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RESEARCH ARTICLE

EFFICACY OF TRANEXAMIC ACID IN REDUCING BLOOD LOSS AND BLOOD TRANSFUSION IN IDIOPATHIC SCOLIOSIS; A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: Tranexamic acid is a synthetic lysine-analogue antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin, it's a well-documented blood sparing agent. However, its routine use in idiopathic scoliosis surgery is poorly documented. The objective of this meta-analysis was to determine TXA's efficacy in reducing blood loss and blood transfusion in idiopathic scoliosis surgery.

Methods: Five databases (*MEDLINE, PUBMED, WEB of SCIENCE, EMBASE and The COCHRANE CENTRAL REGISTER of CONTROLLED TRIALS*) were searched to identify the relevant randomized controlled trials, prospective cohort control, and retrospective controlled trails regarding the TXA efficacy in idiopathic scoliosis surgery. Mean differences (MDs) of blood loss and blood transfusions in TXA-treated group compared to control and/or placebo group were extracted and combined using random-effect meta-analysis model.

Results: A total of 7 studies comprising 426 patients were included in the meta-analysis of blood loss according to the pre-defined selection criteria. TXA-treated group had an overall significantly ($p < 0.005$) less volume of blood loss (ES (MD) = 727.71 mL; CI=281.86 – 1173.56 mL). 6 studies comprising 346 patients were included in the meta analysis of blood transfusion, the TXA-treated group had an overall significantly ($p < 0.001$) less transfusion volume (ES (MD) = 268.30 mL; CI= 105.19 – 431.44 mL).

Conclusion: Patients treated with TXA had a significantly lower blood loss and lower rates of allogeneic blood transfusion than the control group. Further investigation is required regarding the safety of TXA before it can be generalized in the use of idiopathic scoliosis surgery.

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Introduction:-

Idiopathic scoliosis is the commonest type of spinal deformity confronting spinal surgeons.ⁱ With an insidious onset, relentless progression, and a deadly end result. Scoliosis represents a disturbance of the well organized twenty five member intercalated series of spinal segments. It is, at times, grossly oversimplified as mere lateral deviation of the spine, when in reality, it is a complex three-dimensional deformity.ⁱⁱ Two-dimensional imaging systems (plain radiographs or X-ray) remain somewhat limiting, and scoliosis is commonly defined as greater than 10° of lateral deviation of the spine from its central axis.ⁱⁱⁱ Once active intervention is indicated, surgical treatment to achieve solid

bony fusion is the treatment of choice.^{iv} It is well known that one of the main concerns regarding patients undergoing major operative procedures is the risk of increased perioperative bleeding^v and major morbidity and mortality rates are associated with intraoperative blood loss and transfusion, thus the use of antifibrinolytics and other measures to control bleeding is crucial. In response to large volumes of blood loss, patients will face an increase in the need of blood transfusion as well as other measures such as intraoperative blood salvage, hemodilution, and controlled hypotension^{vi}. Tranexamic acid is a synthetic lysine-analogue antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin; at high concentrations it non-competitively blocks plasmin, thus tranexamic acid inhibits the dissolution and degradation of fibrin clots by plasmin^{vii}. It has been implicated in major surgical specialties including cardiac surgery^{viii}, trauma^{ix} and total knee arthroplasty^x. Over the last decade, the use of pharmacological approach to control blood loss has highly been promising and recommended^{xi}. The use of TXA in spinal surgery has been studied and documented^{xii}, but the literature still lacks strong data studying its effectiveness in major spinal procedures. Scoliosis in particular, adolescent idiopathic scoliosis to be specific has a strong impact on patients undergoing scoliosis correction surgery whether it involves posterior or anterior spinal fusion. The procedure itself is not quite simple, in which the surgeon might have to face many objectives and difficulties whether they are intraoperative or postoperative which might include postoperative infection, spinal cord injury, and blood loss associated with major spinal instrumentation and its corresponding procedures. In a retrospective analysis that involved 340 patients and aimed to predict the operative blood loss during spinal fusion of adolescent idiopathic scoliosis, the estimated blood loss was 907 ± 775 mL for posterior spinal fusion, 323 ± 171 mL for anterior spinal fusion, and 1277 ± 821 mL for combined procedures^{xiii}, which emphasize that the blood loss in spinal fusion to correct adolescent idiopathic scoliosis cannot be neglected nor underestimated. The objective of this meta-analysis is to determine if the antifibrinolytic tranexamic acid is effective in reducing the amount of blood loss and allogeneic blood transfusion in patients with idiopathic scoliosis undergoing spinal fusion in order to correct the deformity.

Methods:-

Study Design:-

We conducted a meta-analysis and systematic review according to predefined guidelines provided by the Cochrane Collaboration. Five databases (*PUBMED*, *MEDLINE*, *COCHRANE CENTRAL REGISTER of CONTROLLED TRIALS*, *WEB of SCIENCE* and *EMBASE*) were searched to identify the relevant randomized controlled trials (RCTs), prospective cohort control (PCC), and retrospective control trials regarding the effectiveness of TXA in idiopathic scoliosis surgery.

