Efficacy of interrupted cyclic treatment with prednisolone on cancer pain: a randomized crossover study

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Abstract

Background: Interrupted cyclic treatment with a low oral dose of prednisolone combined with stepladder analgesics would reduce the pain scores in cancer patients with reported less side effects. Following ethical approval, 39 cancer patients were randomized to receive prednisolone 10 mg every other day or every 4th day for 4 successive weeks followed with tapering prednisolone by 2.5 mg every 4 days over 2 weeks after each interval, primary outcome visual analog score (VAS), and other secondary outcomes such as (A) patient demographics; (B) pain scores; brief pain inventory score (BPI), pain severity score (PSS), pain interference score (PIS), analgesia level score, pain level score (PLS), and pain management index (PMI)); and (C) patient safety (adverse effects) with interrupted cyclic treatment with low-dose prednisolone.

Results: Compared with baseline values, patients had statistically significant lower VAS and PSS pain scores at 14 and 28 days after starting the 2 days cyclic treatment with prednisolone. Patients had comparative VAS and PSS pain scores during the 4-day cyclic treatment with prednisolone. Compared with the 4-day cyclic treatment, patients in the 2-day cyclic treatment had significant statistically lower VAS pain scores at 28 days. Adverse effects showed no significant statistical differences during both study sequences.

Conclusion: Interrupted cyclic prednisolone 10 mg combined with stepladder analgesic regimen is effective and safe in terms on improved quality of analgesia for 28 days in cancer patients more when used every 2nd day than every 4th day with appetite improvement during both.

Trial registration: The study protocol was approved by the local Institutional Board Review Committee on 8-11-2019. The study was prospectively registered with the www.clinicaltrials.gov

Keywords: Interrupted cyclic, Prednisolone, Cancer pain, Pain, Cancer, Genomic

Background
Cancer pain is undertreated in one-third of patients (Cleeland et al., 1994). That might be attributed to several factors including inadequate pain management and the assessment tool for measurement of the intensity of pain (Greco et al., 2014). The World Health Organization (WHO) developed the stepladder approach for administering analgesics for cancer patients including the use of non-opioid analgesics, weak opioids, and strong opioids according to the severity of pain (World Health Organization, 2012; Fallon et al., 2018). Several previous researches studied the efficacy of opioids use in cancer pain (Shvartzman et al., 2003). Some investigators reported better analgesia with replacing the weak opioids with administering low doses of oral morphine (Sturdza et al., 2008). The use of glucocorticoids showed some efficacy in treating cancer pain (Haywood et al., 2015) with notable increased appetite (Pufall, 2015), despite there is no current consensus on the ideal type and dosage. These beneficial roles could
be attributed to the anti-nociceptive mechanism (Watanabe & Bruera, 1994), in addition to reducing the peritumoral edema (Kumar et al., 2017). The use of prednisolone, a relatively potent anti-inflammatory agent (more potent than hydrocortisone but less potent than dexamethasone), in a dose range of 20–40 mg/day is associated with unwanted adverse effects including insulin resistance, immune depression, muscle myopathy, and adrenal insufficiency (Miller et al., 2014). Most of these adverse effects are dose-dependent.

Glucocorticoids high doses non-genomic mechanisms including depression of the T lymphocytes, transcellular cycling of calcium and sodium and modulation of neural activity and plasticity could be associated with an immune-suppression (Kumar et al., 2017; Miller et al., 2014; Yasir et al., n.d.).

The use of lower doses of prednisolone would retain the analgesic effects via the delayed genomic mechanisms stimulating the release of anti-inflammatory cytokines such as interleukin 10 (IL-10), nuclear factor-κB (NFκB) inhibitor, and lipocortin-1 (Yasir et al., n.d.).

The effects of low-doses of glucocorticoid on the intensity of cancer pain, fatigability, depressed-mode, and patients’ wellbeing are still not clear (Leppert & Buss, 2012). Sudden cessation of long-term continuous glucocorticoid therapy for more than 3 weeks may result in adrenal insufficiency (Paragliola et al., 2017). However, that is only applicable to daily glucocorticoid use or long-term glucocorticoid therapy.

