A study on the management of corticosteroid side effects in cancer patients

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ABSTRACT

Background

Systemic corticosteroids lead to many adverse effects especially in cancer patients. Preventive measures and treatment options are essential to minimise such side effects.

Objectives

The aims of the study included the evaluation of the prescribers' management of corticosteroid induced hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy, the discussion of possible reasons for non-adherence to guidelines, and the recommendation of interventions to reduce their risk of occurrence.

Method

A retrospective review of the medical records for 156 consecutive patients at oncology out-patients and in oncology wards of Boffa Hospital between the 1st and the 14th September 2014 was performed. Only patients who were on long term corticosteroids (>2 weeks' duration) were considered. Patients younger than 12 years of age or those that were prescribed corticosteroids for antiemetic purposes were excluded from the study. For each of the sampled patients, any management aimed at reducing corticosteroid side effects was compared to the guidelines as stated in an article published in a prominent international journal.

Results

From 156 cancer patients, 55 patients satisfied the inclusion criteria. The mostly addressed side effect was dyspepsia (n=35; 63.6%) followed by proximal myopathy (n=27; 49%), hyperglycaemia (n=24; 43.6%) and lastly oral candidiasis (n=20; 36%). Adherence to guidelines was as follows: hyperglycaemia – haemo-glucose test (HGT) and glycated haemoglobin (HbA1c) (36%); dyspepsia - prescribing of omeprazole (51%) and ranitidine (5%); oral candidiasis - orophargyngeal exam (29%); and proximal myopathy (40% compliance; of which 35% complying with resistance and endurance exercise and 5% complying with steroid dose reduction).

Conclusion

Improvement is required with regards to the management of corticosteroid side effects especially for hyperglycaemia and oral candidiasis. Possible actions that may be taken include strategies to improve guideline awareness, the prescribing of the lowest effective dose, adequate patient education and the implementation of a steroid card.

KEYWORDS

Disease management; adrenal cortex hormones; drug-related side effects and adverse reactions; neoplasms; humans

INTRODUCTION

Corticosteroids have many indications for use in palliative care and oncology, primarily owing to their anti-inflammatory properties (Lussier *et al.,* 2004).

Despite their beneficial effects, long term systemic (oral or parenteral) use of these agents is associated with well known adverse events mainly hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy.

It is therefore the role of the clinician to minimize the risk of such side effects through appropriate active and proactive management, especially in debilitating patients such as cancer patients.

The main aims of the study include:

- To evaluate the prescribers' management of corticosteroid side effects, specifically for hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy;
- To discuss possible reasons for non-adherence to guidelines; and
- To recommend possible interventions to reduce their risk of occurrence.

All this should make the prescriber more aware of corticosteroid side effects in cancer patients as well as providing him with a variety of options for optimally addressing or preventing the manifestation of adverse effects.

For a better understanding of the study, the term "management" will be used to refer to either or both *clinical management* and *pro-active approach*. On the other hand "addressing" a side effect will include one or all of clinical assessment, clinical education, and treatment.

METHOD

Setting and sampling units

The study was conducted between the 1st and the 14th of September 2014 as a retrospective analysis of case notes. Medical notes and treatment regimes for 156 patients were reviewed from Oncology and Palliative Care Outpatients, Day Ward, Oncology Wards and the Palliative Care Unit.

Selection criteria

Inclusion criteria included adult oncology and palliative care patients who were prescribed, or had the intention of being prescribed dexamethasone or prednisolone for more than 2 weeks. Hyperglycaemia, dyspepsia, oral candidiasis and proximal myopathy were assessed due to their high prevalence in cancer patients, ease of management and monitoring.

The exclusion criteria included corticosteroids prescribed for short term intervals as adjuvant antiemetic with chemotherapy. Patients younger than 12 years of age were not included in the study.

When considering such selection criteria, from the 156 case notes that were reviewed only 55 qualified for the study, and hence had their case notes evaluated.

Measuring performance

Performance was measured from the time the patient was first prescribed steroids for a 2-week treatment duration or more.

Performance was measured in terms of:

(1) Clinical assessment for side effect detection,
(2) Clinical education to patient, and
(3) Clinical action in addressing the already manifested side effect

There are no locally established guidelines and hence the guidelines that were used were those stated in a paper entitled "A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy" in the Allergy, Asthma and Clinical Immunology Journal (Liu *et al.*, 2013).

A proforma sheet was produced for each of the side effects previously mentioned and filled in for every patient. Data was processed using Microsoft Excel 2013.

The performance was measured by comparing the management stated in the notes with that of the guidelines. Compliance was calculated as follows: the number of patients on whom an intervention was performed as per guidelines, ***divided by*** the total number of patients sampled (n=55) ***multiplied by*** 100%

Pilot study (10%)

A pilot study was undertaken 2 days prior to the 2-week data retrieval period. Twenty case notes were reviewed of which 6 could be evaluated as they satisfied the selection criteria. The proforma for the 6 patients was effective in measuring performance without major bias. Hence no changes to the original proforma were made other than extending the retrieval time period from two days to a fourteen day time window.

Ethical approval and consent

The study was approved by the Audit and the Data Protection Act committees. Consent was achieved from the Chairman of Oncology/Haematology and all oncologists at Sir Paul Boffa Hospital. The University Research and Ethics Committee was not involved as no human subjects were involved – only case notes were utilised for data retrieval.

