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Characteristics and Treatment of Breakthrought Pain (BTcP) in Palliative Care

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ABSTRACT

Introduction: This research was to follow characteristics of breakthrough pain caused by cancer (BTcP) and other most common sympthoms (ESAS) at patients in advanced stage of cancer disease in palliative care. **Patients and methods:** Prospective study included 433 patients which were treated in Palliative Care Centre in UKC Tuzla, Bosnia and Herzegovina. Group 1 was consisted of 353 patients whose basal cancer pain of intensity 4-7 NRS was treated weak opiates (basal analgetic- fixed combination of tramadol/paracetamol (37.5 mg/325 mg) in initial dose 3x1tbl for pain intensity 4, to 4x2tbl (for pain intensity 7). In Group 2 (80 patients) basal pain of intensity 8-10 was treated strong opiates as basal analgetic (oral morphine and transdermal fentanil). If the previous day were 2 or more breakthrough pain that required ''rescue dose'' of analgetics (tramadol 50-100 mg orally in group 1 ie. Oral morphine 8-12 mg in the group 2), the dose of basal analgetic was increased. **Results:** The total number of reported breakthrough pain in all 433 patients for 10 days of treatment was 3 369 (0.78 BTcP /per patient/day), where at Group 1 patients showed significantly lower BTcP (0.56 BTcP/patient/day). The average intensity of BTcP was 5.91 where in the Group1 was 4.51 while in the Group 2 8.04. 582 (17.28%) was rated grade 7, of which 539 were successfully coupled by strong and 43 (7.39%) successfully coupled by weak opiates. From 556 BTcP who were rated with 8, 540 of them were coupled strong and only 16 successfully coupled by weak opiates. 1967 (58.39 %) of breakthrough pain has occured in the evening hours (18-06 h), while 1402 (41.62%) BTCP occured during day hours (06-18h). Most (1290 or 38.29%) of breakthrough pain lasted less than 10 minutes, 882 (26.18%) between 16 and 20 minutes, 752 (22.32%) between 11 and 15 minutes, 407 (12.8%) between 21 and 30 minutes and 38 (1.13%) lasted longer than 20 minutes. **Conclusion:** Duriong our study, we noted a relatively large number of breakthrough pain with lower intensity (3-6) in patients treated with weak opiates, which are also adversely affected patients satisfaction with pain treatment and required additional doses of analgetics. In the small percentage is possible the breakthrough pain of stronger intensity (7-8) treat by maximum doses of weak opiates.

Keywords: intensity, duration and time breakthrough pain, weak and strong opiates.

1. INTRODUCTION

Breakthrough pain in cancer patients (BTcP) is defined as a temporarily deterioration of pain that occures spontaneously (27%) or can be activated (43%) by movements, laughing, sneezing,coughing, hollow organs distension and psychosocial stimuli, where the main pain is stable and under control.

BTcP is usually connected with bone pain (27%), tumor invasion of the soft tissue (21%) and brachial plexus syndrome (9%) (1-3). In 17-30% of cases BTcP is related to inadequate analgesic treatment, analgetics sub-dosing or too long interval between doses, which leads to so-called 'Pain at the end of dose'. The breakthrogh pain in cancer patients can be caused due to the damage of nerve by cancer or anticancer therapy and BTcP can be classified as nocioceptive,visceral or neuropatic (4). BTcP prevalence is estimated on 50-70% among patients undergoing active oncological treatment, and 70-95% in patients with advanced cancer diseases (5-6). In 92% of patients BTcP is described as severe and intense pain (7-10 per NRS) with fast, paroxysmal beginning (less than 3 min) and average time in achieving 'peak pain' for less than 10 minutes. In 80-90% of cases it lasts from 1 min to 1 hour (typically between 15 and 30 min), and the average frequency in patients in advanced stages of cancer disease is 4-7 pain episodes daily (7-8). Inadequately controlled BTcP causes reduction of confidence in medical treatment efficacy and leads to sleep disorders, anxiety, depression, sense of isolation, fear and

