DOI: 10.7860/JCDR/2024/67235.19073

Case Report

Dentistry Section

Dexamethasone-induced Singultus Post-dental Extraction: A Case Report

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ABSTRACT

Hiccups are involuntary reflexes, usually habitual and self-limiting in nature, experienced by the majority of people at some point in their lives. Persistent hiccups induced by pharmacotherapeutic agents, such as steroids, are considered minor complications. They can cause extreme discomfort and significantly lower the patient's quality of life. This is the first report of persistent severe hiccups after Dexamethasone intramuscular administration in Indian patients post-dental treatment. Hereby, the authors present a case of a 50-year-old male patient with a medical history of Rheumatoid arthritis who was administered 8 mg of dexamethasone Intramuscular (IM) post-extraction. The patient was extremely restless when he reported to the dental clinic, as he had developed persistent hiccups post-24 hours. Neither the home remedies by the patient nor the topical application gel prescribed by the clinician were successful. As intractable hiccups continued for upto 34 hours, immediate action was taken, and the patient was referred to the physician. Pharmacological agents were administered, and the patient's hiccups resolved completely by 42 hours. At the 1-week postoperative appointment, counseling was given on the suspected drug-induced cause of the transient hiccups for his future benefit. There is limited literature in dentistry on the management of drug-induced hiccups, despite the fact that clinicians routinely prescribe steroids postoperatively. The present case report comprehensively discusses the treatment algorithm for managing patients with drug-induced hiccups. Further studies are necessary to investigate the role of potential biomarkers for indicating the susceptibility of patients likely to develop severe persistent hiccups post-administration of steroids.

Keywords: Adverse reactions, Corticosteroid, Drug related side-effects, Hiccups

CASE REPORT

A 50-year-old male patient with a medical history of rheumatoid arthritis for three years reported to a private clinic for extraction. The patient was under a lower dose of methotrexate and sulfasalazine for arthritis. Upon examination, it was noticed that tooth 46 was fractured. The patient mentioned a history of root canal treatment on the same tooth two years prior. Presurgical vital signs were recorded and found to be normal. Intraoral antisepsis was performed with Povidone iodine (7.5% w/v). Local anaesthesia (Lignocaine 2% with 1:200,000 Adrenaline) was administered using an inferior alveolar, long buccal, and lingual nerve block, and the uneventful extraction of tooth 46 was carried out. Due to the complexity of the case, the procedure took a prolonged duration, as a result of which the clinician administered 8 mg (2 mL) of dexamethasone via the intramuscular route to alleviate postoperative inflammation and oedema. Postoperative instructions were explained. Tab Ordent (Ofloxacin (200 mg)+Ornidazole (500 mg) (one tablet BD for 5 days), Tab Diclomol (Diclofenac (50 mg)+Paracetamol (325 mg) (one tablet BD for 5 days), Capsule Omez (Omeprazole 20 mg) (one tablet OD for 5 days) were prescribed, and the patient was escorted from the private clinic. During a telephonic follow-up conducted by the clinician, the patient reported that bouts of intermittent hiccups had developed at a rate of 2-3 per minute over the 24 hours postoperative. Upon complaining of persistent hiccups, the clinician prescribed Mucaine gel (Oxetacaine (10 mg/5 mL)+Aluminium Hydroxide (0.291 gm/5 mL)+Milk of Magnesia (98 mg/5 mL). The patient also attempted home remedies like breathing into a paper bag, swallowing a teaspoon of sugar, and drinking a glass of cold water quickly. Despite these attempts, no relief was achieved, and the patient experienced extreme discomfort for 34 hours. Immediately, the clinician accompanied the patient to the physician, and Injection Reglan (Metoclopramide 10 mg) was administered. The patient's hiccups resolved completely by 42 hours. At the 1-week postoperative appointment, the incident was reviewed with the patient. The onset, duration, and the aggravating factors were discussed. Counseling was given on the suspected drug-induced cause of the transient hiccups for his future reference or benefit.

