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Outcome of Choroid Plexus Cauterization with Endoscopic 3rd Ventriculostomy vs Ventricular Shunting in Management of Hydrocephalus Secondary to Neural Tube Defect

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Abstract: *Background:* Different surgical management of infants suffering neural tube defects (NTD) associated hydrocephalus were reported in the literature. Great debate whether combining endoscopic third ventriculostomy (ETV) with choroid plexus cauterization (CPC) is more effective than ventriculoperitoneal (VP) shuntfor management of congenital hydrocephalus secondary to neural tube defects ininfants younger than 1 year of age. *Purpose:* To evaluate and compare the therapeutic efficacy of ETV combined with CPC versus VP shunts in infants with infantile hydrocephalus associated with NTD. *Methods*: Thirty infants with infantile NTD associated hydrocephalus (de novo), were equally divided and randomly allocated to each intervention group either ETV/CPC or VP shunts). They were monitored for at least 6 months for any sign of raised intracranial pressure (rICP) and/or hydrocephalic metrics (fontanelle quality, HC, and ventricular size) were also documented and compared between two groups. *Statistical Analysis:* The association between intervention group and outcome was tested with Chi-square test and P=0.05 or less was considered statistically significant. *Results:* Of the total thirty patients included in the study, thirteen patients (43.3%) were male and seventeen were female (56.7%) with mean age of 80.3±11.5 days. Twenty patients (66%) were under 6 months of age. The overall success rate in 1-year follow-up was 54% and 60% for VP shunt and ETV/CPC, respectively; with the difference being not statistically significant. *Conclusion*: Combined ETV-CPC is considered a successful surgical option for treatment of infantile hydrocephalus associated with NTD; achieving success rate better than VPS implantation.

Keywords: Endoscopic Third Ventriculostomy, Choroid Plexus Cauterization, Neural Tube Defect, Hydrocephalus

1. Introduction

Hydrocephalusis described as abnormal accumulation of cerebrospinal fluid (CSF) within the brainventricles, as a result of disturbance of CSF formation, flow, or absorption and results in raised intracranial pressure (rICP) leading to abnormal increase in head circumference when occurring in infancy [1, 3, 15].

Neural tube defects (NTDs) are a group of conditions in which an opening in the spinal cord or brain remains from embryonic life resulting in group of disorders including spina bifida, an encephaly and encephalocele. Several factors are implicated in the etiology of hydrocephalus in children with myelomeningocele, like Arnold-Chiari-II malformation, a degree of aqueductal stenosis. The reported incidence ofNTD-associated hydrocephalus following postnatal surgical closure of the MMC defect ranges from 57% to 86% [1, 6, 9, 12].

Many theories tried to explain the pathophysiology of NTD-associated hydrocephalus but it is not fully explained; one theory claimed that inappropriate in-utero CSF outflow through the meningiocele defect leads to under development of normal CSF drainage pathways. These theories constitute the scientific background for the initial several researches both in animals and human aiming at assessment of role of prenatal surgical closure MMC, trying to initiate more hope

that antenatal or earlier surgical closure of the defect would result in better neurological outcome and reduce the incidence of postnatal hydrocephalus [1, 2, 6, 21].

Ventricular CSF shunt drainage, typicallyto the peritoneal cavity (VPS) was the standard surgical treatment for NTD-associated hydrocephalus. However, shunts carrya higher risk of infection and malfunctions that often necessitate surgical revisions. Several reports in the literature addressed the failure rate in cases of neural tube defects treated with VPS. 30% required at least 1 shunt revision and 22% required multiple revisions in case series of 67 children by *Liptak et al.* [24]. Other reports denoted shunt malfunction rates ranging from 14.7% to 64% and shunt infection rates ranging from 2.9% to 15.3% [2, 3, 7, 13, 14, 16].

ETV is an alternative method of hydrocephalus treatment and avoids many common infection and mechanical pitfalls associated with shunting. The reported success rates for ETV asa primary treatment of infantile hydrocephalus in the literature ranged from 29% to 37.5% [10, 11, 12, 20-23].

