Vol 11| Issue 2| 2021 | 39-42.

e-ISSN 2248 – 9142
print-ISSN 2248 – 9134

International Journal of
Current Pharmaceutical & Clinical Research

www.ijcpcr.com

A PROSPECTIVE OBSERVATIONAL STUDY OF DEXAMETHASONE INDUCED HICCUPS IN CHEMOTHERAPY PATIENTS

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ABSTRACT

INTRODUCTION: Corticosteroids are a mainstay of antiemetic regimens for the prevention of acute and delayed emesis. Among the corticosteroids, dexamethasone is the drug used for antiemetic indication and it can induce hiccups. The frequency of occurring hiccups in male and female gender is equivalent, although intractable hiccups occur at a much higher rate in men. MATERIALS AND METHODS: A prospective observational study was conducted for a period of 6 months and a total of 50 patients were observed and the inclusion criteria was the patient's undergoing chemotherapy with dexamethasone antiemetic prophylaxis, adult patients greater than 18 years of age and the exclusion criteria was the patients receiving dexamethasone for any other indications. The outcome measures was development of Hiccups during chemotherapy. The causality assessment of hiccups was done using the Naranjo scale. RESULTS: Out of 50 patients observed in our study, 29 were male and 21 patients were female. A greater proportion of male patients (9 out of 10 patients) developed hiccups and only one female patient developed hiccups and among 10 patients who developed hiccups were receiving different doses of dexamethasone and it concludes that hiccups is not dose related. CONCLUSION: Dexamethasone has been reported to cause hiccups and the dexamethasone induced hiccups is not dose related. If dexamethasone is essential for the treatment, then administering baclofen 5mg three times a day until the last dose of dexamethasone might be an option or replacing Dexamethasone with Methylprednisolone can control Dexamethasone induced hiccups which should be an individualized clinical decision.

Key words: Dexamethasone, Corticosteroids, CINV, Hiccups, Antiemesis.

INTRODUCTION

Chemotherapy drugs are known to cause nausea and vomiting, commonly called as CINV (chemotherapy induced nausea and vomiting). Anti-emetic agents are used to avoid CINV, among which corticosteroids are commonly used.

Corticosteroids were first shown to be efficacious for CINV in the 1980s, and they are now considered a mainstay of antiemetic regimens for the prevention of acute and delayed emesis [1] Although not approved by the FDA for CINV, corticosteroids have been found to be beneficial when used alone for the prevention of nausea and vomiting in patients receiving low emetogenic chemotherapy and to improve efficacy when combined with 5-HT3 receptor antagonists in patients receiving moderately or highly emetogenic chemotherapies [2]

Among the corticosteroids, dexamethasone is the drug used for antiemetic indication and it can be administered as oral tablet or as parenteral, based on emetogenicity of chemotherapy protocol. At the protocol dose, dexamethasone can induce hiccups [3] as side effect and other side effects include indigestion, insomnia, anxiety, etc.

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Several medical conditions have been associated with the development of hiccups and they include gastrointestinal, neurological, pulmonary, psychogenic, cardiovascular, metabolic, anesthesia related and drug induced conditions .[4,5] Although steroid induced hiccups are rare, they are much more frequent with dexamethasone than with other corticosteroids.[6,7] The mechanisms responsible for dexamethasone-induced hiccup (DIH) development are poorly understood, though some suggestions have been made. That is, dexamethasone lowers the synaptic transmission threshold and/or directly binds to corticosteroid receptor on hiccup reflex arc.

Factors associated with dexamethasone induced hiccups are male gender, obesity, young age, elevation in haemoglobin, serum creatinine, uric acid, albumin and body temperature also the use of alkylating class of anticancer agents (as 1st drug) [8]. Other factors include sparkling beverages, air deglutition, gastric distension, changes in food temperature, spices, alcohol, tobacco, central nervous system (CNS) diseases, metabolic disorders, fever, pneumonia, lung tumor, pericardial/pleural effusion, myocardial infarction, gastroesophageal reflux disease (GERD), acute hepatitis, gastric tumors, peritonitis, surgery, chemotherapy, benzodiazepines, corticosteroids, barbiturates and morphine [9].

