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Chrono study: prevalence of breakthrough pain among patients with non-cancer chronic pain in Andalusia,Spain

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ABSTRACT

Objective: The aim of this study was to evaluate the prevalence of breakthrough pain (BTP) in ambulatory patients with non-cancer chronic pain in Spain and to characterize physio-pathology, location, intensity and frequency of BTP episodes.

Methods: Prospective, non-interventional, observational study conducted in 16 pain units of hospitals in Andalusia and Ceuta. Eligible consecutive patients were are asked whether they experience BTP defined as "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite being stable and controlled background pain". On each survey day, the first two patients reporting BTP were further questioned on the clinical characteristics of their BTP (etiology, onset, intensity, frequency and treatment).

Results: A total of 3,209 patients with non-cancer chronic pain were screened to identify 1,118 patients with BTP, which represented a prevalence of 36 %. BTP characteristics were retrieved from 350 patients: mean BTP intensity was 8.3 (± 1.4) on a Visual Analogue Scale (VAS), with a mean of 2 episodes/24 hour (range 1-5/24 h). Pain mechanism was mixed in 149 (42.6%), neuropathic in 91 (26 %) and nociceptive in 72 in (20.6 %) of patients. Significant correlation was found between BTP intensity and both higher background pain ($r = 0.243$, $p < 0.001$), and daily BTP episodes frequency ($r = 0.123$, $p = 0.003$). 78 % of the patients were on opioid treatment. The most frequent were fentanyl citrate (52.6 %) and tramadol (17.4 %).

Conclusions: The prevalence rate of BTP in patients with chronic non-cancer pain is higher than one-third of the patients seen in outpatient hospital pain units in Spain. BTP caused reduced levels of functionality, psychological disorders, and an increase in health care expenditure. Individualization is the key to treatment.

Key words: Breakthrough pain, chronic pain, epidemiology, Spain.

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RESUMEN

Objetivo: El objetivo de este estudio es evaluar la prevalencia de dolor irruptivo (DI) en pacientes ambulatorios con dolor crónico de origen no oncológico y caracterizar la fisiopatología, localización, intensidad y frecuencia de los episodios de DI.

Material y métodos: Estudio observacional, prospectivo y no intervencionista realizado en 16 unidades de dolor ambulatorias de hospitales de Andalucía y Ceuta. Se preguntó a los pacientes consecutivos elegibles si experimentan DI definido como "una exacerbación transitoria del dolor que ocurre espontáneamente, o en relación con un desencadenante predecible o impredecible específico, a pesar del dolor de base estable y controlado". En cada día de la encuesta, los dos primeros pacientes que confirmaron DI fueron preguntados sobre las características clínicas de su PTP (etiología, inicio, intensidad, frecuencia y tratamiento).

Resultados: Se realizó un cribaje a un total de 3209 pacientes con dolor crónico no oncológico para identificar a 1118 pacientes con DI, lo que representó una prevalencia del 36 %. Se obtuvieron las características del DI de 350 pacientes: la intensidad media fue de 8,3 (± 1,4) en una Escala Analógica Visual (EVA), con una media de 2 episodios/24 horas (rango 1-5/24 h). El mecanismo del dolor fue mixto en 149 (42,6 %), neuropático en 91 (26 %) y nociceptivo en 72 (20,6 %) de los pacientes. Se encontró correlación positiva entre una mayor intensidad de DI con el nivel de dolor basal ($r = 0,243$, $p < 0,001$), y el número de crisis diarias de DI ($r = 0,123$, $p = 0,003$), ambas estadísticamente significativas. El 78 % de los pacientes estaba en tratamiento con opioides. Los más frecuentes fueron el citrato de fentanilo (52,6 %) y el tramadol (17,4 %).

