Drug Utilization Study of Diuretics in Children with Hydrocephalus

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Abstrak

Hydrocephalus is a condition characterized by a dynamic imbalance between formation and absorption of cerebrospinal fluid that increases the size of intracranial space of the brain and, in some situations, an extension of the outer space of the brain with or without increased ventricular size. This study aimed to examine the use of diuretics and identify drug therapy problems in hospitalized children with hydrocephalus through the medical record. The study design is observational retrospective with time-limited sampling based on data in medical records at 2010-2013 periods, found 17 of 70 patients using diuretics therapy. There are three categories of diuretic which are used were mannitol (70.6%), acetazolamide (23.5%), and a combination of mannitol and acetazolamide (5.9%). Diuretics can be used for pre-op, post-op, and pre & post-op on all types of hydrocephalus. Still, the specific use of diuretics may be caused by variations in comorbid diagnoses, clinical data, and laboratory data for each patient. Adverse drug reactions are potentially dominant in DTP analysis, and these are 7 of 17 patients. Monitoring of serum electrolytes such as sodium and potassium is needed because it decreases are potential adverse drug reactions of diuretics.
Abstrak dibuat dalam bahasa Indonesia. Abstrak disusun dalam satu paragraf dengan jumlah kata tidak lebih dari 250 kata. Isi mencakup latar belakang, tujuan, metode, hasil, dan simpulan

Keywords: *diuretics, hydrocephalus, child, drug utilization study (DUS).*

Introduction

Hydrocephalus is a condition characterized by a dynamic imbalance between the formation (production) and absorption of cerebrospinal fluid (CSF), resulting in an increase in the size of the intracranial space of the brain and, in some situations, expansion of the extracranial space with or without an increase in the size of the ventricles (1). The incidence of hydrocephalus cases, in general, can be described as a bimodal curve, one of which peaks in the age range of children associated with various congenital malformations (2). The *post-neonatal* infant mortality caused by hydrocephalus is 5.8% (3).

According to research (4), the incidence of hydrocephalus in children and adults is not known for sure, but it is estimated that in every 1000 births, there is an incidence of 0.9-1.5 hydrocephalus. If congenital abnormalities at birth include the cause of hydrocephalus, the incidence of hydrocephalus increases, namely in every 1000 births, there are 1.3-2.9.

Handling hydrocephalus in children is needed because the clinical manifestations caused will result in relaxation of the cranial nerves responsible for eye function so that it can cause dysfunctional eye movements and vision (5). Treatment of hydrocephalus includes medical therapy and actions, namely endoscopic surgery and shunting. Conservative medical treatment aims to limit the evolution of hydrocephalus by reducing fluid secretion from the choroid plexus, such as the use of acetazolamide 100 mg/kg body weight/day; furosemide 1 mg/kg body weight/day. The therapy is still temporary before definitive treatment is applied or if there is the hope of recovery from the hemodynamic disturbance; otherwise, this therapy is not practical for long-term treatment given the risk of metabolic disorders (2).

The most effective drug is acetazolamide alone or combined with furosemide, whereas osmotic agents are no longer used (6). The use of Mannitol in patients with acute renal failure and increased intracranial pressure (ICP) can cause hypervolemia and hyperosmolality, increasing ICP. When used in recommended doses, furosemide is generally well tolerated but at high doses causes excessive diuresis resulting in hypotension, dehydration, and the patient is at increased risk of vascular clot formation. Fluid and electrolyte status should be considered when high-dose therapy is used. All patients should be monitored for signs and symptoms of hypochloremic metabolic alkalosis, hyponatremia, hypokalemia, hypomagnesemia, or hypercalciuria (7). The use of acetazolamide for children can trigger nephrocalcinosis and nephrolithiasis, namely calcium stones, when combined with *loop* diuretics due to increased calcium excretion (8).
Therefore, hydrocephalus in children requires diuretic therapy with appropriate therapeutic effects in drug selection and dosage regimen to predict the possibility of *drug therapy problems* (DTP) from the diuretic therapy used.

