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DISSERTATION

Die Wirksamkeit der Tranexamsäure zur Reduktion des Perioperativen Blutverlusts in der Operativen Therapie Sekundärer Skoliosen

The Efficacy of Tranexamic Acid in Reducing Perioperative Blood Loss in Secondary Scoliosis Surgery

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List of Abbreviations

ap	anteroposterior
APTT	Activated partial thromboplastin time
ASA	American Society of Anesthesiologists
BMI	Body mass index
C7PL	C7 plumb line
CSVL	Central sacral vertical line
CP	Cerebral palsy
DIC	Disseminated intravascular coagulation
DLS	Dorsolaterale Spondylodese
DMD	Duchenne muscular dystrophy
EACA	Epsilon aminocaproic acid
EBL	Estimated blood loss
FDP	Fibrin degradation products
GBV	geschätzter Blutverlust
IOS	Intraoperative salvage
INR	International normalized ratio
MAP	Mean arterial pressure
MCA	Major curve angle

NE	Norepinephrine
NMS	Neuromuscular scoliosis
Pa	posteroanterior
PAI-1	Plasminogen activator inhibitor - 1
PDMS	Patient data management system
PSF	Posterior spinal fusion
PT	Prothrombin time
RBC	Red blood cell
ROTEM®	Rotational thromboelastometry
SMA	Spinal muscular atrophy
TBV	Total blood volume
TEG	Thromboelastogram
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
tTXA	Topical tranexamic acid
TXA	Tranexamic acid

1. Abstract *(Deutsch)*

Hintergrund: Sekundäre Skoliosen entstehen in der Regel bei Kindern als Folge unterschiedlicher Grundkrankheiten und sind aufgrund ihrer starken Progredienz oftmals mittels einer dorsolateralen Spondylodese (DLS) operativ zu korrigieren. Der erhöhte perioperative Blutverlust und Bluttransfusionsbedarf, die durch diese aufwändige Eingriffe entstehen, komplizieren den perioperativen Verlauf. Tranexamsäure (TXA) ist ein Antifibrinolytikum, das derzeit routinemäßig perioperativ bei verschiedenen Eingriffen zur Eindämmung der Blutung eingesetzt wird. In der Behandlung sekundärer Skoliosen gibt es jedoch bis heute keine ausreichende Datenlage, um ihren Einsatz zu empfehlen. In dieser Studie haben wir daher die Wirksamkeit der TXA in der Reduktion des perioperativen Blutverlusts im Rahmen der Durchführung von primären DLS bei sekundären Skoliosen untersucht.

Methodik: Pädiatrische Patient/-innen mit sekundärer Skoliose wurden retrospektiv untersucht, die sich einer primären DLS unterzogen haben. Demographische, chirurgische, radiographische und anästhesiologische Parameter, sowie Laborwerte wurden erhoben und mittels Student T, Mann-Whitney U, oder Chi-Quadrat Tests verglichen. Der geschätzte Blutverlust (GBV) wurde für die perioperative Zeit bis zum ersten postoperativen Tag kalkuliert. Eine multiple lineare Regression wurde verwendet, um unabhängige Prädiktoren des GBV zu analysieren. Verläufe von Hämoglobin und Hämatokrit wurden zwischen den Gruppen verglichen.

Ergebnisse: Von den 66 eingeschlossenen Patient/-innen erhielten 35 intraoperativ TXA und 31 nicht. Die TXA-Gruppe wies einen größeren präoperativen C7-Offset, eine längere Operationsdauer, eine längere Fusionsstrecke und eine niedrigere intraoperativ gemessene minimale Körpertemperatur auf. Die TXA-Gruppe hatte eine höhere

intraoperative Transfusionsrate von Plasmaprodukten ($p < 0,001$), Thrombozytenkonzentraten ($p = 0,016$) und Eigenblut ($p = 0,007$), sowie ein signifikant höheres postoperatives Hämoglobin ($p = 0,038$). Die Gruppen unterschieden sich nicht im perioperativen Verlauf von Hämatokrit ($p = 0,782$) oder Hämoglobin ($p = 0,926$). GBV ($p = 0,554$) und das Verhältnis des GBV zum Gesamtblutvolumen ($p = 0,590$) unterschieden sich nicht zwischen den Gruppen. TXA hatte einen signifikant negativen Effekt auf den GBV ($p = 0.031$). Die Gabe von TXA hat mit der intraoperativ verabreichten Menge an allogenem Blut nicht korreliert ($p = 0.296$).

Schlussfolgerungen: Trotz der längeren Operationsdauer und der größeren Fusionslänge in der TXA-Gruppe, waren der GBV und die allogene Bluttransfusion zwischen den Gruppen ähnlich. Obwohl TXA die perioperative Bluttransfusion nicht signifikant reduziert, hat sie einen signifikant negativen Einfluss auf den GBV und führt zu einem höheren postoperativen Hämoglobinspiegel. Deshalb sollte die intraoperative Anwendung von TXA bei Patient/-innen mit sekundärer Skoliose, die mittels DLS versorgt werden, in Betracht gezogen werden.

2. Abstract *(English)*

Background: Secondary scoliosis occurs in children as a result of various underlying diseases and, due to its strong progression, is corrected surgically via a posterior spinal fusion (PSF). The increased perioperative blood loss and the need for blood transfusions resulting from these complex interventions complicate the perioperative course. Tranexamic acid (TXA) is an antifibrinolytic agent which currently finds routine perioperative use in various interventions for controlling bleeding. There still is no sufficient data to recommend its use in secondary scoliosis surgery. Therefore, in this study, our goal was to examine the efficacy of TXA in reducing perioperative blood loss in secondary scoliosis patients undergoing primary PSF.

Methods: We retrospectively reviewed pediatric secondary scoliosis patients who underwent primary PSF. Estimated blood loss (EBL) was calculated for the perioperative time until the first postoperative day. Demographic, surgical, radiographic, laboratory, anesthesia, and vital parameters were obtained and compared using Student T, Mann-Whitney U, or Chi-squared tests. Multiple linear regression was utilized in controlling for independent predictors of EBL. Hemoglobin and hematocrit courses were compared between groups.

Results: Out of the 66 included patients, 35 received intraoperative TXA, and 31 did not. The TXA group was found to have a significantly larger preoperative C7-Offset, longer surgical time, more fused levels and a lower minimum intraoperative body temperature. The TXA group had a higher intraoperative transfusion rate of plasma products ($p < 0,001$), platelet concentrates ($p = 0.016$), and autologous blood ($p = 0.007$), as well as a significantly higher postoperative hemoglobin ($p = 0.038$). The groups did not differ in their perioperative course of hematocrit ($p = 0.782$) or hemoglobin ($p = 0.926$). EBL ($p =$

0.554) and EBL to total blood volume (p = 0.590) did not differ between groups. TXA had a significant negative effect on EBL (p = 0.031) but did not correlate with allogeneic blood transfusion (p = 0.296).

Conclusions: Despite the longer surgery duration and the greater fusion length in the TXA group, EBL and allogeneic blood transfusion were similar between groups. Although TXA does not significantly reduce perioperative blood transfusion, it has a significant negative effect on perioperative blood loss and leads to a higher postoperative hemoglobin level. Therefore, its use in secondary scoliosis patients undergoing PSF should be taken into consideration.

3. Introduction

3.1 Secondary scoliosis – definition, and classification

The term “scoliosis” is derived from the ancient Greek word *skolios* meaning “curved” or “crooked” and was first used to describe spinal deformity by the Greek physicians Hippocrates and Galen (1, 2). Today, it describes the complex three-dimensional spine deformity comprising abnormal lateral and rotational curvatures (3). There are several ways in which scoliosis is categorized. An initial distinction is made according to the reversibility of the curve by changes in position. If the deformity is fixed, it is referred to as structural scoliosis. This entity differs from functional scoliosis, which arises as spinal compensation for a separate orthopedic deformity (e.g., pelvic obliquity caused by leg-length discrepancy) (4, 5). Structural scoliosis is further classified according to its etiology. The deformity is categorized as primary or idiopathic in 80 percent of cases where it cannot be attributed to any underlying primary condition. In the remaining 20 percent, scoliotic deformity develops secondarily to an accountable pathology or disease and is referred to as secondary scoliosis (6). This heterogeneous condition is broadly categorized according to the three major groups of underlying etiology: neuromuscular, congenital, and syndromic scoliosis, all of which will be further explored in the following section (7). Additionally, secondary scoliosis has been linked to radiation, inflammation as observed in acute transverse myelitis, and spinal surgery. As a result, it may be difficult to classify secondary scoliosis into one of the three primary categories (8, 9).

Due to the nature of the underlying condition, secondary scoliosis mainly arises and progresses at an early age, causing an additional burden for pediatric patients with complicated primary conditions. If the deformity is diagnosed before the age of ten, it is named early-onset scoliosis. This term applies to most secondary scoliosis cases and

idiopathic cases with early development. Further subgroups exist that also take the age of diagnosis into account, such as infantile, juvenile, and adolescent scoliosis. However, these are usually reserved for classifying idiopathic scoliosis in the literature (10, 11).

3.1.1. Causes of secondary scoliosis

Neuromuscular diseases that account for neuromuscular scoliosis (NMS) are either myopathic or neuropathic. Duchenne muscular dystrophy (DMD) and arthrogryposis are two examples of myopathic conditions with a high prevalence of secondary scoliosis. Neuropathic disorders predisposing to scoliosis are caused by either an upper motor-neuron impairment and consequent spastic paresis, as seen in cerebral palsy (CP), or a lower motor-neuron impairment with flaccid paresis, as described in spinal muscular atrophy (SMA).

Scoliosis arises in neuromuscular diseases due to asymmetrical spinal growth caused by various factors such as asymmetric paraplegia and altered muscle tone (12). The sustained curve progression, even beyond completion of spinal growth, is a significant characteristic of NMS, setting it apart from idiopathic scoliosis (13). The curve progression and muscular imbalances may lead to pelvic obliquity, worsening posture, and sitting stability, causing an additional burden for both the patient and caregiver and should be considered while treating the deformity (14-17). Scoliosis occurs in 25 to 70 percent of CP patients, 63 to 100 percent of Friedrichs ataxia patients, 75 to 90 percent of DMD patients, and only 0.3 percent of the general population (12, 18). Patients with NMS are highly comorbid, suffering from seizures, swallowing difficulties, recurrent airway and urogenital infections, poor nutritional status, and inactivity-related osteoporosis, all of which further complicate the course of the disease (19).

Congenital scoliosis occurs in 0.5 to one per 1000 live births and forms at six to eight weeks of gestation during somitogenesis (18, 20). In these cases, scoliosis results from a segmentation or formation disorder of individual vertebrae. Incomplete segmentation of vertebrae results in either a unilateral bony bar between segments or block vertebrae. On the other hand, failure of formation presents as a wedge or hemivertebra (21). Congenital scoliosis may arise with VACTERL association, which is defined as the presence of at least three of the congenital malformations of vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, as well as renal and limb anomalies (22).

A heterogeneous group of primary diseases can cause syndromic scoliosis. Some examples are neurofibromatosis, Down syndrome, and connective tissue diseases such as achondroplasia, osteogenesis imperfecta, Ehlers-Danlos syndrome, and Marfan syndrome (7). Moreover, scoliosis is regarded as one of the major criteria in diagnosing Marfan syndrome. Scoliotic deformity larger than 10 degrees is shown to be prevalent in 63 percent of Marfan syndrome patients (22, 23). Similarly, 52 to 74.4 percent of patients with osteogenesis imperfecta present with scoliosis, while this rate is only at 26 percent in patients with Prader Willi Syndrome, showing that the prevalence of secondary scoliosis varies depending on the primary disease (24, 25).

3.2 Clinical course

The scoliotic deformity is highly progressive in NMS patients with an annual 15-20 degree increase of the major curve angle (MCA) (26). The rapid progression of the deformity in secondary scoliosis may cause chronic back pain and have an extensive impact on physical function, leading to sitting instability and impaired ambulation, both of which limit patients' independence and social participation. In severe cases, upright sitting may entirely depend on hand support, requiring external bracing or seating modifications.

Sitting instability further causes retardation of functional development, as arm and head movements cause postural collapse, limiting activity. Extensive scoliotic concavity may result in costopelvic impingement, leading to pain and skin breakdown in the lateral torso. Pelvic instability causes unequal pressure distribution in the buttock area and may lead to pressure ulcers (27-29). These add to the aforementioned comorbidities, reducing patients' quality of life and complicating care.

Thoracic insufficiency syndrome, defined by Campbell et al. as the inability of the thorax to support normal respiration or lung growth, is one of the feared complications of scoliotic deformity (30). This is commonly caused by fused ribs in congenital scoliosis and can also arise due to rapid curve progression in NMS (31). As alveolar-capillary development ends as late as eight years of age, scoliosis with an early onset and thoracic involvement may have a life-threatening effect on lung development, predisposing patients to restrictive pulmonary disease, pulmonary hypertension, and consequently, right heart failure (32). Reduced lung function also predisposes patients to develop pneumonia and recurring respiratory infections (12).

3.3 Clinical evaluation and imaging

Orthopedic evaluation should include static and dynamic examination of the spine to assess the form and reducibility of the curvature. A concomitant flexion-contracture of the hip should be detected as this may require surgical correction before scoliosis is addressed. Identifying the underlying primary disease via clinical evaluation and genetic testing is critical in understanding and treating deformity. An extensive systemic evaluation is required to detect the diverse comorbidities associated with the primary diseases. These comorbidities may require additional attention and treatment before

surgical intervention, such as cardiac myopathies, as seen in several neuromuscular diseases. Respiratory function needs to be assessed to decide whether to deploy perioperative ventilation exercises or mechanical ventilation in more severe cases. Gastrointestinal problems such as constipation related to wheelchair-ambulation, oral muscle dysfunction, dysphagia, and gastroesophageal reflux should also be detected, as these may compromise nutrition. The suboptimal trophic condition may predispose to postoperative skin ulcers and wound infection, worsening inactivity-related osteoporosis. Overall, the clinical assessment of secondary scoliosis is complex and requires multidisciplinary cooperation (33, 34).

Imaging is a crucial step in the clinical assessment of secondary scoliosis. Due to the three-dimensional geometry of deformity, anteroposterior (ap) or posteroanterior (pa) and lateral view long-cassette radiographs of the entire spine are required to assess the anatomy of deformity in both the frontal and sagittal planes. The standing position is preferred, whereas young patients who cannot stand receive imaging in the supine position. Wheelchair ambulatory patients may remain in the sitting position (35). The standard measurement of scoliosis is achieved via the Cobb angle, which is the angle between the superior endplate of the cephalad end vertebra and the inferior endplate of the caudad end vertebra in the pa radiograph (36). Postural balance is most commonly assessed by examining the C7-offset in the frontal plane, as well as pelvic obliquity (37, 38). Thoracal kyphosis and lumbar lordosis are essential parameters while assessing the sagittal profile.