Conclusiones: La tasa de prevalencia del DI en pacientes con dolor crónico no oncológico es superior a un tercio de los pacientes atendidos en las unidades ambulatorias de dolor hospitalario en España. El DI provoca niveles reducidos de funcionalidad, trastornos psicológicos y un aumento del gasto asistencial. La clave del tratamiento es la individualización.

Palabras clave: Dolor irruptivo, dolor crónico, epidemiología, España.

INTRODUCTION

transitory flare of pain in the setting of chronic pain managed with opioid drugs" (1). Subsequently, this definition has been expanded to "transitory exacerbation of pain that appears, either spontaneously or related with a specific, predictable or unpredictable trigger, despite the existence of a relatively stable, appropriately controlled baseline pain" (2).

Although BTP is perfectly defined for cancer pain, its presence in patients affected by chronic pain of non-neoplastic origin remains controversial and even a subject of debate (3,4). Recent studies regarding the prevalence of BTP in patients with chronic non-cancer pain show enormous differences, ranging between 38% and 80% of patients (5-9). This should be attributed It to the different definitions of BTP used, and to the healthcare environment of the different studies (7,9-11).

In cancer patients, the presence of BTP is associated with greater pain, high levels of anxiety and depression, a worsening of functional state and quality of life, together with less effectiveness of analgesic treatment (1,12,13), and a similar negative impact has been found in studies on patients with chronic non-cancer pain (5-7,13).

There exists consensus among professionals that diagnosis of BTP requires appropriately controlled baseline pain, though the specialized literature does not provide an unequivocal definition of "appropriately controlled" (1-4). Furthermore, BTP is not a single nosologic entity, but instead includes different etiologies, changing physiological mechanisms and clinical characteristics that vary among patients and fluctuate between them as the disease progresses (2,9,14). Accordingly, diagnosis is carried out based mainly on the description given by patients themselves regarding pain patterns, even though they are not aware of the concept of BTP. In Spanish, for example, there is no translation for the polysemic English term "breakthrough" and instead uses the term "irruptivo" , although this adjective does not exist in the dictionary of the Real Academia Española, so we have to know all the potential meanings given, such as "pain flares", pain peaks", "worst pain", etc. Nevertheless, despite all this, there exists clear consensus as to the key attributes of BTP (5-9,15), and in that its existence represents a considerable burden for the healthcare system, negatively affecting both quality of life of patients and their carers (8,9,13,15).

To date, no studies have been published regarding the prevalence of BTP among patients with chronic non-cancer pain in Spain. The objective of this study was to determine the prevalence of BTP among out-patients with non-cancer chronic pain treated by clinicians specialized in pain in Andalusia, Spain. It also sought to evaluate episodes of BTP according to etiology, pathology, temporary patterns and effectiveness of pain treatment in terms of its satisfaction and compliance.

METHODS

Observational, prospective, cross-sectional, non-interventionist study, carried out between May and June 2014 in 16 out-patient pain units of hospitals in Andalusia and Ceuta, Spain.

This study was approved by the Committee of Clinical

Investigation Ethics of the Hospital Universitario Regional de Málaga, and all patients signed their informed consent before their inclusion.

Patients

The eligible population consisted of adults (over 18 years old), with appropriate oral and written comprehension, competent to grant their consent, with etiology of chronic non-cancer pain. Other inclusion/exclusion criteria were not applied. All patients were referred to the pain units by their medical clinician or by other specialists, and were treated as out-patients.

Study design

For this study, a single visit was made, coinciding with the patient's inclusion. Information was gathered in the Case Report From (CRF) designed for this purpose, and all information was filled in by the investigating clinician as from data obtained in the visit, using the patient's clinical background as required.

In this respect, BTP was defined as "a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain." (2). This definition was developed according to the following attributes: background pain must be chronic (duration > 3 months), and controlled (4/10 in a visual analog scale [VAS]), and must have peaks of high intensity pain (VAS 7) and short duration (<60 min), well differentiated from background pain and unrelated with the pain due to end of doses associated with medication.

