The effect of breakthrough pain on heart and lung function during the cancer pain treatment in palliative care

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Abstract

Introduction: The aim of the research was to determine the effect of breakthrough pain (BTP) on heart and lung function in patients whose cancer pain had been treated with strong opiates.

Methods: A prospective study was conducted on 80 patients who were treated in recumbent patients' hospice of Palliative Care Centre (hospice) University Clinical Centre Tuzla. The effect of pain breakthrough on heart function was monitored by blood pressure and pulse measuring outside. The effect on respiratory function was monitored by measuring the respiration number with SpO_2 and pCO_2 and pO_2 capillary blood values outside, during and after relieving pain breakthrough.

Results: Mean value for Karnofsky score for patients upon admission was 47.13 ± 11.05 and on discharge 51.25 ± 11.73. The total number of pain breakthroughs for patients within the 10 days of the treatment was 1396. During the pain breakthrough the mean of systolic pressure was 133.1 mmHg and it was statistically significantly higher than the mean of systolic pressure measured after BTP relief with oral morphine. The mean of diastolic pressure measured outside of pain breakthrough was 75.9 mmHg and after the BTP relief it was 72.9 mmHg. The mean pulse outside of pain breakthrough was 92.7 heartbeats per minute and after the BTP relief 8 9.1 heartbeats per minute.

Conclusion: Pain breakthrough leads to pulse acceleration, increased systolic and diastolic blood pressure and it also affects respiratory function by accelerating the respiration.

Keywords: breakthrough pain, heart and lung function

Introduction

International Association for the Study of Pain – IASP, defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is the most frequent and the most severe symptom of in cancer patients and 75-90% of patients in terminal stage endure pain, the cause of cancer pain can be the cancer itself, cancer therapy or the accompanying disorders related to cancer pain. Tumour cells release endothelin, prostaglandins, alpha tumour necrosis factor (TNF), proteolytic enzymes prostaglandins (E_1 and E_2), proinflammatory cytokines (TNF, IL-1, IL-6), substance P, tumour growth factor and they also activate nociceptors that fire spontaneously and create peripheral sensitization and fast tumour growth of different types of tumours can lead to compression and nerve damage which causes ischemia and direct proteolysis (1). Tumour surgery can lead to nerve damage and neuropathic pain. Chemotherapy induces the release of algogenic cytokines, radiotherapy leads to tissue fibrosis with nerve compression and painful mucositis can be caused both by radio and chemotherapy (2). Breakthrough pain (BTP) is a temporary sudden pain, a subtype of incidental pain that occurs over the "basic" pain during the opiate treatment. It should be differentiated from the weakly controlled basic pain, which is also often a cause of the occurrence of pain breakthrough, also from

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TABLE 1. Differentiation of basal cancer and breakthrough pain

	Basal cancer pain	Breakthrough pain
Onset	Sudden or occurring gradually	Unexpected, sudden, unpredictable
Duration	Persistent, lasts for at least 12 hours daily	From few seconds to several hours, usually around 30 minutes
Characteristics	Dull, painful, sharp	Sharp, shooting, radiant
Treatment	Long-lasting opiates with regular intake	Urgent therapy, immediately releasing or fast-acting opiates, intake according to the need