Preoperative spinal flexibility is evaluated via supine bending radiographs, where the patients are asked to bend in the coronal plane maximally to each side in the supine position. This method is highly dependent on patient cooperation. An alternative is to

perform this assessment under general anesthesia immediately before surgery by applying traction forces on the patient's head and ankles (39).

Magnetic resonance imaging is indicated preoperatively to detect collateral intraspinal abnormalities such as syringomyelia, lipoma, and tethered cord. These are frequent findings in secondary scoliosis and may require neurosurgical intervention before orthopedic surgery.(12) Among the congenital scoliosis patients Bradford et al. examined, 37 percent had such abnormalities.(40) Deployment of computed tomography may be required to examine bone anatomy in complex cases, as in congenital scoliosis.(8)

3.4 Conservative treatment

In general, the deployment of conservative methods yields limited results in secondary scoliosis. Spinal braces allow positional correction of the trunk with the help of rigid supports. Although bracing may help halt curve progression in idiopathic scoliosis, it is effective only in a small subset of NMS patients (41, 42). Olaffson et al. observed that among NMS patients treated with bracing, therapeutic success, which they defined as curve progression of less than 10°, was seen only in ambulatory patients with short deformities, a small curve angle (<40°) and flaccid paresis, as well as in non-ambulatory patients with spastic paresis and short lumbar curves (43). Despite its low efficacy in halting curve progression, bracing finds use as an initial treatment in NMS to improve sitting stability, patient independence, hygiene, and caregiver satisfaction, while delaying surgery (12, 15, 44). Complications may arise, such as skin breakdown and necrosis, as well as impaired pulmonary function in patients with flaccid paresis (45-47). The rigid curve in congenital scoliosis does not respond well to bracing as the deformed vertebrae limit flexibility. Occasionally, bracing may help control compensatory curves, which develop secondarily to the preexisting congenital curve (48).

A further conservative treatment option is serial plaster-casting, administered with or without general anesthesia by applying traction-derotation force to the thorax and axial skeleton. The casts are consecutively exchanged, adapting to the child's growth. This method allows the total correction of idiopathic curves of less than 60° and a delay of surgical intervention in larger idiopathic curves (49). Gussous et al. report that casting also achieves curve correction in secondary scoliosis. However, this correction is significantly less than in idiopathic curves (50). While reporting similar results, Lavalva et al. demonstrate that casting contributes to chest and lung development by improving spinal height while delaying surgical intervention in secondary scoliosis patients (51).

In their retrospective review, Li et al. compared the outcomes of bracing and casting. They reveal that both treatments were statistically similar in eventual surgery requirements and complication rates. Three patients who received casting experienced complications such as skin breakdown, cast soiling from incontinence, and ileus. In contrast, no complications occurred in patients treated with bracing. Additionally, Li et al. also report that bracing only improved idiopathic curves while casting improved curves in both idiopathic and non-idiopathic scoliosis patients (52). These outcomes indicate that casting may constitute a better conservative therapy option than bracing for secondary scoliosis patients. However, along with mentioned complications and limited therapeutical success in secondary scoliosis patients, it is essential to consider if such conservative attempts are worth postponing surgery which is the evident option in secondary scoliosis treatment.

In order to support sitting balance and overall function for wheelchair ambulatory patients, various seating modifications are used. Examples are wheelchairs with custom molded seating and seating shells that support the trunk laterally. These options improve patient comfort and independence, preventing a truncal collapse in the seated position. Clinically relevant improvements to functional measures such as oxygen saturation and blood

pressure have also been reported for custom molded seating (53). On the other hand, no deformity correction is achieved, and fast progressing secondary curves may have already progressed until the measured and customized molded seating is delivered and ready for utilization (12, 28, 44). Therefore, such expensive options should be deployed once the benefit is thoroughly assessed for each individual.

Physiotherapy may also play a vital role in the management of scoliosis. The International Scientific Society on Scoliosis Orthopaedic and Rehabilitation Treatment guidelines of 2016 recommend physiotherapeutic scoliosis-specific exercises as the first step in treating idiopathic scoliosis to limit curve progression (6). However, for secondary scoliosis patients, physiotherapy is only recommended as an adjunct to bracing as it helps reduce the aforementioned negative effect of bracing on respiratory function (54, 55).

Disease-specific treatment approaches may help prevent scoliosis or limit its progression by modifying the underlying disease. An existing option for DMD is the deployment of steroids with a significant delay of scoliosis onset (56, 57). In their non-randomized comparative study, Lebel et al. report that 78 percent of DMD patients who received glucocorticoid therapy did not develop scoliosis of over 20 degrees or underwent corrective spinal surgery after fifteen years of follow-up. This rate was 8.3 percent in their non-treatment group (58). This demonstrates the efficacy of steroids in reducing the need for surgical treatment of scoliosis in DMD patients. Potential complications of steroid therapy, such as long bone fractures, vertebral compression fractures, and cataracts, may necessitate additional surgery and further complicate the course of the disease (14).

In recent years, new gene-targeting drugs such as risdiplam and nusinersen were approved for use in SMA. These drugs reportedly alter the natural history of the disease while improving motor function (59). Thus, they may also bear the potential of affecting

the occurrence and progression of scoliosis in this patient population. Currently, no studies have examined the outcome of scoliosis-onset, magnitude, or progression following gene-targeting drug use in SMA patients.

3.5. Surgical treatment

Curve progression, loss of sitting or standing balance, deformity-caused skin breakdown, worsening cardiac or pulmonary function, and persistent pain set the early indication for surgery in secondary scoliosis. At the same time, idiopathic scoliosis is less likely to progress and require surgical intervention (27, 60). Even in idiopathic cases which qualify for surgical correction, it is feasible to sustain conservative treatment and delay surgery until cease of truncal growth. However, this approach is not always justified in secondary scoliosis, as spinal growth in these patients may further aggravate the deformity (13). Surgical curve correction in secondary scoliosis is achieved via the fusion or non-fusion approach. Both approaches comprise a variety of surgical techniques for which decision-making should be based on each patient´s age, diagnosis, and severity of the deformity (8).

3.5.1. Spinal fusion

In spinal fusion, bony anchors such as pedicle screws, wires, or hooks are placed to the vertebrae or the ribs and are connected to a dual rod construct (35). While the rigid fixation of screws to the vertebrae enables a three-dimensional manipulation of deformity, they are also shown to be superior to hooks and wires in correcting the major curve and improving pulmonary function (61-64).

Spinal fusion can be performed via an anterior, posterior, or a combined anterior and posterior approach. The combined approach was favored in the past for secondary

scoliosis, as the anterior portion of intervention was needed to address rigid deformities, pelvic obliquity, or prevent instrument failure and other implant-related complications. However, this need was overcome through technical progress in spinal implants and operating techniques, leading to an increasing trend for posterior-only fusion and a decline in the combined approach (44). Rumalla et al. report that posterior-only approaches in NMS surgery accounted for 66.2 percent of spinal fusions in 2002, increasing to 90.2 percent in 2011 (65). Fusion is preferred to include both the major curve and secondary curves, which arise cranially and caudally of the major curve. The intention is to achieve optimal curve correction and a stable construct while minimizing the risk of proximal and distal development of scoliosis or kyphosis secondary to fusion. The resulting fusion constructs are usually lengthy, spanning the spine from the upper thoracal vertebrae distally to the lower lumbar vertebrae (66). Extension of fusion distally to include the pelvis can be preferred, especially in non-ambulatory NMS patients. This approach allows controlling pelvic obliquity, achieving sitting stability, and limiting curve progression. However, this approach is subject to discussion in current literature due to an increased risk of pseudoarthrosis, instrument failure, screw instability, and prominence causing skin irritation, pain, and infection (67-69). The surgical procedure may also include osteotomies, expansion thoracoplasty of the concave hemithorax, vertebrectomies, and hemivertebrectomies, depending on the individual anatomy of deformity (19, 70).

Spinal fusion may have numerous benefits for the patient, apart from curve correction. The most prominent improvements noted include the removal of brace or cast, as well as improvements in function, pain, sitting position, pulmonary function, self-image, social role, mental health, quality of life, and caregiver satisfaction (27, 55). In their prospective study where parents of CP patients completed questionnaires postoperatively, Jones et

al. reported significantly improved pain, happiness, and parent satisfaction 12 months following spinal fusion. However, they also reveal no improvement in physical function or school absence, pointing towards possible limitations of corrective surgery.

3.5.2. Growth-friendly constructs

There are a variety of non-fusion approaches, which are categorized into distraction-based, compression-based, and growth-guidance systems. Of the most frequently used, growing rods and vertical expandible titanium rib prosthesis fall under distraction-based systems. These systems allow spinal growth with the help of periodic surgical lengthening. Newer systems have emerged, allowing implant lengthening via magnetic distraction devices to avoid frequent invasive procedures (71). Growth-friendly spinal implants find use mainly in early-onset scoliosis as definitive spinal fusion in these patients would cause a significant impairment of thoracic spinal development (an estimated ten-centimeter loss of thoracic height if fusion is performed at the age of five), leading to further aggravation of the already impending restrictive pulmonary disease and respiratory insufficiency (18, 72). However, it is also essential to consider the potential adverse outcomes of growth-friendly instrumentation. While these constructs may fail to prevent curve progression or thoracic insufficiency syndrome, they also commonly cause infections, rod breakage, and spontaneous spinal fusion, necessitating revision surgery and final spinal fusion (73, 74).

In 2019, Hughes et al. conducted a study in which they constructed a survey consisting of six early-onset scoliosis cases. The survey was sent to 20 experts worldwide. The result was that no consensus was achieved on the treatment method in any of the six cases (75). This reflects the large and increasing number of therapy options available for

secondary scoliosis. The lack of randomized controlled trials in the field further complicates decision-making.

3.6 Complications of posterior spinal fusion

Posterior spinal fusion (PSF) is a major surgery associated with various intra- and postoperative complications. Superficial and deep surgical site infections are among the most common postoperative complications. Many others have been reported, including venous thromboembolism, pulmonary embolism, pleural effusion, pneumothorax, atelectasis, respiratory failure, emesis, paralytic ileus, and implant-related complications (e.g., pseudarthrosis, screw loosening or breakage and loss of correction). Several intraoperative complications occur associated with anchor fixation, such as pedicle fracture and anchor mispositioning. The latter, along with manipulation during surgery, may cause neural injury, leading to temporary or permanent neurological deficit. Other intraoperative complications include dural tearing, seizure, pneumothorax, positioning-related plexopathies, and, most importantly, massive blood loss requiring numerous blood transfusions (76-79).

Upon examining 19,360 cases of pediatric scoliosis from the Scoliosis Research Society database, Reames et al. showed that the rate of complications associated with surgery differs significantly between the subgroups of scoliosis. NMS patients had the highest complication rate with 17.9 percent, followed by congenital scoliosis and other secondary scoliosis patients with 10.6 percent and 14.5 percent, respectively. The lowest complication rate was seen among idiopathic scoliosis patients at 6.3 percent. The reported complications with a higher rate in secondary scoliosis patients were neurologic deficit, death, superficial and deep wound infection, pulmonary non-embolic

complications, non-fatal hematologic complications, dural damage, and implant-related complications (60).

3.7. Blood loss in secondary scoliosis surgery

Massive blood loss is one of the most prevalent complications of spinal fusion surgery. In their retrospective cohort study, Yu et al. reported that 59.7 percent of adolescents with NMS undergoing PSF had blood loss of over 30 percent of total blood volume (80). Edler et al. observed that 65 percent of NMS patients lost more than 50 percent of their total blood volume during PSF surgery (81). Studies examining the efficacy of antifibrinolytic agents, a drug class which will be thematized in the following sections, in reducing blood loss in NMS surgery, report a mean intraoperative blood loss to total blood volume ratio of over 100 percent in their control groups (82-84).

Permissible blood loss is defined as the maximum amount of blood loss a patient can tolerate before reaching a critical postoperative hemoglobin level, which would require further treatment via blood transfusion. The German Society of Anaesthesiology and Intensive Care Medicine defines the lowest allowable postoperative hemoglobin level as 7g/dl (85). A simplified calculation of permissible blood loss, as presented by Gross et al. reveals that a patient with a starting hemoglobin level of 15g/dl would be allowed to lose up to 53 percent of their total blood volume, before reaching the mentioned postoperative hemoglobin threshold of 7g/dl and thus, requiring blood transfusion (86). Considering the blood loss to total blood volume ratios reported by the mentioned studies, it can be concluded that secondary scoliosis patients are highly prone to exceeding permissible blood loss during PSF and requiring blood transfusion perioperatively. This constitutes a major challenge for both the surgical and anesthesia teams in treating

secondary scoliosis patients and makes it crucial to predict and treat massive blood loss in this patient population.

In various studies, several non-modifiable parameters, such as male sex, short stature, low body mass index (BMI), older age, preoperative MCA, and preoperative kyphosis, were shown to correlate with blood loss (80, 87-89). Also, the etiology of scoliosis is shown to predict both perioperative blood loss and blood transfusion requirements. Namely, NMS surgery is associated with a seven times larger risk of blood loss over 50% of total TBV and eight times higher risk of perioperative blood transfusion than idiopathic scoliosis surgery (81, 90, 91). Such relation is unknown for congenital or syndromic scoliosis surgery, as it is poorly investigated in the literature. However, current evidence suggests a similar predisposition for massive blood loss for these patients as well (66, 92).

Several studies point towards intraoperative blood loss as the culprit of several other complications in secondary scoliosis surgery. In their retrospective study, Toll et al. define major complications as those that result in prolonged hospitalization, re-hospitalization, neurological deficit, or revision surgery and found that the prevalence of such major complications was associated with greater intraoperative blood loss (93). Furthermore, Mohamad et al. showed that intraoperative blood loss is associated with an increase in pulmonary complications (16).

The large amounts of intraoperative blood loss in PSF mainly stem from the interruption of intravertebral veins and the decortication of numerous vertebrae, as required for the corrective procedure (94). Various studies reveal that blood loss is associated with fusion length and surgery duration. Therefore, long fusion constructs, lengthy skin incision and extensive surgical time, which are required to correct the advanced secondary scoliosis

curves, further exacerbate perioperative bleeding in these patients (80, 87-89, 92, 95, 96). In their prospective analysis, Modi et al. examined EBL per level fused across four core stages of PSF: dissection, screw insertion, curve correction, and bone grafting. They revealed that NMS patients are subjected to significantly higher blood loss during screw insertion and curve correction than idiopathic scoliosis patients. They attribute this outcome to significantly lower bone quality in their NMS groups, as both surgical phases involve exposing and manipulating bone (97). Accordingly, fusion constructs with high screw density, calculated as the number of inserted screws per level fused (90), compared to those with low screw density, were linked to increased blood loss and longer surgery duration (98-100). Each added screw bears the risk of malposition, neural and vascular impingement, as well as deep wound infection while increasing implant costs (61, 101). High-density constructs may be preferred to achieve a stable construct, maximum curve correction, and successful halt of progression, whereas current literature shows differing results for this correlation (102, 103). Therefore, it is vital to investigate the effects of screw density and fusion length on curve correction, as this knowledge may help achieve a balance between curve correction and limiting adverse outcomes, such as extended surgery duration and blood loss.