Research Methods

Research Material

Medical Record (MR) of Inpatient pediatric with hydrocephalus at Neurosurgery Department RSUD Dr. Soetomo Surabaya as material research. A medical record is a file containing records and documents regarding patient identity, examination, treatment, actions, and other services that have been provided to patients.

Research design

This type of research is a non-experimental (observational) research because it is carried out on events or cause-effect phenomena that have occurred with the cause not due to the treatment of the researcher, with a descriptive design because this study uses general theory to explain a set of data that is carried out retrospectively, using the yearly MR 2010 to 2013. Data collection was carried out by rewriting data from MR and then processing and analysis.

Research Sample

The research sample was patients diagnosed with early or late hydrocephalus in pediatric patients hospitalized at Dr. Soetomo Hospital Surabaya. Patients under 18 years of age were diagnosed with hydrocephalus and receiving diuretic drug therapy for hydrocephalus. The sampling method used was the Time Limited Sampling method. Each patient who met the research criteria was included in the study for a certain period according to the time of the survey.

Place and time of research

The place of the research was in the Inpatient Room of the Neurosurgery Department Hospital Dr. Soetomo Surabaya from March to June 2014 to obtain secondary data on pediatric hydrocephalus patients from January 1, 2010, to December 31, 2013.

Method of Data Processing and Analysis

Data were analyzed descriptively using tables, graphs, and descriptions. The data generated include the percentage of patient demographics, diuretic use, reasons for using diuretics, analysis of DTP (drug therapy problems) that may occur, and the accuracy of dose regimentation and side effects.

Results And Discussion

Characteristics of Research Sample

Table 1 Age and Gender Distribution of Children with Hydrocephalus Patients

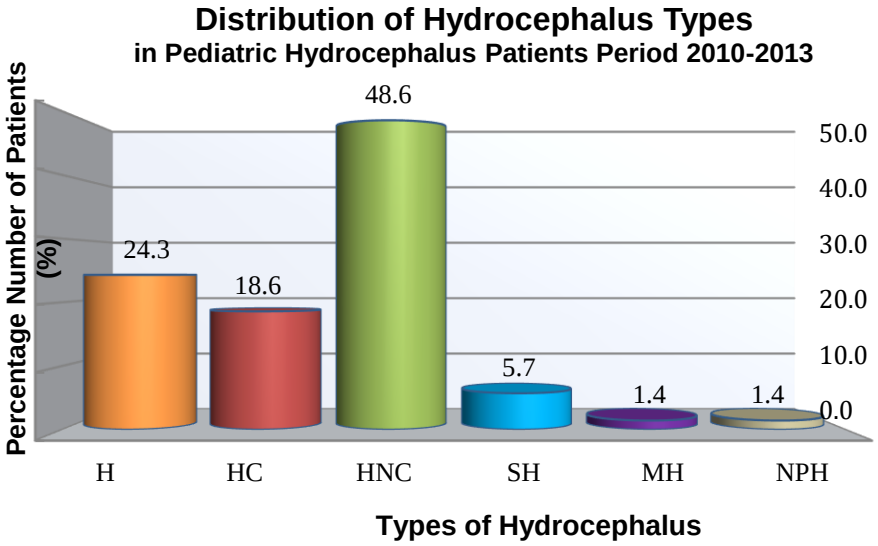
Age	Woman	Man	Total	Percentage (%)
< 1 month (neonate)	4	3	7	10.0
1 - 12 months (*infant)*	11	12	23	32.9
15 years	8	18	26	37.1
6 - 12 years	6	4	10	14.3
13 - 17 years old	0	4	4	5.7
Total	29	41	70	100.0
Percentage (%)	41.4	58.6	100.0	

The number of pediatric patients diagnosed with hydrocephalus from 2010 to 2013, 70 patients with an age range of 1-5 years, had the highest incidence of hydrocephalus, which was 37.1%. Based on gender category, hydrocephalus patients were more boys (58.6%) than girls.