The first CPC was done by Walter Dandy in 1918 and then many case series followed him performing CPC as a stand-alone treatment of infantile hydrocephalus achieving moderate success all over the 20th century [11]. It has been reported that combining ETV with CPC has been shown to treat hydrocephalus more effectively than ETV alone [1]. Achieving a success rate of 76% (mean follow-up 19 months) in a study by *Warf et al.* [5] other reports demonstrated failure rates 28% in the ETV-CPC and 50% with VPS alone with mean follow-up 8.5 years [4].

Many causes attributed to failure of the ETV/CPC technique in management of NTD associated hydrocephalus; insufficient drainage, closed stoma or an enlarged stoma. This may be explained by criteria of MMC that increase the rate of treatment failure like; thickened floor of the ventricle, large massa intermedia, stenotic foramen of Monro, dysplastic ventricular anomalies, and prepontine cistern narrowing with crowded posterior fossa [5, 6, 9, 23].

Wide range of debate about decision-making on the most efficient treatment for NTD associated hydrocephalus; especially the first-line surgical intervention as regard failure rate and complications of each approach; despite the marvelous neurosurgical technical advancement. The goal of our current clinical trial was to comparethe efficacy of both VP shunt and ETV/CPC for the treatment of infantile HCP associated with NTD.

2. Patients and Methods

This randomized control trial was conducted at Neurosurgery Department Mansoura University between 2017 and 2018. The trial was approved by the institutional research board of Mansoura College of Medicine. This study was designed as a single center, unblind, two arm, active control, parallel group, with the aim to evaluate and compare therapeutic efficacy of two surgical modalities for infantile HCP associated with neural tube defect: ETV/CPC versus VP shunt.

Pediatric patients with hydrocephalus admitted to our neurosurgery center were screened for eligibility to be enrolled in the clinical trial. Thirty infants aged up to 1 year were eligible for participation in the trial with infantile hydrocephalus secondary to neural tube defect (de novo) confirmed by magnetic resonance imaging; whose parents or legal guardian signed informed consent form, were included in this study. Patients older than 12 months, patients with active previous shunt implantation, CSF infection, and severe anatomical brain distortion or multiloculated hydrocephalus were excluded from the trial.

Patients were randomly assigned in a non-stratified, simple 1:1 scheme generated at Mansoura University; assignments were concealed in sealed, opaque envelopes, which were opened in the preoperative holding area just before the patient entered the operating room. Patients were equally divided into 2 intervention groups (15 patients each); group (I) were managed surgically by insertion of VP shunt. Group (II) were managed surgically by ETV and CPC.

Detailed medical record for all infant patients was obtained from parents; then all of them were subjected to meticulous neurological examination & assessment. Neuro radiological assessment of hydrocephalic changes in all patients of both groups through Non-contrast computed tomography (NCCT) brain, MRI brain, craniocervical junction and whole spine for assessment of spina bifida and presence of other neural tube defects.

Preoperative variables "hydrocephalus metrics" including (age, fontanelle quality, head circumference (HC), and ventricular size) are collected and compared. As a reference HC was obtained in the standard fashion at the bedside, using a disposable tape measure in centimeter and percentile was calculated. Ventricular size was measured by members of the research team using the FOHR, Evans ratio; measured with CT or MRI brain. Fontanelle quality was classified into 1 of 2 types: A bulging fontanelle was above the level of the surrounding external table of skull. Absence of a bulging fontanelle when the fontanelle was palpated at or below the level of the surrounding external table of skull (flat or concave, respectively).

2.1. Interventions

1. Group (I): Ventriculoperitoneal shunt: VP shunt was done through the standardized protocol of our center using Integra® VP-shunt oblong valve.
2. Group (II): Endoscopic third ventriculostomy/choroid plexus cauterization: All patients were done through standard Kocher's burr hole using rigid endoscope (3.7 mm in diameter, Karl Storz), inserted in right frontal horn into third ventricle. ETV was done in all cases with ensuring continuity with subarachnoid space and complete opening of scarred membranes. Bilateral cauterization of choroid plexusfrom the foramen of Monro to its anterior terminus in the tip of the temporal horn. Septostomy was performed insome cases in order to gain access to the left lateral ventricle. At best, <70% of choroid plexus of each side was cauterized.