Although surgeons may contribute to limiting blood loss by modifying surgical parameters, the measures undertaken by the anesthesia team form the backbone of perioperative patient blood management. In their recent guidelines, the American Society of Anesthesiologists (ASA) summarizes intra- and postoperative blood management in four major steps: patient monitoring, transfusion of allogeneic red blood cells (RBC), reinfusion of intraoperatively salvaged blood and, the targeted treatment of excessive bleeding (104). These steps will be explored in the following sections.

3.8. Monitoring and treating perioperative blood loss

The most rapid way of monitoring blood loss is visual assessment. In case of excessive bleeding, the initial step is to visually differentiate between structural versus hemostatic bleeding. Structural bleeding accounts for 75 to 90 percent of total blood loss during surgery and stems from a definite source such as a damaged vessel, leading to rapid and massive bleeding. In contrast, hemostatic bleeding results from impaired coagulation and is characterized by persistent oozing of blood from multiple sites, not limited to the surgical incision (105). The volume of blood loss should also be determined, as this helps evaluate the need for treatment. However, visual assessment is notoriously inaccurate and frequently leads to underestimating the extent of bleeding. Rothermel et al. report that the surgical, anesthesia and nursing teams are equally inaccurate in their estimation. Years of experience or confidence are reported to have no impact on accuracy. They emphasize that such unreliable estimates are insufficient when setting the indication for blood transfusion (106). Therefore, the use of quantitative methods is recommended by multiple organizations for determining blood loss (32). The two essential qualitative methods are the gravimetric method, which is based on weighing soiled surgical sponges, and the colorimetric method, which utilizes machine-learning models in detecting blood loss amounts by analyzing photographs of surgical sponges (107, 108).

The assessment of postoperative blood loss consists of documenting drain outputs and determining hidden blood loss. The latter corresponds to the volume of intracorporal blood that is no longer in the vascular system, thus not contributing to the circulatory system. Such blood loss can be caused by vascular leakage into the interstitium and blood accumulation in an anatomic or iatrogenic cavity. Hidden blood can only be determined indirectly by subtracting the intraoperatively measured blood loss and the postoperative drain output from total perioperative blood loss (109). Several formulas have been

proposed for calculating perioperative blood loss using well-documented parameters such as pre- and postoperative hematocrit. Lopez-Picado et al. applied five different formulas in calculating blood loss estimates, using data from a previously published study. They revealed that formulas based on anthropometric and laboratory parameters did not result in differing clinical conclusions compared to quantitative blood loss estimation methods (110).

Perioperative blood loss causes anemia via the depletion of red blood cells and hemoglobin. Both hemoglobin and hematocrit are included in point-of-care blood gas analysis results, allowing rapid intraoperative detection of anemia. Blood loss also causes hypovolemia, which results in a drop in blood pressure and a subsequent increase in heart rate. Mean arterial pressure (MAP), which is the average blood pressure in the arterial system throughout one cardiac cycle, is monitored to detect hypotension and is regulated via the administration of vasoconstrictors, such as norepinephrine (NE), and fluids, to maintain perfusion. Hypovolemia, accompanied by anemia, causes tissue hypoxia, which becomes evident in rising serum lactate levels and high anion-gap metabolic acidosis, both of which are also detected via point-of-care blood gas analyses (111-113). If vital organ perfusion is also afflicted, this may be apparent in reduced organ function (*e.g.,* in reduced urine output if kidneys are affected) (104).

Blood transfusion is an essential element of perioperative blood management. Transfused RBC can be of either allogeneic or autologous origin. Autologous RBC is collected either via preoperative donation or intraoperatively by filtering and washing blood suctioned from the surgical field (114). The latter method is referred to as intraoperative salvage (IOS) or cell saving and may cause air embolism with improper application (115). Allogenic blood transfusion carries the risk of various complications, including febrile, cutaneous, hemolytic, and anaphylactic reactions, as well as the

contraction of viral diseases (116). Also, RBC transfusion is associated with increased mortality, postoperative infections, and the incidence of adverse outcomes in children undergoing non-cardiac surgery. Therefore, a restrictive blood transfusion strategy is favored (117). The hemoglobin level of 7 g/dl is the widely accepted threshold for RBC transfusion, while pediatric patients with cardiac disease, severe hypoxemia, active blood loss, or hemodynamic instability benefit from a more liberal transfusion strategy with a higher hemoglobin threshold. Apart from low hemoglobin, blood loss of over 30 percent of TBV, as well as pronounced symptoms of anemia, such as dyspnea and fatigue, also warrant RBC transfusion (118).

3.9 Coagulopathy

Aggressive treatment of perioperative blood loss with RBC and crystalloid fluids may indirectly cause impairment of coagulation and paradoxically contribute to an increase in blood loss. For optimal coagulation function, several physiological criteria need to be met, such as a body temperature of over 34°C, a blood pH level of over 7.15, an ionized calcium level of over 3.6 mg/dl, or 0.9 mmol/l, and appropriate concentrations of thrombocytes and coagulation factor proteins (85).

Massive administration of cold crystalloid fluids and RBC is an important cause of perioperative hypothermia. A drop in body temperature to 33°C results in impaired platelet aggregation, while a further decrease also causes coagulation factor dysfunction (119). Therefore, body temperature should be closely monitored perioperatively via the oral, esophageal, urinary bladder, rectal, ear, or axillary measurements and regulated via cutaneous warming, room temperature regulation, and warming of fluids before intravenous administration.(120, 121)

Anemia and hypovolemia promote tissue hypoxia, which causes high anion gap lactic acidosis. This exacerbates coagulopathy because a change in blood pH from 7.4 to 6.8 causes a 168 percent increase in clot formation time (122). It is important to mention that in patients with liver disease, either due to hypothermia or preexisting disease, lactate is poorly metabolized, causing increased and prolonged acidosis. Citrate, which aids in anticoagulation by binding calcium in stored blood, is a component of packed RBC. Citrate is also poorly metabolized in patients with liver disease and causes both acidosis and hypocalcemia. Patients who receive massive blood transfusion at a rate of more than one packed RBC every five minutes, exceeding the liver's capacity to metabolize citrate, are also susceptible to this transfusion complication, regardless of hepatic function (123).

Lastly, massive fluid resuscitation causes hemodilution and lowers the concentration of the already depleted coagulation factors, thrombocytes, and fibrinogen; worsening coagulation function (124). In summary, massive blood loss necessitates large amounts of RBC transfusion and fluid resuscitation, which in turn cause coagulopathy and increased blood loss, resulting in a vicious cycle (Figure 1). As previously mentioned, secondary scoliosis patients are subjected to high amounts of blood loss accompanied by increased RBC transfusion requirements. It is also shown that PSF surgery is associated with compromised clot formation and stability (94, 125). Therefore, it is crucial to prevent the mentioned vicious cycle in secondary scoliosis patients undergoing PSF by detecting and treating coagulopathy.

Standard coagulation function tests such as the international normalized ratio (INR) and activated partial thromboplastin time (APTT) are utilized in monitoring the intrinsic, extrinsic, and common coagulation pathways. Low fibrinogen and platelet levels indicate systemic clot consumption. Viscoelastic assays are used to assess coagulation function and clot stability. These point-of-care tests will be explored in detail in section 7.2. The

treatment of coagulopathy includes the replenishment of platelets, fibrinogen, and coagulation factors via fresh frozen plasma (FFP) and cryoprecipitate. There are also pharmacologic options that target specific steps of coagulation, such as antifibrinolytic agents (104, 126).

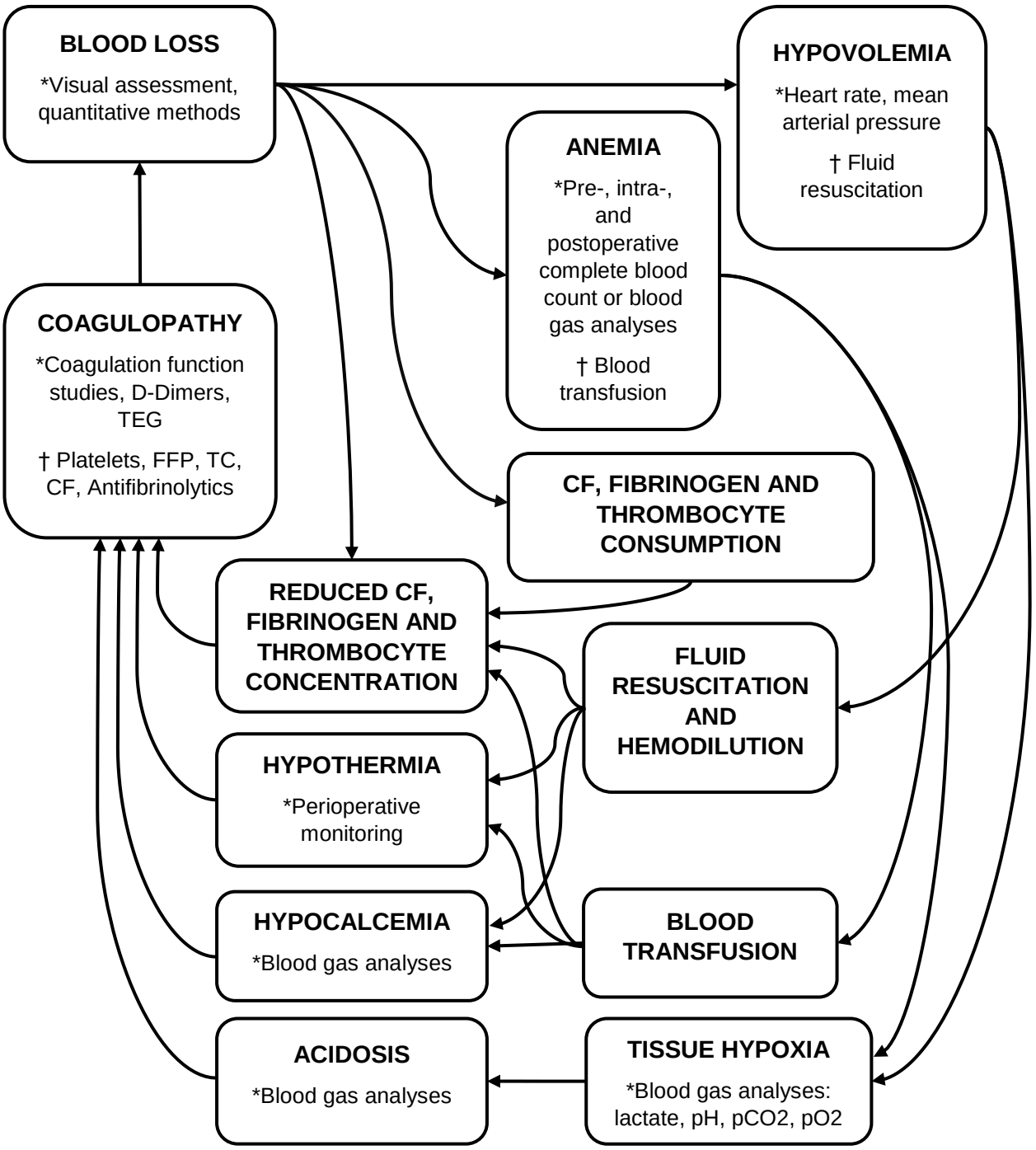

*Figure 1. Diagram demonstrating the vicious cycle leading to uncontrolled blood loss. *Method of diagnosing the respective element. †Treatment of the respective element. CF = Coagulation factors, TEG = thromboelastography, FFP = fresh frozen plasma, TC = thrombocyte concentrate.*

3.10 Antifibrinolytics

Antifibrinolytic agents help reduce bleeding by working against fibrinolysis, a process in which fibrin, the building block of blood clots, is degraded by the proteolytic enzyme plasmin. As a result of fibrinolysis, thrombi are dissolved, allowing vascular flow and sustaining bleeding. Plasmin derives from plasminogen via an activation process in which plasminogen is required to bind tissue plasminogen activator and an insoluble material such as fibrin. The receptors that allow this binding and consequently start fibrinolysis are called lysine-binding sites (127).

Of the antifibrinolytics in use today, aprotinin is a direct inhibitor of plasmin. In contrast, epsilon aminocaproic acid (EACA) and tranexamic acid (TXA) are synthetic lysine-analogs that inhibit plasminogen reversibly and competitively by binding the lysine-binding sites (128). Aprotinin once had a wide range of indications (e.g., in cardiac and orthopedic surgery) as an agent with good efficacy in decreasing perioperative blood loss and transfusion requirements. However, reports on an increased risk of renal failure, myocardial infarction, heart failure, stroke, encephalopathy, and mortality led to its withdrawal by the United States Federal Drug Administration in 2007 and the drug no longer finds use in orthopedic surgery today (129). Therefore, in meta-analyses comparing the three mentioned antifibrinolytics in reducing blood loss and blood transfusions in spinal surgery, aprotinin is underrepresented, while TXA is shown to be superior to EACA (130, 131). In Germany, TXA is the only recommended antifibrinolytic in treating massive intraoperative bleeding and will therefore be the only antifibrinolytic further discussed in this monograph (85).

3.11 Tranexamic acid

The German Federal Institute for Drugs and Medical Devices approves the usage of intravenous TXA for bleeding in the context of various interventions, including otorhinolaryngologic, obstetric, gynecologic, thoracic, abdominal, cardiovascular, and other major surgery. The current guidelines of the European Society of Anesthesiology recommend intravenous TXA in cardiac and non-cardiac pediatric surgery, as well as orthopedic surgery, namely in total hip arthroplasty (THA), total knee arthroplasty (TKA), and major spinal surgery, without further specification for fusion or scoliosis (113). It is worth mentioning that TXA has other routes of administration that are currently off-label, such as oral and topical (132). Research on the use of topical tranexamic acid (tTXA) in scoliosis surgery will be discussed in section 7.6.

Various studies point to the adverse effects of TXA. Zuffrey et al. demonstrated that TXA might promote a hypercoagulable state, leading to postoperative complications, including deep venous thrombosis, acute coronary syndrome, or intracerebral thrombotic events (133). Meanwhile, Ngaage et al. pointed out that the use of TXA may be linked to a tendency toward increased risk of postoperative neurological events, described as stroke, transient ischaemic attack, or delirium (134). In addition to these, there have been reports of hypotension, anaphylactic shock, allergic responses, gastrointestinal issues such nausea, constipation, diarrhea and acute kidney failure. Currently, one of the main contraindications is a history of allergic reactions to TXA. In the United States, a history of thromboembolic events and a predisposition to increased coagulation are regarded as contraindications for TXA use (135-138).

