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ORIGINAL ARTICLE

Does the timing of surgery affect short-term prognosis in newborn infants with meningomyelocele?

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Abstract

OBJECTIVE: To investigate the effect of postnatal primary repair surgery time on short-term (first 30 days) prognosis in newborns with Meningomyelocele (MMC).
METHODS: The study was conducted in the neonatal intensive care unit at a tertiary training and research hospital. The records of 41 MMC neonates were retrospectively reviewed. Demographic and clinical characteristics, surgical time, hospitalization and antibiotic duration, complications and associated anomalies were recorded.
RESULTS: There were 18 newborns in the early surgery (≤3 days) group and 23 newborns in the late surgery (>3 days up to 30 days) group.. There was no difference between groups in terms of birth weight, gestational week, head circumference, sex and type of delivery ($p > 0.05$). The length of hospitalization (17.2 ± 8.2 days vs 24.8 ± 16.1 days, $p > 0.05$) and antibiotic duration (11.8 ± 7.6 days vs 13.8 ± 10.1 days, $p > 0.05$) did not have significant difference. The number of neonates reoperated in the first 30 days was similar in early surgery group and in late surgery group (5 (27.7%) vs 6 (26.1%), $p > 0.05$). The number of patients requiring ventriculoperitoneal shunt was 9 (50%) in the early surgery group and 13 (56.5%) in the late surgery group. Surgical complications such as minor-major wound dehiscence, cerebrospinal fluid leakage, local infection, meningitis and ventriculitis were not statistically different between the groups (9 (50%) vs 8 (34.8%), ($p > 0.05$).
CONCLUSION: Surgical complications were not statistically different between the early and late surgery group, although the presence of surgical complications may be effective in the short-term prognosis of MMC.

Abbreviations:

MMC	- Meningomyelocele
VPS	- Ventriculoperitoneal shunt
CSF	- Cerebrospinal fluid
NTD	- Neural tube defect
USG	- Ultrasonography
CT	- Computed tomography
VP	- Ventriculoperitoneal
SPSS	- Statistical Package for the Social Sciences
CS	- Cesarean section
CNS	- Central nerve system
MOMS	- Management of myelomeningocele study

INTRODUCTION

Among the congenital anomalies of the central nervous system, neural tube defects (NTD) are the most common (Back & Plawner 2011). Although its frequency has decreased with the application of periconceptional folate treatment in developed countries, meningomyelocele (MMC) is still the most common neural tube defect in the world (Phillips *et al.* 2014). Onrat *et al.* have shown the incidence of neural tube defects seen in Turkey was significantly higher compared to that of developed countries, with 3 to 9 per 1,000 live births (Onrat *et al.* 2009).

Meningomyelocele, which is characterized by extrusion of the spinal cord into a sac filled with cerebrospinal fluid, develops in the first 26 days of pregnancy due to a posterior closure defect of the neural canal (Back & Plawner 2011). Although the incidence of MMC in developed countries is decreasing, its frequency also varies according to socioeconomic status, geographical region and race (Rehman *et al.* 2020). In addition to genetic factors, low socioeconomic status, alcohol use during pregnancy, isotretinoin, radiation exposure, antiepileptic (valproate and carbamazepine) medication use in pregnancy, hyperthermia, malnutrition, maternal folic acid, methionine, zinc and selenium deficiency are thought to play a role in NTD formation (Essien & Wannberg 1993; Martínez de Villarreal *et al.* 2006; Zeyrek *et al.* 2009). The most important risk factor identified in NTDs is folic acid deficiency. Preconceptional replacement of folic acid with 0.4 mg/day reduces NTD formation by 60-70% (Martínez de Villarreal *et al.* 2006).

MMC is a clinical condition that may cause lifelong symptoms, depending on the size of the defect, the level of injury to the spinal cord, and associated anomalies, such as disability and absence of sensation in the lower limbs, intestinal and bladder function disorders, and varying degrees of mental retardation (Bowman *et al.* 2009).

Although there are many studies on the timing of surgical repair of meningomyelocele (Naicker *et al.* 2023; Oncel *et al.* 2012)., the number of studies to prevent morbidity is still limited. The aim of this study was to evaluate the effect of timing of postnatal MMC surgery and accompanying clinical factors on short-term prognosis when prenatal surgery is not available and to evaluate the frequency of anomalies in our MMC patient population.