The study consisted of two phases: initially, aimed at identifying the rate of BTP prevalence, and secondly, to evaluate the characteristics of BTP through an in-depth interview with patients selected in the previous stage. Figure 1 describes the flow-chart of the study design.

For the first stage, all patients referred to the pain unit were asked by means of direct questioning (2) whether they experienced peaks of intense pain above their background pain. If the answer was affirmative, they were classified as patients with BTP.

For the second stage, a sample of patients was minimized using the strategy of recruiting the first two identified patients each day as patients with BTP. Each pain unit aimed to recruit 20 patients in the second stage (some units recruited less than 20 patients and some fewer). The patients chosen for the second stage answered a specific questionnaire regarding their pain.

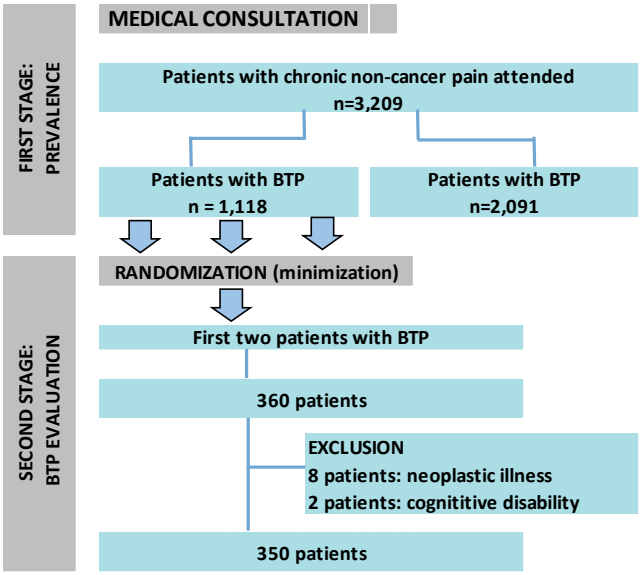

Fig. 1. Patient recruitment and randomization

As an observational, cross-sectional study, all patients continued their medical treatment to regulate background pain, and this meant no alteration to the clinical course.

Statistical analysis

A descriptive analysis of the study variables was carried out. For continuous variables, mean, standard deviation, median, minimum and maximum values are given; for categorical variables, absolute, relative frequencies and percentages are given.

The prevalence of BTP was calculated as the proportion of patients with non-cancer chronic pain who experienced at least one episode of BTP.

To evaluate the differences among sub-groups of continuous variables defined by the presence of BTP or other characteristics, Student's t tests and analysis of variance (ANOVA) were applied; Chi-square analyses and covariance were used to analyze associations among categorical variables. Statistical significance was set at $p < 0.05$. All analyses were carried out using the statistical package for the Social Sciences software (SPSS®), version 15.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Sixteen pain units examined to 3,209 patients with non-cancer chronic pain to identify 1,118 patients affected by BTP. The prevalence of BTP

TABLE I
PATIENT DEMOGRAPHY AND CHARACTERISTICS

Variable	*Patients with BTP (n = 1118)*	*Patients without BTP (n = 2091)*	*Total (n = 3209)*
Age, years			
Mean (SD)	60,3 (14,1)	61,1 (15,3)	61,14 (13,74)
Median, (range)	61 (24-91)	62 (18-94)	62 (18-94)
Gender, n (%)			
Male	396 (35,4 %)	686 (32,8 %)	1.082 (33,7 %)
Female	722 (64,6 %)	1405 (67,2 %)	2127 (66,3 %)

DI: dolor irruptivo. DS: desviación estándar.

stood at 36% of patients. By gender, prevalence was 34.5% among women (714/1.,53) and 37.2% among men (391/661).

Of all patients examined for non-neoplastic chronic pain, 66.2% corresponds women; the sample's age ranged between 18 and 94, and the mean age was 61.14 (± 13.7). Table I shows the demographic characteristics.

