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THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

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Journal:	*International Journal of Clinical Practice*
Manuscript ID:	IJCP-10-10-0536.R1
Wiley - Manuscript type:	Original Paper
Date Submitted by the Author:	11-Dec-2010
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Specialty area:	

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Acknowledgements:

The authors would like to thank Birgit Jaspers for careful review of this manuscript and English editing.

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Background:

WHO-Step-III opioids are often required right from the start of pain therapy in order to achieve sufficient symptom control. Bowel dysfunction, particularly constipation, is one of the most frequent and persistent side effects of opioid therapy, and it is known to cause considerable distress in many patients. The aim of the study was to evaluate whether patients with advanced cancer and moderate to severe cancer pain will benefit from treatment with oxycodone/naloxone prolonged-release tablets (OXN), with particular regard to constipation.

Material and Methods:

In this exploratory, non-randomized, open-label, monocentre study we evaluated the bowel function in palliative care patients treated with OXN. During the treatment phase patients were titrated up to an adequate pain control. The Bristol Stool Form Scale (BSFS) (Type 1-7) and Bowel Function Index (BFI) (0-100) were used to assess consistency and frequency of bowel movements. Global patient satisfaction was assessed with Patient Global Impression of Change Scale (PGIC) (1-7). Statistics: mean±SD, significance $p < 0.05$.

Results:

26 patients (10 males (38.5%)) were included; mean age 70.6±14.0 y, length of stay 22.6±21.2 days. At admission all patients had opioid-induced constipation. During the observation period of 14 days the daily mean dose of OX was 36.2±17.2 mg and of N 15.4±5.3 mg. In 5 cancer patients pain control was not sufficient under the approved maximum total daily dose of 40/20 mg OXN; therefore switching to hydromorphone. BFI improved significantly in 21 patients (72.4±17.0 vs. 36.8±13.4) ($p<0.0001$); stool consistency (BSFS) improved from type 2.0±0.7 to 4.9±1.0 ($p<0.0001$). PGIC at discharge was 1.9±0.8.

Discussion:

Patients with OXN treatment throughout the whole study phase showed a clinically relevant improvement in pain intensity and bowel function as well as increased satisfaction. Well

known disadvantages of laxative treatment might be spared or even circumvented under OXN treatment, if appropriate.

What's already known about this topic?

There are no published data for clinical use of oxycodone/naloxone in patients with advanced cancer

What does this article add?

Data on clinical use of oxycodone/naloxone in patients with advanced cancer and cancer related pain and opioid-induced constipation

Key words: oxycodone, naloxone, opioid-induced constipation, cancer pain, palliative care

Introduction

Chronic pain occurs in up to 70% of patients with advanced cancer [1] and is known to have a significant impact on patients' ability to function and quality of life.[2]

Over the past twenty years opioid use for symptom relief has increased significantly in developed countries.[3] In many countries opioids are now being introduced at earlier stages in palliative care and used in higher doses.[3,4] This appropriate increase in the use of opioids resulted in the development and improvement of management strategies for dealing with unwanted effects such as opioid-induced constipation.

The prevalence of constipation in patients with cancer generally ranges from 70% to 100% .[5-7] Evidence suggests that up to ninety percent of patients treated with opioids will experience chronic constipation and of those receiving standard laxative treatments over half will remain dissatisfied with the outcome.[5,8] Constipation is a distressing complication for oncology patients that is often underassessed and undertreated and may occur as a side effect of tumour growth or an adverse effect of drug therapy. For cancer patients, additional causative factors include gastrointestinal obstruction, electrolyte abnormalities such as hypercalcaemia or hypokalaemia, opioid-analgesic use, other drugs, and other concurrent processes (e.g. organ failure), decreased mobility, and depression.[6,9,10] Physiologic factors that exacerbate constipation are inadequate oral intake of fluids, dehydration, inadequate intake of dietary fibre, or organ failure. Constipation may potentially lead to further symptoms such as nausea and vomiting due to delayed gastric emptying as well as gas distention and abdominal cramps associated with generalised bowel dysfunction.[11]

However, constipation is the most frequent and most persistent side effect of opioid treatment. Unlike other side effects of opioid medication, such as nausea and emesis, there is no, or extremely slow, tolerance build-up to the constipatory effects of opioids and most patients continue to require laxative therapy for the duration of opioid use.[12,13] The (wherever possible

causal) treatment of constipation requires taking a thorough medical history and examination of the patient. Further, sound knowledge of the complex processes in the pathophysiology of constipation and effective mechanisms of laxatives is crucial. Untreated constipation may progress to life threatening complications associated with bowel obstruction.[14]

For improvement of the quality of life of patients with advanced tumour disease optimum control of all distressing symptoms is required, without negative impact on the efficacy of pain control.

