

## Prevalence of the need for sodium intake restriction and the use of laxatives in palliative patients

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### ABSTRACT

**Background:** palliative patients usually have diseases that require a restriction of dietary sodium, although the prevalence of this requirement is unknown. Such conditions, combined with constipation, may mean that the use of laxatives with electrolytes should be avoided.

**Objectives:** to ascertain the prevalence of the need to restrict sodium intake in palliative patients and to analyze the prevalence of constipation and the use of laxatives, including those containing sodium.

**Method:** this was a multicenter retrospective, descriptive, cross-sectional, epidemiological study of both inpatients and outpatients over 18 years of age treated at the palliative care clinic (June 2015-March 2016). Demographic and anthropometric characteristics, diseases associated with dietary sodium restriction and treatments administered were recorded.

**Results:** the study sample consisted of 400 palliative patients, with a mean age of  $77.8 \pm 13.0$  years and 52.2% were male. Of these, 68.3% were inpatients and 31.8% were outpatients. Comorbidities requiring low sodium or a sodium-free diet were found in 87.0% (95% CI: 83.3-90.0) of cases. Only 46.5% (95% CI: 41.5-51.5) of patients had been prescribed a low salt diet. It should be noted that 50.5% (95% CI: 45.5-55.5) of patients required a low sodium diet and suffered from constipation. Laxatives (polyethylene glycol or lactulose-rich products [PEG] with electrolytes in 54% of cases) were taken by 53.8% (95% CI: 48.7-58.7) of patients, 52.1% due to constipation and 42.3% as a prevention due to opioid treatment.

**Conclusions:** a high proportion of the study cohort (87%) had some condition that required dietary sodium restriction and at least half the patients had constipation. The use of laxatives to treat or prevent constipation is common in

palliative patients. A sodium-free laxative is therefore preferred in these patients.

**Key words:** Sodium. Diet. Palliative care. Constipation. Laxatives.

### INTRODUCTION

Palliative care patients are all persons of any age who suffer from an advanced and incurable disease. Palliative care is a way to approach these diseases. It is intended to improve the quality of life of patients by preventing and relieving suffering via early diagnosis, adequate assessment and timely treatment of pain and other physical (such as constipation) or psychosocial problems. Palliative care patients usually suffer from diseases that require dietary sodium restriction, such as heart disease, kidney disease, high blood pressure, hepatobiliary disease or chronic obstructive pulmonary disease (1). There is no reported information to date of the proportion of palliative patients who require low sodium diets. This is important for drug prescription as some prescribed laxatives contain significant amounts of sodium in their formulation.

Constipation is a very common problem in palliative care patients (2), and it is of particular importance due to the high prevalence, ranging from 32% and 87% depending on the underlying disease of the patient (3). It is considered to be one of the ten most troublesome symptoms in these patients and causes suffering, decreased quality of life and, in some cases, increased morbidity and mortality due to bowel perforation (4). The effects of constipation

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include physical problems such as abdominal pain, loss of appetite, fecal impaction and vomiting and also psychosocial disorders (5). One of the most significant causes of constipation in palliative patients is the administration of opioids to treat chronic pain, which is very common in this population. A reduction in the dose of these drugs is often required due to the acute and severe constipation induced by opioids. This reduces the problem with constipation but also the analgesic effect and, as a consequence, patient quality of life (2).

Other clinical conditions that cause constipation in patients on palliative care include chronic obstructive pulmonary disease, heart disease, cancer, depression and hypercalcemia. Other factors known to contribute to constipation include female sex, impaired nutritional status, decreased patient mobility, hospitalization, hemorrhoids and poly-medication in elderly patients (6).

Knowing the dimension of a problem in the healthcare setting is undoubtedly compulsory and also the most efficient way to deal with it from the preventive and therapeutic perspective. This was the premise for designing this study that intended to ascertain the prevalence of the need (based on the underlying disease or concomitant medication) of a low sodium diet and the prevalence of constipation in palliative care patients. This is important information for drug prescription as drugs with a low electrolyte content are ideal for all palliative patients who require a low sodium diet (1,7). Especially when long-term daily medication is required, as with laxatives.

