ORIGINAL ARTICLE

Comparison of the effects of gabapentin and pregabalin on wound healing in rats

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Abstract

Gabapentinoids are effective adjunct drugs for reducing postoperative pain. However, the effects of gabapentinoids on wound healing have not been evaluated yet. In this study we evaluated their effects on wound healing. A total of 17 male Wistar-Albino rats, 250–350 g, were divided into three groups randomly: control group ($n = 5$, 2 ml saline), gabapentin group ($n = 6$, 20 mg/kg gabapentin) and pregabalin group ($n = 6$, 20 mg/kg pregabalin). Until day 13 inflammation scores were significantly lower ($P < 0.05$) and wound healing was significantly better in the control group when compared with gabapentin and pregabalin groups ($P < 0.001$). Inflammation scores were significantly lower in pregabalin group when compared with gabapentin group until day 13. But wound healing was significantly better in gabapentin group than in pregabalin group between days 13 and 21. In conclusion when gabapentin and pregabalin were compared, although pregabalin decreases inflammation scores, gabapentin has better results in wound healing.

Wound healing is a complicated process in which the tissue repairs itself after injury. The four phases of wound healing are hemostasis, inflammation, proliferation and remodelling (1). However, wound healing is a fragile process and is susceptible to failure which can result in the formation of non-healing chronic wounds. Metabolic diseases such as diabetes mellitus, circulatory diseases, infection, some medications and age may contribute to formation of chronic wounds.

Postoperative pain is one of the most common complaints of surgical patients. According to the literature, pain is treated inadequately in approximately half of the patients (2). Pain is caused by multiple mechanisms. Multimodal analgesia regimen is therefore appropriate for treatment of pain. Drug groups such as opioids, local anaesthetics, non-steroidal anti-inflammatory drugs, paracetamol and gabapentinoids are used for pain therapy (3–6). Gabapentinoids are anticonvulsant drugs. Many researches have been conducted to study their role in acute pain treatment (7–9). Gabapentin and pregabalin are two major drugs of the gabapentinoid group. They are increasingly used as part of multimodal analgesia at perioperative period. They decrease opioid use and postoperative pain (10,11). However, the effects of gabapentinoids on wound healing have not been evaluated yet. In this study we evaluate their effects on wound healing.

Material and methods

Afyonkarahisar University Animal Ethics Committee approved this experimental study (Protocol: 211-13, 05·03·2013). All