A major consideration in TXA therapy is the drug`s epileptogenic properties, as it crosses the blood-brain barrier and lowers the seizure threshold by blocking central inhibitory pathways (139). This is the reason why clinicians may refrain from deploying TXA in secondary scoliosis surgery, as many of the primary neuromuscular diseases, such as cerebral palsy, predispose patients to seizures (140). Although studies that examine TXA use in orthopedic surgery in patients with cerebral palsy do not report any TXA-related complications,(83, 141) such studies are rare and include a small number of patients. A history of seizures is currently listed as a contraindication for TXA by the German Federal Institute for Drugs and Medical Devices, along with a history of venous or arterial thrombosis, hyperfibrinolytic condition, and kidney failure (142). Due to the possible complications, it is vital to examine the efficacy of TXA for different patient populations and to set concrete indications to prevent unnecessary application and adverse effects.

Many studies were published, examining the efficacy of TXA on perioperative blood loss and blood product transfusion in pediatric scoliosis surgery. In their systematic review, Yuan et al. included ten such studies and concluded that TXA significantly reduces blood loss, though without a significant effect on transfusion requirements (143). However, these studies either examined adolescent idiopathic scoliosis exclusively or did not differentiate between idiopathic and non-idiopathic scoliosis.

In the literature, studies focusing on the effect of TXA in reducing blood loss exclusively in secondary scoliosis are scarce. This is also mentioned McNicol et al. in their meta-analysis, where they stress the lacking evidence of the effect of antifibrinolytics in secondary scoliosis surgery and call for further research reporting for this population separately (144).

4. Objective

Secondary scoliosis is highly progressive at an early age, causing persistent pain while compromising cardiopulmonary function, posture, balance, and patient autonomy. Over time, these complications increasingly aggravate the primary disease and have an immense impact on patients` quality of life. Surgical treatment via spinal interbody fusion is the sole means of definitively halting curve progression and averting the mentioned complications. Massive blood loss is one of the most frequent intra- and postoperative complications associated with this treatment. This is due to the lengthy dissection, bone exposure, and long surgery duration required for implanting the fusion construct. Moreover, the underlying primary disease predisposes secondary scoliosis patients to larger amounts of blood loss, which may make blood transfusion necessary. Massive blood loss, along with extensive volume resuscitation via crystalloid fluids and red blood cell transfusion, may cause coagulopathy, exacerbating blood loss. Therefore, preventing and treating massive blood loss is decisive in the perioperative management of these patients.

Tranexamic acid is an antifibrinolytic that is proven effective in reducing blood loss in pediatric spinal surgery. However, there is a lack of studies investigating this effect in secondary scoliosis patients. In this retrospective cohort study, we aimed to examine the efficacy of TXA in reducing blood loss and blood transfusion requirements in secondary scoliosis patients undergoing PSF. We also aimed to explore the effect of TXA on perioperative hematological parameters.

In pursuance of a better understanding of massive blood loss in secondary scoliosis patients, our secondary goal was to detect parameters that affect perioperative blood loss and blood transfusion. We also examined perioperative complications in our treatment

groups in order to assess the safety of TXA use. We sought to examine the effect of surgical parameters such as the number of implanted screws on blood loss and on surgical outcome, as the surgeon´s decision-making may have an effect on blood loss either directly or through parameters which effect blood loss.

5. Materials and methods

The study protocol was approved by the Ethical Committee of Charité - Universitätsmedizin Berlin with the application number EA2/207/20, and the study was conducted in accordance with the Declaration of Helsinki.

5.1 Patient inclusion

In this study, we retrospectively reviewed medical records of secondary scoliosis patients under the age of 18, who underwent primary PSF at Charité Campus Mitte, Center for Musculoskeletal Surgery in Berlin, from November 2014 to December 2020. Out of 72 patients meeting these inclusion requirements, five were excluded as the spinal fusion was accompanied by hemi- or total vertebrectomy. One patient was excluded due to a revision surgery within 24 hours of primary surgery. Out of the 66 remaining patients, 35 received intravenous TXA intraoperatively, and 31 did not, making up the “TXA” and the “No TXA” groups, respectively (Figure 2).

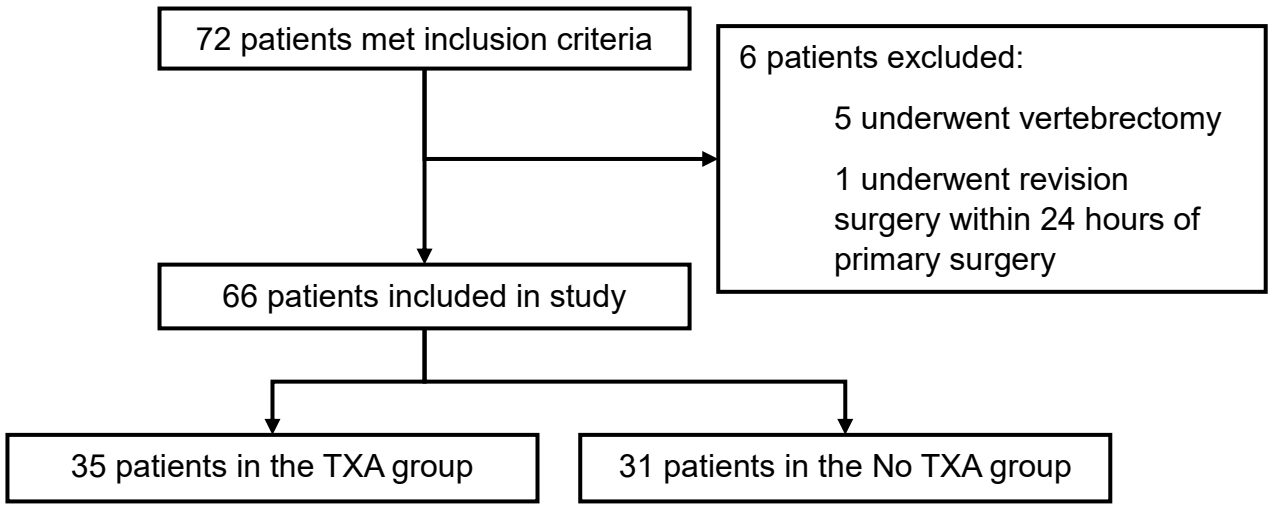

Figure 2. Study cohort diagram. TXA = Tranexamic acid

5.2 Surgical technique

The procedures were performed by one of four orthopedic surgeons and were conducted with the posterior-only approach. All patients received dual rod constructs exclusively with pedicle screws. Rod material was either titanium, chrome, or cobalt-chrome alloy. Patients were in the prone position throughout the procedure. The skin incision was made over the spinous processes. Transverse and articular processes were exposed by dissecting the fascia and the paravertebral muscles. Soft tissue bleeding was minimalized via electrocautery. Screws were inserted into pedicles, followed by verification of correct positioning via lateral and ap x-ray. Subsequently, laminae and spinal processes were decorticated. Chevron and Ponte osteotomies were performed per surgeons' preference in large or inflexible curves. In some patients, thoracoplasty was performed as indicated. The first rod was placed on the concave side, followed by the tightening of screws and bending of the rod to achieve frontal plane correction. The second rod was placed on the convex side, and screws were tightened, followed by local autologous bone grafting to promote bony fusion. Wound closure concluded the surgical procedure. Placed wound drains were removed on the second postoperative day.

5.3 Anesthesiologic management

Anesthetic induction was achieved via the total intravenous approach. Propofol bolus was accompanied by an infusion of an opioid, which was either remifentanil, fentanyl, or sufentanil, and a muscle relaxant: either cisatracurium or rocuronium. Perioperative pain therapy was continued with additional ketamine, piritramide, or morphine, along with non-opioids such as ibuprofen or metamizole. Patient blood management was conducted by the German Society of Anesthesiology and Intensive Care Medicine recommendations: RBC-transfusions were given with a target postoperative hemoglobin level of 7-9g/dl.

Platelet-concentrate transfusion was given at a platelet level below 100.000/µl in case of massive bleeding and 50.000/µl otherwise (85). Patients in the TXA-group received a continuous infusion of 10mg/kg body weight per hour with a TXA concentration of 100mg/ml. Inconsistently, some received a loading dose within a range of 300 to 1000mg. The TXA regimen was initiated according to surgical and anesthetic interdisciplinary decision-making. Anticipation of long surgery duration, extensive fusion, and surgical difficulties was motivational for a pre-incisional prophylactic deployment of TXA. Intraoperative observation of diffuse bleeding was an incentive to start the regimen intraoperatively. Bleeding risk, thromboembolic risk, anemia, blood gas analyses and viscoelastic assay results were also taken into account while deciding for TXA administration.

5.4 Data collection

Preoperative demographic data, including age, sex, height, weight, and the underlying cause of secondary scoliosis, was acquired for both groups using the SAP (Systems, Applications, and Products in Data Processing) patient data management system (PDMS). COPRA 6.2 PDMS was used for acquiring perioperative anesthesiology data such as the ASA grade (which classifies patients according to comorbidity burden) (145), surgical time, average MAP throughout surgery, blood pressure readings, mean and minimum intraoperative temperature, mean, maximum and minimum intraoperative heart rate, the volume of intraoperatively salvaged (IOS) blood transfusion, and the administered volume of TXA, NE, and crystalloid fluids. Blood pressure fluctuation was defined as the difference between the highest and lowest recorded intraoperative MAP (146). Minimum recorded pH and maximum recorded lactate were obtained from perioperative arterial blood gas analyses. Medical charts were ordered from the hospital`s

medical records archive and examined for the intraoperative and postoperative blood product transfusion, including packed RBC, plasma products, and platelet concentrates, as well as the day and time of their administration. Parameters collected from the preoperative laboratory results included hemoglobin, hematocrit, platelets, APTT, INR, and creatinine. Twelve patients, five of whom were female and seven of whom were male, had preoperative laboratory results that were more than a day old before the surgery. Preoperative laboratory data were acquired within four and nine days before surgery for female and male patients, respectively. Hemoglobin, hematocrit, and platelet levels were also obtained from the postoperative first and sixth (± 1) day laboratory results. Postoperative complications until discharge were documented.

5.5 Radiographic parameters and measurements

All patients had pre- and postoperative ap or pa spine radiographs taken in either sitting, supine or erect position. Preoperative images of three patients dated more than six months before the surgery and were, therefore, excluded from the analysis. All postoperative images were acquired before discharge. The parameters measured in the coronal plane included the length of deformity, MCA, and C7 offset. MCA was measured as the greatest angle between the superior endplate of a superior and the inferior endplate of an inferior vertebra. These two vertebrae also set the upper and lower end of deformity. C7 offset was measured as the horizontal distance between the C7 plumb line (C7PL) and the center sacral vertical line (CSVL). C7PL was drawn downwards from the center of the C7 vertebral body. CSVL was drawn upwards starting at the middle of the S1 upper endplate. Both lines were drawn parallel to the vertical edge of the radiograph. Thoracal kyphosis was measured as the angle between the superior endplate of T5 and

the inferior endplate of T12. Lumbar lordosis was measured as the angle between the superior endplate of T12 and the inferior endplate of L5 (Figure 3).

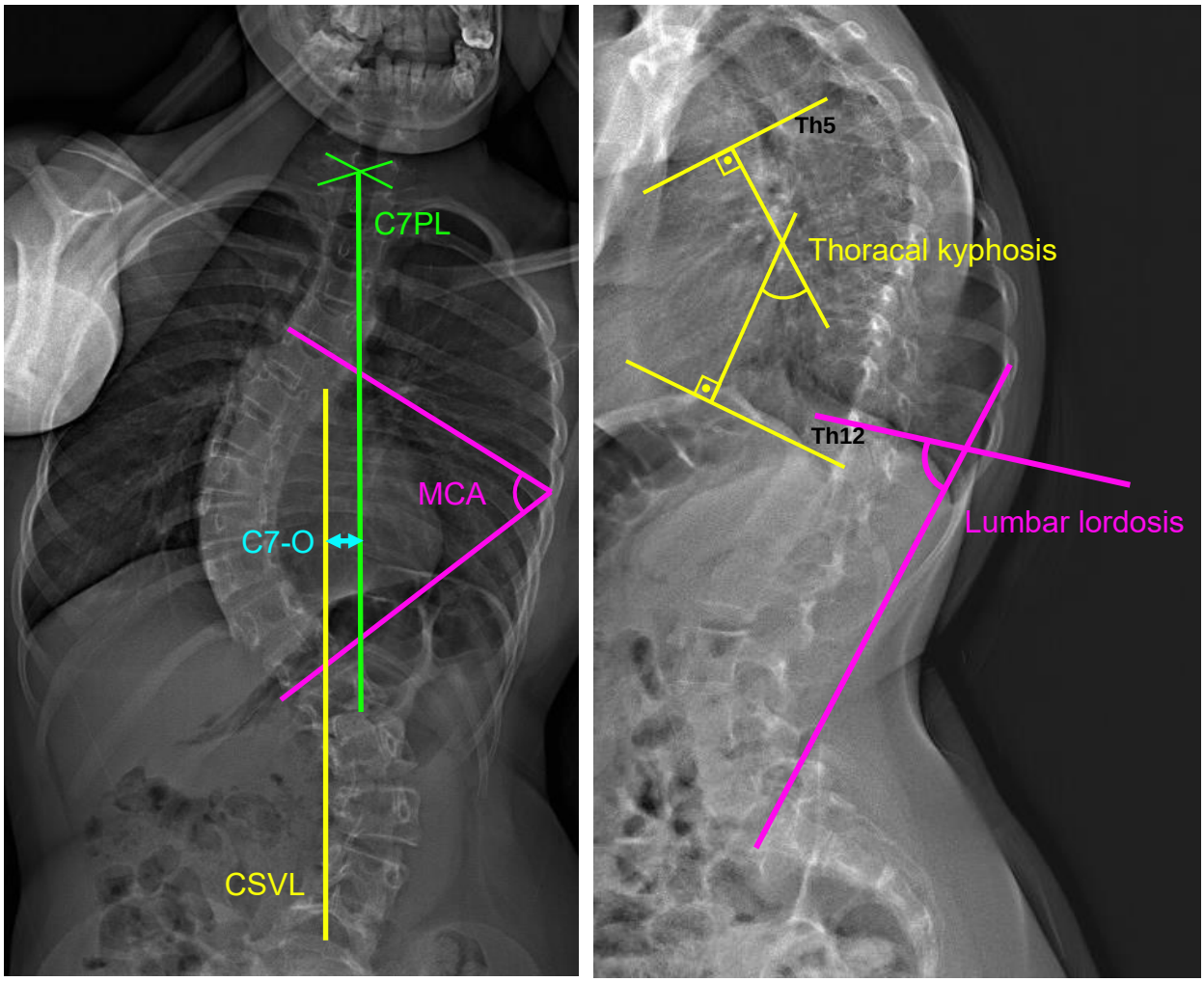

Figure 3. Measurement of radiographic parameters of an 11-year-old female neuromuscular scoliosis patient visualized in preoperative radiographs. The posteroanterior view (left) shows a thoracic dextroconvex curve with a major curve angle of 66 degrees and a C7-offset of 19mm. A thoracal kyphosis of 41 degrees and a lumbar lordosis of 78 degrees is measured on lateral view (right). C7PL = C7 plumb line. CSVL = Central sacral vertical line. C7-O = C7-Offset. Th12 = 12th thoracal vertebra. S1 = First sacral vertebra.