Brief Pain Inventory (BPI) (Fig. 1) (Yamada et al., 1983) is a pain assessment tool that measures both the intensity of pain (sensory dimension) and interference of cancer pain in the patient’s life (reactive dimension). Pain Management Index (PMI) (Sakakibara et al., 2018) is widely used in the assessment of pain management, and negative scores are traditionally considered to indicate inadequate pain management. PMI scores are inversely associated with the proportion of patients with pain interference (PI). However, PMI scores of −1 do not always indicate inadequate pain management; pain management should therefore be evaluated from multiple perspectives.

The investigator hypothesized that the use of low-dose prednisolone at interrupted cyclic intervals in conjunction with the basal stepladder analgesic regimen would improve the quality of pain control in cancer patients with associated less frequent adverse effects.

The present study aimed to study the efficacy of Interrupted cyclic treatment with low-dose prednisolone (10 mg) added to the stepladder analgesic regimen in terms of improved quality of analgesia for 28 days in cancer patients when used every 2nd day than every 4th day with steroid side effects outcomes.

The study outcomes: primary outcome visual analog score (VAS). Secondary outcomes such as (A) patient demographic data (age, gender, occupation, education level, associated comorbidities, the WHO stepladder analgesia level, analgesic drugs used, and type of pain); (B) pain scores; brief pain inventory score (BPI), pain severity score (PSS), pain interference score (PIS), analgesia level score, pain level score (PLS), and pain management index (PMI)); (C) patient safety (adverse effects) of interrupted cyclic treatment with low dose prednisolone in addition to the standard stepladder analgesic regimen in patients with cancer-induced pain.

Methods
Following obtaining the local institutional research board (IRB) ethical committee approval number and patient written informed consent, 39 patients aged 18-75 years who were diagnosed with metastatic cancer were included in this prospective randomized crossover open label study at the Pain Clinic, Oncology Center, College of Medicine. The study was prospectively registered with clinical trial registration. Patients who did not represent regular visits at the pain clinic of the author’s center every other week for a minimum of 3 successive months, refused to participate in the study, or those with severe uncontrolled medical diseases (e.g., organ failure, uncontrolled diabetes, or hypertension), uncontrolled psychiatric illness, or receiving chemotherapy or radiotherapy during the study period were excluded.

Patients were randomly allocated using sequentially numbered computer-generated randomization codes included in closed sealed opaque envelopes into one of two sequences (2 days followed with 4 days intervals or 4 days followed with 2 days intervals) as shown in Fig. 2.

All patients received their basal analgesic regimen throughout the study period based on the WHO stepladder approach, the number and types of cancer ladder analgesics are presented in Table 1.

In the “2 days cyclic interval”, patients received oral prednisolone 10 mg every other day for 4 successive weeks. The “4 days cyclic interval”, in which patients received oral prednisolone 10 mg every 4th day for 4 successive weeks

A washout period was considered after each interval period with tapering prednisolone by 2.5 mg every 4 days over 2 weeks

The study data collection
The primary outcome was the VAS for to assess the severity of pain.

Secondary outcomes included the “efficacy” of interrupted cyclic dosage of glucocorticoids on: (1) the multi-task brief pain Inventory-Short Form questioner (BPI-sf)
(Yamada et al., 1983) which was based on verbal questionnaire provided with the pain physician (Fig 1).

(2) PMI (Sakakibara et al., 2018) was computed by subtracting the pain level from the analgesic level (values ranged from $-3$ (patient with severe pain receiving no analgesic drugs) to $+3$ (patient receiving morphine or an equivalent and reporting no pain)). A negative PMI score was considered as an indicator of inadequate pain management.

(3) PSS (Tegegn & Gebreyohannes, n.d.) as calculated by addition of the values of items $3 + 4 + 5 + 6$ (Fig. 1) divided by 4 yielding severity score out of 10 (1–3 mild pain, 4–6 moderate pain, and 7–10 severe pain).

(4) PIS (Tegegn & Gebreyohannes, n.d.) as calculated by summarizing the scores for questions $9A + 9B + 9C + 9D + 9E + 9F + 9G$ item 9 in Fig. 1) then dividing it by 7, this gives an interference score out of 10.
interference were classified using BPI-sf into four groups; no pain (0), mild pain (1 to 3), moderate pain (4 to 7), and severe pain (8 to 10). Item number 9 (9A–9G, Fig. 1) measured the effect of pain on interfering with patient’s daily activities including general activity, walking, work, mood, enjoyment of life, relations with others, and sleep.

