Advantages of MesoRex shunt compared with distal splenorenal shunt for extrahepatic portal vein occlusion in children

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Master's in Medicine in Paediatric Surgery
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Contents

Declaration

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Abstract

Background:

Portal hypertension (PH) is a common complication of chronic liver or portal vein pathology in children. It is defined as a pathological increase in the pressure of the portal venous system. There are two leading causes for PH in children, pre and post sinusoidal liver disease and pre-hepatic non-cirrhotic portal vein obstruction, also referred to as extrahepatic portal vein obstruction (EHPVO). Management of EHPVO is primarily surgical, with surgical portosystemic shunting representing a safe and effective method for the long-term management of portal hypertension in the paediatric population. Although different shunts have been proposed for EHPVO, both the MesoRex shunt and distal splenorenal shunt have shown the most promising results as effective and definitive approaches to alleviating EHPVO.

Aim:

To review surgical management of extrahepatic portal vein obstruction (EHPVO) at Red Cross War Memorial Children's Hospital (RXH) and compare MesoRex shunt (MRS) with distal splenorenal shunt (DSRS). To determine and compare the shunt success rate, defined as long-term patency at 24 months of the MesoRex shunt and distal splenorenal shunt, the factors that could have influenced the patency of the Rex vein and the effect of these procedures on the long-term synthetic liver function.

Methods:

This study followed a retrospective study design, conducted at a single centre documenting pre- and post-operative data in 21 children, 14 MRS and 7 DSRS, All patients presented to RCWMCH with EHPVO over an 18-year period (2001-2019) were eligible for inclusion either for MRS or DSRS. Exclusion criteria included patients lost to follow up, patients who had atypical shunts not falling into either the DSRS or MRS operation and those with insufficient or missing clinical records over 18 years. Details of patient demographics included age, gender, aetiology, preoperative symptomatology, Rex vein patency, history of neonatal umbilical vein catheterization (UVC), age at shunt surgery and shunt patency were compiled over an average

follow up period of 11 years (2-18). Bloodwork analysis included albumin, prothrombin time (PT), partial thromboplastin time (PTT), International normalized ratio (INR), fibrinogen, total bilirubin, liver enzymes and platelets prior to and two-years-post shunt surgery. Rex vein patency was assessed preoperatively. Statistical significance was determined at $P<0.05$ following a two-tailed t-test.

Results:

Out of 23 patients presenting with EHPVO, two children lost follow up immediately after diagnosis and were excluded. Twenty-one patients were operated on and followed up long term, with 14 patients (66%) in the MesoRex shunt group and seven patients (33%) in the distal splenorenal shunt group. Fourteen of the 15 MesoRex procedures (93%) were deemed successful in comparison to five out of seven (71%) in the distal splenorenal shunt group. Significant improvements were seen in MesoRex shunt recipients regarding the levels of Albumin, PT, PTT, and platelets. The other liver functions measured, including INR, fibrinogen, total bilirubin, ALT, AST, GGT, and ALP, were within the normal physiological range. The distal splenorenal shunt cohort only yielded a significant improvement in the platelet count, increasing from a mean value of 100 to 149.83 ($P = 0.02$). Out of those who showed successful surgical intervention in the long term (14 in MRS and 5 in DSRS cohorts), only one child with MRS experienced 2 episodes of variceal bleeding despite having patent shunt with adequate flow (more than 20cm/second). However, no further surgical intervention was needed, and the bleeding resolved spontaneously.

Conclusion:

This study highlights that MesoRex shunt has a better long-term outcome in extra hepatic portal vein obstruction and improves liver synthetic function and must be considered as the primary definitive intervention. DSRS does control variceal bleeding due to extra hepatic portal hypertension but may have a negative effect on liver function on long term and is only considered when MRS is not technically feasible or as a salvage procedure when MRS fails.

Keywords:

Portal Hypertension, Extrahepatic portal vein occlusion, Variceal bleeding, Portosystemic shunts, Distal Splenorenal shunt, MesoRex shunt.

Chapter 1: Literature Review

Introduction

Portal hypertension (PH) is a common complication of chronic liver and portal vein pathology in children. It is defined as a pathological increase in the pressure of the portal venous system (1). There is no clear consensus on the exact normal portal pressure for the different age groups. Nevertheless, an agreement exists that any increase beyond 11 mmHg is considered pathological and, once established, will have significant morbidity and mortality (2).

There are two leading causes for PH in children, pre and post-sinusoidal liver disease, and pre-hepatic non-cirrhotic portal vein occlusion, also referred to as extrahepatic portal vein obstruction (EHPVO) (3). Omphalitis, neonatal sepsis, repeated abdominal infections, sepsis, abdominal surgery in childhood, neonatal umbilical vein catheterisation, and trauma are known to predispose to EHPVO (4). However, the underlying aetiology of EHPVO in children remains poorly comprehended.

Management of EHPVO in the paediatric population is primarily medical, and control of variceal bleeding by sclerotherapy or banding are essential initial management strategies. Shunts are reserved for those who need them, with non-physiological and physiologic shunts representing a safe and effective method for the long-term management. Several cohort studies have demonstrated significant improvements in growth parameters following shunt surgery, and thus surgical intervention should be actively considered in selected children presenting with PH (5). Although different shunts have been proposed for EHPVO, both the MesoRex shunt and distal splenorenal shunt have shown the most promising results as effective and definitive approaches to alleviating EHPVO due to prehepatic portal vein occlusion. These procedures can reverse PH manifestations with low rates of postoperative morbidity and mortality (6).

Despite the vast number of advances that have been made regarding the treatment of EHPVO, there is limited literature comparing the different surgical management methods of extra hepatic portal hypertension (EHPH) in the paediatric population. A literature search revealed only a single study by Lautz et al. (2013) that compared the MesoRex and distal splenorenal

shunts in the management of EHPH in children (7). Hence, our study aimed to determine and compare the shunt success rate, defined as shunt patency at 24 months of the MesoRex shunt and distal splenorenal shunt. The factors that could have influenced the patency of the Rex vein and the effect of these procedures on the long-term synthetic liver function will also be discussed.

Aetiology

Almost half of children presenting with EHPVO have an idiopathic cause. Most patients present initially with nearly normal liver function only to deteriorate with time indicating that this condition is not completely benign(8-10), however, the metabolic implications of this condition on the liver are not widely explored. In addition, the current literature lacks evidence on whether the metabolic implications of EHPVO that do occur in some patients are direct effects of the impaired portal flow or a result of repeated upper gastrointestinal (GIT) bleeding.