Postoperative ap, pa, and lateral radiographs were used in determining postoperative MCA, C7-offset, thoracal kyphosis, lumbar lordosis, fusion length, the number of spinal levels instrumented (i.e., implanted with one or more screws), and the number of screws implanted (Figure 4). All postoperative radiographs were acquired before discharge. Anchor density was defined as the number of implanted pedicle screws divided by fusion length. The correction rate of the spinal deformity was calculated as (preoperative MCA - postoperative MCA) / preoperative MCA (147).

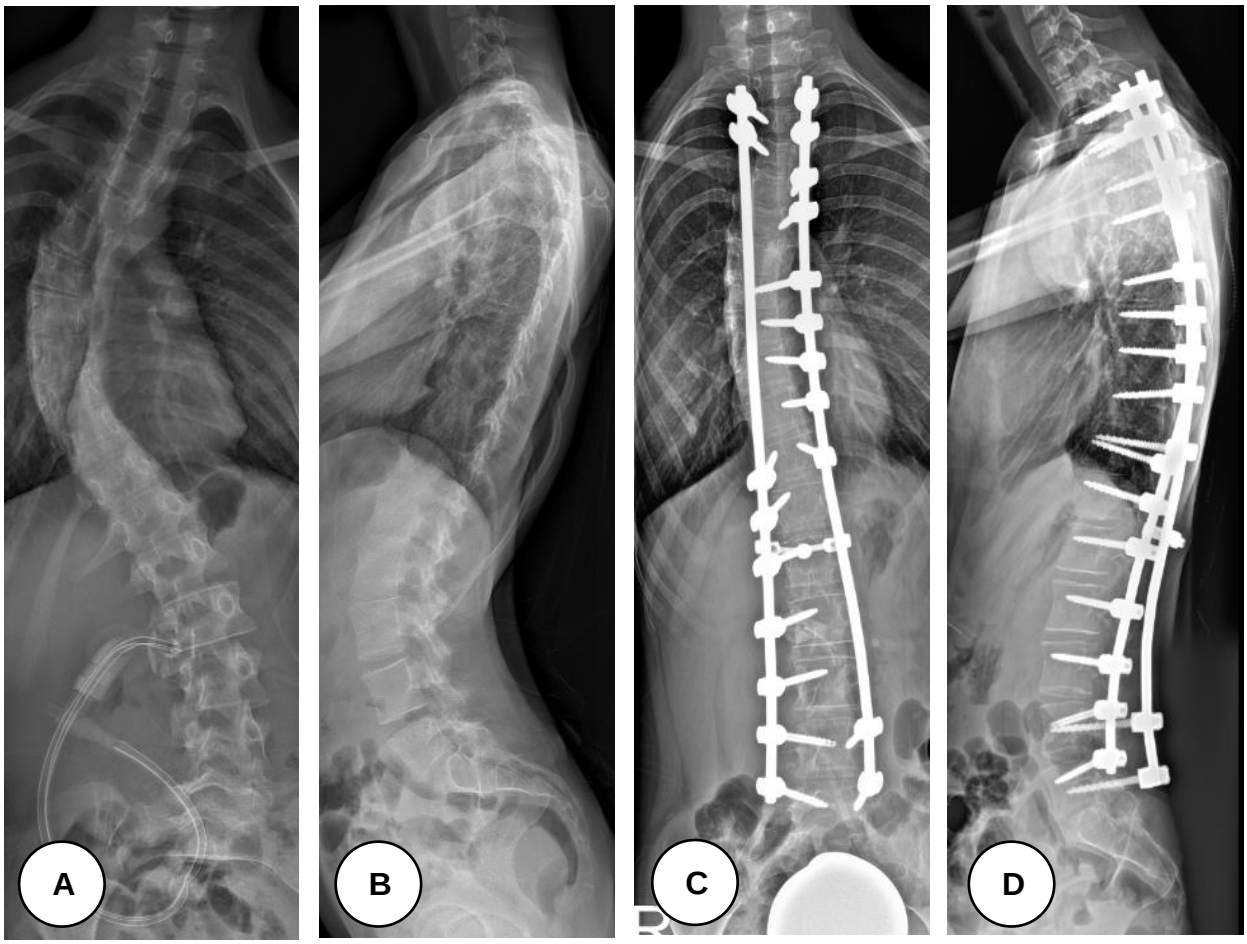

Figure 4 . Pre- and postoperative spinal radiographs of a 12-year-old female with neuromuscular scoliosis. Preoperative ap view (A) shows a main thoracal dextroconvex curve with an MCA of 67 degrees and a C7-offset of 10 degrees spanning from the fifth to the eleventh thoracal vertebra. Preoperative lateral view (B) shows a thoracal kyphosis of 38 degrees and a lumbar lordosis of 74 degrees. Postoperative ap view (C) visualizes a dual-rod construct with a transverse connector at the second lumbar vertebral level. Fusion length is 16 levels with a total of 20 screw anchors corresponding to an anchor density of 1.25 screws per level. MCA is reduced to 30 degrees with a curve correction of 55 percent. Thoracal kyphosis and lumbar lordosis are reduced to 17 and 43 degrees respectively, as seen in the postoperative lateral view.(D) ap = anteroposterior, MCA = major curve angle

5.6 Blood loss estimation

The formula proposed by Camarasa et al. (Figure 5), which calculates perioperative blood loss was used in our study, as our patient population had high transfusion rates and this formula incorporates the transfused allogeneic and autologous blood volume.[148] This formula involved preoperative and postoperative hematocrit, the TBV estimate, and the volume of transfused allogeneic and autologous red blood cells. Unlike the original formula, which defined TBV as 70ml/kg for adult males and 65ml/kg for adult females, we defined TBV as 70ml/kg for our pediatric patient population per prior studies.[96] As a further adaptation to the formula, the follow-up hematocrit used in the calculations was determined on the first postoperative day instead of the fifth. This adaptation was made because the first postoperative day was the only time-point with consistent blood tests for all patients in our included population. For all 35 patients who received IOS blood, cell salvage device outputs were collected to determine the hematocrit of the autologous transfusion. The mean detected hematocrit of 51 percent was applied to patients missing this information. The hematocrit on the first postoperative day was integrated into the calculation.

$$\text{TBL (ml)} = \frac{\text{TRCL (ml)}}{\text{mean H0-H1}}$$

TRCL = ARCL (ml) + VTRC (ml)

ARCL = TBV x (H0 – H1) ; TBV = weight (kg) x 70

VTRC = 1 iu packed homologous blood = 170 ml of red cells

Every 100 ml of concentrated blood from the recovery system corresponded to 51 ml red blood cells

Figure 5. Formulae adapted from the study by Camarasa et al. TBL = total blood loss; TRCL = total red cell loss; H0 = preoperative hematocrit; H1 = hematocrit on 1st postoperative day; ARCL = accepted red cell loss; TBV total blood volume estimate; VTRC = volume of transfused red blood cells.

5.7 Statistical analysis

Pre-, intra- and postoperative data were compared between groups: Student´s-T-test was used for normally distributed continuous parameters. For ordinal parameters and non-normally distributed continuous parameters, the Mann-Whitney U test was applied. The chi-square test was used for nominal parameters. Changes in hematocrit and hemoglobin levels over the three different times of measurement (preoperative, postoperative first day, and postoperative 6th [±1] day) were compared between the TXA and No TXA groups using the two-way repeated-measures analysis of variance. Linear regression analysis was used to examine the effect of different variables on EBL with the bias-corrected and accelerated (BCa) bootstrap confidence interval based on 1,000 bootstrap samples as EBL is generally not normally distributed. Missing values were excluded list-wise for this analysis. Spearman correlation was applied to detect parameters correlating with the EBL to TBV ratio, surgery duration, intraoperative RBC transfusion and curve correction rate. Statistical analyses were conducted using SPSS statistical software version 27 (SPSS Inc., Chicago, IL, USA), and $p < 0.05$ was considered significant.

6. Results

6.1 Demographic and preoperative data

A comparison of demographic and preoperative parameters is presented in Table 1. The TXA group consisted of 16 females (46%) and 19 males (54%). The No TXA group consisted of 16 females (52%) and 15 males (48%). Gender distribution did not differ significantly between the two groups (p=0.632). The mean age at surgery was 13.8 ± 2.3 and 13.8 ± 1.4 years in the TXA and No TXA groups, respectively (p=0.934). Both groups showed a broad spectrum of underlying diseases. DMD was the most common primary disease with 14.3 percent in the TXA-group vs. 16.1 percent in the No TXA-group, followed by CP (11.4% TXA-group vs. 3.2% No TXA-group), spina bifida (11.4% TXA-group vs. 9.7% No TXA-group), and SMA (2.9% TXA-group vs. 9.7% No TXA-group). Both groups did not differ significantly in their mean weight (p=0.963), height (p=0.642), BMI (p=0.643) or ASA score (p=0.568)

Preoperative laboratory data revealed similar a hematocrit (p=0.510), hemoglobin (p=0.336), platelet count (p=0.761), APTT (p=0.943), INR (p=0.633), and creatinine (p=0.178) between the two groups. Preoperative radiographs did not reveal a significant difference in MCA (p=0.260), length of deformity (p 0.893), thoracal kyphosis (p=0.391) or lumbar lordosis (p=0.582) between groups. Mann Whitney U test revealed a significantly greater C7 offset in the TXA group with a mean difference of 15 mm (p = 0.013).

Table 1 Demographic and Preoperative Data in Patients with Secondary Scoliosis Undergoing Spinal Fusion			
Variable	No TXA (N=31)	TXA (N=35)	p-value
Sex (F:M) * (*no.*)	16:15	16:19	0.632
Age at surgery (*years*) †	13.8 ± 1.4	13.8 ± 2.3	0.934
Weight (kg) †	42 ± 14	42 ± 14	0.963
Height (cm) †	149 ± 12.5	150 ± 14	0.642
Body mass index (*kg/m2*) †	18.8 ± 5.0	18.2 ± 4.7	0.643
ASA classification *			0.568
1	0 (0%)	2 (5.7%)	
2	8 (25.8%)	7 (20%)	
3	22 (71%)	25 (71.4%)	
4	1 (3.1%)	1 (2.9%)	
Preoperative radiographic parameters			
Major curve angle (*deg*) † (4/0) ¶	67 ± 21	74 ± 23	0.260
Length of deformity (*levels*) † (4/0)	8 ± 3	8 ± 2	0.893
C7 offset (*mm*) § (4/3)	19 (2-73)	28 (1-135)	**0.013 ‡**
Thoracal kyphosis (*deg*) † (7/9)	29 ± 19	24 ± 22	0.391
Lumbar lordosis (*deg*) † (7/8)	52 ± 26	47 ± 34	0.582
Preoperative laboratory data			
Hematocrit (*%*) †	40.5 ± 3.9	41.2 ± 4.6	0.510
Hemoglobin (*g/dL*) †	13.5 ± 1.5	14.1 ± 1.6	0.336
Platelets ($x10^6/L$) † (0/3)	291 ± 120	283 ± 78	0.761
Activated partial thromboplastin time (*sec*) † (0/5)	35.1 ± 4.2	35.2 ± 4.1	0.943
International normalized ratio § (0/5)	1.06 (0.92 – 1.28)	1.06 (0.92 – 1.23)	0.633
Creatinine (*mg/dL*) § (0/4)	0.46 (0.17 – 0.97)	0.44 (0.16 – 0.70)	0.178

*Pearson chi-square test used to compare groups. †The values are given as the mean and standard deviation, with the Student´s t-test used to compare groups. § The values are presented as the median (range), with the nonparametric Mann-Whitney U test used to compare groups. ‡ Significant. ASA = American Society of Anesthesiologists. ¶ Number of missing data in the (No TXA/TXA) groups.

6.2. Intraoperative and postoperative data

Table 2 demonstrates the comparison of intraoperative and postoperative parameters between groups. The timing of TXA administration varied between 49 minutes before incision to four hours and four minutes after incision. The mean surgical time was significantly higher in the TXA group, with a mean of 249 ± 92 minutes compared to 194 ± 71 minutes in the No TXA group (p=0.009). Surgical intervention parameters were similar in both groups regarding the number of levels instrumented (p=0.962), the number of screws implanted (p=0.060), and anchor density (p=0.668). Fusion length was significantly higher in the TXA group with 15 ± 1 levels compared to 14 ± 2 levels in the No TXA group (p=0.014). Thoracoplasty was performed in two patients in the No TXA group (7%) and seven patients in the TXA group (25%) (p=0.109). Postoperative radiographs did not reveal a significant difference in MCA (p=0.616), C7 offset (p=0.707), thoracal kyphosis (p=0.921), lumbar lordosis (p=0.693) or MCA correction rate (p=0.809) between groups. Laboratory data on the first postoperative day revealed a similar hematocrit (p=0.058) and platelet count (p=0.072). Postoperative hemoglobin was significantly higher in the TXA group with a mean of 9.1 ± 1.3 g/dl compared to 8.4 ± 1.5 g/dl in the No TXA group (p=0.038). Postoperative sixth (±1) day hematocrit (p=0.133) and hemoglobin (p=0.123) were similar in both groups. The median postoperative length of hospital stay was ten days (range 6 - 37) in the No TXA group and 11 days (range 8 – 73) in the TXA group and was significantly different between groups (p=0.024). Neither group had a thromboembolic event recorded postoperatively, until discharge. In the TXA group, three patients had postoperative nausea and vomiting, while this was the case in only one patient in the No TXA group. This difference had no statistical significance (p=0.364).

TABLE 2 Intraoperative and Postoperative Data in Patients with Secondary Scoliosis Undergoing Spinal Fusion			
Variable	No TXA (N=31)	TXA (N=35)	p-value
Surgical time (*min*) †	194 ± 71	249 ± 92	**0.009 ‡**
Surgical intervention data			
Fusion length (levels) †	14 ± 2	15 ± 1	**0.014 ‡**
No. of levels instrumented †	13 ± 2	13 ± 2	0.962
No. of screws implanted †	19 ± 2	20 ± 3	0.060
Anchor density (*screw/level*) †	1.37 ± 0.18	1.35 ± 0.17	0.668
Thoracoplasty (*Y:N*) *	2:29	7:28	0.109
Postoperative radiographic parameters			
MCA (*deg*) §	30 (11-85)	36 (9-97)	0.616
C7 offset (*mm*) § (2/3)	28 (1-60)	23 (0-133)	0.707
Thoracal kyphosis (*deg*) † (0/3)	20 ± 16	20 ± 17	0.921
Lumbar lordosis (*deg*) † (2/3)	49 ± 16	51 ± 18	0.693
MCA change (*deg*) † (4/0)	33 ± 14	36 ± 16	0.395
MCA correction rate † (4/0)	0.50 ± 17	0.49 ± 0.17	0.809
Postoperative day one laboratory data †			
Hematocrit (*%*)	24.8 ± 4.3	26.7 ± 3.9	0.058
Hemoglobin (*g/dL*)	8.4 ± 1.5	9.1 ± 1.3	**0.038 ‡**
Platelets (10^6/*L*)	185 ± 73	155 ± 60	0.072
Decrease in hemoglobin until postoperative day 1 (*g/dL*) †	5.1 ± 1.8	4.7 ± 2.1	0.482
Postoperative day 6 ± 1 laboratory data †			
Hematocrit (*%*) (4/1)	26.9 ± 4.2	28.6 ± 4.4	0.133
Hemoglobin (*g/dL*) (4/1)	9.0 ± 1.5	9.6 ± 1.4	0.123
Postoperative length of stay (*days*) § (1/0)	10 (6-37)	11 (8-73)	**0.024 ‡**

† The values are presented as mean and standard deviation, with the Student´s t-test used to compare groups. § The values are given as the median (range), with the nonparametric Mann-Whitney U test used to compare groups. ‡ Significant. * Pearson chi-square test used to compare groups. MCA = Major Curve Angle. ¶ Number of missing data in the (No TXA/TXA) groups.