The pain interference items were presented with 0–10 scales, with 0 = no interference and 10 = interferes completely.

(5) PLS (Tegegn & Gebreyohannes, n.d.) (absence of pain was scored as “0,” mild pain as “1” moderate pain as “2” severe pain as “3”).

(6) The type of medications used for pain management and percentage of pain relief.

(7) Analgesia Level score ALS (Tegegn & Gebreyohannes, n.d.): 0, no order for analgesic; 1, non-opioid (e.g., NSAID or acetaminophen); 2, weak opioid (e.g., codeine); and 3, strong opioid (e.g., morphine).

(8) Additionally, “safety” was recorded using 1—a simple binary scoring system for the patient’s complaint, 2—myopathy (0 = no myopathy, 1 = present), 3—loss of appetite (0 = no appetite loss, 1 = appetite loss present), 4—insomnia (0 = no insomnia, 1 = insomnia present), and 5—renal function tests.

The study outcomes were recorded before starting prescribing oral prednisolone, at 14th day and 28th day for each study cyclic interval.

Sample size calculation
A pilot study included 20 patients with cancer pain receiving the standard stepladder analgesic regimen with oral prednisolone 10 mg every other day showed that the VAS pain scores were 3.42 ± 0.53 and 2.86 ± 0.69 before and 28 days after start of treatment. An a priori sample size calculation using G power program version 3.0.10 indicated that 31 patients were needed to test the probability of rejecting null hypothesis using two-sided dependent samples t test with an effect size 0.677 and a significance level of 0.05 and a power of 95%. Eight more patients were included to compensate for the expected dropout during the study.
IBM’s SPSS statistics (Statistical Package for the Social Sciences) for windows (version 16) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. Paired t-test for comparing the two sequences to rule out the carryover effect was used for normally distributed continuous data. Chi-square test was used for categorical data using the crosstabs function. All tests were conducted with 95% confidence interval. Data were expressed as mean ± SD, median [inter-quartile range], or number and percentage as appropriate. P value < 0.05 was considered statistically significant. Linear regression for prediction of stage A VAS score at day 28, 21.6% of VAS score day 28 can be predicted by dose of 10 mg given every 2 days (stage A) \( R^2 = 0.216, F = 20.98, p < 0.001 \).

**Table 1** Patients demographics and cancer-cancer treatment criteria

| Variable                          | Numerical          | %    |
|----------------------------------|--------------------|------|
| Age (years)                      | 52.92 ± 11.96      | –    |
| Sex (male/female)                | 16/23              | 41/59|
| Occupation                       |                    |      |
| None                             | 31                 | 79   |
| Government employee              | 3                  | 8    |
| Farmer                           | 1                  | 2.56 |
| Private work                     | 4                  | 10.26|
| Education                        |                    |      |
| Illiterate                       | 22                 | 56   |
| Secondary school                 | 13                 | 33   |
| University                       | 4                  | 10   |
| Comorbidity                      |                    |      |
| No                               | 23                 | 59   |
| Hypertension (controlled)        | 5                  | 13   |
| DM (controlled)                  | 5                  | 13   |
| Both (Hypert. and DM)            | 4                  | 10   |
| Others                           | 2                  | 5    |
| Metastasis                       | 39                 | 100  |
| Number of analgesics             |                    |      |
| One                              | 1                  | 3    |
| Two                              | 1                  | 3    |
| Three                            | 37                 | 94   |
| Type of analgesics (WHO stepladder) |                |      |
| Step 1                           | 0                  | 0    |
| Step 2                           | 33                 | 85   |
| Step 3                           | 6                  | 15   |
| Type of pain                     |                    |      |
| Neuropathic                      | 3                  | 8    |
| Visceral                         | 13                 | 33   |
| Mixed                            | 23                 | 59   |
| PSS-pain level (patient number)  |                  |      |
| Mild                             | 15                 | 29   |
| Moderate                         | 23                 | 10   |
| Severe                           | 1                  | 0    |

Legend: this table shows patient age in (years), sex (male/female), occupation, education, comorbidity, metastasis, number of analgesics, type of analgesics (WHO stepladder), and type of pain. All variables are in number and percentage age in mean ± SD

**Results**

**Patient demographics**

Table 1 showed patients’ characteristics including age, gender, occupation, education level, associated comorbidities, the WHO stepladder analgesia level, and analgesic drugs used. All patients had cancer metastasis and 59% of them had mixed neuropathic and visceral pain (Table 1).