The deranged liver function that underly EHPVO are referred to as the portal biliopathy.
The aetiology of portal biliopathy is proposed to arise from the obstructive impact of the portal vein cavernoma at the porta hepatis. This results in long term cholestasis, with mildly elevated transaminases (11, 12). An additional hypothesis suggests that a prolonged acceleration in the liver ageing process, as a result of a relatively impaired blood supply, leads to a subsequent rise in serum bilirubin (8). The reduced portal hepatic flow, a prominent characteristic of EHPVO, can have a significant influence on hepatocyte functions (13, 14). A large amount of research has proven this through ligation of the portal vein in rodent models. Although the hepatic arterial supply was maintained, the rodent models that had undergone portal vein ligation suffered liver atrophy, growth restriction, and a failure to thrive (15). This emphasises the importance of the portal blood for the growth and function of the liver parenchyma, in addition to general somatic growth. Furthermore, even a partial ligation of the left branch of the portal vein has been shown to result in liver atrophy through hepatocyte volume loss and apoptosis (15). A prospective study of 61 paediatric patients with EHPVO observed both impaired liver growth and physical growth stunting in (51%) across the cohort (16).

Several explanations have been proposed for the implications of the reduced hepatic flow in EHPVO. Firstly, it is suggested that the splanchnic area represents an endocrine system that targets the liver. The reduced portal venous flow deprives the liver of the stimulatory effects

of these splanchnic hormones (14). Substantial evidence has been provided for this hepatotropic effect of portal venous blood across the current literature (14, 17, 18). Secondly, it has been demonstrated that numerous hepatotropic active substances that regulate both liver growth and function originate in the intestine and pancreas. These substances are then carried to the target cells of the liver, the hepatocytes. The transportation of these active substances to the liver relies on the portal blood; hence a reduced flow significantly hinders the functioning of the hepatocytes (14).

The physiological implications of reduced portal blood flow is found to be responsible for the abnormal PT observed in several EHPVO patients (19). A study of 97 paediatric patients by Sherlock and Webb provided evidence that children who have EHPVO for longer durations tend to present with variable grades of liver dysfunction (20).

Diagnosis

The symptoms associated with EHPVO are twofold: those secondary to diminished portal blood flow to the liver and those resulting from the portal hypertension and spontaneous portosystemic shunting.

In contradiction to the widely held belief that the liver function of children with EHPVO is normal, more in depth evaluation is revealing that liver function is broadly affected. The deprivation of portal blood to the liver can influence the hepatic parenchymal functions in patients with EHPVO; more so in patients with prolonged portal hypertension. The liver function can be affected to various degrees. The disruption to this organ is dependent on the duration and degree of portal vein obstruction, with total occlusion of the vein being worse than if cavernomatous transformation bypassing the occlusion has occurred (11, 21). This is thought to be an early manifestation, though subtle that might not get observed in otherwise well child. In this instance, a well-developed collateral circulation between the cavernoma and the intrahepatic portal system results in a less pronounced hepatic dysfunction(22). However, hepatic synthetic function remains affected in EHPVO. This usually presents as impaired coagulation characterised by an elevated serum PT, PTT, INR, and low levels of fibrinogen. In addition, the detoxification role played by the liver can be hindered, resulting in elevated serum ammonia (23).

The clinical diagnosis of EHPH is principally defined by the symptomatology resulting from increased pressure in the portal venous system in the presence of an otherwise normal or preceded by mildly deranged liver function (24). Clinically, it is manifested as oesophageal and/or gastric varices, foregut bleeding, splenomegaly, hypersplenism, growth retardation and neurocognitive impairment (25).

The diagnosis is confirmed with Doppler ultrasonography, contrast-enhanced computed tomography and magnetic resonance angiography of the portal venous system (26), and upper gastrointestinal endoscopy to assess the source of haematemesis or melena.
There are several serum markers that should be looked at when diagnosing EHPVO. The current literature highlights those patients with EHPVO who have an enhanced tendency towards bleeding. The evidence for this lies with the prolonged INR and PTT and the decreased fibrinogen and platelet aggregation. Several studies have also observed an increase in the levels of fibrin degradation products in this patient population (9, 27, 28). Moreover, in addition to the synthesis of coagulation factor VII, protein C and S have been shown to be impaired in EHPVO patients (29, 30).

EHPVO is considered a less severe form of PH when compared to children with hepatic cirrhosis. The latter often have complications of the hyperdynamic circulation associated with liver disease, including high cardiac output, hepatorenal syndrome, and spontaneous bacterial peritonitis(31). However, children with EHPVO have a reduced quality of life due to frequent bleeding episodes, growth retardation, neurocognitive impairment, hypersplenism and splenomegaly (32). Hence, management is crucial to alleviate these manifestations.

In addition to the above-mentioned manifestations, the liver function gradually deteriorates in these children. The observed liver dysfunction arises because of the impaired hepatopetal flow and portal biliopathy, both of which can be successfully reversed following definitive management.

Management

The management of EHPH in children has evolved over several decades from the initial conservative medical management of the bleeding varices using beta blockers, variceal sclerotherapy, and variceal banding, to the surgical management to those patients who will benefit from shunt surgery which itself has been also move forward from non-selective

portosystemic shunt surgery, to the distal splenorenal shunts (DSRS) (Figure 1) and eventually to MesoRex shunts (MRS) (Figure 2). While distal splenorenal shunts partially divert blood away from the liver to the systemic circulation (33), MesoRex shunts restore the hepatopetal blood flow (34).

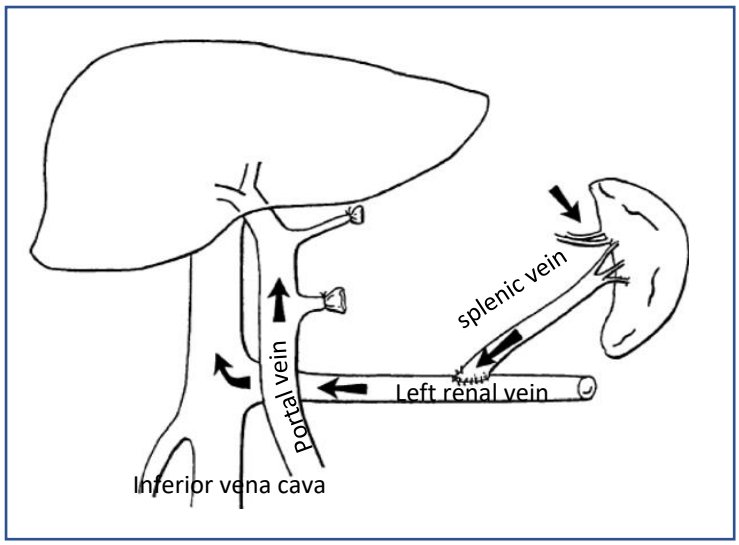

Figure 1: Distal splenorenal shunt anatomy (35)