To evaluate the characteristics of BTP, 360 patients were considered eligible and 350 (97%) provided data for the study. Eight patients were excluded due to eligibility criteria regarding cancer and 2 were excluded due to inability to meet the study requirements.

Characteristics of chronic background pain

Table II shows the main characteristics of background pain in patients with BTP. We can see that the most frequent causes of chronic pain were: osteoarthritis (103/350; 29.4%), lumbar spondylosis (31/350; 8.9%), disk prolapse (27/350; 7.7%), lower back pain (19/350; 5,4%) and post laminectomy syndrome (18/350; 5.1%).
Background pain was mixed in a greater percentage (219/350; 62.6%). The pain mechanism was neuropathic and nociceptive in 74 (21.1%) and 56 (16%) patients respectively.

In total, 327 (93.4%) patients received opioids: the most common (> 10%) were tapentadol (81/327; 23.1%), oxicodone with naloxone (73/327; 20.9%), tramadol (56/327; 16%), fentanyl (45/327; 12.9%) and oxicodone (38/327; 10,9%). Other drugs administered to treat background pain were non-steroid anti-inflammatory drugs (NSAID (182/279; 61.3%), anticonvulsants (196/279; 56%), antidepressants (115/279; 34.2%) and muscle relaxants (41/279; 11.7%). Non-pharmacological

TABLE II
CHARACTERISTICS OF BACKGROUND PAIN IN PATIENTS WITH BTP (N = 350 PATIENTS)

Severity of background pain, mean (SD), median (range)	
VAS 3,1 (0.7); 2.7 (0-4)	
Chronic pain diagnosis	*n (%)*
Osteoarthritis	103 (29.4)
Lumbad spondylosis	31 (8.9)
Disk prolapse	27 (7.7)
Low back painr	19 (5.4)
Post laminectomy syndrome	18 (5.1)
Post-surgical pain	14 (4.0)
Neuralgia	13 (3.7)
Vertebral fracture	10 (2.9)
Peripheral neuropathies	8 (2.3)
Fibromyalgia	6 (1.7)
Others	101(28.8)
Physiopathology of pain	*n (%)*
Mixed	219 (62.6)
Neuropathic	74 (21.1)
Nociceptive	56 (16.0)
Medication	*n (%)*
Opioids	327 (93.4)
– Tapentadol	81 (23.1)
– Oxicodone-naloxone	73 (20.9)
– Tramadol	56 (16.0)
– Fentanyl	45 (12.9)
– Oxicodone	38 (10.9)
NSAID	182 (61.3%)
Other medication	279 (79.7)
Non-pharmacological medication	186 (53.1)

BTP: breakthrough pain. SD: standard deviation.
VAS: Visual

therapies included local anesthetic infiltrations (98/186;.28 %), blockage (49/186. 14 %) and physiotherapy (25/186; 7.1 %).

The patients assessed the treatment positively and, accordingly, 50.1% rated it as "satisfactory" and 32.4% as "very satisfactory". Likewise, the rate of adherence to medication, according to the patients, was high: 95% responded that they always or almost always took their medication. The reasons for non-compliance were adverse effects (7.1%) and the lack of dose (6.3%). Additionally, 12.9% of patients reported having taken medications without prescription. Evaluation of adherence by the doctor came to a level of 95.2% compliance.

Characteristics of BTP

The mean intensity of BTP was 8,3 ± 1,4 VAS, range 7-10. Patients reported a mean of 2 episodes per day (range 1-5), the most frequent interval of duration was from 30 to 45 minutes (28.8%), and the time until the start of significant pain relief was <15 minutes in 54.2% of patients, although the most frequent interval was from 16 to 30 minutes (25.3%). The most common location of BTP was lumbar (45.4%), followed by lower limbs (32.6%) and knees (7.4%), which shows overlapping with regard to background pain (Table III).