Pathophysiology of opioid-induced constipation

Peripheral as well as intrathecal and intraventricular administration of opioids will lead to a prolonged colon passage of the bowel content, since opioid-induced constipation is caused by linkage of the opioid receptors in the gut and the central nervous system.[15,17] The inhibition of the release of acetylcholine from the myenteric plexus leads to a relaxation of the longitudinal musculature of the colon and small intestine. Subsequently, the propulsive motor activity decreases. Furthermore, opioids cause an increase in segmental intestinal contraction. This will cause a prolonged transit of intestinal contents; leading to a withdrawal of water and faecal impaction. Further, the intestinal, gastric, biliary, and pancreatic secretions decrease. An increase in the tonus of the intestinal sphincters and a decrease in the defaecatory reflex add to the constipatory effect. Meissner et al, in a non-randomized controlled study, showed that enteral application of naloxone can reduce opioid-induced constipation without impairing or suspending the pain-relieving effects of the opioid.[18] A combination drug consisting of the opioid oxycodone and the opioid antagonist naloxone has been available for some time.

The aim of the study was to evaluate whether patients with advanced cancer and moderate to severe cancer pain will benefit from the treatment with oxycodone/naloxone prolonged-release tablets (OXN), with particular regard to constipation and assessment of global patient satisfaction.

Methods

In this exploratory, non-randomized, open-label, monocentre study we evaluated the bowel function in palliative care patients admitted to our palliative care unit and switched to OXN during the first 14 days of the treatment period. During the treatment phase patients were titrated up to an adequate pain control (approved maximum total daily dose 40/20 mg OXN). If required, rescue doses of oxycodone (1/6 of the calculated daily dose) for management of breakthrough pain were administered as immediate-release formula. If rescue doses were required more than thrice, basic doses of sustained-release formula of oxycodone (without naloxone) were increased. The total doses of oxycodone – as reported in this paper - included rescue doses.

The Bristol Stool Form Scale (BSFS)[19] (Type 1-7) was used to asses stool consistency. To asses the bowel function a new, validated scale was used: The Bowel Function Index (BFI) (0-100). [20] This score is the mean of three distinct bowel dysfunction components: ease of defaecation (numerical analogue scale [NAS] 0-100; 0= easy/no difficulty, 100=severe difficulty); feeling of incomplete bowel evacuation (0-100); 0=not at all, 100=very strong); and judgement of constipation (0-100, 0=not at all, 100=very strong). A score lower than or equal to 30 is considered to reflect normal bowel function; higher scores indicated poor bowel function. Global patient satisfaction was assessed with the Patient Global Impression of Change Scale (PGIC) (1-7) on day 7 and 14. The intensity of pain was measured using a numeric rating scale (NRS 0-10). The intensity of pain was defined as follows: NRS 0 = no pain, NRS 1-3 = mild pain, NRS 4-7 = moderate pain, NRS > 7 severe pain. Ratings were recorded at rest. Presence of constipation prior to OXN treatment was defined according to the Rome III criteria,[21] which is defined by the presence of two or more of the following symptoms for a period of at least three months: 1. Straining at least 25 percent of the time, 2. Hard stools at least 25 percent of the time, 3. Incomplete evacuation at least 25 percent of the

time, 4. Two or fewer bowel movements per week. All adverse events were also documented and analysed.

Demographic patient- and disease-related data, such as cancer diagnosis or previous illnesses, were documented, including the laboratory values of serum electrolytes (sodium, potassium, and calcium), serum creatinine and CRP and all further clinically relevant laboratory parameters. If patients exhibited discomfort during the study period regarding constipation, oral sodium picosulfate (20 gtt) could be taken as a rescue laxative. If no bowel movement had occurred within 24 h, sodium picosulfate intake could be repeated and, if still unsuccessful after another 24h, an enema could be used.