Table 2 Age and Gender Distribution of Children with Hydrocephalus Patients receiving Medical Therapy (Diuretics)

Age	Woman	Man	Total	Percentage (%)
< 1 month (neonate)	2	1	3	17.6
1 - 12 months (*infant)*	3	2	5	29.5
15 years	2	1	3	17.6
6 - 12 years	4	2	6	35.3
Total	11	6	17	100.0
Percentage (%)	64.7	35.3	100.0	

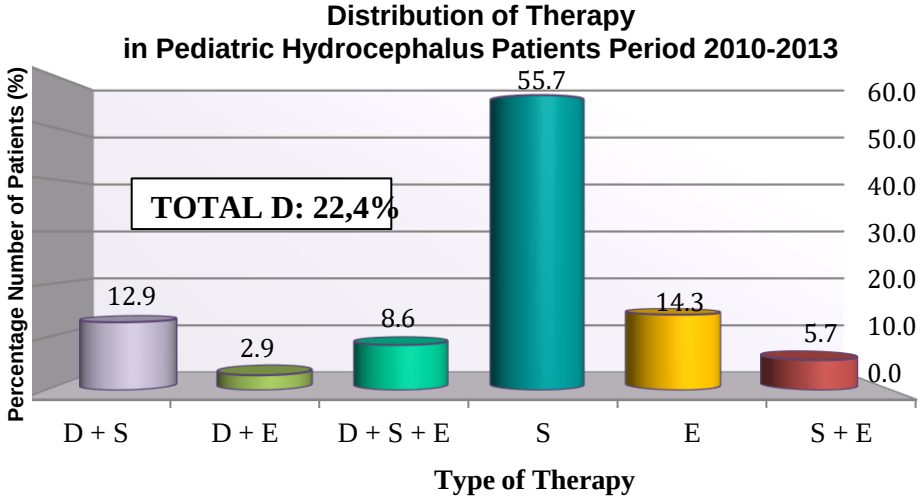
Based on gender, hydrocephalus patients were boys (58.6%) more than girls (41.4%). Several other researchers found no significant difference between male and female patients (9,10,11).



Description: The patient's diagnosis can be accompanied by a simultaneous diagnosis other than hydrocephalus. H: Hydrocephalus, HC: Communicating hydrocephalus, HNC: Non-communicating hydrocephalus, SH: Severe hydrocephalus, MH: Multilobulated Hydrocephalus, and NPH: Normal Pressure Hydrocephalus. Number of patients: 70 patients

Figure 1 Distribution of Hydrocephalus Types in Pediatric Hydrocephalus Patients

Hydrocephalus can be classified into 11 types, namely internal hydrocephalus, external hydrocephalus, communicating hydrocephalus, non-communicating hydrocephalus, obstructive hydrocephalus, symptomatic hydrocephalus, *arrested* hydrocephalus, iatrogenic hydrocephalus, normotensive hydrocephalus, and *ex-vacuo* hydrocephalus (2). In this study, from 70 pediatric hydrocephalus patients, six types of hydrocephalus were found, namely hydrocephalus, communicating hydrocephalus, non-communicating *hydrocephalus, severe hydrocephalus, multilobulated hydrocephalus,* and *normal pressure hydrocephalus*. In this study, non-communicating hydrocephalus (48.6%) was the most common diagnosis in pediatric hydrocephalus patients.



Description: one patient can receive more than one MRS. D: Diuretics, E: Endoscopic Surgery, S: Shunting. The number of patients: 70 patients.

Figure 2 Distribution of therapy in pediatric hydrocephalus patients

The therapeutic management of hydrocephalus can be categorized into three, namely, medical therapy (diuretics), endoscopic surgical therapy, and *shunting* therapy. Endoscopic surgical therapy consists of membrane penetration therapy such as ETV (endoscopic third ventriculostomy*)* and etiological therapy such as tumor excision. *Shunting* therapy consists of VP- *shunt*, and EVD (external ventricle drainage) (2). In this study, the therapeutic management of hydrocephalus can be categorized into six types, and the category of hydrocephalus therapy is dominated by *shunting* therapy (55.7%). Diuretic therapy is not the sole therapy but is an adjunct to definitive therapy. The total number of administration of diuretic therapy (22.4%) was the accumulation of the combination of diuretics and *shunting* (12.9%), the combination of diuretics and endoscopic surgery (2.9%), and the combination of diuretics, *shunting*, and endoscopic surgery (8.6%). Of the 70 pediatric hydrocephalus patients, 17 patients (22.4%) who received diuretic therapy were included in the inclusion criteria and were used as samples in this study.