emergency pain and "crescendo pain". When BTP occurs, basal pain is by definition relatively stable and under control (3). The governing committee of European Association for Palliative Care suggested the use of term "episodic pain" which they divided into two groups –with and without significant basal pain (4). BTP by its intensity has to be severe to unbearable on basis of weak or medium severe pain. Portenoy and Hagen (5) described several characteristics that are important for understanding the BTP: ratio of BTP with fixed dose of opiates, temporal characteristics of BTP (duration period, time of occurrence), the cause of occurrence of BTP, possible predictability of the occurrence and pathophysiology and etiology of BTP (Table 1). BTP occurs in 70-95% of the cases in patients in advanced stage of cancer disease (6). The intensity of BTP is often described as very severe and intensive pain (from 7- 10 according to NRS (Numerical Rating Scale) with fast paroxysmal onset (<3 minutes) and the mean of reaching the "pain peak" in less than 10 minutes. In 80-90% of the cases the duration is from 15 to 30 minutes and the mean frequency in patients in terminal stage of the cancer illness is 4-7 painful episodes a day (7). In 27% of the cases it occurs spontaneously, while the occurrence of the BTP can be accelerated by activities such as movements, laughter, sneezing, coughing, sitting, touch, distension of hollow organs (bowels, urethra) or psychosocial stimuli (8). The cause of the BTP is most often related to bone pain (27%), local soft tissue tumour invasion (21%) and brachial plexus syndrome (9%) , and it can be classified as nociceptive, visceral nociceptive or neuropathic (9). Two key components in treating BTP are: the size of individual salvage dose and tome interval of administering the drug. Most authors agree that the average "salvage dose" should be 10 to 20% of total daily dose of fast-acting strong opiate (10). In 17-30% of the cases, BTP is related to inadequate analgesic treatment, whether it is subdosing analgesics or too long time interval between the doses, which leads to reduction of concentration in the plasma e.g. opiate in the end of dose interval which causes the increase of pain intensity so called end dose insufficiency. At the same time the patients endure BTP not wanting to take fast-acting opiate out of fear of side effects or developing resistance and addiction. The most frequently used drugs in BTP treatment are fast-acting oral opiates with the onset of 20 to 30 minutes after the administration, with maximal effect after 45 to 60 minutes (11). Much better effects in relieving the BTP, because of its fast acting onset, are achieved with transmucosal fentanyl citrate, which passes through the blood brain barrier within 3-5 minutes, with its peak effect within 20-40 minutes with its overall duration from 2-3 hours after the administering the drug (12). Intranasally applied fentanyl citrate spray, relieves the episodic pain significantly faster (within 5-10 minutes) in regard to oral morphine, with safe way of application, without side-effects and good patient tolerance (13). The aim of the research was to establish the effect of BTP on heart and lung function in patients whose cancer pain was treated with strong opiates.

Methods

Patients

A prospective study has been conducted on 80 patients who were treated in recumbent patients' hospice at Palliative Care Centre of Clinical Centre Tuzla in the period of September 2010 to March 2011. Basal Cancer pain (with 7-10 intensity according to NRS) was treated with strong opiates (oral morphine and transdermal fentanyl) whose doses were increased every third day of the treatment by 50%, unless more than two pain breakthrough occurred the previous day, in which case a salvage dose of 8 mg of oral morphine was

required. General condition of the patients was assessed using Karnofsky score upon admission and also after 10 days of treatment. The effect of pain breakthrough on heart function was monitored by measuring the blood pressure (systolic and diastolic) and pulse outside, during and after relieving the BTP with salvage dose of oral morphine. The effect on respiratory function was monitored by measuring the number of respirations, values of SpO_2 measured with pulse oksymeter pCO_2 and pO_2-from ABS medical report, from capillary blood, outside, during and after relieving BTP by salvage dose of oral morphine. The study excluded the following patients; patients allergic to strong opiates, patients who have previously used strong opiates, patients with heavy vomiting that hindered the intake of oral morphine, patients with increased value of pCO_2 due to respiratory insufficiency or as a sign of renal and liver insufficiency.

Statistical analysis

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. For testing the repeated measurements of samples with more than 2 variables, ANOVA for repeated measurements was used. For testing the hypothesis of difference in frequency of parameters of dichotomous scale, the test used was χ^2 test. Statistical hypothesis were tested based on the level of significance of $\alpha = 0.05$ meaning that the difference between samples was considered to be significant if $p < 0.05$.

Results

Mean value for Karnofsky score for all 80 patients upon admission was 47.13 ± 11.05 and on discharge 51.25 ± 11.73, and after relieving the pain Karnofsky score was statistically significantly better ($p = 0.0005$). The total number of pain breakthroughs in all 80 patients within 10 days of treatment was 1396 (1.75 breakthroughs per patient a day). On the first day of treatment, total number of pain breakthroughs was 208 (2.6 breakthroughs per patient a day), on the second day it was 184, and on the third day 186 BTP (2.3 breakthrough/per patient/a day). On the fourth day of the treatment the total of 160 BTP were noted (2.0 breakthroughs/per patient/a day) which is statistically significantly less compared to the first day (p= 0.008). Also, in the following days, the BTP kept reducing and on the tenth day total of 53 BTP was registered (0.66 breakthroughs/per patient/a day), which is statistically significantly less compared to the day of the admission ($p< 0.0001$) (Figure 1).