RESULTS

Corticosteroids were prescribed in 12 known primaries (n=54; 98%). Figure 1 shows the number of patients for each of the primary carcinomas to which a long term corticosteroid was prescribed. The main indications were for nerve pain, control in bone metastases and other metastases mainly of the lung and the liver. With regard to brain primaries, namely astrocytoma and glioblastoma, steroids were indicated due to the direct effect of the tumour on the intracranial pressure (n=5; 9%). Other

indications included decreased appetite (n=6; 11%) and emesis (n=2; 3.7%).

Dexamethasone and prednisolone were the only corticosteroids to be prescribed. Seventy-five per cent (n=41) of all patients were prescribed the former, with the 2mg daily dose being the most prescribed regimen (n=14; 34%). Figures 2a and 2b represent the corticosteroid doses. Treatment duration spanned from 2 weeks to 3 and a half years (Figure 3), with 1 month being the most common treatment duration (n=20; 36%).

Table 1 indicated that the most addressed side effect was dyspepsia (n=35; 64%), followed by proximal myopathy (n=27; 49%), hyperglycaemia (n=24; 44%) and lastly oral candidiasis (n=20; 36%).

Although, for convenience sake, the management of each side effect was classified into clinical assessment, education and action (treatment) it is to be noted that the three interventions could all have been done individually or combined together in the same patient.

Management of hyperglycaemia

Hyperglycaemia was addressed in less than half of the patients (n=24; 44%). Such patients were managed as shown in Figure 4, where monotherapy was the mainstay of treatment. Haemo gluco testing (HGT) was the most common method used to address hyperglycaemia proactively (n=19; 35%).

Management of dyspepsia

Only a pro-active approach was implemented, mainly in the form of gastroprotective agents, of which omeprazole (n=28; 51 %) was preferred over ranitidine (n=3; 9%) and their combination (n=4; 11%) (Figure 5).

Management of oral candidiasis

Oral candidiasis was mainly addressed pro-actively whereby oropharyngeal examination was the most common method (n=16; 29%) to be employed (Figure 6).

Management of proximal myopathy

Both clinical management and a proactive approach were given similar importance. As shown in Figure 7, assessment of lower limb power (n=21; 38%) and physiotherapy referral for quadriceps strengthening (n=19; 35%) were the commonest strategies employed.

Tables 2a and 2b provide a summarised comparative study, including percentage compliance, for each side effect.

DISCUSSION

The importance of long term steroid use in cancer patients

Corticosteroids are commonly used in the treatment of cancer, primarily owing to their anti-inflammatory activities (Rhen and Cidlowski, 2005). Recently it has been found that corticosteroids may have a direct effect on the modulation of tumour biology and angiogenesis as well as on tumour-associated pain (Dietrich *et al.,* 2011). Other benefits include limiting nausea and vomiting and improving appetite in cancer patients.

Side effects related to long term steroid use

In a prospective study the most common side effects associated with corticosteroid use (at 10–30 mg/day of prednisolone and 4-16mg/day of dexamethasone) were oral candidiasis (26% with prednisolone, 37% with dexamethasone), oedema (18% prednisolone, 21% dexamethasone), cushingoid facies (15% prednisolone, 21% dexamethasone), dyspepsia (8% prednisolone, 9% dexamethasone), and weight gain (4% prednisolone, 5% dexamethasone) (Dorffl and Crawford, 2013). A separate study states that hyperglycaemia occurs in a majority of hospitalised patients receiving high doses of corticosteroids (Donihi *et al.,* 2006). Table 3 provides a summary of adverse effects associated with corticosteroid dose.

Table 1: Percentage of patients managed for corticosteroid side effects

Side Effect	Management (%) (n=55)	No management (%) (n=55)
Hyperglycaemia	44	56
Dyspepsia	64	36
Oral Candidiasis	36	64
Proximal Myopathy	49	51

Table 2a: Percentage compliance with management guidelines for hyperglycaemia

Guidelines	Study	Compliance
Proactive Approach • Education about the classic signs and symptoms of hyperglycemia. • Monitoring of glycated haemoglobin, fasting plasma glucose, 2hr plasma glucose using a 75-g oral glucose tolerance test. • Blood glucose should be monitored within 8 hours of the first dose. And then at least 48 hrs after initiation of corticosteroid therapy, regardless of whether or not the patient is diabetic.	**Proactive Approach** • Haemo glucose and glycated haemoglobin testing.	36%
Clinical Management • Management guidelines as in those with pre-established diabetes. If <15mmol/L- metformin, sulphonureas, meglitinides or GLP-1 agonists. Sulphonureas (single dose) for prednisolone regimens and glicliazide MR or glimepride for dexamethasone as this is longer acting. If >15mmol/l insulin and metformin is recommended • Steroid dose reduction leads to improvement • Discontinuation usually leads to complete reversal	**Clinical Management** • Dietary advice • Metformin • Insulatard • Actrapid • Metformin+Glicliazide +Actrapid	13%

Table 2b: Percentage compliance with management guidelines for dyspepsia, oral candidiasis and proximal myopathy

Side effect	Guidelines	Study	Compliance
Dyspepsia	**Proactive Approach** • Use of proton pump inhibitors for gastrointestinal protection in corticosteroid users at high risk of gastrointestinal bleeding or peptic ulcers for example those on non-steroidal anti-inflammatory drugs, cancer patients, history of ulcers or gastrointestinal bleeding, and those with serious comorbidities (i.e., advanced cancer)	**Proactive Approach** • Use of omeprazole, ranitidine or their combination	51%
Oral Condidiasis	**Proactive Approach** • Early recognition of infections through oropharyngeal examination	**Proactive Approach** • Early recognition of infections through oropharyngeal examination • History taking • Regular mouth hygiene **Clinical management** • Miconazole or nysatin with or without the use of mouthwash	29%
Proximal Myopathy	**Clinical Management** • Reduction or discontinuation of steroid use as soon as possible. • Resistance and endurance exercise	**Proactive Approach** • Assessment of lower limb power and advice on the possibility of muscle weakness **Clinical management** • Physiotherapy referral and quadriceps strengthening	40%