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Use of Diuretics

From the number of pediatric hydrocephalus patients who received diuretic therapy, the dominant age range of patients was 6-12 years (35.3%), and the dominant sex was female (64.7%). Medulla blastoma, posterior fossa tumor, supracellular tumor, cerebral tumor (*optic glicon*), ependyoma and *brainstem glioma* are brain tumors. In contrast, multiple cerebral abscesses, meningoencephalitis, and meningitis are infections of the nervous system (2). From the grouping of brain pathologies, in this study, brain tumors and infections of the nervous system were the dominant brain pathologies of the accompanying diagnoses of pediatric hydrocephalus patients, each with 40% incidence.

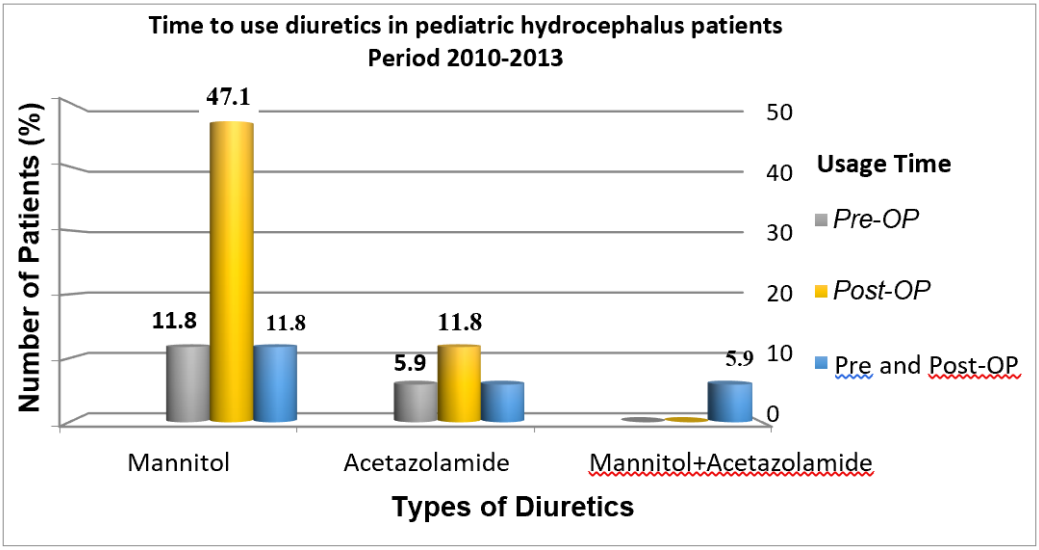
Table 3 Treatment Profile of Children with Hydrocephalus who Received Diuretics

(No.) Initials	Diagnosis	Accompanying Diagnosis	Diuretic Therapy (on the day-)	Surgery (on the day-)	Reasons for using diuretics
(1) ADP	Non-communicating hydrocephalus	Medulla Blastoma, R. Fossa Posterior Tumor.	Mannitol (1-5)	Tumor excision and *VP Shunt* (5), EVD and Trep. ICH evaluation (6)	↑ ICT *pre*-op
(2) AF	Non-communicating hydrocephalus	Brainstem Glioma	Mannitol (1-5)	EVD (18)	↑ ICT *pre*-op
(3) AM	Non-communicating hydrocephalus *Post VP Shunt*	St. Epilepticus ec Meningioense-phalitis + Brain edema	Mannitol (4-6)	Subdural Hygroma (3)	↑ ICT *post*- op
(4) ANA	Non-communicating hydrocephalus *Post VP Shunt*	A cerebral tumor (*optic glicon*)	Mannitol (1-7, 18)	*VP Shunt* (at the time of the previous hospitalization)	↑ ICT *post*- op
(5) AT	Communicating hydrocephalus	Meningioense-phalitis	Mannitol (1, 3-5, 10-11, 14-15)	EVD and *VP shunt* (3), Revision *VP Shunt* (11), Subtemporal dekompr *e* si (13)	↑ICT *pre*-and *post*-op