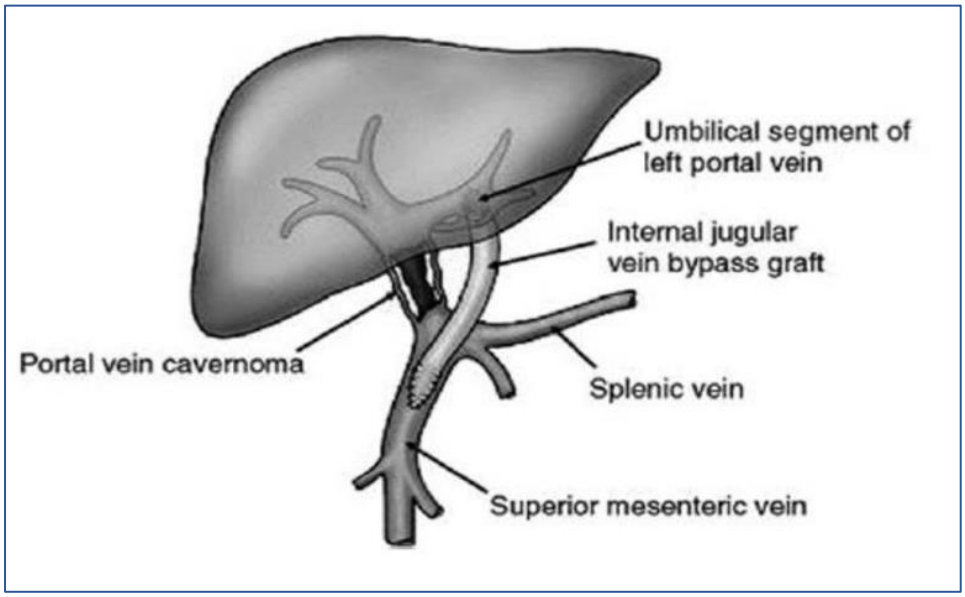

Figure 2: MesoRex shunt anatomy (35)

Conventionally, medical and endoscopic management is usually recommended for EHPVO, and various surgical shunts are used for refractory or complicated cases. Surgery is primarily indicated when endotherapy fails to control bleeding, in presence of gastric or ectopic varices not amenable to endoscopic management.

Variceal band ligation in children is a safe and effective technique to achieve variceal eradication more quickly, with a lower rebleeding rate and fewer complications than sclerotherapy (36-38). Nevertheless, a combination of beta blockers, band ligation followed by sclerotherapy has shown to be superior to either modality in children with EHPVO (39). However, this just manages the symptoms of the increased portal pressure and is not a definitive cure – and thus revolves around multiple treatment sessions and ongoing observations.

As the portal blood flow represents half of the total hepatic blood inflow and 40% of the hepatic oxygen supply. Shunting this volume partially or completely away from the liver through the natural development of portosystemic shunts or surgically created portosystemic shunts will deprive the liver of this flow. Surgical portosystemic shunts in this study is represented by DSRS shunts. DSRS or Warren's shunt is performed by end to side anastomosis of the distal splenic vein to the left renal vein, tying the proximal end of the splenic vein while preserving the spleen (33) (Figure 1). This shunt improves the portal hypertension sequela by reducing portal pressure and resolving any upper GIT bleeding that has resulted from oesophageal and/or gastric varices. Moreover, shunting the portal blood flow will reduce the splenic size and the subsequent effects of hypersplenism, including leukopenia and thrombocytopenia. However, previous studies have shown the potential negative impact of a reduced portal blood flow on synthetic liver function (8, 40).

The definitive surgical procedure to resolve EHPVO, provided the Rex vein is patent, is to perform the mesenteric-left portal bypass (MBP) also known as MesoRex shunt as soon as the diagnosis has been established (34).

Following the availability of advanced physiological shunts such as the MesoRex shunt, the management of EHPVO has subsequently been moving from endotherapy to primary shunt surgery (41), Reserving Further endoscopy for the management of an acute bleeding episode and for prophylaxis to prevent further bleeding (42).

MesoRex bypass is an innovative surgical procedure that has been adopted to restore hepatopetal blood flow, and requires that the umbilical portion of the left portal vein (Rex vein) and superior mesenteric vein are patent (43). This procedure was first described in 1996 as a management approach to EHPVO in liver transplant patients (34). MesoRex bypass restores the portal inflow to the liver through the insertion of a venous graft between the splanchnic vein (superior mesenteric vein) and the end of the intrahepatic left portal vein branch in the Rex fossa (35) (Figure 2).

This approach can be as effective as portosystemic shunts in the prevention of gastrointestinal (GI) bleeding and avoids the prevalent side effects of portosystemic shunts, including hepatopulmonary syndrome (arteriovenous shunting), portopulmonary syndrome (pulmonary hypertension), hepatic encephalopathy, and liver nodules (44, 45). Previous studies have also observed several additional benefits following MesoRex bypass. These include additional metabolic benefits and the cure of portopulmonary syndrome encountered in EHPVO, particularly in those where portosystemic shunts are contradicted (7, 46).

Our study extended beyond the current literature to report on other potential metabolic implications of MesoRex shunt surgery. In this respect, we studied the impact on serum albumin (which has never been reported previously), PTT, fibrinogen, total bilirubin, and other liver enzymes, in addition to INR and platelet count that has been widely reported in previous studies (30).

As EHPVO is a prehepatic vascular insult, initially and in the short term the liver parenchymal morphology, including size, architecture, volume, and echotexture, are reported to be normal (21). However, there is a relative reduction in portal venous flow to the periphery of the liver, alongside a compensatory increase in arterial blood flow (47). These circulatory changes lead to enhanced perfusion of the central liver; thus, over time, the redistribution of the liver parenchymal volume, parenchymal extinction and smooth hepatic atrophy develop. MesoRex shunt results in liver growth and restores the liver mass to normal (48, 49). In contradiction, portosystemic shunts redirect the blood flow away from the portal circulation (50), causing further deprivation of hepatic portal flow. This, in turn, exacerbates liver dysfunction and hepatocyte injury due to accelerated apoptosis (51) and potentiate the effects of naturally developed portosystemic shunts mentioned above.

Chapter 2: Aim and Methods

Aims:

Our study aimed to determine and compare the shunt success rate on patients operated on for EHPVO in our unit. Shunt success defined as shunt patency at 24 months of the MRS and DSRS. Furthermore, to study the possible additional benefits of the MRS over the DSRS as both options are used in the management of EHPVO. We hypothesised that the MRS would be superior to the DSRS in terms of patency, function and metabolic effects. Moreover, effect of these two shunts on the long-term synthetic liver function and variceal bleeding was also investigated. Finally, we extended the study to include The factors that could have influenced the patency of the Rex vein and hence, the eligibility for either MRS or DSRS.

