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A randomized trial of the effects of platelet-rich plasma on postoperative complications after meningomyelocele sac repair

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Abstract. – OBJECTIVE: Meningomyelocele is a common congenital neural tube defect. To reduce complications, we need early surgery and a multidisciplinary approach. In this study, we administered platelet-rich plasma (PRP) to babies with meningomyelocele following corrective surgery to minimize cerebrospinal fluid (CSF) leakage and accelerate the healing of the immature pouch tissue. We compared these with a control group that did not receive PRP.

PATIENTS AND METHODS: Of the 40 babies who had surgery with the diagnosis of meningomyelocele, 20 patients received PRP after surgical repair, and 20 were followed up without PRP. In the PRP group, 10 of the 20 patients underwent primary defect repair, the other 10 underwent flap repair. In the group that did not receive PRP, primary closure was performed in 14 patients and flap closure in six.

RESULTS: In the PRP group, CSF leakage occurred in one (5%) patient, and none developed meningitis. Partial skin necrosis occurred in three (15%) patients and wound dehiscence in three (15%) patients. In the group that did not receive PRP, CSF leakage occurred in nine (45%) patients, meningitis in seven (35%), partial skin necrosis in 13 (65%), and wound dehiscence in seven (35%) patients. The rate of CSF leakage and skin necrosis in the PRP group was significantly ($p<0.05$) lower than that in the PRP group. Furthermore, wound closure and healing were also improved in the PRP group.

CONCLUSIONS: We have shown that PRP treatment of postoperative meningomyelocele infants facilitates healing and lowers the risk of CSF leakage, meningitis, and skin necrosis.

Key Words:
Meningomyelocele, Myelomeningocele, Neural tube defect, Spina bifida, Platelet-rich plasma, Cerebrospinal fluid.

Abbreviations

CSF, cerebrospinal fluid; EGF, epidermal growth factor; IGF-1, insulin-like growth factor; MMC, meningomyelocele; PF-4, platelet-derived factor 4, PDGF, platelet-derived growth factor; PRP, platelet rich plasma; TGF-β, transforming growth factor beta; VEGF, vascular endothelial growth factor.

Introduction

Meningomyelocele (MMC), a form of spina bifida, is the most common congenital anomaly of the central nervous system. It occurs in the first four weeks of pregnancy when the neural tube of the embryo fails to close. Neural tube defects may result in hydrocephalus, hindbrain herniation, and exposure to toxins in the amniotic fluid, with potential morbidity and mortality[1]. Both environmental and genetic factors contribute to the etiology of MMC. The risk of MMC is increasing in the events of maternal exposure to valproate, alcohol, carbamazepine, or isotretinoin, high fever, malnutrition, especially folate or B12 deficiency, diabetes mellitus, or obesity during pregnancy[2]. About 1,427 babies are born with spina bifida each year in the United States (1 in 2,758 births). Lower socioeconomic status and older maternal age are associated with higher neural tube defect incidence. The recurrence rate in subsequent pregnancies is about 2% to 3%[3]. More than 80% of babies born with MMC require a ventriculoperitoneal shunt for hydrocephalus decompression[4]. In 39% of the patients, functional motor deficits are at the affected level or higher, and more than half of these have functional motor deficits two levels higher than the affected level[5].

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The purpose of early closure of MMC defects is to preserve neural tissue function and prevent sepsis.

Platelet-rich plasma (PRP) is an autologous concentration of human platelets obtained from venous blood through proper centrifugation. It contains several growth factors, including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), platelet-derived factor 4 (PF-4), insulin-like growth factor (IGF-1), and transforming growth factor-beta (TGF-β)[1,6]. There are approximately 150-400 $10^3/mm^3$ platelets in the blood, and PRP contains between four and seven times this amount[7]. When whole blood is collected from a patient for the generation of PRP, an anticoagulant is added. This usually contains citrate and disrupts the coagulation cascade by binding to calcium ions[8]. PRP is used in orthopedic indications, wound healing, facial rejuvenation, hair restoration, and other conditions in which tissue renewal is central. The use of PRP for surgical and non-surgical wounds is advantageous, especially in patients with poor wound healing, poor blood supply, and slow cell turnover, and in cases where rapid healing is required.