MATERIAL AND METHODS

This retrospective study was conducted in Adana City Training and Research Hospital with the approval of the local ethics committee (August 2019, 543). The medical records of the newborns diagnosed with MMC between June 30, 2015, and August 1, 2019, in the first 30 days of the postnatal period were systematically examined.

Demographic data, physical examination findings, other congenital anomalies (hydrocephalus, Chiari II malformation, pes equinovarus, renal anomalies, ventricular septal defects, scoliosis), defect localization and size data were recorded. The patients who were operated in the first 3 days of the postnatal period were determined as early surgery group and after 3 (up to 30) days as the late surgery group. Duration of hospital stay, antibiotic use, operation time, surgical and/or disease-related complications (wound infection, dehiscence, CSF leak, ventriculitis-meningitis, shunt infection, convulsion) were recorded. Echocardiography and abdominal-renal USG were performed preoperatively to identify additional anomalies in all patients. In the preoperative period, the patients were evaluated for hydrocephalus based on clinical findings and cranial ultrasonography (USG). Cerebral computed tomography (CT) was performed in patients with ventricular enlargement detected on cranial ultrasound. In cerebral CT, temporal horns larger than 2 mm, obliteration in cerebral sulcus and fissures, expansion of frontal horns and third ventricle were accepted as hydrocephalus. After the meningomyelocele operation, the patients were followed up for increased intracranial pressure, symptoms such as vomiting, abnormal head growth, bradycardia, and sun-setting sign.

VP shunting was inserted when there was clinical and neuroimaging evidence of hydrocephalus. If the MMC area was large intravenous antibiotic prophylaxis was administered to all patients 30 minutes before surgery and 72 hours postoperatively.

Statistical Analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical variables were summarized using counts and percentages, whereas continuous variables were summarized in mean ± standard deviation values. The student's t-test was performed to compare the means of the two groups. For non-normally distributed variables, the Mann-Whitney test was performed. A p-value less than 0.05 was accepted as statistically significant.

Tab. 1. Demographic characteristics, clinical features and treatment periods of MMC patients

	Early (n=18)	Late (n=23)	*p*
Birth weight, g	3251±528	3249±417	>0.05
Gestational weeks	38.3±1.4	38.2±2.0	>0.05
Head circumference, cm	37.5±2.8	37.0±2.4	>0.05
Cesarean section	16(88.9%)	15(65.2%)	>0.05
Female	11(61.1%)	10(43.5%)	>0.05
Antenatal Diagnosis	7(38.9%)	2 (8.7%)	<0.05
Apgar 5. min	9.0±1.0	9.0±0.7	>0.05
Hospitalization duration	17.2±8.2	24.8±16.1	>0.05
Antibiotic treatment duration	11.8±7.6	13.8±10.1	>0.05

RESULTS

Clinical and demographic data of 41 patients are summarized in Table 1. There was no statistical difference between the groups in terms of birth weight, gestational week, sex, and head circumference measurements. A total of 10 (24.4%) patients were referred to our hospital after being born in an external center. All patients (n = 5, 12.2%) who had ruptured MMC sac in the preoperative period were in the early surgery group. There were 9 (22%) patients diagnosed with antenatal meningomyelocele in total, the number in the early surgery group was significantly higher compared to the late surgery group (7 vs 2, $p < 0.05$). There was no difference in terms of hospitalization time (17.2 ± 8.2 vs 24.8 ± 16.1, $p > 0.05$) and duration of antibiotic use (11.8 ± 7.6 vs 13.8 ± 10.1, $p > 0.05$) (Table 1).

The defect size was larger in the late surgery group compared to the early surgery group, but this difference was not statistically significant (5.4 ± 1.1 vs 6.1 ± 2.3, $p > 0.05$) (Table 2). Flap closure was performed by the plastic surgery department because direct closure could not be performed in 5 patients. VP shunt was inserted in 22 patients, whereas in 13 (31.7%) of them, VP shunt was inserted concurrently with MMC surgical repair, and in 9 (22%) of them after the MMC surgical repair. One or more complications due to surgery occurred in 17 (41.4%) patients, but without any statistical difference in surgical complications between the early and late surgery group (9 (50%) vs 8 (34.8%), respectively). Similarly, return to operation room in 30 days was not statistically different in either group (5 (27.7%) vs 6 (26.1%)) (Table 2).

