

EFFICACY OPIOIDS AND OPIOIDS-ADJUVANTS COMBINATION IN BURN PAIN TREATMENT

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Key words: burn pain, morphine, gabapentin.

Summary

Background. Multimodal analgesia, which employs drug combinations that have different action mechanisms in order to improve pain relief, thereby minimizing dose dependent adverse effects, is recommended for burn pain management. Effective adjuncts for analgesia for burn patients still need to be developed.

Aim: To evaluate the efficacy of gabapentin as an adjunct to morphine patient-controlled analgesia (IV-PCA) in pain treatment for burn patients during the 72-h period after injury.

Methods. A prospective randomized controlled study. The pain treatment protocol was standardized with IV-PCA for all of the patients. The treatment patient group received 1200 mg per day of oral gabapentin. Morphine consumption, pain scores, incidence of adverse effects were recorded every 3 h (during the first 24 h after burn) and every 6 h thereafter or during the adverse event cases. Pain was assessed at rest and on movement: flexion in burn of extremity and cough in burn of torso.

Results. During the study period, 53 severe burn patients (TBSA \geq 10%) were included (n=29 in the control group and n=24 in the treatment group). Morphine consumption on the three first days after a burn was significantly lower in the treatment group than in the control group (p<0.001). The total morphine consumption in the treatment group was 28% less than in the control group. The VAS scores were lower in the treatment group as well (p<0.001). No clinically significant adverse effects were documented.

Conclusions. Our results indicate that 1200 mg of gabapentin may be useful as a safe analgesic adjunct

in pain management for effective pain relief with an opioid sparing effect for burn patients during the 72-h period after injury.

Introduction

The pain intensity in the early phase of a burn injury is one of the most excruciating pain sensations that can be experienced [1]. Even in the acute phase of trauma, besides nociception and peripheral hyperalgesia, burn pain is also characterised by central hyperalgesia and neuropathic pain [2, 3]. Due to large area skin nociceptor and surface fibre injury, burn patients experience acute neuropathic pain already during the first days following a burn [4]. Therefore, treatment of burn pain is a complicated task. Until today, opioids remain the gold standard in relieving strong and intolerable pain and preventing innervation of pain receptors and *the wind-up* phenomenon [5]. However, it is clear that they cannot ensure a full-fledged effect on all the pain formation stages [6, 7]. Moreover, large doses of opioids are necessary to achieve satisfactory effect in the treatment of acute burn pain. The role adjuvants play in the treatment of burn pain has not been clarified up till now. Efficacy of gabapentin in the treatment of chronic neuropathic pain [4, 8], postoperative pain [9], pre-operative fear and anxiety [10] has been proven by scientific research and the drug is used in clinical practice, which allows making a conclusion that its inclusion into pain treatment algorithms during the shock period could be beneficial.

Our study was designed to test the hypothesis that gabapentin administration can reduce morphine consumption in patients receiving IV-PCA during the first 72 h post burn injury. We evaluated the pain intensity during the burn injury shock period.

Methods

The Lithuanian University of Health Sciences (former Kaunas University of Medicine) local bioethics committee

approved the study protocol (Kaunas Regional Committee of Biomedical Research, No. BE-2-77).

The study was conducted out in Departments of Anaesthesiology and Plastic and Reconstructive Surgery, Lithuanian University of Health Sciences from March 2010 to December 2012.

This study was a prospective randomized controlled trial with a parallel-groups design. The inclusion criteria were: patients age 18 years and older, a $\geq 10\%$ total body surface area (TBSA) burn of any depth, hospital admission on the first trauma day (24 hours). The exclusion criteria were: pregnancy, history of allergy to morphine or gabapentin, regular use of an analgesics for chronic pain treatment, regular use of any anti-epileptic or anti-psychotic medications, kidney and/or liver insufficiency, acute alcohol intoxication, and admission to the intensive care unit due to cardiovascular instability and/or respiratory insufficiency requiring respiratory support.