ETV/CPC treatment failure was defined as the need of any subsequent surgical procedure for hydrocephalus treatment. Shunt failure was defined as progressive head enlargement, anterior fontanel distension, new or worsening symptoms of rICP, new or worsening of abnormal eye findings, or progressive ventriculomegaly on neuroimaging.

2.2. Follow up Protocol

1. Postoperative follow-up CT brain within first 24 hours; to exclude postoperative sequelae.
2. Clinical evaluation for checking CSF leakage, rICP or tense pseudo MMC.
3. Regular outpatient visits at 2 weeks and 1, 3, 6, and 12 months after the procedure with head circumference measurements performed at each visit.
4. Full postoperative MRI study, including sagittal T2-weighted SPACE or FIESTA images; typically obtained at 6 months and at 1 year after surgery to assess evidence for ETV patency and to obtain detailed measurements for FOHR determination. In addition, the changes ($value_{6months}$–$value_{preoperative}$) in hydrocephalus metrics (fontanelle quality, HC, and ventricular size) were also documented and compared between groups.

2.3. Statistical Analysis

The collected data were coded, processed & analyzed using IBM SPSS Statistics Program (Version 21) for Windows. The appropriate statistical tests will use discipline analysis using mean±SD for parametric continuous data, median and interquartile range for non-parametric continuous data and numbers and proportions for description of categorical data. Qualitative variables as sex distribution and underlying disease were reported as proportion (percentage). Quantitative variables as age were reported as mean± standard deviation. The association between two qualitative variables as intervention group and outcome was tested with Chi-square test and P=0.05 or less was considered statistically significant.

3. Results

A total number of 30 patients suffered HCP associated with NTD were eligible for the study. Of the total number; 13 were males (43.3%) and17were females (56.7%) with the mean age of 80.3±11.5 days (range=1 days to 8 months). 20 patients (66%) were under 6 months of age. The patients' demographic data (age, sex, and associated anomalies) between two intervention groups was not statistically significant (P>0.05).

Pre-operative clinical examination demonstrated that all our cases in both groups had bulged AF, signs of rICP (sunset appearance, vomiting, and failure to thrive) and the HC was above 2SD in all cases. All our cases had HCP (by Evans' ratio, FOHR: more than 0.3 of both); with no statistical difference between both groups as regard the initial neuroradiological screening (P=0.589). Only one infant had occipital encephalocele in group I while 2 had encephaloceles in group II. All patients underwent repair of encephalocele and meningomyelocele prior to interventions for management of hydrocephalus (table 1).

Table 1. *Clinical and radiological hydrocephalic metrics in both groups; initial and postoperative follow-up 6 months and 1 year.*

Parameter		Group I (VPS)			Group II (ETV & CPC)		
		Preop.	Postop. (6 months)	Postop. (1 year)	Preop.	Postop. (6 months)	Postop. (1 year)
Clinical variables	Fontanelle quality:						
	Bulging	100%	55%	33%	100%	35%	10%
	Not bulging	0%	45%	67%	0%	65%	90%
	OFC:						
	Above 2SD	100%	60%	40%	100%	50%	30%
	Below 2SD	0%	40%	60%	0%	50%	70%
	Signs of ICT	100%	40%	20%	100%	30%	5%
Radiologic hydrocephalic metrics	Evans ratio >0.3	100%	70%	40%	100%	60%	20%
	FOHR >0.3	100%	70%	40%	100%	60%	20%

Clinical and Surgical Outcome

In group (I) cases; at 6 months and 1 year follow up: AF became tense in (55%, 33%) of cases respectively, OFC became below 2 SD in (40%, 60%) respectively, signs of rICT still noticed in (40%, 20%) of infants respectively, and MMC was repaired in all cases. Radiologically, ventriculomegaly (by Evan's ratio & FOHR) recorded in 70%, 40% respectively (Figure 1).

In group II cases; at 6 months and 1 year follow up: AF was tense in (35%, 10%) of cases respectively, HC still below 2SD in (50%, 70%) of cases respectively, and MMC was repaired in all cases with 40% had CSF leak, and signs of rICP still noticed in (30%, 5%) of cases respectively. Radiologically, ventriculomegaly (by Evan's ratio & FOHR) recorded in (60%, 20%) respectively (Figure 2).