Total complications, additional anomalies, localization of meningomyelocele and neurological status of the study population are summarized in Table 3.

The most common anomaly accompanying MMC was hydrocephalus, seen in 22 (53.7%) patients followed by talipes equinovarus in 20 (48.8%) patients, and Chiari II malformation detected in 5 patients (12.2%).

The most common localization was the lumbosacral region (34.1%) and the lumbar region (26.8%). After MMC repair surgery, minor dehiscence was observed in 6 (14.6%), major dehiscence in 3 (7.3%), CSF leakage in 3 (7.3%), meningitis and ventriculitis in 3 (7.3%), and local infection in 2 (4.8%) patients (Table 3). No patients died in either group.

None of the mothers had received folic acid supplementation in the preconception period, and only

Tab. 2. MMC defect size and surgical data

	Early (n=18)	Late (n=23)	*p*
Defect size (cm)	5.4±1.1	6.1±2.3	>0.05
Defect size > 5 cm	9 (50.0%)	16 (69.6%)	>0.05
Patients with associated ≥1 anomalies	12 (66.7%)	16 (69.6%)	>0.05
Surgical procedure Direct closure Flap application	18 (%43) 17 (94.4%) 1 (5.6%)	23 (%57) 21 (91.3%) 2 (8.7%)	>0.05
Ventriculoperitoneal shunt Simultaneous Shunting Delayed Shunting	9 (50%) 5 (%27.7) 4 (%22.2)	13 (56.5%) 8 (%34.8) 5 (%21.7)	>0.05
Patients with ≥1 surgical complications	9 (50%)	8 (34.8%)	>0.05
Return to operation room in 30 days	5 (27.7%)	6 (26.1%)	>0.05

Tab. 3. Total complication, additional anomalies, localization of meningomyelocele and neurological status of the study population

		Total (n, %)	Early (n, %)	Late (n, %)
Total Complications	Minor dehiscence	6 (14.6)	2 (4.9)	4 (9.7)
	Major dehiscence	3 (7.3)	2 (4.9)	1 (2.4)
	CSF leakage	3 (7.3)	2 (4.9)	1 (2.4)
	Meningitis and ventriculitis	3 (7.3)	2 (4.9)	1 (2.4)
	Local infection	2 (4.8)	1 (2.4)	1 (2.4)
Accompanying Anomaly	Hydrocephalus	22 (53.7)	9 (21.9)	13(31.8)
	Talipes equinovarus	20 (48.8)	10(24.4)	10(24.4)
	Chiari II malformation	5(12.2)	2 (4.9)	3 (7.3)
	Hydronephrosis	3 (7.3)	1 (2.4)	2 (4.9)
	Ventricular septal defect	3 (7.3)	3 (7.3)	-
	Renal Agenesis	1 (2.4)	1 (2.4)	-
	Anal atresia	1(2.4)	-	1(2.4)
Location	Thoracic	7 (17)	3 (7.3)	4 (9.7)
	Thoracolumbar	9 (21.9)	4 (9.7)	5 (12,2)
	Lumbar	11(26.8)	6 (14.6)	5 (12,2)
	Lumbosacral	14(34.1)	5 (12.1)	9 (22)
Neurologic Status	Normal	5 (12.2)	3 (7.3)	2 (4.9)
	Paraparesis	17 (41.5)	6 (14.6)	11 (26.9)
	Paraplegic	19 (46.3)	9 (22)	10 (24.3)

CSF: Cerebrospinal fluid

22 mothers were supplemented from the mid-first trimester. There was no change in lower extremity motor strength in the preoperative and postoperative neurological examinations between the two groups. After primary repair surgery, VP shunt placement was performed in 9 patients and reoperation was performed due to complications in 2 patients.