DISCUSSION

Hiccups, or "Singultus," are involuntary reflexes, usually mild, habitual, and brief in nature, experienced by most people at some time in their life [1,2]. The "hiccup" sound is produced due to sudden, uncontrolled contractions of the diaphragm, followed by immediate inspiration and closure of the glottis over the trachea. Primarily based on duration, they are classified as acute/transient (less than 48 hours), persistent (longer than 48 hours), and intractable (longer than 1 month) [3,4]. They resolve spontaneously but occasionally become prolonged in some postoperative patients, causing distress as it hinders their nutrient and sleep needs. Recent analysis revealed an alarming 4000 admissions yearly in the United States of America (USA) for hiccups [5]. Out of these patients, temporary singultus composed 44.1% of patients, persistent hiccups 36.9%, and intractable 19% [6]. A telephone-based study further highlighted that 127 patients had developed dexamethasone-induced hiccups postoperatively. In light of this, as clinicians, authors should be mindful while prescribing steroids and should be well [7].

Hosoya R et al., investigated the influence of medicines and patient characteristics on hiccups using a large-sized Japanese Adverse Drug Event Report (JADER) database between April 1, 2004, and January 20, 2016 [8]. More than 95% of patients in the hiccup group were men. The explanation is that the specificity of steroid receptors in the brain and pituitary gland may influence male dominance in dexamethasone-induced hiccups. The means (±Standard Deviation) of age, height, and weight were 57.7±14.9 years, 163.3±7.9 cm, and 58.7±9.9 kg, respectively. The results obtained showed that advanced age, greater height, and greater weight were all significant factors positively influencing the onset of hiccups.

The present study could not establish a definitive relationship between dexamethasone doses and the induction of hiccups. Patients receiving medications intravenously are more frequently

observed by physicians than those receiving oral medications, and the former group is more likely to report adverse effects. High-dose dexamethasone crosses the blood-brain barrier, activates steroid receptors in the hypothalamus and hippocampus, and stimulates the efferent pathway of the hiccup reflex arc [9].

The present case report highlights intramuscularly injected dexamethasone-induced hiccups in a male from Maharashtra. It is surprising that this known but rare side-effect is reported very few times in dental literature, despite the frequent use of dexamethasone in managing postoperative inflammation. This may reflect that the adverse effect is rare, or that clinicians have generally been unaware of it. The male predilection in present study is similar to a previously reported study [8].

In dental literature, only one case report highlighted episodic cognitive dysfunction as an adverse reaction in an 18-year-old female who had briefly taken dexamethasone [10]. The patient in this case report was taking low doses of methotrexate and sulfasalazine for rheumatoid arthritis. In line with our case reports, two cases of dexamethasone-induced hiccups were reported in Abakaliki, Nigeria. Both patients developed persistent hiccups following the use of oral dexamethasone for the treatment of inflammatory conditions. The hiccups only stopped following discontinuation of the dexamethasone. They reported the side effect because it was severe, persistent, and unbearable, significantly diminishing their quality of life [11].

Benzodiazepines and corticosteroids are the drug classes most commonly mentioned in the literature as being connected to hiccups. Garvey D studied postoperative cases of hiccups and came to the logical conclusion that the aetiologic factor was probably drug-related [12]. Hiccups have been reported to start between one hour to 18 hours and may last from 1 to 109 days [13]. The postulated mechanisms related to drug-induced hiccups are that they influence the hiccup center in the central limb. Dexamethasone is thought to lower the midbrain's threshold for synaptic transmission, eventually causing hiccups [14]. Although they are rare, hiccups are much more frequent with dexamethasone than with other corticosteroids. The dosages of dexamethasone reported as causing hiccups also varied, ranging from 8 to 40 mg orally, 8 to 20 mg intravenously, and 8 to 15 mg epidurally [15,16].