> **Key Messages**
> - in this study we evaluated the effects of gabapentinoids on wound healing
> - a total of 17 male Wistar-Albino rats, 250–350 g, were divided into three groups randomly: control group ($n = 5$, 2 ml saline), gabapentin group ($n = 6$, 20 mg/kg gabapentin) and pregabalin group ($n = 6$, 20 mg/kg pregabalin)
> - wound healing was significantly better in the control group at days 3, 9 and 13 ($P < 0·001$) and at day 5 in the control and gabapentin groups ($P < 0·001$)
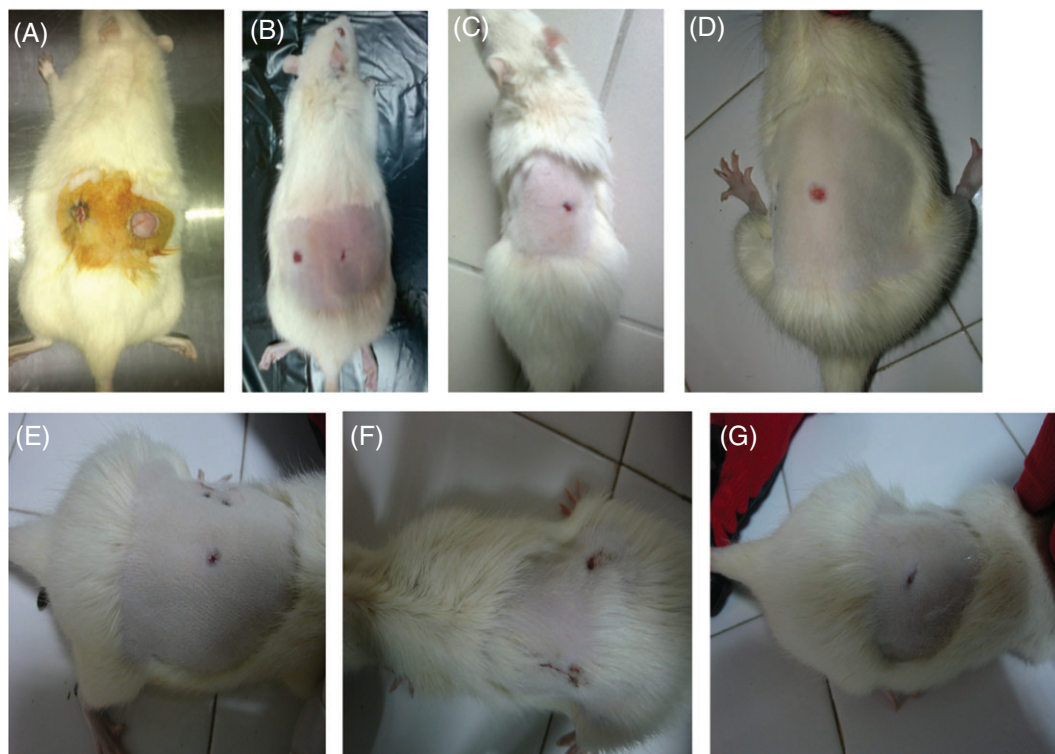
Figure 1 (A) Day 0, control group; (B) day 9, pregabalin group; (C) day 9, control group; (d) day 9 gabapentin group; (E) day 21, control group; (F) day 21 pregabalin group and (g) day 21, gabapentin group.
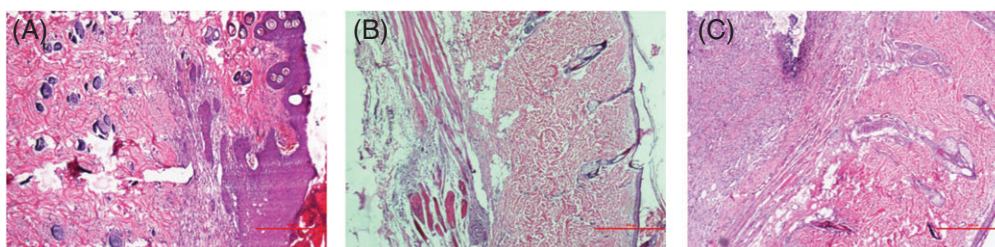

Figure 2 Histopathological sections on day 9. (A) Control group: normal epidermis; (B) pregabalin group: epidermal thinning and moderate inflammation and (C) gabapentin group: epidermal thinning, severe inflammation and connective tissue accumulation.

the experimental manipulations and postoperative care were administered in concordance with National Institutes of Health Guide for the Care and Use of Laboratory Animals. A total of 17 male Wistar-Albino rats, aged 5 months and weighing between 250 and 350 g were divided into three groups randomly: control group ($n = 5$), gabapentin group ($n = 6$) and pregabalin Group ($n = 6$). All the rats were housed in individual cages at 25°C with alternating 12 hour light–dark cycles. All had free access to standard laboratory diet and water. The rats were premedicated with 10 mg/kg intraperitoneal (ip) Xylazine HCl (Rompun vial, 23·32 mg/ml, Bayer Turkish Chemistry Industry Ltd.C., Istanbul, Turkey), and anaesthetised with ip 100 mg/kg Ketamin HCl (Ketalar vial, 50 mg/ml, Eczacibasi Medicine and Commerce A.C., Istanbul, Turkey).

