TXA after severe TBI: Learning and memory benefits are prominent only in males

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BACKGROUND: Tranexamic acid (TXA), a commonly used pharmacotherapy, appears to preserve blood brain barrier integrity after traumatic brain injury (TBI) in males, but whether TXA confers equivalent neurocognitive benefit in female and male subjects after TBI remains unknown. We hypothesized that TXA unequally affects male and female learning and memory post-TBI.

METHODS: CD1 male (M, n = 24) and female (F, n = 24) mice underwent controlled cortical impact (TBI) or sham craniotomy (Sh), receiving either TXA (60 mg/kg) or saline (placebo [P]) i.v., 1 hour later. For 14 days, mice underwent Morris water maze testing where improved learning/memory was indicated by traveling a shorter distance/reaching or crossing into target zones with greater frequency (Z1, platform quadrant; Z5, platform, Z6; Z7, concentric peri-platform zones). Brains were collected for tissue water determinations and neurological recovery was quantified daily using the Garcia neurological test and Neurological Severity Score across 14 days.

RESULTS: Post-TBI TXA improved male spatial learning (crossing frequency into Z6 and Z7 [$p < 0.01$]; latency to Z1 [$p < 0.01$], Z5 [$p < 0.01$], Z6 [$p < 0.01$], and Z7 [$p < 0.01$]). Tranexamic acid improved female learning solely in one parameter (Z7 latency; $p < 0.01$). Tranexamic acid improved male memory (frequency into Z5 [$p = 0.02$] and Z6; duration in Z1 [$p = 0.01$] and Z7 [$p = 0.04$] and swimming velocity [$p < 0.01$]). In females, TXA improved memory solely in one parameter (Z1 duration; $p = 0.02$). Tranexamic acid reduced only male cerebral edema.Tranexamic acid enhanced male mice Garcia Neurological Test scores early (first 3 days) and female mice scores, late (Day 11). Tranexamic acid only improved male Neurological Severity Score on Days 8 to 11.

CONCLUSION: Post-TBI TXA benefits males more than females. Traumatic brain injury should be studied separately in males and females to identify sex-specific mechanisms of injury and recovery. (*J Trauma Acute Care Surg.* 2026;00: 00–00. Copyright © 2026 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Tranexamic acid; traumatic brain injury; sex; Morris water maze; learning.

Traumatic brain injury (TBI) preclinical inquires have been historically explored and reported using male animals. However, in clinical care, such as sports-related concussions, reports increasingly indicate a preponderance of female cases, with some suggesting a 2-fold greater incidence in females than males.[1] One reason for this could be cultural, as women may be more willing to report an injury than men.[1,2] Nonetheless, most clinical TBI studies report overwhelmingly male majority populations (likely since males are more prone to injury than females) but then assume that results can be extrapolatable to women. Sex is underinvestigated as a fixed variable but appears to significantly impact TBI outcomes and potential therapeutic agent or care pathway development.[3]

The influence of sex in injury-related social dysfunction has not been well studied.[4] Cognitive outcome studies that include females yield unique results and seem to demonstrate an asymmetric impact on females. For example, TBI increases the risk of psychiatric disorders in females, reaching 17% greater frequency than in males over a 10-year span.[5] In contrast, other clinical inquiries document essentially similar cognitive outcomes based on sex with the exception of visual memory, for which recovery was better in women.[6]

Applied therapeutics may influence observed outcomes either independently or based on interaction with host elements driven by sex. Tranexamic acid (TXA) is an antifibrinolytic that influences both blood-brain barrier integrity and neutrophil trafficking into cerebral parenchyma.[7–12] Despite the well-established benefits of TXA in life-threatening hemorrhage and TBI, prehospital use seems less utilized, and also appears to be less frequently administered to women and the elderly.[13,14] These observations shroud the impact of specific therapeutics and their intersection with sex regarding outcomes. Since it

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remains unclear if rescue agents like TXA function differently based on sex, it is reasonable to explore that interaction in a preclinical model that balances sex across injury and treatment groups. We therefore evaluate the neurocognitive effects of post-severe TBI TXA and hypothesize that TXA influences neurocognitive recovery differently in male and female mice despite identical injury and postinjury management.

METHODS

Experimental Design and Study Groups

Experimental procedures were approved by the Institutional Animal Care and Use Committee and conducted in accordance with national guidelines for laboratory animal welfare. CD1 male and female mice weighing 25 to 30 g (Charles River Laboratories, Wilmington, MA) were acclimated in standard housing facilities with regular light and dark cycles and received chow and water *ad libitum*. All mice underwent a craniectomy on Day 0, followed by controlled cortical impact (CCI) or no injury (Sh [sham]; Fig. 1).