A systematic review by Steger M et al., elaborated on the management of hiccups, including a systematic review of reported efficacy and safety of pharmacological treatments [17]. Treatment of 341 patients with persistent or intractable hiccups was reported in 152 published studies. Pharmacologic treatments, including steroid rotation, chlorpromazine, metoclopramide, haloperidol, and baclofen, have been reported to stop hiccups [17]. Alternative methods such as hypnosis and acupuncture have also been used for persistent and intractable hiccups. A variety of invasive procedures, such as peripheral anaesthetic blocks to nerves involved in the putative 'reflex arc', surgical disruption, or stimulation of vagal afferents or phrenic efferent nerves, have been applied for intractable cases of hiccups that fail to respond to pharmacological therapy [18].

A comprehensive review recently recapitulated the current understanding of epidemiological data, pathophysiological mechanisms, and therapeutic modalities of drug-induced hiccups. Clinical evaluation of intractable hiccups includes obtaining history regarding symptom duration, triggers, and illicit drug use. When treatment is indispensable, it should be directed toward a specific aetiology, if known, which may range from the simple treatment of Gastroesophageal Reflex Disease (GERD) with a Proton Pump Inhibitors (PPI) to neurosurgery for the removal of a Central Nervous System (CNS) lesion. Monotherapy will be ineffectual in all patients, and patients frequently need to try several different options before finding a viable regimen [19-21]. If hiccups fail to resolve with medical management, then interventional approaches should be considered. Recent evidence is building to support the safe and efficacious use of peripheral phrenic nerve block and C3-C5 targeted epidural for refractory cases [22,23]. The detailed physical management, non pharmacological, and pharmacological treatment modalities have been summarised in [Table/Fig-1-3], respectively [17,19,24-27].

Nasopharyngeal stimulation	Vagal stimulation	Respiratory manoeuvres
Intranasal application of vinegar	Cold compress to face	Breathe in a closed bag for 1 minute, and/or hold your breath for a few seconds
Inhalation of 'smelling salts' or similar stimulant/irritant (e.g., ammonia, ether)	Carotid massage	Re-breathing (hypercapnia)
Oropharyngeal stimulation (e.g., ice water)	Induced fright	Valsalva manoeuvres
Ingestion of a spoon of sugar	Forced eructation	
Deviation of nervous stimulus-sneeze with black pepper	Induced vomiting	CPAP-respiration
	Squatting on the floor	

[Table/Fig-1]: Physical management.
CPAP: Continous positive airway pressure

Pharmacological therapy	Level of evidence	Mechanism of action	Notes to be taken into consideration
Recommended (typical dose/day)			Common or important side-effects and safety concerns
Proton pump inhibitors 1. Omeprazole 20 mg twice a day 2. Domperidone (3×10 mg)	2b 5	Suppression of underlying GERD/ oesophagitis	Empiric PPI should be considered Neurological side-effects, hyperprolactemia, cardiac arrhythmia
Baclofen (3×5-20 mg/day)	2b	Gamma aminobutyric acid (GABA) analogue leads to blockage in synaptic transmission	First line of choice of drugs in suspected aetiology Potential ataxia, delirium, dizziness, and sedation Caution with use in renal impairment
Anti-convulsant drugs Earlier used a. Valproate dose titration to 20 mg/kg/day b. Carbamazepine, 3-4×100-300 mg/day c. Phenytoin 3×100 mg/day **Currently used** a. Pregabalin/Gabapentin (2×75-150 mg/day) b. Nifedipine (60-80 mg/day)	4	Enhances GABA transmission centrally aiding blocking the hiccup stimulus Additionally produces a blockade of neural calcium channels, synergistically increasing release of GABA leading in modulation of diaphragm. Reversing the abnormal depolarisation inhiccup reflex arc	Wide range of doses is reported Neurological and mood disturbance, Liver failure, weight gain Coarse facies, neurological and mood disturbance Adverse effects are sedation, virtual disturbance, clumsiness Hypotension, headache, respiratory oedema Substantial risk of inducing hypotension
Antipsychotic medications a. Chlorpromazine upto (4×25-50 mg/day)	4	Acts centrally by dopamine antagonism in the hypothalamus	Only United States Food and Drug Administration (US FDA) approved pharmacologic for hiccups Side-effects include sedation, postural hypotension and neurological side-effects to some extent
Prokinetic agents Metoclopramide (3×10 mg)	2b	Dopamine antagonist Helps empty stomach by stimulation of gastrointestinal motility	Risk of significant side-effects (tardive dyskinesia) Neurological side-effects