Table 3: Adverse effects associated with steroid dosage regimen (Hanks et al., 1983)

Adverse Effect	Corticosteroid type and dose for adverse effects
Hyperglycemia	Low-dose dexamethasone (0.5-2 mg/day)
Infection	Low-dose predmisone (10 mg/day)
Myopathy	Low-dose predmisone (10 mg/day)
Osteoporosis	Low-dose predmisone (10 mg/day)
Oedema	Low-dose predmisone (10 mg/day)
Weight gain	Low-dose predmisone (10 mg/day)
Dyspnoea	Low-dose predmisone (10 mg/day)
Cushingoid facies	Low-dose dexamethasone (0.5-2 mg/day)

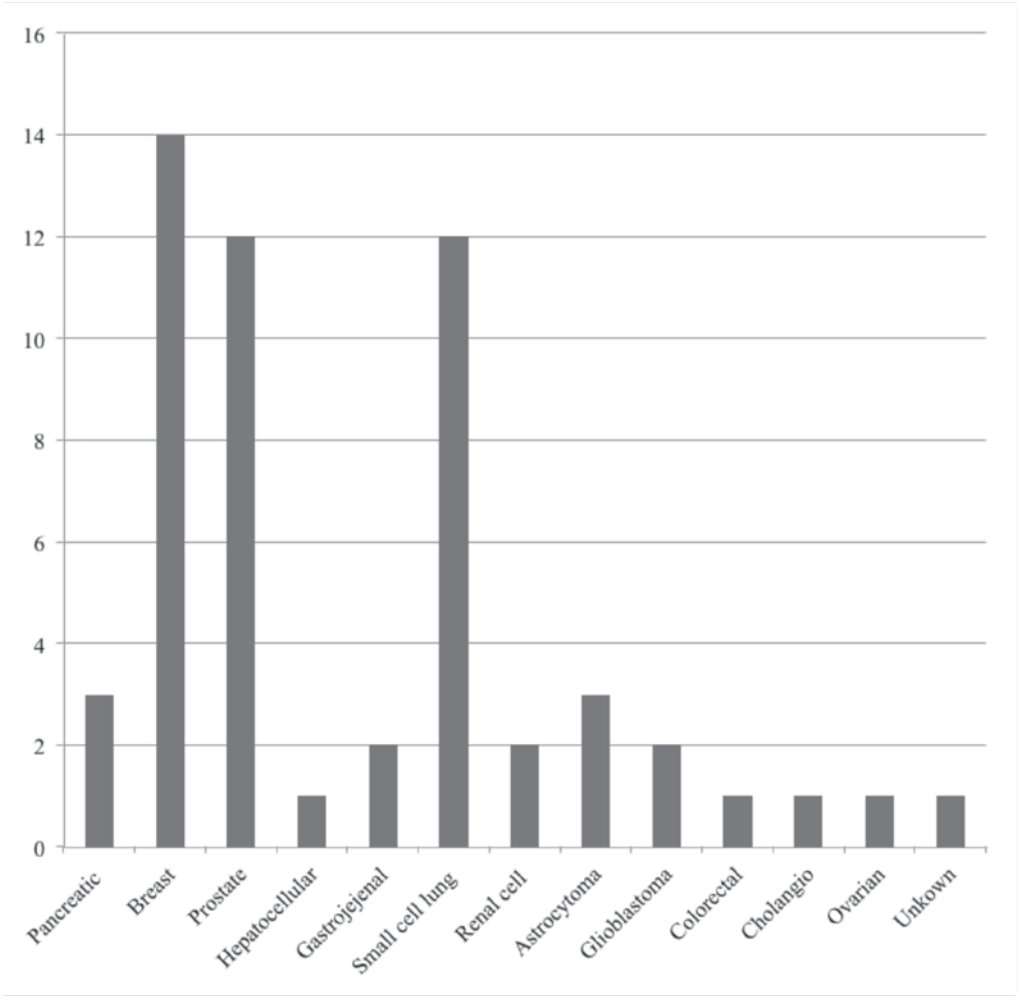


Figure 1: Number of patients (n=55) that were prescribed long term corticosteroids for each of the diagnosed primary carcinomas

Figure 2a: Number of patients (n=41) that were prescribed dexamethasone by different doses

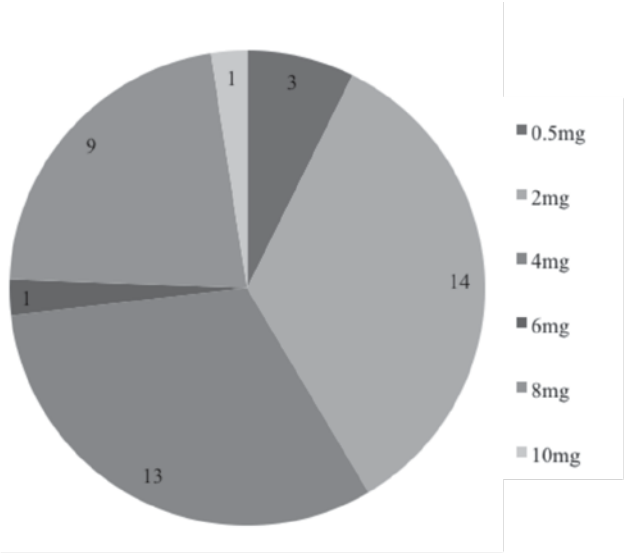


Figure 2b: Number of patients (n=14) that were prescribed prednisolone by different doses