## PATIENTS AND METHODS

This was a multicenter retrospective, cross-sectional, descriptive, epidemiological study in both inpatients and outpatients over 18 years of age that were seen at the palliative care clinic from June 2015 to March 2016. The study was submitted to the Ethics Committee of the Fundación Jiménez Díaz on the 29<sup>th</sup> of January 2016 and was approved on the 9<sup>th</sup> of March 2016. All patients were provided care according to standard clinical practice. Participating centers included: Fundación Jiménez Díaz (Madrid), Hospital Universitario Infanta Elena (Valdemoro, Madrid), Hospital Universitario Rey Juan Carlos (Móstoles) and Hospital General de Villalba (Collado Villalba, Madrid). As this was an anonymized, retrospective, observational study, informed consent from patients was not considered as necessary. The ethical principles of the Declaration of Helsinki of the World Medical Association were followed.

Patients were consecutively recruited. Data collected from the electronic clinical histories of each hospital included: demographic characteristics (age, sex, origin), anthropometric data (weight, height, body mass index [BMI]), diseases associated with dietary sodium restriction (congestive heart failure, kidney disease, acute renal failure, chronic renal failure, nephrotic syndrome, edematogenic glomerulonephritis, diabetic nephropathy, kidney stones, renal hypertension, hepatobiliary disease, ascites, liver cirrhosis and chronic obstructive pulmonary disease), current diet and treatments administered (laxatives, morphine derivatives, corticosteroids and other drugs associated with constipation).

The need for a low sodium or sodium-free diet was defined as presence of a diagnosis of at least one of the following conditions or medications that require dietary sodium restriction: congestive heart failure, kidney disease, acute renal failure, chronic renal failure, nephrotic syndrome, edematogenic glomerulonephritis, diabetic nephropathy, kidney stones, renal hypertension, ascites, liver cirrhosis, chronic obstructive pulmonary disease or long-term corticosteroid treatment. The Roma IV criteria were used to define constipation (8-10).

The recruitment of 385 patients receiving palliative care was planned in order to estimate a 50% prevalence of patients who required a low sodium or sodium-free diet with a precision of 5%, a 95% confidence interval and a power of 80%. Variables in the overall sample were analyzed and some of the characteristics were compared between inpatients and outpatients. Frequencies, percentages and confidence intervals were used to summarize categorical variables for the descriptive analysis, and the mean and standard deviation was used for quantitative variables. A Chi-square test or a Fisher exact test, as appropriate, was used to compare qualitative variables between inpatients and outpatients. A value of  $p < 0.05$  was considered as statistically significant. The SAS 9.3 software was used for statistical analyses.

## RESULTS

All recruited patients were included in the analysis. The study sample consisted of 400 patients with a mean age of  $77.8 \pm 13.0$  years and a male to female ratio of 52.2%/47.8%. Of the total patient cohort, 68.3% were inpatients and 31.8% were outpatients. Unemployed or retired subjects, housewives or students accounted for 48.3% of the patients. The mean patient weight was  $68.9 \pm 17.0$  kg and the mean height was  $164.3 \pm 9.1$  cm. The mean BMI was  $25.1 \pm 4.6$  kg/m<sup>2</sup> (Table 1).

Eighty-seven percent (95% CI: 83.3-90.0) of patients required low sodium or sodium-free diets. Constipation was reported by 56.8% (95% CI: 51.7-61.7) of patients. Thus, 50.5% (95% CI: 45.5-55.5) of patients required a low sodium or sodium-free diet and also had constipation. At the time of the visit, 46.5% (95% CI: 41.5-51.5) of patients had been prescribed a low-salt diet. Table 2 shows the prevalence of diseases associated with a low sodium or sodium-free diet and use of the different treatments, both for the overall cohort and by type of care.

**Table 1.** Sample characteristics. Comparative data of inpatients and outpatients

	Total	Outpatients	Inpatients
Total patients, n (%)	400	127 (31.7)	273 (68.3)
Age (years), mean (SD)	77.8 (13.0)	78.1 (12.0)	77.7 (13.4)
Female, n (%)	191 (47.8)	53 (41.7)	138 (50.5)
Weight (kg), mean (SD)	68.9 (17.0)	70.9 (20.2)	68.1 (15.7)
Height (cm), mean (SD)	164.3 (9.1)	165.9 (10.1)	163.8 (8.8)
BMI (kg/m <sup>2</sup> ), mean (SD)	25.1 (4.6)	25.3 (4.7)	25.0 (4.7)

SD: standard deviation.

