts mainly at spinal and supraspinal levels to inhibit excitatory interneurons [8].

The present study was carried out to assess and compare the analgesic effect of the previous three drugs: tizanidine, diclofenac and gabapentin.

In this study the analgesic effect of these drugs and their combinations was studied and compared on experimentally induced acute inflammatory pain and chronic neuropathic pain in male albino rats.

MATERIALS AND METHODS

Animals

128 adult male albino rats weighing 150–200 gm were used in this study. Animals were purchased from the Faculty of Veterinary Medicine, Zagazig University, Egypt. Rats were allowed standard pellet diet and tap water. They were kept at a constant temperature (23 ±2°C) and a light/ dark (12 h: 12 h) cycle. Rats were randomly assigned to experimental groups. All tests were performed between 8.00 and 15.00 h. The experiments were performed in the pharmacology department laboratory, faculty of medicine, Zagazig University. Experimental design and animal handling were performed in accordance with protocols approved by the local experimental ethics committee guidelines of the Egyptian Society of Neuroscience, the Ethical Committee of the Faculty of Medicine, Zagazig University, for Animal Use and the guidelines of the US National Institutes of Health on animal care. Experiments complied with the ARRIVE guidelines and was carried out in accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) .

Drugs and chemicals:

Tizanidine powder **[Novarts Co., Egypt].**

Diclofenac Na 75mg ampoule **[Novarts Co., Egypt].**

Gabapentin powder **[Pfizer Co., Egypt].**

Carrageenan powder **[Sigma co., Egypt].**

Thiopental, 500mg vial **[Sigma co., Egypt].**

Tizanidine and Gabapentin were dissolved in normal saline just before injection [9],[10].

Carrageenan was dissolved in distilled water just before injection [11].

Tools:

Analgesia Meter 11TC Model 390 Paw Stimulator {Woodland hills, C.A., U.S.A}.

Induction of acute inflammatory pain:

This occurs by local sub-planter injection of carrageenan (0.05 ml of 1% suspension) [12] 2hrs before injection of the drugs. Then the animal was exposed to the analgesia meter to measure the reaction times.

Induction of chronic neuropathic pain:

This occurs by unilateral ligation of the sciatic nerve in the thigh under general anesthesia by intraperitoneal (i.p.) injection of thiopental, 40 mg/kg [13]. In sham operated group, the nerve was dissected and isolated at the mid-thigh without ligation to evaluate the effect of surgical intervention on the reaction time [14].

Experimental design

Acute inflammatory pain:

64 rats were classified into: **Control group:** injected with distilled water. **Control post-carragenan group, Diclofenac group:** injected with 0.24 ml ip diclofenac (30 mg/kg) [15]. **Gabapentin group:** injected with 0.2 ml ip gabapentin (100 mg/kg) [9]. **Tizanidine group:** injected with 0.2 ml ip tizanidine (1 mg/kg) [16]. **Gabapentin-diclofenac group**, **Tizanidine-gabapentin group and Tizanidine-diclofenac group.**

In the control group reaction time was measured after injection with distilled water. In the control post-carrageenan group reaction time was measured after 2 hours of carrageenan injection. In other groups drugs were injected

2hrs post carrageenan and reaction time was measured after 30, 60, 90 and 120 min. of injection of the drugs.

Chronic neuropathic pain:

64 rats were classified into: **Control group:** injected with distilled water. **Sham operated group, Sciatic nerve ligation groups: Diclofenac, Gabapentin, Tizanidine, Gabapentin-diclofenac, Tizanidine-gabapentin and Tizanidine-diclofenac.** All drugs were administered by i.p. injection and the same doses as acute pain.

Before the operation of sciatic nerve ligation all groups received ip injection with saline and the reaction times were measured (as a control pre-operative). Two weeks after the operation the animals received ip injection of distilled water and the reaction times were measured (as a control post-operative). The drugs were injected and after 30, 60, 90 and 120 min. the reaction times were measured.

Statistical analysis:

The obtained Continuous variables were tabulated as means± SD. Comparison between different groups were made using one way analysis of variances (one-way ANOVA) followed by Post-Hoc (least significant difference"LSD") tests [17]. The differences were considered to be significant when $p < 0.05$.