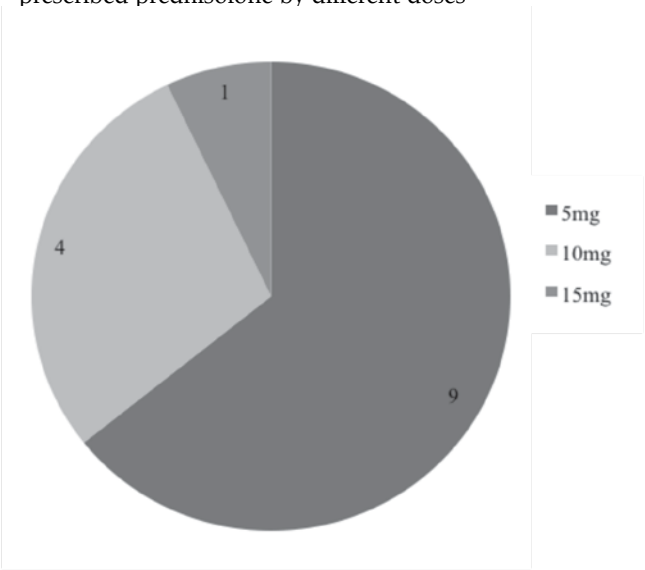
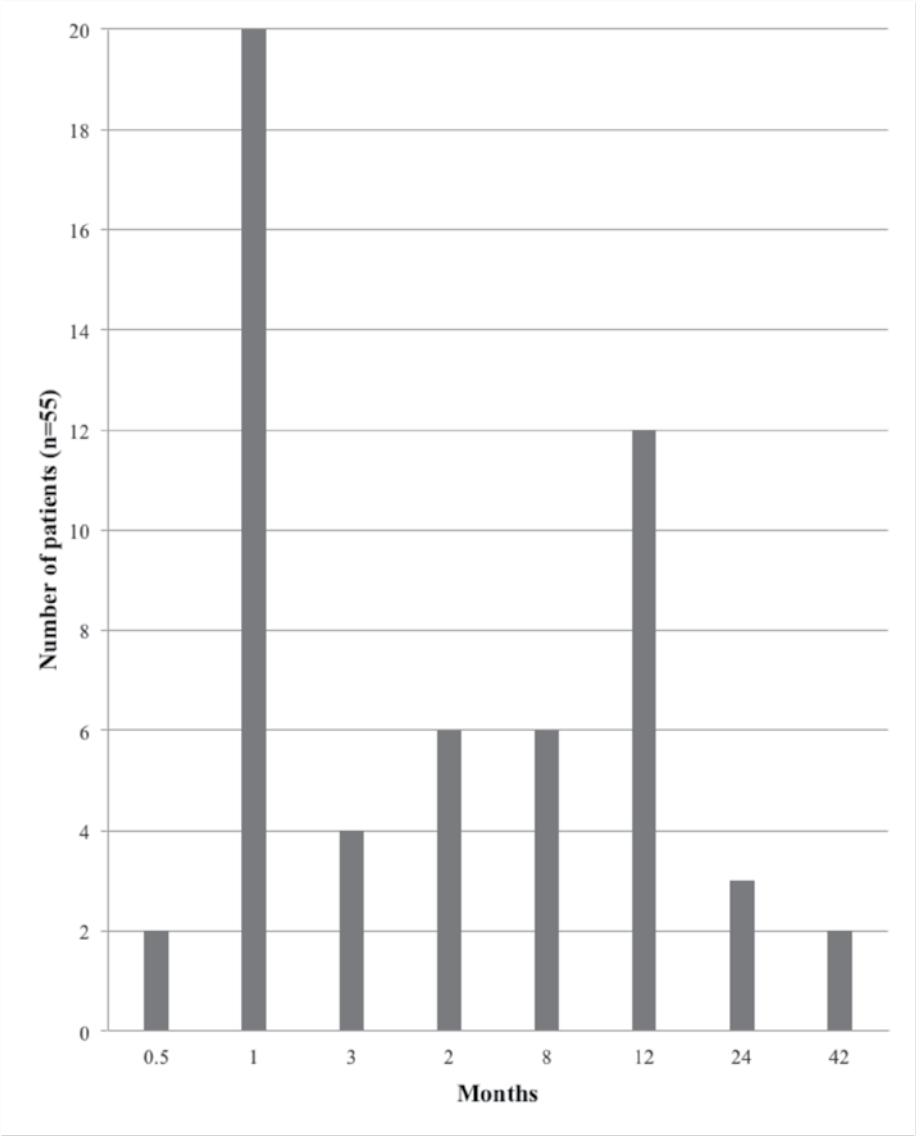


Figure 3: Treatment duration (months) of corticosteroid therapy (n=55)