**Pain scores**

Compared with baseline values, patients had statistically significant lower VAS and PSS pain scores at 14 days and 28 days after starting the 2-day cyclic treatment with prednisolone [VAS 3.31 ± 0.83 and 3.1 ± 0.64 at 14 days and 28 days, respectively vs. 4.49 ± 1.02 at baseline, \( P < 0.001 \), PSS 3.7 ± 0.67 and 3.46 ± 0.52 at 14 days and 28 days, respectively vs. 4.56 ± 0.75 at baseline, \( P < 0.001 \)] (Table 2). Patients had comparative VAS and PSS pain scores during the 4-day cyclic treatment with prednisolone (Table 2). Compared with the 4-day cyclic treatment, patients in the 2-day cyclic treatment had significant statistically lower VAS pain scores at 28 days (Table 4), a result documented after linear regression analysis (Table 5) for prediction of stage A VAS score at day 28, 21.6% of VAS score day 28 can be predicted by prednisolone dose of 10 mg given every 2 days (stage A). Compared with the baseline values, the scores PIS, PLS, ALS, and PMI showed no significant statistical differences in both study sequences (Table 2).

**Glucocorticoid side effects** Myopathy, insomnia, renal function (serum creatinine), and liver function (AST, ALT) were similar during the two cyclic intervals with no significant differences compared to basal and in between both study stages comparison (Tables 3 and 4). Appetite loss was significantly decreased in both stage A 64.1% \( P \leq 0.001 \) and stage B 82% \( P = 0.006 \) compared to basal value of 100% (Table 3), with no significant difference between stage A when compared to stage B \( P = 0.74 \) (Table 4).
Discussion

The present study results demonstrated lower VAS pain scores for 28 days during the 2-day cyclic interval treatment with oral prednisolone 10 mg, combined with basal stepladder analgesic regimen, for 4 weeks followed with gradual tapering down over 2 weeks this analgesic effect, linear regression analysis for prediction of stage A VAS score at day 28, 21.6% of VAS score day 28 can be predicted by prednisolone dose of 10 mg given every 2 days (stage A).

Table 2 Pain measurement variables (stage analysis)

| Variable | Basal | 14 days | P value | 28 days | P value |
|----------|-------|---------|---------|---------|---------|
| VAS      |       |         |         |         |         |
| Stage (A)-Glucocorticoid every 2nd day | 4.49 ± 1.02 | 3.31 ± 0.83 | ≤ 0.001 | 3.1 ± 0.64 | ≤ 0.001 |
| Stage (B)-Glucocorticoid every 4th day | 3.59 ± 0.68 | 3.58 ± 0.55 | 0.453 | 3.74 ± 0.59 | 0.507 |

Pain severity score (PSS)

| Stage (A)-Glucocorticoid every 2nd day | 4.56 ± 0.75 | 3.7 ± 0.67 | ≤ 0.001 | 3.46 ± 0.52 | ≤ 0.001 |
| Stage (B)-Glucocorticoid every 4th day | 3.54 ± 0.38 | 3.54 ± 0.43 | 0.678 | 3.62 ± 0.34 | 0.354 |

Pain interference score (PIS)

| Stage (A)-Glucocorticoid every 2nd day | 5.98 ± 1.58 | 5.26 ± 1.59 | 0.449 | 5.27 ± 1.43 | 0.213 |
| Stage (B)-Glucocorticoid every 4th day | 5.48 ± 1.36 | 5.38 ± 1.39 | 0.223 | 5.36 ± 1.39 | 0.663 |

