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Hiccup as a side effect of epidural injection: A literature review

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ABSTRACT

Epidural injections are invasive procedures for pain management, perioperative anesthesia, and labour analgesia. These procedures are generally safe with minor side effects such as hiccups. Scientists explain the pathophysiology of hiccups by the disruption of hiccups “reflex arc”. However, to this day, it remains incompletely understood. Hiccup, an involuntary spasm of the diaphragm and respiratory organs, where a sudden closure of the glottis results in a gulping sound, may differ from acute, self-limiting to intractable. After our thorough analysis, twenty-three papers met the criteria of this work, where 30 patients reported hiccups as a complication of epidural injections. In most cases, physicians injected steroids with anesthetic agents in mixed injectables. Dexamethasone, betamethasone, bupivacaine, and lidocaine were the most frequent drugs in injections. The onset of hiccups was most often between 6 and 24 hours post-procedure. The duration was most frequently up to 2 days, however, many patients complained about hiccups for longer than that. The majority of the patients were older than 50. Most of the patients were males. If hiccups did not resolve spontaneously, the first line of treatment was mostly physical treatment. When it failed, the most common drug treatments were chlorpromazine, metoclopramide, and baclofen. These drugs are mentioned in unofficial treatment recommendations in the literature; however, physicians often chose to treat patients according to their own beliefs rather than following established treatment schemes. This work implies that hiccups as a direct complication of epidural injections requires more clinical awareness.

Keywords: Hiccups, Singultus, Epidural injection, Epidural space, Intractable hiccups

1. INTRODUCTION

Epidural space occurs both within the spinal canal and brain. It extends between the dura mater, which is the outermost membrane surrounding the spinal cord, and the bones. More specifically, a bony vertebral column in the spine or a skull in the brain. Epidural space is considered a potential space. It can potentially fill with fluid or air. It is a crucial area for procedures, including administering epidural anesthesia or epidural steroid injections in pain management. Generally, these

procedures are safe and serious complications are very rare (Cohen et al., 2021; Pountos et al., 2016). There have been a few reports of hiccups being a side effect of procedures such as epidural steroid injections, epidural anesthesia or epidural opioid injection (Abubaker et al., 2018; Odonkor et al., 2017; Zhang et al., 2018; Mena et al., 2024; Loomba et al., 2012; Anijar, 2017).

Hiccup is an involuntary spasm of the diaphragm and respiratory organs, with a sudden closure of the glottis resulting in a characteristic gulping sound. Hiccup can be acute, lasting less than 48 hours, persistent, lasting over 2 days, or intractable, lasting more than one month. Although the incidence of hiccups after those procedures is not common, it may be highly under-reported (Pountos et al., 2016). In the majority of cases, it does not state any threat to a patient, mainly being short and self-limiting episodes (Errante et al., 2005). However, an episode of long hiccup can be physically devastating (Wilcox et al., 2009). Because of insufficient data regarding hiccup as a complication of epidural injection, there is a need for a comprehensive insight into this topic. Taking this into account, the authors of this work have attempted to shed some light on this matter. To our knowledge, this work is the latest comprehensive review of hiccup as a side effect of epidural injections.

Aim

This literature review aims to explore hiccup as a direct complication of epidural injections. It also confronts how the patients were treated versus what is presented in the literature.