Search Strategy and Data Source:-

Interrelated randomized controlled trials (RCTs), prospective cohort control, and retrospective control trials were distinguished in the MEDLINE and EMBASE, PUBMED, WEB of SCIENCE databases and the COCHRANE CENTRAL REGISTER of CONTROLLED TRIALS from January 1960 through December 2016. Key words used in the search included “antifibrinolytics”, “tranexamic acid”, “cyklokapron”, “aprotinin”, “trasylol”, “epsilon aminocaproic acid”, “amicar” and, “spinal curvatures”, “kyphosis”, “scoliosis”, “lordosis”, “anterior fusion” “posterior fusion”, “randomized controlled trial”, and “comparative study”, “prospective” and “retrospective”.

Inclusion and Exclusion Criteria:-

All the studies were included in accordance to all criteria included mutually based on criteria from 1 to 5 as follows; (1) randomized controlled trials, prospective cohort control and/or retrospective control; (2) subjects who underwent spinal fusion including cervical, thoracic and lumbar scoliosis correction surgery irrespective of anterior or posterior approach; (3) the route of intervention was TXA intravenous (IV) administration in the treatment (experimental) group, accompanied with matched control group and (4) the primary outcome measures should include one of the following outcomes: volume of total blood loss reported outcomes including intraoperative, postoperative, and total blood loss (primary outcomes); and (5) the outcomes that were described included the number of patients receiving blood transfusion, volumes of transfusion packed cells.

Studies should be excluded if they:-

(1) had no interventions of which was described above; (2) studies that included patient with a history of coagulation disorder or recent intake of anticoagulation drugs (one month). (3) Patients with severe cardiopulmonary, renal, and hepatic dysfunction and (4) did not contain any of the outcomes mentioned above (5) involved procedures in idiopathic scoliosis patient other than primary deformity correction.

Literature Search Results:-

The internet literature search on TXA yielded a total of 88 studies; PubMed (n=25); Medline (n=24); Cochrane Central Registered Controlled Trials (n=18); EMBASE (n=15) and Web of Science (n=16). Of these 88, only 25 articles were found to be relevant articles on scoliosis corrective surgery regardless of approach. Although all 25 studies were relevant, only 7 were selected for data extractions. The remaining 19 studies did not meet the inclusion criteria and/or did not contain the required information.

Data Extraction:-

Eligible articles were reviewed independently by 2 investigators. The titles and abstracts of the references were read. Any disagreement on a controversial study was settled by discussion and consensus with a third author. The collected data included the first authors' name, publication date, region/ethnicity, genotyping method and the total number of cases and controls.

Bias Risk Assessment:-

The included studies were assessed for risk of bias by 2 independent researchers and a managing reviewer. Methodological domains were graded individually according to (1) study's design; (2) specific to randomization sequence; (3) adequacy of the methods; (4) level of accuracy of the measurements of blood volumes; (5) appropriateness of the statistical tests used for reporting results. The included studies were graded accordingly (A) adequate = methods were reported and appropriate; (B) inadequate = methods were reported but inappropriate; or (C) unclear = methods were not reported. In addition, all efforts were made to ensure the implementations of Cochrane guidelines for literature search.