Study Design

This study followed a retrospective descriptive design, conducted at a single tertiary centre, Red Cross War Memorial Children's hospital/ Cape Town. The children included in this study underwent either MesoRex shunt or distal splenorenal shunt surgery for EHPVO over an 18-year period (2001-2019). During this period, twenty-three patients presented with EHPVO. The standard preoperative assessment methods and the surgical technique described by De Ville De Goyet for Mesorex shunt (34), and by Dean Warren for distal splenorenal shunt (33) were utilised in this study. Ethical permission was obtained from the human research and ethics committee/University of Cape town / HREC REF 107/2019. (Appendix 1)

Inclusion and exclusion criteria:

All patients presented to RCWMCH with EHPVO over an 18-year period (2001-2019) were eligible for inclusion either for MRS or DSRS. Exclusion criteria included patients lost to follow up, patients who had atypical shunts not falling into either the DSRS or MRS operation and those with insufficient or missing clinical records over 18 years.

Criteria for MRS:

1- EHPVO with patent superior mesenteric vein
2- Patent Rex vein

3- Patent right and left internal jugular vein, as one of them will be utilized as an interposition venous graft.

Criteria for DSRS:

1- EHPVO that is extended to the superior mesenteric vein.
2- Obliterated Rex Vein.
3- Patent splenic vein
4- Patent left renal vein

Consent requirements

As this was a retrospective descriptive study, and no additional patient interventions occurred, consent was not required for this study.

Data Collection

A comprehensive overview of the patient demographics was compiled (Appendix 2), including age, gender, aetiology, preoperative symptomatology, Rex vein patency, age of shunt surgery and shunt patency. In addition, this study analysed the resolution of the upper gastrointestinal symptomatology and the synthetic liver function. Data collection additionally included platelets count, prothrombin time (PT), partial thromboplastin time (PTT), international normalised ratio (INR), fibrinogen, albumin, total bilirubin, and liver enzymes prior to and two-years post shunt surgery for both MesoRex shunt and distal splenorenal shunt groups. Rex vein patency was assessed preoperatively, with wedged hepatic vein portography, Doppler ultrasound, CT angiography, conventional angiography, or direct exploration at the time of surgery (52).

All information was obtained from patient records, Division of Paediatric Surgery surgical procedures data base, Radiology PACS system and the National Health Laboratory service patient results portal.

Pre-operative venous assessment

Rex vein patency was assessed preoperatively with wedged hepatic vein portography, CT angiography, conventional angiography, Doppler ultrasound, or direct exploration at the time of surgery.

Postoperative Regime

The existing hospital post-operative protocol was followed for patients undergoing surgery. The in-hospital postoperative regime consisted of prophylactic subcutaneous low molecular weight heparin at 0.5 mg/kg daily. On day four, oral antiplatelet medication introduced, specifically acetylsalicylic acid (aspirin), were started at a 1mg/kg/day and continued for six to twelve months. Doppler ultrasonography was performed routinely to assess shunt patency on days zero, one, three and seven, then at six weeks and continued quarterly for a year and then annually. Shunt patency was established annually by Doppler ultrasonography to assess if a good flow is shown, defined as a minimum flow rate of 20 cm/second for a least 24 months postoperatively and cessation of further upper GIT bleeding (53). Esophagogastroduodenoscopy was performed only in the event of further upper gastrointestinal bleeding. In addition to a routine annual clinical assessment, full blood count and liver function tests were performed.

Statistical Analysis

Statistical analysis, following data collection, was performed using the SPSS software package. Basic descriptive statistics were then used to characterise and compare the patient cohort, including mean values, standard deviations, ranges, and percentages. Liver function and platelet values were assessed with contingency tables. This included Chi-squared statistics (X^2), Fisher's exact test and Mann-Whitney-U-Test. A two-tailed test p-value of less than 0.05 was deemed significant.

Chapter 3: Results

Patient Characteristics

A total of 23 patients with EHPVO were recorded during the study period. The average age was 5 years (range 2 - 12), with a male to female ratio of 1.1:1 (12 male patients and 11 female patients).

With respect to aetiology, 14 patients (60%) gave a history inclusive of a risk factor for EHPVO: 5 patients (22%) had a history of UVC as an infant, one patient (5%) had a history of abdominal tuberculosis, with periportal lymphadenitis in addition to UVC, two patients (9%) had omphalitis, five patients (22%) had a liver transplant, and one patient (5%) had abdominal TB. The remaining nine patients (39%) were deemed idiopathic EHPVO as no risk factors were identified.

Two patients (9%) were lost to follow-up soon after a diagnosis of EHPVO was established. Amongst the remaining 21 children with EHPVO, all showed increased splenic size at presentation. Only one child presented with splenomegaly, leukopenia, and thrombocytopenia (hypersplenism). All others presented with upper GIT bleeding, either due to gastric varices in two (10%) or secondary to oesophageal varices in the others (90%). There was an overall average of 4 episodes of variceal bleeding (range:1-7). Further bleeding was controlled with either injection sclerotherapy in 17 (80%), band ligation in 2 (10%) or both in one child (5%). Complications reported for children who underwent sclerotherapy included 2 (10%) mild oesophageal strictures that resolved spontaneously, 4 (20%) children experienced temporary dysphagia and 8 (40%) reported retrosternal chest pain immediately post sclerotherapy.

Table 1: **Demographic data, aetiology, type of varices and diagnostic modalities used for 23 patients presented with EHPVO. Note: patient's number 18 and 19 lost follow up after the diagnosis of EHPVO was established, No shunt surgery performed for both.**

Patient number	Age in years	gender	Aetiology of EHPVO	Esophageal varices	Gastric varices	Rex vein detection	Shunt type	Duration of f/u in months
1	4	F	idiopathic	Y		WHVP	MRS	24
2	7	M	idiopathic		Y	WHVP	DSRS	133
3	3	M	Liver Tx	Y		CT Angio	MRS	180
4	11	M	Idiopathic		Y	WHVP	MRS	129
5	1	F	Liver Tx	Y		WHVP	MRS	164
6	2	F	Liver Tx	Y		WHVP	MRS	175
7	5	M	Liver Tx	Y		WHVP	MRS	148
8	3	M	UVC	Y		WHVP	MRS	174
9	9	M	Omphalitis	Y		WHVP	MRS	135
10	5	M	Omphalitis	Y		WHVP	MRS	167
11	3	F	Idiopathic	Y		WHVP	DSRS	172
12	7	M	Idiopathic	Y		WHVP	MRS	165
13	7	M	Idiopathic	Y		WHVP	MRS	147
14	5	F	TB	Y		CT Angio	MRS	218
15	8	M	TB+UVC	Y		Exploration	MRS	130
16	5	M	Idiopathic	Y		Doppler u/s	DSRS	151
17	9	F	Idiopathic	Y		Direct Angio	MRS	58
18	/	F	UVC+omphalitis	Y		/	/	/
19	/	F	Idiopathic			/	/	/
20	3	F	UVC	Y		Direct Angio	DSRS	82
21	2	F	Liver Tx	Y		CT Angio	MRS	130
22	3	M	UVC+omphalitis	Y		Exploration	DSRS	188
23	4	F	UVC	Y		Exploration	DSRS	164

WHVP: wedged hepatic vein portography, UVC: umbilical vein catheterisation, TB: tuberculosis portal lymphadenitis, liver Tx: liver transplant, Y: yes

Preoperative Findings

In all patients, the splenic, superior mesenteric vein and left renal vein were patent on doppler ultrasound. Wedged hepatic vein portography (WHVP) showed a patent Rex vein in 15 patients (70%), and an occluded Rex vein in 6 (30%) patients. Intraoperatively, and during Rex vein

exploration, one child who showed patent Rex vein on WHVP turned to have an obliterated vein on exploration, and one was flagged as having obliterated vein turned to have a patent Rex vein. The imaging pattern on WHVP provided an overall sensitivity of 80% and a specificity of 95% in predicting the Rex vein patency.