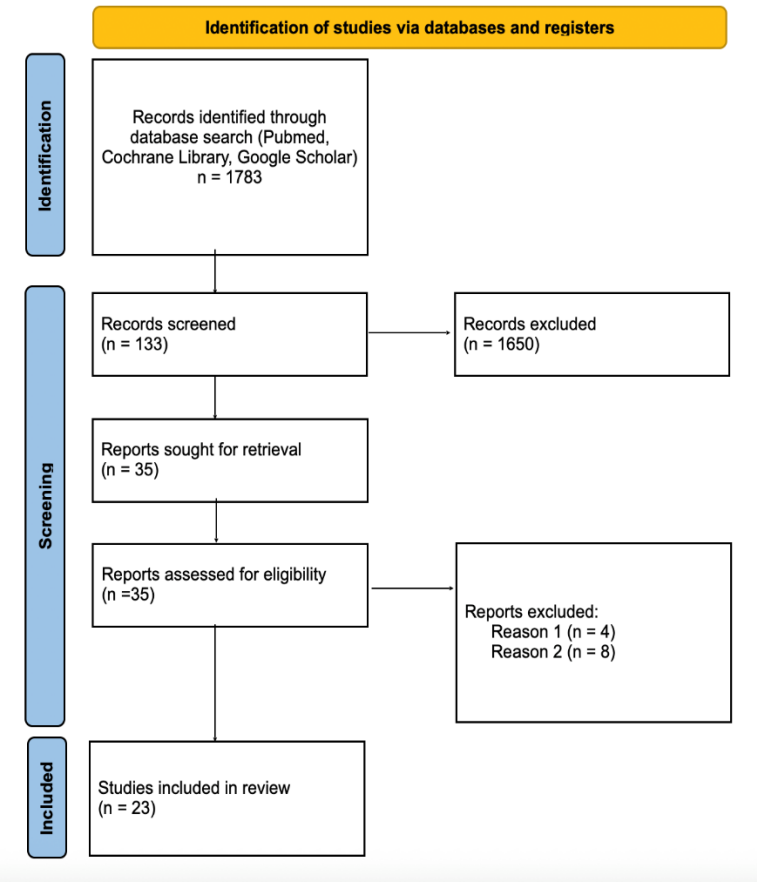


Figure 1 PRISMA Chart

2. REVIEW METHODS

We reviewed all published case reports, case series and posters of hiccups after epidural injections, which met our including and excluding criteria. Studies included were published between 2001 and 2024 in Pubmed, Cochrane library and Google Scholar. From the collected data, we described the associations between sex, age, substance injected, etiology, onset of hiccups, duration of hiccups, level of spine where physicians gave the injection and the management. We did not take the publication year into consideration in

including/excluding criteria. It is because there are very few cases of this kind which are published, so that every single patient is an invaluable addition to our database. The selection criteria were:

- Inclusion criteria:*
- Case reports/series and posters with keywords: Hiccups, Singultus, Epidural injection, Epidural space, Intractable hiccups
 - Case reports/case series where hiccup was a complication of epidural injection

- Exclusion criteria:*
- Non-English studies (Reason 1)
 - Studies where it was impossible to extract enough information about particular patients (Reason 2)

Three researchers separately conducted a comprehensive search in PubMed, Cochrane Library, and Google Scholar to find all the matching works. Cumulatively, we included twenty-three studies in this literature review (Figure 1). The further purpose was to analyze the collected data. The main points included information about patients, such as sex, age, number of injections, reason for injection, substance injected, local anesthetic (if given), onset of hiccups, duration of hiccups, management of hiccups, and level of injection.

3. RESULTS & DISCUSSION

Twenty-three papers have met the criteria of this work, where the epidural injection directly led to hiccups. Some of them present the case of more than one patient, and in one case, a patient got both epidural injection for pain management and an epidural anesthesia later in life. Out of twenty-three papers, 25 patients got an epidural steroid injection, and 1 of them also underwent epidural anesthesia. Apart from this one patient who got an epidural anesthesia with hiccup afterwards, we included three more patients in this work. Additionally, we took 2 cases of epidural opioid injection into consideration. To sum up, 30 patients are under investigation in this work. As some people got an injection more than once, in total 52 injections were done and one analgesia during labour, where firstly, the physician inserted the epidural catheter and then administered three doses of anesthetic.

Table 1 and 2 present clear and readable results of all the included information about patients. Of all the 30 patients, only four were females. 2 of these females had an epidural anesthesia before an operation, one a labour analgesia and one an epidural opioid injection for back pain. In other words, there are only men who had hiccups after epidural steroid injection in our database. Of 3 patients with hiccup after epidural anesthesia, 2 were women and of 2 patients with hiccup after epidural opioid injection, 1 was a women. Lastly, there is only one case of a woman who had hiccup after labour analgesia.

Table 1 - Presentation of patients (no. of injections, sex, age)				
Author	Patient number	No. of injections	Sex	Age
(Abubaker et al., 2018)	1	1	Male	60
(Ritz et al., 2018)	2	1	Male	62
(Ege, 2024)	3	2	Male	50
(Colorado & Decker, 2017)	4	2	Male	69
	5	3	Male	48
	6	3	Male	30
	7	2	Male	35

(Abbasi et al., 2012)	8	2	Male	48
	9	1	Male	32
	10	3	Male	63
	11	2	Male	38
(Odonkor et al., 2017)	12	2	Male	72
(Kanniah, 2009)	13	3	Female	30
(Zhang et al., 2018)	14	1	Female	70
(Kaydu, 2017)	15	1	Male	43
(Slipman et al., 2001)	16	2	Male	31
(Beyaz, 2012)	17	1	Male	61
(Mena et al., 2024)	18	1	Male	49
(McAllister et al., 2005)	19	6	Male	65
(Loomba et al., 2012)	20	1	Male	44
(Ruan et al., 2007)	21	1	Female	65
(Anijar, 2017)	23	1	Male	63
(Nikiforova, 2016)	24	1	Female	81
(Shah et al., 2006)	25	3	Male	46
	26	2	Male	62
(Shafiq et al., 2006)	27	2	Male	53
(Lee et al., 2011)	28	1	Male	46
(Kim et al., 2020)	30	1	Male	54