6.3 Hemoglobin and hematocrit course

Time had a significant effect on hematocrit ($F(1,118) = 231.721$; $p < 0.001$) and hemoglobin ($F(1,118) = 221.183$; $p < 0.001$), with the highest mean hematocrit and hemoglobin measured preoperatively and the lowest mean hematocrit and hemoglobin measured on the first postoperative day. Both groups had a significant between-subjects-effect for hematocrit ($F(1,59) = 4.460$, $p= 0.039$) and hemoglobin ($F(1,59) = 5.736$, $p=0.020$), with the TXA group having a higher mean hematocrit and hemoglobin than the No TXA group throughout all three times of measurement. However, time and group interaction was insignificant for both hematocrit ($p = 0.782$) and hemoglobin ($p = 0.926$) (Figures 6, 7).

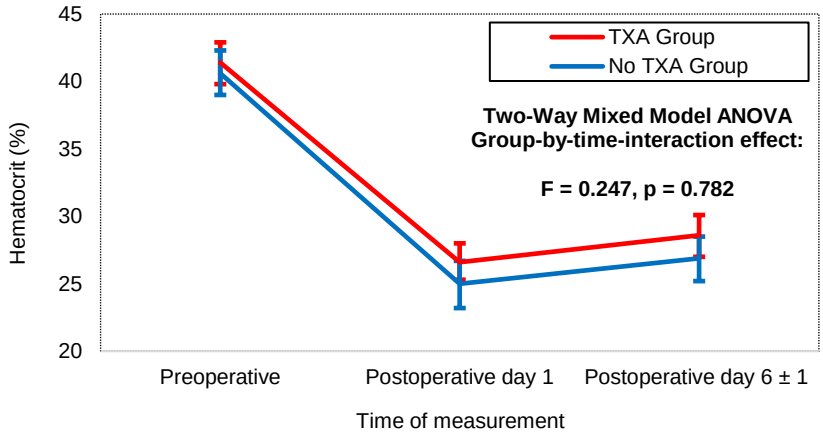

Figure 6. Changes in hematocrit levels over different times of measurement in the TXA group and the No TXA group. The error bars represent the 95% confidence interval.

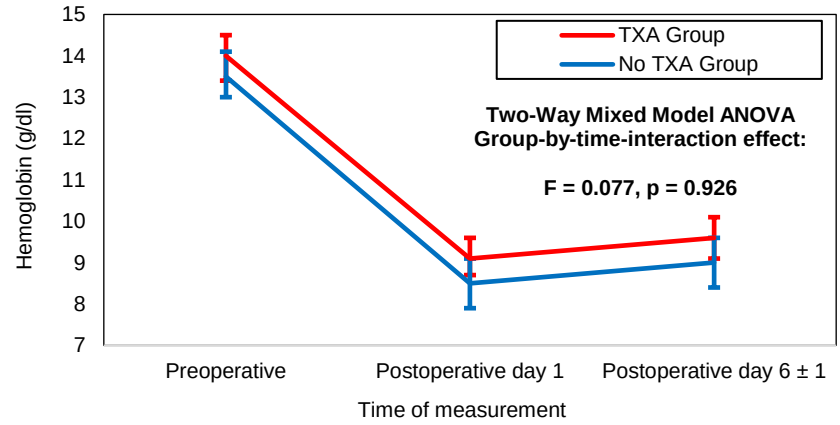

Figure 7. Changes in hemoglobin levels over different times of measurement in the TXA group and the No TXA group. The error bars represent the 95% confidence interval.

6.3. Anesthesiologic parameters and blood products

A comparison of intraoperative anesthesiologic parameters between the groups is demonstrated in Table 3. Both groups did not differ significantly in intraoperatively administered crystalloid volume (p=0.776) and volume per kg weight (p=0.913). The fraction of patients who received iv NE intraoperatively was similar in both groups (p=0.116). The groups did not differ in perioperatively measured MAP (p=0.577), blood pressure fluctuation (0.627), mean heart rate (p=0.544), maximum recorded heart rate (p=0.615), minimum recorded heart rate (p=0.715), minimum recorded pH (p=0.239), maximum recorded lactate (p=0,785), mean temperature (p=0.060). The minimum recorded temperature differed significantly (p=0.008) between the two groups. The No TXA group had a minimum recorded temperature of 35.3 ± 0.9°C, whereas, in the TXA group, it was 34.6 ± 1.1°C, thus lower by 0.7°C.

TABLE 3 Intraoperative Anesthesiologic Parameters in Patients with Secondary Scoliosis Undergoing Spinal Fusion			
Variable	No TXA (N=31)	TXA (N=35)	p-value
Total administered crystalloid §			
ml	3000 (1500-6000)	3000 (1000-7000)	0.776
ml/kg	80 (38-172)	78 (21-224)	0.913
Norepinephrine administration (*no. [%] of patients*) *	21 (68%)	17 (49%)	0.116
MAP (mmHg) †			
Mean	73 ± 6	72 ± 6	0.577
ΔMAP	45 ± 18	47 ± 17	0.627
Heart rate (bpm) †			
Mean	83 ± 12	81 ± 12	0.544
Maximum	105 ± 17	107 ± 19	0.615
Minimum	63 ± 16	62 ± 9	0.715
Minimum recorded arterial blood pH †	7.37 ± 0.07	7.35 ± 0.07	0.271
Maximum recorded lactate *(mg/dl)* †	9 ± 4	10 ± 6	0.570
Temperature (°C)			
Mean †	35.9 ± 1.0	35.5 ± 0.9	0.061
Minimum †	35.3 ± 0.9	34.6 ± 1.1	**0.008 ‡**

*Pearson chi-square test used to compare groups. §The values are given as the median (range), with the nonparametric Mann-Whitney U test used to compare groups. †The values are presented as the mean and standard deviation, with the Student's t-test used to compare groups. ¶ Number of missing data in the (No TXA/TXA) groups. ‡ Significant. MAP = mean arterial pressure. ΔMAP = Blood pressure fluctuation, defined as the difference between the highest and lowest recorded intraoperative MAP.

Intra- and postoperatively transfused blood products are demonstrated in Table 4. A significantly higher percentage of patients in the TXA group received intraoperative blood product transfusions compared to the No TXA group except for packed RBC (p=0.508). IOS autologous blood was administered to 24 patients (68%) in the TXA group and 11 patients (35%) in the No TXA group (p=0.007). The TXA group received a significantly higher IOS blood transfusion volume than the No TXA group (p=0.009). Plasma products were administered to 27 patients (77%) in the TXA group, and eleven patients (35%) in the No TXA group (p=0.001). The TXA group received a higher volume of plasma products than the No TXA group (p<0.001). Platelet concentrates were administered to six patients (17%) in the TXA group and no patients (0%) in the No TXA group (p=0.016). Postoperatively, a similar percentage of patients in both groups received packed RBC (p=0.163), plasma products (p=0.579), and platelet concentrates (p=0.931).

TABLE 4 Transfusion of Blood Products for Patients with Secondary Scoliosis Undergoing Spinal Fusion			
Variable	No TXA (N=31)	TXA (N=35)	p-value
Transfusion of cell salvage blood			
no. (%) of patients *	11 (35%)	24 (68%)	**0.007 ‡**
ml § (0/1) ¶	0 (0 – 565)	200 (0 – 2341)	**0.009 ‡**
Transfusion of packed red blood cells			
Intraoperative (*no. [%] of patients*) *	17 (55%)	22 (63%)	0.508
Intraoperative (*310 ml*) §	1 (0-3)	1 (0-8)	0.293
Postoperative (*no. [%] of patients*) *	22 (71%)	19 (54%)	0.163
Postoperative (*310 ml*) §	1 (0-3)	1 (0-3)	0.255
Transfusion of plasma products			
Intraoperative (*no. [%] of patients*) *	11 (35%)	27 (77%)	**0.001 ‡**
Intraoperative (*220 ml*) §	0 (0-6)	3 (0-21)	**< 0.001 ‡**
Postoperative (*no. [%] of patients*) *	7 (23%)	10 (29%)	0.579
Postoperative (*220 ml*) §	0 (0-4)	0 (0-8)	0.482
Transfusion of platelet concentrates			
Intraoperative (*no. [%] of patients*) *	0 (0%)	6 (17%)	**0.016 ‡**
Intraoperative (*240 ml*) §	0 (0-0)	0 (0-2)	**0.016 ‡**
Postoperative (*no. [%] of patients*) *	1 (3%)	1 (3%)	0.931
Postoperative (*240 ml*) §	0 (0-1)	0 (0-1)	0.931

*Pearson chi-square test used to compare groups. §The values are given as the median (range), with the nonparametric Mann-Whitney U test used to compare groups. ¶ Number of missing data in the (No TXA/TXA) groups. ‡ Significant.

6.4. Blood loss

Table 5 demonstrates the EBL calculations for both groups. Total EBL (p = 0.531), EBL to TBV fraction (p = 0.422), EBL per minute (p = 0.234) and EBL per level fused (p = 0.871) did not differ significantly between groups. Median EBL for the TXA and No TXA group was 2058 ml (Range: 1019 – 4170ml) and 2602 ml (Range: 810 – 9262ml) respectively.

TABLE 5 Estimated Blood Loss for Patients with Secondary Scoliosis Undergoing Spinal Fusion

Variable	No TXA (N=31)	TXA (N=35)	p-value
Total EBL (*mL*) (0/1)§	2058 (1019 – 4170)	2602 (810 – 9262)	0.554
EBL to TBV fraction (0/1)	0.82 (0.26 – 1.28)	0.84 (0.23 – 3.13)	0.590
EBL per minute (*mL/min*) (0/1)	12.8 (4.7 – 27.5)	8.7 (2.9 – 36.2)	0.196
EBL per level fused (*mL*) (0/1)	168.0 (63.7 – 278.0)	152.9 (54.0 – 617.5)	0.783

§ The values are given as the median (range), with the nonparametric Mann-Whitney U test used to compare groups. EBL1 = Estimated blood loss until postoperative day 1. TBV = Total blood volume estimate.

Multiple linear regression modeling based on the 1000-sample bootstrapping method for the relationship between EBL and age, sex, weight, preoperative major curve magnitude, surgery duration, fusion length, TXA administration, minimum intraoperative pH level, minimum intraoperatively recorded body temperature, as well as the volume of intraoperative plasma and platelet transfusions is presented in Table 6. A significant negative influence of TXA administration (B=-602.185 [BCa 95% CI: -1027.301, -90.701], p=0.031) and a significant positive influence of weight (B=31.962 [BCa 95% CI: 9.942, 54.184], p=0.006) and intraoperative plasma transfusion (B=185.265 [BCa 95% CI: 22.195, 312.568], p=0.028) were revealed. Age (p=0.409), sex (p=0.926), preoperative

main curve magnitude (p=0.235), surgery duration (p=0.516), fusion length (p=0.066), minimum intraoperative pH level (p=0.954), minimum recorded intraoperative temperature (p=0.923) and the number of intraoperatively transfused platelet concentrates (p=0.290) did not significantly predict EBL.

TABLE 6 Multiple Linear Regression Modeling for Estimated Perioperative Blood Loss in Secondary Scoliosis Patients Undergoing Primary Spinal Fusion

Variable	B	BCa 95% CI	p-value
Age at surgery (*years*)	68.900	-96.641 – 205.511	0.409
Sex (*0=female, 1=male*)	27.274	-390.967 – 425.582	0.926
Weight (*kg*)	31.962	15.639 – 52.215	**0.006‡**
Preoperative major curve angle (*deg*)	8.228	-4.082 – 19.493	0.235
Surgery duration (*min*)	-1.127	-4.424 – 1.693	0.516
Fusion length (*levels*)	104.187	-2.568 – 212.359	0.066
TXA administration *(0=no, 1=yes)*	-602.185	-1112.580 – -110.955	**0.031‡**
Minimum recorded arterial blood pH	-129.819	-4704.808 – 3050.969	0.954
Minimum recorded body temperature (*°C*)	18.447	-400.640 – 377.795	0.923
Volume of intraoperatively transfused plasma products (*220ml*)	185.265	21.258 – 326.870	**0.028‡**
Volume of intraoperatively transfused platelet concentrates (*240ml*)	597.703	-382.260 – 2009.147	0.290

BCa = bias-corrected and accelerated. CI = Confidence interval ‡ Significant.

EBL to TBV fraction was significantly associated with the surgery duration (r_s = 0.265, p = 0.033). No significant association was found for fusion length (p = 0.607), number of implanted screws (p = 0.083), preoperative MCA (p = 0.201) and MCA correction rate (p = 0.950). Surgery duration also correlated with preoperative MCA (r_s = 0.284 , p = 0.025) and the number of implanted screws (r_s = 0.308 , p = 0.012).

RBC transfusion correlated significantly with surgery duration (r_s = 0.376, p = 0.002). There was no significant association with age (p = 0.464), sex (p = 0.634), preoperative MCA (p = 0.292), fusion length (p = 0.343) or TXA administration (p =0.296).

There was no correlation between MCA correction rate and anchor density (r_s = -0.142, p = 0.271) or between MCA correction rate and number of implanted screws (r_s = -0.001, p = 0.993).

The TXA and No TXA groups had no significant differences regarding complications until discharge. No thromboembolic events or hypersensitivity to TXA were recorded in either group. Four patients in the TXA group and one in the No TXA group had gastrointestinal complications such as nausea, vomiting, and gastroesophageal reflux (p=0.209). Four patients in the TXA group and three in the No TXA group had systemic inflammatory response syndrome postoperatively (p=0.818). Pneumonia was seen in two patients in the TXA group and one in the No TXA group (p=0.628). Pleural effusion was documented in two patients in the TXA group and no patient in the No TXA group (p=0.177). Two patients in the TXA group and one in the No TXA group had a urinary tract infection (p=0.628). Position-related neuropraxia was seen in one patient in the TXA group and one in the No TXA group (p=0.931). Two patients in the No TXA group and no patient in the TXA group had a seizure (p=0.127). Perioperatively, two patients in the TXA group and no patient in the No TXA group had a hemorrhagic shock (p=0.177). Single cases of

complications were recorded, such as respiratory insufficiency, urinary retention, shunt dislocation, dysphagia, superior mesenteric artery syndrome, intestinal dystonia, and IV-site inflammation in the TXA group (p=0.343). In the No TXA group, single cases of rod dislocation, superinfection of hematoma, atelectasis, and pancreatitis were recorded (p=0.284).