Seventy-seven patients were screened for eligibility. Six patients did not meet the inclusion criteria, five patients declined participation, and one patient had a language barrier. Overall, 65 patients agreed to participate and gave written consent. The patients were assigned by a computer-generated randomization sequence into one of the two groups: control (M) or gabapentin (G). Randomization was straight and was not adjusted according clinical status of the patient. Twelve patients did not complete the protocol and were excluded from the analysis. Twenty-nine patients in the control (M) group patients and twenty four patients in the gabapentin (G) group patients completed the protocol, and their data were analyzed.

All patients were treated by a burn specialist and received burn injury management according to our local protocol. Morphine IV-PCA was started in all of the patients immediately after admission to the hospital. In addition, G group received oral gabapentin 1200 mg per day for three days.

PCA pumps (Perfusor fm B. Braun, B. Braun Melsungen AG) were connected to each patient via a dedicated IV line or non-reflux valve. These were placed at or below the patient's heart level to avoid siphoning. The morphine concentration was standardized to 1 mg/ml in normal saline. The PCA pumps were programmed as follows: the initial dose was 2 mg every 5 min (target VAS ≤ 30 mm), each additional IV bolus of morphine was 1 mg with a lockout interval of 5 min for the first 6 hours, and 8 min thereafter. The 1 hour maximum dose limits were 0.1 mg/kg for the patients who were less than 65 years of age and 0.075 mg/kg for the patients who were 65 years old or above [11].

One gram of IV acetaminophen was allowed to be used

as an antipyretic.

The patients were continuously monitored for cardio-respiratory function (e.g., mean arterial blood pressure, pulse rate, breathing rate, and SpO₂), pain and sedation, as well as adverse effects, such as pruritus, nausea, vomiting, and dizziness. The follow-up data were recorded every 3 h (during the first 24 h after burn) and every 6 h thereafter or during the adverse event cases. Pain was assessed at rest and on movement: flexion in burn of extremity and cough in burn of torso. The first measurement was at the time of hospital admission before start of treatment (0 h). Pain was assessed by a 100 mm VAS (0 mm=no pain, 100 mm=worst pain imaginable). A five-point sedation scale was used to evaluate and quantify sedation: 1-awake, 2-drowsy, 3-awakening by verbal stimulus, 4-awakening by physical stimulus, and 5-hardly possible to be awakened (*Wilson E.*) [12]. Nausea and vomiting were also registered (where 0=no nausea, 1=nausea only, 2=nausea and vomiting). Other adverse effects, such as pruritus, dizziness and visual disturbances, were scored as present or absent.

After the 72-h study period, the patients used PCA morphine as long as indicated or were treated with oral morphine.

Data collection was carried out by independent observer who was not informed about group allocation of patients.

Statistical analyses

The primary outcome measures were daily morphine consumption during the first, second and third treatment days and the cumulative morphine dose. The secondary outcome measures were pain at rest and on movement and the adverse effects. To determine the size of study groups, we performed the analysis only for the primary outcome. The sample size calculation was based on the data from our pilot study, which assumed a minimum difference of 15 mg in the total morphine consumption. A calculation based on $\alpha = 0.05$ and a power of 80% yielded a sample size of 22 patients per group using a two-tailed test. The morphine consumption, pain score, summary scores from questionnaire are summarized by presenting medians and interquartile ranges (25th and 75th percentiles) of their values. The Mann Whitney U test was used to compare their values in control and gabapentin groups. Categorical data were analysed using Chi-square test and Fisher's exact test as appropriate and the results are presented as numbers and percentages. Spearman's correlation coefficient was also used, taking into account the variable distribution. Odds ratio (OR) and confidence intervals (95%CI) were used to estimate the odds of the adverse effect. The difference was considered statistically significant when $p < 0.05$.

Results

The two groups were homogeneous according to patient age, body mass index (BMI), burn size and type of burn, hospital admission length. There were more females in the gabapentin (G) group. ($2=5.09$, $p=0.024$) (Table 1.).