sometimes the decision on the rejection of further medical treatment compromising the quality of life of patients (9-10). Any increase in the pain intensity or appearance of pain before regular opiate dose, needs to be carefully considered, following the possible causes of BTcP, such as its characteristics (11). The breakthrough pain treatment involves the usage of additional so-called 'Rescue doses' which should be recorded and included in the following day in adjusted doses of regular analgesic therapy. In most cases, BTcP can be successfully controlled by combination of pharmacological and non-pharmacological therapeutic measures (12). Oral opioid preparations of short-acting are recommended as first-line BTcP treatment because they are easy to use, they act relatively fast and most physicians have a lot of experince in their usage (13). The main deficiency of BTcP oral treatment is the slow onset of action (20-30 min) with maximum effect only after 45-60 min (14). The sublingual drug application would undoubtedly speed up the effect of a medicin, but morphine, because of its hydrophobicity, absorbes through the mucuos membrane and the effect of sublingual application is then not faster than oral (15). The much faster onset of activity is achieved by using a type of oral transmucosal composition of fentanyl citrate, which is 80 % of the non-ionized form, absorbed through mucuos membrane, in 3-5 min passes through the blood brain barrier, with the peak effects of 20-40 min and the total duration of 2-3 hours after the use (16-19). Better effects in the BTcP treatment are achieved using fentanyl in the form of: 1) sublingual tablets (SLF) (20); 2) intranasal fentanyl spray (INFS) (21-22) and 3) fentanyl buccal soluble film(FBSF) (18).

The aim of this research was to follow characteristics of breakthrough pain (BTcP) caused by a cancer and other most common sympthoms (ESAS) at patients in advanced stage of cancer disease, in palliative care.

2. PATIENTS AND METHODS

Prospective study included 433 patients treated in Palliative Care Centre, UKC Tuzla, Bosnia and Herzegovina. General condition of patients was assessed Karnofski score during admission and after 10 days of treatment and dominant following symptoms by ESAS scale daily for 10 days. Group 1 included the patients (353) whose basal cancer pain was of 4-7 intensity per NRS treated by weak opiates (basal analgetic - fixed combination of tramadol/paracetamol (37.5 mg/325 mg) in the inital dose of 3xtbl for pain intensity 4, up to 2xtbl for pain intensity 7). In group 2 (80 patients) basak pain of intensity 8-10 was treated strong opiates as basal analgetic (oral morphine preparates and transdermal fentanyl). Dialy (10 days) breakthrough pain was evidented and if previous day existed 2 or more breakthrough pain that demanded „rescue dose" of analgetics (tramadol 50-100 mg per os in group 1 i.e. oral morphine 8-12 mg in group 2), basal analgetics dose was increased.

The study didn't include patients that were alergic to opiates or if they had uncontroled vomittng that interfered with the oral analgetics application. This study can conducted in accordance with declaration from Helsinki. Statistical analysis was conducted using biomedical application software called MedCalc for Windows version 9.4.2.0. For testing the repeated measurement of paired samples, depending on the distribution of variables, paired T-test and Wilcoxon tests were used.

3. RESULTS

The research was conducted by 433 patients, average age 60.08 ± 10.15 age (from 24 to 87 years), of which 261 (60.28%) male and 172 (39.72%) female patients. 142 (32.79%) had verified metastatic changes in bones, while at 291 (67.21%) patients didn't have bone metastasis ($p<0.0001$)(Table 1). Among patients 33.1% were the patients with lung tumor, 21.1% were with digestive tract patients, 15.6% were patients with ORL tumor, 15.1 % were breast tumor patients while patients with other tumors were less than 10% (Table 2). Mean value for Karnofski score for all 433 patients during the reception was 46.63 ± 10.46 and during the release of patients was 54.11 ± 11.7 which is statistically significantly better ($p< 0.0001$). There was no statistically significant difference between mean values for Karnofski score between patients of group 1 and group 2 neither the first day of treatment ($p=0.64$), nor the tenth day of treatment ($p=0.946$).

Characteristics of breakthrough pain (BTcP)

The total number of recorded breakthrough pain in all 433 patients for 10 days was 3 369 (0.78 BTcP/per patient/dialy), where at group 1 patients (treated by weak opiates) were recorded statistically less ($p< 0.0001$; 0.56 BTcP/patient/day)when compared with group 2 patients (treated by strong opiates) with recorded 1.75 BTcP/patient/day. In group of patients treated by strong