Results:

Effect of diclofenac (30 mg/kg) on acute pain (table 1): Diclofenac produced a significant increase in the mean reaction time (MRT) after 60 and 90 min. (7.9 ± 0.46 sec. and 6.19 ± 0.42 sec.) respectively compared to carrageenan group. Meanwhile there were non-significant increase in the MRT after 30 and 120 min. (4.34 ± 0.22 and 4.24 ± 0.15 sec.) respectively.

Effect of gabapentin (100 mg/kg) on acute pain (table 1): Gabapentin produced a significant increase in the MRT after 30, 60and 90 min. (7.5±1.21, 7.05±0.95, 6.12±0.87 sec.) respectively compared to carrageenan group. Meanwhile non-significant increases in the MRT after 120 min. (3.95 ± 0.56 sec.) was observed.

Effect of tizanidine (1 mg/kg) on acute pain (table 1): Giving tizanidine ip significantly increased the MRT after 30 and 60 min. (3.93 ± 0.27 and 5.42 ± 0.32 sec.) respectively compared to the carrageenan group. Meanwhile there were non-significant increases in the MRT after 90 and 120 min. (3.52 ± 0.29 and 3.51 ± 0.26 sec.) respectively.

Percentage changes in MRT compared to the post-carrageenan control after ip injection of diclofenac, gabapentin and tizanidine on acute pain (table 2): Diclofenac and gabapentin produced significant increase in the percentage changes of MRT after 30, 60 and 90 min. (18.9 ± 0.71 %↑and 114.29 ± 0.7 %↑),(116.44± 5.01%↑ and 101.43 ±6.33 %↑) and (69.59± 3.17 %↑ and 74.86 ± 3.18 %↑) compared to tizanidine (29.7 ± 1.61 %↑), (78.88± 1 %↑) and (16.17 ± 1.3 %↑) respectively. Meanwhile there were non-significant differences between the different groups at 120 min. (16.16 ± 1.92%↑, 12.86 ± 3.17%↑ and 15.84± 3.1 %↑) respectively.

Effect of ip gabapentin (100 mg/kg) and diclofenac (30 mg/kg) on acute pain (table 1): Gabapentin and diclofenac produced significant increase in the MRT after 30, 60 and 90 min. (7.05 ± 0.36, 8.65 ± 0.28 and 5.78 ± 0.34 sec.) respectively compared to the post-carrageenan control. Meanwhile there were non-significant increases in the MRT after 120 min. (3.98 ± 0.16 sec.).

Effect of ip gabapentin (100 mg/kg) and tizanidine (1 mg/kg) on acute pain (table 1): Gabapentin and tizanidine produced significant increase the MRT after 30, 60 and 90 min (8.18 ± 0.42, 7.6 ± 0.31 and 6.44 ± 0.23 sec.) respectively compared to the carrageenan group. Meanwhile there were non-significant increases in the MRT after 120 min. (3.85 ± 0.24).

Effect of ip tizanidine (1 mg/kg) and diclofenac (30 mg/kg) on acute pain (table 1): Diclofenac and tizanidine produced significant increase in MRT after 30, 60 and 90 min (4.73 ± 0.14, 8.58 ± 0.19 and 6.28±0.46 sec.) respectively compared to the carrageenan

group. Meanwhile there were non-significant increases after 120 min (4.05 ± 0.18 sec.).

Percentage changes in the MRT compared to the post-carragenan control after ip injection of {gabapentin+ diclofenac}, {gabapentin + tizanidine} and {diclofenac + tizanidine} on acute pain (table 3): After 30 and 60 min. they all produce significant increase in the percentage changes of the MRT compared to the post-carrageenan control (93.15 ± 1 %↑, 122.28 ± 6.96 %↑ and 25.13 ± 1.61 %↑) and(136.99 ± 2 %↑,106.52 ± 1.92 %↑ and 126.98 ± 3.81 %↑) respectively.

At 90 min. both the (gabapentin + diclofenac), and (diclofenac + tizanidine) produced non-significant differences in the percentage changes of the MRT (58.36 ± 3.22 %↑) and (66.14±3.17 %↑) respectively. But they significantly differ from (gabapentin + tizanidine) (75 ± 1.7 %↑).

At 120 min. the 3 combinations produced non-significant increase (9.04 ± 0.7 %↑) (4.62 ± 1.2 %↑) and (7.14 ± 1.51 %↑) respectively.