In this study, we assessed whether the administration of PRP during the MMC pouch repair procedure can improve infant outcomes. This was measured by its ability to reduce CSF leakage, meningitis, local infection, skin necrosis, wound dehiscence, and hydrocephalus, and to accelerate the healing of the underdeveloped pouch tissue. These outcomes were compared with those of an MMC control group who did not receive PRP during surgery.

Patients and Methods

40 infants with a diagnosis of MMC who were operated on at our neurosurgery clinic between February 2020 and May 2021 were included in this study. PRP was administered to 20 of the patients, and 20 were followed up without PRP. All babies were born at term and fed with breast milk. All infants in the study were followed up in the neonatal intensive care unit. The mean birth weight was 2,990 grams. In the PRP group, 10 of the 20 patients underwent primary defect repair and 10 underwent flap repair. In the non-PRP group, 14 patients underwent primary closure and 6 underwent flap closure. All operations were performed under general anesthesia. Blood was taken from each patient and the platelets were separated by centrifugation at 3,200 rpm for five minutes in a 2-cc whole blood centrifuge device. The plasma was separated with the buffy coat layer. During MMC sac repair, a neural plate was formed and the dura was then made using opposing flaps from the fascia. After hemostasis was achieved, the defect was repaired and PRP was applied from the wound edge. The prepared PRP was applied to the dura and pouch repair and under the skin flap wound line (Figure 1).

Statistical Analysis

Descriptive statistics were expressed as means, standard deviations, medians, ranges, frequencies, and ratios. The distribution of variables was measured with the Kolmogorov-Smirnov test. Independent sample *t*-tests and Mann-Whitney U tests were used for the analysis of independent quantitative data. Chi-square tests were used in the analysis of qualitative independent data, and the Fischer's test was used when the Chi-square test conditions were not met. A *p*-value below 0.05 was accepted as statistical significance. Analyses were performed using SPSS 27.0 software (IBM Corp., Armonk, NY, USA).

Results

PRP was used with 20 of the 40 patients in our sample who were born with MMC and operated on. Of the 40 patients, 20 were male, and 20 were female. Birth weights ranged from 1,990 to 3,840 grams. The skin defect diameter of the MMC ranged from 3 to 10 cm^2. Operation times ranged from 40 to 150 minutes. During the operations, total blood loss ranged from 10 to 60 ml. The defect level of the 40 MMC patients was the lumbar region in 22 patients, the lumbosacral region in two patients, and the thoracolumbar region in 16 patients. All patients were term deliveries. CSF leakage occurred in 10 patients. Nine (45%) of these were from the non-PRP group and one (5%) was from the PRP group. Local infection was seen in three patients, two (10%) of whom were in the non-PRP group and one (5%) from the PRP group. Partial skin necrosis was seen in 16 patients, 13 (65%) from the non-PRP group, and three (15%) from the PRP group. Total skin necrosis was not observed in any of the patients. Wound dehiscence occurred in 10 patients, seven (35%) from the non-PRP group, and three (15%)