Twenty-five patients, who got an epidural steroid injection, had 47 injections in total. Some of the patients only had a steroid in an injection and others, steroid and an anesthetic agent in a mixed injectate. Ten of these 25 patients were over 60 years old at that time, nine were over 40 years old, and no one was younger than 30 years old. Only two glucocorticosteroid injections did not result in hiccups. These 2 injections refer to one patient. He had a history of 5 epidural injections on different days and the first 3 were both glucocorticosteroid and anesthetic drug with hiccups as a complication and the next 2 were only glucocorticosteroid, where no hiccups occurred. In case of mixed injectables, only three injections did not lead to hiccups. It relates to 2 patients, where in one case a patient got three injections with glucocorticosteroid and anesthetic drug and hiccup happened only after the third one and in another case a man got two injections in between one month, one was an epidural injection and another one was a cervical selective nerve root block and hiccup happened only after the second one. Because a selective nerve root block is not an epidural injection, it was not included in this work. There is no information about their comorbidities or long-term medications. The only difference was the levels of injection.

Table 2 - Presentation of patients (substances injected, characteristics of hiccups, treatment used and the levels of injection)

Patient number	No. of injection	Substance	Onset and duration of hiccups	eatment	Level of injection
1	1	Methylprednisolone, Bupivacaine, Xylocaine	Onset: 3 h Duration: 13d	Haloperidol, Metoclopramide, Gabapentin	C7-T1
2	1	Betamethasone	Onset: Next morning Duration: 1d	Physical treatment, Thorazine	C7-T1
3	1	Betamethasone, lidocaine	Onset: 10h Duration: 6d	No treatment	L5-S1
	2	Betamethasone	Onset: 15h Duration: 7d	No treatment	L5-S1
4	1	Dexamethasone, lidocaine	Onset: Next day Duration: 6d	Physical treatment, Baclofen	L5-S1
	2	Dexamethasone, lidocaine	Onset: Next day Duration: 16h	Baclofen	L5-S1
5	1	Betamethasone	Onset: 18-24h Duration: 1d	Physical treatment	C6-C7
	2	Betamethasone	Onset: 18-24h Duration: 1d	Physical treatment	C6-C7
	3	Betamethasone	Onset: 18-24h Duration: 1d	Physical treatment	C6-C7
6	1	Betamethasone, lidocaine	Onset: 18-24h Duration: 1d	Physical treatment	L4-L5
	2	Betamethasone, lidocaine	Onset: 18-24h Duration: 1d	Physical treatment	L4-L5
	3	Betamethasone, lidocaine	Onset: 18-24h Duration: 1d	Physical treatment	L4-L5
7	1	Betamethasone, lidocaine	Onset: 12-18h Duration: 5-6d	Physical treatment	L5-S1
	2	Betamethasone, lidocaine	Onset: 12-18h Duration: 5-6d	Physical treatment	L5-S1
8	1	Betamethasone	Onset: next morning Duration: 1d	Physical treatment	C6-C7

	2	Betamethasone	Onset: next morning Duration: 1d	Physical treatment	C6-C7
9	1	Betamethasone, lidocaine	Onset: Immediate Duration: 12h	Physical treatment, Chlorpromazine	L5-S1
10	1	Dexamethasone, lidocaine	No hiccup	No treatment	L3-L4
	2	Dexamethasone, lidocaine	No hiccup	No treatment	L3-L4
	3	Dexamethasone, lidocaine	Onset: 12h Duration: 1d	Physical treatment	L3-L4
11	1	Betamethasone, lidocaine	Onset: Immediate Duration: 1d	Physical treatment	L5-S1
	2	Triamcinolone, lidocaine	Onset: Immediate Duration: Few h	Physical treatment	L5-S1
12	1	Dexamethasone, lidocaine	Onset: Few hours Duration: 36h	Physical treatment	L4-L5
	2	Dexamethasone, lidocaine	Onset: Immediate Duration: 5d	Physical treatment	L4-L5
13	1	Levobupivacaine, alfentanil	Onset: A few minutes Duration: 1h	No treatment	L3-L4
	2	Levobupivacaine	Onset: A few minutes Duration: 2h	No treatment	L3-L4
	3	Levobupivacaine, diamorphine	No hiccups	No treatment	L3-L4
14	1	Lidocaine, bupivacaine	Onset: 30m Duration: 1-2h	Physical treatment, Chlorpromazine, Metoclopramide, Right phrenic nerve blockade	L2-L3
15	1	Celestone, Bupivacaine	Onset: 20h Duration: 3d	Chlorpromazine	Sacral hiatus
16	1	Betamethasone, xylocaine	Onset: 15h Duration: 3.5d	Physical treatment, Chlorpromazine, Metoclopramide	T11-T12
	2	Betamethasone,	Onset: 18h	Metoclopramide	T11-T12