The study protocol was reviewed and approved by the Research and Ethics Committees of the Medical Association of North Rhine, Germany, and was in accordance with the recommendations found in the Helsinki Declaration of 1975. The written consent of all patients was obtained.

Inclusion Criteria

Included were: patients with opioid-induced constipation, i.e. patients with a history of constipation, defined according to the Rome III criteria, since onset of opioid treatment without accompanying laxative treatment; patients who could provide informed consent and who were 18 years of age or older, with documented diagnosis of advanced, terminal cancer or other terminal incurable disease, and who were likely to improve from pain therapy with oxycodone/naloxone.

Exclusion Criteria

Exclusion criteria included contraindications regarding switching to oxycodone hydrochloride and/or naloxone hydrochloride, age <18 years, communication problems, diagnosed significant structural abnormalities of the gastrointestinal tract or gastrointestinal

diseases/diseases with impact on the gastrointestinal tract, missing consent, or patients in the pre-final phase; defined as patients with a life expectancy of a few days or hours.

Data Analysis and Statistics

Data were anonymized and inputted into an Excel 5.0 database. The programme SPSS was used for statistical evaluation. Descriptive methods (mean±SD (range) and medians (1/3 quartiles), respectively, were used. Comparative tests (Wilcoxon) were employed. The P values cited were two-sided, and P values <0.05 were judged as statistically significant.

Results

All patients tolerated the study session well. Of the 26 patients included in this trial (age 70.6±14.0 years) 10 (38.5%) were male. Diagnoses at admission were breast cancer (n=6), colon cancer (n=6), prostate cancer (n=4), carcinoma of the lung (n=3), urothelial cancer (n= 3), ovarian cancer (n=2) and carcinoma of unknown primary (CUP) (n=2). Observation period was 14 days. Patients' demographic and disease-related data is shown in *table 1*. The type of pain was somatic in 14 (53.8%) patients and visceral in 10 (38.5%). Two patients were suffering from somatic pain with neuropathic components All patients were pre-treated with opioids (WHO step III) and had opioid-induced constipation. Laxatives were not used or prescribed prior to their admission and since intake of opioids. Of the 26 patients in this study 11 were pre-treated with fentanyl TTS, 8 with oxycodone, 6 with morphine and 1 with hydromorphone for symptomatic pain control. Mean oral morphine equivalent dose at admission was 53.1±23.8 mg. At admission, opioid pre-treatment was discontinued and switched to oxycodone/naloxone (daily mean dose 36.2±17.2 mg OX/15.4±5.3 mg N). PGIC in mean at on day 7 was 3.5±1.0 and on day 14 was 1.9±0.8 (p<0.0001) *(figure 3).*

BFI improved significantly in 21 patients (72.4±17.0 vs. 36.8±13.4) (p<0.0001), changes are shown in *figure 1*; stool consistency (BSFS) improved in mean from type 2.0±0.7 to 4.9±1.0 (p<0.0001) (*figure 2*).

Furthermore, there was a significant decrease in the intensity of pain at rest (NRS 5.7±2.2 vs. 2.6±1.3 (p<0.0001) *(figure 4).*

In 5 cancer patients (2 of them with neuropathic pain components) with severe pain, pain control was not sufficient under OXN therapy with the – at the time of the study - maximal licensed daily dose of 40/20 mg; therefore these patients were switched to hydromorphone.

Spontaneous bowel movements increased during therapy with OXN in all patients: reported movements of 1.0±0.7 / week prior to admission vs. 3.6±0.8 / week on day 14 (p<0.0001).

As anticipated with opioid analgesics, the most common class of adverse events was gastrointestinal. Nausea (n=9) and abdominal pain (n=5) were the most frequently reported adverse events during the first five days of therapy with OXN. Two of the patients reported suffering from treatment-related diarrhoea for four, respectively five, days. Gastrointestinal infections could be excluded in both patients. None of the patients reported worsening of constipation during the therapy with OXN. Opioid withdrawal symptoms could be excluded. Use of rescue laxative was documented in four patients during the first four days: three patients had one intake of 20 gtt sodium picosulfate and in the fourth patient another sodium picosulfate intake as well as the use of an enema was required.