Morphine consumption

Morphine consumption was significantly lower in the gabapentin group than in the control group during all three study days (day1, day 2, day 3 $p<0.001$) (Figure 1). The total morphine consumption was reduced from a median of 88 mg (interquartile range 77-104) in the control group to

Table 1. Patients' characteristics

p value – Mann-Whitney U test (age, BMI, hospital admission length) and Chi-square test (burn size, burn type, gender). Data are presented as the medians (25th and 75th percentiles), numbers and percentages. *statistically significant ($p<0.05$)

Characteristic	Control group (M) n=29	Gabapentin group (G) n=24	p value
Age (year)	45 (39.5-56.5)	47 (35-55.75)	0.872
BMI (kg/m ²)	25.51 (24.34-28.52)	25.57 (24.02-27.38)	0.657
Hospital admission length	32 (24-54)	46.5 (32.5-56)	0.186
Burn size			
<25%	13 (44.8)	9 (37)	0.115
25-50%	12 (41.4)	14 (58.3)	
>50%	4 (13.8)	1 (4.2)	
Gender			
Male	24 (82.7)	13 (54.2)	0.024*
Female	5 (17.3)	11 (45.8)	
Burn type			
Hot water	9 (31)	5 (20.8)	0.820
Flame	18 (62.1)	17 (70.8)	
Another (chemical, electrical)	2 (6.9)	2 (8.3)	

Table 2. Incidence of adverse effects

Statistically significance $p<0.05$, * the exact Fisher test. Data are presented as the numbers, percentages and OR (confidence intervals). ^a The patients responded to oxygen therapy, no patient required naloxone administration. ^b Urinary catheters were placed for monitoring fluid therapy and diuresis

Adverse effects	Control group (M) n=29	Gabapentin group (G) n=24	OR (Confidence interval)	Chi-square p
Desaturation (<90%) ^a	2 (6.9)	2 (8.3)	-	1.00
Nausea and vomiting	4 (13.8)	2 (8.3)	-	0.68
Pruritus	4 (13.8)	3 (12.5)	-	0.89
Urinary retention	0	0	-	-
Urinary catheters ^b	19 (65.5)	15 (62.5)	-	0.76
Sedation				
(2 grade episodes)	5 (17.2)	12 (50)	4.8 (1.372;16.72)	0.011
(3 grade episodes)	0	4 (16.7)		0.036*
Dizziness	2 (6.9)	7 (29.2)	5.6 (1.031; 24.96)	0.032
Visual disturbances	0	4 (16.7)	-	0.036*

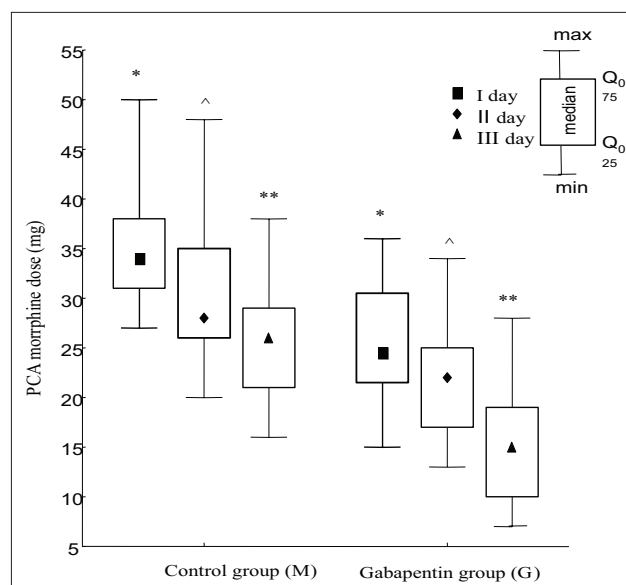


Figure 1. Morphine consumption in the control (M) and gabapentin (G) groups during the 3 treatment days. (Median, 25th and 75th percentiles, * $p<0.001$, ^ $p<0.001$, ** $p<0.001$).