DISCUSSION

The current approach to the timing of MMC surgical repair is in favor of early surgery (Naicker *et al.* 2023). However, it is necessary to have an appropriate time interval to obtain comprehensive information about the patient's clinical condition and to plan surgical reconstruction adequately. Prenatal diagnosis, detailed examination, and delivery of MMC patients in centers where early surgery can be performed is ideal. Approximately one quarter of our patients (10 patients) were born in an external center and were referred to our hospital at the post delivery period.

Cases with hydrocephalus constitute approximately 85-90% of patients with MMC (Samuels *et al.* 2009). In our study, the number of MMC patients who had accompanying hydrocephalus was 24 (58.5%). In 15% of cases accompanied by hydrocephalus at birth, signs of increased intracranial pressure (vomiting, dehiscence, sun-setting eyes, stretched fontanel) or brain stem dysfunction (apnea, sucking-swallowing disorder) may be observed. Chiari II malformation is common, especially in patients with brain stem dysfunction and urgent treatment is required (Lee *et al.* 2022). In our patients, we were only able to have CT scan of the brain as neuroimaging due to which we observed low Chiari II malformation rate. In patients with NTD, ventriculoperitoneal shunt (VPS) is needed in at least 80% of patients to prevent neurocognitive and motor dysfunction caused by the accompanying Chiari II malformation and hydrocephalus (Siahaan *et al.* 2023). But The timing of treatment of hydrocephalus accompanying MMC is still controversial due to factors such as infection, intellectual development, and shunt dysfunction. Early shunt placement has been reported to improve rapid intracranial pressure in the presence of severe hydrocephalus and to improve wound healing faster in the MMC repaired area, also shortening hospital stay, preventing CSF leakage and protecting the brain from progressive ventricular dilatation) (Miller *et al.* 1996; Chadduck & Reding 1988; Norkett *et al.* 2016). It is anticipated that shunt placement time may affect the rate of shunt infection, and that shunt placement reverses the flow of cerebrospinal fluid and allows fluid from the lumbar region to travel to the ventricles to facilitate infection. Therefore, infective complications were observed more

frequently in patients with simultaneous shunt placement with MMC repair than those with late shunt placement (Gurbuz & Yuksel 2020). Öktem *et al.* reported that VP shunt placement after MMC repair reduces wound infection, CSF leakage, and shunt infection in patients, in their study comparing VP shunt placement in the same and different sessions with MMC repair (Öktem *et al.* 2008). The approach to treating hydrocephalus days or weeks after MMC primary surgical repair is more often preferred. According to the literature, our hydrocephalus rate was lower. In our study, the number of patients requiring VPS placement was 22 (53.7%), of which 13 (31.7%) patients had concurrent, and 9 (21.9%) patients late VPS insertion; there was no statistical difference between the groups in terms of the number of patients requiring VPS. Early VPS placement was performed in patients with symptoms of symptomatic hydrocephalus and brain stem dysfunction (sucking swallowing disorder, apnea).

In our study, of the patients who developed surgical complications, 8 (44.4%) patients were in the early surgery group and 7 (30.4%) patients were in the late surgery group. CNS infections (ventriculitis and meningitis) were observed in 3 (7.3%) patients. In the literature, ventriculitis and meningitis independent of shunt infection have been reported as 4-12.5% in MMC patients (Ammirati & Raimondi 1987; Brau *et al.* 1990; Shehu *et al.* 2000).

The most common site of MMC is lumbar with 60-70% (Padmanabhan 2006). In a study increased diameter of meningomyelocele sac was associated with poor prognosis because of the greater amount of neural tissue within the sac. According to the literature, sac localization in babies with larger diameter of sacs did not change prognosis but increased infection rates and hospitalization duration (Eseoğlu *et al.* 2017). In our study, 26.8% of the localizations where MMC was seen, were in the lumbar region, and together with the lumbosacral region, it made up 60.9% of the cases. Defect size was greater in the late surgery group than the early surgery, but it wasn't statistically significant between two groups.