The frequency of occurring hiccups in male and female gender is equivalent, although intractable hiccups occur at a much higher rate in men.

High dose therapy with corticosteroids especially with dexamethasone, can induce hiccups that may persist for hours to days [10]. Hence we conducted a observational study to ascertain the incidence of dexamethasone induced hiccups in chemotherapy patients

MATERIALS AND METHODS:

A prospective observational study was conducted for a period of 6 months and a total of 50 patients were observed and the inclusion criteria was the patients undergoing chemotherapy with dexamethasone antiemetic prophylaxis, adult patients greater than 18 years of age and the exclusion criteria was the patients receiving dexamethasone for any other indications.

The outcome measures was development of Hiccups during chemotherapy. The causality assessment of hiccups was done using the Naranjo scale

RESULTS:

Baseline characteristics

Age wise distribution:

12 out of 50 patients in our study were in the age group of 18-30 years and 20 patients were among the 30-50 years category and 18 were among the 50-80 age group.

Gender Wise Distribution

Out of 50 patients observed in our study, 29 were male and 21 patients were female.

Incidence Of Hiccups Based On Gender

The incidence of the hiccups in the patients is characterized based on the gender of the patients

In our study, there was a greater proportion of male patients (9 out of 10 patients) developed hiccups and only one female patient developed hiccups after dexamethasone premedication in our study.

Causality Assessment Of Hiccups

The causality assessment of the patient who developed hiccups was done using the Naranjo scale 8 out of 10 patients who developed hiccups were in the category of probable and 2 were in the definite category. Among the probable category, 7 patients had a causality assessment score of 8 and 1 patient had a score of 7.

Incidence Of Hiccups Based On Dexamethasone Dose

5 out of 10 patients who developed hiccups received 8 mg of dexamethasone premedication and 2 patients received 4 mg and 20 mg of dexamethasone in each category and 1 patient received 12 mg of dexamethasone

Table 1: Age Wise Distribution

CHARACTERISTICS	NUMBER OF PATIENTS (N=50)	PERCENTAGE (%)
AGE (Years)		
18-30	12	24
30- 50	20	40
50-80	18	36

Table 2: Other Baseline Characteristics

CHARACTERISTICS	NUMBER OF PATIENTS (N=50)	PERCENTAGE (%)
CANCER TYPE DISTRIBUTION		
ALL	10	20
AML	4	8
CML	8	16
HL	7	14

NHL	10	20
HEPATOSPLENIC T-CELL LYMPHOMA	1	2
MULTIPLE MYELOMA	8	16
BURKITT'S LYMPHOMA	2	4
CHEMOTHERAPY REGIMEN		
R-CODOX	1	2
HIDAC	4	8
CYTARABINE+ DAUNORUBICIN	5	10
GMALL 07/03 INDUCTION	12	24
FLAG-IDA	1	2
BEAM CONDITIONING	5	10
ICE	1	2
HIGH DOSE MELPHALAN	5	10
CYCLO-POM-DEXA	4	8
CYCLO-BORTEZOMIB-DEXAMETHASONE	4	8
R-CHOP	8	16