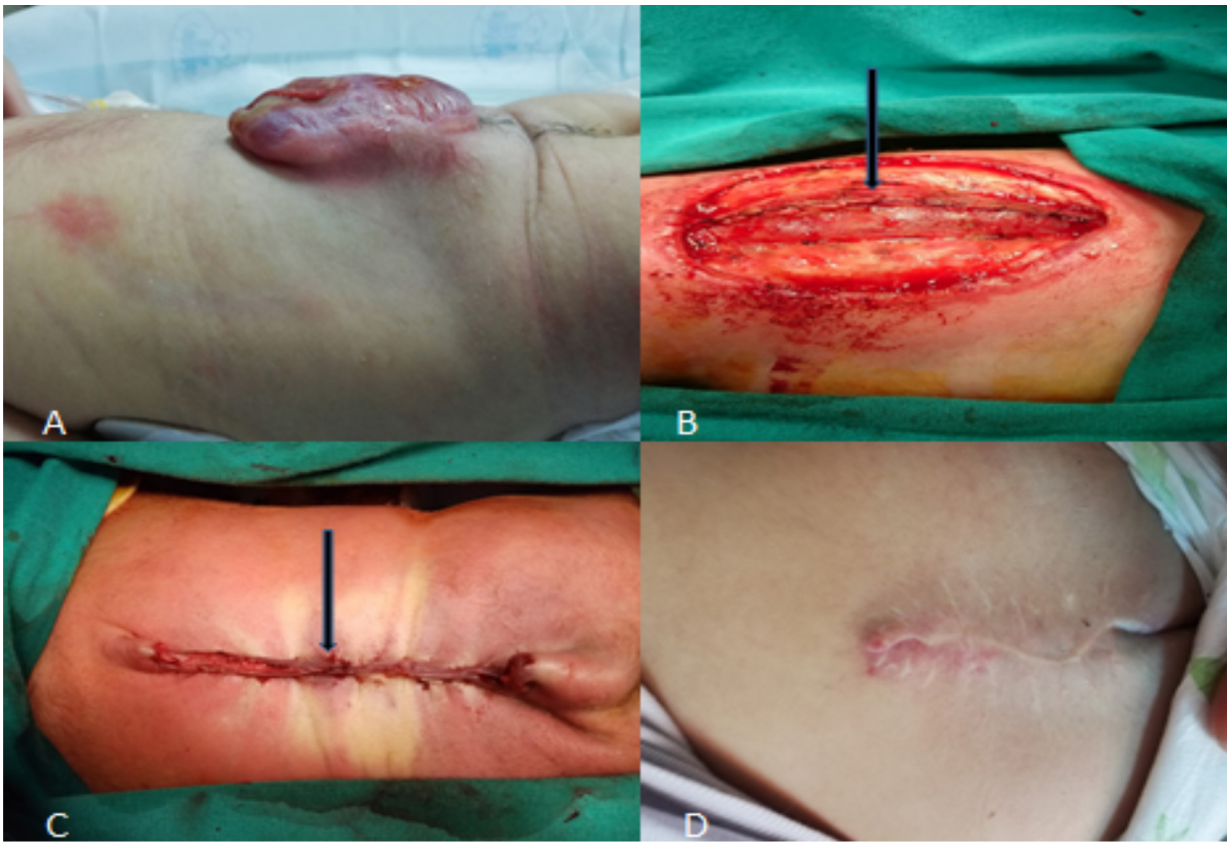

Figure 1. Pictures of the patient diagnosed with Lumbar Meningomyelocele, to whom we applied platelet-rich plasma (PRP) during the operation. **A**, Before the operation. **B**, During the operation, spread some platelet-rich plasma (PRP) over the dura. **C**, After the operation, some platelet-rich plasma (PRP) was also infused under the skin. **D**, 3 months after the operation.

from the PRP group. Hydrocephalus was seen in 23 patients, 15 (75%) from the non-PRP group and eight (40%) from the PRP group (Figure 2). Of the 20 non-PRP patients, the skin defect was closed primarily in 14 (70%) and repaired with flaps in six (30%) patients. Half (10, 50%) of the 20 patients administered PRP, had their skin defects closed primarily, and half (10, 50%) had their skin defects repaired with flaps (Table I).

Discussion

MMC is a variant of spina bifida and the most common form of neural tube defect[9]. It is a serious condition with lifelong complications that greatly affect the quality of life[10]. MMC manifests in many ways, including weakness, hypoesthesia, paraplegia, anesthesia, bowel/bladder dysfunction, spinal and lower extremity deformities, and hydrocephalus[9]. The mortality rate in spina bifida patients is approximately 1% per year between the ages of 5 and 30. The higher the lesion, the higher the morbidity and mortality. One of the biggest risk factors for neural tube defects is folic acid deficiency in the mother while the infant is in utero. It has been reported that daily intake of folic acid at a dose of 0.4 mg reduces the rate of neural tube defects in newborns by 60%-70%[11].

When the baby is born, the lesion should be carefully evaluated with the baby on its side or face down. It should be covered with a moist dressing or plastic wrap to prevent heat loss. The MMC should be closed as soon as possible, ideally within the first 48 hours after birth, in postnatal surgery to reduce the risk of infection[12,13]. The clinical features of MMC depend on the level of damage and the presence of hydrocephalus and brain anomalies. Newborns may remain asymptomatic until up to six weeks old. If there is hydrocephalus, clinical manifestations of increased intracranial pressure (increased head circumference, irritability, lethargy, and a limited upward gaze) may be observed[14].