Pain level score (PLS)

| Stage (A)-Glucocorticoid every 2nd day | 1.1 ± 0.307 | 1.1 ± 0.22 | 0.395 | 1.1 ± 0.38 | 0.432 |
| Stage (B)-Glucocorticoid every 4th day | 1.1 ± 0.35 | 1.2 ± 0.54 | 0.383 | 1.2 ± 0.54 | 0.383 |

Analgesia level score (ALS)

| Stage (A)-Glucocorticoid every 2nd day | 2.13 ± 0.34 | 2.13 ± 0.34 | 1 | 2.13 ± 0.34 | 1 |
| Stage (B)-Glucocorticoid every 4th day | 2.13 ± 0.34 | 2.13 ± 0.34 | 1 | 2.13 ± 0.34 | 1 |

Pain management index (PMI)

| Stage (A)-Glucocorticoid every 2nd day | 1.1 ± 0.35 | 1.1 ± 0.42 | 0.777 | 1.1 ± 0.46 | 0.572 |
| Stage (B)-Glucocorticoid every 4th day | 1.1 ± 0.51 | 1 ± 0.65 | 0.672 | 1 ± 0.65 | 0.672 |

Legend: this table shows significant decrease in VAS and PSSC after 14 days and 28 days compared to basal values after oral glucocorticoid dosing once a day every other day as adjuvant to WHO stepladder analgesics with no significant difference as regards PIS, PLS, ALS, and PMI. Data were in mean and standard deviation. Cross tab chi-square statistical test was used for comparison of non-parametric data and t test for parametric data. P value was significant if < 0.05. Linear regression analysis for prediction of VAS score 28 indicated that 21.6% of VAS score day 28 can be predicted by dose of 10mg given every 2 days (stage A) \[
R^2 = 0.216, F = 20.98, p < 0.001
\]

Table 3 Glucocorticoid side effects

| Variable | Basal value | Study result | P value |
|----------|-------------|--------------|---------|
| Myopathy (yes/no) | | | |
| Stage (A)-Glucocorticoid every 2nd day | 11/28(28.2%) | 6/33(15.38%) | 0.170 |
| Stage (B)-Glucocorticoid every 4th day | 11/28(28.2%) | 9/30(30.0%) | 0.604 |

Appetite loss (yes/no)

| Stage (A)-Glucocorticoid every 2nd day | 39/0(100%) | 25/14(64.1%) | ≤ 0.001 |
| Stage (B)-Glucocorticoid every 4th day | 39/0(100%) | 32/7(82%) | 0.006 |

Insomnia (yes/no)

| Stage (A)-Glucocorticoid every 2nd day | 13/26(33.3%) | 6/33(18.18%) | 0.065 |
| Stage (B)-Glucocorticoid every 4th day | 13/26(33.3%) | 8/31(25.6%) | 0.202 |

Serum creatinine

| | 0.92 ± 0.22 | 1 ± 0.23 | 0.063 |
| AST | 22(10–72) | 32(17–126) | 0.391 |
| ALT | 22(9–49) | 29(13–129) | 0.292 |

Legend: this table shows significant decrease in appetite loss after oral glucocorticoid adjuvant to WHO stepladder analgesics compared to basal values with no significant difference as regards myopathy, insomnia, kidney function (serum creatinine), and hepatic function (AST, ALT). Data are in median and range except for serum creatinine is in mean and standard deviation. Myopathy, loss of appetite, and insomnia were in number and percent%. Cross tab chi-square statistical test was used for comparison of non-parametric data and t test for parametric data. P value was significant if < 0.05.
That could be attributed to the analgesic properties of prednisolone via the delayed genomic mechanisms with releasing the anti-inflammatory cytokines (Yasir et al., n.d.) in addition to suppression of inflammation nociceptors activation (Leppert & Buss, 2012), and pro-inflammatory cytokines.

In contrast, a Cochrane review (Haywood et al., 2015) included 1926 participants in 15 studies demonstrated weak analgesic effects of using glucocorticoids for pain control in cancer patients. That might be explained with the use of dexamethasone in these included studies with interruption for only 1 week.