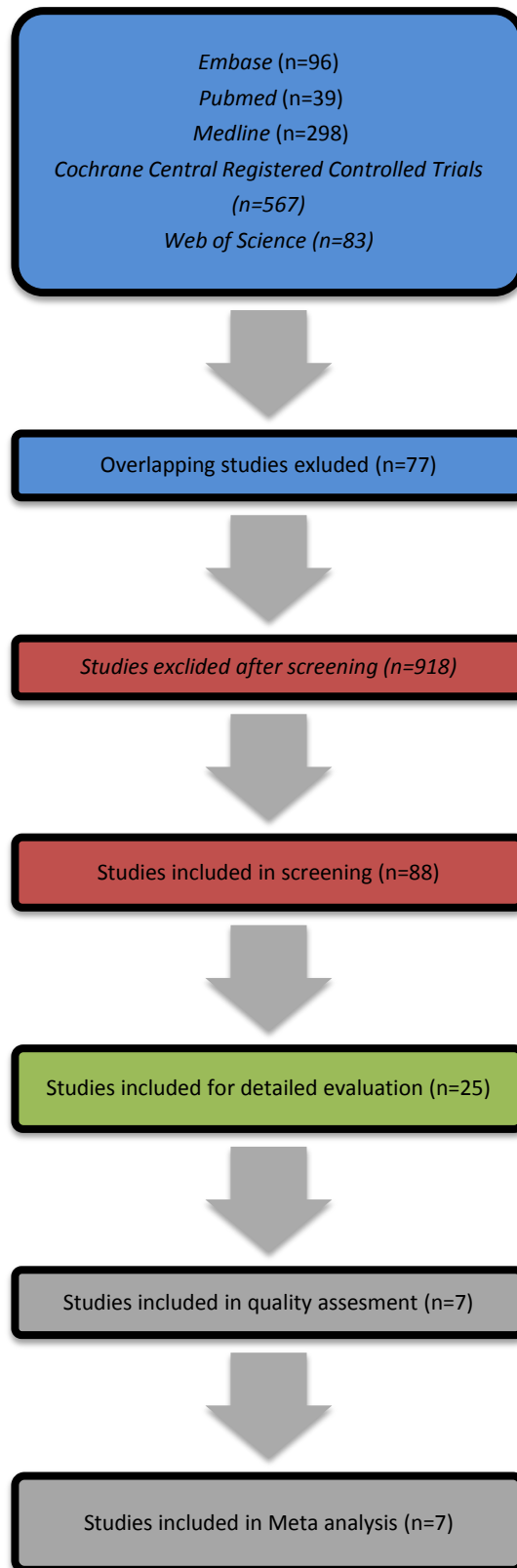
Statistical Analysis:-

The effect size (mean differences - MD) of blood loss and blood transfusions in TXA-treated group compared to control and/or placebo group were extracted and combined using random-effect meta-analysis. Heterogeneity parameters (I², r² and Q²) were used to evaluate the variability among studies relative to the overall effects size. Forest-Plot was generated to display the range of each study relative to the overall range of the model.

Results:-

After full text review of the relevant 25 studies, only 7 qualified studies were used in the meta-analysis for blood loss. (*Neilipovitz et al., 2001; Navil et al., 2005; Kaabachi et al., 2007; Grant et al., 2009; Yagi et al., 2012; Bobby et al., 2015; Vinicius et al., 2015*).

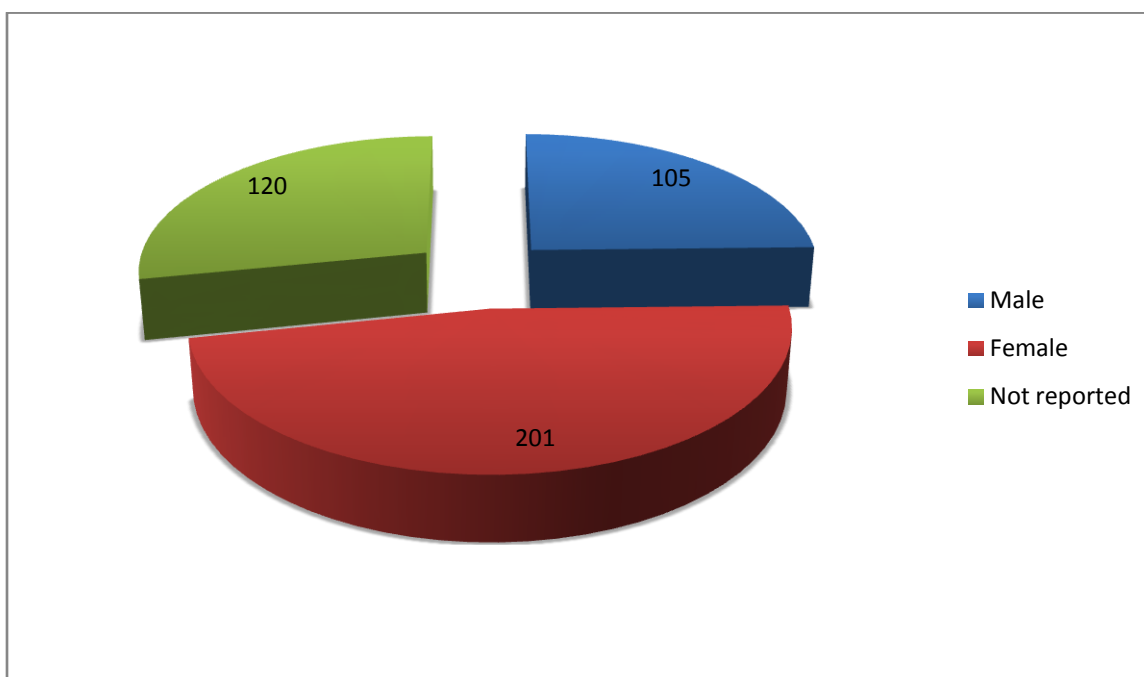
Additionally, 6 studies (*Neilipovitz et al., 2001; Navil et al., 2005; Grant et al., 2009; Yagi et al., 2012; Bobby et al., 2015; Vinicius et al., 2015*) were included in the final analysis for blood transfusion. The basic gender and anthropometric characteristics of the studies are involved in this meta-analysis presented in Table (1), Graph (1) and Graph (2).