One hour later, all animals received a single tail vein intravenous injection of either (0.07 mL) normal saline (NS) (placebo [P]) (Baxter Healthcare Corporation, Deerfield, IL) or TXA (60 mg/kg) (AuroMedics Pharma LLC, E. Windsor, NJ). Tranexamic acid 60 mg kg^{-1} dosing reflects the murine pharmacokinetic profile in which the plasma half-life is approximately one-third that of humans, and replicates the area-under-the-curve achieved by a 2-g bolus in a 70-kg adult.[15]

Forty-eight mice were assigned to one of six groups (n = 8/group): (1) female + sham craniectomy + placebo (FSh + P); (2) female + CCI + placebo (FTBI + P); (3) female + CCI + TXA (FTBI + TXA); (4) male + Sham + placebo (MSh + P); (5) male + CCI + placebo (MTBI + P); (6) male + CCI + TXA (MTBI + TXA). Convenience sampling was used to denote group animal numbers, a practice supported by previous reports using identical Morris water maze and data analyses. Animal research data reporting guideline requirements were completed for in vivo experimentation in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) 2.0 guidelines to ensure transparency, reproducibility, and methodological rigor in preclinical animal research (Supplemental Digital Content 1, http://links.lww.com/TA/F90).

Severe TBI

Controlled cortical impact created a severe and reproducible brain injury using an established model.[16] On Day 0, mice were anesthetized with intraperitoneal ketamine (Mylan Institutional, Rockford, IL), xylazine (Akorn, Lake Forest, IL), and acepromazine (Beohringer Ingelheim, Duluth, GA) (KXA: 100, 10, 1 mg/kg, respectively). Subcutaneous bupivacaine (Fresenius Kabi USA, Lake Zurich, IL; 0.5 mg/mL) and buprenorphine-XR (Ethiqa XR, Fidelis Animal Health, North Brunswick, NJ; 1.3 mg/mL) provided extended analgesia. Mice were placed prone in a stereotactic device; a 4-mm diameter circular tracing on the left hemisphere was marked between the sagittal, bregma, and lambda sutures using a trephine. A dental drill (Henry Schein, Melville, NY) created a transcortical craniotomy without dural breach. After bone flap removal, a controlled cortical impactor (AMS201, AmScien Instruments, Richmond, VA) was used to create a standardized severe TBI injury on the left parietotemporal cortex, utilizing standard parameters: 3 mm diameter impactor tip, impact velocity of 6 m/s, cortical deformation depth of 1.0 mm, dwell time of 104 msec.[17] Sham mice underwent an identical craniectomy without CCI. Following hemostasis, scalp closure covered the exposed dura.

Body Weight Loss Recovery and Neurological Improvement

Post-TBI body weight loss/gain serves as a marker of recovery. Animal body weights were recorded immediately prior to the initial craniectomy (W0), and daily (W1, W2, W3, etc.) through Day 14. Weight loss/gain was expressed as a ratio ([W0-W*x*]/W0) × 100%, where 'x' represents the day after craniotomy.

Global neurological recovery was gauged with two scores averaged daily. First, the Garcia Neurological Test (GNT) assessed motor, sensory, reflex, and balance ability to a maximum of 18 points.[18] Second, the neurological severity score (NSS) evaluated 10 tasks: circle exit, seeking behavior, monoparesis, straight walk, startle reflex, beam balance, beam walk (3, 2, and 1 cm beam), and round stick balance. The maximum score was 13 points with a higher score indicating worse recovery.[19]

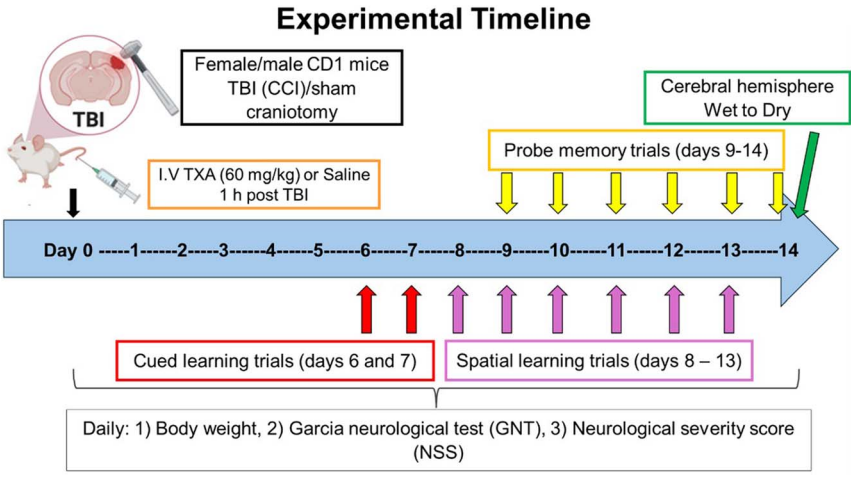

Figure 1. Experiments timeline.

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Morris Water Maze

Starting on post craniotomy Day 6, mice began daily swimming exercise trials in a Morris water maze (MWM) (Supplemental Digital Content 2, http://links.lww.com/TA/F91). The MWM consists of a circular plastic tank (100 cm diameter, 50 cm high) filled with 22°C water, which is divided into four quadrants with a 10-cm diameter platform (10% tank diameter) in the center of the north quadrant (Zone 1, Z1) (Supplemental Digital Content 2, http://links.lww.com/TA/F91). Zone 5 is the area of the pool where the platform is, regardless of whether it is above (cued trials) or below (spatial trials) the surface, or even completely absent (probe trials). Zones 6 and 7 were larger concentric zones delineated around Zone 5, 18 and 24 cm in diameter (Supplemental Digital Content 2, http://links.lww.com/TA/F91). All MWM trials were conducted and scored by a single operator.