Groups		Group 1**		Group 2***		
Number of patients (433)		353		80		
Age		58.75 ± 10.02		62.11 ± 9.61		
Gender	M (%)	211 (48.73)		50 (11.55)		
	F (%)	142 (32.79)		30 (6.93)		
Subgroups		Bone metastasis		Bone metastasis		
Yes		No	Yes		No	
Gender	M (%)	63 (29.86)	148 (70.14)	M (%)	18 (36.00)	32 (64.00)
	F (%)	39 (27.46)	103 (72.54)	F(%)	22 (73.33)	8 (26.67)

Table 1. General and demographic characteristics of patients *Mean value Patients treated **weak opiates; ***strong opiates

Topographic localisation of tumor							
Tumor site	Head and neck		Thorax		Abdomen and Pelvis		
Number of patients (%)	75 (17.3)		214 (49.4)		144 (33.3)		
Clinical localisation of tumor							
Primary tumor	ORL	Skin	Lungs	Breast	Digest.	Ginekol.	Urolog.
Broj pacijenata (%)	67 (15.6)	14 (3.1)	143 (33.1)	65 (15.1)	91(21.1)	21 (4.7)	32 (7.3)

Table 2. Cancer localization (topographic and clinical) and bone metastasis

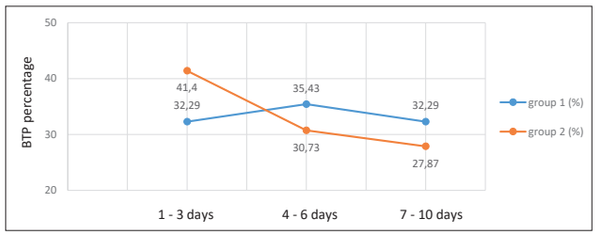


Chart 1. Number (%) breakthrough pain by groups

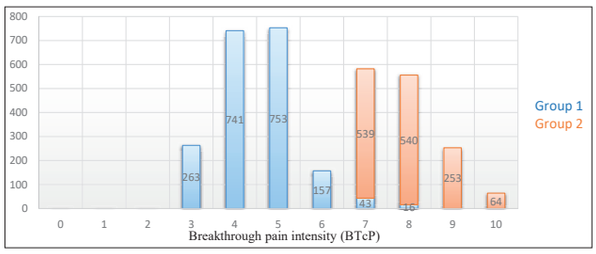


Chart 2. BTcP intensity groups

opiates (group 2), during first three days of treatment, 578 (4.4%) BTcP or 2.41/BTcP/pat/day were registered, which is statistically remarkably more when compared to group 1, in which in the same interval period registered 637 BtcP (32.29%) or 0.60 BTcP/pat/day. In the following two interval periods there were no statistically significant difference in BTcP number in group 1 and group 2 patients (Chart 1). 1 408 (41.79%) BTcP were recored at 142 patients with verified bone metastasis or 0.992 BTcP/patient/day, while at 291 patients without verified bone metastasis 1 961 BTcP or 0.676 BTcP/patient/day were recorded which is statistically remarkably less (p<0.0001). The average intensity of BTcP was 5.91, where in group 1 was 4.51 and 8.04 in group 2. Out of totally registered 3 369 breakthrough pain, 582 (17.28%) were graded by 7, of which 539 (92.61%) were successfully couple by strong opiates and 43 (7.39 %) by weak opiates. It is similar for 556 (16.5%) BTcP which were graded by grade 8, of which 540 (97.12%) were coupled by strong opiates and only 16 (2.88%) were successfully coupled by weak opiates (Chart 2). Of totally 1973 registered BTcP at group 1 patients (treated by weak opiates), the most of them were graded by grade 5 (753 or 38.17%), and then by grade 4 (741 BTcP or 37.56 %). Significantly less BTcP(263 or 13.3 %) is graded by grade 3, then by grade 6 (157 or 7.96 %), grade 7 (43 or 2.18%) and the least grade it by grade 8 (16 or 0.81%). There were no BTcP graded by 1, 2, 9 and 10 (Chart 2). At group 2 patients (treated by strong opiates), of totally 1396 registered BTcP, 540 or 38.68 % were graded by 8. 539 or 38.61 % by grade 7. Significantly less (p<0.0001) BTcP is graded by 9 (253 or 18.12%) and grade 10 (64 or 4.58%). There were no BTcP graded by 1 to 6 (Chart 2).

