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EFFICACY OF TRANEXAMIC ACID TO REDUCE HEMORRHAGE AND BLOOD TRANSFUSION IN MAJOR ORTHOPEDIC SURGERIES: A META-ANALYSIS

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ABSTRACT

Background & Purpose: The Tranexamic Acid (TXA) has been used successfully to prevent bleeding in more than one specialty along with liver, cardiac, prostate, and dental surgeries. The Aim of this work is to provide cumulative data about the efficacy of tranexamic acid (TXA) to reduce hemorrhage and blood transfusion in major orthopedic surgeries. **Methods:** A systematic search was performed of PubMed, Cochrane library Ovid, Scopus & Google scholar to identify Orthopedic surgery RCTs, clinical trials, and comparative studies, which studied the outcome of TXA group versus Control group of orthopedic surgery patients. A meta- analysis was done using fixed and random-effect methods. Primary outcome was total blood loss. Secondary outcomes were intra and post-operative amount of blood loss. **Results:** A total of 7 studies were identified

involving 557 patients, with 287 patients in TXA group, and 270 patients in Control group. Regarding primary outcome measures, random-effects model of the meta-analysis study showed highly significant decrease in mean total blood loss in TXA group ($p < 0.01$). Regarding secondary outcome measures, random-effects model of the meta- analysis study showed significant decrease in mean intra-operative blood loss in TXA group ($p < 0.05$). The random-effects model of the meta-analysis study showed non-significant difference in mean post-operative blood loss ($p > 0.05$). **Conclusion:** To conclude, TXA significantly decreases blood loss and blood transfusion requirements in patients undergoing orthopedic surgery.

KEYWORDS: TXA, Hemorrhage, Orthopedic Surgery.

INTRODUCTION

Major orthopedic operations which includes general knee arthroplasty, total hip arthroplasty, and spinal surgery are associated with full-size blood loss.[1]

Bone and smooth-tissue bleeding (600-1500 cc) constitute the most commonplace purpose of postoperative morbidity after general knee arthroplasty (TKA), growing transfusion necessities up to 50% and prolonging length of hospitalization. furthermore, the substantial adoption of antiplatelet and anticoagulant dealers to reduce thromboembolic events in patients undergoing TKA has substantially improved bleeding threat.[2]

A selection of blood-conserving techniques have been advanced to reduce blood loss and put up-operative transfusion rates, together with controlled hypotension, intra-operative blood salvage, local anesthesia, navigation, minimally invasive surgery (MIS), use of drain, and the use of erythropoietin and antifibrinolytic agents.[3]

A 30% discount in blood transfusion requirements because of a lower with the aid of one-third in blood losses has been verified with TA in orthopaedic surgical procedure. but, TA is used in only 17% of patients meeting theoretical criteria for this treatment, because of the huge variability in administration regimens (dose, duration, and route).[4]

Antifibrinolytics were utilized in orthopedic surgical treatment via an intravenous (IV) route, resulting in a 50% reduction in the rate of transfusions.[5]

Fibrinolysis is initiated by way of surgical trauma and similarly by the use of a tourniquet. This accelerated fibrinolytic interest can also boom blood loss after TKA, at the least for the

duration of the early postoperative hours. TXA produces antifibrinolytic results by way of inhibiting the activation of plasminogen to plasmin. TXA blocks the lysine binding websites of plasminogen to fibrin, displacing plasminogen from the fibrin surface and resulting inside the inhibition of fibrinolysis.[6]

TXA has been used successfully to prevent bleeding in more than one specialties along with liver, cardiac, prostate, and dental surgeries.[1]

TXA is an artificial antifibrinolytic agent that attaches to the lysine binding site of plasminogen and blocks the attachment of plasminogen to the fibrin surface. thus, plasminogen activation is averted and fibrinolysis is delayed.[7]

AIM OF THE STUDY: The Aim of this work is to provide cumulative data about the efficacy of tranexamic acid (TXA) to reduce hemorrhage and blood transfusion in major orthopedic surgeries.

METHODS

This review was done using standard methods mentioned within the Cochrane handbook and in agreement with the (PRISMA) statement guidelines.[8]

Identification of Studies

- An initial search carried out throughout the PubMed, Cochrane library Ovid, Scopus & Google scholar using the following keywords: Tranexamic Acid, Hemorrhage, Orthopedic Surgery.
- We will consider published, full text studies in English only. Moreover, no attempts were made to locate any unpublished studies nor non-English studies.