**Table 2.** Prevalence of diseases associated with a low sodium or sodium-free diet and the use of the different treatments. Comparative data of inpatients and outpatients

	Total	Outpatients	Inpatients	p*
Total patients, n (%)	400	127 (31.7)	273 (68.3)	
Need for low sodium or sodium-free diet, n (%)	348 (87.0)	104 (81.9)	244 (89.4)	0.038
Constipation, n (%)	227 (56.8)	55 (43.3)	172 (63.0)	< 0.001
Need for low sodium or sodium-free diet and constipation, n (%)	202 (50.5)	48 (37.8)	154 (56.4)	< 0.001
Low-salt diet, n (%)	186 (46.5)	74 (58.3)	112 (41.0)	0.001
<i>Diseases associated to low sodium or sodium-free diet, n (%)</i>				
High blood pressure	241 (60.3)	86 (67.7)	155 (56.8)	0.037
Congestive heart failure	93 (23.3)	23 (18.1)	70 (25.6)	0.097
Chronic renal failure	82 (20.5)	16 (12.6)	66 (24.2)	0.008
COPD	80 (20.0)	21 (16.5)	59 (21.6)	0.237
Ischemic heart disease	78 (19.5)	28 (22.0)	50 (18.3)	0.381
Acute renal failure	29 (7.3)	7 (5.5)	22 (8.1)	0.361
Ascites	27 (6.8)	3 (2.4)	24 (8.8)	0.017
Liver cirrhosis	16 (4.0)	2 (1.6)	14 (5.1)	0.091
Diabetic nephropathy	15 (3.8)	3 (2.4)	12 (4.4)	0.319
Heart surgery	10 (2.5)	2 (1.6)	8 (2.9)	0.419
Kidney stones	5 (1.3)	1 (0.8)	4 (1.5)	1.000
Nephrotic syndrome	2 (0.5)	0 (0.0)	2 (0.7)	1.000
Edematogenic glomerulonephritis	1 (0.3)	0 (0.0)	1 (0.4)	1.000
<i>Treatments, n (%)</i>				
Laxatives	215 (53.8)	50 (39.4)	165 (60.4)	< 0.001
Morphine derivatives	186 (46.5)	46 (36.2)	140 (51.3)	0.005
Long-term corticosteroid treatment	95 (23.8)	19 (15.0)	76 (27.8)	0.005
Enemas	82 (20.5)	17 (13.4)	65 (23.8)	0.016
Other drugs potentially causing constipation	193 (48.3)	51 (40.2)	142 (52.0)	0.027
Opioids	91 (47.2)	19 (37.3)	72 (50.7)	0.099
Diuretics	88 (45.6)	12 (23.5)	76 (53.5)	< 0.001
Anticholinergics	28 (14.5)	0 (0.0)	28 (19.7)	0.002
Antianemics	22 (11.4)	14 (27.4)	8 (5.6)	< 0.001
Calcium channel blockers	17 (8.8)	16 (31.4)	1 (0.7)	< 0.001
Antiepileptics	16 (8.3)	0 (0.0)	16 (11.3)	0.044

COPD: chronic obstructive pulmonary disease. \*p calculated using a Chi-square or Fisher test with a statistical significance level of 0.05.

The prevalence of the different diagnoses that required a low sodium diet was significantly greater in inpatients (inpat.) as compared to outpatients (outpat.) (Table 2). Overall, the proportion of patients with any of the diseases that required a low sodium diet was higher in inpatients as compared to outpatients, except for high blood pressure and ischemic heart disease. Significant differences were only seen with regard to high blood pressure (outpat. vs inpat.: 67.7% vs 56.8%,  $p = 0.037$ ), chronic renal failure (inpat. vs outpat.: 12.6% vs 24.2%,  $p = 0.008$ ) and ascites (inpat. vs outpat.: 2.4% vs 8.8%,  $p = 0.017$ ).

The proportion of patients who took any treatment was significantly higher in inpatients as compared to outpatients

(Table 2). With regard to laxatives, the proportion of patients who took products rich in lactulose or polyethylene glycol (PEG) with electrolytes was significantly higher in inpatients as compared to outpatients (outpat. vs inpat.: 22.0% vs 44.8%,  $p = 0.001$ ). This was also true for the proportion of patients taking laxatives on a daily basis (outpat. vs inpat.: 64.0% vs 86.1%,  $p = 0.001$ ).