		xylocaine	Duration: 1d		
17	1	Triamcinolone acetate, Bupivacaine	Onset: 15h Duration: 3d	No treatment	L4-L5
18	1	Dexamethasone, Lidocaine	Onset: Few h Duration: 12d	Baclofen, Chlorpromazine	C6-C7
19	1	Triamcinolone, Bupivacaine	Onset: 1h Duration: 5-7d	No information	L2-L3
	2	Triamcinolone, Bupivacaine	Onset: 1h Duration: 5-7d	No information	L2-L3
	3	Triamcinolone, Bupivacaine	Onset: 1h Duration: 5-7d	No information	L2-L3
	4	Triamcinolone	No hiccups	No treatment	L2-L3
	5	Triamcinolone	No hiccups	No treatment	L2-L3
	6	Lidocaine, epinephrine, Bupivacaine, Fentanyl	Onset: 5h Duration: 9d	No treatment	L2-L3
20	1	Morphine, Hydromorphone	Onset: 12h Duration: 7.5d	Physical treatment, Baclofen, Change of morphine into hydromorphone	L3-L4
21	1	Morphine, Hydromorphone	Onset: 12h * Duration: 7d *	Physical treatment, Chlorpromazine, Change of morphine into hydromorphone	L2-L3, L3-L4
22	1	Dexamethasone, Lignocaine, Ropivacaine	Onset: Next day Duration: 4d	Physical treatment	L4-L5
23	1	Dexamethasone	Onset: 4d Duration: 8d	Baclofen	C7-T1
24	1	Levobupivacaine	Onset: 15m Duration: 9h	Physical treatment, Metoclopramide and midazolam	L2-L3
	1	Betamethasone, Bupivacaine	Onset: Evening Duration: 5d	No treatment	L4-L5

25	2	Betamethasone, Bupivacaine	Onset: No info Duration: No info	Metoclopramide	L4-L5
	3	Betamethasone	Onset: No info Duration: No info	No information	L4-L5
26	1	Betamethasone, Bupivacaine	Onset: Next day Duration: 1.5d	No treatment	L4-L5
	2	Betamethasone	Onset: Next day Duration: Instantly	Metoclopramide	L4-L5
27	1	Steroid	Onset: Few h Duration: Instantly	Chlorpromazine	L5-S1
	1	Steroid	Onset: Few h Duration: Instantly	Chlorpromazine	L5-S1
28	1	Steroid	Onset: Evening Duration: 4d	Physical treatment	T5-T6
29	1	Betamethasone, Ropivacaine	Onset: 4h Duration: no information	No treatment	L5-S1
	2	Betamethasone	Onset: 3h Duration: 15d	Metoclopramide, Chlorpromazine	L5-S1
30	1	Dexamethasone, mepivacaine	No hiccups	No treatment	C7-T1

* After intrathecal pump administration

The first injection was at C7-T1 and the second one at C5-C6. A majority of glucocorticosteroids injected were methylprednisolone, betamethasone and dexamethasone. In 1 case, celestone was used and in 3 cases, triamcinolone. Anesthetic agents mainly were lidocaine, bupivacaine, xylocaine, and levobupivacaine. Hiccups occurred most often after lumbar injections, then consequently after cervical, thoracic, and sacral injections. Patients reported that the onset of hiccups after injections was most often between 6 hours and 24h (25 patients), then before 6 hours passed (14 patients) and exceptionally over 24 hours (1 patient). The duration of hiccups was most frequently under 2 days (20 patients), between 2 and 7 days (15 patients), and seldom over 7 days (4 patients). There was no information about the onset of 2 patients' hiccups, and the duration of 3 patients' hiccups. In the case of 11 patients with hiccups after steroid injection, hiccups resolved spontaneously without any treatment methods used. The first option of treatment in a majority of cases was a physical treatment. If a physical treatment did not work, the second option was a drug treatment. Chlorpromazine and metoclopramide were administered most frequently. Baclofen, haloperidol, gabapentin and thorazine constituted only a minor part of administered medicines.

There were three patients with hiccups after epidural anesthesia. Their age was consecutively 70, 65 and 81 years. A 65-year old was a man. The anesthetics used were lidocaine and bupivacaine in 2 cases and levobupivacaine in one case. All of the 3 injections were at L2-L3 level.

Patients reported the onset of hiccups consecutively after 30 minutes, 5 hours, and 15 minutes, and the duration was consecutively 1-2h, 9 days, and 9 hours. The first and the third patients required both physical and drug treatment to stop the hiccups, whereas the second patient did not have a treatment at all. The drugs were chlorpromazine and metoclopramide in the first case and metoclopramide with midazolam in the third one. The first patient also had a blockade of the right phrenic nerve, which led to gradual stoppage of hiccup within 5 minutes.