Table 3: Incidence of Hiccups Based on Gender

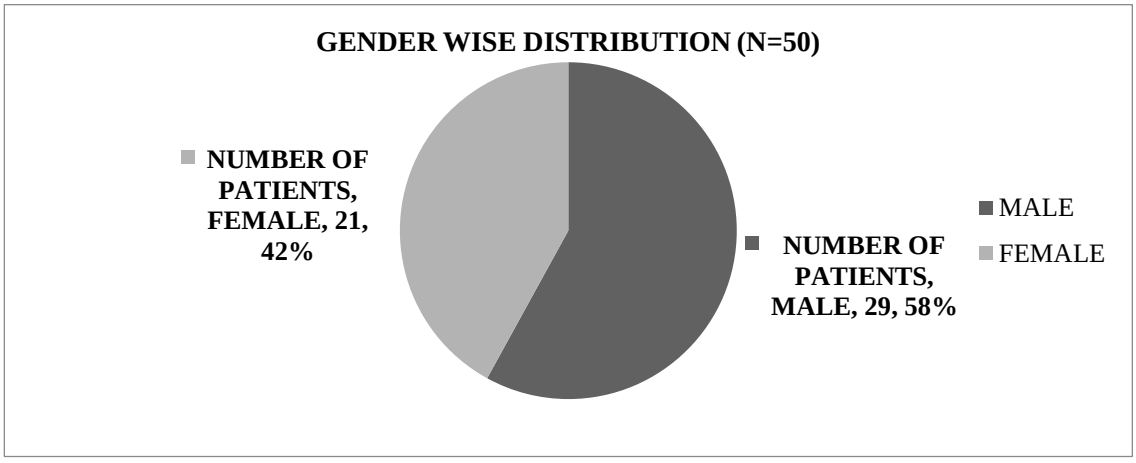
GENDER	NUMBER OF PATIENTS DEVELOPED HICCUPS N(%)	MEDIAN DURATION (RANGE)
Male	9 (90)	4 hours (4 hours- 1 day)
Female	1 (10)	8 hours (8)

CATEGORIES BASED ON SCORE	NUMBER OF PATIENTS (N=10)	PERCENTAGE(%)
DEFINITE	2	20
PROBABLE	8	80
POSSIBLE	0	0

(NOTE: DEFINITE- ≥9 : PROBABLE- 5-8 : POSSIBLE – 1-4)

DEXAMETHASONE DOSE	NUMBER OF PATIENTS (N=10)	PERCENTAGE (%)
4 mg	2	20
8 mg	5	50
12 mg	1	10
20 mg	2	20

Figure 1: Gender Wise Distribution



DISCUSSION

Dexamethasone: one among the corticosteroid is widely used as an essential medication in haematology protocol indicated for the prevention of chemotherapy induced nausea and vomiting. Hiccups can be almost intolerable and significantly diminish the quality of life in patients.

The literature search revealed some reports of dexamethasone induced hiccups. vardy et al reported that 25% of patients with cancer had hiccups after dexamethasone administration, Hiccups in this report are presumed to be DIH because no other drugs administered to the patient are known to induce hiccups other than dexamethasone, which is in concordance with our study that, there are no other drugs/ plausible etiology for hiccups.

The incidence of hiccups was higher among the male gender in our study which is in concordance with the systematic review [2] which reported DIH (dexamethasone induced hiccups) development is significantly associated with a male gender. And this finding is consistent with [11] a case report which suggested that the reason for male predilection could stern from higher male prevalence of the risk factors for hiccups.

One fascinating aspect is that the development of hiccups among the patients, were not proportional to the dose of dexamethasone. Since regardless of the dose of dexamethasone, patient development the hiccups which is consistent with [11] which reported the side effect because it was severe, persistent, and intolerable as their quality of life was significantly diminished. The hiccups persisted despite reduction of the dose of dexamethasone to 6 mg daily. This suggests that the dexamethasone induced hiccups may not be dose related, which is ascertained with our study.

CONCLUSION

Dexamethasone has been reported to cause hiccups. Although hiccups are not life-threatening, they are important because they can be almost intolerable and significantly diminish quality of life in patients. Discontinuation of dexamethasone or switching from dexamethasone to other corticosteroids have been reported to relieve hiccups, but there is no conclusive reports.

As evident from our study, the dexamethasone induced hiccups is not dose related. If dexamethasone is essential for the treatment, then administering baclofen 5mg three times a day until the last dose of dexamethasone might be an option or replacing Dexamethasone with Methylprednisolone can control Dexamethasone induced hiccups, which should be an individualized clinical decision.

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