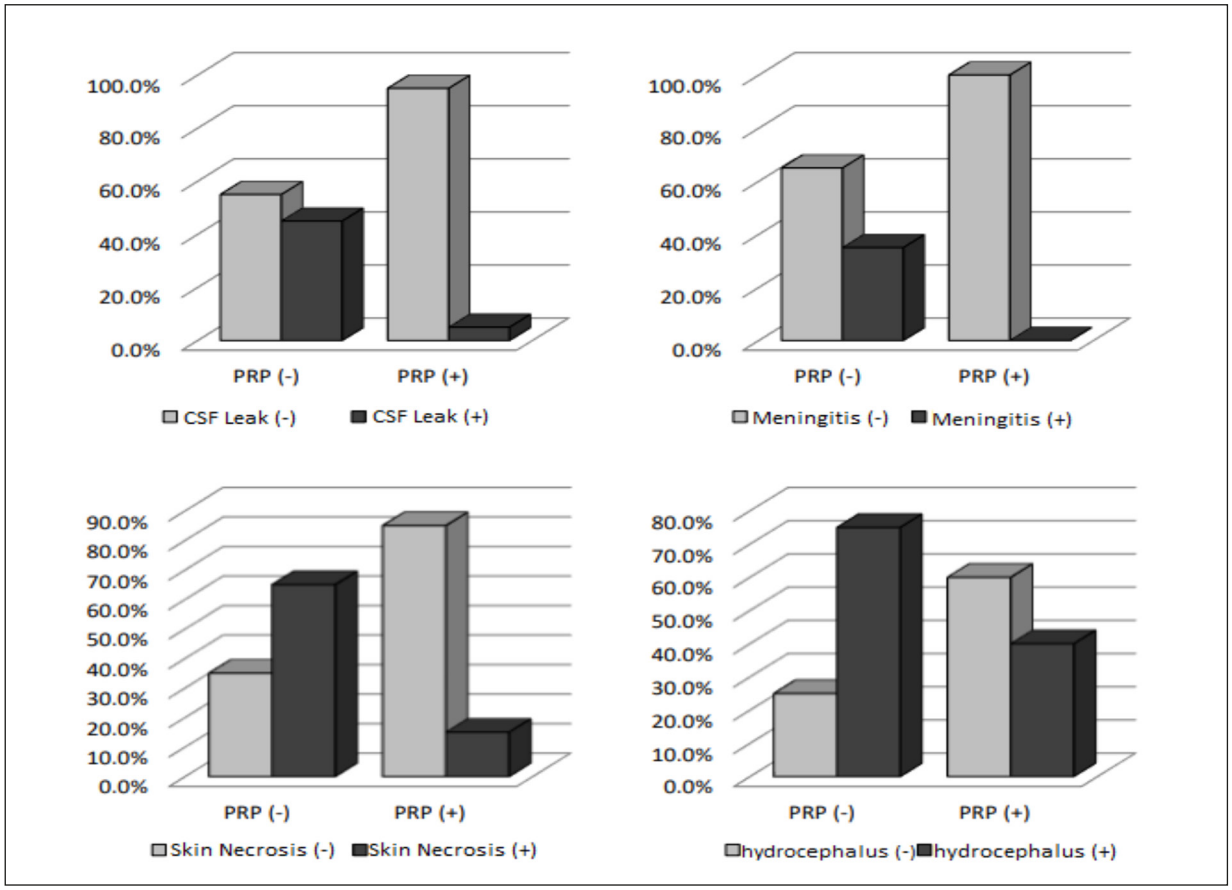

Figure 2. Rates of cerebrospinal fluid leakage, meningitis, skin necrosis, and hydrocephalus in post-surgical repair meningomyelocele patients receiving, or not receiving, platelet-rich plasma (PRP). CSF, cerebrospinal fluid leakage; PRP (+), patients receiving platelet-rich plasma; PRP (−), patients not receiving platelet-rich plasma.

Long-term complications associated with MMC include learning difficulties and cognitive impairments, seizures, paralysis and loss of sensation below the lesion site, decreased mobility due to muscle weakness, neurogenic bladder and frequent urinary tract infections, intestinal dysfunction, pressure ulcers due to sensory impairment, scoliosis, contractures, hip dislocation, and other orthopedic problems[14].