Time of occurence of breakthrough pain (BTcP)

Analysing the time of occurence of BTcP at all 433 patients, it has been found that 1967 (58.39%) breakthrough pain came up in evening and night hours (from 18 – 06 hours) and that it is statistically remarkably more (p<0.0001) regarding the 1402 (41.61%) BTcP that are registered in daily hours (from 06 – 18 hours). The most, 1 116 (33.13 %) of BTcP is recorded in time from 18 to

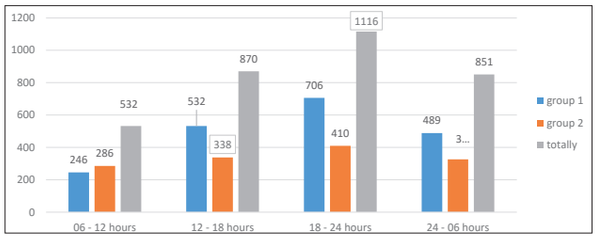


Chart 3. Time of occurence of breakthrough pain in group 1 and group 2 patients

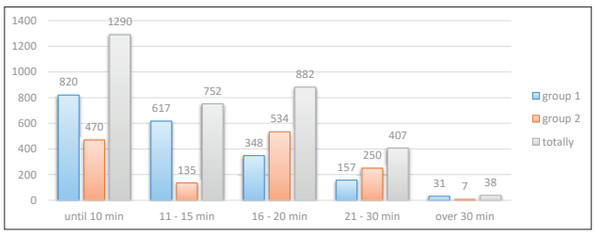


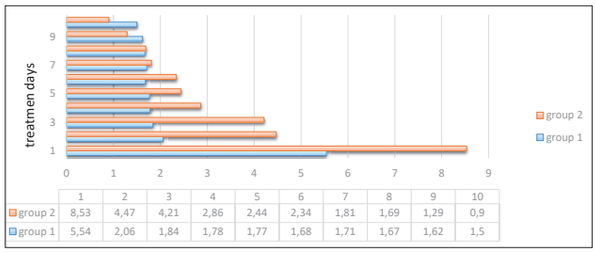
Chart 4. The breakthrough pain duration (BTcP) of group 1 and group 2 patients

24 hour, and comparing it with other time periods, we can see that in period of 24 to 06 hours is recorded 851 (25.26 %) BTcP; in period od 12 to 18 hours 870 (25.82 %) BTcP (p<0.0001), and the least breakthrough pain (532 or 15.79 %) in period between 06 to 12 hours (p<0.0001). (Chart 3). Analyzing the biggest number of breakthrough pain according to groups is registered in time from 18 to 24 hours (716 in group 1 and 410 in group 2), and the least in time between 06 to 12 hours (246 in group 1 and little more in group 2, that is 286)(Chart 3). Out of totally 3369 breakthrough pain registered at all 433 patients, the most of BTcP (1290 or 38.29%) lasted less than 10 minutes, 882 (26.18%) between 16 and 20 minutes, 752 (22.32%) between 11 and 15 minutes (p=0.0002), 407 or 12.08% between 21 and 30 minutes (p<0.0001) and 38 (1.13%) lasted longer than 30 minutes (Chart 4).

In group 1 statistically more BTcP lasted less than 10 minutes (820 or 41.56 %) when compared to 470 or 33.67 % in group 2 (p<0.0001). At the same time there is significantly more BTcP in period between 11 and 15 minutes at patients in group 1 (617 or 31.27%) comparing to group 2 (135 or 9.67%) (Chart 4). Conversely to that, in group 2 most of BTcP lasted between 16 and 20 minutes [(534 or 38.25%), while the same duration was recorded at 348 (17.64%) BTcP in group 1, which is statistically less (p<0.0001)], and between 21 and 30 minutes [(250 or 17.91%) in group 2 compared to 157 or 7.96 % in group 1 (p<0.0001)](Chart 4).

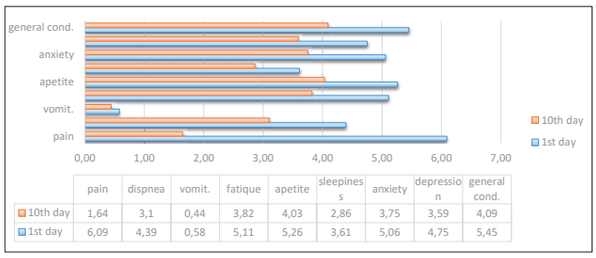
Impact of pain and pain treatment by opiates on accompanying symptoms by ESAS scale