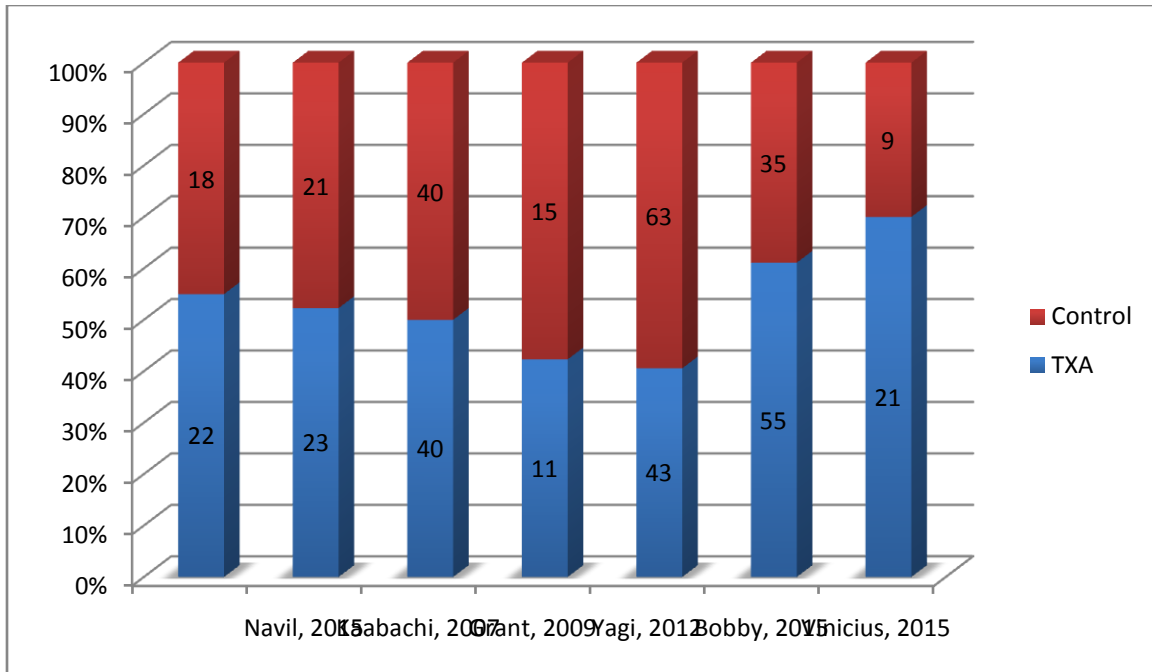


Flow chart 1:-showing the process of the Literature review

Table 1:- Basic Characteristics of the Studies Involved in the Meta-analysis of the Present Study

Studies	Gender		Age (yrs)		Weight (kg)	
	Male	Female	TXA	C/P	TXA	C/P
Neilipovitz, 2001	17(12/5)	23(10/3)	14.1 \pm 2.1	13.7 \pm 2.5	41.8 \pm 16.7	50.6 \pm 20.2
Navil, 2015	30(17/13)	14(6/8)	13.6 \pm 1.8	14.0 \pm 2	59.4 \pm 18.3	52.4 \pm 15.7
Kaabachi, 2007	Not reported		11-20		Not reported	
Grant, 2009	15(8)	11(11/0)	15.4 \pm 2.2	14.7 \pm 2	58.0 \pm 10.8	50.3 \pm 8.6
Yagi, 2012	43(3/40)	63(4/59)	15.2 \pm 2.9	15.5 \pm 3	43.9 \pm 8.1	43.8 \pm 6.8
Bobby, 2015	0	55/35	15.2 \pm 2.6	15.3 \pm 3	45.3 \pm 8.9	42.9 \pm 7.8
Vinicius, 2015	Not reported		18.6 \pm 4.4	21.61 \pm 8	55.5 \pm 6.1	51.8 \pm 5.9

**Graph 1:-**Overall Gender variation in Meta-Analysis .



Graph 2:- Number of patients in tranexamic acid group (TXA) and Control group.

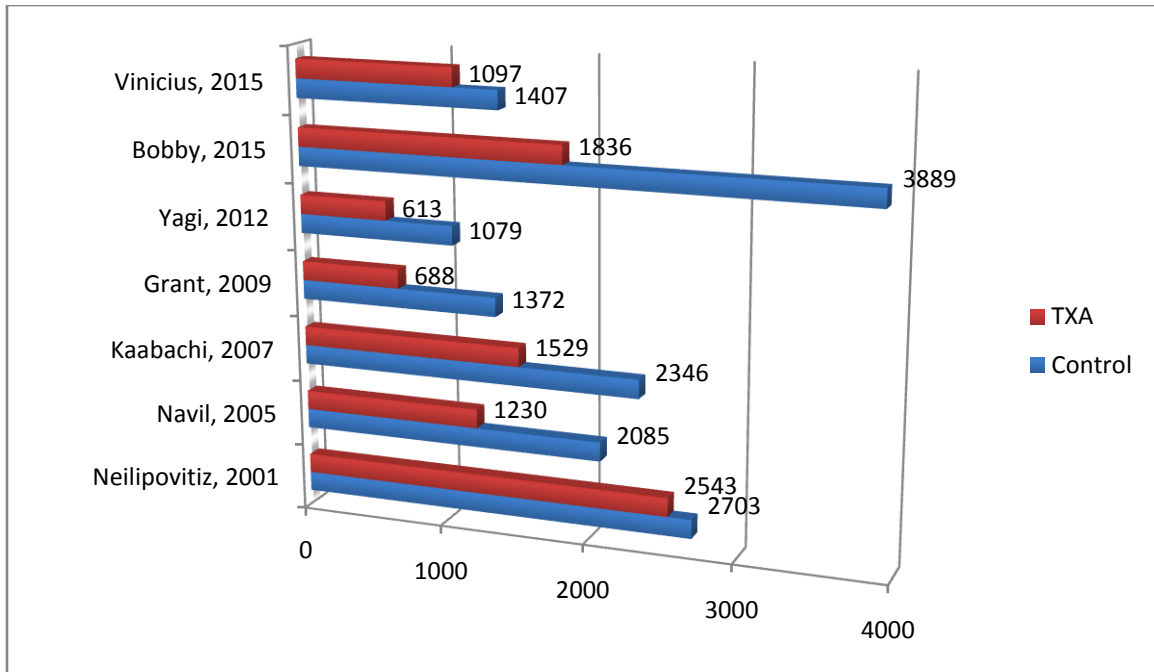
Meta-analysis for Blood Loss Volume (BLV):-