MMC requires spinal cord repair, dural closure, and reconstruction of the skin defect. Anatomical repair of these structures is vital to the reduction of complications. The most common early complications of MMC are CSF leakage, meningitis, hematoma, seroma, wound infection, wound dehiscence, and skin necrosis.

PRP therapy was introduced into clinical practice in the 1980s and 1990s. It has gained popularity in regenerative medicine and other specialties, with applications extending to cardiology, dentistry, and maxillofacial surgery. In the latter field, Marx et al[8] evaluated the effects of PRP on bone maturation rates and bone density in bone graft reconstructions of mandibular continuity defects. They found that adding PRP to grafts increased bone formation[8]. PRP therapy has become an extremely attractive treatment within sports medicine because of its effects on tissue regeneration and repair, which can speed up the recovery time of injured athletes, allowing them to return to sports. PRP has been found beneficial for tendon, ligament, muscle, and cartilage healing and is used as an injectable biologic used for strengthening[15]. The healing benefits of PRP are useful in the treatment of damaged tendons, ligaments, and cartilage that have poor blood circulation and/or slow cell turnover. The three phases of wound healing are inflammation, proliferation, and remodeling. The initial inflammatory phase is characterized by hemostasis, in which platelets provide the material for clot formation and release growth

Table I. Demographic characteristics of postsurgical repair meningomyelocele patients with and without platelet-rich plasma (PRP).

		PRP (–)			PRP (+)			*P*
		Average ± ss/n-%		Median	Average ± ss/n-%		Median	
Gender	Women	13	65.0%		7	35.0%		0.058χ^2
	Man	7	35.0%		13	65.0%		
Birth weight		3,195 ± 436		3230	2,806 ± 477		2,750	**0.011***t*
Gestational week	Term baby	20	100.0%		20	100.0%		1.000χ^2
Defect diameter (cm^2)		5.20 ± 1.32		5	5.30 ± 1.59		5	0.813m
Operation time (min)		73.00 ± 31.43		60	78.75 ± 39.37		55	0.764m
Blood loss (ml)		32.00 ± 8.49		30	37.00 ± 14.36		33	0.172m
MMC level	Lumbar	12	60.0%		10	50.0%		0.750χ^2
	Lumbosacral	0	0.0%		2	10.0%		0.487χ^2
	Thoracolumbar	8	40.0%		8	40.0%		1.000χ^2
CSF leakage	(−)	11	55.0%		19	95.0%		**0.003**χ^2
	(+)	9	45.0%		1	5.0%		
Meningitis	(-)	13	65.0%		20	100.0%		**0.004**χ^2
	(+)	7	35.0%		0	0.0%		
Local infection	(−)	18	90.0%		19	95.0%		1.000χ^2
	(+)	2	10.0%		1	5.0%		
Skin necrosis	(−)	7	35.0%		17	85.0%		**0.001**χ^2
	(+)	13	65.0%		3	15.0%		
Wound dehiscence	(−)	13	65.0%		17	85.0%		0.144χ^2
	(+)	7	35.0%		3	15.0%		
Hydrocephalus	(−)	5	25.0%		12	60.0%		**0.025**χ^2
	(+)	15	75.0%		8	40.0%		
Primary closure	(−)	6	30.0%		10	50.0%		0.197χ^2
	(+)	14	70.0%		10	50.0%		

χ^2, Chi-square test; m, Mann-Whitney U test; MMC, meningomyelocele; PRP, platelet-rich plasma; CSF, cerebrospinal fluid leakage; PRP (+), patients receiving platelet-rich plasma; PRP (−), patients not receiving platelet-rich plasma, *t*, *t*-test.

factors that activate and attract inflammatory cells such as neutrophils and macrophages. The proliferation phase is characterized by the construction of an extracellular matrix through granulation, contraction, and epithelialization. Finally, the remodeling phase focuses on the production of collagen and scar tissue. Physiological progression through these stages of wound healing is governed by growth factors and cytokines, which are released and modulated by components of the blood that are prolific in PRP[16].