CRITERIA OF ACCEPTED STUDIES

- **Types of studies**

The review will be restricted to RCTs, clinical trials, and comparative studies, either prospective or retrospective, which studied the outcome of TXA group versus Control group of blood loss of orthopedic surgeries patients.

- **Types of Participants**

Participants will be patients undergoing major orthopedic surgeries.

- **Types of Outcome Measures**

1. Average total blood loss (1ry outcome)
2. Average intra-operative blood loss (2ry outcome)
3. Average post-operative blood loss (2ry outcome)

Inclusion criteria

- ✓ English literature.
- ✓ Journal articles.
- ✓ Between 2009 until 2019.
- ✓ Describing blood loss in either TXA group or Control group.
- ✓ Human studies.

Exclusion criteria

- ✓ Articles describing other types of hemostatic drugs or agents.
- ✓ Irrelevance to our study.

Methods of the Review

■ **Locating Studies**

Abstracts of articles identified using the above search strategy will be viewed, and articles that appear of fulfill our inclusion criteria will be retrieved in full, when there is a doubt, a second reviewer will assess the article and consensus will be reached.

■ **Data extraction**

Using the following keywords: Tranexamic Acid, Hemorrhage, Orthopedic Surgery, data will be independently extracted by two reviewers and cross-checked.

Statistical analysis

Statistical analysis done using MedCalc ver. 18.11.3 (MedCalc, Ostend, Belgium). Data were pooled and odds ratios (ORs) as well as standard mean differences (SMD), were calculated with their 95 per cent confidence intervals (CI). A meta-analysis was performed to calculate direct estimates of each treatment, technique or outcome. According to heterogeneity across trials using the I^2-statistics; a fixed-effect model ($P \geq 0.1$) or random- effects model ($P < 0.1$) was used.

Study selection

We found 134 record; 104 were excluded based on title and abstract review; 30 articles are

searched for eligibility by full text review; 8 articles cannot be accessed or obtain full text; 10 studies were reviews and case reports; the desired agents not used in 5 studies leaving 7 studies that met all inclusion criteria (Fig. 1).

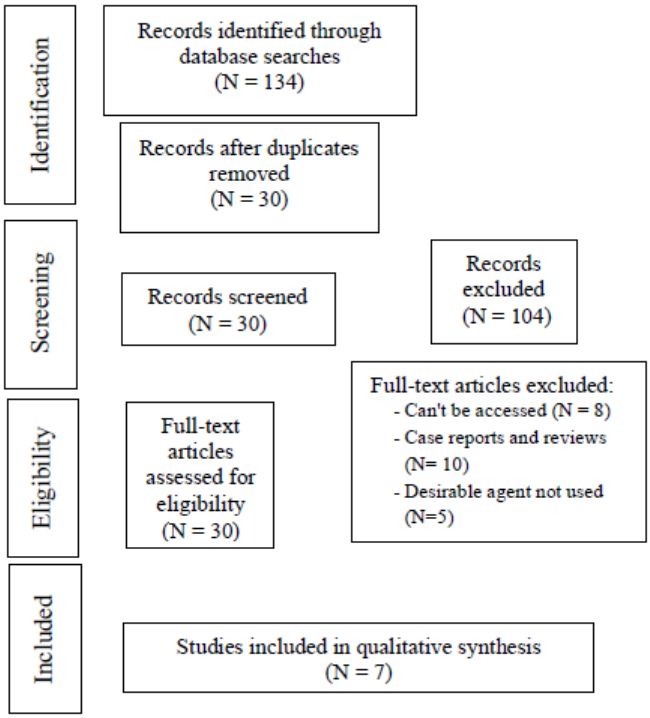

Figure 1: Flow chart for study selection.

RESULTS

Descriptive analysis of all studies included (Tables 1, 2).

Table 1: Patients and study Characteristics.

N	Author	Type of study	Number of patients			Type of surgery
			Total	TXA group	Control group	
1	Rajesparan et al., 2009	Prospective	73	36	37	Hip
2	Lin et al., 2011	Retrospective	100	50	50	Knee
3	MacGillivray et al., 2011	Prospective	40	20	20	Knee
4	Tsutsumimoto et al., 2011	Retrospective	40	20	20	Spine
5	Roy et al., 2012	Retrospective	50	25	25	Knee
6	Friedman et al., 2016	Retrospective	194	106	88	Hip and Knee
7	Gupta, 2019	Prospective	60	30	30	Hip

#Studies were arranged according to publication year.