Discussion

Opioids are currently the mainstay of pain management for patients with cancer pain.[1,22] Successful pain management requires that analgesia is achieved without excessive tolerability issues that would jeopardize the overall improvement in the patients' quality of life.

While many opioid side effects occur at the beginning of pain treatment and are attenuated or disappear over time, constipation and related symptoms, including nausea, abdominal pain or

even dizziness, persist or can even become worse.[15,23] Consequently, a high proportion of patients receiving opioids require one or more laxative treatments.[22] However, even the most aggressive laxative regimens are often ineffective, as they do not target the underlying mechanisms of opioid action in the gastro-intestinal tract [22] and can cause additional side effects.

Opioid-induced constipation is a frequent symptom in patients with advanced illness receiving analgesic treatment with opioids and is mediated predominantly by opioid receptors in the gut. Sykes [24] demonstrated in a prospective study of 498 hospice inpatients with advanced cancer that laxatives were required by 87% of patients taking oral strong opioids. Pappagallo [22] demonstrated that approximately 40% patients taking opioids for non-cancer origin experienced constipation related to opioid therapy. Wirz et al [25] demonstrated in a retrospective study that constipation occurred in 42.7% of palliative care patients and laxatives were administered to 74.3 % of these patients. All too often sufficient pain therapy will be discontinued because of opioid-induced constipation.

Opioid-induced constipation has to be treated rigorously or, as far possible, avoided altogether by means of prophylactic treatment. Unfortunately, even though prophylaxis is recommended as standard regimen in patients receiving opioids for pain control on a regular basis, this has not yet become part of the medical routine in Germany, as was experienced by the patients included in this study. None of these patients was given prophylactic laxative treatment together with their opioid medication in the primary care setting. However, although many treatment strategies are available, opioid-induced constipation still poses therapeutic challenges particularly in the treatment of patients with poor health status and advanced illness. Thorough knowledge of the pathophysiology of the symptom opioid-induced constipation is essential for targeted treatment. An alternative therapeutic strategy to conventional oral laxatives has evolved by selectively blocking peripheral opioid-receptors

while maintaining desired action of opioids on central receptors that mediate analgesia. At the time of the study, the combination drug OXN was being introduced to the German market. As it is well-known that it adds to quality of life when the number of drugs that need to be taken can be kept as small as possible, the effectiveness of this alternative treatment was studied in patients who had not received laxative treatment previous to admission to our palliative care unit.

Since the adverse effects of opioids on gastro-intestinal function are believed to be predominately mediated by interactions between opioids and opioid receptors in the gastro-intestinal tract,[15,26] a potential therapeutic target is to selectively antagonize the gastro-intestinal adverse effects caused by opioids by co-administering an opioid antagonist that has limited systemic bioavailability. [22] Oxycodone is a pure opioid agonist exerting its analgesic effect primarily through μ-opioid receptors in the central nervous system. [16,17] It is available in immediate-release and prolonged-release preparations; prolonged-release oxycodone provides a fast onset of analgesia within 1 hour and pain relief for a 12-hour period. [27] The first attempt to selectively target opioid receptors in the periphery was made with naloxone.[15] Naloxone is a pure competitive antagonist of opioid receptors in both the central and peripheral nervous system and devoid of any intrinsic agonist activity. After oral administration, naloxone has negligible systemic bioavailability (approximately 2%) due to extensive first-pass hepatic metabolism.[28] It inhibits the action of opioids locally in the gastro-intestinal system, without interrupting the centrally mediated analgesic effect of the opioid administered concomitantly. [8-31]

Prolonged-release oxycodone/naloxone is the first analgesic therapy to combine oxycodone, a strong opioid, with naloxone, an opioid antagonist, in an oral prolonged-release tablet [23]. Its

use is indicated in moderate to severe pain, which can be adequately managed only with opioid analgesics. [23]