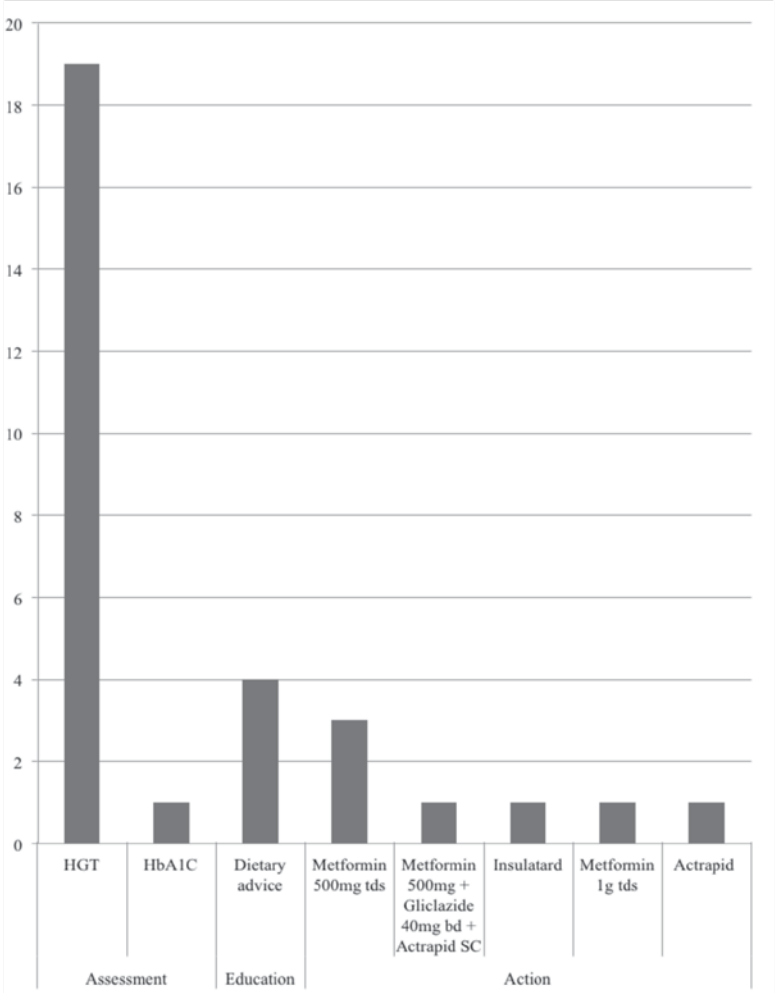


Figure 4: Management of hyperglycaemia (n=55)

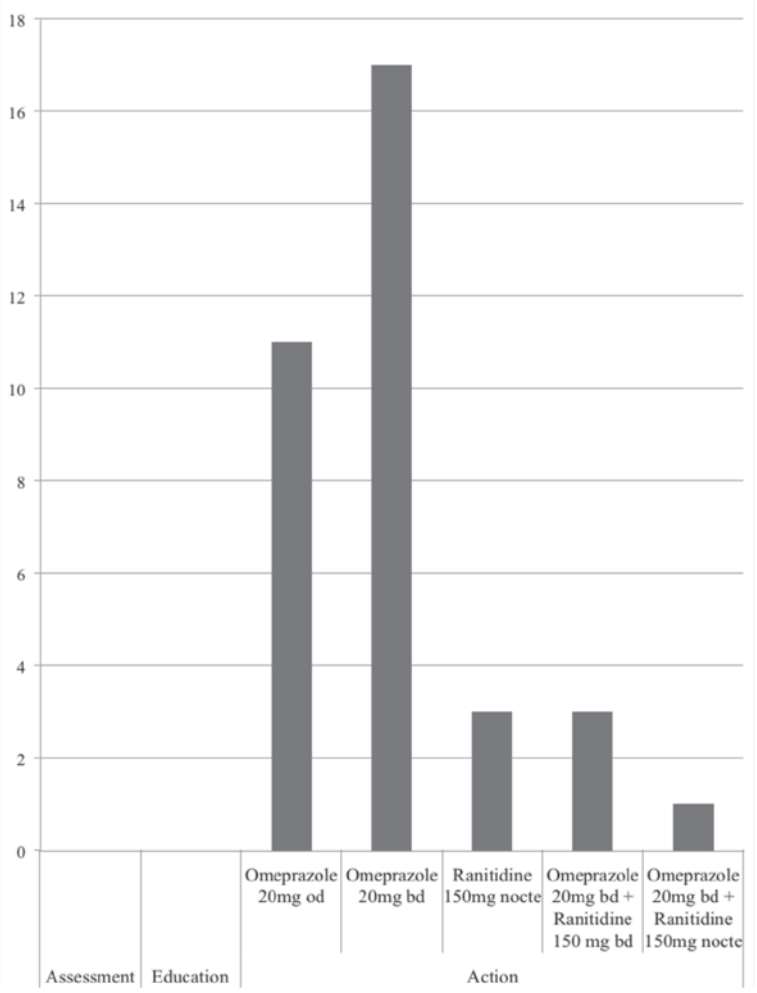


Figure 5: Management of dyspepsia (n=55)

Figure 6: Management of oral candidiasis (n=55)