The dorsal surface hair of all rats was shaved bilaterally and the rats were disinfected. No prophylactic or therapeutic antibiotic was administered; 2 cm skin incision was made to the right side of the dorsum of all the rats and then sutured with 2-0 prolene (Dogsan,Trabzon, Turkey) and two mattress sutures in sterile conditions; 1.5 cm diameter round-shaped, full thickness skin patch was removed from the left side of the dorsum of all the rats and dressed with sterile gauzes. All the surgical procedures were performed under aseptic conditions by the same surgeon; 20 mg/kg of gabapentin (Neurontin®; Pfizer, New York) and 20 mg/kg of pregabaline (Lyrica®; Pfizer) diluted with 2 ml saline was administered orally to the gabapentin and pregabaline groups, respectively, by orogastric tube, and only saline was administered to the control group 1 day before the surgery and 9 days after the surgery, once a day. Sutures at the incision sites of all the rats were removed at day 9 and sampling was carried out from the scar tissue under anaesthesia (with same anaesthesia protocol) for histopathological evaluation. Rats were euthanised with ip thiopental 150 mg/kg and tissue sampling
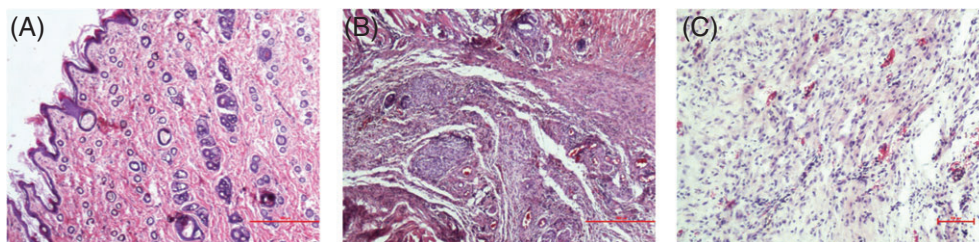
Figure 3 Histopathological sections on day 21. (A) Control group: normal tissue; (B) pregabalin group: moderate inflammation, connective tissue accumulation and vascularisation and (C) gabapentin group: mild vascularisation.

was carried out from scar tissue at day 21 (Figures 1–3). Evaluation of the round-shaped scar tissue healing was done by copying the scar shape on acetate and calculating the surface area at days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Pathological method

Tissue samples were fixed in 10% formaldehyde solution for 24 hours. They were processed and embedded in paraffin blocks and were cut into 5 μm sections with a microtome. After deparaffinisation, sections were prepared for staining with haematoxylin and eosin. A semi-quantitative evaluation was performed in light microscopy at 10× and 40× by two distinct pathologists blinded to the study groups. During the pathological assessment epidermis and dermis were evaluated. Epidermis was evaluated regarding thinning and inflammation [grade 0 = normal (−), grade 1 = mild (+), grade 2 = moderate (++) and grade 3 = severe (+++)]. Dermis was evaluated for the thinning and existence of inflammatory cells in addition to new vessel formation, accumulation of connective tissue matrix and collagen fibres [grade 0 = normal (−), grade 1 = mild (+), grade 2 = moderate (++) and grade 3 = severe (+++)].

Statistical analysis

Data were analysed with the SPSS 16·0 (SPSS Inc, for Windows) software package. A one-way analysis of variance (ANOVA) test was used to compare the wound areas between groups. Test significance levels within and between groups were checked using Duncan's test. For the scores and non-normally distributed variables, comparison between groups was carried out by the Kruskal–Wallis test. Descriptive results are expressed as means ± standard deviation. For all comparative tests, a value of $P < 0.05$ was considered significant.

Results

No animals died in control, gabapentin and pregabalin groups during study period. The thinning, inflammation, new vessel formation, accumulation of connective tissue matrix and collagen fibres were significantly lower in control group compared with pregabalin and gabapentin groups on day 10 in the dermis and epidermis ($P < 0.05$). These were also significantly lower in pregabalin group than gabapentin group on day 10 in the dermis and epidermis ($P < 0.05$). Although there were no significant differences between groups on day 21, the scores were lower in control group than other groups (Table 1).