63.5 mg (49.5-71) in the gabapentin group ($p<0.001$). No rescue analgesic medication was required during the study. However, acetaminophen was given in cases of fever (temperature higher than 38.5°C). Doses of acetaminophen did not differ between the groups (median value was 3 (2-4) g in group M and 3 (1.25-4) g in group G, $p=0.678$).

Pain scores. Starting from 6 hours after initiating pain treatment, the patients of control group experienced more intensive pain than the gabapentin group patients at rest and on movement during the 72-h period after burn ($p<0.001$) (Figure 2).

Adverse effects. No patient required IV-PCA discontinuation due to persistent troublesome opioid-induced adverse effects. Gabapentin related adverse effects episodes, such as somnolence, dizziness, and visual disturbances, were documented in the gabapentin (G) group more often (Table 2). These adverse effects were not clinically significant and did not require disconti-

uation of therapy with gabapentin.

Discussion

Multimodal analgesia, which employs drug combinations that have different mechanisms of action to improve pain relief and thereby minimize the dependent adverse effects, is recommended for burn pain management. Effective adjuncts for analgesia in burn patients must be identified. Our results indicate that 1200 mg of gabapentin may be useful as a safe analgesic adjunct in pain management for effective pain relief with an opioid sparing effect for burn patients during the 72-h period after injury.

The efficacy of gabapentin in reducing opioid consumption has been documented in hysterectomy [13], spinal surgery [14], after mastectomy and breast surgery [15], and knee arthroplasty cases [16]. Several meta-analyses and systematic reviews have demonstrated the efficacy and safety of preoperative gabapentin in multimodal pain management [17,18].

Rimaz S et al. found that a single preoperative dose of 1200 mg of gabapentin as an adjunct to morphine analgesia decreased the total postoperative morphine consumption and postoperative pain scores at rest and on movement after burn wound