At 1 year follow up group (I) cases achieved overall success 54%. With statistical significance was recorded between preoperative clinical data and 1-year follow-up data (p=0.049) indicating clinical improvement. While, group (II) cases achieved 60% success with statistical significance recorded between preoperative clinical data and 1 year follow up data (p=0.021). But there was no statistical significance between the two groups as regards clinical outcomes (p=0.618).

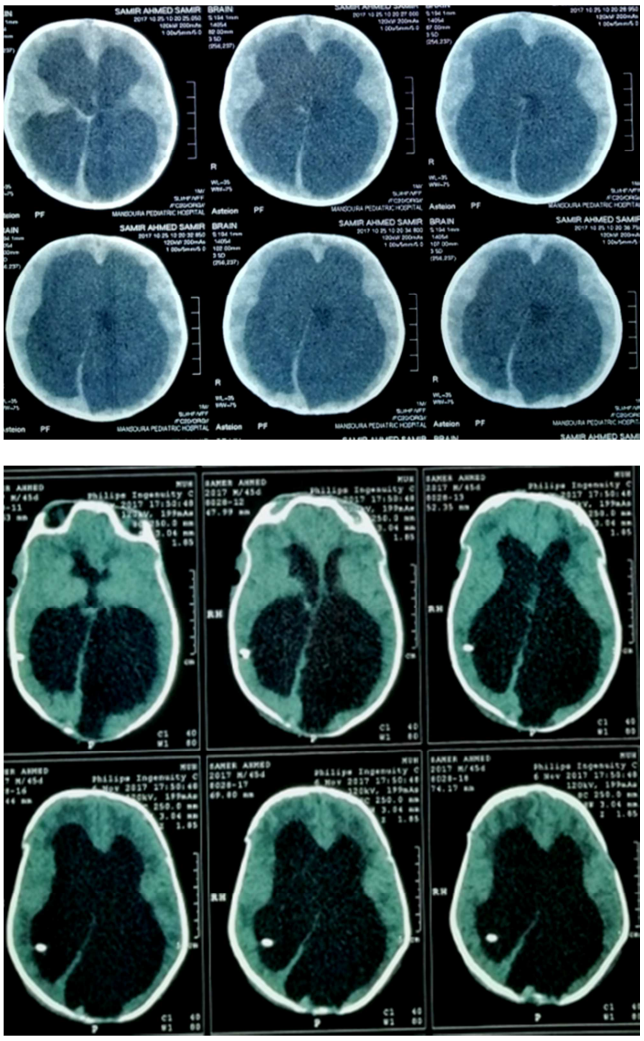
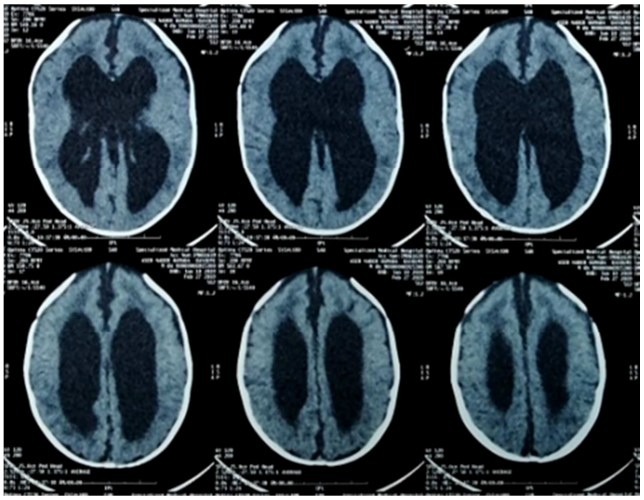


Figure 1. *2-month old male infant with congenital communicating hydrocephalus, managed by VP-shunt. Left: preoperative axial CT scan of brain in a 2 months old male infant with congenital communicating hydrocephalus. Right: postoperative follow up axial CT scan after VP shunt.*