Table 2: Summary of Outcome Measures In All Studies.

N	Author	Primary Outcome		Secondary outcomes			
		Total Blood Loss		Intra-operative blood loss		Post-operative blood loss	
		TXA group	Control group	TXA group	Control group	TXA group	Control group
1	**Rajesparan et al., 2009**	1372	1683	376.4	354.3	---	---
2	**Lin et al., 2011**	833	1453	---	---	478	556
3	**MacGillivray et al., 2011**	678	918	---	---	---	---
4	***Tsutsumimoto et al., 2011***	264.1	353.9	49.1	63.4	132	211
5	***Roy et al., 2012***	401	870	109.6	194	---	---
6	***Friedman et al., 2016***	750	1000	---	---	---	---
7	***Gupta, 2019***	732.3	690.6	326.1	556	---	---

The included studies published between 2009 and 2019. Regarding the type of included studies, 3 studies (out of 7 studies) were prospective, while 4 studies were retrospective.

The total number of patients in all the included studies was 557 patients, with 287 patients in TXA group, and 270 patients in Control group.

Regarding orthopedic surgeries, 3 studies conducted hip surgeries, 4 studies conducted knee surgeries, while 1 study conducted spine surgeries.

Meta-analysis (Fig. 2, 3, 4)

Data were divided into two groups:

1) TXA group
2) Control group

Meta-analysis study was done on 7 studies which described and compared the 2 different groups of patients; with overall number of patients (N=557).

Patients who achieved favorable outcomes were pooled:

Each outcome was measured by

✓ **Standard Mean Difference (SMD)**

- For average total blood loss (1ry outcome)
- For average intra-operative blood loss (2ry outcome)
- For average post-operative blood loss (2ry outcome)

Regarding primary outcome measure,

We found 7 studies reported total blood loss with total number of patients (N=557).

I^2 (inconsistency) was 93% with highly significant Q test for heterogeneity ($p < 0.01$), so random-effects model was carried out; with overall SMD= -1.05 (95% CI -1.77 to 0.33).

The random-effects model of the meta-analysis study showed highly significant decrease in mean total blood loss in TXA group compared to Control group ($p = 0.004$).

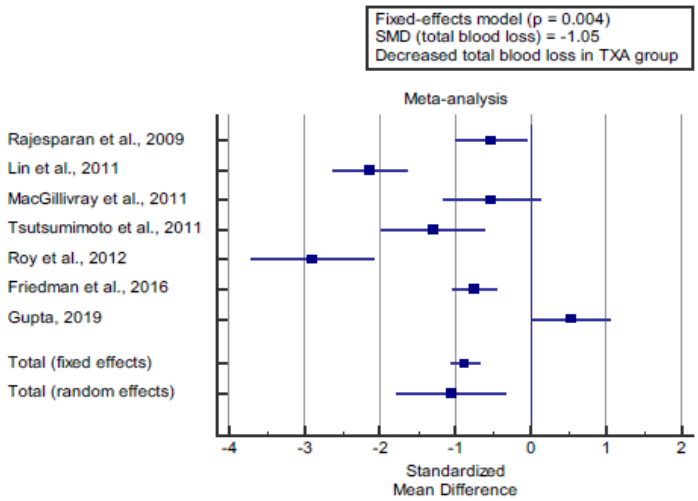

Figure 2: Forest plot of (total blood loss) on TXA group vs Control group - Mean difference.

Regarding secondary outcome measure,

We found 4 studies reported intra-operative blood loss with total number of patients (N=223).

I^2 (inconsistency) was 96% with highly significant Q test for heterogeneity ($p < 0.01$), so random-effects model was carried out; with overall SMD= -1.83 (95% CI -3.64 to -0.03).

The random-effects model of the meta-analysis study showed significant decrease in mean.