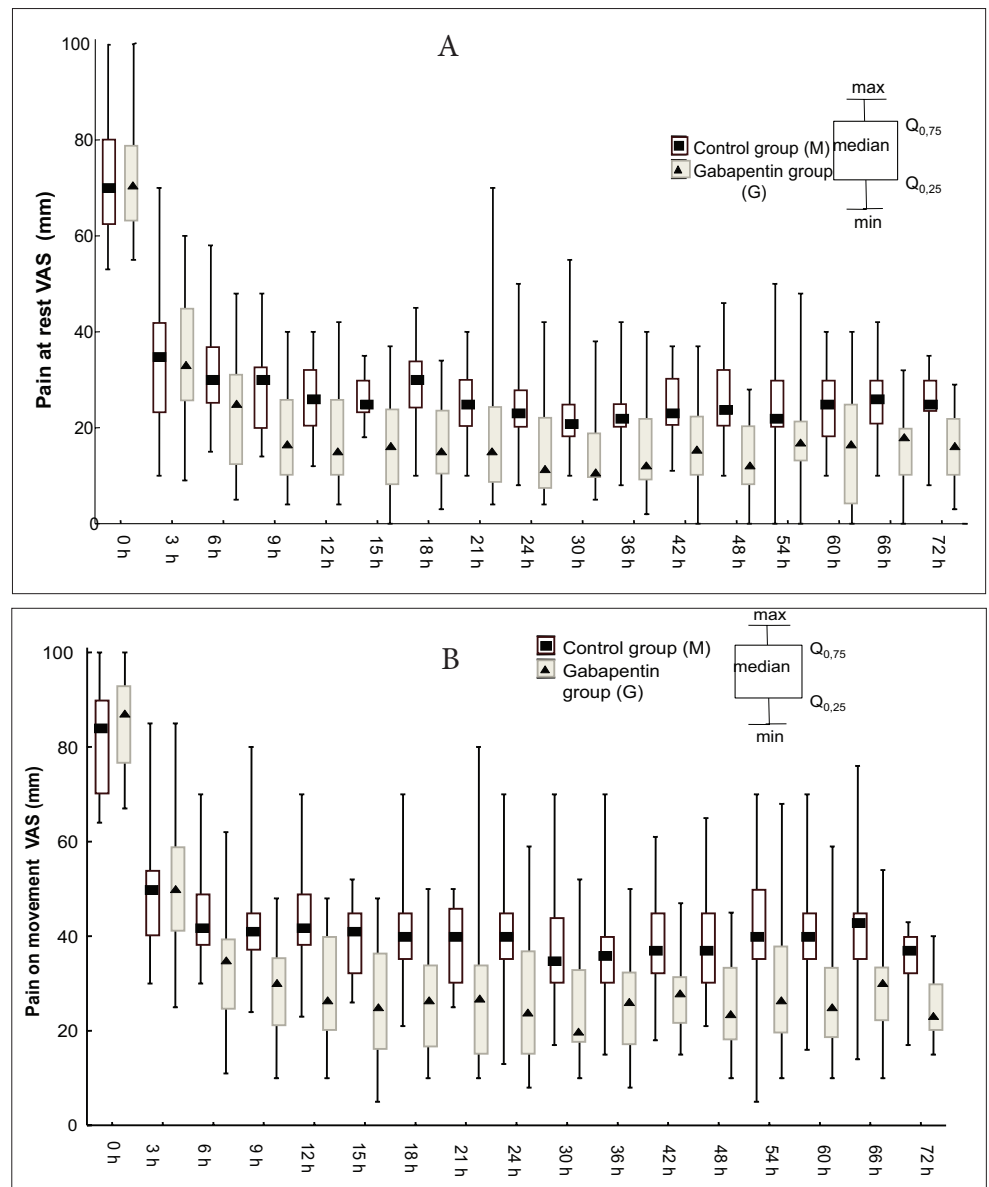


Figure 2. Pain intensity at rest (A) and on movement (B) during every 3 h (first day after burn) and 6 h (second and third treatment day) of follow-up.

Panel A: at rest $p=0,88$ and $p=0,377$ at 0 h and 3 h, respectively, $p < 0,001$ at 6-72 h.

Panel B: on movement $p=0,768$ and $p=0,302$ at 0 h and 3 h, respectively, $p < 0,001$ at 6-72 h.

debridement [19]. In an observational study by Cuinet et al., an opioid-sparing effect of gabapentin was reported. A daily oral dose of 2400 mg of gabapentin for 21 days, starting on the 3rd post-burn day (i.e., following the shock phase) reduced the opioid requirements in burn patients [3]. Our results are in line with these two studies despite a different study design.

However, our results differ from reported by Wibbenmeyer L et al. [20], who were unable to show a reduction in opioid consumption with gabapentin administration during the

acute burn injury period. The daily opioid requirements did not differ between the groups; but the study protocol had substantial differences, including burn sizes that were greater than 5% of the total body surface area and a study drug titration schedule that consisted of 1200 mg of gabapentin on the first study day and 300 mg thrice daily (900 mg) on study days 2 and 3. It is clear that the administration of gabapentin in conjunction with systemic analgesia requires further investigation with respect to the timing and duration of administration.

We found that the pain intensity both at rest and on movement was not significantly different between the groups at the 0 – and 3-h follow-up period. After a single oral dose of gabapentin, the mean maximum plasma concentration is attained in 2 – 3 h [18], and this fact may have influenced this result.

Pain has a mainly nociceptive character in the acute burn injury period. Peripheral hyperalgesia, central hyperalgesia, and neuropathic pain are also important pain components [3, 4, 21] in this period. The burn injury damages and partially destroys nerve structures. According to this fact, neuropathic pain can occur directly or after a period of time [5]. A Gray P et al. demonstrated that neuropathic pain was detected within 1 to 7 days after a burn injury [4].