The effect of BTP on cardiovascular system

During the BTP, mean value of systolic pressure in all 80 examinees (in 1396 measurements) was 133.1 mm Hg (from 115 do 165 mm Hg) and was statistically significantly greater ($p< 0.0001$) than systolic pressure mean measured in a state of stabile, controlled pain (outside BTP) when the mean was 120.4 mm Hg (from 100 to 140 mm Hg). After relieving BTP by salvage dose of oral morphine the mean of systolic pressure was 114.5 mm Hg (from 80 to 140 mm Hg) and was statistically significantly lower ($p<0.0001$) compared to the systolic pressure during the BTP (Figure 2). The mean of diastolic pressure in all 80 examinees, monitored outside BTP was 75.9 mm Hg (from 60 to 95 mm Hg). During the BTP the mean of diastolic pressure (in 1396 measurements) was 84.7 mm Hg (from 70 to 130 mm Hg) and was statistically significantly higher ($p<0.0001$) compared to measuring outside BTP. The value of diastolic pressure after relieving the BTP with salvage dose of oral morphine was 72.3 mm Hg (from 50 to 95 mm Hg) and was statistically significantly lower ($p< 0.0001$) compared to diastolic pressure during the BTP (Figure 2). Measured outside BTP, mean pulse in for all 80 patients was 92.7 heartbeats per minute (From 78 to 110 heartbeats per minute). During the BTP statistically significant pulse acceleration occurs ($p< 0.0001$) so the mean rises to 102.2 heartbeats per minute (from 83 to 120 heartbeats/min), followed by significant pulse slow down after relieving the BTP with oral morphine ($p< 0.0001$), so the mean shows 89.1 heartbeats per minute (from 64 to 107 heartbeats/min) (Figure 2).

The effect of breakthrough pain on respiratory system

The mean number of respirations, measured in a state of stabile, controlled pain was 13.6 per minute (from 12 to 16), with statistically sig-