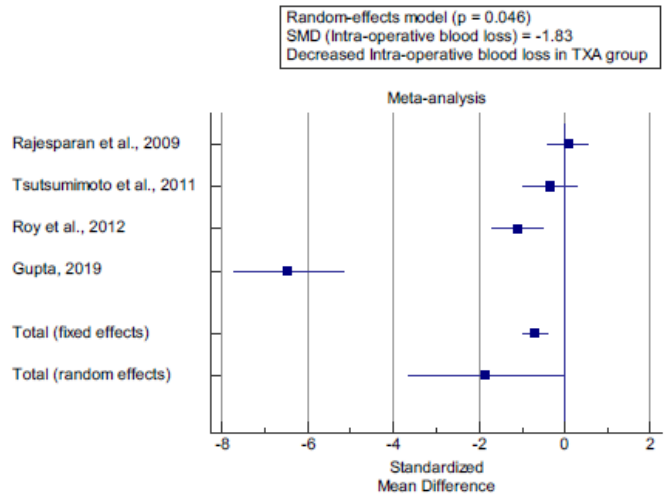

Figure 3: Forest plot of (Intra-Operative Blood Loss) on TXA group vs Control group – Mean difference.

Regarding secondary outcome measure,

We found 2 studies reported post-operative blood loss with total number of patients (N=140).

I^2 (inconsistency) was 91% with highly significant Q test for heterogeneity ($p < 0.01$), so random-effects model was carried out; with overall SMD= -1.04 (95% CI -2.43 to 0.35).

The random-effects model of the meta-analysis study showed non-significant difference in mean post-operative blood loss in TXA group compared to Control group ($p > 0.05$).

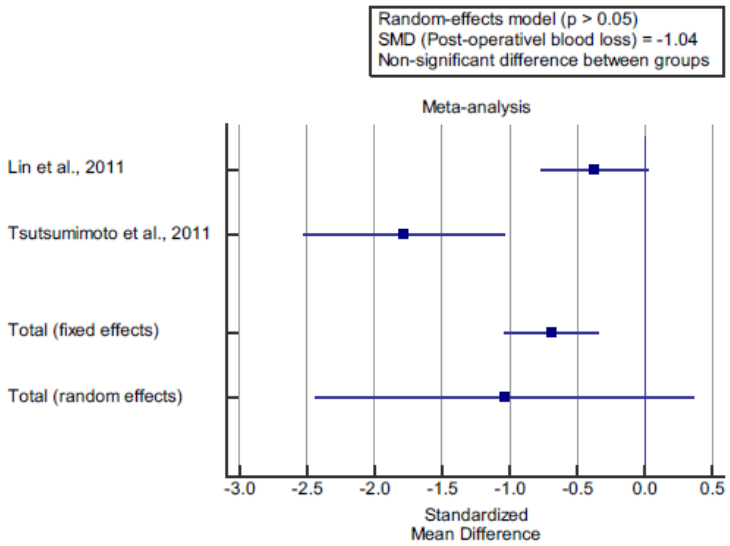

Figure 4: Forest Plot of (Post-Operative Blood Loss) on TXA Group vs Control group – Mean difference.

DISCUSSION

The Aim of this work is to provide cumulative data about the efficacy of tranexamic acid (TXA) to reduce hemorrhage and blood transfusion in major orthopedic surgeries.

Regarding orthopedic surgeries, 3 studies conducted hip surgeries, 4 studies conducted knee surgeries, while 1 study conducted spine surgeries.

Regarding Meta-analysis of outcome measures; Data were divided into two groups: **(TXA group and Control group)**.

Regarding primary outcome measure, we found 7 studies reported total blood loss with total number of patients (N=557).

The random-effects model of the meta-analysis study showed highly significant decrease in

mean total blood loss in TXA group compared to Control group (p = 0.004) which came in agreement with ***Huang et al. 2014***[1] and with ***Wind, Barfield, and Moskal 2013***[9] and with ***Bidolegui et al. 2014.***[2]

Huang et al. 2014[1] reported that a total of 46 randomized controlled trials regarding 2925 patients had been included. using TXA reduced general blood loss through a median of 408.33 mL, intraoperative blood loss by means of a mean of 125.65 mL, postoperative blood loss via a mean of 214.58 mL, the wide variety of blood transfusions in keeping with affected person via 0.78 U, and the volumes of blood transfusions in keeping with affected person by means of 205.33 mL. TXA caused a considerable reduction in transfusion requirements (relative risk, 0.51), TXA drastically reduced blood loss and blood transfusion necessities in patients undergoing orthopedic surgical procedure.