(6) AU	*Multilobular* hydrocephalus	-	Acetazola-mid (8-12, 14-15, at subsequent hospitalized 2-9)	*VP Shunt* (7), revised *VP Shunt* (14), revised *VP Shunt* and endoscopy (9 at next hospitalized)	↑CSF *pre*-and *post*-op
(7) HWN	Non-communicating hydrocephalus	Meningioense-phalitis	Mannitol (1-2, 5-6)	EVD and *VP Shunt* (3)	↑ICT *pre*-and *post*-op
(8) DS	Communicating hydrocephalus	Meningioense-phalitis	Mannitol (1-3)	*VP Shunt* (1)	↑ICT *post*- op
(9) H	Communicating hydrocephalus	Multiple cerebral abscess + meningitis + dangerous type omsk + urinary tract infection	Mannitol (27-39, 44)	EVD (1), abscess evacuation, cwd mastoidectomy S, and revision of EVD (9)	↑ICT *post*- op
(10) L	*Severe post-VP shunt* hydrocephalus	Meningioence-phalocal *post* excision celle, secondary ASD Koci, combustio gr IIA	Acetazole-mid (70-78)	EVD (26)	↑CSF *post*- op
(11) MDP	Communicating hydrocephalus	St. epilepticus ec. meningio-encephalitis + bronchopneumonia.	Mannitol (1-4)	EVD (2)	↑ICT *pre* and *post*- op
(12) N	Non-communicating hydrocephalus	Stenosis Aquaductus Sylvii	Acetazole-mid (5, 8)	ETV (12)	↑CSF *pre*- op
(13) PWS	Non-communicating hydrocephalus	Medulla blastoma	Acetazole-mid (1-2) Mannitol (1-2, 4-6)	*VP Shunt* (3)	↑CSF *pre*-op ↑ICT *pre*-and *post*-op
(14) R	Communicating hydrocephalus	St. Epilepticus ec. Meningio-encephalitis, cerebral edema	Mannitol (3-10)	EVD (5)	↑ICT *pre*-and *post*-op
(16) W	Non-communicating hydrocephalus	Meningioense-falocele rupture + sepsis	Acetazole-mid (47-53)	EVD and *VP Shunt*	↑CSF *post*- op
(17) ZAP	Non-communicating hydrocephalus	supracellular tumor	Mannitol (20)	*VP Shunt* (1), Tumor excision (17), *Subdural Hygroma* (23), and *Subdural Peritoneal* (30)	↑ICT *post*- op

Description: ↑ increase, ICP: Intracranial pressure, CSF: Cerebrospinal fluid, OP: Surgery.

Based on the time category of diuretic use, mannitol was dominantly used *post*-op (47.1%), acetazolamide was dominantly used *post-op* (11.8%), and the combination of mannitol & acetazolamide was used *pre* & *post*- OP (5.9%). Loop diuretics (furosemide) were not used in pediatric hydrocephalus patients in this study**.** Diuretic therapy is given not only pre-op but can also be given post-op and pre- & *post*-op, as evidenced by the 3-time categories of diuretic use obtained in this study. Based on the time category of diuretic use, mannitol and acetazolamide were dominantly used *post*-op (47.1% and 11.8%), while the combination of mannitol and acetazolamide was used *pre* & *post*-op (5.9%).