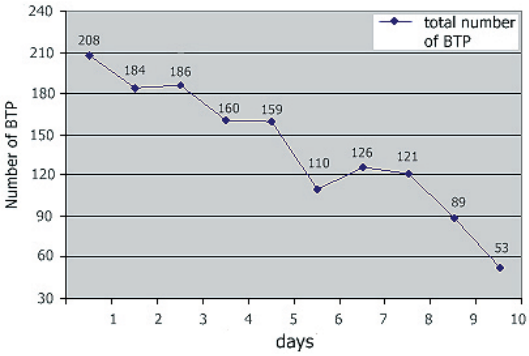

FIGURE 1. Number of BTP through days of treatment in all examinees

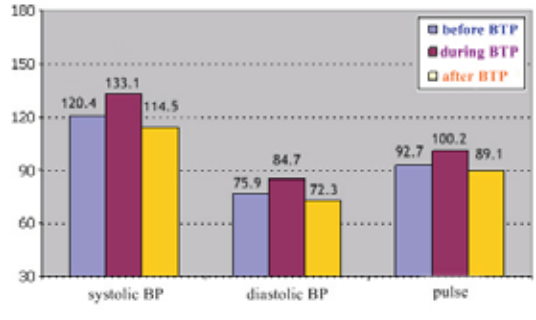

FIGURE 2. The values of blood pressure and pulse depending on BTP

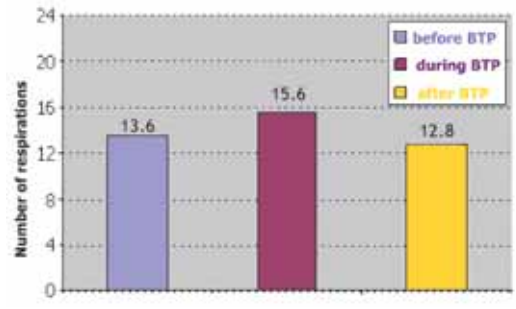

FIGURE 3. The mean of respirations per minute depending on the number of BTP

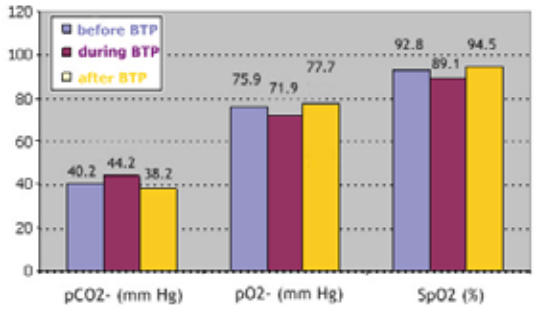

FIGURE 4. The mean of pCO_2, pO_2 and SpO_2 depending on BTP

nificant respiration acceleration (p<0.0001) during the BTP to the mean of 15.6 per minute (from 12 to 21 respirations per minute). Relieving BTP with salvage dose of oral morphine significantly slows down the respiration speed (p<0.0001) so the mean number of respirations per minute is 12.8 (from 11 to 16) (Figure 3). The mean of partial pressure of carbon dioxide in capillary blood (pCO_2) in all 80 patients outside BTP was 40.2 mm Hg (from 29.6 to 51.1 mm Hg) while during the BTP statistically significant (p< 0.0001) increase of pCO_2 to the mean of 44.2 mm Hg occurred (from 30.2 to 57.2 mm Hg), and relieving BTP with salvage dose of oral morphine significantly reduces the mean of pCO_2 mm Hg (from 28.3 to 51.1 mm Hg) (Figure 4). Partial pressure of oxygen (pO2) in capillary blood in all patients outside BTP in mean was 75.9 mm Hg (from 62.7 to 91.6 mm Hg) and is statistically significantly higher (p< 0.0001) than pO_2 mean during BTP, which was 71.9 mm Hg (from 55.7 to 88.4 mm Hg) on mean. By relieving the pain by salvage dose of oral morphine the ventilation improves so the mean of pO_2 was 77.7 mm Hg (63.1 to 92.7 mm Hg), which is statistically significantly higher (p< 0.0001) than during BTP (Figure 4). The saturation mean (SpO_2%) measured with pulse oximeter in all 80 patients, monitored outside BTP was 92.8 % (from 83 to 96%) only to be statistically significantly smaller during the BTP (p<0.0001) when it was 89.1 % (from 79 to 96%) and after relieving BTP with oral morphine, the mean SpO_2 94.5% (from 84 to 98%) and it was statistically significantly higher (p<0.0001) compared to the means of SpO_2 during BTP but also before the onset of BTP (Figure 4).

Discussion

In the study that monitored the effects of cancer pain treatment with transdermal fentanyl within

the period of 3 months, Karnofsky score was relatively constant during the treatment, with the mean of 69 ± 2 on the first day, 68 ± 2 at the end of the second month and 69 ± 2 at the end of the study (14). In our study, mean value of Karnofsky score for all 80 patients upon admission was 47 ± 11.05 and upon release 51.25 ± 11.73, so after relieving the pain Karnofsky score was significantly better (p=0.0005). The study of Marinangeli and associates on 48 patients in advanced stage of carcinoma showed, contrary from our study, that after the opiate treatment with the average duration of 76.66 ± 41.15 and significant reduction of pain intensity (p = 0.04), statistically significant reduction of Karnofsky performance status occurs (from 58.92 ± 5.56 upon admission, with the reduction of – 24.04) and the degree of life quality, shows deterioration of general condition (15). In our study, after relieving the pain with strong opiates, dyspnea was statistically significantly reduced (p< 0.0001; 4.41 ± 2.13 compared to 1.95 ± 1.43. BTP significantly accelerates respiration, but no considerable difference was noted compared to the number of respirations before the BTP (13.6/min) and after relieving the pain with strong opiates (12. 8/min). A study published for palliative care units in Japan states that dyspnea occurs in 29 to 74% of the patients, regardless of the type of carcinoma in terminal stage of the illness, in which respiratory depression treated by morphine is defined as deceleration of breathing by more than 10% and it reduces SpO_2 by more than 5. The mean dose of morphine used was 65 mg/per day/per patient (in our study 52.42 mg within all ten days of the treatment.) Also, in our study, there was no significant difference in the number of respirations (p= 0.117) before and after the application of morphine. In this study the mean of oxygen saturation (SpO_2%) measured by pulse oximeter was around 88% before, and up to 98% after the morphine treatment (p=0.125), and as well as in our study there was no statistically significant difference. This study concurrently draws a conclusion that if the morphine is applied in the form of nebulizer (if it is inhaled) it relives the breakthrough pain or sudden onset of dyspnea significantly faster and it has far less system side effects (constipation, drowsiness etc.) (16). In random double-blind controlled study conducted in Switzerland in older patients in which dyspnea was treated with 5 mg s.c. of morphine, measuring taken 45 minutes after the treatment show, like in our study, a significant (p<0.01 reduction of pain intensity [(according to VAS scale: 57.8 ± 16 before compared to 32.8 ± 15 after the morphine treatment, while in the placebo group control measuring shows aggravation of pain from 50.6 ± 18 before, compared to 51.1±15 after the application of the placebo)]. The number of respirations after the morphine treatment was smaller (-2 ± 2.2), while in the placebo group there was no difference in the number of respirations (p=0.02) compared to experimental and placebo group. In this particular study, as well as in our study, there was no significant difference in blood oxygen saturation before and 45 minutes after the morphine treatment (0 ± 1.5). The study concludes that the morphine reduces dyspnea in patients suffering from cancer without any significant side-effects, with the use of one quarter of regular 4-hour dose of morphine used in pain treatment (17). A study by Estefan and associates follows similar parameters in 30 patients in terminal stage of cancer disease that is not dependent on oxygen therapy. There was no statistically significant change (p = 0.14) in values of end-tidal CO_2 (values before 33.39 ± 5.0 compared to means after 34.79 ± 5.7 mm Hg) after the morphine treatment which lead to significant reduction of pain intensity. In our study as well, there is no significant change in the mean of partial pressure in the capillary blood (pCO_2) before and after the treatment with oral morphine [39.9 mm Hg (from 29.6 to 51.1 mm Hg) before compared to 38.2 mm Hg (from 28.3 to 50.8 mm Hg) after the treatment], although, contrary to the Estefan and associates study, the means of pCO_2 in our study were somewhat higher after the treatment (18). A Study conducted at St. Christopher Hospice monitors the effect of oral morphine on respiratory function in 31 patients. All patients received over 100 mg morphine sulphate a day in the average doses of 30 mg for every 4 hours (from 20 to 90 mg). The diagnoses of cancer were set approximately 11 moths (from 3 to 174 months) before the admission to hospice. Following the value of respiratory parameters blood PH was in the range from 7.33 to 7.48, pCO_2 from 25.8 to