A 30-year-old woman who suffered from hiccup after epidural analgesia had an epidural catheter inserted at L3-L4 level at first. Then, three doses of anesthetics were administered through that catheter. The first dose was levobupivacaine and hiccup started within a few minutes. Then levobupivacaine was continuously administered with alfentanil in fractionated doses. Hiccup resolved spontaneously after one hour. Six hours later, physicians added more levobupivacaine for breakthrough pain. Hiccup started within a few minutes after another dose was given and stopped after two hours spontaneously. After C-section, levobupivacaine with diamorphine administered for postoperative pain did not lead to hiccups.

The first patient who suffered from hiccup after opioid epidural injection, firstly had a 24-hour infusion of morphine as a trial. After the trial, a morphine pump was administered. Hiccup occurred 12 hours after the pump administration. He had a physical treatment and baclofen, but only 2 hours after changing morphine to hydromorphone in a pump, it resolved. The total duration of the hiccup was 7.5 days. The second patient had a 7 days long trial of opioid infusion. Then, after these 7 days, a pump was implanted. Around 12 hours after the pump implantation, a hiccup occurred. The methods of treatment were physical treatment methods and chlorpromazine, but only 16 hours after changing morphine to hydromorphone in a pump, it stopped. Two patients undergoing epidural opioid injection were 44 and 65 years old, respectively. The first one was a man; the other was a woman.

A long-lasting hiccup may be a burden, leading to exhaustion, tiredness, undernourishment, weight loss, dehydration, and in extreme cases, death (Wilcox et al., 2009). There are many reports of persistent/intractable hiccups and its debilitating influence on people's daily lives. An abundance of possible etiologies responsible for this phenomenon have been discovered (Nikiforova, 2016). Making a correct diagnosis and determining the exact etiology can often be challenging. This is why many physicians do not know what is the reason for tormenting hiccups and call it idiopathic. Furthermore, persistent/intractable hiccups are relatively uncommon. If they happen, patients rarely report them. When it comes to the exact mechanism of this symptom, scientists have been trying to explain it for years. To this date, they have not fully determined it. Some proposed mechanisms seem to reasonably explain the pathomechanism of hiccups. Many case reports still puzzle scientists over, though. Acute hiccups do not generally last long and subside spontaneously in a majority of cases. Persistent/intractable hiccups may be way more troublesome for patients. With the help of a variety of treatment methods, physicians can alleviate patients' distress.

Pathomechanism

Bailey was the first to state in 1943 that hiccups develop due to a "reflex arc". Three main compounds of hiccups "reflex arc" have been unveiled. One is an afferent limb comprising of phrenic nerve, vagus nerve and sympathetic nerve fibres from levels T6-T12. There is also a central processor and an efferent limb, where the phrenic nerve travels to the diaphragm whereas accessory nerves travel to intercostal muscles. When the phrenic nerve stimulates the diaphragm, it leads to unilateral or exceptionally bilateral contraction.

On the other hand, stimulated accessory nerves lead to contraction of the intercostal muscles. Of these 3 components of hiccups "reflex arc", the central processor is still the least explored. It is somewhere between the cervical spine and brainstem, possibly including upper spinal cord (C3-C5), the brainstem nearby respiratory centre, the reticular formation and the hypothalamus. The characteristic sound of hiccup occurs due to the closure of the glottis, which is stimulated by a recurrent laryngeal branch of the vagus nerve. Gamma-aminobutyric acid (GABA) and dopamine are among the few defined neurotransmitters taking part in this process (Steger et al., 2015; Abubaker et al., 2018). This knowledge explains why inhibitors of these substances are useful in the management of hiccups. Steroids in epidural injections may change the volume, composition or pressure of cerebrospinal fluid as well as induce a systemic effect on organism, leading to hiccups (Dickerman et al., 2003; Odonkor et al., 2017). Additionally, the advantage of parasympathetic activity by blocking the sympathetic chain along the thoracic vertebrae or stimulation of the phrenic and vagus nerves by a solution injected may play a role (Ritz et al., 2018). Among all steroids, dexamethasone was the most frequent one to result in this symptom. (Go et al., 2017) Apart from glucocorticosteroids, hiccups can also be provoked by anesthetic agents such as propofol,

midazolam, bupivacaine, ropivacaine and lidocaine via different ways. Among these ways are anesthetic agents administered intravenously, epidurally during epidural anesthesia or by nebulization (McAllister et al., 2005; Neeno et al., 1996). There have been cases of persistent hiccups as a complication of steroid epidural injection with or without local anesthetic and cases where local anesthetic alone induced hiccups (Ege, 2024; Zhang et al., 2018). Zhang et al., (2018) presented a case, where a patient suffered from continuous hiccup during hysterectomy with epidural injection of anesthetics. He proposed that uterine stretching during operation caused stretching of contents of abdominal cavity, and it all led to stimulation of phrenic nerves and diaphragm spasm.