It needs to be realised; however, that the opioid-antagonist naloxone can easily cross the blood-brain barrier and hence, despite its low oral bioavailability, can reverse analgesia.[15] Thus the therapeutic range of naloxone is rather narrow because of the need to titrate peripherally versus centrally active doses.[30] Despite of this limitation, a combination of oral oxycodone and naloxone at the weight ratio 2:1 has been licensed in Germany, given that a phase II trial had shown that the combination has low potential to induce opioid-induced bowel dysfunction whereas the analgesic effect is preserved.[18]

The primary objective was to investigate whether patients with advanced cancer with moderate to severe malignant pain and opioid-induced constipation receiving oxycodone /naloxone (prolonged-release) had clinically significant improvement in symptoms of constipation as measured by BFI, BSFS and PGIC. A secondary efficacy variable was to assess the average pain intensity using the numeric rating scale. Our study results demonstrate that 21 patients receiving OXN achieved a significant change and improvement in bowel function, especially with respect to constipation over 14 days treatment period. Stool consistency was generally improved in all patients after 14 days. The improvement in bowel function was achieved without affecting the analgesic efficacy of the oxycodone component. The results of this study add also further support to the data from Colluzi et al.,[32] demonstrating the efficacy of the oxycodone/naloxone (prolonged-release) combination with respect to both bowel function and analgesic efficacy in patients with advanced cancer. Although this study investigated the efficacy of oxycodone/naloxone (prolonged-release) in patients with chronic cancer-pain, oxycodone is verifiably also an effective treatment option for non-malignant pain as proven in phase II and III trials.[32-35] Identical results to these phase II and III trials[32-35] were achieved in our study population.

The adverse events seen in this study are consistent with the expected adverse event profile of opioids. As with other opioid analgesics, the most common adverse event, observed in our study, was of gastrointestinal nature, except constipation. However, further analysis revealed no safety concerns arising from the use of oxycodone/naloxone (prolonged-release) in higher doses than used in this study.

The reported abdominal pain might indicate an increase in gut motility. Importantly, the incidence of diarrhoea was generally low.

Limitations of the study

We are well aware of the fact that the non-randomised, non-control group design is a limitation of the study. Nevertheless is this the first prospective study of OXN in patients with chronic cancer pain in the palliative setting. The study was designed to assess bowel function over a 14 days time period. Two weeks may be too short a period for observing differences in constipation regarding to long term use of oxycodone/naloxone prolonged-release tablets. Also, the assessed patient group was not very large. However, at the time of the study, the licensed maximum daily dose of OXN was 40/20 mg in Germany. Few cases of insufficient analgesia under doses up to 60-80 mg OXN treatment of patients with severe pain were experienced in clinical practice and reported in the literature.[34] Therefore an extremely cautious inclusion process of palliative care patients was clinically and ethically required. The recently licensed new maximum daily dose that is twice as high as before will allow including more patients in the palliative setting.

Conclusions

The treatment with oxycodone/naloxone prolonged-release tablets produced a clinically significant improvement in BFI and BFSF in our study population without a negative impact

on the analgesic efficacy of the oxycodone component, as evidenced by pain intensity scales and assessment of global patient satisfaction. The most frequent adverse events associated with oxycodone/naloxone (prolonged-release) are consistent with those reported for strong opioid analgesics. Taken together, these results demonstrate that the fixed combination tablet of oxycodone/naloxone (prolonged-release) provides an improved treatment option for patients with moderate to severe cancer pain. The recently licensed increased maximum daily dose of 80/40mg will allow including more patients from palliative care settings in OXN treatment. Randomised investigations are desirable.

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Table 1: ***Demographics (n=26)***

	n (%)	
Sex	male	10 (38.5)
	female	16 (61.5)
Age (mean) years	70.6±14.0	
Duration of stay (mean) days	22.6±21.2	
Karnofsky Index (median) %	50 % (20-80) %	
Type of pain	somatic	14 (53.8)
	visceral	10 (38.5)
	somatic with neuropathic pain components	2 (7.7)
Daily dose (mean) mg	oxycodone	36.2±17.2
	naloxone	15.4±5.3
Bowel Function Index (BFI) (mean)	admission	72.4±17.0
	day 14	36.8±13.4
Bristol Stool Form Scale (BSFS) (mean)	admission	2.0±0.7
	day 14	4.9±1.0
Laboratory values at admission	sodium mval/l	139.0±5.0
	potassium mval/l	4.0±0.7
	calcium mval/l	3.9±0.7
	creatinine mg/dl	1.0±0.5
	CRP mg/dl	10.1±8.3
Patient Global Impression of Change Scale (PGIC) (mean)	day 7	3.5±1.0
	day 14	1.9±0.8