For most common symptoms in advanced stage of cancer disease (following the Edmonton scale for grading symptoms) in all 433 patients of both groups, the average score, calculated at the first day of reception of patients was 4.48±0.89 (40.31±8.08 as sum of average values of all symptoms), and after 10 days of treatment 3.01±0.82 (27.09±7.38),which is statistically better result comparing to reception day. Average value of pain for all 433 patients for the first day of treatment was 6.09±1.39



	1	2	3	4	5	6	7	8	9	10
group 2	8,53	4,47	4,21	2,86	2,44	2,34	1,81	1,69	1,29	0,9
group 1	5,54	2,06	1,84	1,78	1,77	1,68	1,71	1,67	1,62	1,5

Chart 5. Average pain intensity according to treatment days of all patients and group



	pain	dispnea	vomit.	fatique	apetite	sleepiness	anxiety	depression	general cond.
10th day	1,64	3,1	0,44	3,82	4,03	2,86	3,75	3,59	4,09
1st day	6,09	4,39	0,58	5,11	5,26	3,61	5,06	4,75	5,45

Chart 6. Intensity of the most common symptoms first and tenth day od tretment

which is statistically remarkably more (p<0.0001) regarding the average pain intensity on the tenth day of treatment (1.64±0.68). In group 2 patients pain intensity was remarkably larger during first 6 days of treatment comparing to group 1 patients, from 7-th to 9-th day there were no significantly remarkable diference, while the pain intensity was significantly smaller at 10th day of treatment (p<0.0001) at patients who were treated with strong opiates (Chart 5). The average values of dispnea at all patients at the first day of treatment was 4.39±1.86 and at the tenth day it was 3.10±1.63 (p<0.0001). Vomitting intensity at the reception was 0.58±0.98 and tenth day of treatment it was 0.44 ± 0.72, and there were no statistically significantly remarkable diference (p=0.015), while the average value for fatique at the reception was 5.11±1.52, and tenth day it was 3.82±1.48 (p < 0.0001). The appetite at the tenth day of treatment was considerably better (4.03±1.55 v 5.26 ±1.61 first day; p < 0.0001) (Chart 6). Sleepines was considerably less expressed at the tenth day of treatment (2.86±1.42)(p<0.0001) comparing to the first day of treatment (3.61±1.34). The average value of anxiety during the first day of tretment was 5.06±1.57 and tenth day it was 3.75±1.45 (statistically considerably less p< 0.0001), while the average value of depression was statistically considerably less at the tenth day (3.59±1.39) comparing the first day of treatment (4.75±1.45) (p<0.0001). At the reception, the average of estimated general condition was 5.45±1.45 which is statistically remarkably worse grade (p<0.0001) compared to average result at the tenth day (p<0.0001) (Chart 6).

4. DISCUSSION

By symptom treatment, average value for Karnofski score in our study has improved from 46.63±10.46 at the reception to 54.11±11.7 at the release. In a study that has been following up the effects od treatmen of cancer pain by strong opiates (transdermal fentanyl), Karnofski score was relatively constant during the treatment, with average value of 69±2 at the first day and 68±2 at the end of second month (23). The study od Marinangelio and its cooperates (2004) at 48 patients with advanced cancer has showed, contrary to our study, that after the pain treatment with opiates despite the considerably reduction of pain intensity (p=0.04), comes to statistically considerable reduction of Karnofski perfomance status (from 58,92 ± 5,56 at the reception, with the reduction of -24.04) and measure of quality of life which supports the worsening of general condition (24).

In our study, at patients whose elementary pain was treated by strong opiates (group 2) 1.75 BTcP/patient/day was registered, with average intensity of 8.04 (NRS), which is considerably larger the number and the intensity BTcP when compared to group 1 patients (elementary pain treated by weak opiates) [(0.56 BTcP/patıent/day of average intensity of 4.51 (NRS)]. From 582 (17.28%) BTcP which were graded by grade 7, 539 (92.61%) were coupled by strong opiates and 43 (7.39%) by weak opiates. Similarly, from 556 (16.5%) BTcP which were graded by grade 8, 540 (97.12%) were coupled by strong opiates and only 16 (2.88%) were successfully coupled by weak opiates. Most of BTcP in group 1 were graded by grade 5 (753 or 38.17%) or 4 (741 BTcP or 37.56%) and in group 2 by grade 8 (540 or 38.68 %) or grade 7 (539 or 38.61%).