Table 1 Control, pregabalin and gabapentin groups wound surface area changes at measurement days*

Day	Control ($n = 5$) Wound surface area (cm^2)	Pregabalin ($n = 6$) Wound surface area (cm^2)	Gabapentin ($n = 6$) Wound surface area (cm^2)
0	1·77	1·77	1·77
1	1·50 ± 0·08[a]	1·73 ± 0·09[b]	1·54 ± 0·09[a]
3	0·95 ± 0·10[b]	1·17 ± 0·22[a]	1·24 ± 0·27[a]
5	0·81 ± 0·11[a]	0·97 ± 0·32[b]	0·82 ± 0·15[a]
7	0·71 ± 0·08	0·80 ± 0·22	0·79 ± 0·14
9	0·35 ± 0·08[b]	0·41 ± 0·16[a]	0·42 ± 0·09[a]
11	0·24 ± 0·04	0·30 ± 0·08	0·33 ± 0·09
13	0·17 ± 0·06[b]	0·24 ± 0·06[a]	0·27 ± 0·07[a]
15	0·07 ± 0·04[a]	0·20 ± 0·07[b]	0·17 ± 0·06[c]
17	0·03 ± 0·02	0·08 ± 0·05	0·07 ± 0·03
19	0·003 ± 0·005	0·05 ± 0·21	0·01 ± 0·02
21	0	0·02 ± 0·02	0·003 ± 0·005

*The values with different letters (a, b and c) in the same line show statistical significance ($P < 0.001$).

Table 2 Mean (SD) histopathological scores of the groups at days 9 and 21*

	Day 9		Day 21	
	Epidermis	Dermis	Epidermis	Dermis
Control ($n = 5$)	0·2 ± 0·4[a]	0·4 ± 0·8[a]	0·2 ± 0·4	0·4 ± 0·5
Pregabalin ($n = 6$)	0·6 ± 0·5[ab]	1·8 ± 0·7[b]	0·6 ± 1·2	1·16 ± 1·16
Gabapentin ($n = 6$)	1 ± 0[b]	2·8 ± 0·4[c]	0·3 ± 0·5	0·8 ± 0·4

*The different letters (a, b and c) in the same column show statistical significance ($P < 0.05$).

Healing of the round-shaped scar wounds was also evaluated by copying the scar shape on acetate and by calculating the surface area and decreased surface area at days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21 in the three groups (Table 2). According to these calculations wound healing in the control group was significantly better than pregabalin (PGB) and gabapentin (GBP) groups at days 3, 9 and 13 ($P < 0.001$). At day 5 wound healing in the control and GBP groups was significantly better than PGB group ($P < 0.001$). At day 21 control group scar tissue was healed completely; however, in PGB and GBP groups, scar tissues did not close completely but these disclosures were not statistically significant. On the other hand, healing in GBP group was better than PGB group at days 13, 15, 17 and 19.

Discussion

The permanent or temporary loss of existent physiological properties due to the loss or failure of integrity of the skin and mucosal structures is called a wound. Healing period begins from the second the trauma happens and goes on for days, months even years. The healing capacity of a wound depends on its depth, and the health and nutritional status of the organism (12). Davidson reported that after exposure to the anaesthesia and surgery combination, many of the immune system functions deteriorated (13). There are many medications used during the perioperative period, for example, intravenous anaesthetics, inhalational anaesthetics and local anaesthetics, opioids, non-steroids, muscle relaxants, corticosteroid, antiemetics and gabapentinoids. Their effect on the healing capacity is a very important subject. Local anaesthetics, opioids, corticosteroids and some of the anaesthetics were evaluated for their effects on wound healing. Although gabapentinoids are commonly used for postoperative pain relief during the perioperative period, their effect on wound healing is still unknown.