Over a fourth of patients (100/350; 28.6%) suffered predictable or incidental BTP. The pain mechanism was mixed in 149 (42.6%), neuropathic in 91 (26%) and nociceptive in 72 (20.6%) of patients. When the data was adjusted for the study, covariance showed that neuropathic pain associated with greater intensity of BTP in comparison with nociceptive pain (8,3 ± 1,2 versus 7.9 ± 1,7; p = 0,008), although it lacked information in 38 patients (10,.%).

Table IV shows the correlation between pain intensity and controlled variables, that is, the intensity of background pain, the number of daily episodes and the time when significant pain relief begins. There was a low positive correlation between the level of background pain (r = 0,2.3, p <0.01), and the number of daily crises (r = 0.123, p = 0.003) which was statistically significant.

All patients were in treatment for BTP and 273 (78%) took opioids. The most frequent were fentanyl (184/350; 52.6%) and tramadol (61/350; 17.4%).

As regards routes of administration, sublingual was the most used (118/267; 44.2%), followed by oral (117/267; 43.8%), transmucosal (16/267; 6,0%), nasal (15/267; 5,6%) and intravenous (1/267; 0.4%). In 6 patiens, this information was not available. Other drugs used were metamizol (10.0%), paracetamol (8.6%) and ibuprofeno (6.0%).

Data regarding satisfaction with the treatment for BTP showed that 217 patients were satisfied (66.4), while 110 (33.7%) were not. Data was missing for 23 patients. Adherence, according to the assessment of doctors patients, was classified as 76.0% and 75.7%, respectively. The main reasons for non-compliance were lack of doses (8.3%), side effects (4.9%) and lack of efficiency (4.6%). Finally, 11.7% of patients reported having taken medications without prescription. For the purposes of this study, we do not evaluate the perceived effects of medication or any other treatment for BTP.

TABLE III
DESCRIPTPON OF BREAKTHROUGH PAIN EPISODES

Pain intensity,mean (SD); median (range)	
VAS 8,3 (1,4); 8,2 (7-10)	
Location of pain	*n (%)*
Lumbar	159 (45.4)
Lower limbs	114 (32.6)
Knee	26 (7.4)
Upper limbs	19 (5.4)
Cervical spine	17 (4.9)
Shoulders	15 (4.3)
Type of pain	
Incidental	100 (28.6)
Spontaneous	83 (23.7)
Mixed	165 (47.1)
Missing data	2
Number of daily episodes	
1-2	297 (84.9)
3-5	51 (14.6)
Missing data	2
Duration of episodes	
0-14 min	66 (19.0)
15-29 min	80 (23.8)
30-45 min	100 (28.8)
45-60 min	95 (27.4)
Missing data	3
Time tro pain relief	
1-5 min	29 (8.7)
6-10 min	77 (23.2)
11-15 min	74 (22.3)
16-30 min	84 (25.3)
> 30 min	68 (20.5)
Missing data	18

DISCUSSION

Breakthrough pain is a heterogeneous condition which needs to be addressed by evaluating each patient in detail so as to identify the exact nature of the pain (including frequency and other temporal characteristics, severity, location and quality), in order to understand its

TABLE IV
CORRELATION BETWEEN CLINICAL VARIABLES AND GREATER BREAKTHROUGH PAIN (BTP) INTENSITY

Variable	*Correlation coefficient (r)*	*p-value*
Background pain intensity	0.243	< 0.001
Time to achieve analgesia	0.132	0.055
Number of daily episodes	0.123	0.003

relationship with background pain, co-morbid conditions and prior treatments. From this evaluation, reasonable inferences should be derived regarding the BTP's etiology and its physiopathology. In our study, the prevalence of BTP was 36%, a lower percentage than the figures of 48% to the 80% found in previous studies (5,6,8,11,15). This lesser prevalence is in keeping with greater knowledge of the subject. In the case of BTP of a neoplastic origin, a recent systematic review shows that, in the last 20 years, the more the subject has been studied, more the rate of prevalence has fallen (16).