Gender distribution, the average duration of the reparative operation, the amount of bleeding, and the primary closure rate did not differ significantly between the PRP and non-PRP groups ($p>0.05$). The average birth weight was significantly lower in the PRP group than in the non-PRP group ($p<0.05$). There was a significant difference in MMS region distribution between the groups ($p>0.05$).

Rehman et al[17] found that the most frequent complication resulting from CSF leakage is meningitis in 16 (11%) and then seven (5%) cases in a separate trial. Demir et al[18] have reported infection rates of 11%. Other research[17] found infection in 13.5% of patients and CSF leaks in 23.7%, with many of these patients eventually requiring CSF diversion. Preoperative neurological deficits were

observed in 87 (58%) patients and deterioration was observed in eight (5.4%) patients with initially normal strength. Five (3.3%) patients developed paraplegia, and three (2%) had paraparesis after surgery.

Demir et al[18] studied MMC defect repair and found that 18 (16.4%) of 91 newborns developed meningitis/shunt infections, and 12 (11%) developed surgical wound infections. Open neural placodes not covered by any pseudomembrane (myeloschisis), the use of external ventricular drainage, and flap transposition were deemed important relative risk factors for the development of meningitis. It was observed that deep surgical wound infection was not correlated with operation time or wound surface area[18]. Lien et al[19] found a rate of skin flap dehiscence of 20%, skin flap dehiscence rate was 4%, a rate of skin flap necrosis of 2%, rates of CSF leakage and meningitis of 0%, and a rate of skin and subcutaneous tissue infection of 7%[19].

In our study, the rate of CSF leakage in the PRP group was significantly (p<0.05) lower than in the non-PRP group. The literature supports this finding. The meningitis rate in the PRP group was significantly (p<0.05) lower than in the PRP group. However, the meningitis rate in the non-PRP group was higher than that observed in the literature, while the rate in the PRP group was lower. The rate of local infection did not differ significantly (p>0.05) between the groups. The rate of local infection in both groups was reflective of the rates seen in the literature. The rate of skin necrosis in the PRP group was significantly (p<0.05) lower than in the non-PRP group. The rate of skin necrosis in the non-PRP group was higher than that in similar studies, while the rates in the PRP group were similar to those in other studies. The rate of wound dehiscence did not differ significantly (p>0.05) between groups. The rate of wound dehiscence in the non-PRP group was higher than that in similar studies, while our PRP group rates of wound dehiscence were in accordance with those in other studies[15,16].

Khan et al[20] conducted a study of PRP treatment with MMC in which 79 MMC patients had a defect size of <5 cm^2, 68 had a defect size of 5-10 cm^2, and nine patients had a defect size of >10^2 cm. Infection of the surgical wound occurred in 21 of their patients (13.5%), while wounds healed satisfactorily in 135 patients (86.5%). CSF leakage occurred in 37 patients (23.7%) and completely healed in 119 patients (76.3%). Postoperative fever was observed in 141 patients (90.4%), while 15 patients (9.6%) remained fever-free. Postoperative hydrocephalus was observed in 35 patients (22.4%) compared to 121 patients (77.6%) without postoperative hydrocephalus[20]. Defect diameters did not differ significantly (p>0.05) between our PRP and non-PRP groups. The size of the defects in our study was roughly equivalent to those described by Khan et al[20]. The rate of hydrocephalus in our PRP group was significantly (p<0.05) lower than in the non-PRP group. Hydrocephalus rates in both groups were higher than have been found in other studies[9,13,19,20].

Conclusions

MMC affects the health and quality of life of sufferers in infancy, childhood, adolescence, and adulthood. It is a challenge for individuals, families, and society. Early surgery and a multidisciplinary approach offer the best chance of good outcomes and survival. PRP has been found useful in many areas of medicine. Our study has demonstrated that PRP can effectively reduce CSF leakage, meningitis development, and skin necrosis in MMC infants, for whom early repair and healing are especially important. We hope that this study will provide a useful contribution to the literature and clinical practice with this patient group.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

This study was conducted in accordance with the tenets of the Declaration of Helsinki 1964. The study was approved by the Van Yüzüncü Yıl University Clinical Research Ethics Committee Presidency of (No.: 22.06.2021-08).

Informed Consent

The authors declare that this report does not contain any personal information that could lead to the identification of the patients and/or volunteers. Signed statements of informed content to participation and publication were obtained from participants before the study.

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