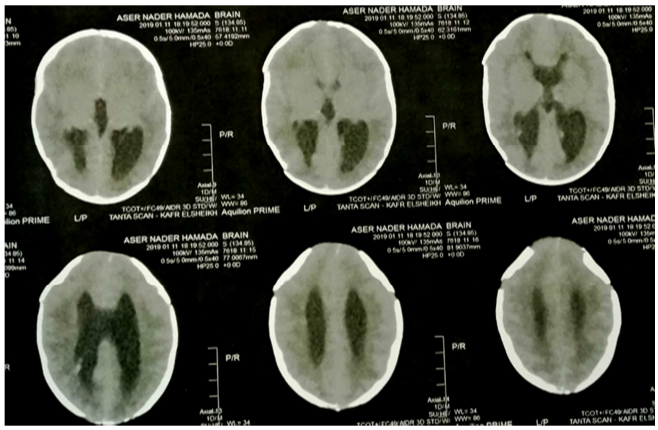


Figure 2. *3 months old female infant with congenital communicating hydrocephalus managed by CPC/ETV. Left: Preoperative axial CT scan of brain in a 3 months old female infant with congenital communicating hydrocephalus. Right: Postoperative follow up axial CT scan after CPC / ETV.*

We reported a heterogenous group of complications in our series: In group (I);7 cases were complicated (46%); one case of shunt over drainage resulted in bilateral chronic subdural hematoma that was managed by burr-hole evacuation and shunt ligation, two cases of CSF leakage from cranial wound due to proximal obstruction managed by shunt revision within first week of surgery. 2 cases of shunt infection managed by removal of shunts at 1 month and the other treated by CSF tapping and appropriate antibiotic administration. two cases of shunt malfunction (obstruction) treated by revision 1 year postoperative. In group (II): 6 cases complicated (40%) three cases of CSF leakage from the wound; one case was shunted two weeks later and other two cases shunted three month later. One case obstructed ETV stoma shunted three month later, two cases infected; both were shunted two and three month later. No statistical significance was recorded between the two groups (p=0.593) as regard the complications after 1 year follow-up (Table 2).

Table 2. *Perioperative and outcome parameters follow-up in both groups.*

Parameter	Group (I) (VPS)	Group (II) (ETV& CPC)
Total (n, %)	15 (100%)	15 (100%)
Successful (n, %)	8 (54%)	9 (60%)
Failed (n, %)	7 (46%)	6 (40%)
Overdrainage (SDH)	1	0
C. S. F leak	2	3
Obstruction	2	2
Infection	2	1
Operative time (average)	40 min	60 min
Postoperative complication	30%	10%

4. Discussion

Hydrocephalus is one of the most prevalent and debilitating associated clinical complications with the infants with NTDs. Ventricular CSF shunting, typically to the peritoneal cavity is the gold standard surgical management for NTD-associated hydrocephalus. Nevertheless, VPS revisions may often be indicated as it carries a risk of

infection and malfunction; as reported in some researches shunt malfunction rates ranging from 14.7% to 64% and shunt infection rates ranging from 2.9% to 15.3% [15, 21, 22].

Several reports in literature investigated the assumed risk factors predisposing to shunt malfunction [18, 19]. In a series of 170 children; higher incidence of shunt complications in first postoperative year reported in cases associated thoracic and cervical MMCs [16]. In other report of 189 hydrocephalic MMC patients; 64% first-shunt failure rate due to obstruction (70%), infection (24%), or loculated ventricles (4%) [17]. In our trial shunt failure reported in 7 cases (46%); shunt over drainage (6.6%) CSF leakage (6.6%), shunt infection (13.3%), shunt malfunction (obstruction) (13.3%).

Shunting complications as infection and obstruction or malfunction has been managed by introduction of ETV as an alternative method for treatment of NTD associated hydrocephalus. The first small trial was published in 1981 by *Natelson et al.*[21] who had a case series of 20 patients with NTD associated infantile hydrocephalus; 9 received a shunt with ETV and 11 received a shunt alone; No revisions were needed in the shunt-ETV group. Later in 1996; larger series patients managed by ETVs as a solo treatment for hydrocephalus was published. In 64 patients with NTD associated hydrocephalus; the reported overall ETV success rate was 72% [22]. Other studies reported a direct correlation of an ETV success rate with older patient age; and ETV was not contraindicated due to a prior VPS malfunction or infection [1, 12, 20, 23]. In another trials; the reported success rates for ETV as a primary treatment ranged from 29% to 37.5% [9, 10, 22, 23]. Long-term ETV outcomes after 5 years follow-up demonstrated ETV success rates of 53.3% and 64.3% when used as a first or second treatment modality, respectively [15].