Effect of ip diclofenac (30 mg/kg) on chronic pain (table 4): Giving diclofenac ip significantly increased the MRT compared to the post-operative control after 30, 60 and 90 min. (9.05±0.57, 13.1 ± 0.83 and 15.06 ± 0.59 sec.) respectively. Meanwhile there were non-significant increase after 120 min. (7.48 ± 0.56 sec.).

Effect of ip gabapentin (100 mg/kg) on chronic pain (table 4): Giving gabapentin ip significantly increased the MRT after 60 and 90 mins. (17.15 ± 1.15 and 12.42 ± 1.77 sec.) respectively compared to the post-operative control. Meanwhile MRT was non-significant after 30 and 120 mins. (8.09 ± 1.02 and 5.81 ± 0.38 sec.).

Effect of ip tizanidine (1 mg/kg) on chronic pain (table 4): Tizanidine ip produced non-significant increases in the MRT after 30, 60, 90 and 120 min (4.75 ± 0.32, 5 ± 0.39, 5.34 ± 0.49 and 4.8 ± 0.29 sec.) respectively compared to the post-operative control (4.7 ± 0.29 sec.).

Percentage changes in MRT compared to the control post-operative after ip injection of diclofenac, gabapentin and tizanidine on chronic pain (table 5): The percentage changes of the MRT were significantly increased after 30, 60 and 90 min. of ip injection of diclofenac and gabapentin compared to the corresponding values produced by tizanidine at the same times (43.65 ± 4.21 %↑ ,40.2 ± 3.18 %↑ ,and 1.06 ± 0.31 %↑), (107.94± 2.24 %↑, 197.23 ±0.71 %↑and 6.38± 1.14 %↑) and (139.05± 2.86 %↑, 115.25 ± 4.78 %↑and 13.62 ± 1 %↑) respectively. Meanwhile at 120 minutes the percentage changes in the reaction times of diclofenac (18.73 ± 2.61 %↑) significantly differ from both gabapentin and tizanidine which produce non-significant increase compared to themselves and to their post-operative control (0.69 ± 0.07 %↑) and (2.13 ± 0.31 %↑) respectively.

Effect of gabapentin (100 mg/kg) and diclofenac (30 mg/kg) ip injection on chronic pain (table 4): Gabapentin + diclofenac ip produced significant increase in MRT compared to the post-operative control after 30, 60 and 90 min. (15.59 ± 1.44, 24.01 ± 1.45 and 13.45 ± 0.85 sec.) respectively. Meanwhile there were non-significant increases after 120 min. (5.5±0.48 sec.).

Effect of gabapentin (100 mg/kg) and tizanidine (1 mg/kg) ip injection on chronic pain (table 4): Giving gabapentin + tizanidine ip significantly increased the MRT compared to the post-operative control (6.63 ± 0.22, 8.78 ± 0.45 and 7.7 ± 0.47 sec.) after 30, 60 and 90 min. respectively. Meanwhile there were non-significant increases after 120 minutes (4.15 ± 0.25 sec.).

Effect of tizanidine (1 mg/kg) and diclofenac (30 mg/kg) ip injection on chronic pain (table 4): Diclofenac + tizanidine ip produced significant increase in MRT compared to the post-operative control after 30, 60 and 90 min. (5.83 ± 0.29, 8.08 ± 0.71and 9.15 ± 0.65 sec.) respectively. Meanwhile there were non-significant increases after 120 min. (4.28 ± 0.23 sec.).

Percentage changes in MRT compared to the post-operative control after ip injection of {gabapentin + diclofenac}, {gabapentin + tizanidine} and {diclofenac+ tizanidine} on

chronic pain (table 6): All the values are significant to each other after 30,60 and 90 min. (208.1 ± 2.7 %↑, 70 ± 7.07 %↑ and 39.47 ± 4.25 %↑),(374.51 ± 3.41 %↑, 125.13 ± 8.06 %↑ d 93.3 ± 3.3 %↑) and (156.81 ± 3.53 %↑,97.44 ± 2.72 %↑ and 118.9 ± 2.7 %↑) respectively. Meanwhile at 120 min., all combinations produced non-significant increase compared to themselves and to their post-operative control (8.69±0.7%↑),(2.56 ± 2.12 %↑) and (2.39 ± 0.71 %↑) respectively.