As regards the glucocorticoid effects on the general condition of patient with metastatic cancer, our study results showed highly significant decrease in appetite loss (64.1%), (82%) during both study stages (A and B) respectively compared to basal value (100%), $P$ value $\leq 0.001$, 0.006 respectively. Prednisolone 10 mg single oral dose improved the cancer patient appetite whenever used every 2nd day or 4th day, this could be attributed to anti-inflammatory properties and ability to counteract pain, nausea, and other toxic effects of cytotoxic chemotherapy. However, perhaps the most important benefit of glucocorticoids is derived from the suppression of adrenal androgen synthesis (Tannock et al., 1989). On the other hand, glucocorticoids also improve the quality of life of patients with prostate cancer by providing pain relief, stimulating appetite and improving fatigue, which was strongly associated with reduced lean body mass and strength in cancer cachexia and anorexia (Willcox et al., 1984).

In line with our results, Miller et al. 2014 (Miller et al., 2014) reported that prednisolone at 20 to 40 mg/day is known to stimulate the appetite in cancer induced anorexia in palliative medicine. But this high dose has its drawbacks including insulin resistance, immune suppression, muscle myopathy, and risk of adrenal insufficiency. In opposition to our results, Exton et al. 2009 (Mensah-Nyagan et al., 2008) documented that there has been little evidence in literature for glucocorticoid effectiveness in cancer-induced anorexia, depressed mood, and poor general well-being and dyspnea; long-term use of oral glucocorticoids is associated with serious side effects, including osteoporosis, metabolic disease, and increased risk of cardiovascular disease (De Vries et al., 2007; Vegiopoulos & Herzig, 2007).

The present study was designed to test the efficacy and safety of using lower daily dose of prednisolone given at an interrupted cyclic fashion to reduce the glucocorticoid-induced side effects. Bruera et al. (Bruera et al., 1985) studied the analgesic efficacy of using a larger daily dose regimen of prednisolone (32 mg/day in divided doses) for 20 days in 40 patients with advanced cancer in a crossover design. All the patients were then given methylprednisolone for 20 days. They reported similar decreased VAS pain scores to our results. Lundström and colleague (2006) (Lundström & Furst, 2006) In a Swedish survey, compared to this present study found that 82% of patients had range from very good to some effect, the positive response came within a week and lasted for more than 4 weeks, of these patients, 81% used glucocorticoids for more than 4 weeks—a shorter period than our study— together with glucocorticoids daily use.

Similar with the present study, Tannock et al. (Tannock et al., 1989) reported favorable analgesic efficacy of low prednisolone doses (7.5–10 mg daily dose) in one-third of the studied 37 metastatic prostatic cancer patients.

Hypothesis in this present study was constructed up on adding interrupted cyclic low daily doses of glucocorticoid prednisolone to the cancer analgesia WHO

### Table 4 Study stages comparison; pain scores, and side effects

| Variable                  | Stage (A) Glucocorticoid/2nd day | Stage (B) Glucocorticoid/4th day | $P$ value |
|---------------------------|---------------------------------|---------------------------------|-----------|
| VAS at:                   |                                 |                                 |           |
| 14 days                   | $3.31\pm 0.83$                  | $3.58\pm 0.55$                  | 0.081     |
| 28 days                   | $3.1\pm 0.64$                   | $3.74\pm 0.59$                  | $\leq 0.001$ |
| Pain severity score (PSS) at: |                                 |                                 |           |
| 14 days                   | $3.7\pm 0.67$                   | $3.54\pm 0.43$                  | 0.344     |
| 28 days                   | $3.46\pm 0.52$                  | $3.62\pm 0.34$                  | 0.1       |
| Myopathy                  | $6/33(15.38\%)$                 | $9/30(15.38\%)$                 | 0.389     |
| Appetite loss             | $25/14(64.1\%)$                 | $32/7(82\%)$                    | 0.74      |
| Insomnia                  | $6/33(15.38\%)$                 | $8/31(20.5\%)$                  | 0.555     |