Trials were video recorded using a digital camera mounted above the maze and equipped with video tracking software (Ethovision, Noldus, Leesburg, VA) that analyzed travel parameters (distance, time, quadrant crossings, etc.). Analyzed parameters included: latency in seconds (s) (the time to arrive at a given zone), distance traveled to reach the zone (in cm), absolute duration spent in Zone 5 (in s, only in probe trials), percent time spent in a given zone (only in probe and cued trials), and frequency of crossing into a given zone (number of times crossing into a Zone). Swimming velocity was measured in cm/s. Results are reported as a cumulative of all days unless otherwise specified.

Cued Learning Trials

Eight cued trials were conducted on postcraniotomy Days 6 and 7 (4 per day) to acclimate mice to the maze and establish the purpose of reaching the platform. During cued trials the platform is placed 1 cm above water level and is colorfully adorned with a red flag on the platform center making it highly visible (Supplemental Digital Content 2A, http://links.lww.com/TA/F91). No additional visual cues are included in these trials. Platform location was randomly changed and mice were randomly placed in the maze at different starting positions (north [N], east [E], south [S], and west [W]). The trial ends when the mouse either reaches the platform or after 60 seconds of swimming without reaching the platform. Mice that fail to reach the platform are gently retrieved and immediately placed on the platform to establish the platform as the objective. After 15 seconds on the platform, mice were removed from the maze, placed under a heat lamp, rewarmed, and rested for 10 minutes between trials.

Spatial Learning Trials

Spatial learning was assessed on Days 8 to 13 (4 trials/day × 6 days) to determine if mice could learn to reach the platform solely guided by colorful wall cues anchored at maze cardinal points (N, S, E, W). In these trials, the platform is submerged 1 cm below the surface in the center of Zone 1 (N) and devoid of the flag, rendering it invisible to the swimming mouse (Supplemental Digital Content 2B, http://links.lww.com/TA/F91). Each trial utilizes a different starting point with the mouse facing outward to prevent visual platform location during MWM entry. Similar to cued learning trials, mice that failed to reach the platform within 60 seconds were removed and placed on the platform for 15 seconds, followed by rewarming.

Probe Memory Trials

Probe memory trials were performed on Days 9 to 14 (1/day on Days 9–13; 4 trials on Day 14). The platform is now absent, but wall cues remain in place as for the spatial trials (Supplemental Digital Content 2C, http://links.lww.com/TA/F91). Probe trials evaluate the animals' long-term memory of platform position relying on visual cues. Mice are released at different starting points and allowed to swim for 30 seconds to assess how rapidly and frequently they swim to where they remember the platform to be located. Following this, mice are again rewarmed and rested period.

Brain Water Content

After Morris water maze trial exercises on Day 14, mice were euthanized and injured cerebral hemispheres were procured. Hemisphere wet weight (WW) was immediately recorded followed by dry weight (DW), which was measured after 72 hours of dehydration at 70°C. The percentage of tissue water content (edema) was calculated using a wet-to-dry ratio (% tissue water content = $[(WW - DW)/WW] \times 100\%$).

Statistical Analysis

Data are presented as means ± SEM and were analyzed using Prism software (GraphPad Software, San Diego, CA 2022). Intergroup differences were evaluated using analysis of variance with Bonferroni correction for multiple comparisons; statistical significance was assumed for $p < 0.05$.

RESULTS

Body Weight Loss Recovery and Neurological Improvement

Weight loss followed by weight recovery occurred in all animals across 14 days, with no significant differences among groups.

Garcia Neurological Test scores in injured TXA-treated female mice demonstrated improved neurologic recovery but later only, significantly on Days 7, 9, and 11 (post-TBI Day 11: FTBI+TXA: 17.4 ± 0.2 vs. FTBI+TXA: 18.0± 0.0, $p < 0.01$) (Fig. 2A). In injured male mice, GNT scores were improved early, in the first 3 days following TXA administration and most pronounced on Day 2 (MTBI+TXA: 16.3 ± 0.4 vs. MTBI+P: 14.5 ± 0.3, $p < 0.01$) (Fig. 2). Neurological Severity Scores demonstrated significant TXA-related improvements but only in males, not females. This was particularly manifest in the final 7 days, reaching maximal improvement on Day 8 (MTBI+TXA: 0.6 ± 0.3 vs. MTBI+P: 4.1 ± 0.9, $p < 0.01$) (Fig. 3).

Morris Water Maze

Cued Learning

There were no statistically significant intergroup differences regardless of treatment or sex during Days 6 and 7 cued learning trials as animals were getting acclimated to the Morris water maze.

Spatial Learning

Tranexamic acid improved female MWM spatial learning performance for only one parameter: the time to reach Zone 7 (z7 latency: FTBI+TXA: 10.2 ± 1.2 s vs. FTBI + P: 19.9 ± 2.1 s, $p < 0.001$). Tranexamic acid in males also improved z7 latency