The debate about the optimal time for MMC repair has gained a new dimension with the increasing experience of intrauterine surgery. Since 1997, experimental procedures for prenatal repair of MMC have begun to increase the experience of fetal surgery (Yamashiro & Farmer 2021). Approximately 80% of NTDs require VPS in the postnatal period in order to prevent the destruction of hydrocephalus on brain tissue and to prevent deterioration of neurocognitive development (Adzick & Walsh 2003). Prenatal surgery provides significant improvement in hindbrain herniation and reduces the risk of Chiari II malformation (Kabagambe *et al.* 2018; Yamashiro *et al.* 2019). In initial studies, prenatal surgery was shown to reduce the need for VPS in the first year (Adzick *et al.* 2011). Tulipan *et al.*(2003) showed that they reduced the risk of hydrocephalus significantly (85.7% control vs. 54.8% study group) with prenatal surgery performed at 25 weeks of gestation or less, when compared to the traditional method. The safety and efficacy of intrauterine surgery were evaluated in a randomized controlled MOMS (Management of Myelomeningocele Study) study comparing prenatal and postnatal surgery. In this large multicenter study, intrauterine surgery reduced shunt requirement and improved motor outcomes at 30 months but was associated with maternal and fetal risks like preterm delivery and uterine dehiscence at delivery (Adzick *et al.* 2011). Intrauterine MMC surgery continues to be performed in experienced centers (Pastuszka *et al.* 2022), however postnatal traditional surgery is widely performed all over the world.

Early aggressive treatment approach in postnatal MMC surgery reduces early morbidity and mortality rates. Oncel *et al.* (2012) demonstrated that early surgery (<5 days) shortened hospital stay and antibiotic treatment time and reduced complication rates. In the long term, it is reported that cognitive functions are better, need for long-term care and incidence of urinary incontinence are reduced and early surgery positively affects neurogenic bladder prognosis, and thus urinary tract function. Preoperative rupture of MMC, postoperative dehiscence, and incidence of neurodevelopmental retardation 1 year after delivery showed improved outcome after immediate surgical intervention after birth (mean time of surgery after birth 1 h 30 min) (Pinto *et al.* 2009). In our study, there was a tendency to shorter duration of hospital stay and antibiotic treatment in the early surgery group. The number of prenatally diagnosed patients in the early surgery group was higher than those in the late surgery group. There were no significant differences between the groups in terms of the number of patients who developed surgical complications and total complications. The return to the operating room within 30 days was also similar in both groups. In our study, we believe the fact that all patients who developed preop MMC sac rupture being in the early surgery group (<3 days) was important in terms of not showing significant difference between the early and late surgery groups. In addition, low hydrocephalus rate in our cases is one of the factors that caused no difference in prognosis. The fact that the number of surgical complications and the number of patients requiring reoperation were similar in both groups may have led to a less favorable prognosis in the early surgery group than expected.

Our study had many limitations. Most importantly, the number of patients included in the study was limited, it was retrospective, and a single-center study. The inclusion of a single center in the study was an advantage as perioperative interventions and treatments were standard. Computed tomography and cranial USG could only be performed on our patients as cerebral imaging. In our study, we were able to evaluate short-term results and thus, one of the major limitations

of the study was the lack of evaluation of the long-term outcome of a clinical condition, especially for MMC which is a major cause of lifelong morbidity.

In conclusion, surgical timing of MMC remains important considering the morbidity risks. National policy on prenatal follow-up of pregnancy and folic acid supplementation should be formulated and implemented to prevent NTD development. In countries where MMC is frequently observed, intrauterine surgery is not yet widespread. Early surgery in the first 48 h of life is recommended in the literature for MMC patients. As in our study, antenatal diagnosis rate is low in newborns with MMC in developing countries. The number of centers that can perform early surgical intervention in these babies is also limited. Therefore, more sensitivity in postnatal care may reduce the development of secondary complications such as infection in these patients. In our study, surgical complications and the number of patients requiring reoperation were similar between the early surgery group and the late surgery group, for the reasons named in discussion. These results suggest that early discovery of surgical complications may be as effective as the timing of surgery in determining the short-term prognosis of MMC, which emphasizes the necessity of postoperative care and long term follow-up.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval for this study was received from the Adana City Training and Research Hospital Clinical Research Ethics Committee (August 2019, 543).

CONSENT FOR PUBLICATION

Not applicable.

COMPETING INTERESTS

No conflict of interest was declared by the authors.

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