Table (1):Effect of ip. injection of diclofenac (30 mg/kg), gabapentin (100 mg/kg), tizanidine (1 mg/kg) and their combinations on acute inflammatory pain in rats

Group N=8	Control normal MRT±SE	2 hr post-carrageenan MRT±SE	At 30 min. MRT±SE	At 60 min. MRT±SE	At 90 min. MRT±SE	At 120 min. MRT±SE
Diclofenac treated	**10.75±0.37 A**	**3.65±0.31 B**	**4.34±0.22 B**	**7.9±0.46 C**	**6.19±0.42 D**	**4.24±0.15 B**
Gabapentin treated	**9.71±0.71 A**	**3.5±0.67 B**	**7.5±1.21 AC**	**7.05±0.95 AC**	**6.12±0.87 CD**	**3.95±0.56 BD**
Tizanidine treated	**11.1±0.35 A**	**3.03±0.32 B**	**3.93±0.27 C**	**5.42±0.32 D**	**3.52±0.29 BC**	**3.51±0.26 BC**
gabapentin + diclofenac	**10.7±0.64 A**	**3.65±0.26 B**	**7.05±0.36 C**	**8.65±0.28 D**	**5.78±0.34 E**	**3.98±0.16 B**
gabapentin + tizanidine	**10.34±0.31 A**	**3.68±0.34 B**	**8.18±0.42 C**	**7.6±0.31 C**	**6.44±0.23 D**	**3.85±0.24 B**
tizanidine + diclofenac	**10.2±0.38 A**	**3.78±0.2 B**	**4.73±0.14 C**	**8.58±0.19 D**	**6.28±0.46 E**	**4.05±0.18 BC**

* Values represent the mean of the reaction times (MRT) in sec. ± standard error (SE).
* Values without common subscript capital letters are significantly different in relation to each other.
* N =the number of animals in each group.

Table (2): Percentage changes in the mean reaction times after ip injection of diclofenac (30 mg/kg), gabapentin (100 mg/kg) and tizanidine (1 mg/kg) on acute inflammatory pain induced by carrgeenan in rats:

Group (N=8) Time	Diclofenac treated	Gabapentin treated	Tizanidine treated
At 30 min.	**18.9 ± 0.71 %↑ A**	**114.29 ± 0.7%↑ B**	**29.7 ± 1.61 %↑ C**
At 60 min.	**116.44± 5.01%↑ A**	**101.43 ±6.33%↑ B**	**78.88± 1 %↑ C**
At 90 min.	**69.59± 3.17 %↑ A**	**74.86 ± 3.18%↑ A**	**16.17 ± 1.3 %↑ B**
At 120 min.	**16.16 ± 1.92%↑ A**	**12.86 ± 3.17%↑ A**	**15.84± 3.1 %↑ A**

* Values represent percentage increase of the mean of the reaction times in sec. in relation to the post-carrageenan control ± standard error (SE).

* In the same horizontal line values without common subscript capital letters are significantly different in relation to each other.
* N = the number of animals in each group.
* %↑ = percentage increase in the MRT in relation to the post-carrageenan control.

Table (3): Percentage changes in the MRT compared to the post-carragenan control after ip injection of {gabapentin (100 mg/kg) + diclofenac (30 mg / kg)}, {gabapentin (100 mg/kg) + tizanidine (1 mg/kg)} and {diclofenac (30 mg / kg) + tizanidine (1 mg/kg)} on acute inflammatory pain induced by carrageenan in rats

Group (N=8) Time	Gabapentin+diclofenac Treated	Gabapentin+tizanidine treated	Tizanidine+diclofenac Treated
At 30 min.	93.15 ± 1 %↑ A	122.28 ± 6.96 %↑ B	25.13 ± 1.61 %↑ C
At 60 min.	136.99 ± 2 %↑ A	106.52 ± 1.92 %↑ B	126.98 ± 3.81 %↑ C
At 90 min.	58.36 ± 3.22 %↑ A	75 ± 1.7 %↑ B	66.14 ± 3.17 %↑ A
At 120 min.	9.04 ± 0.7 %↑ A	4.62 ± 1.2 %↑ A	7.14 ± 1.51 %↑ A

* Values represent percentage increase of the mean of the reaction times in sec. in relation to the post-carrageenan control ± standard error (SE).
* In the same row values without common subscript capital letters are significantly different in relation to each other.
* N = the number of animals in each group.
* %↑ = percentage increase in the MRT in relation to the post-carrageenan control.