The fifteen children with a patent Rex vein subsequently underwent MesoRex shunt surgery. The left internal jugular vein was utilized in all MesoRex shunts as the interposed conduit except one. This child had a reduced size liver transplant post Budd-Chiari syndrome, presented with EHPVO one year later. Intraoperatively, during MRS surgery, the superior mesenteric vein was quite dilated and tortuous. A direct roux loop side to side anastomosis between the superior mesenteric vein and Rex vein was performed. A successful MRS was demonstrated for this child on subsequent follow up. One child was salvaged with a distal splenorenal shunt due to early Rex shunt thrombosis. The onset of this was within 12 hours post-surgery. The 6 children with a non-patent Rex vein (5 on preoperative imaging and one at exploration) received a distal splenorenal shunt.

Postoperative Findings

Twenty-one patients were followed up long term, with 14 patients (66%) in the MesoRex shunt group and 7 patients (33%) in the distal splenorenal shunt group, including the child who had a salvage splenorenal shunt. The average follow-up in the MesoRex shunt cohort was 136 months (22-218 months) and 129 months (82-188 months) in the DSRS group (P = 0·689). Fourteen of the 15 MesoRex procedures (93%) were deemed successful in comparison to five out of seven (73%) in the Distal splenorenal Shunt group (P = 0·001). One of the 15 children who received a Rex shunt had reduced shunt flow (15cm/second) at early follow up (first six months), resulting in two episodes of upper GI bleeding. This, however, on further follow up, resolved spontaneously without further intervention needed.

Amongst the seven children who received a distal splenorenal shunt, two presented with ongoing symptoms of upper gastro-intestinal bleeding. Doppler Imaging showed impaired shunt stream due to a blocked or reduced flow, which required further sclerotherapy and anticoagulation. In addition, one of these children developed marked splenomegaly, with the family refusing further surgical intervention.

Two years post shunt surgery all children successfully treated with either MRS or DSRS showed reduced splenic size. The exact size reduction was not quantified in this study as measurements were not in standard planes throughout the study period.

Metabolic Implications: Liver Function and Platelets Value

Preoperative bloods and blood results at the 2 years post-operative follow up were analysed for the two cohorts. Among the MesoRex shunt group, the statistical analysis showed a significant improvement in the serum albumin, with this increasing from a mean of 32.87g/dl preoperatively to 39g/dl 2 years post-MesoRex surgery (P = 0.025). PT and PTT showed a significant change from a mean of 14.6 to 12.6 (P = 0.04) and from 35.6 to 31.7 (P = 0.018), respectively. In addition to the significant improvement in the platelet count from a mean value of 98.13 preoperatively to 182.07 2 years postoperatively (P = 0.01). There was also a mild improvement in the serum fibrinogen from a mean value of 2.04 g/dl to 2.44 g/dl; however, this was not statistically significant (P = 0.180). Table 1 depicts the liver function and platelet values prior to and 2 years post-shunt surgery for both the MesoRex and distal splenorenal shunts.

The other liver functions measured, including INR, total bilirubin, ALT, AST, GGT, and ALP, although, showed mild improvement among MRS group, it did not reach a significant level and were within the upper or lower reference normal physiological range.

The distal splenorenal shunt cohort only yielded a significant 2-year improvement in the platelet count, however, it was less than the improvement seen among MRS group, increasing from a mean value of 100 to 149.83 (P = 0.02). Despite a mild prolongation of PT and PTT values in this cohort, the liver synthetic function did not show noticeable changes (Table 1). Other liver function parameters did not show significant change and were within normal reference values before and after shunt surgery.

Table 2: Liver function and platelet values prior to and 2 years post-shunt surgery for both MRS and DSRS.

Value	Pre-operative (mean)		Postoperative (mean)		P value	
	MRS	**DSRS**	**MRS**	**DSRS**	**MRS**	**DSRS**
Albumin	32.8	31.0	39.0	32.16	0.025	0.61
PT	14.6	14.39	12.6	13.6	0.04	0.53
PTT	35.6	34.0	31.79	39.56	0.018	0.18
INR	1.9	1.27	1.2	1.2	0.24	0.42
Fibrinogen	2.04	2.14	2.44	2.12	0.15	0.87
Total Bili	17.93	10.6	14.5	14.66	0.16	0.11
ALT	49.86	37	36.33	38	0.06	0.23
AST	47.2	40	42.0	48.5	0.54	0.79
Platelets	98.13	100.0	182.06	149.0	0.01	0.02

Significance of UVC

History of UVC was observed as a predictor of an obliterated Rex vein. Amongst our cohort, six patients had a history of UVC. Of this population, only two patients showed a patent Rex vein 33%, (P = 0.03). These patients were eligible for a MesoRex shunt; however, one of them experienced shunt thrombosis immediately after surgery and proceeded to urgent distal splenorenal shunt, the other had reduced MRS flow at 6 months follow up with further 2 episodes of variceal bleeding that resolved spontaneously.

Of the 23 patients that presented with EHPVO, 17 were without a history of UVC. 2 of these were lost to follow up. Thirteen of the remining 15 had a patent Rex vein (86% patency rate compared with 33% in the group with a history of UVC) and received a MesoRex shunt – all were patent on follow up.

Chapter 4: Discussion

Overview of findings:

This study investigated the overall success rate of MesoRex shunts compared with the traditional distal splenorenal shunt used to treat EHPVO (33, 34, 50, 54). We report our single centre experience with the physiologic MesoRex shunt and selective portosystemic shunt, spanning 20-years, for the treatment of paediatric EHPH secondary to extra hepatic portal vein obstruction. Our findings confirm that children with EHPVO have a mild impairment in synthetic liver function and liver-dependent coagulation factors on presentation. This is manifested by low serum albumin, elevated INR, PT, PTT, and reduced fibrinogen. Following restoration of the hepatopetal blood flow to the liver with a MesoRex shunt, a long-term improvement is seen in the levels of serum albumin, PTT, and INR. However, these findings are not observed in patients that received a distal splenorenal shunt even though both cohorts have shown no ongoing variceal bleeding post shunt surgery. The negative impact of EHPVO on synthetic liver function was successfully reversed following MesoRex shunt surgery in this cohort. This has not been reproduced amongst DSRS group. Furthermore, our findings highlight the risk of previous UVC on the patency of the Rex vein. This should facilitate the selection of patients when considered for either of these two procedures.