52.1 mm Hg, pO_2 from 48.3 to 123.5 mm Hg and HCO_3 from 13.3 to 28.3 mmol/l. The study concludes that the appropriate dose of titration of oral morphine (regardless of its plasma level) relieves pain well and in addition to that it provides safety from developing respiratory depression in cancer pain. In our study, relieving the pain leads to reduction of pCO_2 (from 44.6 mm Hg to 38.2 mm Hg), the increase of mean of pO_2 (from 71.4 mm Hg to 78.1 mm Hg), and also the increase of SpO_2 from 89.1% during the breakthrough pain to 94.5% after relieving the breakthrough pain (19).

While the effect of acute pain on heart function has been studied thoroughly, there are few studies that talk about the effect of chronic pain on blood pressure and heart frequency. The research by Radosh et al. (2009) follows the impact of chronic pain treatment efficiency on heart function. The research was conducted on 37 patients whose pain was determined by numerical scale (from 0 to 10), and the treatment, depending on pain intensity was conducted accordingly to the guidelines of tree level scale. The pain intensity during the first check-up was on average 8 (from 6, 0 to 10, 0), during the first control check-up 5 (from 2.7 to 6.5) and 4 (from 2.5 to 5.3) during the third examination which is statistically significantly less (p<0.001). The mean of systolic pressure was, as in our study as well, significantly reduced (p<0.001) after relieving the pain, at the control check–up compared to the first examination [130 (from 120 to 148 mm Hg) compared to 150 (from 130 to 160 mm Hg)]. The mean of diastolic pressure was significantly reduced (p<0.007) at the control check-up [90 (out of 80 to 98 mm Hg) compared to 80 (from 80 to 88 mm Hg)] which corresponds with the results of our study, while contrary to the results of our study, in this research there was no significant difference in the heart function frequency [p = 0.821; 78 (72 to 83 per minute) compared to 78 (71 to 83 per minute)] (20).

Conclusion

Breakthrough pain, as an "acutization" of chronic cancer pain affects the cardiovascular system leading to pulse acceleration, increase of systolic and diastolic blood pressure. Breakthrough pain affects the respiratory function by leading to respiration acceleration, the increase of pCO_2 values, and the reduction of pO_2 and SpO_2 values, without statistically significant difference in relation to mentioned parameters before the onset of breakthrough pain. By using modern fast-acting opiates such as transmucosal fentanyl citrate or internasal fentanyl citrate spray, the breakthrough pain is much more easily intercepted (within 5- 10) minutes and by doing that the effect of BTP on cardiovascular and respiratory system is reduced.

Competing interests

The authors declare that they have no conflict of interest.

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