Table (4): Effect of ip. injection of diclofenac (30 mg/kg), gabapentin (100 mg/kg), tizanidine (1 mg/kg) and their combinations on chronic neuropathic pain in rats

Group N=8	Control pre-operative MRT±SE	control post-operative MRT±SE	At 30 min. MRT±SE	At 60 min. MRT±SE	At 90 min. MRT±SE	At 120 min. MRT±SE
Diclofenac treated	10.34±0.57 A	6.3±0.34 B	9.05±0.57 AD	13.1±0.83 C	15.06±0.59 E	7.48±0.56 BD
Gabapentin treated	11.39±0.91 A	5.77±0.42 B	8.09±1.02 B	17.15±1.15 C	12.42±1.77 A	5.81±0.38 B
Tizanidine treated	10.37±0.39 A	4.7±0.29 B	4.75±0.32 B	5±0.39 B	5.34±0.49 B	4.8±0.29 B
gabapentin + diclofenac	10.6±0.34 A	5.06±0.46 B	15.59±1.44 C	24.01±1.45 D	13.45±0.85 C	5.5± 0.48 B
gabapentin + tizanidine	10.56±0.3 A	3.9±0.21 B	6.63±0.22 C	8.78±0.45 D	7.7±0.47 E	4.15±0.25 B
tizanidine + diclofenac	10.26±0.26 A	4.18±0.14 B	5.83±0.29 C	8.08±0.71 D	9.15±0.65 AD	4.28±0.23 B

* Values represent the mean of the reaction times (MRT) in sec. ± standard error (SE).
* Values without common subscript capital letters are significantly different in relation to each other.
* N =the number of animals in each group.

Table (5): Percentage changes in the mean of the reaction times compared to the control post-operative after ip injection of diclofenac (30 mg / kg), gabapentin (100 mg/kg) and tizanidine (1 mg/kg) on chronic (neuropathic) pain induced by right sciatic nerve ligation.

Group (N=8) Time	Diclofenac treated	Gabapentin treated	Tizanidine treated
At 30 min.	43.65 ± 4.21 %↑ A	40.2 ± 3.18 %↑ A	1.06 ± 0.31 %↑ B
At 60 min.	107.94±2.24 %↑ A	197.23 ±0.71 %↑ B	6.38± 1.14 %↑ C
At 90 min.	139.05±2.86 %↑ A	115.25 ±4.78 %↑ B	13.62 ± 1 %↑ C
At 120 min.	18.73 ± 2.61 %↑ A	0.69 ± 0.07 %↑ B	2.13 ± 0.31 %↑ B

* Values represent percentage increase of the mean of the reaction times (MRT) in sec. in relation to the control post-operative ± standard error (SE).
* At the same horizontal line values without common subscript capital letters are significantly different in relation to each other.
* N = the number of animals in each group.
***** **%↑** = percentage increase in the reaction times in relation to the post-operative control.

Table (6): Percentage changes in the mean of the reaction times compared to the post-operative control after ip injection of {gabapentin (100 mg/kg) + diclofenac (30 mg / kg)}, {gabapentin (100 mg/kg) + tizanidine (1 mg/kg)} and {diclofenac (30 mg / kg) + tizanidine (1 mg/kg)} on chronic (neuropathic) pain induced in rats by sciatic nerve ligation

Group (N=8) Time	Gabapentin+diclofenac treated	Gabapentin+tizanidine treated	Tizanidine+diclofenac Treated
At 30 min.	208.1 ± 2.7 %↑ A	70 ± 7.07 %↑ B	39.47 ± 4.25 %↑ C
At 60 min.	374.51 ± 3.41 %↑ A	125.13 ± 8.06 %↑ B	93.3 ± 3.3 %↑ C
At 90 min.	156.81 ± 3.53 %↑ A	97.44 ± 2.72 %↑ B	118.9 ± 2.7 %↑ C
At 120 min.	8.69 ± 0.7 %↑ A	2.56 ± 2.12 %↑ A	2.39 ± 0.71 %↑ A

* Values represent percentage increase of the mean of the reaction times (MRT) in sec. in relation to the post-operative control ± standard error (SE).
* At the same horizontal line values without common subscript capital letters are significantly different in relation to each other.
* N = the number of animals in each group.
***** **%↑** = percentage increase in the MRT in relation to the post-operative control.