Finally, of the 215 patients (53.8% of the total) who took laxatives, 52.1% used them due to constipation, 42.3% as a prophylaxis because of opioid treatment and 5.6% for other reasons. Laxatives were taken daily by 80.9% and sporadically by 11.2% of patients and were not combined with other laxatives in 87.0% of cases. The most commonly used lax-

ative was PEG with electrolytes (with sodium) (54.0%), followed by lactulose (38.1%) and paraffin/picosulfate (14.4%). Stimulant laxatives were used by 18.6% of patients, while 31.6% used enemas combined with the laxative. The use of laxatives is described in table 3.

## DISCUSSION

Palliative patients often experience constipation due to different reasons, the use of opioids is one of the most relevant. These patients could benefit from the use of sodium-free laxatives if sodium restriction is required due to certain comorbidities. However, there are no data reported to date in this regard.

This observational, retrospective study has proven the initial hypothesis: 87.0% of palliative patients, who represent an elderly population with multiple diseases, suffer from disorders that require low sodium content in their diets. In addition, 50.5% of these patients had constipation. Only 46.5% of patients who required a low-sodium diet were already following this type of diet. Therefore, it is important to emphasize the interest of these data in this group of

patients, as the use of laxatives is common and they are the first-line drugs used to prevent or treat constipation in these patients (11-13). Therefore, clinical practice guidelines recommend that a laxative is prescribed from the start of opioid treatment in order to prevent constipation (14). Laxatives are widely used by all types of people. In the United States, the acute treatment for constipation at hospitals significantly increased from 1997 to 2010, with a consequent increase in total expenditure (from 188 million dollars in 1997 to 851 million in 2010). Elderly patients were found to have the highest prescription rate of laxatives on discharge from hospital (15). Palliative care patients are usually elderly; the mean patient age in this study was 77.8 years.

There are a wide variety of laxatives with different mechanisms of action in the pharmaceutical market: bulk-forming, osmotic, stimulant or emollient laxatives (15). There is currently no agreement with regard to the specific drug to treat constipation caused by opioids, which is one of the most important factors for the development of constipation in palliative patients (14). PEG, lactulose and sodium picosulfate are considered to be well tolerated. Methylalntrexone is also used when patients are at risk of gastrointestinal perforation (16).

**Table 3.** Use of laxatives. Comparative data of outpatients and inpatients

	Total	Outpatients	Inpatients
Total patients, n (%)	400	127 (31.7)	273 (68.3)
Patients with laxatives, n (%)	215 (53.8)	50 (39.4)	165 (60.4)
<i>Indication, n (%)</i>			
Treatment of constipation	112 (52.1)	30 (60.0)	82 (49.7)
Prevention for opioid treatment	91 (42.3)	19 (38.0)	72 (43.6)
Hepatic encephalopathy	9 (4.2)	1 (2.0)	8 (4.8)
Intestinal pseudo-obstruction	3 (1.4)	0 (0.0)	3 (1.8)
<i>Frequency, n (%)</i>			
Daily	174 (80.9)	32 (64.0)	142 (86.1)
2 or more times/week	14 (6.5)	5 (10.0)	9 (5.5)
Less than 2 times/week	3 (1.4)	0 (0.0)	3 (1.8)
Sporadically	24 (11.2)	13 (26.0)	11 (6.7)
<i>Number of laxatives used, n (%)</i>			
1 laxative	187 (87.0)	43 (86.0)	144 (87.3)
2 laxatives	24 (11.2)	7 (14.0)	17 (10.3)
3 or more laxatives	4 (1.9)	0 (0.0)	4 (2.4)
Number of laxatives used, mean (SD)	1.2 (0.4)	1.1 (0.4)	1.2 (0.4)
<i>Laxatives used, n (%)</i>			
PEG with electrolytes	116 (54.0)	19 (38.0)	97 (58.8)
Lactulose	82 (38.1)	28 (56.0)	54 (32.7)
Paraffin/picosulfate	31 (14.4)	4 (8.0)	27 (16.4)
Other laxatives	27 (12.6)	7 (1.4)	20 (12.1)
Stimulant laxatives, n (%)	40 (18.6)	5 (10.0)	35 (21.2)
Laxative combined with enemas, n (%)	68 (31.6)	15 (30.0)	53 (32.1)

SD: standard deviation; PEG: polyethylene glycol.