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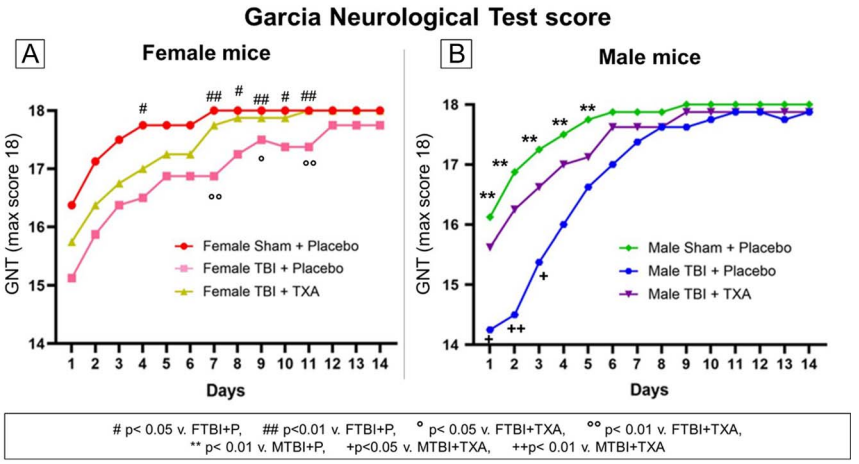

Figure 2. Functional animal neurological recovery over 14 days evaluated by the GNT that evaluates motor, sensory, reflex, and balance ability to a maximum sum of 18 points. *(A)* GNT in female animals, *(B)* GNT in male animals.

(MTBI+TXA: 10.7 ± 1.2 s v. MTBI + P: 28.4 ± 1.8 s, $p < 0.0001$) (Supplemental Digital Content 3A, http://links.lww.com/TA/F92) but also improved performance in five additional spatial learning parameters including latency to z1 (Fig. 4A), z5 (Fig. 4B), and z6 (Supplemental Digital Content 3B, http://links.lww.com/TA/F92) as well as number of male mice crossing into z6 (Fig. 4C) and z7 (Supplemental Digital Content 3C, http://links.lww.com/TA/F92). No other spatial learning parameters demonstrated significant differences between groups in either sex mouse.

Probe Memory

In memory probe trials, TXA improved female mice performance in the time duration spent in z1 (FTBI+P: 6.3 ± 0.5 s vs. FTBI+P: 4.2 ± 0.4 s, $p = 0.02$; SD3A). TXA increased z1 time duration in males as well (MTBI+TXA: 8.3 ± 0.5 s vs. MTB + P: 9.7 ± 0.5 s, $p = 0.01$; Supplemental Digital Content 4A, http://links.lww.com/TA/F93) but also improved male mice performance in four additional probe memory parameters: z7 time duration (Fig. 5A), z5 crossings (Fig. 5B, $p = 0.01$), and z6 crossings (MTBI + TXA: 1.9 ± 0.1 events vs. MTBI + P: 1.2 ± 0.1 events, $p = 0.01$) (Supplemental Digital Content 4B, http://links.lww.com/TA/F93). In addition, only male mice demonstrated greater swimming velocity in memory probe trials (Fig. 5C). No other probe memory parameters demonstrated significant differences between groups in either sex mouse.

Brain Water Content

At 14 days, the injured cerebral hemisphere of TXA-treated males was found to harbor less edema with significantly less water content as compared with untreated injured males (MTBI+TXA: 77.8 ± 0.2 vs. MTBI+P: 78.6 ± 0.3, $p = 0.02$) (Fig. 6). There were no such differences in cerebral edema across female groups (FTBI+TXA: 77.6 ± 0.1 vs. FTBI+P: 77.8 ± 0.1, $p > 0.999$).

DISCUSSION

In the current study, we evaluated sex-related effects of post-TBI Tranexamic acid on learning and memory using a

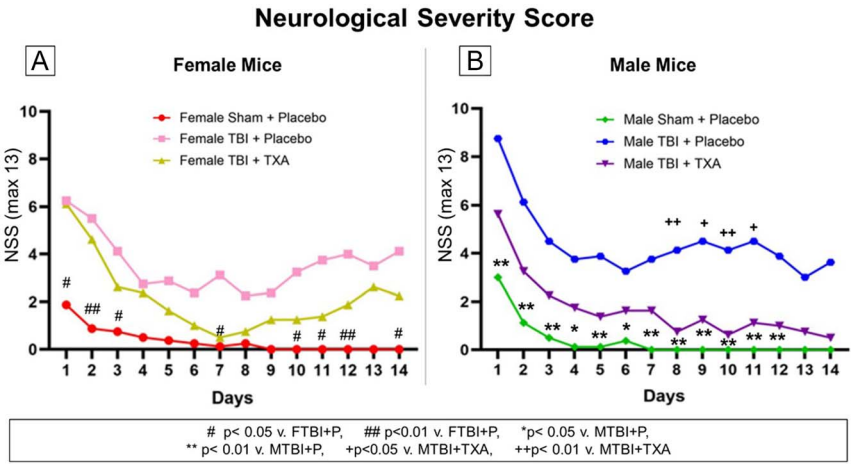

Figure 3. NSS over 14 days, which evaluates the neurological recovery through ten tasks (exit circle, seeking behavior, monoparesis, straight walk, startle reflex, beam balance, beam walk, and round stick balance). The maximum score is 13, which indicates a worse outcome. *(A)* NSS in female animals, *(B)* NSS in male animals.