Defoaming agents Simethicone 125 mg QID	2b	Helps break gas bubbles in the gut and gastric distention is present	Not to be advised in patients taking quinolone antibiotics
Methylphenidate (6 to 20 mg per day i.v.)	2b	Mild CNS stimulant Cessation of hiccups through inhibition of dopamine and norepinephrine uptake	Emerging as a possible treatment for intractable hiccup in cancer patient
Lidocaine (1 mg/kg i.v.)	2b	Hiccup suppression due to properties of bronchodilation or being a central stimulant	Not sufficient evidence regarding the effect of lidocaine on suppression of hiccups Risk of cardiovascular and neurologic toxicities
Amitriptyline initial 1×25-100 mg/night	5	Reduces abnormal gastric or diaphragmatic mobility, through more central effects on the hiccup reflex arc	Sedation, dry mouth, constipation, cardiac arrhythmia in overdose consider if visceral hypersensitivity appears to be causative factor
Steroid rotations a. 15 mg i.v. dexamethasone changed to125 mg i.v. methylprednisolone b. Oral dexamethasone (8 mg) was replaced with 30 mg of prednisolone (BID) Medication combination Low doses of Olanzapine and Baclofen Olanzapine (2.5 mg/kg/day) and Baclofen (5 mg/kg/day)	2b		

[Table/Fig-2]: Pharmacological therapy.
The levels of evidence and their role in evidence-based medicine [27]
1a- Systematic review (with homogeneity) of Randomised Control Trails (RCTs)
1b- Individual RCT
1c- All or null study
2a- Systematic review (with homogeneity) of cohort study
2b- Individual cohort study
2c- 'Outcomes' research, ecological studies
3a- Systematic review (with homogeneity) of case control studies
3b- Individual case control study
4- Case series
5- Expert opinion without explicit critical appraisal or based on physiology bench research

Non pharmacological therapy	Level of evidence	Mechanism of action	Concerns
Hypnosis [24]	5	Psychogenic effect	
Acupuncture [25]	4	Regulation of thoracic viscera and effects on gastrointestinal motility through modulation of local blood flow, neurotransmitter signalling and inflammation	Possibility of transmission of infectionby use of unsterilised needles
Nerve block (C3 to C5, phrenic, vagal nerve) [26]	5	Direct interruption/ pacing of hiccup reflex arc	Nerve damage, pneumothorax
Implantation of vagal nerve stimulator or neuromodulation device [27]			Risk of surgery, nerve damage, unwanted side-effects of vagal stimulation
Neurological side-effects (acute dystonia, akathisia, tardive dyskinesia), impaired glucose tolerance, weight gain, increased mortality due to thrombotic and cardiovascular events			