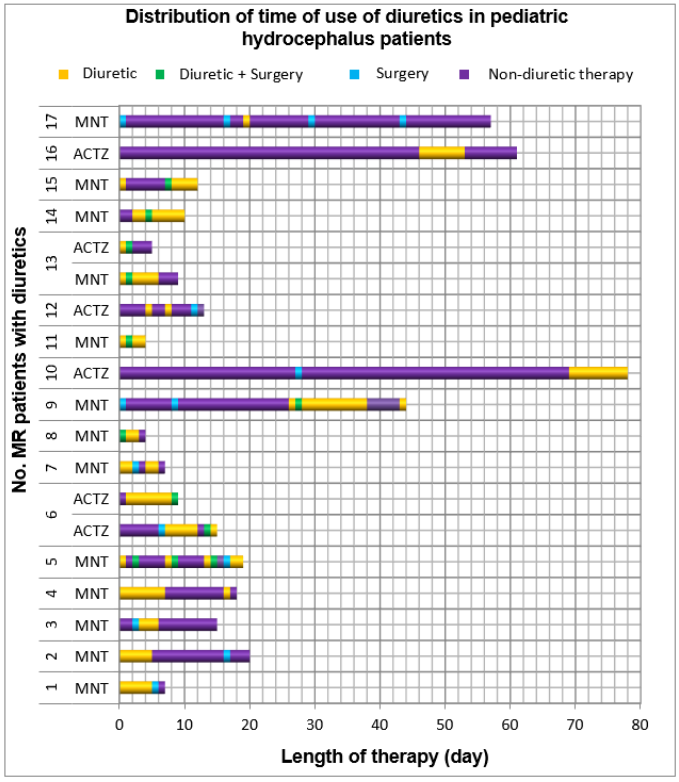
Description: Number of patients: 17 patients

Figure 3 Time to use diuretics in pediatric hydrocephalus patients

Although diuretics can be used *pre*-op, *post*-op, *pre* & *post*-op, diuretics are not used routinely every day during hospitalization. Diuretics are used according to clinical conditions and patient laboratory data. According to clinical situations and patient laboratory data, diuretics can be discontinued and resumed with different doses. Mannitol can reduce ICP because mannitol acts on the blood-brain barrier and relatively reduces intracranial volume. The effect associated with a decrease in ICP is the dehydrating effect of the brain by reducing the accumulation of fluid in the interstitial space so that the volume of brain tissue is relatively reduced. The rheological effect will increase microcirculation, thereby improving the penetration ability of red blood cells, which will ensure tissue oxygenation and maintain the Na^+ pump (2).

Acetazolamide can reduce CSF production through inhibition of the local activity of carbonic anhydrase in the choroid plexus. Inhibition of carbonic anhydrase via acetazolamide increases cell pH in the choroid plexus. An increase in cell pH leads to a slowdown in the uptake of Na^+ and Cl^-, which usually occurs by parallel Na-H and Cl-HCO_3 exchangers located on the side of the blood membrane. Acetazolamide can also block the anion channel in the apical membrane responsible for the extrusion of Cl^- and HCO_3^-. The effect is a decrease in the *vectorial* transport of NaCl from the blood to the CSF. Consequently, CSF formation is inhibited because Na + and Cl - transport in the choroid plexus into the ventricles is a significant determinant of fluid shape (12). Acetazolamide therapy and mechanical ventilation in children with hydrocephalus can improve the VP shunt's tolerance and minimize respiratory harm (13).