Patient characteristics and presentation:

Twenty-three patients, with an average age of 5 years (range 2 - 12) were included in the study. This patient population is younger than most series in the literature that report ages at the time of shunt between 6 and 8 years of age (7, 55).

It is not possible to tell the exact reasons for the lower age at shunt in our cohort, but it is postulated that this is because our unit does not rely on lengthy variceal eradication programs that require patients to attend on multiple occasions over many months and progress to shunt if these fail, Another reason for this is this is a group often resides outside big centres with difficulty accessing tertiary health care facilities and there is a chance of fatal bleeding, away from a centre where emergency treatment can be initiated. Hence, we rather progress to definitive shunt early in the management.

With respect to aetiology, 60% of our patients gave a history inclusive of a risk factor for EHPVO including UVC, abdominal tuberculosis with periportal lymphadenitis, omphalitis, and liver transplant. The aetiology of EHPVO influences the subsequent management of this condition; however, given the lack of comprehension in current literature surrounding this topic, determining the predisposing factors of EHPVO remains a significant challenge. Among the studies that explored the underlying risk factors for EHPVO, the one performed by Sarin and Agarwal (56) compared seven studies that assessed aetiology of portal vein thrombosis in infants and children. In most cases the cause could not be identified and where it could be, the majority of cases showed direct injury to the umbilical vascular system (omphalites and / or umbilical vein catheterization) or intrabdominal and umbilical sepsis to be a contributor. However, there also seemed to be a relationship between various causes suggesting a coexistent transient prothrombotic state that might result in extra hepatic portal vein thrombosis at the time of insult or shortly afterwards. With regard to umbilical vein catheterization, the predisposing factors that increase the potential risk for portal vein obstruction are later insertion, catheter dwell time over 3 days, catheter misplacement, trauma on catheter insertion site, type of solution infused and catheter related sepsis (56).

In our cohort, we could not identify any potential underlying aetiology in 40% of our paediatric patients. In the remaining 60% of patients, we identified a diverse range of possible predisposing factors. UVC and post liver transplant were the most prevalent causes in this cohort, with these presenting in six and five children, respectively. Moreover, we identified two children with neonatal omphalitis, two with periportal tuberculous lymphadenitis, in which one patient had a history of both TB and UVC. These findings are compatible with the current literature.

EHPVO can present as early as six weeks after birth as well as manifest in childhood. Clinical presentation depends on recent or chronic onset of clinical disease and age of presentation. The most common clinical features are haematemesis; often massive and usually not associated with major hepatocellular dysfunction. Gastrointestinal bleed is usually recurrent before a patient seeks medical attention. Patients can present with haematemesis and melena from conventional esophageal and / or gastric varices and can also bleed from ectopic varices or may present with obscure GI bleeding or bleeding from the biliary tract(57).

Hematemesis from bleeding varices was the commonest presenting symptom in our cohort (95%). Variceal bleeding is the most serious complication of portal hypertension in children (58, 59). EHPVO may not be discovered until gastrointestinal haemorrhage develops (60).

Clinical splenomegaly was present in all our patients. Enlarged spleen is one of the classic findings of noncirrhotic EHPH together with esophageal varices and normal liver architecture (61). Thus, the possibility of EHPVO should be suspected and a Doppler ultrasound performed in children and adolescents with upper gastrointestinal bleeding and / or isolated finding of splenomegaly during clinical examination.

The management of variceal bleeding in children is a challenging and less well-established treatment modality owing to a paucity of good evidence that can be used to evaluate the risk and benefits of a particular strategy. Nowadays, endoscopic variceal band ligation is the primary choice for the management of variceal bleeding in children. This treatment may, however, be technically challenging in very young and small children, and sclerotherapy is recommended as an alternative approach in these cases (62). Our series showed that injection sclerotherapy had a higher association with the development of complications than band ligation.

Preoperative imaging of the Rex vein:

In the surgical management of EHPVO Once the diagnosis has been established, and provided that the child is in stable hemodynamic status, identifying patent Rex vein is the next critical step. The preoperative evaluation of a patient with EHPVO includes an accurate assessment of the portal venous flow proximal to the occlusion and intra hepatic left portal outflow. The former is readily assessed by ultrasound and contrast enhanced MRI. However, investigating the outflow of the intrahepatic portal vein represents a diagnostic challenge. For this purpose, conventional angiography, Doppler ultrasound, contrast-enhanced CT, contrast-enhanced MRI and wedged hepatic vein portography (WHVP) has all been used with different accuracies and invasiveness.

Choosing the best modality depends on the availability and comfortability of the radiologist interpreting the results. In our centre, WHVP is considered the gold standard for the assessment of Rex vein patency in preparation for MesoRex shunt surgery. The sensitivity and specificity

of WHVP of 80% and 95% respectively is comparable to results of a previous study by Lawson et al. (2011) (52).

Use of the left internal jugular vein:

The left internal jugular vein (IJV) lies lateral and anterior to both the internal and common carotid arteries. Found at the junction of the neck and thorax, this vein joins the subclavian vein to form the brachiocephalic vein (63). The IJV is chosen as a vascular autograft over other conduit alternatives in the standard MesoRex shunt technique (64). For this reason, it is crucial that physicians avoid left sided central venous catheterization when resuscitating a child with EPHVO, and that anaesthetists are familiar with this as well.

A large case series by Sherif et all, assessed children with EHPVO that were treated with a MesoRex shunt using left internal jugular vein as interposition graft. A success rate of ninety-one per cent was observed, over a median duration of eight years (range, 5.3-8.8 years) (65). The study highlighted the superiority of venous autografts over synthetic grafts. This institution thus highly recommends using the left internal jugular vein as a shunt conduit in MRS surgery whenever this is technically possible.

Superiority of MesoRex shunt versus distal splenorenal shunt

We observed an overall success rate of shunt surgery 83% (19 patients of the 21 evaluated) across the two shunt groups, with MesoRex shunt approach yielding a superior success rate compared to distal splenorenal shunt (93% versus 73% respectively). This underpins our decision to preferentially adopt the MesoRex shunt as the primary definitive technique, reserving the distal splenorenal shunt for patients where a MesoRex shunt was not technically feasible or when the MesoRex shunt fails.

It is of note that one child in our cohort was salvaged with a distal splenorenal shunt due to early Rex shunt thrombosis. However, the reasons for this single operative failure of the MesoRex shunt was thought to result from the surgical technique or an inadequate diameter Rex vein as opposed to the MesoRex shunt itself.