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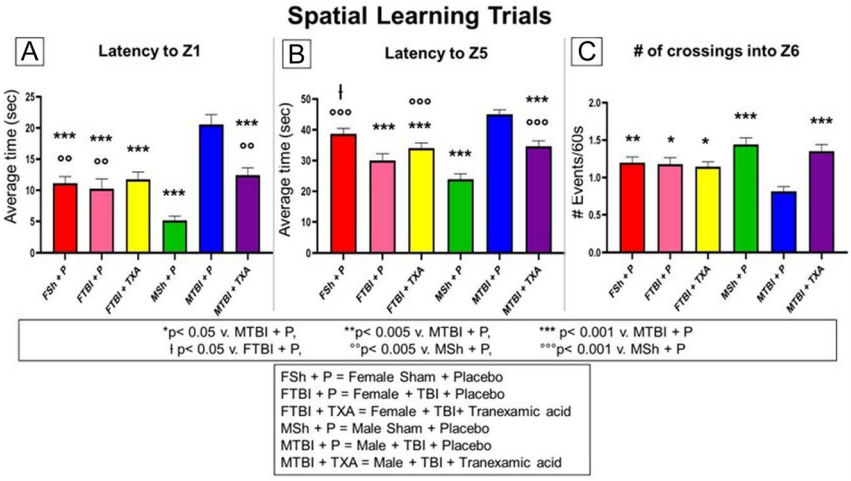

Figure 4. Spatial learning trials *(A)* Mean time required for mice to reach Zone 1 (north quadrant) for the first 60 seconds of swimming. *(B)* Mean time required for mice to reach Zone 5 (platform). *(C)* Mean number of crossing into Zone 6 (area of 18 cm surrounding the platform) for the first 60 seconds of swimming.

validated severe TBI murine model. While TXA demonstrated certain benefits in both females and males, we observed that males benefited from TXA treatment across a broader range of neurocognitive recovery parameters. Improved NSS were only noted in males while GNT improvements occurred early in males and late in females—these results provide evidence of sex-linked divergence despite identical injury and care profile. Functional assessments that interrogated learning and memory also cement that TXA's benefit is principally aligned with male sex. Since TXA is clinically used regardless of sex, especially for those with severe TBI as well as for those with hemorrhagic shock, our data cast doubt on the expectation of similar benefit and similarly enhanced outcomes in female populations.

Severe TBI survival often engenders substantial morbidity including neurocognitive impairment.[20,21] Moderate to severe TBI survivorship is prominently marked by deficits in attention, processing speed, memory, and executive functioning.[22,23] Indeed, neurocognitive recovery underpins progress to regaining independence or requiring aid that spans complete care to aid in activities of daily living. Learning and memory are two key aspects of that recovery, even when motor strength and coordination are both intact. Memory loss and impairment are profound sequelae of TBI compared with other cognitive functions, particularly after injury to the anterior temporal lobe and hippocampus. Recovery is slow and certain deficits may persist for 2 years following moderate TBI and up to 10 years after severe injury.[23,24] Peri-injury therapeutics that reduce the neurocognitive impact of moderate or severe TBI have historically been quite limited and this has prompted investigation into novel approaches ranging from neuropharmacology to neural stem cell implantation.[25,26] Our data suggest that development of such therapeutics should consider sex-specific differences, thereby expanding the model of pharmacogenomics in developing effective agents on the basis of genetic signatures.[27]

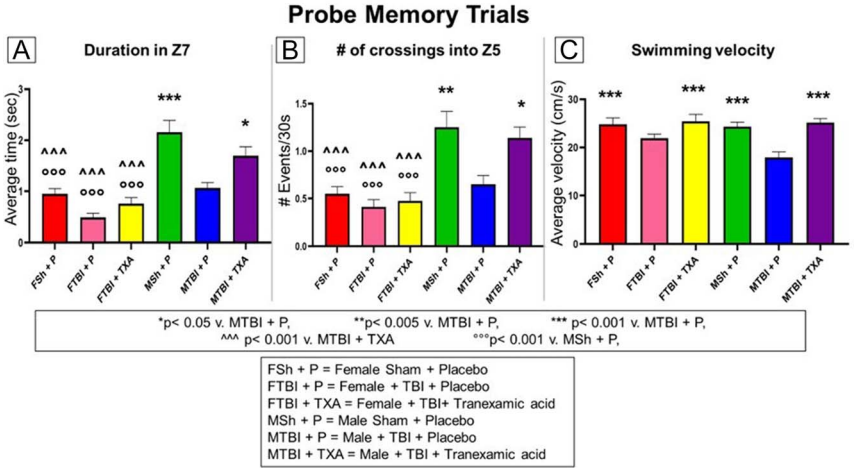

Figure 5. Probe Memory Trials *(A)* Time the animal spent into Zone 7 (area of 24 cm surrounding the platform) during the 30 seconds of swimming. *(B)* Mean number of times the animal crossed into Zone 5 during the 30 seconds of swimming. *(C)* Mean velocity of animal swimming during 30 seconds of swimming.