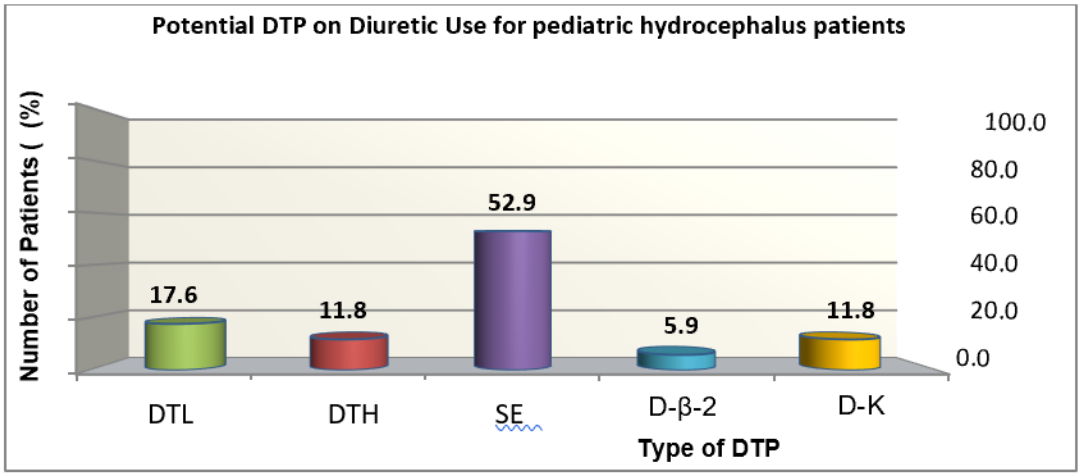
In this study, mannitol was used in cases of hydrocephalus with increased intracranial pressure due to obstruction of fluid flow (by a brain tumor and inflammation by infection of the nervous system) and cerebral edema. Acetazolamide is used in cases of hydrocephalus with impaired fluid flow (by aqueductal stenosis and meningioencephalocele) and *multilobular* hydrocephalus. The combination of mannitol and acetazolamide is used in cases of hydrocephalus with increased intracranial pressure due to a brain tumor (liquor flow obstruction). Based on the relationship between diuretic use and the pathology or etiology of hydrocephalus, it is proven that hydrocephalus patients with accompanying pathology or etiology also require etiological therapy such as endoscopic surgery in addition to the use of diuretics.



Description: On the day of the use of diuretics, the patient also used non-diuretic drugs. The number of patients: 17 patients. MNT: Mannitol, ACTZ: Acetazolamide, D: Diuretics, S: surgery.

Figure 4 Time distribution of diuretic use in pediatric hydrocephalus patients during hospitalized

Potential DTP Analysis



Description: DTL: Dose Too Low, DTH: Dose Too High, SE: Side Effects of Diuretic Drugs, D-β-2: Diuretic-β-2 Adrenergic Agonist Interaction, D-C: Diuretic-Corticosteroid Interaction. One patient can have more than one potential DTP. Number of Patients: 17 patients

Figure 5 Potential DTP on the use of diuretics for pediatric hydrocephalus patients

Based on the analysis of potential DTP, there were four categories of potential problems with diuretic therapy for pediatric hydrocephalus patients: too high a dose, too low a dose, drug side effects, and drug interactions. Diuretic-β-2 adrenergic agonist interactions and diuretic-corticosteroid interactions fall into drug interaction problems.

Table 4 Calculation of Doses Too Low

Number of MR patient	Types of Diuretics	Initials (BB)	Dosage Regimentation	Observed dose / day (mg)	Dosage/day Literature (mg)
(6)	Acetazolamide	AU (5 kg)	1dd50mg 1dd50mg	50 50	125-500 150-600
(10)	Acetazolamide	L (3.7 kg)	3dd10 mg	30	92.5-370
(12)	Acetazolamide	N (8.9 kg)	3dd70mg	210	222.5-890

Description: literature dose for acetazolamide 25mg/kg/day not maximum 100 mg/kg/day (15). BB: body weight in kg.

Diuretic doses were too low in 3 patients (17.6%). According to the DTP classification, the causes of too high and low doses are wrong dose, inappropriate frequency, inappropriate duration, inappropriate administration, and drug interactions (17). In this case, a dose that is too low is potentially caused by an incorrect dose because the patient's eGFR (*estimated glomerulus filtration rate*) value is still within the normal range, so a dose reduction if it is suspected of impaired renal function, should not be performed. The diuretic dose was too high in 2 patients (11.8%). Based on the analysis of eGFR, there was no decrease in eGFR with too high a dose. Patients are at risk for acute renal failure if a decrease in the eGFR value of more than 25% (15). However, there was a decrease in serum potassium with the use of too high a dose of mannitol, so that the use of too high a dose of diuretics is still a potential DTP in this study.