Lautz et al. compared the effectiveness of MesoRex bypass and portosystemic shunt for reversing the characteristic symptoms of EHPVO in children, including variceal bleeding,

hypersplenism, and metabolic abnormalities. A total of 65 children with idiopathic EHPVO were considered for MesoRex bypass between 1997 and 2010. It was observed that almost all patients had complete relief of their variceal bleeding (MesoRex bypass 96%, portosystemic shunt 100%). On the other hand, improvements in platelet count, the INR, and the serum ammonia level were all significantly greater following MesoRex bypass than a portosystemic shunt. Among patients with below average (standard deviation z-score <0) preoperative weight for age, the improvement in weight-for-age z-score was greater after meso-Rex bypass (þ0.84 0.98) than PSS (þ0.17 0.79, p 1⁄4 0.044). Median duration of follow-up was 4.45 years after meso-Rex bypass and 1.8 years after PSS (7).

In this study, we reproduced some aspects of these results, and extended our research to explore other parameters that have not been analysed by Lautz et al. We reproduced the superiority of the MesoRex shunt over distal splenorenal shunt in relieving the variceal bleeding, with only one child out of fourteen (7%) who received MRS presenting with further variceal bleeding while two children out of seven (37%) who underwent DSRS presented with variceal bleeding at 2 years follow up. Furthermore, we reported significant improvement in the platelet count from a mean value of 98.13 preoperatively to 182.07 2 years postoperatively (P = 0.0001) in MRS group, compared with an increase from a mean of 100 to 149 (P = 0.02) pre and post DSRS respectively, highlighting the significant differential increase between the two shunts (P = 0.04). INR showed reduction from a mean of 1.9 pre MRS to a mean of 1.2. However, this did not reach a significant level (P = 0.24), and this might be due to the smaller size of the cohort, compared with almost unchanged value in children with DSRS.

We extended our study to include other parameters that reflects the synthetic liver function, in addition to the liver enzymes. PT and PTT showed a significant change from a mean of 14.6 to 12.6 (P = 0.04) and from 35.6 to 31.7 (P = 0.018) respectively in children with MRS. While PT went down from 14 to 13 (P = 0.53) in DSRS group, interestingly, PTT among DSRS children showed increase from 34 seconds to 39.5 seconds. Although this was not statistically significant, however, due to the small study sample it is difficult to reach a conclusion here, but it might reflect procoagulants deficiencies which could be due to shunting of the portal flow away from the liver.

Furthermore, a significant improvement in the serum albumin was noticed, with this increasing from a mean of 32.87g/dl preoperatively to 39g/dl 2 years post-MesoRex surgery (P = 0.025).

In addition, there was also a mild improvement in the serum fibrinogen from a mean value of 2.04 g/dl to 2.44 g/dl; however, this was not statistically significant (P = 0.15). These changes have not been seen amongst children underwent DSRS, which is to the best of our knowledge has never been reported in literature with direct comparison between MesoRex shunt and distal splenorenal shunt.

Serum albumin levels are dependent on the rate of albumin synthesis, the amount secreted from the liver cell, the distribution in body fluids, and the level of degradation. Hypoalbuminemia results from a derangement in one or more of these processes. Albumin synthesis begins in the nuclei of the hepatocytes, where genes are transcribed into messenger ribonucleic acid (mRNA). The mRNA is secreted into the cytoplasm, where it is bound to ribosomes, forming polysomes. These polysomes are responsible for synthesis of pre-albumin then albumin from the amino acids that made available via portal circulation. The flow of substrate (amino acids) form the intestinal villi subsequent to absorption affects certain functions of the liver, including protein synthesis (66). Reduction in the portal flow secondary to EHPVO results in diminution of the amino acids supply to the hepatocytes, hence, decreased albumin and other protein synthesis. This restoration of portal blood flow to the liver may be the reason for long term serum albumin levels rising.

Finally, liver transaminases have shown mild improvement two years after MRS with Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) went down from 49 and 47 preoperatively to 36 and 42 (P = 0.06) and (P = 0.54) respectively, However, none of them reached a significance level. No changes appreciated among DSRS cohort. This improvement is believed to be due to the combined effects of resolution of the portal biliopathy, decompression of the portal circulation and restoration of hepatopetal flow.

Collectively, these findings demonstrate that both MesoRex bypass and the selective portosystemic shunt represented here by DSRS are capable of effectively relieving symptoms in EHPVO. However, MesoRex bypass demonstrated superiority regarding the alleviating of hypersplenism and offered additional metabolic benefits. These findings contrast with the recently published meta-analysis (55), which did not reveal superiority for either MRS or PSS, however, in this meta-analysis, only one study compared directly between both shunts and confirmed the better results of MRS regarding the metabolic outcome (7). The paucity of well

conducted trials in this area justifies future multicentre studies and studies that examine long-term outcomes and directly compare MRS with DSRS.

Impact of UVC on Extrahepatic PH shunt surgery:

History of UVC was observed as a predictor of an obliterated Rex. Of the 6 patients with a history of UVC, 4 had an obliterated Rex vein, 1 had a failed MRS shunt most likely due to a narrowed Rex vein, and 1 had initial reduced shut flow and subsequent bleeding which eventually settled. Thus, a previous neonatal umbilical catheter is a predictor of an obliterated Rex vein and possible MesoRex shunt failure. However, due to the small numbers it was impossible to comment on the role of UVC on the long-term patency of MesoRex shunt. Similar findings have reported a success rate of MesoRex shunts as low as 10% in patients with a history of UVC during the neonatal period (44, 67). Guérin et al recommended that MesoRex bypass be exclusively performed in patients without a previous history of UVC (44).

Collating this evidence, we hypothesize that the UVC is one of the primary causes of obliterated Rex vein in the paediatric population and hence, EHPVO. Moreover, it represents an independent risk factor for MesoRex shunt failure. This arises following UVC-induced local injury and thrombosis in the Rex vein. The thrombus then propagates towards the left portal vein, before moving eventually to the main portal vein trunk resulting in EHPVO. The clinical implications of these findings are vast for patients with a history of UVC and, given the poor performance of MesoRex shunts in this instance, a more conservative approach might be warranted for disease management in this cohort. In other words, delaying MesoRex shunt surgery until the patient's endoscopic treatment fails may enable the underlying varices to be managed through an alternative measure as opposed to ending up with a distal splenorenal shunt.

Conclusion

MesoRex shunt has an improved long-term outcome in extra hepatic portal vein obstruction and improves liver synthetic function. Distal splenorenal shunt does control variceal bleeding due to portal hypertension but may have a negative effect on liver function in the long term and should only be considered when MesoRex shunt is not technically feasible or as a salvage procedure when MRS fails.