***Figure 1**. Bowel Function Index (BFI) in palliative care patients (n=26) at admission and on day 14 during therapy with oxycodone/naloxone.*

Wilcoxon-Test $p<0.0001$

Bowel Function Index:

1. Ease of defecation (NAS) during the last 7 days:
   0 = easy / no difficulty - 100 = severe difficulty
2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days:
   0 = not at all - 100 = very strong
3. Personal judgment of patient (NAS) regarding constipation during the last 7 days:
   0 = not at all - 100 = very strong

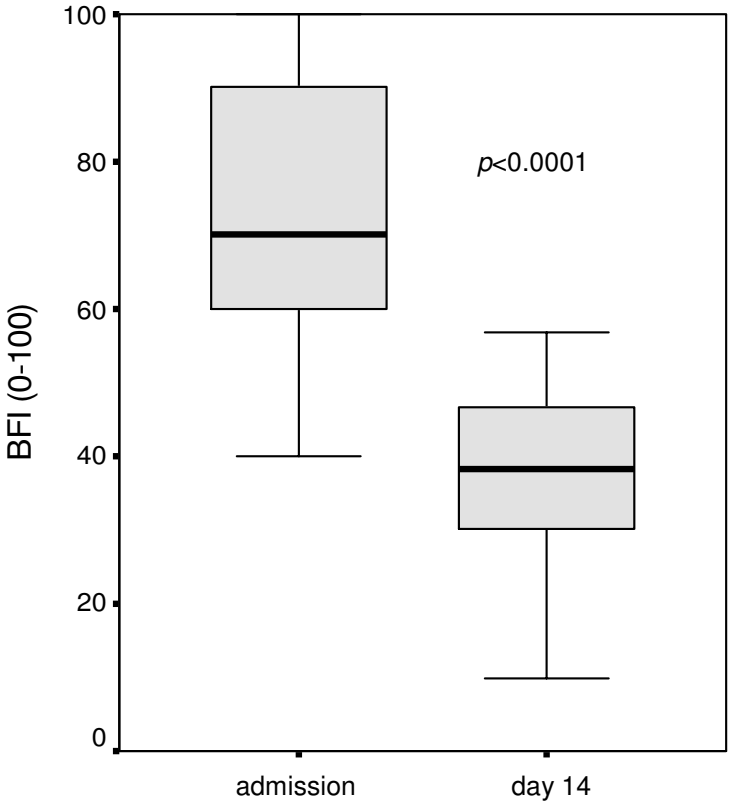
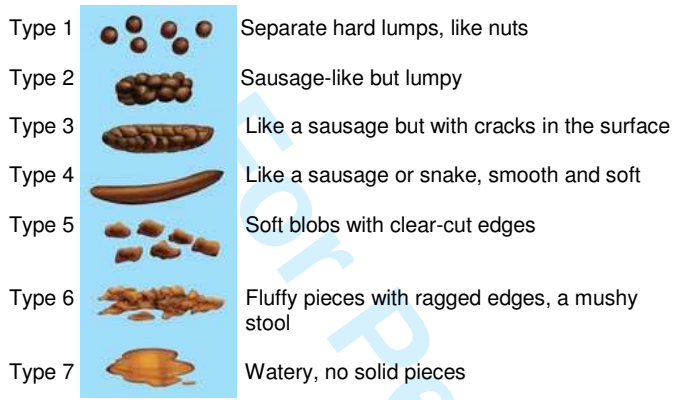


Figure 2: *Bristol Stool Form Scale (BSFS) in palliative care patients (n=26) at admission and on day 14 during therapy with oxycodone/naloxone*
Wilcoxon-Test p<0.0001