Healing process is influenced by the degree of inflammation, which is the key step in wound healing. Inflammation is a natural reaction to injury and it is essential for tissue repair. Inflammatory reactions are initiated by multiple factors such as trauma, infection, metabolic dysfunction and surgery. Inflammation is the first acute response of the tissue to the trauma. This phase is characterised by increased vascular permeability, chemotaxis of the cell from the circulation to the wound site, local release of cytokines and growth factor and activation of migration of cells (14). Although the wound healing process is divided into four phases it is a continuous process and phases overlap each other. The presence of more mature capillary vessels in the vicinity of the wound and large amount of collagen fibre provides better tissue oxygenation and nutrition which is adequate for wound healing process (15). So the drugs that effect any of these phases have influence on wound healing.

Inhalational anaesthetics are major anaesthetic drugs for general anaesthesia. Their effects on wound healing and inflammation have been evaluated by several researchers. Yang *et al.* reported that inhalational anaesthetics, especially isoflurane, cause abnormal calcium release from the endoplasmic reticulum via excessive activation of inositol 1,4,5-trisphosphate (IP_3) receptors so they may induce cell damage (16). Also isoflurane, halothane and enflurane attenuate the inflammatory response by decreasing release of proinflammatory cytokines (17). Lee *et al.* reported that the exposure to sevoflurane over 4 hours affects early period of wound healing, leading to delayed wound size reduction, and decreased expression of transforming growth factor-β_1 (TGF-β_1) and basic fibroblast growth factor (bFGF) on the wound surface (18). They also found that 8 hours exposure to sevoflurane caused delayed wound healing compared with the oxygen (18). Consequently it can be assumed that the patient who has been subjected to general anaesthesia with inhalational anaesthetics is under risk of delayed wound healing as the exposure time gets prolonged. So we used ketamin and xylazin for anaesthesia of the animals in this study to avoid the effects of inhalational anaesthetics on inflammation and wound healing.

Local anaesthetics is another drug group which is a touchstone for anaesthesia practice; their effects on surgical wound healing were also evaluated (19,20). There are conflicting results in the literature about local anaesthetics on wound healing. Chiang *et al.* reported that local anaesthetics have proinflammatory effects and cause delayed resolution of inflammation (21). Lidocain can reduce inflammatory responses and protect tissues from local injury in certain settings; on the other hand, it impairs polymorphonuclear apoptosis and macrophage phagocytosis, thus delaying the resolution of inflammation (21) and cause a delay in wound healing. However Eroglu *et al.* evaluated the effects of lidocaine/prilocaine cream on wound healing and concluded that it had no adverse effect on incisional wound model (22). Also Nykanen *et al.* concluded that eutectic mixture of lidocaine/prilocaine cream does not affect wound healing adversely and is comparable to 1% lidocaine infiltration in a single blind prospective rat model (23). Zeren *et al.* reported that levobupivacaine impairs wound healing during the early period and has positive effect during later periods of wound healing (24). Feder *et al.* showed that lidocaine, bupivacaine and ropivacaine had concentration-dependent cytotoxic effect on fibroblasts (25).

Opioids are also used frequently during intraoperative and postoperative period for pain relief. They can interfere during the different stages of inflammation, decrease inflammation via vasoconstriction and decrease neuropeptide release (26). Corticosteroids, a frequently used drug group at perioperative period, decrease inflammation, thus affecting cell migration, proliferation and angiogenesis (27). And as a result corticosteroids cause delayed wound healing by inhibiting the inflammatory phase and collagen synthesis (28).