For intraoperative blood loss, a total of 7 studies comprising 426 patients were included in the meta-analysis according to the pre-defined selection criteria, described in the methods section. (Table 1) summarized the characteristics and weight effect of the 7 studies included for blood loss (BLV).

Table 2:- Studies Profile, Effect Size, Confidence Intervals and Weight for Blood Loss (MBL).

Study (Author&Yr)	Control		TXA		MD	Confidence Interval		Weight
	N	MBL	N	MBL		LL	UL	
Neilipovitz, 2001	18	2703	22	2453	250	-623.734	1123.734	10.81
Navil, 2005	21	2085	23	1230	855	301.848	1408.152	14.40
Kaabachi, 2007	40	2346	40	1529	817	374.214	1259.786	15.64
Grant, 2009	11	1372	15	688	684	-64.316	1432.516	12.16
Yagi, 2012	63	1079	43	613	466	346.818	585.182	18.26
Bobby, 2015	35	3889	55	1826	2063	1205.244	2920.536	10.98
Vinicius, 2015	19	1407	21	1097	310	91.979	526.421	17.72

As shown in (Table 2), all studies' profile for both TXA and control groups included effect size (MD), upper and lower limits of the confidence intervals (CI) and weight. Graph (3) illustrated the Mean blood loss in both control and TXA. Clearly observed overlap in Forest's Plot among the CI's for all studies that indicated generalized homogeneity (Figure 1). The overall model results indicated that the effect size of blood volume loss was 727.71mL with confidence interval (CI) ranged from 281.86 – 1173.56 ml which was significant (p<0.005), implying that the use of TXA caused a substantial reduction in blood loss volume during operation. The model also displays a 95% CI for the between-studies variance estimate implying perfect overlap, hence the observed scatter is due to sampling error, and the null hypothesis is rejected. It can be concluded that the true effects of TXA in all studies are identical. This was also true as $I^2 = 90.34\%$ (Table 3), implying more than 90.34% of the proportion of blood loss volume reduction inducted by TXA, treatment effect (Table 3).



Graph 3:- Mean Blood Loss volume (ml).