On one hand, it could be the case that the definition of BTP adopted in the study may explain the variation in prevalence, as was already shown by a study on cancer-based BTP (17). In a recent work with chronic patients with cancer and non-cancer pain, which meticulously addressed the clinical characteristics of BTP as elements for developing a diagnostic tool, a prevalence of 38.4% was found in non-cancer patients and 32.4% in cancer patients, which would coincide with the findings of our study, though it is also lower than the literature reports (9). We should highlight the fact that this study has only considered BTP perceived as severe or unbearable (7/10 on a VAS scale), in accordance with the most recent recommendations (18). Another factor to bear in mind is the study's healthcare environment. In this respect, works carried out in ambulatory clinics showed the lowest rates of prevalence (5,9,16,19). Other studies suggest that pain specialists may be more qualified to recognize this clinical condition (20) than other medical specialists or non-medical interviewers (5,8).

As regards the characterization of BTP in our sample, the most frequent location was lumbar, coinciding with foregoing works (8,13). Similarly, the number of daily episodes (mean 2) and their duration (> 30 minutes in 53% of patients) is similar to the results of other studies in chronic non-cancer patients (5,6,8,11,21), while typology (spontaneous and incidental), showed a similar percentage, in line with previous studies carried out on cancer-based BTP (21,22).

Controlling background pain is an inevitable requirement to diagnose BTP, though it refers to different clinical matters. In this respect, studies show that a reduction in the intensity of background pain did not reduce the prevalence of BTP (18,22-24), though it did reduce the intensity and frequency of episodes (23,24). In our sample, we found that the intensity of BTP is significantly correlated with a larger number and higher limits of what is considered adequately controlled background pain, even if the correlation was low because the relationship was causal. It is worth noting that 82.5% of patients were satisfied with the medication for background pain, while this figure falls to 66.4% for BTP treatment, making the adherence rate fall from 95% to 76%. In this respect, we should highlight the fact that using opioids for background pain averaged at 93.4% of patients, falling to 78% for treatment of BTP, even though analgesic opioids are considered the current standard for treating BTP (2,4,10,16,22,24,25).

BTP must be treated early and appropriately. The ideal remedy is fast-acting, short half-life medication to avoid opiate toxicity, and easy to administer (25), always bearing in mind the patient's preferences. Fentanyl is the medication that best adapts to these requirements, and is the most prescribed medication in our study, achieving a good level of adhesion and satisfaction. As regards the route of administration, sublingual was the most valued, and this also coincides with other works on patient preferences (25,26).

This study has some limitations that should be considered upon evaluating the results. Perception of pain is an eminently subjective experience, and we evaluate BTP exclusively on the basis of data provided by the patient, and which could be subject to bias regarding misunderstanding of concepts, or with their own expectations about treatment. Furthermore, this study is only based on data gathered during a single interview in the pain unit. We should also note that end-of-dose pain has not been addressed and, ultimately, lack of data regarding certain characteristics of the BTP and the observational design do not lead to solid conclusions as to the causal relationship between variables. We should also mention, although there are issues that go beyond the objectives of this study, lack of control or evaluation or evaluating drug use or abuse disorders.

In conclusion, this study offers new information regarding the prevalence and characteristics of non-cancer breakthrough pain in ambulatory hospital pain units in Spain. Our results show that more than a third of patients with chronic pain suffer BP and, accordingly, show lower levels of functionality, higher levels of psychological disorders and even higher healthcare costs. The key to treatment is indvidualization, using both pharmacological and non-pharmacological criteria.

CONFLICTS OF INTEREST

The study was sponsored by Kyowa Kirin Farmacéutica, S.L.U. AJJL is an employee of Kyowa Kirin Farmacéutica, S.L.U. The authors state that there are no other conflicts of interests.

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