Legend: this table shows highly significant decrease in VAS at 28 days in stage A compared to stage B [better analgesia] after oral glucocorticoid dosing once a day every other day as adjuvant to WHO step ladder analgesics with no significant difference as regards myopathy, appetite loss, and insomnia in between the study stages. Data were in mean and standard deviation except for myopathy, appetite loss, and insomnia were in number and percent%. Cross tab chi-square statistical test was used for comparison of non-parametric data and t test for parametric data. $P$ value was significant if $<0.05$.
Riccardi, 2009 (Ayroldi & Riccardi, 2009) reported a monomodulatory cytokine. Further study by Ayroldi and Riccardi (2009) documented that glucocorticoids via genetic mechanisms stimulates the release of anti-inflammatory cytokines. In line with our result, Couper et al. 2008 (Couper et al., 2008) documented that glucocorticoids anti-inflammatory actions via genetic induction stimulates IL-10 production, a potent anti-inflammatory and immunomodulatory cytokine. Further study by Ayroldi and Riccardi, 2009 (Ayroldi & Riccardi, 2009) reported glucocorticoid genetic protein induction inhibits the function of nuclear factor-κB (NFκB) inflammatory cytokine and activator protein 1 (AP-1) (Table 5).

κ function of nuclear factor-
glucocorticoid genetic protein induction inhibits the

This table shows that 21.6% of VAS score day 28 can be predicted by dose of 10 mg given every 2 days (stage A)

| Model | Unstandardized coefficient | Standardized coefficient | t | p  |
|-------|----------------------------|--------------------------|---|----|
|       | B                          | Std.Error                | Beta | 11.124 * 0.001 |
|       | Group                      | 0.321                    | 0.140 | 0.0465 |
|       |                             |                          |                                 | 4.580 * 0.001 |

R² = 0.216

F = 20.98, p * 0.001

protocol drugs, leads to cancer pain analgesia improvement A result supported by Clark, 2007 (Clark, 2007) who documented that glucocorticoids via genetic mechanisms stimulates the release of anti-inflammatory cytokines. In line with our result, Couper et al. 2008 (Couper et al., 2008) documented that glucocorticoids anti-inflammatory actions via genetic induction stimulates IL-10 production, a potent anti-inflammatory and immunomodulatory cytokine. Further study by Ayroldi and Riccardi, 2009 (Ayroldi & Riccardi, 2009) reported glucocorticoid genetic protein induction inhibits the function of nuclear factor-κB (NFκB) inflammatory cytokine and activator protein 1 (AP-1) (Table 5).

Conclusion
The use of interrupted cyclic treatment with prednisolone 10 mg combined with stepladder analgesic regimen is effective and safe in terms on improved quality of analgesia for 28 days in cancer patients more when used every 2nd day than every 4th day with appetite improvement during both.

Limitations
The use of a fixed does of prednisolone over the study period is still a naive idea. It needs to be studied through a randomized controlled study including a larger number of patients.

Recommendations
The author recommends the use of interrupted cyclic treatment with low doses of prednisolone (10 mg every other day), in conjunction with the standard stepladder analgesic drugs, for 4 weeks for treating cancer pain. Further studies including larger numbers of participants are needed to evaluate the safety and effectiveness of glucocorticoids for the management cancer pain in adults.

Abbreviations
VAS: Visual analogue score; PSS: Pain severity score; PIS: Pain interference score; ALS: Analgesia level score; PMI: Pain management index; WHO: World Health Organization; BPI: Brief pain inventory score; PIS: Pain interference score; ALS: Analgesia level score; PLS: Pain level score; IRB: Institutional research board; BPI-sf: Brief pain Inventory-Short Form questioner; NFκB: Nuclear factor-κB; AP-1: Activator protein 1

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Author’s contributions
The study idea, design, data collection, data analysis, the literature search, manuscript editing, final manuscript review, and the study publication were done by the single author (coauthor). The author read and approved the final manuscript.

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Availability of data and materials
The analyzed data are included in the tables. The details are available from the corresponding author upon a reasonable request.

Declarations
I declare that I intend to submit the manuscript to “Ain-Shams Journal of Anesthesiology”, and that it is not currently under consideration elsewhere.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Faculty of Medicine Mansoura University with a number R.19.10. 656.R1 on 8-11-2019 and a written consent was signed by all participants. The study was prospectively registered with the www.clinicaltrials.gov (Identifier: NCT04162379).

Consent for publication
A consent for publication of personal data was not applicable.

Competing interests
The authors declare that he has no competing interests.

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