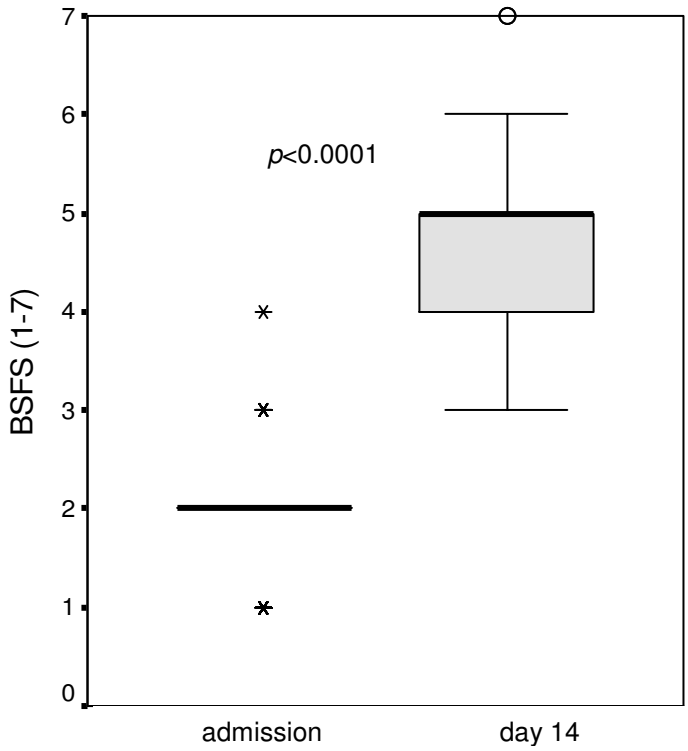


Figure 3: *Patient Global Impression of Change Scale (PGIC) in palliative care patients and on day 7 and 14 after start of treatment, respectively*

Wilcoxon Test: p<0.0001

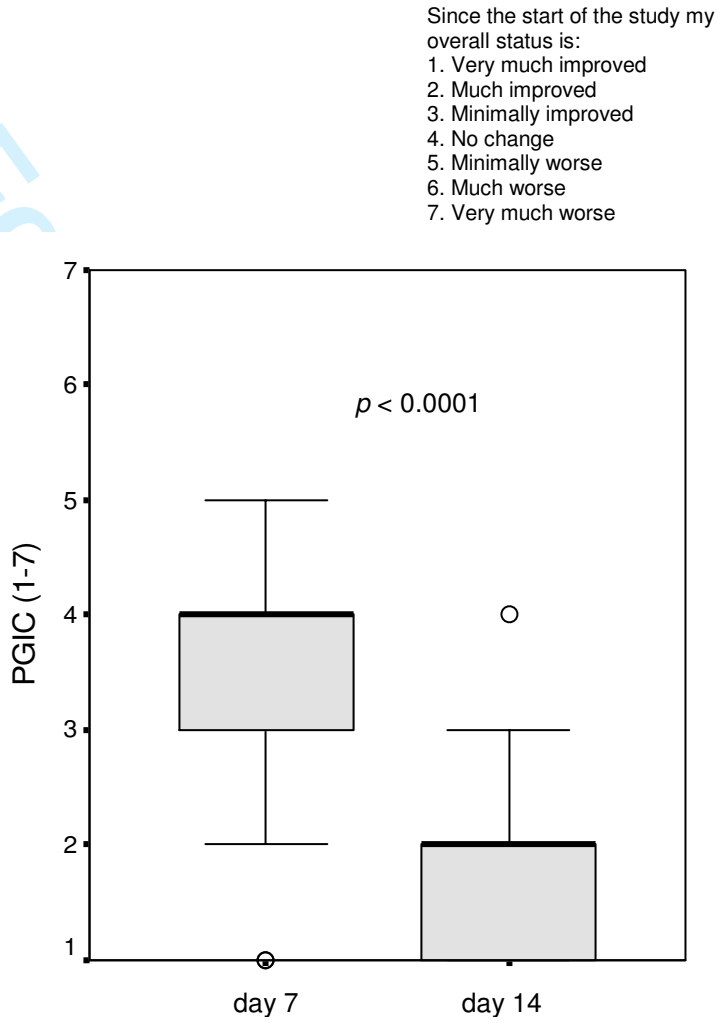


Figure 4: *Changes in intensity of pain at rest and at admission and on day 14 during therapy with oxycodone/naloxone (p<0.0001) (Wilcoxon Test) (n=21)*