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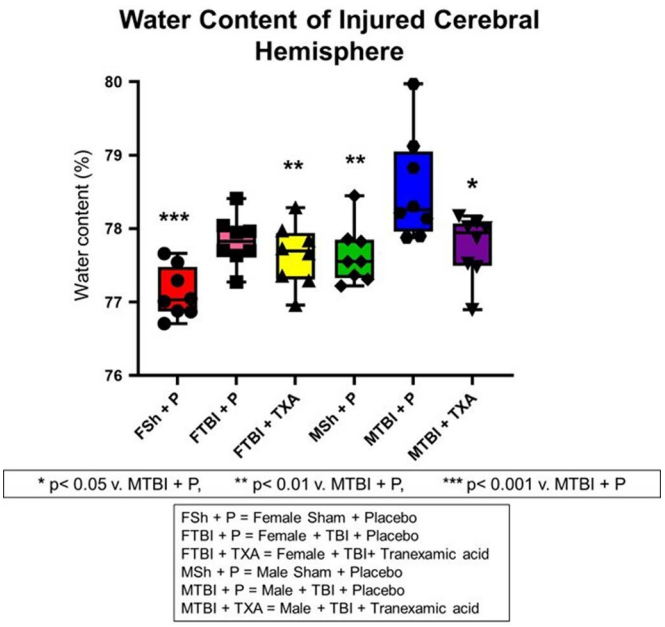

Figure 6. Ipsilateral hemisphere brain water content at 14 days measured by wet-to-dry analysis.

Traumatic brain injury is increasingly identified in women, perhaps due to enhanced participation in contact sports enlistment in the military, as well as augmented reporting of intimate partner violence.[3,28] Our current preclinical results would anticipate a fairly uniform difference between male and female neurocognitive outcomes after TBI; instead, human results are inconsistent when parsed by sex.[28] For example, sex did not appear to influence severe TBI outcomes in data from the Chinese Head Trauma Study collaborators, while others note enhanced cognitive recovery in women.[23,24,29] Studies that document improved neurocognitive recovery in females often anchored their observations in the purported protective action of a sex-based hormonal milieu. Nonetheless, a recent prospective multicenter exploration of progesterone therapy (ProTECT trial) failed to secure benefit after acute TBI compared with P, potentially dislodging the protective hormone theory.[30,31] This suggests that factors beyond hormonal influences contribute to female resilience after brain injury, such as processes that impact blood-brain barrier integrity, post-injury inflammatory cell trafficking and parenchymal infiltration, which may provide a mechanism to explore to understand divergent sex-related outcomes.[32] Of course, those mechanisms will likely rely on a multi-'omics approach as it is unlikely that a single element bears responsibility for successful neurocognitive recovery. Nonetheless, certain omic interactions may serve as more suitable targets for pharmacotherapeutic agents.[33]

Tranexamic acid helps arrest hyperfibrinolysis that is prevalent following injury but also interfaces with a variety of host pro and counter inflammatory processes such as cytokines and the complement system.[34] Since inflammation is tethered to maladaptive neurocognitive outcomes, it is plausible that TXA would reduce parenchymal inflammation and enhance cerebral healing.[35–37] In one clinical study, for example, injured military combatants treated with TXA achieved improved Glasgow Coma Scale scores despite no evidence of altered intracranial hemorrhage progression.[28] Unfortunately, other such military studies were unable to find any beneficial effects.[38] Given that most military studies address men, the data is likely not extrapolatable to injured women.

Neurocognitive recovery is a complex process that may be conceptualized using a time-based evaluation of neural component regenerative potential. Such potential is considered at its peak early following TBI but is influenced by a variety of factors that are not amenable to clinician manipulation such as age and injury severity, but potentially also sex.[39] On the other hand, specific therapies may be selected based on sex if there were data to drive such intervention; unfortunately, most studies that examine TXA have been performed in only males. For example, earlier work that explored rapid TXA administration after severe TBI documented enhanced BBB integrity, reduced injured hemisphere edema, and improved neurocognitive outcomes [7,8,11].

Preclinical studies enable equal allocation of treatment(s) across groups that sustain identical injury; unsurprisingly clinical care data is plagued by great heterogeneity. For instance, while TXA reduces post-TBI mortality similarly in men and women across a number of studies, women are less likely to receive TXA treatment in routine practice regardless of injury severity or hemorrhagic shock risk.[40] An inclusion allocation bias that led to treatment allocation disparity was evident within studies, such as CRASH-2 and CRASH-3 where both studies included only 20% females.[36,37] It is important to investigate whether certain therapies are better aligned with one sex—a task impeded by unequal sex allocation across treatment groups when interrogating clinical data.

While we explored sex-related outcome differences following TBI and TXA administration, our study is preclinical and has important limitations. Although it employed a controlled TBI model, mice have a different physiology to that of humans, making the direct translation to clinical human studies uncertain. Our study lasted for 2 weeks after injury and as such, longer-term outcomes were not explicitly addressed. Nonetheless, when equating human and murine lifespans one may equate one human year to nine mouse days. A 14-day follow-up in mice approximates 1.5 human years and is sufficient to capture medium-term cognitive sequelae that often follow traumatic brain injury.[41] Extending observation to 42 days (≈4.5 human years) in future studies would allow evaluation of longer-term durability and late-emerging effects. The estrous cycle of the female mice was not captured, nor were female sex hormone concentrations measured.[39] These aspects may inform additional explorations now that a sex-based differential effects seem feasible to explore within this model architecture. Finally, TBI was established via CCI, a focal and blunt mechanism that may be rather different from other TBI mechanisms (penetrating, blast TBI) regarding outcomes and responses to TXA. In addition, TBI was the sole injury and therefore may not reflect outcomes following multiple injuries but may instead provide a platform from which to explore that influence.