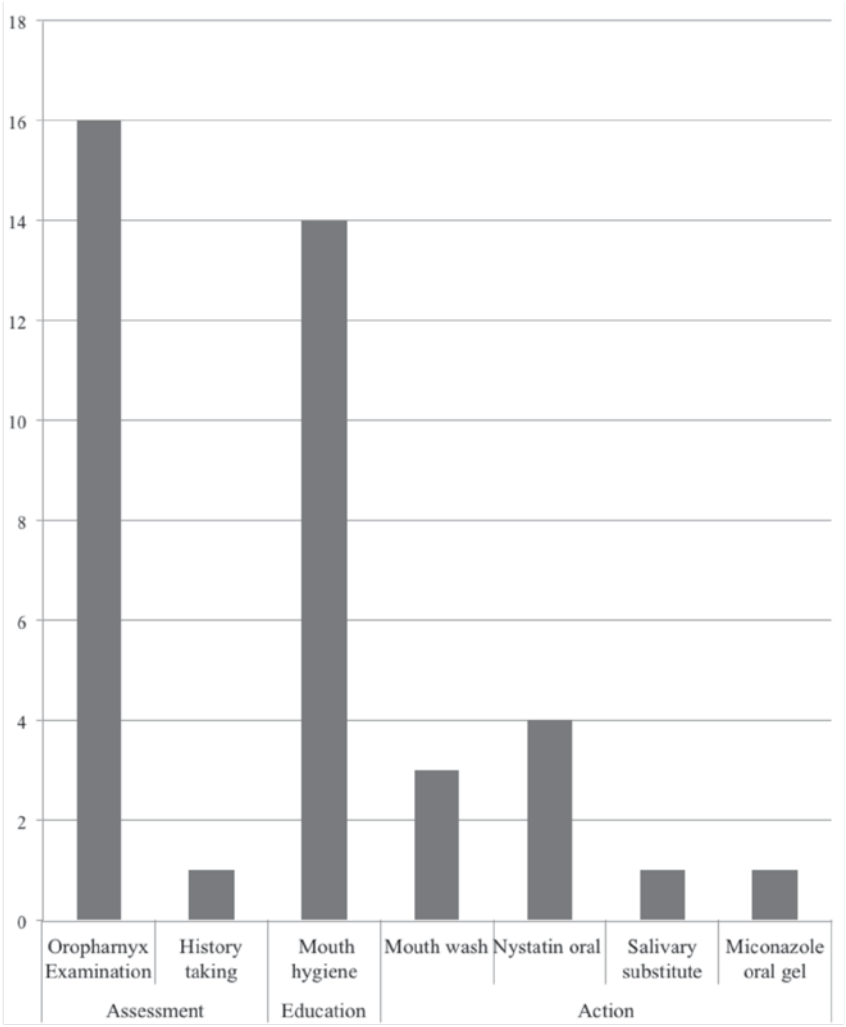
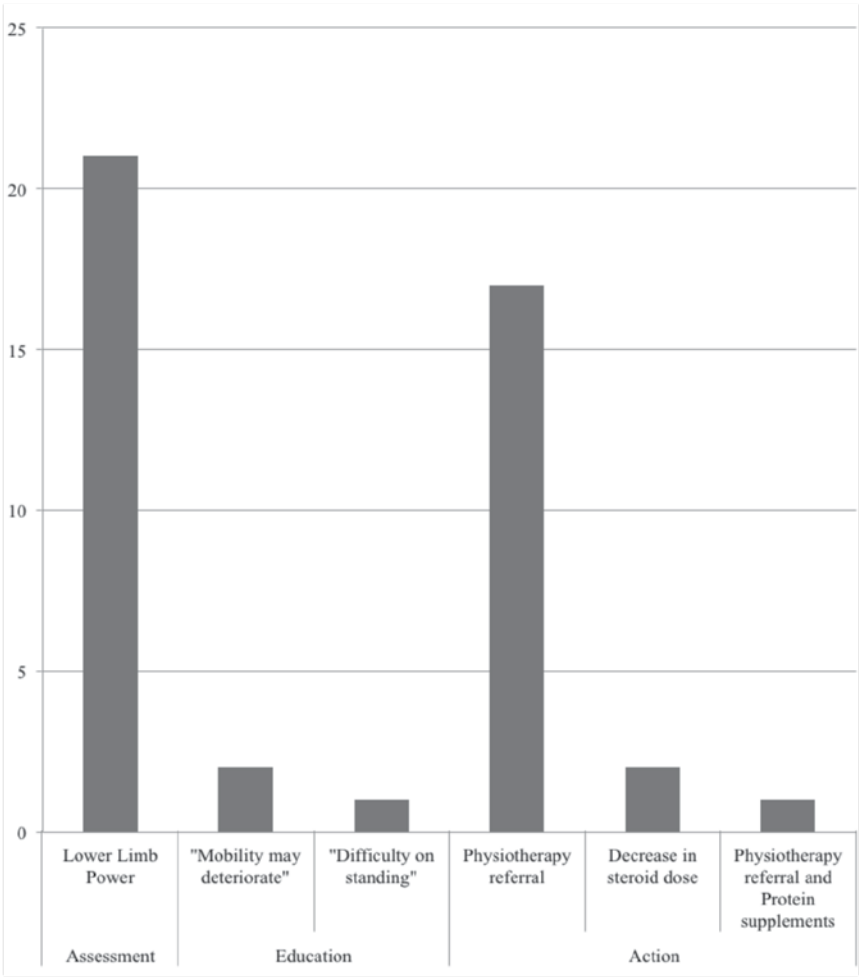


Figure 7: Management of Proximal Myopathy (n=55)



As described previously the indications of corticosteroid therapy require relatively potent corticosteroids with long term and high dose regimens. In this study the mostly prescribed steroid was dexamethasone (75%) at a dosage regimen of 2mg daily (34%) for 1 month (36%).

1. Hyperglycaemia

Glucocorticoids decrease glucose utilisation and increase hepatic glucose production, leading to hyperglycaemia; nonetheless the development of frank diabetes in a previously normal patient is uncommon (Moghadam-Kia and Werth, 2010). The effects of glucocorticoid administration on glucose levels are observed within hours of steroid exposure and appear to be dose dependent (Liu *et al,* 2013).

From the results of this study, less than half of the patients on long term steroids (43.6%) were managed for hyperglycaemia in any way. One reason for this might be that most of the steroid doses were not high enough to cause any concern among physicians. A less likely reason might also be that there was lack of awareness or lack of documentation among physicians.