Wind, Barfield, and Moskal 2013[9] reported that TXA infusion established a significant decrease in blood transfusion (P < 0.01).

Bidolegui et al. 2014[2] reported that, there were no need to transfuse blood in the TXA group, whereas 32% of the control group required blood transfusion (p < 0.01).

Regarding secondary outcome measure, we found 4 studies reported intra-operative blood loss with total number of patients (N=223).

The random-effects model of the meta-analysis study showed significant decrease in mean intra-operative blood loss in TXA group compared to Control group (p = 0.046) which came in disagreement with ***Zhang et al. 2012***[3] and agreement with ***Konig, Hamlin, and Waters 2013 Konig, Hamlin, and Waters 2013.***[10]

Zhang et al. 2012 reported that There were no statistically significant differences in decreasing intra-operative blood loss between TXA and control groups.

Konig, Hamlin, and Waters 2013[10] reported that health center length of live was also considerably shorter in sufferers in each surgical groups while TXA turned into used, losing by using 6 days in THA sufferers, and dropping via 4 days in TKA sufferers. No patients required an intraoperative blood transfusion. No sufferers had thromboembolic complications.

Regarding secondary outcome measure, we found 2 studies reported post-operative blood loss with total number of patients (N=140).

The random-effects model of the meta-analysis study showed non-significant difference in mean post-operative blood loss in TXA group compared to Control group ($p > 0.05$) which came in disagreement with ***Bali, Prabhakar, and Dhillon 2011***[11] and with ***Alshryda et al. 2013***[7] and with ***Konig, Hamlin, and Waters 2013.***[10]

Bali, Prabhakar, and Dhillon 2011[11] reported that however, the postoperative Hb become observed to be decrease within the control group as compared to the TEA group and this difference turned into located to be statistically big ($P < 0.01$), the entire postoperative drain output become found to be decrease in sufferers who received TEA as compared to the manage group (275 ml vs. 810 ml) and this relation become additionally located to be statistically widespread ($P < 0.01$).

Alshryda et al. 2013.[7] The postoperative Hb level was significantly higher (difference, 0.83 g/dL; $p < 0.01$) in the tranexamic acid group in comparison to the placebo group.

Konig, Hamlin, and Waters 2013[10] reported that topical TXA significantly decreases postoperative blood loss and transfusion risk in orthopedic surgery patients.

CONCLUSION

To conclude, TXA significantly decreases blood loss and blood transfusion requirements in patients undergoing orthopedic surgery.

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Conflict of interest

None.

Authorship

All the listed authors contributed significantly to conception and design of study, acquisition, analysis and interpretation of data and drafting of manuscript, to justify authorship.