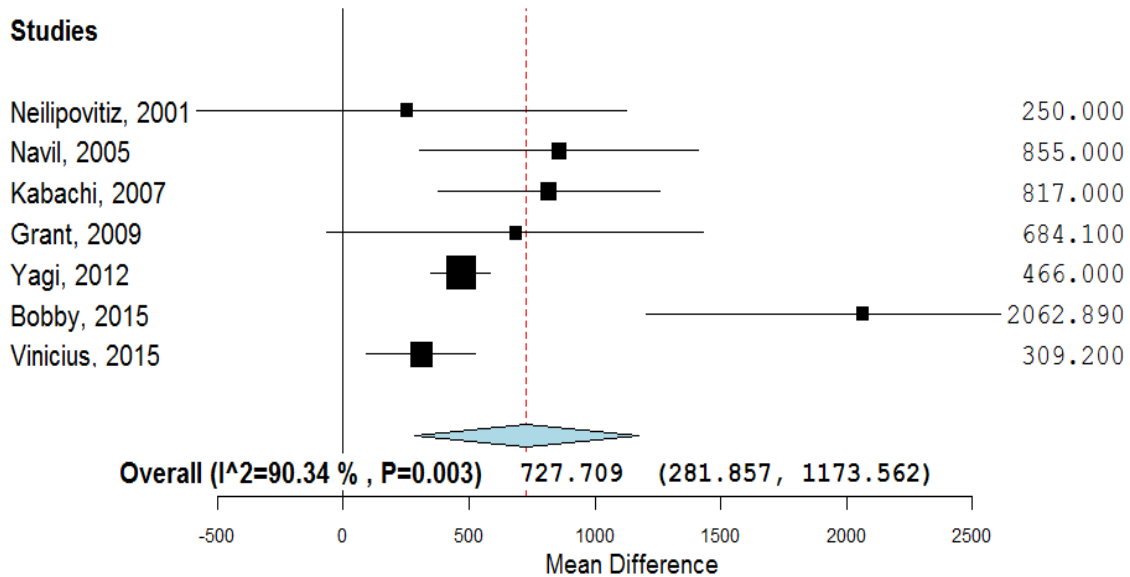


Figure 1:-Forest plot displaying PL meta-analysis

Table 3:- Heterogeneity Measures of Blood Loss

Source	Value	df	p-value
Cochrane Q	20.05	6	0.001
I ² (%)	90.34		

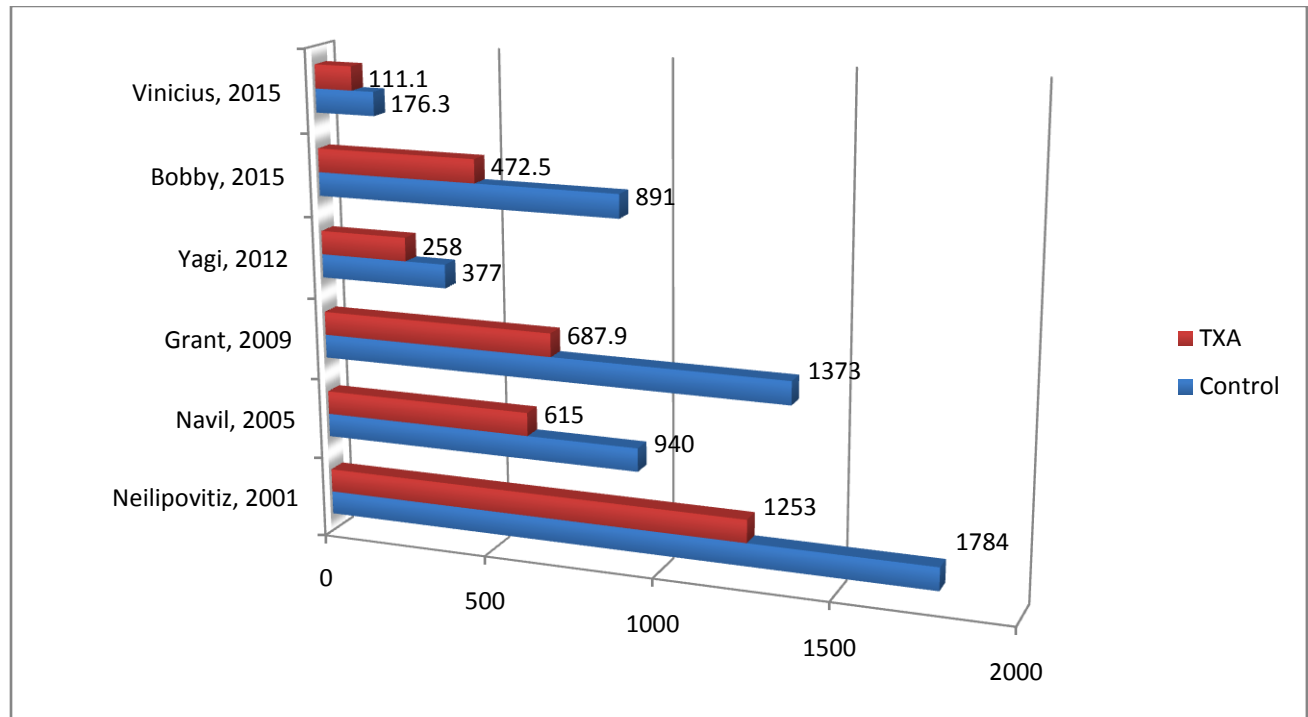
Meta-analysis for Blood Transfusion:-

For post-surgical blood transfusions, a total of 6 studies comprising 346 patients were included in the meta-analysis according to the pre-defined selection criteria, mentioned in the methods section. (Table 4) summarized the characteristics and weight effect of the 6 studies included for blood loss. Graph (4) also summarizes the mean blood transfusion. As can be seen from (Table 3), all studies' profile for both TXA and control groups that included

sample size, mean blood transfusion volume (BTV), effect size (MD), upper and lower limits of the confidence intervals (CI) were overlapped as observed in Forest Plot (Figure 2) and that indicated generalized homogeneity. The overall model results indicated that the effect size of blood volume transfusion (BVT) was 268.30 mL, with confidence interval (CI) ranged from 105.51 – 431.41 ml which was significant ($p < 0.001$), implying that the use of TXA induced substantial reduction in blood transfusion postoperatively. As observed from Forest Plot (Figure 2), an overlap among all the CI's of all studies exists. The observed scatter is due to sampling error, and the true effects of TXA in all studies are identical. This is also true as $I^2 = 72.27\%$, implying more than 72.27% of the proportion of blood transfusion reduction induced by TXA, treatment effect (Table5).

Table 4:- Studies Profile, Effect Size, Confidence Intervals and Weight for Blood Transfusion (BVT).