Comparing to guidelines: proactive approach

Thirty-six per cent of patients were proactively managed according to guidelines only through HGT and HbA1c monitoring. No mention was made of whether the blood glucose levels were pre or post dose. Nonetheless there was no mention of any educational advice given with regards to the classic signs of hyperglycaemia. It is to be noted that educational advice could have been mentioned but not documented.

Comparing to guidelines: clinical management

Glycaemic targets for patients with corticosteroid-induced diabetes should be individualised, but for most patients, fasting plasma glucose and 2-hour plasma glucose targets of 4.0-7.0 mmol/L and 5–10 mmol/L respectively, are recommended (Cheng *et al,* 2013).

Thirteen per cent of patients were actively managed according to guidelines but compliance of this was only partial as insulin and metformin were given only to patients who had pre-existing diabetes and not specifically to those with steroid induced diabetes of levels >15mmol/L. Thus oral hypoglycaemics, as monotherapy, were the mainstay of treatment in this case. Such management would have been improved if a referral to a multidisciplinary diabetes team was conducted (Liu *et al,* 2013).

None of the clinicians resorted to a decrease in steroid dose or discontinuation of treatment as suggested by the guidelines. This may have been due to the fact that the benefit of steroid use at a therapeutic level outweighed the risks of hyperglycaemia.

It can be said that more is desired with respect to proactive management as the tests done are minimally invasive, non time-consuming and reliable. From the clinicians' point of view, awareness of glucose level cut-off points and steroid pharmacokinetics is paramount for optimal pharmacological glucose control. Patients should always be made aware of the most common clinical signs of hyperglycaemia so that help is sought immediately as this would allow prompt action to be employed.

2. Dyspepisa

The use of systemic glucocorticoids is associated with gastrointestinal (GI) side effects including gastritis, peptic ulceration and gastrointestinal haemorrhage (Moghadam-Kia and Werth, 2010). Recent evidence suggests that the risk of peptic ulcer disease due to corticosteroid alone is low, but increases significantly when these agents are used in combination with non-steroidal anti-inflammatory drugs (NSAIDs) (Hawkey & Longman, 2003).

In this study, dyspepsia was found to be the side effect which physicians were mostly aware of. It was found that protection was mostly offered to those patients with a high risk of GI bleeding or peptic ulcers. As stated by Hawkey & Longman (2003), corticosteroids act only as an NSAID specific risk magnifier and hence this may give rise to the debate of whether corticosteroids on their own increase risk of gastritis. This lack of clarity in evidence-based material might explain the rationale why a gastro-protective agent was not commonly prescribed in patients that have no history of gastritis, ulceration or GI bleeding.

Comparing to guidelines: proactive approach

As per the guidelines, management was only in the proactive form, with omeprazole being the most commonly prescribed. When compared to H_2 receptor antagonists, the proton pump inhibitors are a superior treatment modality for ulcer healing due to their ability to effectively control acid (Meijia and Kraft, 2009). No evidence based rationale was found that state that ranitidine and omeprazole combination therapy is more effective than omeprazole on its own.

Physicians may also have opted more for omeprazole since its dosage form is in capsule form and hence easier to swallow than ranitidine. Another reason for prescribing omeprazole could

have the physicians' awareness of the recommended prophylactic use of 20mg omeprazole in steroid induced ulcers (Lanza *et al,* 2009).

It is to be noted that patient advice with regards to lifestyle and steroid administration was not performed or not documented.

3. Oral candidiasis

Corticosteroids have been shown to affect T-cells by inducing thymocyte apoptosis after polyclonal T-cell activation, leading to reduced function of the immune system (Herold, McPherson and Reichardt, 2006).

Owing to the immunosuppressive effects of corticosteroids, patients may be at increased risk for increased risk of topical bacterial and fungal infections (Systemic steroids, 2014).

Hence it can be said that prednisolone and dexamethasone doses of more than 10mg and 1.5mg respectively can lead to a significant risk of oral candidiasis (Poetker and Reh, 2010).

The study shows that only 36% of patients on long term steroids where addressed for potential oral candidiasis, making it the least managed steroid induced side effect. Seventy-one per cent of patients of the same cohort were taking prednisolone or dexamethasone doses that were greater than 10mg and 0.5mg respectively and hence would have warranted a form of management (see Table 3). Reasons for this could be either failure of documentation or lack of clinicians' awareness.

Comparing to guidelines: proactive approach

Compliance to guidelines was achieved in 29% of patients of whom an orophargyngeal exam was conducted prior to commencement of corticosteroid therapy. Reasons for physicians not performing an oropharyngeal examination may be lack of awareness or failure to document. Oral candidiasis is mainly diagnosed clinically and hence awareness among physicians to look for clinical signs during follow up or before increasing corticosteroid dose is essential. Other proactive management actions that were performed by the physicians but not mentioned in guidelines included mouth hygiene and further history taking.

Comparing to guidelines: clinical management

The guidelines do not specify any form of active management but the study indicated that 16 % of patients were prescribed either a mouth wash or a form of a topical antifungal. This lack of compliance may be due to the fact that the guidelines were not formulated specifically for cancer patients. As in this case, active management may be appropriate in immunosuppressants secondary to carcinomas (Liu *et al.,* 2013), but routine primary prophylaxis is not recommended. However, if recurrences are frequent or severe, oral fluconazole can be used for either oropharyngeal or vulvovaginal candidiasis (Kaplan *et al.,* 2009).

Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including nystatin suspension or miconazole oral gel. Routine general advice about maintaining oral hygiene is always appropriate at any steroid regimen prescribed.

4. Proximal myopathy

Glucocorticoids have a direct catabolic effect on skeletal muscle (Sun *et al.,* 2008). Onset of symptoms usually takes several weeks, and patients typically present with proximal muscle weakness and atrophy in both the upper and lower extremities (Moghadam-Kia and Werth, 2010).