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REFERENCES

1. Huang, F.; Wu, D.; Ma, G.; Yin, Z.; Wang, Q. The Use of Tranexamic Acid to Reduce Blood Loss and Transfusion in Major Orthopedic Surgery: A Meta-Analysis. *Journal of Surgical Research*, 2014; *186*(1): 318–327. https://doi.org/10.1016/j.jss.2013.08.020.
2. Bidolegui, F.; Arce, G.; Lugones, A.; Pereira, S.; Vindver, G. Tranexamic Acid Reduces Blood Loss and Transfusion in Patients Undergoing Total Knee Arthroplasty without Tourniquet: A Prospective Randomized Controlled Trial. *Open Orthop J.*, 2014; *8:* 250–254. https://doi.org/10.2174/1874325001408010250.
3. Zhang, H.; Chen, J.; Chen, F.; Que, W. The Effect of Tranexamic Acid on Blood Loss and Use of Blood Products in Total Knee Arthroplasty: A Meta-Analysis. *Knee Surg Sports Traumatol Arthrosc*, 2012; *20*(9): 1742–1752. https://doi.org/10.1007/s00167-011-1754-z.
4. Irisson, E.; Hémon, Y.; Pauly, V.; Parratte, S.; Argenson, J.-N.; Kerbaul, F. Tranexamic Acid Reduces Blood Loss and Financial Cost in Primary Total Hip and Knee Replacement Surgery. *Orthopaedics & Traumatology: Surgery & Research*, 2012; *98*(5): 477–483. https://doi.org/10.1016/j.otsr.2012.05.002.
5. Konig, G.; Hamlin, B. R.; Waters, J. H. Topical Tranexamic Acid Reduces Blood Loss and Transfusion Rates in Total Hip and Total Knee Arthroplasty. *The Journal of Arthroplasty*, 2013; *28*(9): 1473–1476. https://doi.org/10.1016/j.arth.2013.06.011.
6. Charoencholvanich, K.; Siriwattanasakul, P. Tranexamic Acid Reduces Blood Loss and Blood Transfusion after TKA: A Prospective Randomized Controlled Trial. *Clin Orthop Relat Res.*, 2011; *469*(10): 2874–2880. https://doi.org/10.1007/s11999-011-1874-2.
7. Alshryda, S.; Mason, J.; Vaghela, M.; Sarda, P.; Nargol, A.; Maheswaran, S.; Tulloch, C.; Anand, S.; Logishetty, R.; Stothart, B.; et al. Topical (Intra-Articular) Tranexamic Acid Reduces Blood Loss and Transfusion Rates Following Total Knee Replacement: A Randomized Controlled Trial (TRANX-K). *The Journal of Bone and Joint Surgery-American Volume*, 2013; *95*(21): 1961–1968. https://doi.org/10.2106/JBJS.L.00907.
8. Liberati, A.; Altman, D.; Tetzlaff, J.; Mulrow, C.; Gøtzsche, P.; Ioannidis, J.; Clarke, M.; Devereaux, P.; Kleijnen, J.; Moher, D. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Healthcare Interventions. *Bmj*, 2009; *339*.
9. Wind, T. C.; Barfield, W. R.; Moskal, J. T. The Effect of Tranexamic Acid on Blood Loss and Transfusion Rate in Primary Total Knee Arthroplasty. *The Journal of Arthroplasty*, 2013; *28*(7): 1080–1083. https://doi.org/10.1016/j.arth.2012.11.016.
10. Konig, G.; Hamlin, B. R.; Waters, J. H. Topical Tranexamic Acid Reduces Blood Loss

and Transfusion Rates in Total Hip and Total Knee Arthroplasty. *The Journal of Arthroplasty*, 2013; *28*(9): 1473–1476. https://doi.org/10.1016/j.arth.2013.06.011.

11. Bali, K.; Prabhakar, S.; Dhillon, M. Tranexamic Acid for Control of Blood Loss in Bilateral Total Knee Replacement in a Single Stage. *Indian J Orthop,* 2011; *45*(2): 148. https://doi.org/10.4103/0019-5413.77135.
12. Rajesparan, K., Biant, L.C., Ahmad, M. and Field, R.E., The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. *The Journal of bone and joint surgery. British volume*, 2009; *91*(6): 776-783.
13. Lin, P.C., Hsu, C.H., Chen, W.S. and Wang, J.W., Does tranexamic acid save blood in minimally invasive total knee arthroplasty?. *Clinical Orthopaedics and Related Research®*, 2011; *469*(7): 1995-2002.
14. MacGillivray, R.G., Tarabichi, S.B., Hawari, M.F. and Raoof, N.T., Tranexamic acid to reduce blood loss after bilateral total knee arthroplasty: a prospective, randomized double blind study. *The Journal of arthroplasty*, 2011; *26*(1): 24-28.
15. Tsutsumimoto, T., Shimogata, M., Ohta, H., Yui, M., Yoda, I. and Misawa, H., Tranexamic acid reduces perioperative blood loss in cervical laminoplasty: a prospective randomized study. *Spine*, 2011; *36*(23): 1913-1918.
16. Roy, S.P., Tanki, U.F., Dutta, A., Jain, S.K. and Nagi, O.N., Efficacy of intra-articular tranexamic acid in blood loss reduction following primary unilateral total knee arthroplasty. *Knee Surgery, Sports Traumatology, Arthroscopy*, 2012; *20*(12): 2494-2501.
17. Friedman, R.J., Gordon, E., Butler, R.B., Mock, L. and Dumas, B., Tranexamic acid decreases blood loss after total shoulder arthroplasty. *Journal of shoulder and elbow surgery*, 2016; *25*(4): 614-618.
18. Gupta, D., COMPARATIVE EVALUATION OF TRANEXAMIC ACID AND HEMOCOAGULASE ON BLOOD LOSS IN ORTHOPEDIC HIP SURGERIES. *Global Journal For Research Analysis*, 2019; *8*(8).