DISCUSSION

Concerning gabapentin, the current results are in accordance with that obtained with **Abdel-Salam and Sleem,** [18] who evaluated the effect of gabapentin in animal models of acute nociceptive pain. They found that, the reaction

time in a hot plate assay was prolonged by gabapentin. However a study by **Kansal et al., [19]** showed that oral gabapentin didn't produce any marked effect on early phase response of formalin test which represents acute pain. This conflict can be explained on the basis of lower oral doses used in **Kansal's** study 50mg/kg while in the current study higher doses of gabapentin 100mg/kg were used.

Regarding diclofenac, the results of the present study are combatable with that of **Agarwal and Kansal, [20]** who found that diclofenac, at a dose of 5, 10 and 20mg/kg, i.p., produced significant analgesic effect in formalin test, both in phase (1 and 2).

Concerning tizanidine, results of the present study cope with that obtained with **Yazicioglu et al., [21]** who concluded that the addition of tizanidine in postoperative pain therapy decreased postoperative pain, analgesic consumption and improved the return to normal activity. The analgesic effect of tizanidine can be explained on the base that α_2-agonists change neuronal ion channel functioning through multiple mechanisms and finally lead to central modulation of nociceptive transmission.

Combination of gabapentin and diclofenac in acute pain was studied by **Narai et al., [22]** who revealed that gabapentin and diclofenac may be useful for reducing postoperative pain in a rat postoperative pain model. In contrary, **Mao and Gold [23]** found that gabapentin as an addtional therapy neither result in better pain relief, less opioid use, better functional recovery, nor did a combination of gabapentin and meloxicam in pain relief.

The analgesic effects of tizanidine and gabapentin in acute pain was studied by **Tak and Chalkoo, [24]** who demonstrated the good pharmacotherapeutic response to tizanidine in case of persistent myofascial pain, even in more severe cases. The results also suggest that gabapentin is a good alternative in tizanidine resistant patients.

In addition, **Altan et al., [25]** concluded that combination therapy with skeletal muscle relaxants and NSAID is beneficial for pain relief in patients with low back pain as pain and muscle spasm frequently co-exist in acute back pain.

Indeed, **Agarwal and Elsi, [26]** showed that gabapentin is well established for chronic non-pelvic pain conditions, for example, post-herpetic neuralgia, diabetic neuropathy, fibromyalgia, etc which is in line with the present study

Regarding the effect of diclofenac in chronic neuropathic pain the results of the present study cope with **Ahmed et al., [27]** who concluded that 1.5% topical diclofenac may serve as an effective treatment option for patients with neuropathic pain as NSAIDs could modulate the mechanisms of neuropathic pain and provide effective analgesia.

In parallel with the present results, **Park and Moon, [28]** revealed that skeletal muscle relaxants have a limited role for chronic pain treatment. In contrary, **Pei et al., [29]** investigated the anti-nociceptive effect of tizanidine on spared nerve injury induced neuropathic pain. They found that intrathecal administration of tizanidine for 3 consecutive days after injury significantly attenuated the mechanical and thermal hyperalgesia. The findings reported by **Pei et al., (2018)** are in contrast with the results of the current work regarding the analgesic effect of tizanidine in neuropathic pain and this controversy may be attributed to the difference in the route of administration of tizanidine where in the present study tizanidine was given ip in a single dose but in **Pei et al., (2018)** study tizanidine was given intrathecal for 3 consecutive days after injury.

Concerning the drug combination of gabapentin and diclofenac the present results cope with **Ibrahim et al., [30]** who revealed that combination therapy of low dose of either diclofenac with gabapentin showed higher analgesic effect compared with their individual high doses.

Regarding combination of gabapentin and tizanidine, the present results cope with **Cheng [31]** who stated that the addition of α_2-agonists

might enhance GABAergic and glycinergic antinociception and have been applied to chronic pain.

Concerning combination of diclofenac and tizanidine, the addition of a skeletal muscle relaxant to NSAID may be more effective than the analgesic alone. Indeed, **Chou,** [32] concluded that, there was insufficient evidence to determine whether skeletal muscle relaxants are effective for chronic low back pain**.**

In conclusion, tizanidine has analgesic effect in acute pain and potentiated the effect of diclofenac and gabapentin. The later drugs have analgesic action both in acute inflammatory as well as chronic neuropathic pain.

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