The dose-dependent adverse effects of opioids may interfere with the analgesia plan and may lead to a reduced quality of pain relief. Respiratory depression, which is the most important side effect of morphine PCA, may be more common when a background infusion is added [11]. We did not use a background infusion and no patient required naloxone for respiratory depression. Many studies with gabapentin report common side effects, such as somnolence, dizziness, and visual disturbances [18, 22]. The use of higher dose of gabapentin increased the incidence of adverse effects [23]. Sedation is frequent during acute pain treatment with gabapentin according to a meta-analysis by Ho K et al. [24]. Our study results regarding sedation are similar. The dizziness and visual disturbance incidences were comparable with results from other studies [18, 22]. No patient in our study withdrew due to adverse effects. The present study did not find any serious adverse events that would limit the use of 1200 mg gabapentin in burn pain treatment during shock period.

It is important to acknowledge the limitations of the present study. First, although this trial was randomised, however not double blinded. Second, our study was limited by its short therapeutic intervention duration. The gabapentin effects were monitored only for a 72-h period after injury. Admittedly, burn treatment and continuous pain lasts much longer. Moreover, therapeutic procedures, such as dressing

changes and burn wound debridement, induce additional pain episodes that might contribute to the causality between acute and chronic burn pain.

Conclusions

Our study shows that gabapentin is a safe and effective adjunct in multimodal pain management in the shock period for burn patients. An opioid-sparing effect and reduce pain intensity scores were documented.

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OPIOIDŲ BEI OPIOIDŲ IR ADJUVANTŲ DERINIO VEIKSMINGUMAS GYDANT NUDEGIMO SKAUSMĄ

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Raktažodžiai: nudegimo skausmas, morfinas, gabapentinas. Santrauka

Įvadas. Nudegusiems pacientams tinkama daugiaveiksnė analgezija, derinant skirtingas grandis veikiančius analgetikus nulemtų veiksmingesnį skausmo gydymą, kartu sumažintų nuo dozės priklausomų šalutinių poveikių dažnį. Ieškoma efektyvių adjuvantų, papildančių analgezijos derinius, gydant nudegimo sukeltą skausmą.

Tikslas. Įvertinti adjuvanto gabapentino veiksmingumą, gydant nudegimo skausmą morfino infuzija paciento kontroliuojamos analgezijos (PKA) metodu pirmas 72 val. po nudegimo.

Metodika. Atliktas perspektyvusis atsitiktinių imčių klinikinis tyrimas. Visi tyrime dalyvavę pacientai gydyti paciento kontroliuojama analgezija morfinu. Gabapentino (G) grupės pacientai gavo 1200 mg gabapentino per dieną. Morfino suvartojimas, skausmo intensyvumas, analgezijai skiriamų šalutiniai vaistų poveikiai stebėti ir registruoti kas tris valandas pirmąją parą po nudegimo, antrą ir trečią tyrimo dienas duomenys registruoti kas 6 val. Skausmo intensyvumas vertintas ramybėje ir judant.

Rezultatai. Tyrime dalyvavo 53 pacientai, nudegę daugiau kaip 10 proc. kūno paviršiaus ploto (kontrolinėje grupėje n=29 ir gabapentino grupėje n=24). Morfino suvartojimas visas tris tyrimo dienas reikšmingai mažesnis gabapentino grupėje nei kontrolinėje grupėje (p<0,001). Suminė morfino dozė gabapentino grupėje 28 proc. mažesnė lyginant su kontroline grupe. Žemesni skausmo intensyvumo balai nustatyti gabapentino grupėje (p<0,001). Kliniškai reikšmingų šalutinių vaistų poveikių nenustatyta.

Išvada. Mūsų tyrimo rezultatai parodė, kad gabapentinas yra saugus ir efektyvus adjuvantas, gydant nudegimo sukeltą skausmą. 1200 mg gabapentino reikšmingai sumažino opioidų dozę ir skausmo intensyvumą nudegusiems pacientams pirmas 72 val. po nudegimo.

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