7. Discussion

7.1 Tranexamic acid in secondary scoliosis surgery

Secondary scoliosis patients are highly comorbid, and their overall well-being deteriorates over time due to the rapid curve progression, causing pain and affecting breathing and posture. Spinal interbody fusion is the only available treatment option that offers a definitive correction and halt of curve progression. This procedure is associated with massive blood loss which increases perioperative morbidity and necessitates treatment with allogeneic blood transfusion. TXA, which is an antifibrinolytic agent, is proven effective in pediatric spinal surgery in reducing blood loss. However, in the current literature, evidence for this effect in secondary scoliosis patients is limited. Therefore, in this retrospective study, our primary objective was to investigate the effect of TXA on perioperative blood loss in secondary scoliosis patients undergoing PSF.

Our results reveal a negative effect of TXA on EBL and higher hemoglobin levels on the first postoperative day upon perioperatively administering intravenous TXA. Furthermore, no thromboembolic events or TXA-hypersensitivity were recorded in our treatment group. To our knowledge, this is the largest study, to this day, to examine the efficacy of TXA in secondary scoliosis patients. Our results are aligned with existing studies concerning the effect of TXA on blood loss. We conclude that perioperative intravenous TXA is a safe option for limiting blood loss in secondary scoliosis surgery.

While our TXA and No-TXA groups did not differ significantly in preoperative demographic and laboratory data, a significant difference was noted in four parameters: preoperative C7-offset, surgery duration, fusion length, and minimum intraoperatively recorded temperature. Surgery duration and fusion length were shown to cause increased blood loss in previous studies(87), whereas intraoperative hypothermia is linked to coagulation

function abnormalities, further exacerbating blood loss (85). This discrepancy between groups reflects our patient blood management strategies, where an increased blood loss would be an incentive to deploy the TXA regimen. As current literature shows that all three parameters correlate with blood loss, a higher blood loss would be expected in the TXA group. Instead, the TXA group had significantly higher postoperative hemoglobin, while the hemoglobin and hematocrit courses were similar between groups. A linear regression model was calculated while controlling for the three deviating intraoperative parameters to reduce bias. Intraoperative plasma transfusion was the only positive predictor of blood loss. This was expected, as excessive blood loss requires plasma transfusion instead of excessive crystalloid fluid resuscitation, in an attempt to prevent coagulopathy. Our model revealed TXA administration to be the only negative predictor of blood loss. Thus, a significant reduction in blood loss may have been masked by longer surgery duration, longer fusion length, and lower minimum body temperature in the TXA group. Accordingly, surgery duration was significantly associated with blood loss in our patient population. However, while our groups did not differ in perioperative homologous RBC transfusion, a significant effect of TXA on transfusion was also not detected. Our TXA group was transfused significantly more autologous blood, which is also due to our patient blood management strategies.

To our knowledge, only four studies exist which examine the efficacy of TXA exclusively in secondary scoliosis patients. The results reported in these studies are presented in Table 7. In contrast to our study, which included different causes of secondary scoliosis, all four limited their patient population to a specific syndrome or neuromuscular disease. Consonantly with our results, all studies confirm a significant reduction of either EBL or the EBL to TBV fraction upon administering intravenous TXA perioperatively. However, varying results on decreased transfusion requirements are reported.

Table 7. The Present Study Compared With Studies Examining the Efficacy of TXA in Reducing Blood Loss and Transfusion Requirements in Secondary Scoliosis Surgery					
	Present study	Shapiro 2007 (82)	Dhawale 2012 (83)	Chou 2021 (84)	Ikwuezunma 2021 (149)
Disease	Secondary scoliosis	DMD-Scoliosis	CP with spinal deformity	SMA-Scoliosis	MFS-Scoliosis
Study type	retrospective	retrospective	retrospective	retrospective	retrospective
Determined blood loss	perioperative	intraoperative	intraoperative	intraoperative	intraoperative
Number of included patients (N)	66	56	70*	30	52
TXA loading dose	0-1000 mg	100 mg/kg	100 mg/kg	100mg/kg	N/A
TXA maintenance dose (mg/kg/h)	10	10	10	10	N/A
EBL in TXA group (ml)	2331 (810 – 9262)	1944 ± 789	1301	1327 ± 685	1023 ± 534
EBL in No TXA group (ml)	2058 (1019 – 4170)	3382 ± 1795	2684	2024 ± 1673	1436 ± 1022
Is the EBL difference significant?	No (p=0.531)	Yes (p<0.001)	Yes (p<0.001)	No (p=0.174)	Yes (p=0.001)
EBL/TBV in TXA group (%)	84 (29-300)	47 ± 28	N/A*	52 ± 18	27 ± 16
EBL/TBV in No TXA group (%)	78 (26-128)	112 ± 67	120 ± 80	107 ± 95	36 ± 21
Is the EBL/TBV difference significant?	No (p=0.422)	Yes (p<0.001)	N/A	Yes (p=0.011)	No (p=0.05)
Significant reduction of allogeneic RBC transfusion in TXA group?	No	Yes	No	Yes	No

*The epsilon-aminocaproic acid subgroup in this study is excluded from the displayed parameters.
DMD = Duchenne Muscular Dystrophy, CP = Cerebral Palsy, SMA = Spinal Muscular Atrophy, MFS = Marfan syndrome, EBL = Estimated blood loss, EBL/TBV = EBL to total blood loss fraction, RBC = Red blood cells

The earliest of these studies was conducted by Shapiro et al. They retrospectively examined pediatric DMD patients with secondary scoliosis undergoing PSF.(82) A similar number of patients as our study was included, with a similar mean age at surgery. Compared to our patient population, a smaller mean preoperative MCA was observed with 45 and 51 degrees in the No TXA and TXA groups, respectively. Our No TXA and TXA groups had larger mean preoperative MCA, namely 67 and 74 degrees, respectively. This discrepancy may have been caused by the heterogeneous makeup of our patient population considering primary disease. The surgical technique was also different as all patients received sublaminar wire-fixation. In contrast to our study, blood loss was calculated using quantitative measurements. Sponges were weighed, and the blood volume from surgical field suction and cell salvage system reservoir was taken into account. While it was not stated how the TXA administration was decided, the two parameters that complicated the comparison between our groups, surgical time and fusion length, were similar in both groups. A lower mean EBL in the TXA group (1944ml) and a higher mean EBL in the No TXA group (3382ml) were reported, compared to our TXA (2638ml) and No TXA (2229ml) groups, respectively. Furthermore, Shapiro et al. also detected a correlation between surgery duration and the EBL to TBV ratio in the No TXA group. In contrast, such correlation was absent in the TXA group, showing the efficacy of TXA in limiting the effect of surgery duration on intraoperative bleeding. However, in our study, such correlation was found in both the No TXA and TXA groups. Shapiro et al. also revealed less autologous and homologous blood transfused in the TXA group, which was not the case in our study population.

A similar study was conducted by Dhawale et al., examining pediatric CP patients who underwent spinal surgery (83). In this multicenter study, 84 patients either received no antifibrinolytic or were administered either TXA or EACA intraoperatively. Although both

antifibrinolytics were included in this study, results for TXA were reported separately, allowing a comparison with our results. A further difference to our study is that four patients who underwent kyphosis correction were also included. Moreover, three types of fusion constructs were applied: all-screw constructs, all-sublaminar wire constructs, or hybrid constructs where sublaminar wires were utilized for proximal fixation and screws were implanted for distal fixation. Blood loss was estimated by the anesthesiologist from sponges, suction canisters, cell salvage, and surgical drapes. Similar to Shapiro et al., they also report a lower mean EBL in their TXA group (1301ml) and a higher EBL in their No TXA group (2684ml) compared to the TXA and No TXA groups in our study, respectively. Similar to our study, no efficacy of TXA in reducing homologous RBC transfusion was shown. However, like Shapiro et al., this study also revealed the efficacy of TXA in reducing intraoperative autologous blood transfusion.

A recent retrospective study by Chou et al. reports similar results (84). In this study, a significant reduction of blood loss upon TXA administration is reported in SMA patients with secondary scoliosis undergoing PSF. The patient population in this study did not consist exclusively of pediatric patients. However, their No TXA and TXA groups did have a mean age similar to our study population, with 14.5 and 12.7 years respectively, but with a broader distribution. Patients in this study were recruited over 27 years. The TXA group consisted of their most recent patients because TXA was given to all patients after 2009 and to none before that year. This division bears a high risk of bias, e.g., due to a potential increase in the surgeons´ competence and possible changes to the surgical setting over time**.** On the other hand, such division may have allowed possible disparities between the TXA and No TXA groups to be overcome, as evident in the similar surgical time between the groups, in contrast to our study. Furthermore, Chou et al. limited the patient population to a long fusion construct from the second or third thoracic vertebra to

the pelvis. In contrast, the fusion length in our patient population varied from 7 to 16, which reflects our heterogeneous patient population with various primary diseases. Another difference in our study is that Chou et al. used a hybrid construct consisting of proximal sublaminar wires and distal screw fixation. In contrast, screws were the only anchors in our study. Though not statistically significant, Chou et al. report higher mean blood loss in their No TXA group (2638 ml) and lower mean blood loss in their TXA group (1327 ml), which is parallel with the findings of Shapiro et al. and Dhawale et al. They also report significantly less EBL to TBV ratio in the TXA group compared to the No TXA group with a mean of 52.1 percent and 106.7 percent respectively. In comparison, our TXA group had a higher EBL to TBV ratio with 84 percent, and our No TXA group had less, at 78 percent. Like Shapiro et al., Chou et al. also report a significant reduction in homologous RBC transfusion. In addition, they also reported less crystalloid infusion in the TXA group, whereas this was not the case in our study. While the higher crystalloid infusion in their No TXA group may reflect the need to compensate for the higher blood loss and subsequent blood pressure drop, it is also worth considering that excess in crystalloid administration may favor bleeding as clotting factors are diluted. The time of crystalloid and TXA-infusion would be decisive in understanding this relation but was not mentioned in the study.

In their recent study, Ikwuezunma et al. were the first to examine the efficacy of TXA exclusively in non-neuromuscular syndromic scoliosis surgery. They only included Marfan syndrome patients and reported ahead of publishing a significant reduction in EBL and EBL/TBV in their TXA group. With a mean EBL of 1023 ml in their TXA group and 1436 ml in their no TXA group, they report less blood loss in both groups compared to the TXA and No TXA groups in our study, as well as the mentioned studies, respectively. This divergence may reflect the effect of underlying disease on blood loss. As previously

mentioned, higher blood loss in NMS surgery compared to non-neuromuscular cases was proven (96). However, to our knowledge, no study with a direct comparison of blood loss between neuromuscular and syndromic scoliosis patients exists. Ikwuezunma et al. also reveal no change in allogeneic RBC transfusion upon TXA administration as parallel to us and the study by Dhawale et al.

In summary, all four studies report significantly lower EBL and EBL to TBV ratios upon TXA administration. These results are parallel to ours, as they also confirm the negative effect of TXA on blood loss in secondary scoliosis surgery. All three NMS studies reported higher blood loss in their No-TXA groups than ours. Our study did not reveal any effect of TXA on allogeneic RBC transfusion. This finding is parallel to that of Dhawale et al. and Ikwuezunma et al. but contradicts Shapiro et al. and Chou et al. Therefore, the efficacy of TXA in reducing transfusion requirements in secondary scoliosis patients remains unclear.

It is important to note that neither published study had discrepancies in surgery duration and fusion length between treatment and control groups. This may be the reason why these studies were able to demonstrate lower blood loss in their TXA groups. The lack of intergroup discrepancy in the studies by Shapiro et al. and Dhawale et al. may have been caused by differing decision-making in TXA administration. It is noteworthy that in all three studies, the TXA group received a loading dose of 100mg/kg followed by a maintenance dose of 10mg/kg per hour. Only the maintaining dose was consistent in our study, and the loading dose varied between 0 and 1000mg. Such heterogeneity of the drug´s indication and dosing regimen across institutions results from the scarcity of research on TXA use in secondary scoliosis surgery and, consequently, lacking guidelines.

Another critical point is that all three studies included spinal fusion constructs with sublaminar wire fixation. Previous studies show conflicting results as to whether screw-only, sublaminar wire-only, and hybrid constructs differ in the amount of blood loss.(150-153) Therefore we believe our study is better suited for making conclusions on the efficacy of TXA in reducing blood loss in screw-only spinal fusion. A final central point setting our studies apart is that while all mentioned studies determined reported intraoperative blood loss, we utilized perioperative blood loss in our analysis. We will be discussing the difference between the two approaches in the next section.

7.2 Perioperative blood loss

In studies assessing blood loss associated with surgery, only intraoperative blood loss and the blood volume in postoperative drains are regarded. However, hidden blood loss is usually overseen or omitted. Upon applying the aforementioned calculations in determining hidden blood loss, studies reveal hidden blood loss to account for 26-60 percent, 49 percent, and 42 percent for THA, TKA, and adult PSF procedures, respectively (154). In their retrospective study, Wang et al. reveal hidden blood loss to account for 53.9 percent of total blood loss in pediatric scoliosis surgery. They report that hidden blood loss of 850 ml and higher was an independent risk factor for postoperative transfusion requirements.

With that regard, we believe it is essential to assess the efficacy of TXA in reducing perioperative blood loss as well. All studies examining the efficacy of TXA in secondary scoliosis surgery uniformly report a significant reduction in intraoperative blood loss. However, there is a lacking consensus on its efficacy in reducing transfusion requirements, which might result from undetermined hidden blood loss accounting for an

increased postoperative transfusion requirement. A separate calculation of hidden blood loss and intraoperative blood loss would be needed to address this problem.

7.2 Fibrinolysis as the driving force of bleeding in spinal fusion

Up to this point, we sought the answer to whether TXA reduces blood loss in secondary scoliosis surgery. Our results align with the mentioned studies conducted in the last years and show this to be the case. The next step in supporting our conclusion is to examine the mechanism of bleeding in secondary scoliosis surgery and understand how and to what extent TXA can address this. Therefore, considering that the effect of TXA on blood loss stems from its inhibitory effect on fibrinolysis, it is crucial to comprehend the physiology of this process and its role in causing blood loss in spinal surgery.