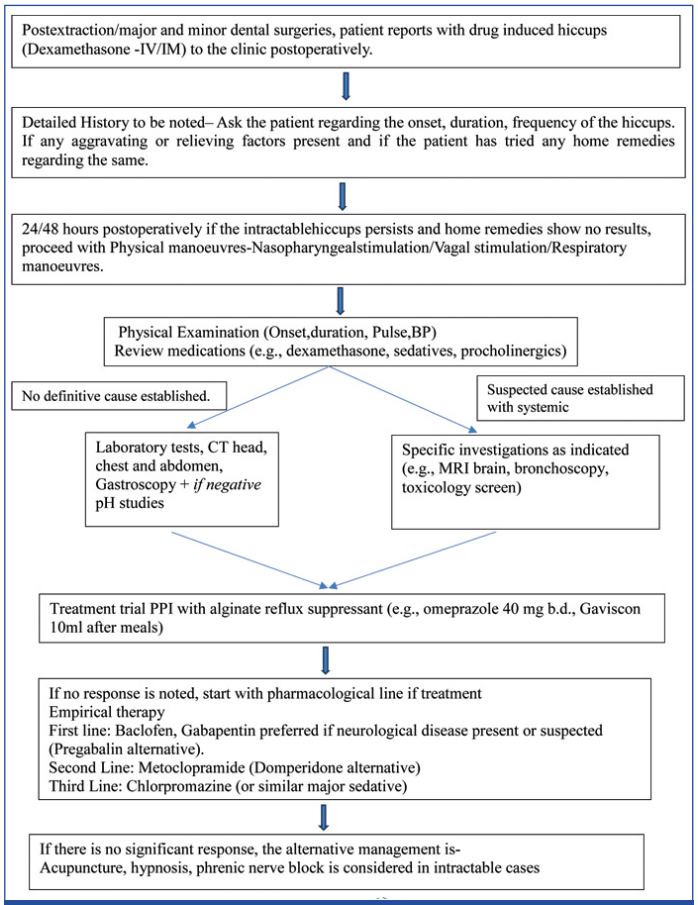
[Table/Fig-3]: Non pharmacological therapy [24-27].

Clinicians should be aware of this known but rare adverse effect of dexamethasone as it could be severe, distressing, and negatively impact patient care. There is a need for a high index of suspicion whenever a patient develops hiccups while taking dexamethasone. Various pharmacological and non pharmacological treatment modalities are available to treat dexamethasone-induced hiccups. The present article has compiled all the evidence-based data and suggested a specific protocol to be followed when a patient reports postoperatively with dexamethasone-induced hiccups to the clinic [Table/Fig-4] [17-19,28].

Future studies are needed to investigate potential biomarkers that can help indicate who is susceptible to the induction of severe, persistent hiccups by steroids.

CONCLUSION(S)

As clinicians, we should be vigilant about possible side effects when prescribing steroids in medicine and dentistry. The present case paper highlights the correlation between hiccups and steroid treatment in a postoperative setting.



[Table/Fig-4]: Treatment protocol-diagnosis,investigations and management of drug-induced hiccups.

REFERENCES

[1] Hung YM, Miller MA, Patel MM. Persistent hiccups associated with intravenous corticosteroid therapy. J Clin Rheumatol. 2003;9(5):306-09.
[2] Siddiqui JA, Qureshi SF, Allaithy A, Mahfouz TA. Intractable hiccups (Singultus) of psychogenic origin- A case report. J Behav Health. 2019;8(1):20-23.