Scientists have also proposed that hiccups may be the result of swallowing a lot of cold air, as a manifestation of anxiety before surgery (Wilcox et al., 2009). Nikiforova's possible explanation of this phenomenon is sympathetic blockade after lower thoracic/upper lumbar level of epidural space. This blockade would result in a parasympathetic dominance and an array of physiological changes leading to hiccups (Nikiforova, 2016). Epidural anesthesia can also affect diaphragmatic activity. Thoracic epidural anesthesia increases diaphragmatic activity by interrupting an inhibitory reflex of phrenic nerve motor drive by directly differentiating visceral sensory pathways or reducing diaphragmatic load as a result of increased abdominal compliance (Manikian et al., 1988). It is not fully known whether hiccups are directly a complication of local anesthetic or physiological changes in epidural space.

Epidemiology

Acute hiccups occur frequently and are commonly experienced by children, but also by adults. Mainly, it does not require pharmacological treatment and self-limits. In most cases the etiology is unknown and it is called idiopathic. On the other hand, persistent and intractable hiccups are rather incidental and may indicate that some comprehensive diagnostics are required. The exact incidence of persistent and intractable hiccups is not precisely known. In one retrospective review, 55 of 100,000 patients attending a general hospital received a primary diagnosis of hiccups (Cymet, 2002). Approximately 3% of the healthy population suffers from recurrent hiccups. The same problem can be associated with 10% of patients with gastroesophageal reflux disease (GERD) and 20% with Parkinson's disease (Khorakiwala et al., 2008). Moreover, of patients with advanced cancer, 3.9%-4.8% have been reported to experience hiccups. What is interesting is that hiccups can occur prenatally (Bagdure et al., 2011). When it comes to acute hiccups caused by non-CNS (Central Nervous System) diseases, clear male dominance has been demonstrated. In CNS etiology this discrepancy diminishes (Lee et al., 2016). Persistent and intractable hiccups are much more noticeable in men (Fisher, 1967). No racial, geographic, or socioeconomic variation in hiccups has been documented (Rajagopalan et al., 2021).

Etiology

Researchers have identified over 100 causes of hiccups, most of them are gastrointestinal disorders such as gastroesophageal reflux disease, central nervous system disorders (stroke, multiple sclerosis, tumours) or cardiovascular disorders (myocardial ischemia or pericarditis). There are also benign causes, more common, for instance carbonated beverages, air swallowing or overeating, all three leading to gastric distention, but apart from them also alcohol intake, smoking, sudden temperature changes. All of them may influence hiccups "reflex arc" by affecting any of the three components (afferent, central, efferent limbs). A short, self-limiting hiccups due to a benign cause mostly does not put patients into jeopardy. Still, patients with persistent/intractable hiccup should undergo a complex diagnostics to rule out a potential organic etiology. Due to the immensity of reasons for hiccups, it is relatively tough to diagnose every patient. Table 3 presents the extent of diseases, factors, etc., ever associated with hiccups (Rajagopalan et al., 2021; Cersosimo & Brophy, 1998; Stuth et al., 2000). The causes of hiccups can be divided into central and peripheral. Central causes such as stroke, trauma or infection (encephalitis, meningitis) affect the central processor. Peripheral causes include lesions along the "reflex arc", gastroesophageal reflux disease, ischemic heart disease or bronchitis. Besides, other etiologies are possible such as iatrogenic (bronchoscopy), drug induced (opioids, benzodiazepines, chemotherapy) or psychosomatic (anxiety, fear, stress) (Brañuelas et al., 2016; Cersosimo & Brophy, 1998). Referring to drug-induced hiccups, glucocorticosteroids are also among those that can lead to hiccups via different ways of administration, including oral, epidural, intra-articular, or intravenous (Abbasi et al., 2012; Abubaker et al., 2018; Errante et al., 2005; Lee et al., 2013). According to one research, glucocorticosteroids reduce the threshold for transmission in synapses in the midbrain, inducing hiccups (Davis, 1970).