It was found that half of the patients on long term steroids were managed for proximal myopathy. Lower limb power assessment, physiotherapy referrals and quadriceps strengthening were the most common forms of management respectively. Patient education was observed only in 5% of patients most probably because of failure in documentation. It is vital to clarify to the patient the fact that weakness is due to corticosteroid effect rather than due to cancer progression.

In those patients that were not managed, prednisolone doses were less than 10mg and the likelihood of side effect manifestation is very low. But 43 % of such patients were on average daily dexamethasone doses greater than 1.5mg (equivalent to 10mg prednisolone) - see Table 3. This means there may be lack of knowledge with regards to steroid dosing and proximal myopathy.

Comparing to guidelines

According to the guidelines only clinical management is to be considered. Compliance was mostly noted when it came to resistance and endurance exercises. Some literature suggests that aerobic exercises and resistance training may help to prevent weakness or reduce its severity (Foye, 2015).

A proactive approach, a low steroid dose, low potency or insufficient regimen duration for steroid-induced myopathy may have reduced steroid manifestation and hence in practice this might have led

to less manifestations and hence less clinical management. Other possibilities for non-adherence may be lack of awareness and failure to document.

The main treatment recommendations for steroid myopathy are a decrease in the dose of steroid to below a threshold level or the discontinuation of the corticosteroid's use. Alternate-day dosing could also be considered (Gupta and Gupta, 2013). But again reduction in steroid dose was an uncommon choice with physicians. Physicians may have opted out of this option as benefits of corticosteroid use may have outweighed the risks of proximal myopathy manifestation or worsening of the condition.

Limitations

Many limitations were encountered in the study. Firstly, the guidelines to which the results were compared were not specifically formulated for cancer patients but for patients with inflammatory and immunological conditions that required long term systemic corticosteroid use. Due to time constraints only the most common clinically encountered side effects were considered. Osteoporosis, skin atrophy and psychiatric side effects were not assessed. Furthermore, although differences in monitoring and care exist between adults and children, only the adult population was sampled.

With regards to data collection, this was based only on what the clinicians had documented, and hence may not reliably reflect the actual intention of the prescriber. For example advice may have been given by the clinician but not necessarily documented.

Although the cancer type, steroid doses and duration of treatment were recorded, in view of time constraints, the effect of such steroid regimens on the manifestation of type and severity of side effect were not evaluated. It was also assumed that the side effects were purely long-term corticosteroid induced and not affected by other causes, e.g. comorbidities (cancer), drug interaction, etc.

Recommendations

This study has shown that hyperglycaemia, oral candidiasis, heartburn and proximal myopathy may often be overlooked in cancer patients who are on long-term steroids. If proactive and / or active management is to be provided, it is vital that patient assessment, education and appropriate treatment is sought.

From the study several recommendations can be highlighted that would help to improve the management of steroid side effects. Firstly, awareness amongst physicians of the above-mentioned guidelines is essential if they are to be followed and applied accordingly. These should be clear, regularly updated, well disseminated and enforced. One practical way to ensure this would be to make these management guidelines available on Mater Dei's Intranet (Kura) were they can be clear, easy to use regularly updated. Regular audits, the availability of hard copies on the wards and education campaigns are other ways by which awareness can be increased among prescribers.

Secondly, from the prescribers' side, documentation of any signs of corticosteroid side effects in medical notes is vital as their presence may affect the patient's management plan. This will also help when reviewing corticosteroid doses on weekly bases. Dexamethasone should be given as single morning dose, or if a higher dose needed give in 2 divided doses, the second being no later than 2 p.m. to minimise risk of sleep disturbance.

Thirdly, patients should be informed about the common corticosteroid side effects and advised on lifestyle modification strategies that may help reduce the risk of these events. If discharged home, the physician should instruct patients to seek medical advice in the case corticosteroid side effect manifestations (Princess Alice Hospice Guidelines for corticosteroid use in palliative care, 2008).

Patients on systemic steroids for >3 weeks must be given a steroid card so that it can be shown to all healthcare professionals involved in their care and management (North of England Cancer Network palliative care guidelines, 2013). This should include the indication for steroid use and the plan for dose reduction and monitoring. At end of life, if corticosteroids are prescribed for specific severe or serious symptom, these should be continued at the most convenient subcutaneous dose. If prescribed for 'general well-being' or appetite stimulation they should be discontinued.

The provision of educational leaflets may facilitate delivery of information to patients as well as save the clinician's time. Furthermore, the assistance of allied health care professionals in the clinical assessment and education prior to the patient's consultation with the physician may assist in the awareness of corticosteroid side effects.

CONCLUSION

Much has still to be done in order to implement management as proposed by guidelines for steroid induced side effects, especially when it comes to treatment

and prevention of steroid induced hyperglycaemia and oral candidiasis. These adverse effects are particularly important as they tend to be more severe and commoner in cancer patients than in the rest of the population.

Management should involve more careful patient monitoring and implementation of preventive measures, including the use of lower potency agents and the lowest effective dose required for management of the underlying condition. Management should also involve the treatment of the manifested side effects as well.

Furthermore, patients should be informed more about the side effects associated with systemic corticosteroid use and should be advised on lifestyle modification strategies that may help reduce the risk of these events. Patients should also be instructed to seek medical attention if they experience signs and symptoms of steroid-related side effects and should also be advised to carry a steroid treatment card that can be shown to all healthcare professionals involved in their care and management. Differences in the monitoring and care of adults versus children should also be noted.

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