Limitations

Despite the strengths of this study, there are several limitations that must be considered. Firstly, A small sample size made it difficult to come up with a solid conclusion. However, this is not a commonly performed procedures and these numbers are comparable to most of other studies in literature discussing this pathology.

Data concerning ALP and GGT was missing in several of the cohort; therefore, comparing the implications of a MesoRex shunt to a distal splenorenal shunt in this regard proved challenge. The decision was made to exclude these two parameters because of insufficient data. Further studies should ensure that the impact of these management approaches on ALP and GGT is investigated. Secondly, the study design followed a retrospective review over a 20-year period. This carries significant limitations regarding bias and the selection of patients. Moreover, the data collection was deficient in several demographic criterion, including patient growth and nutritional status, limiting the statistical analysis.

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Appendices:

Ethics:

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HREC REF: 107/2019

Prof A Numanoglu
Department of Paediatric Surgery
Red Cross Memorial Children's Hospital
Rondebosch

Dear Prof Numanoglu

PROJECT TITLE: RETROSPECTIVE REVIEW OF THE MESO-PORTAL BYPASS FOR EXTRAHEPATIC PORTAL VEIN OCCLUSION (MMED CANDIDATE: DR. O KHAMAG)

Thank you for your response, addressing the issues raised by the Human Research Ethics Committee (HREC).

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 May 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr O Khamag will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210308-007

Data collection forms:

Data Capture sheet				
Demographics	Participant number			
	DOB		GENDER	
Aetiology	UVC		Omphalitis	
	TB		Intra abdo sepsis	
	post liver Tx EHPH			
Presentation	Symptoms			
Scope findings	Upper GI scope			
	Sclerotherapy		Band ligation	
	Post sclerotherapy stricture?			
	Post sclerotherapy Dysphagia?		Post sclerotherapy chest pain	
Pre and post bloods	PT1		PT2	
	PTT1		PTT2	
	INR1		INR2	
	FIBRINOGEN1		FIBRINOGEN2	
	PLATELET1		PLATELET2	
	TOTAL BILI1		TOTAL BILI2	
	ALT1		ALT2	
	AST1		AST2	
	GGT1		GGT2	
	ALP1		ALP2	
	ALBUMIN1		ALBUMIN2	
Rex workup	Rex vein detection pre op			
	Rex vein on angio?			
Shunt surgery	Surgery date		Age at surgery	
	Diagnosis		Operation	
	Indication		Planned procedure	
	Procedure		Interposition graft	
	Reason for deviation			
Follow up	Post op shunt flow		Graft patency on follow up	
	Action needed?			
	Post op spleen size		Post op chylous ascites	
	Length of follow up till Dec 2019		Further GI bleed	

Conflict of interest

Date: 17th November 2021

To whom it concerns

Advantages of MesoRex shunt compared with distal splenorenal shunt for extrahepatic portal vein occlusion in children.

Conflict of Interest Statement

I declare no conflict of interest in preparation or subsequent publication of this material.

Yours sincerely,

Dr O Khamag
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Red Cross War Memorial Children's Hospital
Cape Town, South Africa
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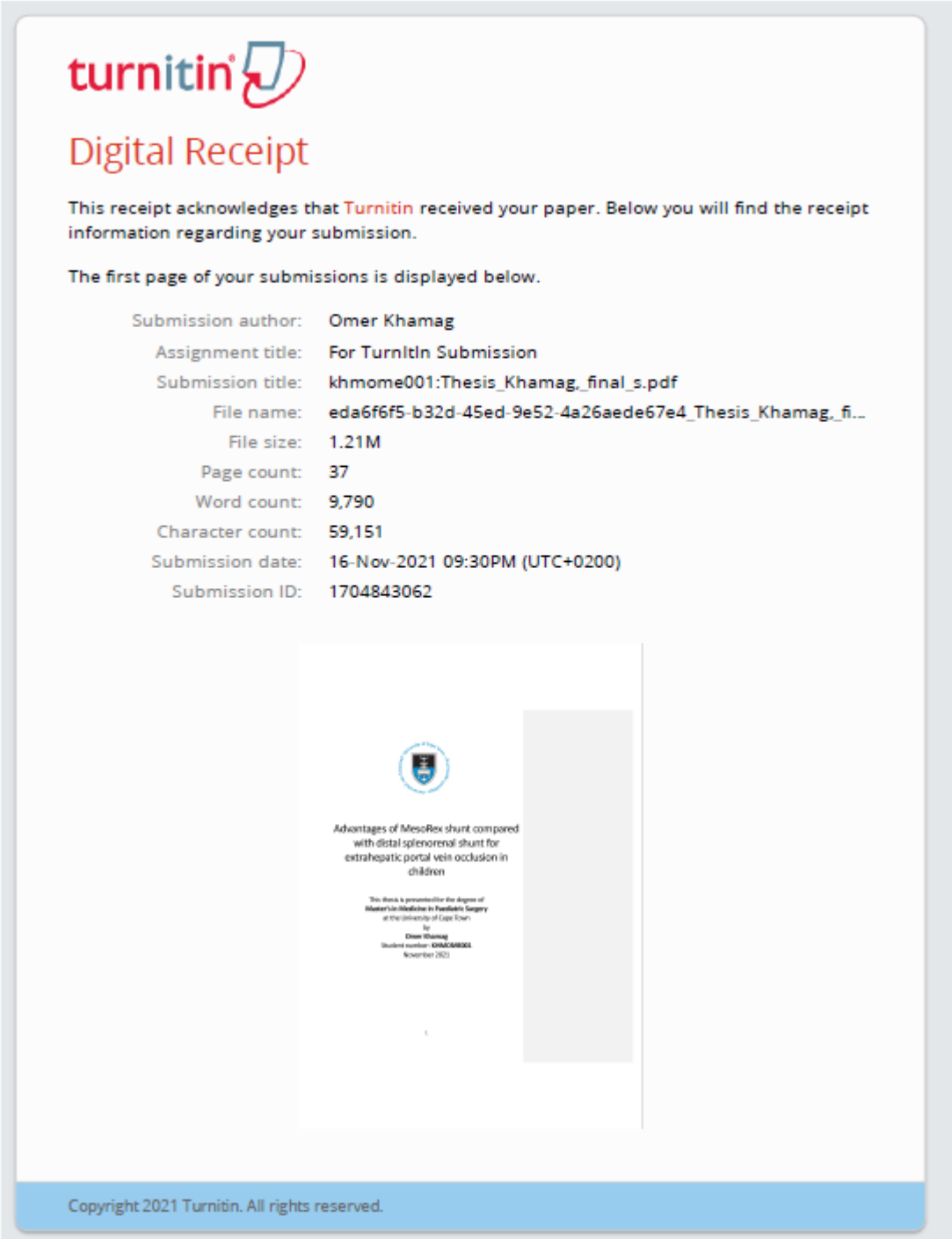

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