Table 3 - The etiology of hiccups

Peripheral pathway	
Gastrointestinal disorders	Gastroesophageal reflux disease (GERD), H. pylori infection, Esophageal tumours, Hiatus hernia, Gastric distention, Gastritis, Gastric carcinoma, Gastric volvulus, Gastric distention, Esophagitis, Pancreatitis, Pancreatic cancer, Gallbladder disease, Inflammatory bowel disease, Bowel obstruction, Hepatitis, Aerophagia, Abdominal abscess, Peptic ulceration
Cardiovascular disorders	Myocardial ischemia, pericarditis, atrial pacing, aortic aneurysm, post-myocardial infarction
Pulmonary disorders	Bronchitis, pneumonia, Asthma, Tuberculosis, Bronchial carcinoma, Pulmonary embolism
Otolaryngologic disorders	Goiter, Neck cyst, Rhinitis, Otitis, Pharyngitis, Endotracheal intubation, Foreign body, Herpes zoster
Thoracic lesions	Mediastinal tumour, Lymphadenopathy, Pleural effusion, Empyema, Diaphragmatic tumour,
Other	Ascites, Pelvic tumour, Intestinal obstruction
Central pathway	
Vascular disorders	Stroke, Infarct, Aneurysm, AV malformations
Neoplasm	Astrocytoma, Cavernoma, Brain stem tumours
Trauma	Traumatic Brain Injury
Inflammation	Neuromyelitis optica, Multiple sclerosis
Infection	Encephalitis, Meningitis, Temporal arteritis, Neurosyphilis
Other	Syringomyelia, Hydrocephalus, Parkinsonism
Other causes	
Surgical	Bronchoscopy, Tracheostomy, Thoracic or abdominal surgeries, Central Venous Catheterization, Anesthetic Agents
Drugs	Steroids, Opioids, Benzodiazepines, Macrolides, Chemotherapy, Antipsychotic medications, Ethanol
Metabolic disorders	Hyponatraemia, Hypokalaemia, Hypocalcaemia, Hypocapnia, Uraemia, Diabetes Mellitus
Psychogenic disorders	Anxiety, Excitement, Stress, Sleep deprivation, Fear

Treatment

Acute hiccups are most frequently self-limiting episodes, which do not require further examination or professional treatment. Ultimately, the most effective hiccup therapy, especially for persistent and intractable hiccups, is making a correct diagnosis and treating it. The examples are tumour operations or drug treatment of gastroesophageal reflux disease (GERD) (Chang and Lu, 2012). However, apart from eradicating the underlying condition resulting in hiccups, it is necessary to introduce an effective treatment. There are various methods to treat hiccups. The most important are physical treatment, drug treatment, and nerve block (Zhang et al., 2018).

Among physical methods there is a nasopharyngeal stimulation (drinking a glass of water, inserting a tube to irritate the back wall of the pharynx for 20 seconds or applying other irritants such as vinegar or ammonia), vagal stimulation (induced vomiting, induced fright, massage of the carotid sinus or a cold compress to face) and respiratory maneuvers (Valsalva manoeuvre, cough, holding one's breath, breathing with a help of bag and CPAP-respiration) They are generally only working as a solution for short hiccups attacks (Steger et al., 2015; Brañuelas et al., 2016). Researchers explain these methods by interrupting the reflex arc, which, during hiccups, repetitively generates diaphragmatic contractions. Studies have shown that these manoeuvres help by decreasing the frequency of hiccups as arterial pCO₂ goes up (Davis, 1970). There are also anecdotal treatments such as drinking carbonated beverages, meditation or digital rectal examination. Due to a lack of research regarding these methods, we do not include them in this work (Turkyilmaz & Eroglu, 2008). If physical methods do not work, pharmacological drug treatment is usually the second choice. There is insufficient data to create official treatment guidelines, despite numerous studies analyzing large numbers of patients. Before prescribing a medicine for hiccups, a physician should collect a complete medical history regarding actual medications and comorbidities to avoid possible drug interactions and side effects of the treatment (Rajagopalan et al., 2021). It is of great importance to ask whether a patient has ever suffered from hiccups, especially after invasive procedures such as epidural injections or has a predisposing condition, because if hiccup occurs during the operation, there may be very severe consequences afterwards (He et al., 2025).

A continuous hiccup during an operation is a rare phenomenon, but if it occurs, it may negate the effort of surgeons (Zhang et al., 2018). Stuth et al., (2000) reported a case where hiccups during the operation resulted in a pulmonary edema. Other researchers, Rullo et al., (2007) reported a case where continuous hiccup caused left common iliac artery perforation. A few medications are reportedly effective in treatment of persistent/intractable hiccups. A majority of them work by influencing dopaminergic and GABA-ergic receptors (Steger et al., 2015). Here we enlist the following drugs with a brief description of each. Chlorpromazine is a centrally acting dopamine antagonist. It can be administered orally or intravenously and is the only medication approved by FDA for treatment of intractable hiccups (Friedgood & Ripstein, 1955). Other neuroleptics like haloperidol, a dopamine antagonist, and olanzapine, a postsynaptic serotonergic receptors antagonist, are effective but have side effects such as sedation, mood disturbance, dizziness (Ives et al., 1985; Alderfer & Arciniegas, 2006). Benzodiazepines suppress the repetitive, myoclonic contractions of diaphragm when given in high doses, for instance midazolam in a continuous infusion at the rate of 10-60 mg/24h (Wilcock & Twycross, 1996).