As previously mentioned, fibrinolysis describes the process in which blood clots, made up of interconnected fibrin molecules are lysed with the help of the serine protease plasmin. This process is physiological and allows vascular patency and the maintenance of circulation. However, excessive fibrinolysis also referred to as clot instability, may arise in specific settings, such as major surgery, and favor blood loss. Systemic excess of fibrinolysis primarily results from the imbalance between its activators, such as tissue plasminogen activator, and inactivators, such as plasminogen activator inhibitor-1 (PAI-1) and antiplasmin. In the surgical setting, such an imbalance is usually generated by the increased endothelial production of the mentioned activators as a reaction to vascular injury, hypoperfusion, and several other factors associated with surgery. Systemic fibrinolysis can also arise secondarily to hypercoagulation, as seen in major trauma and surgery. In this case, excessive and prolonged coagulation physiologically initiates fibrinolysis. However, the inhibitors of fibrinolysis are depleted, causing fibrinolysis to derail. This mechanism is similar to disseminated intravascular coagulation (DIC) in that

excessive coagulation is the starting cause of fibrinolysis. However, unlike DIC, coagulation does not arise pathologically and instead due to tissue damage associated with trauma or surgery. A third potential cause of fibrinolysis in surgical procedures is the dilution of antifibrinolytic proteins due to volume substitution with crystalloid fluids and RBC concentrates in case of excessive bleeding (155, 156).

Fibrinolysis can be detected via various diagnostic methods, such as viscoelastic assays and quantifying the biomarkers of fibrinolysis, which are fibrin degradation products (FDP) and D-Dimers. Unlike coagulation studies such as APTT and INR, these methods are not well-standardized or routinely deployed in the everyday perioperative setting. This is why the assessment and analysis of fibrinolysis are absent in this study and similar studies with a retrospective approach.

Viscoelastic assays provide a convenient option as they facilitate point-of-care coagulation monitoring during surgery and allow consequent intervention upon detection of hyperfibrinolysis. Thromboelastography (TEG) and rotational thromboelastometry (ROTEM®) are examples of viscoelastic assay platforms currently available for clinical use. Though with low sensitivity, these systems allow an interpretation of fibrinolysis via measuring the parameters of LY30 or LI30 in TEG or ROTEM®, respectively. Although calculated differently, both values correspond to the extent of clot lysis at 30 minutes after maximum clot stability, meaning a greater LY30 would point towards increased fibrinolysis (157, 158). The current ESA guidelines recommend the deployment of viscoelastic assays in both pediatric and major orthopedic surgery in diagnosing hyperfibrinolysis (113). This approach allows targeted treatment of excessive fibrinolysis with antifibrinolytics such as TXA.

As previously mentioned, TXA is indicated in major orthopedic surgery, such as in TKA and THA, along with spinal surgery. Meta-analyses confirm the efficacy of TXA in reducing blood loss and transfusion requirements in both TKA and THA (159, 160). In understanding the role of fibrinolytic dysfunction in postoperative thromboembolism and excessive bleeding, both of which are inherent in total joint arthroplasty procedures, Guler et al. enrolled patients undergoing TKA or THA. They measured the previously mentioned biomarkers of fibrinolysis perioperatively. Their results show increased D-dimers and PAI-1 and decreased antiplasmin in the arthroplasty group compared to the control group, indicating increased fibrinolysis (161). In their recent study, Zhang et al. compared two different TXA regimens (a single preoperative dose vs. six perioperative doses) and placebo in patients undergoing TKA. They showed that the TXA regimens significantly decreased blood loss. While the six-dose regimen achieved a greater reduction than the one-dose regimen, it also significantly reduced perioperative FDP and D-dimer levels (162). In brief, we can see that fibrinolysis in arthroplasty is successfully treated with TXA, allowing reduction of blood loss and transfusion.

A similar approach was taken for pediatric scoliosis surgery by Bosch et al. Their prospective study included 58 adolescent idiopathic scoliosis patients undergoing PSF and examined their perioperative coagulation profiles. D-dimer and FDPs were included along with platelet count, APTT, and INR in calculating a fibrinolysis score. Their results revealed that fibrinolysis score was associated with EBL per level fused and blood transfusion requirement, suggesting that fibrinolysis is the driving force of blood loss in PSF (125). In a more recent prospective study, Bosch et al. analyzed the effect of TXA on blood loss and RBC transfusion for idiopathic scoliosis patients undergoing PSF while utilizing TEG. Their results reveal that TXA significantly reduces the RBC transfusion rate, fibrinolysis score, and LY30. They also found fibrinolysis score to be associated with

blood transfusion rate. They conclude that TXA effectively limits fibrinolysis in PSF, supporting its administration in this patient population (163).

To our knowledge, there is just one study that examined the coagulation profile of individuals with secondary scoliosis undergoing PSF in such depth. In their prospective study, Brenn et al. compared coagulation profiles and viscoelastic assays of idiopathic scoliosis patients and CP patients with scoliosis undergoing spinal fusion. The only difference they identify is the longer PT and APTT in CP patients, though within laboratory norms, and an earlier start of increased bleeding in CP patients compared to idiopathic scoliosis patients, pointing towards a disparate nature of bleeding in this patient population (164). The purpose of this study was to explore possible coagulation function abnormalities in the secondary scoliosis group rather than assess fibrinolysis, which is why no fibrinolysis biomarkers were measured and reported. Also, TEG results were limited to coagulation parameters, while fibrinolysis parameters such as LY30 were omitted. We believe that, apart from further studies assessing the efficacy of TXA in reducing blood loss in secondary scoliosis surgery, studies that aim toward understanding the role of fibrinolysis in this patient population are needed. Despite views that excessive fibrinolysis is not required for TXA to reduce bleeding (156), we believe this approach to be even so validated; since a confirmation of fibrinolysis to be the primary driving force of bleeding in secondary scoliosis surgery may be an incentive to consider the prophylactic application of TXA in this patient population. This idea is also supported by the fact that rapid diagnosis of hyperfibrinolysis in case of extensive bleeding during surgery is complicated due to the low sensitivity of currently available viscoelastic assays, making it challenging to limit TXA administration only to cases with confirmed fibrinolysis.

7.3 Optimal tranexamic acid-regimen

A second important consideration regarding TXA treatment is the regimen. It was previously pointed out that the loading dose was inconsistent in our treatment group. This discrepancy is due to the lacking consensus on the optimal TXA regimen in the literature. In their systematic review, Wang et al. report both the loading and maintenance doses vary across studies examining TXA efficacy in scoliosis surgery, namely between 10-100 mg/kg (or 1-2 g) and 1-10 mg/kg/h (or 10-100 mg/h) respectively (130). While Yuan et al. report a similar disparity in their systematic review, they also reveal via a subgroup analysis that a high-dose TXA regimen, which they define as higher than 20 mg/kg, does not result in a distinctly lower intraoperative blood loss (143). Consonantly, in their systematic review, Yang et al. included studies examining TXA efficacy in spinal surgery. Upon defining the high dose regimen as higher than 15 mg/kg, they revealed the low dose regimen to be as effective in reducing blood loss. They conclude the efficacy of TXA to be dose-independent (165). Several prospective RCTs exist, comparing high versus low doses of TXA in pediatric scoliosis surgery, albeit with opposing results. Hasan et al. included idiopathic scoliosis patients, prospectively comparing a high dose regimen of 30 mg/kg + 10 mg/kg/h with a low dose regimen of 10 mg/kg + 1 mg/kg/h. They reveal low-dose TXA to be as effective as high-dose TXA in limiting surgical blood loss and transfusion requirements (166). In a similar study, Johnson et al. retrospectively compared the efficacy of a high dose TXA regimen of 50 mg/kg + 5 mg/kg/h with a low dose TXA regimen of 10 mg/kg + 1 mg/kg/h in idiopathic scoliosis surgery. They reveal the high dose regimen achieved significantly less blood loss than the low dose regimen with 695 ml versus 968 ml ($p=0.01$), respectively. This disagreement complicates decision-making and results in the mentioned heterogeneity in TXA regimens in and across institutions.

Current ESA guidelines recommend a loading dose of 20-25 mg/kg and an optional maintenance dose of 1-2 mg/kg/h, while the German Society of Anesthesiology and Intensive Care Medicine recommends a loading dose of 15-20 mg/kg or 1-2 g and an optional maintenance dose of 1-5 mg/kg/h.(85) However, these recommendations are made for patients with diffuse intraoperative or trauma-induced bleeding without age-related specification. Rozen et al. report that pediatric patients require a lower TXA concentration than adults for the complete in-vitro inhibition of fibrinolysis. Therefore, we believe that it is requisite for the optimal TXA regimen to be determined separately for pediatric patients (167).

In their recent review, Goobie et al. point out the lacking consensus across in-vitro studies on the optimal plasma concentration of TXA for the complete inhibition of fibrinolysis while also mentioning the absence of in-vivo studies addressing the same problem. They attribute this to the lack of feasible tools with good sensitivity and specificity in detecting fibrinolysis. As a result, the target plasma concentration of TXA varies in the literature, with a range of 10 to 150 µg/ml. They conclude that proposed TXA regimens resulting from pharmacokinetic models based on target plasma concentrations need validation via randomized prospective trials (168).

7.6 Is topical tranexamic acid an option for secondary scoliosis surgery?

The final aspect of perioperative TXA treatment which needs to be discussed is the route of administration. As previously described, TXA is not limited to systemic administration and is used as a topical agent in orthopedic surgery. It was previously shown that tTXA effectively reduces blood loss and transfusion requirements in TKA and THA surgery, and a combined intravenous and topical application was shown to be superior in that regard (169-172). Systematic reviews show that tTXA is also efficient in spinal surgery in limiting

perioperative blood loss (173, 174). To this day, two distinct ways of administering tTXA were shown to be effective in pediatric scoliosis surgery: In their prospective study, Dong et al. compared exclusive intravenous TXA with combined intravenous and topical TXA in idiopathic scoliosis patients undergoing spinal fusion. Following skin closure, they applied tTXA retrogradely through the postoperative drain in the operating room, with subsequent clamping to allow local drug action. They revealed blood drain volume and duration to be significantly lower in the combined tTXA-group, while transfusion rates were similar. However, they do not report intraoperative or perioperative blood loss, so it remains unclear if this method would limit hidden blood loss (175). George et al. assessed a different method, where surgical laps were soaked with tTXA and used for wound-packing intraoperatively. Compared to no tTXA, this method showed significantly lower intraoperative blood loss and transfusion rate (176). To our knowledge, only one study assessed the efficacy of tTXA in secondary scoliosis surgery. In their recent retrospective cohort study, Weissmann et al. compared four different intravenous and topical TXA combinations. Idiopathic scoliosis and NMS patients received either no TXA, exclusively intravenous TXA, exclusively tTXA, or combined intravenous and topical TXA. Topical TXA was applied intraoperatively, similar to George et al. The results show the combined approach to be superior in limiting blood loss. In contrast, the transfusion rate did not differ between groups. However, a subgroup analysis revealed that NMS patients did not have significantly different postoperative blood loss depending on the TXA group, unlike intraoperative blood loss (177). To conclude, it seems tTXA bears the potential of being an appropriate adjunct to intravenous TXA for limiting blood loss in scoliosis surgery. However, studies on this subject are sparse, and further investigation is needed to assess its efficacy in secondary scoliosis patients.

7.7 Optimizing surgical planning for reducing blood loss

Our analysis shows no effect of screw density on curve correction. This result is parallel with the study by Quan et al. (102). It is important to mention, that both our studies utilized postoperative radiographs before discharge in assessing curve correction. In contrast, studies that examined radiographs from follow-ups over a year following spinal fusion, report a positive correlation between anchor density and curve correction (61, 103). This may point toward the efficacy of high-density constructs primarily in halting curve progression rather than achieving immediate curve correction.

Our results also revealed screw count to be associated with longer surgery duration and surgery duration was correlated with blood loss. However, no direct relation between screw count or high screw density with intraoperative blood loss was made. These results are not sufficient in making a deduction on whether these surgical parameters can be optimized to reduce blood loss.

7.8 Limitations

Our study had several limitations: (1) the treatment groups differed in major operative parameters due to the clinical reality and the retrospective approach of our study. This bias was overcome by running a linear regression model. (2) The TXA group had an inconsistent loading dose. Thus, the effect of TXA on blood loss may have been underestimated. (3) Intraoperative blood loss and drain outputs were not consistently documented, limiting our primary outcome to perioperative blood loss. (4) The follow-up hematocrit, used to calculate blood loss, was measured on the first postoperative day, as was consistently measured in our institution. Considering that postoperative drains were removed on the second postoperative day, this may have led us to underestimate perioperative blood loss. (5) Inconsistent documentation was not limited to drain outputs

and intraoperative blood loss and was also encountered in several other perioperative parameters. Our solution was to exclude patients with a missing parameter from the analysis of that individual parameter.

7.9 Conclusion

Overall, despite existing proof of the efficacy of TXA in reducing blood loss in secondary scoliosis surgery, further questions need to be answered to standardize the use of TXA in this patient population:

1. Other retrospective studies are needed that assess the efficacy of separate secondary scoliosis subtypes. Current literature is limited and bears initial proof only for DMD, CP, SMA, and Marfan syndrome patients. Furthermore, these studies include a small number of patients; hence there is a need for multicenter studies or systematic reviews.

2. The role of fibrinolysis must be further explored in perioperative bleeding in secondary scoliosis patients via utilizing viscoelastic assays and determining additional parameters such as D-dimers and FDPs. If fibrinolysis is eventually the leading cause of bleeding in these patients, this finding will support the prophylactic use of TXA.

3. Further studies should include calculating perioperative blood loss to assess hidden blood loss and determine whether it can be sufficiently reduced via intraoperative TXA or perioperative tTXA.

4. The efficacy of tTXA is also not adequately investigated in secondary scoliosis patients, and its use as an adjunct to intravenous TXA should be evaluated.

5. Further in-vitro and in-vivo studies are needed in determining the drug's target plasma concentration for inhibiting fibrinolysis to set an optimal TXA regimen. These steps should

be followed by prospective randomized controlled trials to implement a standardized perioperative TXA treatment in secondary scoliosis patients undergoing PSF.

Our study provides initial evidence for the significant negative effect of TXA on perioperative blood loss in secondary scoliosis patients. In this regard, our results are aligned with the current literature, while a reduction of transfusion requirements is still debated. Overall, TXA is a safe option for reducing perioperative blood loss in secondary scoliosis patients and should be integrated into the patient blood management strategies in PSF surgery. Further studies are required to standardize the regimen, as well as the route and time of application.

8. Literature

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Statutory Declaration

“I, Ali Eren Güven, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic The Efficacy of Tranexamic Acid in Reducing Perioperative Blood Loss in Secondary Scoliosis Surgery (*Die Wirksamkeit der Tranexamsäure zur Reduktion des Perioperativen Blutverlusts in der Operativen Therapie Sekundärer Skoliosen*), independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me.”

Date Signature

Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

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Bescheinigung

Hiermit bescheinige ich, dass Herr *Ali Eren Güven* innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: 11.02.20
- Termin 2: 17.12.20
- Termin 3: 06.01.21
- Termin 4: 18.08.22

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Prüfung der Normalverteilung
- Unabhängiger t-Test und Mann-Whitney-U-Test
- Zweifach wiederholte gemessene ANOVA
- Lineare Regression mit Bootstrapping-Verfahren

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 19.08.2022

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