Higher rates of ETV failure in first year of life are explained by many theories. Early onset of ETV failure due to insufficient CSF absorption by arachnoid villi in infants in presence of active CSF flow and then HCP would remain. ETV failure might be also caused by obstruction of the fenestrated stoma. This obstruction might result from either arachnoid membrane formation or gliosis which is more common in infants [1, 6, 12].

Combination of both ETV/CPC was established to enhance the efficacy and success rate of intervention. CPC can enhance the success rate of ETV through decreasing the CSF production based on the fact of the insufficient CSF absorption in infants [1, 5, 8]. *Warf et al.* [5] in a series of 93 East African infantile patients with MMC who received ETV-CPC, the procedure demonstrated a success rate of 76% with no need for additional surgery (mean follow-up 19 months). *Beuriatet al.* evaluated 70 patients with MMC: 32 with ETV-CPC, 20 with ETV-VPS, and 18 with VPS alone and the recorded failure rates were 28% in the ETV-CPC group, 35% in the ETV-VPS group, and 50% with VPS alone (mean follow-up 8.5 years) [4]. In another study, the combination of CPC increased the ETV success rate from 46% to 66% as well [15]. The combination of ETV/CPC was also reported to have success rate of about 52%–66% elsewhere [1, 8, 17]. The success rate in our series was 60% which is concomitant with the published series.

In our current single-center trial, an experienced neurosurgeon performed all the surgical procedures; the internal validity of the study was enhanced by assessment of the outcomes by different neurosurgeon. In our current study, we selected infantile hydrocephalus secondary to NTD which was studied by few reports in the literature. The overall success rate was 54% and 60% in VPS and ETV/CPC, respectively; which demonstrates the overall efficacy of ETV/CPC as the primary and sole treatment for NTD associated infantile hydrocephalus in comparison to the standard technique (VPS) in Egyptian population. ETV/CPC offered a valuable and successful surgical option with better clinical and radiological outcome than VPS, with fewer complications. The results are like those reported from Uganda that suggested that more than half of all infants presenting for initial treatment of hydrocephalus can be successfully treated in this way [1, 5, 8].

Technique of ETV/CPC still not familiar to many institutes and surgeons, which represented the main problem in considering it as the main procedure for management of NTD associated infantile hydrocephalus. Our recent trial strongly recommends (ETV & CPC) as a safe and effective method which can be used as a primary surgical modality for managing HCP secondary to neural tube defect as also recommended by other study series [5, 15, 20, 22].

Future further larger case studies trials will be necessary to validate these results in other centers and to investigate the long-term consequences of treating infantile hydrocephalus by ETV/CPC compared with shunt placement.

5. Conclusion

The combined use of ETV with CPC is advocated; based on our results; as a better surgical management option for congenital infantile hydrocephalus associated with neural tube defects rather than shunt implantation as it has lower rate incidence of subsequent infection and other complication. Using ETV/CPC reduce the financial burden of shunts and its long-term complication especially in developing countries. We recommend shunts for patients with high risk of ETV/CPC failure (prepontine cistern scarring, difficult creating stoma at the floor of third ventricle).

6. Ethical Consideration

After approval of the local Institutional Research Board (IRB), Faculty of Medicine, Mansoura University (MS/17.11.120), an informed and written consent was submitted from all parents of children who participated in this study. In addition, all the research participants are free not to participate or to leave the research at any time, without penalty and appropriate documents will clarify that issue.

7. Limitation of the Study

The main limitation of our current study is the small sample size, but we are planning to expand this series into larger sample size multi institutional Cohort to detect the true effect of both interventions.

Conflicts of Interest

There are no conflicts of interest.

Abbreviations Used in This Paper

NTD=Neural tube defect; CPC=choroid plexus cauterization; ETV=endoscopic third ventriculostomy; MMC=myelomeningocele; VPS=ventriculoperitoneal shunt; FOHR=frontooccipital horn ratio; rICP=raised intracranial pressure; HCP=Hydrocephalus; CSF=cerebrospinal fluid. HC=Head circumference.

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