Table 5 Calculation of Doses Too High

Number of MR patient	Types of Diuretics	Initials (BB)	Dosage Regimentation	Observation dose (g)	Literature Dose (g)
(13)	Acetazolamide	PWS (6 kg)	3dd250mg	0.75	0.15-0.6
	Mannitol		LD 100cc	20	1.5-18
			4dd30cc	24	1.5-18
(15)	Mannitol	TN (27 kg)	LD 200cc	160	6.75-108
			MD 6dd100cc		6.75-108

Description: literature dose for IV mannitol 1-2 dd 0.25-1.5g/kg (14). LD: loading dose. MD: maintenance dose.
BB: body weight in kg.

Calculation of the diuretic dose is calculated based on the patient's weight. The literature used as a dose comparison was drawn from the *British National Formulary for Children* 2009 (14) for mannitol and the Diagnosis and Management of Neurological Disease (15) for the dose of acetazolamide. The dose of mannitol used is indicated for increased intracranial pressure, and the dose of acetazolamide is indicated for hydrocephalus.

Table 6 Potential Drug Interactions

No.	Drug Interaction	Interaction Forms (21)
1	Diuretics-Corticosteroids, (Acetazolamide – Dexamethasone) and Acetazolamide – Methyl prednisolone	Diuretics that cause K^+ loss when given concomitantly with corticosteroids will cause increased K^+ loss
2.	Diuretics β -2 Adrenergic Agonists, (Mannitol – Albuterol)	Concomitant use of mannitol with albuterol may increase the risk of hypokalemia. Risks may exist even when albuterol is administered by oral inhalation directly into the lungs, and if used in excess

Description: The interaction of Acetazolamide-Dexamethasone, Acetazolamide-Methyl prednisolone, and Mannitol-Albuterol is *moderate* (clinically significant enough. Usually, the combination is avoided and used only in special circumstances (18).

Potential drug interactions were diuretic-corticosteroids in 2 patients (11.8%) and diuretic-β-2 adrenergic agonist therapy in 1 patient (5.9%) of the total 17 patients. Therapeutic management of the patient when co-administered with diuretic-corticosteroid drugs and diuretic-β-2 adrenergic agonists is close monitoring for the risk of hypokalemia, especially when high doses of corticosteroids are administered. The patient may require potassium supplements. Patients are advised to notify their doctor if they experience signs of electrolyte disturbances such as weakness, lethargy, muscle aches, cramps, palpitations, and irregular heartbeats (18).

Table 7 Potential Diuretic Side Effects

Types of Diuretics	Side effects	Percentage (%)	Number of Patients
Mannitol	↓Na^+	53.8	7
	↓K^+	69.2	9

Description: ↓ decrease. In one patient there can be more than one kind of side effect. The percentage was calculated from the number of patients who used mannitol (13 patients).

The side effect of diuretic drugs is a potential DTP that is dominant in diuretics for pediatric hydrocephalus patients, namely 52.9% (9 patients). In this study, a possible side effect observed was a decrease in serum sodium and potassium with mannitol use. This is because the decline in serum sodium and potassium in the use of mannitol often occurs while the use of acetazolamide is rare (7, 19). In addition, this study was limited to a retrospective method so that the side effects of using acetazolamide, such as *taste disturbance* (20), could not be observed directly.

Conclusions and Suggestions

The use of diuretics in pediatric hydrocephalus patients is not alone but is combined with actions, namely *shunting* and/ endoscopic surgery. This study's potential drug-related problems (DTP) are too low a dose, too high a dose, drug interactions, and drug side effects. Drug side effects are the dominant potential DTP in the use of diuretics for pediatric hydrocephalus patients, namely 9 out of 17 patients. Medical therapy (diuretics) can be used before, after, and before & after the procedure in all types of hydrocephalus, but the reason for using diuretics can be specific due to variations in comorbid diagnoses, clinical data, and laboratory data for each patient.
Monitoring serum electrolyte levels such as sodium and potassium due to decreased serum sodium and potassium is a potential side effect of using diuretics for pediatric hydrocephalus.

Acknowledgement

After getting a proper ethical permit, this research was conducted in Dr. Soetomo Hospital Surabaya. The researcher fully bears research costs without any conflict of interest.

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