Studies (Author & Year)	Control		TXA		MD	Lower	Upper	Weight (%)
	N	BVT	N	BVT				
Neilipovitiz, 2001	18.00	1784.00	22.00	1253.00	531.00	29.89	1032.12	7.78
Navil, 2005	21.00	940.00	23.00	615.00	325.00	-35.06	685.06	12.06
Grant, 2009	15.00	1373.00	11.00	687.90	685.10	108.34	1261.86	6.28
Yagi, 2012	63.00	377.00	43.00	258.00	119.00	30.43	207.57	26.95
Bobby, 2015	35.00	891.00	55.00	472.50	418.50	264.78	572.22	23.23
Vinicius, 2015	19.00	176.30	21.00	111.10	65.20	-81.13	211.53	23.69



Graph 4:- Mean Blood Transfusion .

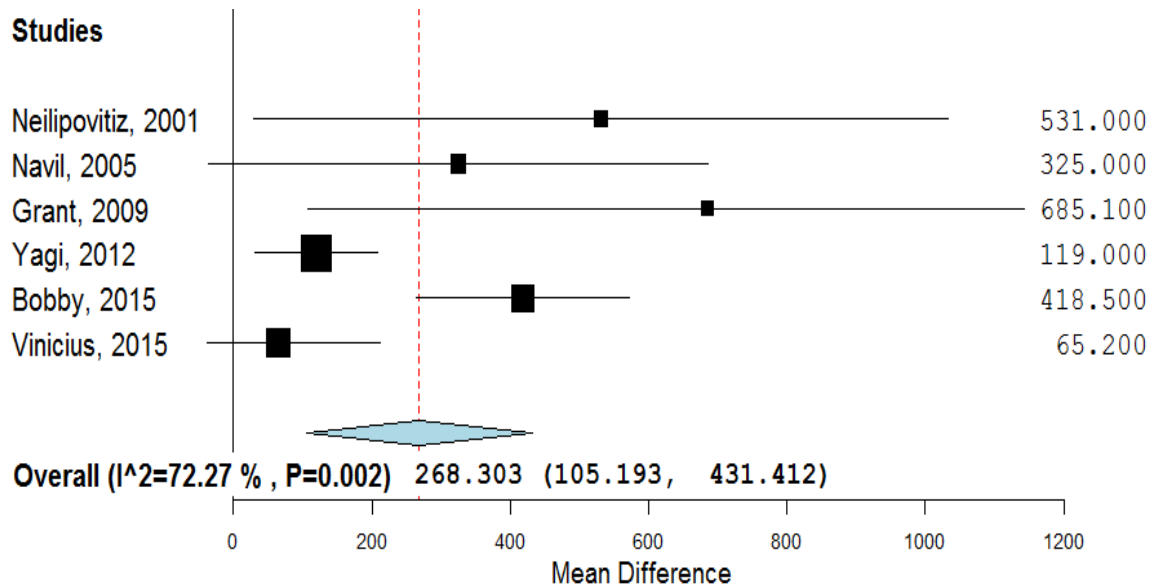


Figure 2:-Forest Plot Displaying PL meta-analysis for Blood Transfusions

Table 5:- Heterogeneity Measures of Blood Transfusion

Source	Value	df	p-value
Cochrane Q	18,87	5	0.001
I ² (%)	72.27		

Discussion:-

This study is ultimately a step forward to generalize the use of Tranexamic Acid in spinal surgery, scoliosis reduction. The results showed positive outcomes and significant differences in terms of blood reduction and transfusions, potentially making TXA the drug of choice. Despite its effectiveness, studies on its prophylactic use in scoliosis surgery are limited. Subsequently, not one article has yet been published in Saudi Arabia. Questions arise on the role of TXA in perioperative blood reduction and postoperative allogeneic transfusion. Having said that limitations can be found in this study due to the inclusion of retrospective studies. However, similar benefits of blood loss reduction and transfusion under the use of TXA have been documented in various surgical specialties such as in total knee arthroplasty^{xiv} and radical surgery^{xv} to that of spine surgeries. In addition, adverse effects play major role when selecting a drug. David T. Neilipovitz et al.,^{xvi} evaluated the risks in a randomized-control trial revealing no cases of clinical thrombotic events or hemodynamic instability. Another study showed the safety of TXA use in scoliosis surgery upon postoperative examination detecting no clinical evidence of deep venous thrombosis¹⁷. Subsequent to these two studies, numerous other studies support its perioperative safety as shown in the studies included in our meta-analysis (Table 6). Another point to add is the presence of co-morbidity. Patients with preexisting renal or hepatic disorders, bleeding diathesis, or coagulation abnormalities are most commonly excluded from studies due to their vulnerability and susceptibility to adverse events. On the other hand, safe use of TXA can be achieved in variant situations such as adjusting the dosage for patients with renal insufficiency¹⁸.