Gabapentin and pregabalin have been used in the treatment of postsurgical pain, neuropathic pain, epilepsy, spasticity and anxiety. In recent years gabapentin and pregabalin have been used widely for acute postsurgical pain treatment. They were found to be effective in reducing acute postoperative pain (10,11). Chang *et al.* have reported gabapentin to be a safe and efficacious drug for the treatment of postoperative pain (29). They help to decrease opioid use and reduce postoperative pain (10,11). Pregabalin is also considered an alternative drug for opioid dependence, and prevent hyperalgesia (30). And additionally perioperative administration of gabapentinoids is effective in reducing incidence of chronic postsurgical pain (31). Gabapentin and pregabalin have been proposed to have mechanism of action of gabapentinoids and inhibit α (2)/δ subunit of inactivated voltage-dependent calcium channels. Also gabapentin inhibits glutamate release, increases the activity of voltage gated N-methyl-ᴅ-aspartate receptors and inhibits the activity of voltage-gated potassium channels (32,33). However, it is still not clear if these mechanisms play a role in analgesic effects of gabapentinoids.

Pregabalin decreases calcium influx thus decreasing secretion of excitatory neurotransmitters, such as glutamate, noradrenalin and substance P (34). Yong Ha *et al.* evaluated pregabalin in a rat model of spinal cord injury and concluded that it has neuroprotective effect and this effect is attributed to its anti-inflammatory and antinociceptive effects (35). But

the mechanism of the anti-inflammatory effect is still unknown. Substance P is a potent vasodilator. It can cause degranulation of mast cells and induce chemotaxis of neutrophils and lymphocytes (36). The inhibition of substance P by gabapentinoids may be one of the causes of their anti-inflammatory effect.

Gabapentin treatment increased peritoneal macrophage migration and carrageenan induced paw oedema, thus suggesting that gabapentin is a proinflammatory factor (37). The inflammation scores are higher in the gabapentin group in our study also. So it can be deduced that gabapentinoids can interfere at different stages in the inflammatory cascade. In the literature, gabapentin and pregabalin are used for treatment of pain in a wide variety of dose ranges (29,37–39). We studied the effects of 20 mg/kg dose and found that it has a negative effect on wound healing. Higher doses must be evaluated in future studies.

Postoperative day 9 is the proliferative phase of the wound healing; collagen and fibroblast synthesis increased during this period (40). So the sutures were removed during this period (7–10 days) (41). Day 21 is the remodelling phase of the wound healing (40). So the first sampling was performed at day 9 and second one at day 21.

Inflammation scores were significantly lower and wound healing was significantly better in the control group than pregabalin and gabapentin groups until day 13. Inflammation scores were significantly lower in pregabalin group when compared with gabapentin group until day 13. This may be the cause of elongation of inflammatory phase of wound healing and the consequent delay in wound healing process. Camara *et al.* reported that gabapentin accentuates nerve and peripheral inflammatory response, which could be mainly due to an independent central nervous system-mediated mechanism and raise some concerns about inflammatory side effects when used clinically (37).

Although gabapentinoids have been widely used for postoperative acute pain treatment, they especially pregabalin should be avoided in patients with poor wound healing risk, or if fast healing is essential. In such patients retinoic acid, which significantly increases the hydroxyproline content at normal levels, may improve the healing process (28).

This study has some limitations. Rat skin morphology and characteristics do not completely simulate the human skin as wound contraction occurs more rapidly than epithelisation (38). Rats have loose skin and this property allows wound contraction to play a significant role in closing rat skin wounds, and finally faster wound contraction than epithelisation results in faster healing time of rat wounds (38). And the environment of human wounds cannot be imitated in experimental animals absolutely.

Conclusion

Our results suggest that although gabapentinoids are effective drugs for postoperative acute pain treatment they should be avoided especially in patients with poor wound healing risk. Gabapentin delayed wound healing prominently during first 10 days but pregabalin effect is seen between day 10 and 21 and it has more prominent negative effect on wound healing. Additional studies are needed on different doses of gabapentinoids and their effect at the molecular level on inflammation, collagen structure and wound tension strength.

Author contributions

TBS helped design the study, conduct the study, analyse the data and wrote the manuscript. ZKS helped design the study and analyse the data. MK helped with all experimental examinations. AS analysed all the histopathological data.

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