The study has been done on patients treated in palliative care, in which fast-acting oral morphine for breakthrough pain control was used, states the average number of breakthrough pain of 2.9 (1-5.5) by patient per day, with average intensity BTcP of grade 7 (by NRS) (25). Korean study from 2016, done on 609 patients, states that the frequency of BTcP is 29.1% (177), where the mean value and median BTcP were 1.95 and 2. The duration of BTcP at 110 patients was up to 10 minutes, at 29 patients it was between 11 to 20 minutes, at 5 patients between 21 to 30 minutes, at 3 patients between 31 and 60 minutes and at 6 patients longers than 60 minutes (26).

Zeppetelle and co.,(2000) state that the average frequency of breakthrough pain was graded 4 daily (between 1 and 14), where the BTcP in the 16 % of cases was evaluated as mild (1-3 per NRS), in 46 % as medium strong (grades 4,5,6), in 36% as strong (grades 7,8 and 9) and in 2% as nondurable (grade 10) BTcP, with average duration of 35 minutes (span between 15 and 60) (27). Davies and co. (2008) (11) while exploring 120 patients older than 18 years in different stage of malignancies, at 87 patients (72.5%) registered BTcP with the average frequency of 2 breakthrough pain daily (span between 1 and 10), with average duration of breakthrough pain episodes of 10 minutes (between 5 seconds and 360 minutes), with intensity BTcP to 4 per NRS at 10 patients, to 6 at 45 patients and between 7 and 10 at 31 patients.

The research conducted in Poland, with survey done by 135 doctors that treat the patients in palliative stage of disease, shows that 98.32% of doctors diagnosed breakthrough pain, whose frequency was between 2 (43% of doctors) and 4 episodes daily (7.41% doctors). The most common duration of breakthrough pain was 15 to 30 minutes (27.4%), then up to 5 minutes (23%) and be-

tween 5 to 15 minutes (17.8%), until three doctors didn't plead about duration of breakthrough pain. In pain therapy patients usually used morphy (96.3%), fentanyl (78%), NSAIL (73%), tramadol (66%) and acetaminofen (61%) (28). Out of totally 3369 breakthrough pain registered at our patients (433), 1967 or 58.39% were registered in night hours (from 18 to 06 hours), of which 1116 (33.13%) were registered in period of 18 to 24 hours and 851 (25.26%)between 24 to 06 hours. Between 12 and 18 hours 870 (25.82%) BTcP were registered, and the least of them (532 or 15.79%) between 06 and hours. Fine and Busch's study states opposite results in which 86% patients felt increased pain intensity and bigger BTcP during day, while only 45 % patients felt pain during the night (25). Similary, the Bruere and co. Study states that 45 out of 61 patients (76%) have received most of its additional „rescue" doses od narcotis for BTcP between 10 and 22 hours, which shows that at this patients the larger breakthrought pain number (from total average of 2.17 BTcP/patient/day) is registered in that period (29). In our study 1408 (41.79%) BTcP is registered at 142 patients with verified bone metastasis or 0.992 BTcP/patient/day, while at 291 patients without verified bone metastasis 1961 BTcP is registered or 0.674 BTcP/patient/day, which is statistically considerably less ($p<0.0001$). Also, the Radbruch and co. studies agree that bone metastasis are the cause of enlargement of intensity breakthrough pain, which is harder to control (30, 31).

5. CONCLUSION

The most of this research was aimed at breakthrough pain (BTcP) which occure during the treatment between middle to strong basal cancer pain (6-10 per NRS) by the strong opiates, although we were during our study recorded relatively large number of breakthrough pain of smaller intensity (3-6) at patients treated with weak opiates, and which are also adversely impacted at the satisfaction od patients by pain treatment and demanded additional doses of analgetics. In a smaller percentage it is possible to treat breakthrough pain of stronger intensity (7 and 8) with maximum doses of weak opiates (in case that patients rejects to take strong opiates, opiofobies etc) althought there is a better effect when introducing strong opiates as rescue doses. Bone pain caused by metastasis in advanced stage of cancer disease is the cause of larger number of breakthrough pain of bigger intensity with the need of introducing addiotional terapy next to opioid preparates. The most breakthrough pains were registered in period between 18 and 24 hours, although the cause is not completely clear.

- Conflict of interests: none declared.

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