It should be noted that these patients require daily laxatives use throughout their lives. Hence, long-term laxatives use, such as PEG or lactulose should be preferred, as stimulant laxatives, such as picosulfate or bisacodyl, should only be used sporadically as they cause habituation. Moreover, stimulant laxatives should be used with caution in patients at risk of developing water and electrolyte disorders, such as the elderly and patients with heart failure or treated with diuretics or corticosteroids (17). More evidence is available for PEG and lactulose as compared to stimulant laxatives for the treatment of constipation and they also have an adequate safety profile (18). PEG is considered to be the osmotic laxative of choice, with a 1A level of evidence (19) for the management of chronic constipation due to the greater efficacy and tolerability as compared to lactulose (20,21). PEG products with electrolytes (including sodium) and no electrolytes are available in the Spanish market. The choice of the laxative should be individualized for each patient (22).

As shown in this study, a large proportion of the population required dietary sodium restriction. Excess sodium intake is widely agreed to increase the risk of high blood pressure and thus, cardiovascular disease (23). In clinical practice, this is taken into account in order to reduce salt in food but not in relation to other sodium sources, such as drugs (24). In industrialized countries, most dietary salt (75.0%) comes from precooked or packaged food and cold cuts, which contain food additives such as sodium glutamate or benzoate. The remaining 25% comes from sodium that is naturally present in food, common salt, some carbonated mineral waters and certain drugs. Thus, sodium ingested with food and drugs often widely exceeds the amount recommended for the general population and may represent a risk for health (25).

Few studies have assessed the contribution of drugs to sodium intake, which is especially important in patients at greater risk who take more drugs due to their disease. These drugs may exacerbate the chronic condition. It is important that physicians know the potential contribution of drugs that contain sodium in more vulnerable patients, so that they can prescribe drugs appropriately (26).

Studies have reported that a 50% reduction in the sodium content of drugs given to inpatients would shorten their hospital stay by one day (27) and would decrease the costs of hospitalization due to heart failure by 5.6 billion dollars per year (28,29). According to another report, a 9.5% reduction in sodium intake would result in a decrease in mean systolic pressure by 1.25 mmHg in people aged 40-85 years (26). A retrospective study analyzed 82 patients admitted to the Intensive Care Unit due to acute heart failure. These patients were found to ingest on average  $4.0 \pm 5.0$  g/day of sodium from non-dietary sources (drugs), which correlated with longer hospital stays. Thus, when a mean amount of 1.2 g of sodium daily was administered, hospital stay increased to five days and when given 2.6 g/day, hospital stay was prolonged to ten days (24). Finally, a nested case-control study conducted in the general population of the United Kingdom assessed the long-term use of sodium-containing drugs and the development of cardiovascular disorders. The results showed that patients who took sodium-containing drugs had a 16% greater risk of developing cardiovascular events (OR = 1.16, 95% CI: 1.12-1.21) and the risk of a stroke and high blood pressure was even

higher, 1.22 (1.16-1.29) and 7.18 (6.74-7.65), respectively. Caution is therefore required when drugs containing sodium are prescribed, and an adequate benefit/risk assessment should be performed (23).

It may be argued that dietary measures may not be so relevant in palliative patients, in whom quality of life would be the most important goal. However, if laxatives and other types of non-sodium drugs were as effective as those with sodium, their use would be more adequate according to our study data. To date, this was apparently not considered when the treatment was prescribed.

The main limitation of this study is that it was not population-based and there is no guarantee that the study sample is representative of patients seen at palliative care clinics at the national level. However, the study recruited a wide group of patients from four different types of palliative care clinics in the Madrid region. On the other hand, causal associations are difficult to establish due to the cross-sectional nature of the study. However, the study had a purely descriptive objective and was not intended to establish this type of relationship between variables. A high proportion of the study population (87%) had some disorder that required dietary sodium restriction and at least half of the patients suffered from constipation. The use of laxatives to treat or prevent constipation is common in palliative patients. Thus, a sodium-free laxative should be preferred in such patients.

## ETHICAL RESPONSIBILITIES

**Protection of persons:** the authors state that no experiments in human beings have been performed for this study.

**Confidentiality of data:** the authors state that they have followed the protocols of their work centers regarding the publication of patient data. Data collection was fully anonymized.

## CONFLICTS OF INTEREST

Doctors Gándara del Castillo, Herrera Abián, Vicente Martín, and Fraile Vicente state that they have received an economic compensation for their collaboration in this article from Laboratorios Casen Recordati. The corresponding author, Delgado Juárez, works as a medical advisor at Laboratorios Casen-Recordati.

The authors state that neither the affiliation nor the economic compensation affect the objectivity of the study results. This study was funded by Laboratorios Casen-Recordati.

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