[3] Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. Am J Hosp Palliat Care. 2003;20(2):149-54.
[4] Marinella MA. Diagnosis and management of hiccups in the patient with advancedcancer. J Support Oncol. 2009;7(4):122-27,130.
[5] Cole J, Plewa M. Singultus (hiccups): StatPearls, StatPearls Publishing, 2019. https://www.ncbi.nlm. nih.gov/books/NBK538225/. Accessed 1 July 2019.
[6] Eroglu O. The effect of gender differences in protracted hiccups. Niger J Clin Pract. 2018;21(10):1356-60.
[7] Ehret CJ, Le-Rademacher JG, Martin N, Jatoi A. Dexamethasone and hiccups: A 2000-patient, telephone-based study. BMJ Supportive & Palliative Care. 2021;13:e790-93.
[8] Hosoya R, Uesawa Y, Ishii-Nozawa R, Kagaya H. Analysis of factors associated with hiccups based on the Japanese Adverse Drug Event Report database. PLoS One. 2017;12(2):e0172057.
[9] Maeda R. JADER from pharmacovigilance point of view. Jpn J Pharmacoepidemiol. 2014;19(1):51-56.
[10] MacKay S, Eisendrath S. Adverse reaction to dental corti- costeroids. Gen Dent. 1992;40(2):136-38.
[11] Eze CO, Nnaji TO, Nwobodo MU. Persistent hiccups following use of oral dexamethasone: A report of two cases from Abakaliki, Nigeria. Case Reports in Clinical Medicine. 2020;9(9):282-87.
[12] Garvey D. Post-operative hiccups. Proceedings of UCLA HealthCare. 2000;4:19-21.
[13] Abbasi A, Roque-Dang CM, Malhotra G. Persistent hiccups after interventional pain procedures: A case series and review. PMR. 2012;4(2):144-51.
[14] Lee GW, Oh SY, Kang MH, Kang JH, Park SH, Hwang IG, et al. Treatment of dexamethasone-induced hiccup in chemotherapy patients by methylprednisolone rotation. Oncologist. 2013;18(11):1229-34.
[15] Cersosimo RJ, Brophy MT. Hiccups with high dose dexamethasone administration: A case report. Cancer. 1998;82(2):412-14.
[16] Kang JH, Hui D, Kim MJ Kim HG, Kang MH, Lee GW, et al. Corticosteroid rotation to alleviate dexameth- as one-induced hiccup: A case series at a single institution. J Pain Symptom Manage. 2012;43(3):625-30.
[17] Steger M, Schneemann M, Fox M. Systemic review: The pathogenesis and pharmacological treatment of hiccups. Aliment. Pharmacol. Ther. 2015;42(9):1037-50.
[18] Peacock ME. Transient hiccups associated with oral dexamethasone. Case Case Rep Dent. 2013;2013:426178.
[19] Polito NB, Fellows SE. Pharmacologic interventions for intractable and persistent hiccups: A systematic review. J Emerg Med. 2017;53(4):540-59.
[20] Popa SL, Surdea-Blaga T, David L, Stanculete MF, Picos A, Dumitrascu DL, et al. Supragastric belching: Pathogenesis, diagnostic issues and treatment. Saudi J Gastroenterol. 2022;28(3):168.
[21] Reichenbach ZW, Piech GM, Malik Z. Chronic hiccups. Curr. treatm. opt. gastroenterol. 2020;18:43-59.
[22] Nausheen F, Mohsin H, Lakhan SE. Neurotrans- 27. mitters in hiccups. Springerplus. 2016.
[23] Arwani R, Alikhan MM, El Halabi M, Bhuta R. Intractable hiccups and belching: Approach, evaluation, and treatment. Current Treatment Options in Gastroenterology. 2023;21(3):307-19.
[24] Al-Mahrouqi T, Al-Sabahi F, Al-Harrasi A, Al-Balushi N, Al-Sinawi H. Psychogenic hiccups in an older adult: A case report and literature review. J Taibah Univ Medical Sci. 2023;18(3):560-65.
[25] Zhang Y, Jiang X, Wang Z, He M, Lv Z, Yuan Q, et al. Efficacy of acupuncture for persistent and intractable hiccups: A protocol for systematic review and meta-analysis of randomized controlled trials. Medicine. 2021;100(8):e24879.
[26] Zhong Y, Deng J, Wang L, Zhang Y. Phrenic nerve block combined with stellate ganglion block for postoperative intractable hiccups: A case report. J Int Med Res. 2023;51(8):03000605231197069.
[27] Tariq K, Das JM, Monaghan S, Miserocchi A, McEvoy A. A case report of Vagus nerve stimulation for intractable hiccups. Int J Surg Case Rep. 2021;78:219-22.
[28] Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast. Reconstr. Surg. 2011;128(1):305.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 29, 2023
- Manual Googling: Nov 17, 2023
- iThenticate Software: Dec 13, 2023 (20%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Aug 26, 2023**
Date of Peer Review: **Oct 24, 2023**
Date of Acceptance: **Dec 15, 2023**
Date of Publishing: **Feb 01, 2024**