When weighing the risks and benefits, dose regimens should be taken in consideration. Not having an established optimal dose can be quite challenging. In high dose versus low dose study, the group of patients on a loading dose of 50mg/kg and a maintenance dose of 5mg/kg/h had a lower estimated blood loss than those who were on a loading dose of 10mg/kg and a maintenance dose of 1mg/kg/h by P=0.01 difference.¹⁹ Nevertheless, high doses of drug raise great concern regarding toxicity, and to which extent of increase can the drug safely be administered. In a TXA study of different dose regimens, Jing-Ming Xie et al.,²⁰ declared that a loading dose of 100mg/kg with a maintenance dose of 10mg/kg/h, double of which mentioned in the previous study, showed no signs of renal toxicity, seizures, DVT, or MI upon assessment. Conclusively, TXA is a safe drug though an optimum dose is greatly recommended for exploration. Further to be considered is the etiology of the disorder, secondary scoliosis, neuromuscular or congenital etiologies, manifested greater blood loss tendency than that of idiopathic etiology, though the mechanism behind the increase bleeding is undetermined²¹. With such variables, study's results may be

deviated. To illustrate, various measures should be taken in order to minimize the high amount of blood loss experienced in patients' with Duchenne Muscular Dystrophy undergoing posterior spinal fusion such as deliberate hypotension technique and patient positioning, yet with the use of TXA, minimal of 740ml blood reduction and 2135ml maximum is to be expected²¹. Which happens to make TXA the advanced management of neuromuscular scoliosis.

Moreover, hospitals' protocols on autologous blood transfusion, hemoglobin level, and the use of cell saver can bias the study's results. In Ho Yong Choi et al.,²² study on the effectiveness and safety of TXA in spinal deformity surgery, same blood transfusion guidelines were used for both TXA group and control group, allogeneic transfusions were preformed to maintain hemoglobin level between 7-8 mg/dl. In some institutions, anesthesia protocols are standard in scoliosis surgery which leads to limitations in the study²³. As well, in randomized-control trials, patients' demographic data such as age, gender, body mass index, medical history vary between the two groups contributing to alteration in the results, but such differences are minor and of little or no clinical relevance. Furthermore, Scoliosis surgery is based on medical criteria. Skeletal maturity, degree of curvature, and progression of the curvature are included when considering the surgery²⁴. However, patients as young as 8 years old may undergo idiopathic scoliosis surgery. Hence, introducing a drug for study in a vulnerable age group can be demanding leading to limited studies of TXA in spine surgery. More emphasis on its safety and significant efficacy on both patients and hospitals is crucial. According to the CRASH 2 trial²⁵, TXA administration is remarkably cost-effective in low, middle, high income settings directly, and indirectly by reducing the cost of additional hospital stays. In other circumstances, economical saving by decreasing the costs of treatment for allogeneic transfusions' side-effects is promising.

When covering the intraoperative aspect of TXA use, surgeons' and anesthesiologists' preferences are taken into account. In surgery for instance, intraoperative transfusion is based on the surgical team's decision such when hemoglobin level reaches 7.0g/dl or less²⁶ and the TXA dose to be administered is under the anesthesiologist's preference. David T. Neilipovitz et al.,¹⁶ study conducted a short questionnaire at the end of the surgery that was completed by the attending surgeon rating the level of surgical difficulty on a visual analogue scale of 0 (no difficulty) to 10 (extremely difficult) and the operative conditions in term of bleeding, 0 (negligible bleeding) to 10 (massive bleeding). The results were similar for both TXA group (n=22) and the control group (n=18)¹⁶. However, upon perspectives, results may respectfully fluctuate. One of the most significant advantages health practitioners will face with the use of TXA is the decline in number of cases of blood-borne infections and immunologic reactions associated with blood transfusions as such cases present to be challenging for surgeons. In our results, a notable reduction of blood transfusion was seen in patients treated with TXA, that happens to make TXA a deal breaker when measuring the consequences. From anesthesia's point of view, it has been addressed that the use of TXA with regional and general anesthesia has no complications²⁷. In fact, the use of TXA with epidural anesthesia followed 65% of reduction in blood loss²⁷. It is clear that TXA plays a tremendous role in the decline of perioperative blood loss and allogeneic transfusions. Thus, this meta-analysis will help guide future scoliosis management and further study exploration on its use in spine surgeries.

Table 6:-Post-Surgical Risks

No.	Author	Post-surgical Risk
1	Neilipovitz, 2001	Safe procedure
2	Navil, 2005	Safe procedure
3	Kaabachi, 2007	No data regarding risks
4	Grant, 2009	No data regarding risks
5	Yagi, 2012	No interoperative complications
6	Bobby, 2015	Safe procedure
7	Vinicius, 2015	Not mentioned

Conclusion:-

Although the number of the patients of each of the study included in this meta-analysis is relatively small, tranexamic acid has been shown to effectively reduce blood loss and blood transfusion in idiopathic scoliosis correction surgery. Further multi-center double blinded randomized control trials involving a larger number of patients is required to confirm the efficacy and safety of tranexamic acid in idiopathic scoliosis surgery.

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