CONCLUSION

This study identifies sex-related differences in the effects of post-TBI TXA therapy. Although TXA has some beneficial impact on both sexes, learning and memory are asymmetrically

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enhanced in males, which is associated with reduced cerebral edema, also only in males. These observations seem to relate to previously identified mechanistic differences in male versus female response to TBI and TXA therapy underpinned by improved vascular integrity and reduced inflammation. Therefore, TBI should be deliberately and separately studied in males and females to enhance understanding of differences in physiology and recovery. Such improved understanding, in turn may guide development of sex-specific therapeutics.

AUTHORSHIP

All authors have reviewed and approved the final article version. P.S.C., G.A.B., and J.L.P. participated in the conception and study design. P.S.C., E.K., L.J.K., J.L.P. participated in the literature review. P.S.C., E.K., A.K., M.C., D.A., A.G. participated in the data acquisition. P.S.C., L.J.K., J.L.P. participated in the data analysis and interpretation. P.S.C., J.L.P., L.J.K. participated in the drafting of the article. P.S.C., L.J.K., E.K., A.K., M.C., P.B., M.C., A.G., D.A., D.M., D.S., G.B., J.L.P. participated in the critical revision.

DISCLOSURE

Author disclosure forms have been supplied and are provided as Supplemental Digital Content (http://links.lww.com/TA/F89).
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REFERENCES

1. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic brain injury: an overview of epidemiology, pathophysiology, and medical management. *Med Clin North Am*. 2020;104(2):213–238.
2. de Freitas Cardoso MG, Faleiro RM, de Paula JJ, Kummer A, Caramelli P, Teixeira AL, et al. Cognitive impairment following acute mild traumatic brain injury. *Front Neurol*. 2019;10:198.
3. Späni CB, Braun DJ, Van Eldik LJ. Sex-related responses after traumatic brain injury: considerations for preclinical modeling. *Front Neuroendocrinol*. 2018;50:52–66.
4. Semple BD, Dixit S, Shultz SR, Boon WC, O'Brien TJ. Sex-dependent changes in neuronal morphology and psychosocial behaviors after pediatric brain injury. *Behav Brain Res*. 2017;319:48–62.
5. Rauen K, Späni CB, Tartaglia MC, Ferretti MT, Reichelt L, Probst P, et al. Quality of life after traumatic brain injury: a cross-sectional analysis uncovers age- and sex-related differences over the adult life span. *Geroscience*. 2021;43(1):263–278.
6. Moore DW, Ashman TA, Cantor JB, Krinick RJ, Spielman LA. Does gender influence cognitive outcome after traumatic brain injury? *Neuropsychol Rehabil*. 2010;20(3):340–354.
7. Culkin MC, Bele P, Georges AP, Santos P, Niziolek G, Kaplan LJ, et al. Dose-dependent tranexamic acid blunting of penumbral leukocyte mobilization and blood–brain barrier permeability following traumatic brain injury: an in vivo murine study. *Neurocrit Care*. 2024;41(2):469–478.
8. Culkin MC, Bele P, Georges AP, Lopez AJ, Niziolek G, Jacovides CL, et al. Early posttraumatic brain injury tranexamic acid prevents blood-brain barrier hyperpermeability and improves surrogates of neuroclinical recovery. *J Trauma Acute Care Surg*. 2023;95(1):47–54.
9. Culkin MC, Coons M, Bele P, Thaploo A, Georges AP, Anderson E, et al. Delayed tranexamic acid after traumatic brain injury impedes learning and memory: early tranexamic acid is favorable but not in sham animals. *J Trauma Acute Care Surg*. 2024;96(1):26–34.
10. Gando S, Shiraishi A, Wada T, Yamakawa K, Fujishima S, Saitoh D, et al. Effects of tranexamic acid on coagulofibrinolytic markers during the early stage of severe trauma: a propensity score-matched analysis. *Medicine (Baltimore)*. 2022;101(32):e29711.
11. Daglas M, Galle A, Draxler DF, Ho H, Liu Z, Sashindranath M, et al. Sex-dependent effects of tranexamic acid on blood-brain barrier permeability and the immune response following traumatic brain injury in mice. *J Thromb Haemost*. 2020;18(10):2658–2671.
12. Medcalf RL, Keragala CB. Fibrinolysis: a primordial system linked to the immune response. *Int J Mol Sci*. 2021;22(7):3406.
13. Girardello C, Carron PN, Dami F, Darioli V, Pasquier M, Ageron FX. Evaluation of the prehospital administration of tranexamic acid for injured patients: a state-wide observational study with sex and age-disaggregated analysis. *Emerg Med J*. 2024;41(8):452–458.
14. Nicholson H, Scotney N, Briscoe S, Kirby K, Bedson A, Goodwin L, et al. Factors that influence the administration of tranexamic acid (TXA) to trauma patients in prehospital settings: a systematic review. *BMJ Open*. 2023;13(5):e073075.
15. Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA*. 2020;324(10):961–974.
16. Bele P, Thaploo A, Coons M, Culkin MC, Santos P, Martinez-Quinones P, et al. Daily quetiapine after severe TBI improves learning and memory. *J Trauma Acute Care Surg [Internet]*. 2024; [cited 2024 Sep 13]; Available from: https://journals.lww.com/10.1097/TA.0000000000004400.
17. Smith DH, Soares HD, Pierce JS, Perlman KG, Saatman KE, Meaney DF, et al. A model of parasagittal controlled cortical impact in the mouse: cognitive and histopathologic effects. *J Neurotrauma*. 1995;12(2):169–178.
18. Garcia JH, Wagner S, Liu KF, Hu XJ. Neurological deficit and extent of neuronal necrosis attributable to middle cerebral artery occlusion in rats. Statistical validation. *Stroke*. 1995;26(4):627–634 discussion 635.
19. Khalin I, Jamari NA, Abdul Razak N, Hasain Z, Mohd Nor MB, Zainudin MBA, et al. A mouse model of weight-drop closed head injury: emphasis on cognitive and neurological deficiency. *Neural Regen Res*. 2016;11(4):630.
20. Thompson HJ, LeBold DG, Marklund N, Morales DM, Hagner AP, McIntosh TK. Cognitive evaluation of traumatically brain-injured rats using serial testing in the Morris water maze. *Restor Neurol Neurosci*. 2006;24(2):109–114.
21. Menon DK, Schwab K, Wright DW, Maas AI. Position statement: definition of traumatic brain injury. *Arch Phys Med Rehabil*. 2010;91(11):1637–1640.
22. Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am*. 2014;37(1):1–11.
23. Cristofori I, Levin HS. Traumatic brain injury and cognition. *Handb Clin Neurol*. 2015;128:579–611.
24. Zec RF, Zellers D, Belman J, Miller J, Matthews J, Femeau-Belman D, et al. Long-term consequences of severe closed head injury on episodic memory. *J Clin Exp Neuropsychol*. 2001;23(5):671–691.
25. Hering C, Shetty AK. Extracellular vesicles derived from neural stem cells, astrocytes, and microglia as therapeutics for easing TBI-induced brain dysfunction. *Stem Cells Transl Med*. 2023;12(3):140–153.
26. Gao Y, Liu N, Chen J, Zheng P, Niu J, Tang S, et al. Neuropharmacological insight into preventive intervention in posttraumatic epilepsy based on regulating glutamate homeostasis. *CNS Neurosci Ther*. 2023;29(9):2430–2444.
27. Pirmohamed M. Pharmacogenomics: current status and future perspectives. *Nat Rev Genet*. 2023;24(6):350–362.
28. Haynes N, Goodwin T. Literature review of sex differences in mTBI. *Mil Med*. 2023;188(5–6):e978–e984.
29. Chinese Head Trauma Study Collaborators. Chinese Head Trauma Data Bank: effect of gender on the outcome of patients with acute traumatic brain injury. *J Neurotrauma*. 2021;38(8):1164–1167.
30. Wright DW, Kellermann AL, Hertzberg VS, Clark PL, Frankel M, Goldstein FC, et al. ProTECT: a randomized clinical trial of progesterone for acute traumatic brain injury. *Ann Emerg Med*. 2007;49(4):391–402, 402.e1–2.
31. Wright DW, Yeatts SD, Silbergleit R, Palesch YY, Hertzberg VS, Frankel M, et al. Very early administration of progesterone for acute traumatic brain injury. *N Engl J Med*. 2014;371(26):2457–2466.
32. Santos Carlin P, Kaplan L, Coons M, Bele P, Culkin M, Kauffman A, Augustin D, Georges A, Bass G, Johnson V, Smith D, Pascual J. Post-TBI tranexamic acid benefits demonstrate sex dependence. *Presented at 54th Western Trauma Association Annual Meeting*. 2025; Whistler, British Columbia, Canada.
33. Vandereyken K, Sifrim A, Thienpont B, Voet T. Methods and applications for single-cell and spatial multi-omics. *Nat Rev Genet*. 2023;24(8):494–515.
34. Barrett CD, Kong YW, Yaffe MB. Influence of Tranexamic acid on inflammatory signaling in trauma. *Semin Thromb Hemost*. 2020;46(2):183–188.
35. Guo Y, Li J, Hagström E, Ny T. Beneficial and detrimental effects of plasmin (ogen) during infection and sepsis in mice. *PloS One*. 2011;6(9):e24774.
36. Syrovets T, Lunov O, Simmet T. Plasmin as a proinflammatory cell activator. *J Leukoc Biol*. 2012;92(3):509–519.
37. Hastings S, Myles PS, Medcalf RL. Plasmin, immunity, and surgical site infection. *J Clin Med*. 2021;10(10):2070.

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38. Walker PF, Bozzay JD, Johnston LR, Elster EA, Rodriguez CJ, Bradley MJ. Outcomes of tranexamic acid administration in military trauma patients with intracranial hemorrhage: a cohort study. *BMC Emerg Med*. 2020;20(1):39.
39. Mollayeva T, Mollayeva S, Pacheco N, D'Souza A, Colantonio A. The course and prognostic factors of cognitive outcomes after traumatic brain injury: a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2019; 99:198–250.
40. Nutbeam T, Roberts I, Weekes L, Shakur-Still H, Brenner A, Ageron FX. Use of tranexamic acid in major trauma: a sex-disaggregated analysis of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2 and CRASH-3) trials and UK trauma registry (Trauma and Audit Research Network) data. *Br J Anaesth*. 2022;129(2):191–199.
41. Dutta S, Sengupta P. Men and mice: relating their ages. *Life Sci*. 2016;152: 244–248.

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