Baclofen is a muscle relaxant, a GABA-B agonist, which inhibits transient relaxations of lower esophageal sphincter and diaphragm with its effect on vagal nerves both centrally and peripherally (Ramirez & Graham, 1992; Twycross, 2003; Walker et al., 1998). Gabapentin, carbamazepine, and valproic acid are anti-epileptic drugs, which increase the GABA transmission centrally (valproic acid) or modulate diaphragmatic excitability by increasing endogenous GABA-mediated inhibition (Tegeler & Baumrucker, 2008; McFarling & Susac, 1974; Jacobson et al., 1981). Among other drugs, there is metoclopramide, which lowers esophageal sphincter tightening effect, dopamine antagonists like domperidone and nefopam, cisapride, a 5-HT₄ agonist, nifedipine, a calcium channel blocker which interrupts the reflex arc by reversing the abnormal depolarization, methylphenidate, an inhibitor of dopamine and norepinephrine reuptake, carvedilol, which acts on the afferent sympathetic component of the reflex arc and amantadine (Wang & Wang, 2014; Duffy et al., 1992; Mukhopadhyay et al., 1986; Maréchal et al., 2003; Bilotta & Rosa, 2003; Stueber & Swartz, 2006; Wilcox et al., 2009). Interesting is that lidocaine is a treatment for hiccups with its effect on the irritant sensory afferents (Cohen et al., 2001; Neeno & Rosenow, 1996; Rajagopalan et al., 2021).

Some case reports presented a possibility of combination therapy, where Petroianu et al., (1997) proposed cisapride, omeprazole, and baclofen (COB) to be an effective therapy. In another study, Petroianu et al., (2000) also added gabapentin to the previous combination with even better results. Steger et al., (2015) published a research paper, where he presented recommendations for treatment of persistent and intractable hiccups. According to these recommendations, baclofen, gabapentin and pregabalin are a potential first line treatment, metoclopramide and domperidone a second line treatment, while chlorpromazine a third line treatment. If both physical and pharmacological treatment fail, there are also other methods to treat intractable/persistent hiccups. Physicians

perform a procedure called phrenic nerve block to blockade the hiccups “reflex arc” and stop the hiccup. It is usually performed under ultrasound guidance due to the nerve's thinness (Kang et al., 2010).

Calvo et al., (2002) reported a case of five cancer patients who underwent phrenic nerve block with ultrasound guidance for intractable hiccups. Successfully, hiccups resolved without side-effects. Unfortunately, phrenic nerve block may also affect the respiratory function of an organism. In one work, it decreased FEV1, FVC and PEF by 12%, 13% and 12% respectively. However, patients with normal respiratory function should not be disqualified from this procedure (Zhang et al., 2018). Speaking more about the phrenic nerve, in the case of coronary by-pass surgery related hiccup, radiofrequency ablation of phrenic nerve was successful to treat the symptom (Kang et al., 2010). Payne et al., (2005) reported that left vagal afferent blockade via nerve stimulation may be applied to stroke-related intractable hiccups if phrenic nerve block fails. If a patient has many injections planned and there is a history of hiccup after one, switching from one steroid to another may be a solution to prevent its future occurrence (Abbasi et al., 2012).

4. CONCLUSION

Hiccup's relationship with epidural injections is still not fully explored. Current knowledge explains the Patho mechanism of hiccups by the hiccups “reflex” arc and a diversity of etiological factors affecting it. In our work, a majority of patients who got an epidural steroid injection were men. Due to a small number of patients undergoing epidural anesthesia, analgesia, or opioid injection with hiccups afterwards, conclusions about the sex advantage are unreliable. The age of patients was majorly over 50. Most of the interventions resulting in hiccups were epidural steroid injections with a steroid and an anesthetic agent in a mixed injectate. The removal of an anesthetic agent from a mixed injectate prevented hiccups in only one case. Steroid rotation also did not stop the hiccup recurrence. Two patients experienced hiccups after some injections but not after others. Analyzing all the collected research papers, it is not possible to explain this phenomenon. Chlorpromazine and metoclopramide were the most frequent drugs used for treating hiccups. According to unofficial recommendations in literature, they are the second and third line of treatment, meaning that physicians choose medications according to their preferences due to a lack of official guidelines.

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Author contributions

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Informed consent

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Ethical approval

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Conflict of interest

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Data and materials availability

All data associated with this work are present in the paper.

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